## SPECIFIC AIMS

Survivors of childhood cancers face multiple late effects of their initial cancer therapy. One of the most consequential is the occurrence of a subsequent neoplasm (SN). Subsequent breast cancer is the second most common type of SN, following non-melanoma skin cancers, among survivors of childhood cancer, and the associated risk factors and incidence have been well-described.[1-3] Among survivors of childhood cancer who received chest radiotherapy for their primary malignancy, cumulative breast cancer incidence estimates at age 40 years have ranged from 13-35%.[4-6] Given the previous frequent use of chest radiotherapy in Hodgkin lymphoma (HL), this population of survivors has been studied in detail. Their risk for breast cancer is 4-5 fold greater than the general population[4,7,8] and this elevated risk persists into the 5th and 6th decades of life.[9,10] Recently, it was reported that breast cancer risk is increased among certain groups of survivors not previously treated with chest radiotherapy, specifically those with a primary childhood cancer diagnosis of leukemia or sarcoma and those treated with alkylating agents and anthracyclines.[11]

Although much attention has been given to subsequent breast cancer risk among survivors, there are limited data on treatment, treatment-related toxicities, survival and physician decision making for these challenging SNs. Survivors of childhood cancer have previously been exposed to therapies, including radiation and/or anthracyclines, which may limit their ability to receive standard-of-care breast cancer therapy. Compared to primary breast cancer patients, survivors of adult and pediatric HL that developed breast cancer were more likely to undergo mastectomy and less likely to receive radiation.[12,13] Overall survival (OS) after breast cancer for HL survivors was inferior to those without a prior cancer history,[12,13] with increased risk for mortality secondary to cardiovascular causes and non-breast cancer SNs.[12] Although these analyses of breast cancer in HL survivors provide valuable data and enhance understanding of breast cancer outcomes among cancer survivors, much remains unknown. Specifically, analyses have not focused on childhood cancer survivors, so prior treatment exposures and co-morbidities were likely quite different. Furthermore, the focus on HL survivors prohibits generalizability to survivors of other childhood cancers because of their older age at diagnosis and treatment homogeneity.

The Childhood Cancer Survivor Study (CCSS) is a multi-institution cohort of 24,363 5-year survivors of childhood cancer diagnosed between 1970-1999 with detailed treatment, survival and validated SN data. At present the CCSS contains 486 cases of subsequent breast cancer. The CCSS includes extensive follow-up and comprehensive data on the primary and secondary cancers, and thus provides a unique opportunity to address the identified knowledge gaps. *We hypothesize that survivors of childhood cancer diagnosed with a subsequent breast cancer will experience inferior OS and event-free survival (EFS) following breast cancer treatment, will receive therapy that deviates from the standard of care for individuals with primary breast cancer of the same age and disease stage, and that childhood cancer survivors will experience higher rates of treatment-related toxicity compared to women with a primary breast cancer receiving similar therapy.* We will address these hypotheses through the following specific aims:

**Specific Aim 1: Survival Following Subsequent Breast Cancers.** Quantify OS and EFS among CCSS participants with breast cancer and compare with SEER OS estimates, and with OS and EFS in an age-, breast cancer stage- and treatment era-matched comparison cohort of women with primary breast cancer. *Hypothesis:* OS and EFS will be inferior among women treated for subsequent breast cancer compared to women treated for primary breast cancer with similar stage and disease characteristics.

**Specific Aim 2: Treatment and Treatment-Related Toxicity for Subsequent Breast Cancer.** Compare prescribed treatment and breast cancer treatment-related toxicity between CCSS participants with breast cancer and a comparison cohort of women with primary breast cancer, matched on age, breast cancer stage and treatment era. Explore differences between subsequent breast cancer treatment and National Comprehensive Cancer Network treatment guidelines. *Hypothesis:* Women treated for subsequent breast cancer will be less likely to be prescribed treatment with anthracyclines or radiation and will experience more treatment-related toxicity compared to women treated for primary breast cancer.

**Specific Aim 3: Treatment Decision Making for Subsequent Breast Cancer.** Perform semi-structured interviews with medical and radiation oncologists to understand drivers of treatment decision-making, and use responses to create a broad-reaching survey for distribution to medical and radiation oncologists. *Hypothesis:* Treatment decisions will be highly variable and will be strongly influenced by the survivors' previous treatment exposures and by the provider's practice setting.

This project will provide data necessary to **improve outcomes** in this high-risk and vulnerable population. Understanding the drivers of decisions and the way women with subsequent breast cancers are treated will guide educational interventions and development of treatment guidelines for subsequent breast cancer.

