I. STUDY TITLE: Impact of radiotherapy breast dose and dose-volume metrics on subsequent breast cancers in female childhood cancer survivors: A Report from the Childhood Cancer Survivor Study

II. WORKING GROUP AND INVESTIGATORS:

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Secondary Working Group: Epidemiology/Biostatistics

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III. Background And Rationale:

Treatment for childhood cancer has significantly advanced in recent decades, with the 5-year survival rate now reaching 85%[1]. It is estimated that approximately 15,000 children will be diagnosed each year in the United States, introducing approximately 13,000 additional childhood cancer survivors every year into a population that currently exceeds a half-million[1,2]. While an overwhelming majority of children will survive their primary cancer, they are at risk for various treatment-related late adverse conditions occurring decades after their diagnoses. One of the most prominent and devastating late effects is the development of subsequent cancers, with approximately 20% of survivors experiencing at least one subsequent neoplasm within 30 years following their initial diagnosis[3].

Studies have clearly established a strong association between radiation therapy (RT) and the development of subsequent cancers[4–8], with subsequent breast cancer (SBC) being the most frequently observed among female childhood cancer survivors, excluding nonmelanoma skin cancer[9]. One of the most significant treatment related SBC risk factors is chest-directed RT with many studies reporting increased risk with increased dose to the chest. The highest SBC risk has been observed in survivors of childhood Hodgkin lymphoma treated with high doses of chest-directed RT [10]. Over twenty years ago, Travis et al. in a case control study of SBC in Hodgkin lymphoma survivors (ages < 30 years at diagnosis) reported 3.2- and 8.0-fold statistically significant increased risks for doses > 4 Gy and 40 Gy, respectively to the site of the SBC[4]. Of note is that the Travis cohort were treated with radiation techniques, doses, and volumes not currently used, and specific breast dose mapping (dosimetry) was not performed. In another case-control study of females in the Childhood Cancer Survivor Study (CCSS), Inskip et. al. reported a linear dose response as a function of RT dose to the site of the SBC with risks being 11-fold higher for doses > 40 Gy, while those whose treatment delivered a sterilizing dose to the ovaries of greater than 5 Gy had only a 3.4-fold risk [5]. While these studies were seminal works, case-control studies do not directly estimate absolute risks or cumulative incidence rates, which are critical for developing personalized surveillance or treatment planning guidelines. Additionally, dose to the site of the SBC is difficult to translate into patient-specific surveillance guidelines or use as breast dose constraints in RT treatment planning for newly diagnosed females.

Over the past three decades, as imaging techniques have improved to allow more accurate delineation of tumor volumes, RT has become increasingly conformal, reducing the dose to healthy tissues. For Hodgkin lymphoma patients, the volume of breast tissue irradiated during RT has dramatically decreased as the standard of care has evolved from conventional mantle field irradiation to 3D conformal techniques to intensity modulated photon therapy and proton therapy. While past investigations have shown that chest RT doses < 20Gy, as is common with contemporary therapy, have reduced risk for SBC[11], more recent studies have found that despite contemporary therapy methods using more conformal RT with lower doses for Hodgkin lymphoma, the risk for breast cancer still remains higher for this group than the general population[12]. Such findings have sparked heightened interest in better understanding the dose-volume effect in SBC risk. For example, does irradiating large volumes of tissue to lower doses or small volumes to higher doses confer more risk? This knowledge gap was recently highlighted in the Pediatric Normal Tissue in The Clinic (PENTEC) Reports[13,14]. A recent SBC case-control study of mostly adult survivors (30% ages 11 to 20 and 70% ages 21 to 40) of Hodgkin lymphoma reported a statistically significant linear dose-response relationship with mean breast dose and positive associations with several dose-volume metrics[15]. However, breast and breast-dose volume metrics have not been considered as SBC risk factors solely among survivors of childhood cancer (ages less than 21 years at diagnosis) with a broad range of primary cancer diagnoses.

Investigating the dose-volume effect on a cohort level is essential to provide population-based absolute risks and dose-response relationships across the full spectrum of radiation exposures and patient characteristics, enabling evidence-based treatment planning and the development of clinically relevant dose constraints for pediatric radiation oncology. However, most childhood cancer survivor cohorts with long-term follow-up are mainly comprised of individuals treated with conventional 2D RT, and thus breast doses or dose-volume metrics

are not available in their historic medical records. In the absence of these metrics, studies have leveraged the available data to derive surrogate approximation metrics. De Bruin et al. considered a cohort of over 1,000 female Hodgkin lymphoma survivors (28% ≤ 20 years) and found that those treated with mediastinal RT fields compared to those treated with full mantle fields (with the former and latter considered surrogates for small and large breast volumes, respectively) had a lower risk of developing an SBC[11]. However, a limitation of that study was that they only considered field type and not dose to each field. Following that work, Moskowitz et al. evaluated SBC risk among 1,230 female CCSS survivors treated with any chest-directed RT considering both field type and field dose. They reported elevated SBC risk for those treated with low dose (median 14 Gy, range 2 to 20 Gy) whole lung fields (surrogate for large breast volume treated), as well as high dose (median 40 Gy) mantle fields (also a surrogate for large volume), i.e., large volumes of breast treated is an important risk factor for SBC[16]. In a more recent, larger cohort study, Henderson et. al. quantified the risk of SBC for 11,550 females in the CCSS and evaluated how rates changed as treatment exposures evolved over 3 decades. Chest-directed RT was included as a risk factor, with chest maximum target dose estimated by summing the delivered target doses for all overlapping chest fields. This study reported that exposure to chest RT was associated with higher breast cancer risk and that high-dose anthracyclines and chest RT have an interactive effect.[9] Using chest target dose, rather than dose to the breast, does not account for the fact that the tumor volume in the chest may not overlap with the breast volume and therefore does not always represent dose to the tissue at risk for breast cancer that can be translated clinically for radiotherapy treatment plan optimization in newly diagnosed girls and adolescents. While the case-control study of Hodgkin lymphoma survivors (ages 11 to 40) by Roberti et. al. reported a positive association with mean dose and dose-volume metrics[15], breast dose reconstructions for that study did not account for dosimetric differences between fully developed and underdeveloped/developing breasts among survivors treated as adults versus as children/adolescents.