## SIGNIFICANCE

Survival following a diagnosis of childhood cancer has improved dramatically over the course of the last four decades, such that it now exceeds 80%[14] and by the year 2020, it is estimated that there will be 500,000 survivors of childhood cancer living in the United States.[15] Despite increased rates of survival, survivors of childhood cancer experience an average of 17 chronic health conditions, 5 of which are severe and potentially life threatening.[16] This is nearly double the rate seen in the general population and many of these conditions are late health complications, or "late effects," secondary to their previous cancer therapy.[16] One of the most challenging categories of late effects is the development of a subsequent neoplasm (SN). Presently, approximately 20% of survivors will experience at least one SN by 30 years from their initial childhood cancer diagnosis,[1] and risk of developing a SN remains elevated compared to the general population even into the 5th and 6th decades of life.[10]

The development of SNs among survivors of childhood cancer has been well-studied, with the first reports dating back to the 1960s and the treatment-related risk factors are well-documented.[17-20] Therapeutic radiation as part of treatment for a childhood malignancy is strongly associated with solid SN risk,[1,21] and in many types of SNs including cancers of the breast, central nervous system (CNS) and sarcomas, there is a clear dose-response relationship.[22-24] Subsequent breast cancers are the second most frequently observed SN exceeded only by non-melanoma skin cancers.[3] Along with their known association with therapeutic radiation,[6] secondary breast cancers have also been associated with chemotherapeutic exposures, including alkylating agents and anthracyclines, in women not previously treated with chest irradiation.[11] Subsequent breast cancers are frequently seen after a primary diagnosis of Hodgkin lymphoma, one of the most common malignancies of children and young adults, and a malignancy that historically was treated with high-dose radiation.[4,7] Strikingly, the cumulative risk for breast cancer at age 50 following a diagnosis of Hodgkin lymphoma is comparable to that observed among women who carry a *BRCA1* gene mutation (35% vs. 31%, respectively; Figure 1).[6]

Figure 1. Cumulative risk for breast cancer in Hodgkin lymphoma survivors and BRCA mutation carriers.[6]

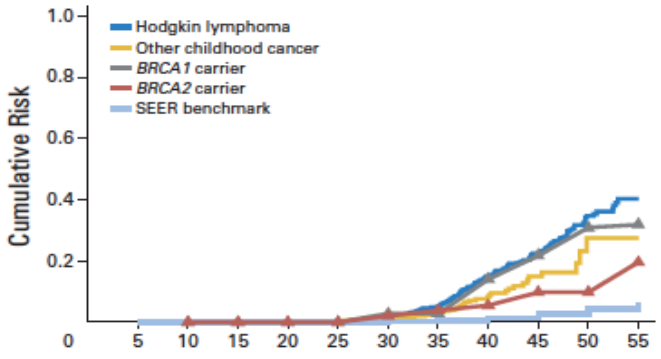
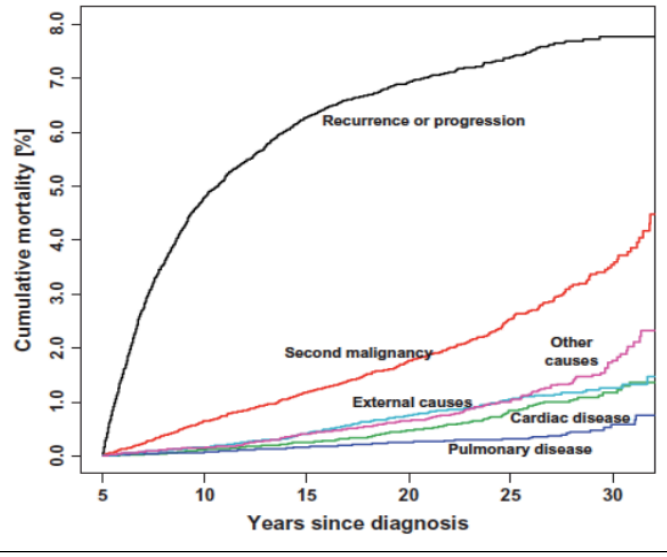



Figure 2. Cause-specific cumulative mortality, based on time since diagnosis. Red line shows subsequent malignancy.[25]




Despite a growing understanding of why subsequent breast cancers develop in survivors of childhood cancer, and well-defined treatment protocols for primary breast cancers, much remains unknown about how subsequent breast cancers are medically managed. Mortality from subsequent malignancies exceeds deaths from other medical causes or disease recurrence by 20 years from initial childhood cancer diagnosis[25] (Figure 2) and it is not clear whether this is secondary to the subsequent malignancy itself, to toxicities from therapy for the subsequent malignancy or to other disease-related complications. Medical decision making for these SNs is complicated by multiple factors. Notably, because of treatments received for the primary childhood malignancy, such as high cumulative doses of anthracycline chemotherapy or high-dose mantle field or chest radiation, or total body irradiation (TBI), many survivors experience long-term chronic health conditions that may alter the treatment that can safely be delivered for a subsequent cancer. The St. Jude Lifetime Cohort recently reported that by age 50 years, the cumulative incidence of a chronic health condition among survivors was 99.9%, with an average of 4.7 severe conditions per survivor.[16] These chronic conditions, along with prior treatment exposures, limit the survivors' ability to tolerate standard-of-care breast cancer therapy.