Risk of SBC associated with breast dose and dose volume-metrics has not previously been reported for any cohort comprised solely of long-term survivors whose age at diagnoses spanned from infancy to 20 years and who were diagnosed with different types of primary cancers. This lack of reported associations is largely due to the challenges associated with reconstructing breast doses for thousands of young girls and adolescents treated in the pre-CT era of RT whose breasts were at different stages of development at the time of their RT. For the CCSS to carry-out such a study, our methodology to estimate organ doses by reconstructing survivors' RT on age-matched phantoms needs refinement to address the unique challenges of breast dosimetry across a wide age distribution. Foremost among the challenges is that the 6,016 females in the CCSS who received RT spanned all five Tanner stages including nipple, bud, underdeveloped, developing, and fully developed breasts. Complete cohort dosimetry requires estimating doses for the nipple, breast bud, and underdeveloped breasts for development stages 1, 2, and 3 respectively, as well as breast doses for stages 4 and 5. The MD Anderson Late Effects (MDA-LE) computational phantom that we use for dose reconstruction has a cuboid geometry, which is appropriate for calculating doses for internal organs and organs near the surface of the phantom[17]. The nipples, breast buds, and underdeveloped breasts lie very close to the surface of the chest and thus the existing methodology can be used for dose reconstructions for survivors who were in development stages 1, 2, or 3 (at the time of RT). Additionally, for survivors at development stages 4 and 5 at the time of RT, but <u>not treated with chest-directed RT</u>, our existing methodology can be used to calculate out-of-field breast doses because there is little change in stray radiation dose with depth in phantom. For survivors who were at development stages 4 or 5 at the time of RT and <u>treated with chest-directed RT</u>, our existing methodology cannot accurately calculate breast dose or dose volume metrics due to the inability to add organs anterior to the phantom's surface as is the case for developing and fully developed breasts. Therefore, for this study we developed and validated a pediatric population average breast model for a CT-based age-scalable phantom. The complete dosimetry plan for this study is described in the Dosimetry section of this proposal.

Significance: To our knowledge, no other study comprised of solely survivors whose age at diagnoses spanned from infancy to 20 years, has established SBC dose-response relationships for specific breast dose and dose-volume metrics, and also taken ovarian dose and other breast cancer risk factors into account. As treatments

continue to become significantly more conformal, prescribed dose to the tumor or max chest dose becomes an increasingly less accurate metric of the dose that the volume of the breasts may have received during treatment. Therefore, risk estimates based on less conformal RT prescription doses are less applicable, especially when HL treatments today typically use lower RT doses, 10-25 Gy vs 35-45 Gy. While useful for screening and follow up care, prescription doses cannot be incorporated into treatment planning of current and future patients. Reconstructing actual breast doses and developing dose-response models from dose-volume metrics will allow us to obtain more applicable risk models for clinical translation in the modern treatment era. Specifically, our findings could provide valuable information that ultimately can be clinically translated for risk-tailored guidelines, which could be used both prospectively in contemporary treatment planning as potential breast dose-volume constraints for newly diagnosed girls and adolescents and retrospectively to better refine post-treatment surveillance strategies for current patients and future survivors.

STUDY POPULATION:

The population for this study includes all 5-year female survivors in the CCSS (N = 12,338) diagnosed with their initial cancer from 1970 – 1999, at under 21 years of age. Detailed information on primary diagnosis, age at diagnosis, and subsequent cancer development is outlined in the Appendix. Of the 12,338 5-year female survivors in the CCSS, 755 breast cancer cases were reported among 608 survivors. All subsequent breast cancer cases were classified as either non-invasive (N = 218) or invasive SBC (N = 537) via pathology reports, and must have occurred at least 5 years after their initial childhood cancer diagnosis.

DOSIMETRY FOR SURVIVORS TREATED WITH RADIATION THERAPY

All breast dosimetry will be performed by the CCSS Radiation Physics Center at MD Anderson. Breast staging at the time of RT, which is not available for the CCSS, will be approximated based on median age of entry into the five stages of breast development and considering race and ethnicity. This methodology was used in a prior CCSS SBC case-control study[5] and based on data from Sun et al (**Appendix 1**).[18]

Each survivor's RT (N=6,016) will be reconstructed on an age-scaled phantom with one of three breast dosimetry models (**Figure 1**) selected according to estimated breast development at the time of their RT, i.e., nipple/bud (stage 1 and 2), underdeveloped breast (stage 3), and developing/developed breast (stage 4 or 5). The nipple/bud and underdeveloped breast models were previously established and have been used in prior CCSS studies. The developing/developed breast model is a population-based model developed specifically for this study (**Appendix A4**). One of two computational phantoms will be used for dose reconstructions, either the MD Anderson Late Effects Phantom (MDA-LE) or the 15-year-old female International Commission on Radiological Protection (ICRP) CT-based phantom selected based on criteria below. Phantoms and their organs will be scaled to the age at the time of RT using an in-house age scaling algorithm.[19]

- When the nipple/bud or underdeveloped breast models are selected (stage 1-3), dose reconstructions will be carried-out using the MDA-LE phantom for survivors treated with any radiotherapy, i.e., chest and non-chest-directed RT (**Figure 1a**).
- When the developing/developed breast model is selected (stage 4-5), dose reconstructions will be carried-out using the MDA-LE phantom for survivor's treated with non-chest directed RT (**Figure 1b**) and the ICRP phantom for survivors treated with chest-directed RT (**Figure 1c**).

Dose reconstructions will use beam parameters previously abstracted from survivors' historic radiotherapy records, e.g., prescription dose, beam type, energy, configuration and laterality, field type, field size, and field blocking. Additionally, ovarian doses were previously calculated for all females in the CCSS and will also be used in the analyses.

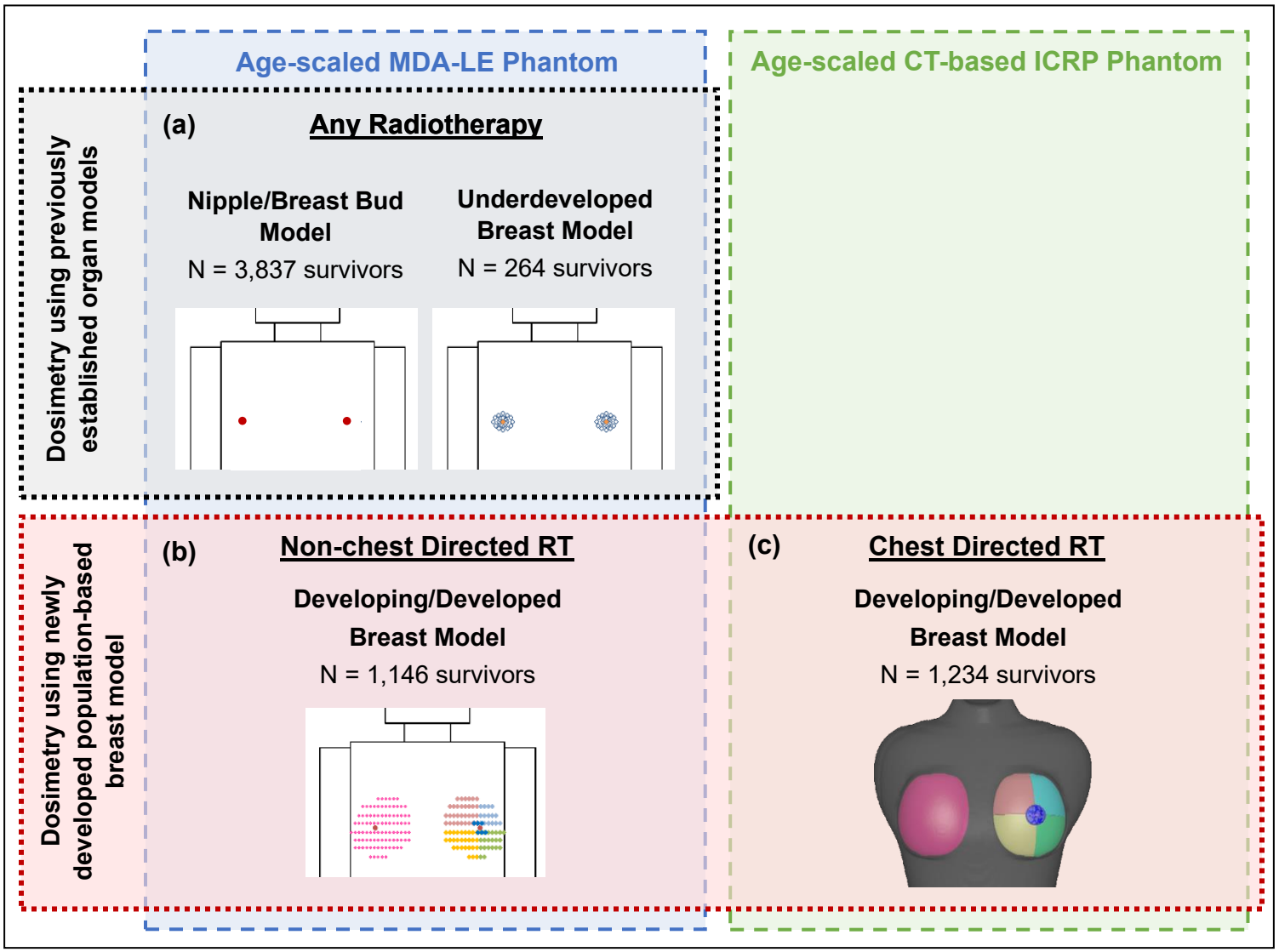


Figure 1: illustration of survivor specific breast dosimetry plan based on selection of breast model (determined by breast development at the time of RT) and type of RT (determines which phantom to be used for dose reconstruction). Categories are not mutually exclusive.

Use of Breast Dosimetry in Analyses

For all individuals treated with RT, we will calculate mean dose and dose-volume metrics to the left and right nipple/bud, underdeveloped breast, and developing/developed breast. We will report mean dose, maximum dose, and dose-volume metrics, i.e., percent volume receiving greater than or equal to X Gy (V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy}). These breast-specific RT metrics will be used in dose-response analyses of any SBC for the entire study population. Those not treated with RT will be the reference group

For a subpopulation of survivors whose breasts were estimated to be developing or developed at the time of their RT, six breast subregion mean doses will also be calculated (nipple and areola, central region, upper-inner, lower-inner, upper-outer, and lower-outer quadrants). For each breast subregion, mean doses to that subregion will be used in dose-response analyses where the SBC site location is specified (C50.0 – C50.5). Note that for some subregions, there may be too few SBC for analyses.