Few previous studies have presented detailed treatment data on breast cancer occurring in long-term cancer survivors, and none have focused specifically on survivors of childhood cancer. Prior studies examining

subsequent breast cancers have focused on survivors of Hodgkin lymphoma, combined all adult and adolescent cases, and reported on limited case series.[8,12,13,26] Compared to primary breast cancer patients, breast cancers in Hodgkin lymphoma survivors were more likely to be diagnosed by screening and were more likely to be bilateral.[13] In addition, treatment was more likely to include mastectomy and less likely to include radiation.[12,13] Milano and colleagues reported that Hodgkin lymphoma survivors with a subsequent breast cancer experienced inferior overall survival compared to women with a primary breast cancer, in part because of excess deaths from cardiac disease and other subsequent cancers. In addition, women with localized breast cancer with a history of Hodgkin lymphoma had worse breast cancer-specific survival.[12] Although these studies are informative in describing breast cancer among Hodgkin lymphoma survivors, there are several critical gaps in knowledge. ***First***, the majority of available data on subsequent breast cancers are from individuals diagnosed with Hodgkin lymphoma as adults, such that data from the 10-20% of pediatric Hodgkin lymphoma survivors cannot be separated from individuals exposed to primary cancer therapy at older ages. This is important because the tissue response to therapeutic exposures during peak periods of growth and development may be very different from what is seen in adults. ***Second***, previous series have been limited to Hodgkin lymphoma survivors and little is known about survivors of other types of cancer who may have been exposed to different therapies. Forty percent of subsequent breast cancers among survivors of childhood cancer occurred after diagnoses other than Hodgkin lymphoma. ***Third,*** there has not been a description of chemotherapy used in this population or how therapy delivered differs from contemporary standards of care. These data are necessary to understand recurrence rates, toxicity and survival among this unique population, all of which will inform the development of appropriate treatment guidelines for this high-risk cancer population.

To address these knowledge gaps, we propose to study individuals from the Childhood Cancer Survivor Study (CCSS) that have developed subsequent breast cancers. The CCSS is a North American retrospective cohort study of 24,362 5-year survivors of childhood cancer from 31 centers who were diagnosed with their initial cancer between 1970-1999 at <21 years of age. This group is well-characterized, with detailed information on their primary childhood cancer diagnosis, cancer therapies for the childhood cancer, including surgery, chemotherapy, and radiation, and validated subsequent cancer diagnoses. The CCSS Coordinating Center has extensive experience with successfully tracking survivors and obtaining medical records. This study will be the first, to our knowledge, to address treatment of, and toxicities and survival following subsequent breast cancer in a large population of long-term survivors of childhood cancer. We will perform detailed medical record review of CCSS participants with breast cancer, construct a geographically diverse, age-, race and ethnicity-, breast cancer stage-, and treatment era-matched comparison cohort of women with primary breast cancer to analyze differences in survival and toxicity, and use a qualitatively-driven mixed methods approach to understand predictors of treatment decision making by medical and radiation oncologists. No other cohort in North America is of comparable size or has the level of detailed primary cancer treatment and SN data to permit a similar study. Our findings will provide valuable data for developing future treatment guidelines for this vulnerable and medically complex population and will identify targets for education and intervention among oncology providers.

## INNOVATION

This study leverages the resources of the CCSS, a large retrospective cohort study with comprehensive data on treatment and SNs, with a combination of quantitative and qualitative analyses to create new knowledge on the outcomes of women with subsequent breast cancers following a childhood cancer diagnosis, how they are treated and how they tolerate therapy. The number of survivors of childhood cancer in the United States is expected to reach 500,000 by the year 2020,[15] many of whom will be at risk for a subsequent breast cancer. This first-of-its-kind study will inform the development of much needed treatment guidelines and will identify targets for education and intervention among survivors and providers.

## APPROACH

### Preliminary Work

***Work from the University of Minnesota.*** We recently performed an exploratory analysis of women with a history of adolescent and young adult Hodgkin lymphoma who received therapeutic chest radiation treated at a University of Minnesota-Fairview Health System affiliated clinic or hospital between 1969 and 2003 who were subsequently diagnosed with breast cancer (N=42). Treatment and toxicity data were abstracted from the medical record for a subgroup (N=15). Detailed data were abstracted regarding Hodgkin lymphoma diagnosis and treatment, including radiation fields and prescribed dose and chemotherapy regimens, and also breast

cancer data, including diagnostic data, tumor characteristics, and treatment and outcomes information. Radiation therapy was only prescribed as treatment for one patient with breast cancer. Approximately 20% of women did not tolerate chemotherapy as prescribed and required dose modifications or discontinuation, and 33% required use of growth factor. Although the sample was small, the feasibility of this approach, including collecting necessary details on subsequent breast cancer characteristics and treatment from clinics not affiliated with the University was demonstrated and confirmed the importance of studying subsequent breast cancer treatment and treatment-related toxicity in additional populations, including those treated for their primary cancer as children.