IV. SPECIFIC AIMS:

Specific Aim 1: Quantify standardized incidence ratios (SIRs) and absolute excess risks (AERs) for subsequent breast cancer (SBC) using updated RT dose metrics

Objective: To update previously reported SIRs and AERs for SBC in the CCSS cohort using the most recent data freeze, stratifying by survivor demographics and treatment exposures including newly available organ-level breast dose and dose-volume metrics.

Hypothesis: Detailed breast dose and dose-volume metrics will refine SIR and AER estimates and identify new treatment-risk associations not captured by prior surrogate metrics (i.e. prescription dose, chest max total dose).

Specific Aim 2: Estimate cumulative incidence and incidence rate ratios (IRRs) for SBC and develop multivariable dose-response models

Objective: To update previously reported cumulative incidences and IRRs for SBC and construct multivariable regression dose-response models that quantify SBC risk as a function of breast dose and dose-volume metrics, adjusting for confounding variables identified through univariate analyses.

Hypothesis: SBC risk will increase with increasing mean breast dose, greater low-dose exposure to large volumes (e.g. V_{5Gy} when V_{20Gy} = 0%), and higher doses to small volumes (e.g. $V_{10Gy} – V_{40Gy}$), after adjusting for confounding variables including mean ovarian dose (≥5 Gy vs. <5 Gy). The following novel breast dose and dose volume metrics will be considered:

- Mean RT breast dose
- Highest subregion mean dose across 6 defined breast regions
- V_{5Gy} when V_{20Gy} = 0 (low dose to large volumes)
- V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy} (high dose to small volumes)

Specific Aim 3: Evaluate excess relative risk (ERR) per Gy for SBC based on continuous breast dose

Objective: To construct linear and quadratic ERR models for SBC risk based on continuous mean RT dose to the breast , adjusting for ovarian dose (≥5 Gy vs. <5 Gy) and other known risk factors.

Hypothesis: ERR will increase with increasing mean RT breast dose, and that the relationship will be more accurately captured when breast development stage is considered. Ovarian dose and other clinical covariates will modify this risk.

V. Analysis Framework:

Aim 1: We will estimate age- and calendar-year-adjusted standardized incidence ratios (SIRs) and absolute excess risks (AERs) for subsequent breast cancer (SBC) among female childhood cancer survivors, using general population rates from the Surveillance, Epidemiology, and End Results (SEER) Program. Survivors will be considered at risk beginning five years after their primary childhood cancer diagnosis.

To improve upon previous analyses, we will incorporate newly derived, patient-specific breast dose metrics—including mean dose to the whole breast and breast subregions (defined by ICD-O-3), as well as dose-volume metrics such as V_{5Gy} and V_{20Gy}. Cumulative incidence of SBC will be estimated while accounting for death and prophylactic mastectomy as competing risks. SIRs and AERs will be calculated for the overall cohort (N = 12,338) and stratified by radiation exposure status (e.g., RT yes vs. RT no), conventional surrogate metrics (e.g., chest maxTD), and newly available organ-level breast dose categories (**Appendix 3 Table 3**). Additional stratification will include age at diagnosis, attained age, treatment era (in 10-year intervals), and hormone- and treatment-related factors listed in the analysis framework.

Aim 2: We will evaluate the association between radiation exposure and subsequent breast cancer (SBC) incidence using cumulative incidence and multivariable piecewise exponential models. Cumulative incidence curves will be estimated across key survivor characteristics (e.g., RT exposure, dose levels, demographic factors), accounting for death and prophylactic mastectomy as competing risks. To quantify relative risk, we will construct piecewise exponential models estimating incidence rate ratios (IRRs) for individual risk factors (**Appendix 3 Table 4**). Models will be adjusted for attained age using cubic splines (five knots at 15, 20, 25, 30, and 40 years), as well as age at primary cancer diagnosis, sex, and race/ethnicity, based on a priori confounder assumptions.

The incorporation of a population-based pediatric breast model into our age-scalable computational phantom allows for organ-level dose reconstruction across the entire cohort. For survivors who received RT, this enables inclusion of precise dose predictors such as mean whole-breast dose, breast subregion doses mapped to SBC location (**Appendix 3 Table 5**), and dose-volume metrics (e.g., V_{5Gy}, V_{20Gy}) in our models. These refined predictors overcome previous limitations that relied on surrogate measures like field type or prescription dose, and provide metrics directly translatable to clinical RT planning.

Univariate analyses will be used first to evaluate risk factors; those factors significant at $p < 0.1$ will be included in multivariable models. Multivariable models will also adjust for non-treatment risk factors, and analyses will be restricted to survivors with complete covariate data. The reference group for all comparisons will consist of survivors not exposed to the treatment variable being assessed.

Two-sided p-values < 0.05 will be considered statistically significant. All analyses will be performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Aim 3: We will construct ERR models to quantify the association between RT dose and SBC risk. The primary model will use a linear form, $e^{\beta X}(1 + Kd)$, where:

- *X* is a vector of covariates including demographics (attained age, sex, race/ethnicity, smoking history, and year of diagnosis) and chemotherapy doses (anthracycline dose, platinum
- dose, and alkylator dose)
- *d* is the mean RT dose to the breast as a continuous variable in Gy
- *K* is the percentage increase in the excess rate per Gy.