***Work from the CCSS.*** Within the CCSS, we have identified 486 women with subsequent breast cancer diagnoses (Table 1). Subsequent breast cancer cases were initially self-reported via questionnaires and are then validated through review of pathology reports by a pathologist and an oncologist. Other medical records or death certificates were used for validation when pathology reports were not available. Only SNs occurring ≥5 years following the childhood cancer diagnosis are included for analyses. The CCSS is the only cohort in North America that could address the questions posed in this study, and based on a small pilot Dr. Turcotte performed abstracting charts already on-hand at the CCSS Coordinating Center of 10 survivors with breast cancer, the proposed aims can feasibly be completed. Breast cancer details, including histology, stage, hormone receptor status, laterality and location was available in all 10 charts. Treatment data, including surgery, chemotherapy regimens (if used), radiation dose, was clearly identified in 8, 9, and 7 charts, respectively. Toxicity data, including use of growth factor, fever and neutropenia episodes, peripheral neuropathy, and therapy dose reductions and/or omissions were described in 7 of 10 charts. Abstractions were performed on charts that were previously pursued by the CCSS Coordinating Center; no attempts were made to obtain additional records to fill in missing data. Although charts were not complete for all variables of interest on initial review, this pilot demonstrated feasibility of abstracting data from medical charts from a variety of outside centers for the purpose of addressing these study aims.

Table 1. Characteristics of women with breast cancer in CCSS.

| **Characteristics** | **N = 486 (%)** |
|---|---|
| Childhood cancer diagnosis | |
| Leukemia | 43 (8.8) |
| CNS | 9 (1.9) |
| Hodgkin lymphoma | 310 (63.8) |
| NHL | 17 (3.5) |
| Wilms | 9 (1.9) |
| Neuroblastoma | 4 (0.8) |
| Soft tissue sarcoma | 28 (5.8) |
| Bone | 66 (13.6) |
| Previous treatment with chest XRT | |
| Yes | 346 (71.2) |
| Previous treatment with TBI | |
| Yes | 4 (0.8) |
| Previous anthracycline exposure | |
| None | 300 (61.8) |
| 1-100 | 9 (1.9) |
| 101-300 | 87 (17.9) |
| >300 | 90 (18.4) |
| Year of breast cancer diagnosis | |
| 1995-2000 | 106 (21.8) |
| 2001-2005 | 111 (22.8) |
| 2006-2010 | 120 (24.7) |
| 2011-2016 | 149 (30.7) |
| Age at breast cancer diagnosis | **N, mean (SD)** |
| 18-29 | 35, 25.9 (3.0) |
| 30-39 | 232, 35.7 (2.7) |
| 40-49 | 204, 44.0 (2.8) |
| >/=50 | 14, 51.7 (0.9) |

Dr. Turcotte has extensive experience working with the CCSS SN data. In 2012, she reviewed and validated all existing SN cases in the CCSS. Since then, she and her mentor, Dr. Neglia, have prospectively reviewed and validated all SN cases. Dr. Turcotte has also successfully initiated studies through the CCSS and has experience collaborating with a multi-site, multidisciplinary team to complete these studies. In 2015, she published a high-impact analysis in the *Journal of Clinical Oncology* of late-occurring subsequent cancers among survivors of childhood cancer, which demonstrated risk for SNs persisting into the 6$^{th}$ decade of life.[10] She then published an analysis of changes in SNs over time in *JAMA* and was the first to demonstrate reductions in SNs attributable to reductions in radiation therapy exposure over time.[3] She has co-authored two additional CCSS published manuscripts on the topic of subsequent breast cancers.[27,28]

**Research Design**

**Specific Aim 1: Survival Following Subsequent Breast Cancer.** There are minimal data on overall (OS) and event-free survival (EFS) following a subsequent breast cancer diagnosis among survivors of childhood cancer. We hypothesize that OS and EFS following breast cancer diagnosis will be inferior among survivors of childhood cancer, in part because of increased risk for mortality from non-breast cancer causes compared to women with primary breast cancer diagnoses and also because we hypothesize that they are less likely to receive anthracycline chemotherapy or therapeutic radiation, which may compromise long-term cure. This aim will be addressed by comparing OS and EFS among women from the CCSS cohort who have developed

subsequent breast cancer with a comparison cohort of women, matched on age, race and ethnicity, breast cancer stage and 5-year treatment era, and also with SEER OS estimates, based on disease stage. This will be carried out as an ancillary study through the CCSS. This has been reviewed and approved by the study's Steering Committee and by the CCSS principal investigator, Dr. Gregory Armstrong (see letter of support).

***Study Population:*** The CCSS is a North American retrospective cohort study of 24,362 5-year survivors of childhood cancer from 31 centers diagnosed with their initial cancer between 1970-1999 at less than 21 years of age. Participants had a primary diagnosis of leukemia, central nervous system malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney malignancy, neuroblastoma, soft tissue sarcoma or bone tumor. Participants completed a baseline and up to 4 follow-up questionnaires (https://ccss.stjude.org/tools-and-documents/questionnaires/expanded-cohort-questionnaires.html). Detailed data on primary childhood cancer diagnosis, previous surgeries, chemotherapy agents and cumulative doses, and radiation site(s) and cumulative doses were collected at the time of cohort enrollment. SNs were identified through self or proxy report and were then validated by pathology report review. Human subjects committee approval was granted at all participating institutions prior to recruitment. Detailed description of CCSS methodology is published elsewhere.[29]

Female participants in the CCSS cohort that have a confirmed diagnosis of breast cancer (Invasive Ductal Carcinoma [IDC], Ductal Carcinoma In Situ [DCIS], Invasive Lobular Carcinoma [ILC], Lobular Carcinoma In Situ [LCIS]), diagnosed between 1995 and 2016, occurring when the survivor is 18 years of age or older will be included. Breast cancer must have occurred at least 5 years after initial childhood cancer diagnosis. Participants must have treatment data available from their primary childhood cancer treatment and must provide informed consent (via self or proxy, if deceased) for release of medical records for their subsequent breast cancer. Potential participants (or spouse or next of kin, if deceased) who have not yet provided informed consent, but who meet other eligibility criteria will be approached for consent to obtain medical records related to treatment for their subsequent breast cancer. CCSS subsequent breast cancer population descriptive data are summarized in Table 1.

A cohort of women with primary breast cancer will be constructed for comparison with the participants from the CCSS with breast cancer. The comparison cohort will be geographically diverse, consisting of women diagnosed at the University of Minnesota, Duke University or the University of Chicago (see letters of support). By selecting three sites, we will increase racial and ethnic diversity and will increase the potential diversity of breast cancer management styles. We will match the comparison cohort 1:1 from the pool of all three centers, based on age at diagnosis (within 5 years), race and ethnicity, breast cancer histology, stage, hormone receptor status, and year of diagnosis (within 5 years), with an approximately equal number sampled from each center. If an appropriate match cannot be identified at the initially selected site, attempts will be made at one of the other two sites. This will be carried out with close collaboration from Dr. Yasui (biostatistics co-mentor), Dr. Neglia (primary mentor), Dr. Blaes (co-mentor) and collaborating centers. Women included in the comparison cohort with a primary breast cancer diagnosis cannot have a history of previous malignancy or underlying serious medical condition.

***Participant Data:*** We will use previously abstracted CCSS data including patient year of birth, year of childhood cancer diagnosis, type of childhood cancer, history of other non-breast cancer SNs (yes/no, type), reported cardiac dysfunction, and vital status. Treatment related data from the initial childhood cancer diagnosis include: cumulative anthracycline exposure, cumulative alkylating agent exposure (reported as a cyclophosphamide equivalent dose[30]), history of TBI (yes/no), non-TBI therapeutic radiation body sites (chest, abdomen, pelvis, extremities, etc.), and cumulative therapeutic radiation exposure dose from the radiation dosimetry conducted by the Radiation Dosimetry Center of the CCSS at MD Anderson Cancer Center. Organ dysfunction and chronic health reported prior to the onset of breast cancer will be collected and graded according to Common Terminology Criteria for Adverse Events [CTCAE] (version 4). Breast cancer variables will include: age at breast cancer diagnosis, year of breast cancer diagnosis, breast cancer histology, laterality, involved breast quadrant(s), stage and TNM status, non-breast sites of disease involvement, hormone receptor status (estrogen receptor, progesterone receptor), and HER2 status. Vital status and cause of death will be collected for cases and the comparison cohort using data from National Death Index.

***Data Analysis:*** Overall (OS) and event-free survival (EFS) will be estimated using the Kaplan-Meier method.[31] OS and EFS in women with subsequent breast cancers will be compared to Surveillance, Epidemiology, and End Results Program (SEER) estimates, based on breast cancer stage, and also to the matched comparison cohort. We will examine whether differences exist in survival outcomes based on primary childhood cancer diagnosis, initially comparing Hodgkin lymphoma to all other diagnoses together, using the log-rank test. If

sample size permits, comparisons with specific primary diagnoses (leukemia, bone cancer) will be analyzed. Cox regression models will be used to adjust for the influence of chronic health conditions and childhood cancer treatment exposures on survival.