To evaluate potential nonlinear dose-response relationships, we will also consider ERR models in quadratic form, $e^{\beta x}(1 + K_1 d + K_2 d^2)$. Model comparisons will be conducted using likelihood ratio tests and Akaike Information Criterion (AIC) scores to determine the best-fitting dose-response relationship. Additionally, interaction terms will be tested for key covariates (e.g., mean ovarian dose) to assess their modifying effect on SBC risk. To account for potential survivor bias, a left-truncated survival analysis will be applied, ensuring that

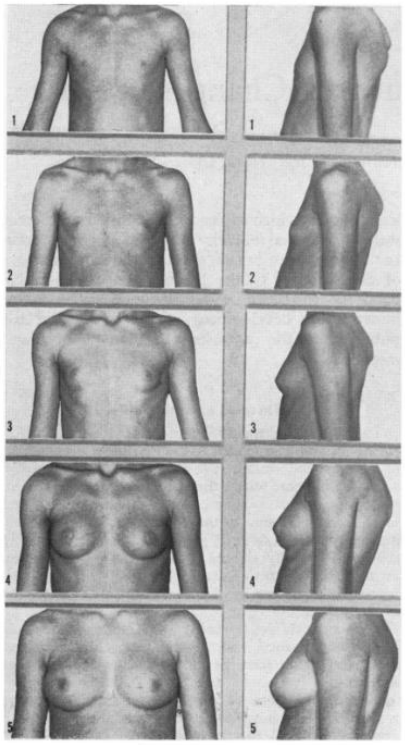
person-years are only counted from five years post-treatment onward. Results will be reported in figures similar to Bates. et. al. 2023 (**Appendix 3 Figure 3**).

Dose Binning and Thresholds:

- Radiation therapy will be binned in 5 Gy bins for all preliminary SBC analyses and collapsed to larger bins if subgroup N are too small.
- Chemotherapy will be binned as:
  - Anthracycline in chest RT, (Y/N):
    - None
    - 1 – 249
    - ≥ 250
  - Cyclophosphamide equivalent dose (CED) in chest RT (Y/N):
    - None
    - 1 – 5999
    - 6000 – 17,999
    - ≥ 18,000

APPENDIX

A1: Breast Development Staging (approximation)

Breast Development Stage (Sun et al. 2002)[18]		Breast Structure	Age Range (yrs)	
			Race: Non-black	Race: Black
	**B1**	Nipple	< 10	< 9.5
	B2	Bud	≥ 10 to <12	≥ 9.5 to < 11
	B3	Underdeveloped	≥ 12 to < 13	≥ 11 to < 12
	B4	Developing	≥ 13 to < 15.5	≥ 12 to < 14
	B5	Developed	≥ 15.5	≥ 14

Breast development staging at the time of RT, which is not directly recorded in the CCSS, will be approximated based on the median age of entry into the five Tanner stages of breast development, stratified by race and ethnicity, as reported by Sun et al. This methodology was previously used in a CCSS SBC case-control study[5]. In the CCSS cohort, data on physical indicators of puberty such as Tanner stage, age at menarche, or body mass index (BMI)—which could otherwise aid in assigning breast developmental stage—are either not collected or not consistently reported across the entire cohort. As a result, the only variable reliably available for all participants is age at the time of RT. Therefore, to ensure consistency and applicability across the full cohort, we have adopted age-based thresholds derived from the Sun et al. study to assign breast development stages in this analysis.

A2: Analysis Framework:

1. Outcome of interest: confirmed diagnosis of invasive breast cancer or DCIS/LCIS
2. Population: all females enrolled in the CCSS cohort
3. Predictor variables to be analyzed:

Non-treatment Variables

- Primary cancer diagnosis
- Age at primary cancer diagnosis
- Location of subsequent breast cancers
    - Using ICD-0-3 site based on Surveillance, Epidemiology, and End Results (SEER) Program coding for breast cancer (see Appendix A4)
- Treatment era
    - 1970-1979
    - 1980-1989
    - 1990-1999
- Family history of breast cancer
- Age at menarche
- Age at menopause
- Tobacco history (answers to baseline survey questionnaire O1, O2, O3, etc.)
- Alcohol use history (answers to baseline survey questionnaire O1, O2, O3, etc.)

Treatment Variables

Entire Study Cohort

- Any radiation therapy (RT)
- Any chest RT
- Chest MaxTD
- Ovary dose
- Any chemotherapy
- Any alkylating agent
- Any anthracycline
- Any platinum agent
- Any procarbazine agent
- Alkylating dose (CED - cyclophosphamide equivalent dose)
- Cumulative anthracycline (based on doxorubicin equivalents)
- Cumulative platinum dose
- Procarbazine cumulative dose

All Survivors treated with RT

- Chest MaxTD
- Whole breast RT mean dose (i.e. nipple, bud, underdeveloped, developing, developed breasts)
- Percent Volume of the breast receiving at least X Gy (i.e., V_{XGy}):
    - V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy}
    - V_{5Gy} when V_{20Gy} = 0%
- For breast stages 4 – 5 (developing and developed breasts):
    - RT mean dose to breast subregions upper inner and outer quadrants (UIQ and UOQ), lower inner and outer quadrants (LIQ and LOQ), central region, and nipple and areola (C50.0 – C50.8).
- Ovary Mean RT Dose (if left ≠ right, use higher)

A3. Sample Tables/Figures:

Table 1: Characteristics of Females in the Childhood Cancer Survivor Study Cohort