***Sample size consideration:*** Based on desired power of 80% and $\alpha$=0.05, using 5-year OS of 90% in the comparison cohort[32], and a plan to sample 1:1, our sample size of 486 cases and comparison cohort participants will allow us to detect a 6-8% difference in OS, or a minimally detected RR=0.6 (Table 2).

Table 2. Sample size considerations for Aim 2.

| *Rate in comparison group* | *Rate in cases* | *RR* | *N per group* |
|---|---|---|---|
| 90% | 88% | 0.8 | 3215 |
| 90% | 86% | 0.7 | 1199 |
| **90%** | **84%** | **0.6** | **555** |
| **90%** | **82%** | **0.5** | **284** |
| 90% | 78% | 0.4 | 153 |

***Potential Limitations and Expected Outcomes:*** It is anticipated that matching will be imperfect. By including a multi-center contemporarily treated comparison cohort, we hope to optimize our chances of matching the geographically diverse CCSS cohort. The age at breast cancer diagnosis is younger among the CCSS participants with breast cancer than in the general population. If this difference limits our ability to match on other characteristics, we will consider removing that matching criteria to enhance our ability to match on other characteristics better to best capture differences between women with primary and subsequent breast cancer.

**Specific Aim 2: Treatment and Treatment-Related Toxicity for Subsequent Breast Cancer**. As described above, there has not been a comprehensive report of how women are treated for subsequent breast cancers occurring after a diagnosis of childhood cancer, nor has it been described how they tolerate subsequent breast cancer therapy. Among women with early stage primary breast cancer, oncologists' treatment recommendations have been highly concordant (95%) with the National Comprehensive Cancer Network (NCCN) treatment guidelines.[33] We hypothesize that women with a history of childhood malignancy will be prescribed therapy that is different from a matched comparison cohort of women with similar breast cancer characteristics and stage and is also discordant from the therapies described in the contemporary standard of care guidelines, as defined by the NCCN. We anticipate these differences will include more frequent omission of therapeutic radiation and anthracyclines because of their previous exposures. It is further hypothesized that women with subsequent breast cancer will experience increased breast cancer treatment-associated toxicity compared to women diagnosed with primary breast cancer. This is predicted in part because of their previous treatment exposures from their childhood cancer and resultant baseline chronic health conditions.

***Study Population:*** Using the same population of women with subsequent breast cancers from the CCSS and the comparison cohort identified for aim 1, we will further examine those women for whom detailed breast cancer treatment data are available in their medical records.

***Participant Data:*** We will use previously abstracted CCSS data as described in aim 1, including patient demographics, childhood cancer diagnosis and treatment data, baseline chronic conditions graded based on CTCAE criteria. Breast cancer variables will be abstracted from the medical records of CCSS participants and comparison cohort members and will include disease characteristics described in aim 1. Medical records, including pathology reports, imaging studies, chemotherapy/treatment records, radiation records, progress notes, hospital admission and discharge summaries, will be requested for all participants based on the center/treating physician they identified as the site of diagnosis and/or treatment for breast cancer. Treatment data will be abstracted using a standardized medical record abstraction form (MRAF) designed by Dr. Turcotte and her mentoring team. She will perform all chart abstractions to ensure consistent methods are used for all patient records. Abstracted data will include: type of surgery (lumpectomy, mastectomy), cumulative dosing of any chemotherapy agents, use of selective estrogen receptor modulators (SERMs) and type of SERM prescribed, use of HER2 receptor blockers, treatment with radiation (yes/no, type), and field(s), number of fractions and cumulative radiation dose. A subset of 50 randomly selected record abstractions (~10%) will be validated by Drs. Neglia and Blaes to minimize bias. Differences identified between reviewers will be discussed and reconciled and if abstractions are consistently >5% different between reviewers, an additional 50 abstractions will be validated until abstractions are consistently <5% different.

To assess breast cancer treatment-related toxicity, the following information will be abstracted from the medical records of CCSS participants and breast cancer comparison cohort: duration of each treatment cycle, documented infections (culture positive bacterial, fungal viral infections), admissions for fever and neutropenia (number of admissions and duration of each admission), prophylactic use of granulocyte colony growth factor (GCSF), chemotherapy dose reductions, discontinuation of therapy or omitted chemotherapy agents or cycles, surgical complications, radiation-induced skin changes, other radiation-associated toxicity (ex: radiation-

induced brachial plexopathy), any reported end-organ toxicities (abnormal liver function tests, echocardiogram abnormalities, GFR changes; organ involved and if available, grade of abnormality based on CTCAE criteria).