Characteristics	Female cohort members with SBC (N = 608)		Female cohort members without SBC (N = 11,730)	
	Median	**IQR**	**Median**	**IQR**
Age at last follow-up (years)				
Duration of follow-up from primary diagnosis to last contact (years)				
	N*	**%**	**N***	**%**
Primary Diagnosis: Leukemia CNS tumor Hodgkin lymphoma Non-Hodgkin lymphoma Wilms tumor Neuroblastoma Soft-Tissue Sarcoma Bone Tumor Total				
Age at Primary Cancer Diagnosis (years): Less than 1 1 – 3 4 – 7 8 – 10 11 – 14 15 - 20 Total				
Age at end of follow-up (years): 0 – 19 20 – 29 30 – 39 40 – 49 50+ Total				
Age at menarche (years): Less than 11 11 – 13 14 – 16 Greater than 16				
Age at menopause (years): Still menstruating at last contact Less than 20 20 - 29 30 – 39 Greater than 40 Unknown due to hysterectomy Missing				
Race (N; %): White, non-Hispanic Black, non-Hispanic Hispanic Other Unknown All cases				
Family History of any Cancer:				

No Yes				
First Degree Relative With Breast Cancer: No Yes				
Treatment Era: 1970 – 1979 1980 – 1989 1990 – 1999				
Vital Status: Alive Dead				
Radiation Therapy No Yes				
Chest Radiation No Yes				
Mean Breast Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Nipple and Areola Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Central Breast Region Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Upper Inner Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Lower Inner Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Upper Outer Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Mean Lower Outer Quadrant Dose (Gy) None 0.1 < 5 5 < 10				

10 < 15 ≥ 20				
V_{5Gy} (%) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
V_{10Gy} (%) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
V_{20Gy} (%) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
V_{30Gy} (%) None 0.1 < 5 5 < 10 10 < 15 ≥ 20				
Ovarian Dose (Gy) < 5 ≥ 5				
Total Body Irradiation No Yes				
Chemotherapy No Yes				
Alkylating Agents No Yes				
Platinum Agents No Yes				
Anthracyclines No Yes				
Procarbazine No Yes				
Stem Cell Transplant No Yes				

Abbreviations: SBC – subsequent breast cancer; IQR – interquartile range; V_X – % volume receiving at least X Gy

*Data are median (IQR) or N (%). Percentages are reported among participants with known values.

Table 2: Clinical and Pathologic Characteristics of Subsequent Breast Cancer (SBC) Cases

Characteristics	Female cohort members with SBC (N = 608)	
	Median	**IQR**
Age at Primary Diagnosis of Childhood Cancer		
Time from Primary Diagnosis to SBC		
Age at SBC		
	N*	**%**
Age at Diagnosis of SBC (years): 10 – 19 20 – 29 30 – 39 40 – 49 Greater than 49		
†Anatomical site of SBC – Based on site ICD-0-3 code C50.0 Nipple and areola C50.1 Central portion of breast C50.2 Upper-inner quadrant C50.3 Lower-inner quadrant C50.4 Upper-outer quadrant C50.5 Lower-outer quadrant C50.6 Axillary tail of breast C50.8 Overlapping lesion of breast C50.9 Breast, unspecified		
SBC Receptor Status: ER + PR + HER-2 Unknown		
Radiation Therapy Yes No		
Chest Radiation Therapy Yes No		
Mean Breast Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Mean Nipple and Areola Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Mean Central Breast Region Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Mean Upper Inner Quadrant Dose (Gy) None 0.1 < 5 5 < 10		

10 < 15 ≥ 20		
Mean Lower Inner Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Mean Upper Outer Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Mean Lower Outer Quadrant Dose (Gy) None 0.1 < 5 5 < 10 10 < 15 ≥ 20		
Cause of Death of SBC Participants Primary cancer Subsequent breast cancer Other subsequent malignancy Cardiac toxicity External causes All cases		

Abbreviations: SBC – subsequent breast cancer; IQR - interquartile range

† Anatomical site of subsequent breast cancer based on Surveillance, Epidemiology, and End Results (SEER) Program site recode definitions from the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3

Table 3. **Standardized incidence ratios and absolute excess risk for SBC**

	No. Observed	No. Observed† (considering weights)	No. Expected	SIR (95% CI)	AER/10,000 PY (95% CI)
All subjects					
Age at Primary Cancer Diagnosis					
Less than 1					
1-3					
4-7					
8-10					
11-14					
15-20					
Attained Age (years)					
5-14					
15-24					
25-34					
35-44					
45-54					
55+					
Race/ethnicity					
White, non-Hispanic					
Black, non-Hispanic					
Hispanic					
Other					
First Degree Relative with Breast Cancer					
No					
Yes					
Primary diagnosis					
Leukemia					
CNS					
Hodgkin Lymphoma					
Non-Hodgkin Lymphoma					
Wilms Tumor					
Neuroblastoma					
Soft Tissue Sarcoma					
Bone Cancer					
Treatment Era					
1970s					
1980s					
1990s					

Any RT					
No					
Yes					
Chest RT					
No					
Yes					
Mean Breast Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{5Gy} when V_{20Gy} = 0%					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{20Gy}					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Any chemotherapy					
Yes					
No					
Any alkylating Agents					
Yes					
No					
Any platinum Agents					
Yes					
No					
Any anthracyclines					
Yes					
No					
Alkylating agent dose (CED, mg/m^2)					
None					

<6000					
≥6000					
Platinum-based dose					
None					
<450					
≥450					
Anthracycline dose					
None					
0.1<250					
≥250					

Abbreviations: SBC - subsequent breast cancer ; No - number; CI - confidence interval; SIR - standardized incident ratio; AER - absolute excess risk; RT - radiation therapy; PY - person-year; CCSS - Childhood Cancer Survivor Study

† Observed values will be reported with decimal places as these values consider weights.