***Data Analysis:*** Descriptive statistics will be reported for the CCSS and breast cancer comparison cohort populations. Breast cancer treatment data will be summarized for all breast cancer cases. We will examine if the stage at diagnosis, the method of detection (routine screening vs. self-exam vs. other), surgical approach, or treatments prescribed vary based on decade of breast cancer diagnosis. Differences in type of surgery, cumulative dosing of chemotherapies, and cumulative dosing of therapeutic radiation will be compared between CCSS breast cancer patients and age-, race and ethnicity-, breast cancer stage-, and treatment era-matched comparison cohort participants. As an exploratory analysis, therapy delivered to CCSS subsequent breast cancer cases will also be compared to treatment era-specific NCCN Clinical Practice Guidelines (first introduced in 1995), based on breast cancer clinical stage and histology. We will identify the proportion of survivors in whom radiation or anthracycline
therapy was omitted or dose reduced when it would otherwise have been standard of care, and to quantify the number of women being treated with mastectomy vs. breast-conserving approaches. Additional logistic regression analyses within CCSS cases will examine whether previous anthracycline, alkylating agent and radiotherapy exposure significantly influenced whether an individual with subsequent breast cancer received standard of care breast cancer treatment, considering both yes/no, as well as cumulative doses of exposures.

Differences in number and distribution of types and CTCAE grades of on-therapy toxicities experienced, between CCSS participants and the comparison cohort will be evaluated, stratified by breast cancer stage. Using logistic regression, we will evaluate if specific previous therapeutic exposures or baseline organ dysfunction increase risk for breast cancer treatment-related grade 3 or greater toxicities among survivors of childhood cancer. We will describe the number of women with subsequent breast cancer that successfully completed prescribed therapy without treatment-related modifications and will determine if specific characteristics are predictive of successful completion of therapy.

***Sample size consideration:*** Based on desired power of 80% and $\alpha$=0.05, using $\geq$ grade 3 CTCAE neutropenia estimate of 40% in the comparison cohort, and a plan to sample 1:1, our sample size of 486 cases and comparison cohort participants will allow us to detect an 8-12% difference in toxicity, or a minimally detected RR=1.6 (Table 3).

Table 3. Sample size considerations for Aim 2.

| *Rate in comparison group* | *Rate in cases* | *RR* | *N per group* |
|---|---|---|---|
| 40% | 44% | 1.2 | 1939 |
| **40%** | **48%** | **1.4** | **566** |
| **40%** | **52%** | **1.6** | **289** |
| 40% | 55% | 1.8 | 185 |
| 40% | 57% | 2.0 | 134 |

***Potential Limitations and Expected Outcomes:*** This aim is dependent on obtaining detailed treatment records from multiple treating institutions, based on participants' recall of their treating physician and medical center. The CCSS Coordinating Center has extensive experience and an established history of success in tracking down medical records regarding SNs, with an overall success rate of 83% in their most recent follow-up survey. Based on a recent pilot review of CCSS records that have already been obtained, >70% were inclusive of the desired data. With this level of available chart detail prior to additional patient record tracking by the CCSS Coordinating Center, we are confident we will accomplish the outlined aim of describing therapeutic differences between women with subsequent breast cancer vs. the comparison cohort. By relying on medical records, it is possible that toxicities will be incomplete. This will potentially be more problematic in CCSS cases compared to the comparison group, since the collaborating investigators at comparison cohort sites will be able to review the full medical record for toxicity detail and within CCSS we are dependent on what records are submitted from outside sites. It does appear, based on the pilot review of 10 CCSS records, that comprehensive on-therapy records will be available for the majority of cases, permitting a detailed assessment of toxicity. Since Dr. Turcotte will not be blinded to any characteristics about the CCSS participants or comparison cohort, the validation of a random sample of abstracted records will help overcome potential biases.

**Specific Aim 3: Treatment Decision Making for Subsequent Breast Cancer.** Treatment planning and recommendations for subsequent breast cancer are made by the treating medical oncologists and radiation oncologists, and presently there are no standard-of-care treatments or guidelines for women in this unique scenario. The limited available data on subsequent breast cancer management and heterogeneous reported approaches make medical decision making difficult for providers who may not frequently manage survivors of childhood cancer. For this aim, we will survey practicing medical oncologists and radiation oncologists, both in academic and community settings, to better understand how previous therapeutic exposures, other health

conditions/late effects, and providers' own experiences shape treatment decision-making and recommendations for women with subsequent breast cancer. We hypothesize that treatment decisions will be highly variable and will be strongly influenced by the survivors' previous treatment exposures and by the provider's practice setting.

***Study Population:*** We will request a list of physician names and email addresses, filtering for specialty in medical oncology and radiation oncology and participation in direct patient care, from a commercial vendor (SK&A, Irvine, CA) that has an up-to-date, comprehensive list of practicing U.S. physicians. The vendor has estimated approximately 7,600 available names and contacts. This will allow access to a broad population of medical oncologists and radiation oncologists from diverse practice settings (academic and private) and from a broad geographic distribution. The vendor-supplied sample will be enriched for medical oncologists and radiation oncologists practicing at the 49 National Cancer Institute (NCI) comprehensive cancer centers by performing internet searches at those centers for individuals who identify a specialization in breast cancer care.

***Participant Data:*** Semi-structured interviews will be performed by Dr. Turcotte following training and pilot interviews with University of Minnesota physicians performed under the observation of Dr. Carolyn Porta (K08 co-mentor). Physicians selected for the interview will be identified from the list described above and will represent a geographically diverse group of medical and radiation oncologists practicing in both academic and private settings, intentionally selecting physicians that are early, mid and later career, and equally sampling males and females. Interviews will be used to assess knowledge, comfort and perceived challenges in managing subsequent breast cancer. Questions will be open-ended with probes available. Directed content analysis will be used to identify major themes.[34] The number of interviews needed to be performed will depend on saturation of content themes, meaning interviews will be performed until no new themes arise within the last two interviews and the identified themes and concepts are replicated by multiple interviewees. A minimum of 15 interviews will be performed, but it is anticipated that 20-30 interviews will be completed.

These themes will then be used to design a multiple choice, vignette-based survey. The survey will be distributed to the 7,600 medical and radiation oncologists described above. The survey will be conducted using the modified Dillman method, initially via email with follow-up mailings and phone call reminders to non-responders. A gift card incentive will be offered for participation.[35] The survey will initially be delivered via an email link to the web-based University of Minnesota Qualtrics survey system. This secure survey tool has complex survey capabilities for survey design and allows for collection of both qualitative and quantitative data (https://survey.umn.edu/qualtrics-u-of-m). The surveys will consist of a series of 6 clinical vignettes, each followed by a series of questions about how they would manage specific aspects of the vignette patient's care. The vignettes will be created based on the major themes identified in the semi-structured interviews and will be refined using an iterative design process, with the guidance of a medical oncologist with expertise in breast cancer and cancer survivorship. Content validation will occur both through review by content experts as well as by physicians outside the target audience. Consultation will be sought through the Minnesota Center for Survey Research within the Office of Measurement Services at the University of Minnesota to ensure the survey design and sampling techniques are optimized. The survey will confirm physician participation in direct patient care. Responses will be multiple choice and respondents will be asked to select one answer per question. The opportunity to include written comments will be provided at the end of each vignette. We will also request basic demographic information including age, sex, geographic location of medical practice, practice setting (academic, private), physician specialty (radiation or medical oncology), area of cancer specialty (breast, non-breast specialized, general). Based on previous surveys of a similar physician population, we anticipate a response rate of 40-60%.[36,37]

***Data Analysis:*** For the semi-structured interview data, directed content analysis,[34] as described above, will be performed. Descriptive statistics will be presented for respondent demographic and practice characteristics. Relative frequencies will be calculated for each vignette question. Differences in responses will be assessed based on respondent age, practice location and specialty. Any comments will be qualitatively summarized.

***Potential Limitations and Expected Outcomes:*** Survey studies are frequently limited by the response rate, which can lead to non-response bias. There is also the potential for survey bias, where respondents may provide answers that differ from their true opinions. We will attempt to overcome these limitations by using evidence-based strategies for survey distribution, incentives and reminders.[35] We will also perform the semi-structured interviews to help formulate survey questions, thereby examining themes identified by medical and radiation oncologists rather than the principal investigator. Sampling biases will be overcome, in part, by using an established commercial vendor (SK&A) with a track record of providing a comprehensive list of accurate and frequently updated physician contact and practice data.

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

This project will address a significant knowledge gap in the field of SNs in survivors of childhood cancer. The population of survivors of childhood cancer continues to grow, and as survivors age into adulthood the risk for developing subsequent malignancies is increased. Presently, although the incidence and risk factors for subsequent breast cancers are well understood and additional work on genetic susceptibility is ongoing,[27] standard treatment practices are not established. Completion of the proposed aims will lead to increased knowledge on how survivors with subsequent breast cancers are currently treated, how they tolerate therapy and how their survival compares to women with primary breast cancers. Data from this study can be leveraged for the process of developing initial treatment guidelines and will provide guidance to medical and radiation oncologists on whether specific therapies (chest radiation, anthracyclines) can be safely delivered. Survey data from treating physicians can be used to develop targeted educational interventions. There are multiple directions for future federal funding that will enhance the management and quality of life of this vulnerable and high-needs population. As the principal investigator of this project, I will lead all aspects of the proposed aims, including subject identification and recruitment, study design, and the analysis and presentation of data. This work will allow for valuable interactions with an experienced mentoring team, including Drs. Joseph Neglia, Anne Blaes, Yutaka Yasui, and Carolyn Porta, along with input from Dr. Smita Bhatia and the leadership of the CCSS. The skills in study design, mixed methods study methodology and study leadership developed with this study, along with my current skill set, will leave me well-positioned to lead novel and high-impact survivorship studies. I envision this project as a transition point from mentored physician scientist to independent investigator and will demonstrate this through a planned R01 submission during the final year of this study.

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