Table 4. **Cumulative incidences and Incident rate ratios (IRR) by treatment exposure**

RT- Metric	Survivors with SBC N (%)	Survivors without SBC N (%)	Cumulative Incidence (95% CI)	Adjusted IRR (95% CI)	P
Any RT					
No					
Yes					
Chest RT					
No					
Yes					
Body Region RT Max Target Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Breast Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Nipple and Areola Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Central Breast Region Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Upper Inner Quadrant Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Lower Inner Quadrant Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Upper Outer Quadrant Dose (Gy)					
None					
0.1 < 5					

5 < 10					
10 < 15					
15 < 20					
≥ 20					
Mean Lower Outer Quadrant Dose (Gy)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{5Gy} (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{10Gy} (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{20Gy} (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{30Gy} (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{40Gy} (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
V_{5Gy} when V_{20Gy} = 0 (%)					
None					
0.1 < 5					
5 < 10					
10 < 15					
15 < 20					
≥ 20					
Any chemotherapy					
No					
Yes					

Any alkylating agent					
No					
Yes					
Any platinum-based agent					
No					
Yes					
Any anthracycline					
No					
Yes					
Alkylating agent dose (CED, mg/m^2)					
None					
<6000					
≥6000					
Platinum-based dose					
None					
<450					
≥450					
Anthracycline dose					
None					
0.1<250					
≥250					

Table 5. Incident rate ratios (IRR) subpopulation analyses

Type of Data	RT- Metric	Survivors with SBC N (%)	Survivors without SBC N (%)	Adjusted IRR (95% CI)	P
Highest of the Mean Breast Dose among the 6 subregions (Gy)	**Dose (Gy)**				
	None				
	0.1 < 5				
	5 < 10				
	10 < 15				
	15 < 20				
	≥ 20				

Parallel tables will be created for all survivors, those with ovary dose ≥ 5Gy, and <5 Gy

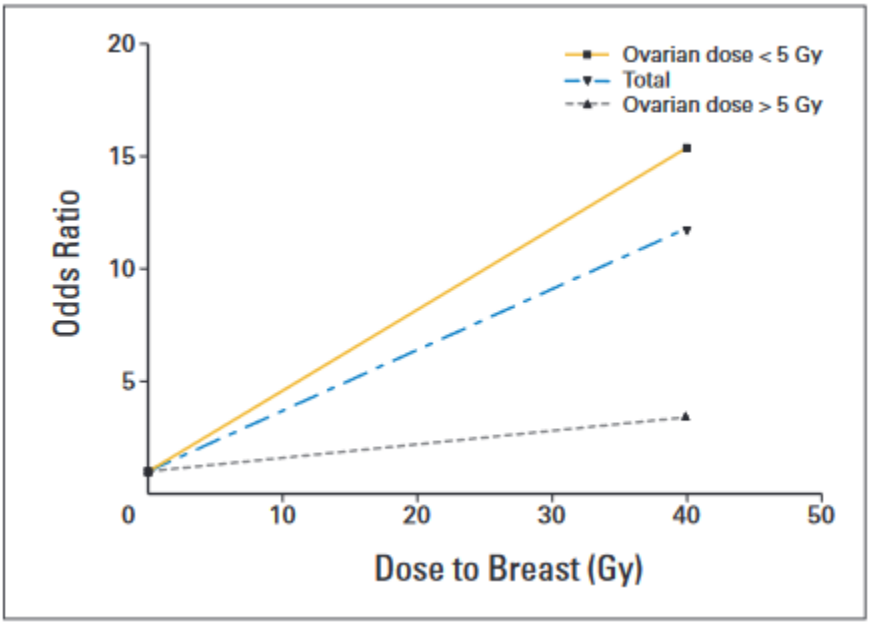


Figure 2: Example from Inskip et al. (2009) of how we will plot stratified IRR for this study. Breast cancer risk by radiation dose to the breast and ovary.

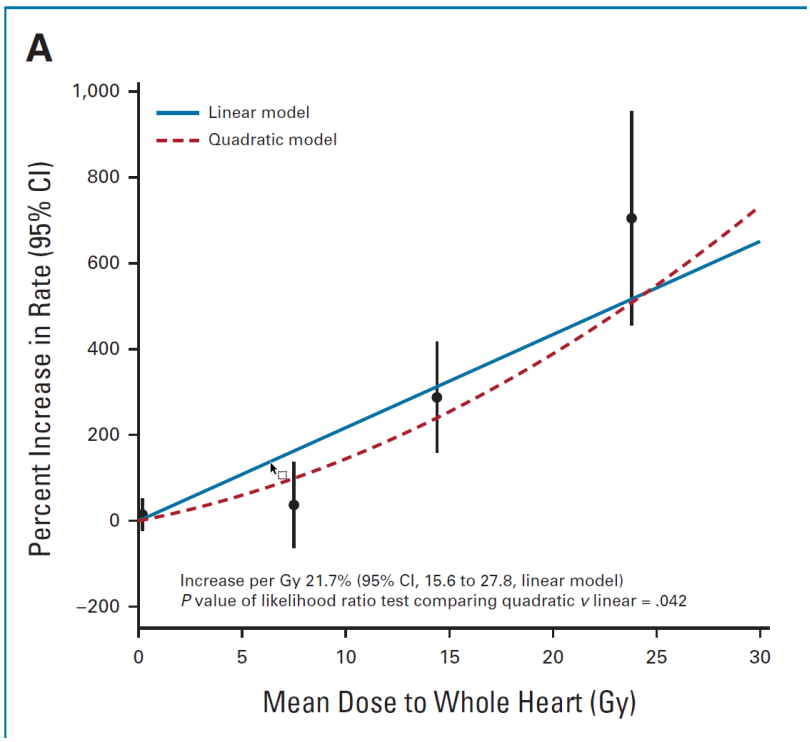


Figure 3: Example from Bates *et al.* (2023)[20] of how we will plot the ERR for this study. ERR dose-response models between mean whole heart radiation dose and risk of coronary artery disease. The solid and dotted lines are the fitted lines from the linear and quadratic ERR models, respectively. The circles show adjusted excess relative rate estimates when the mean whole heart doses were categorized as <5, 5 to <10, 10 to <20, and 20 Gy or more, that is, not assumed linear or quadratic changes, and plotted at the categories' mean doses, with vertical lines representing their associated 95% CIs. ERR, excess relative rate.[20]
In our study, we will also consider ERR/Gy stratified by ovarian dose > 5Gy and ≤ 5 GY.

A4. Additional Dosimetry Details:

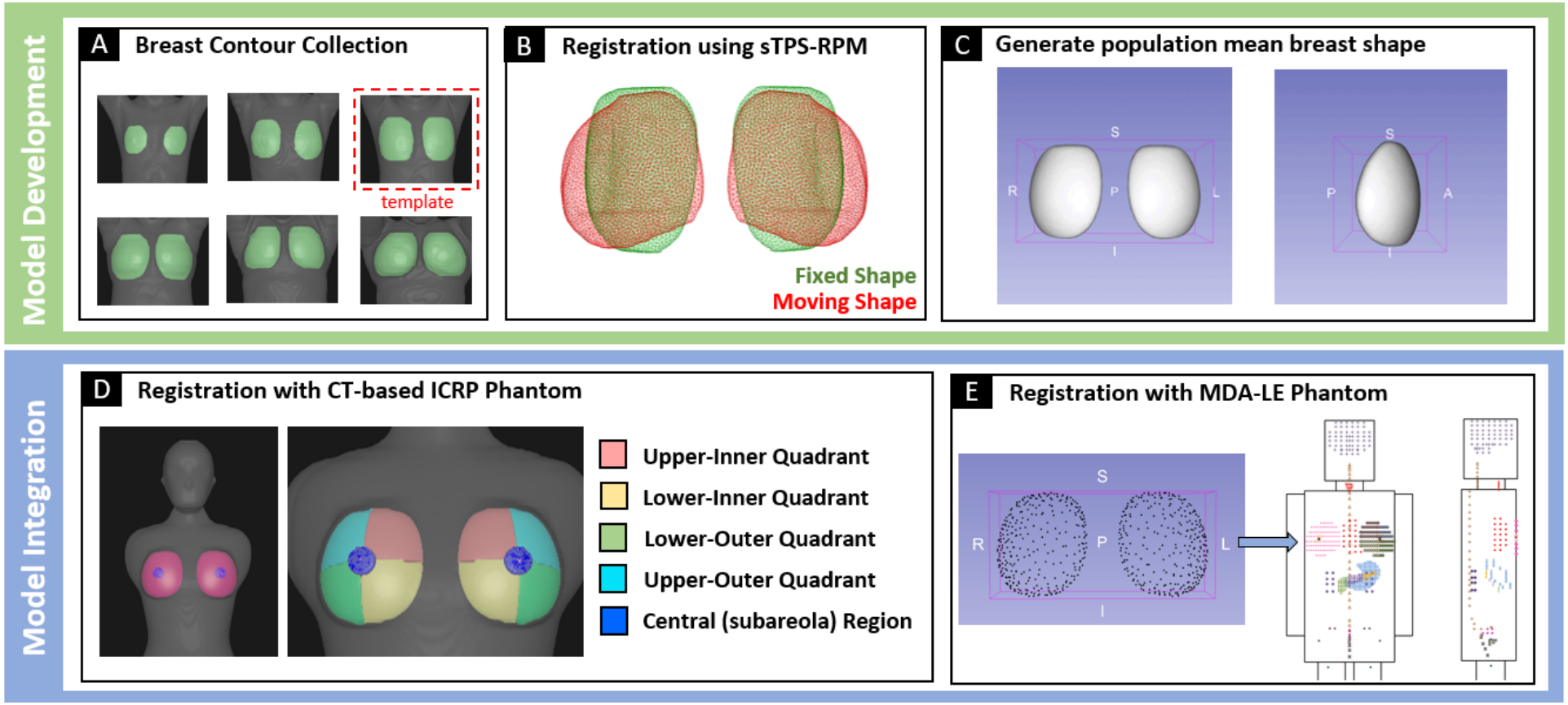


Figure 4: Population-mean adolescent breast model representing breast development stages 4 and 5. (A-C) An enhanced breast model was developed using breast contours from a population of 71 female pediatric patients' (ages 12 to 21 years) whole-chest CTs. (D) The breast model was then integrated into the CT-based ICRP 15 year old female computational phantom[21–23], where the breast was further separated into corresponding breast subregions as defined by ICD-0-3. This breast model in the ICRP phantom will be used when reconstructing chest-directed RT in RayStation for CCSS participants who were in breast development stage 4 or 5 at the time of their RT. (E) Additionally, the population-based adolescent breast model was converted from a 3D organ contour to a 3D grid of points, collapsed to a single plane, and then integrated into the chest wall of the MDA-LE phantom. This breast model in the MDA-LE phantom will be used when reconstructing non-chest directed RT (i.e. stray radiation) using a pre-established dose reconstruction methodology. Both phantoms can be scaled to the survivor's age at time of RT using an in-house age-scaling algorithm[19].

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