1. STUDY TITLE

Cost-effectiveness of the Children's Oncology Group's Long-term Follow-up Screening Guidelines for breast cancer in female chest-irradiated survivors of pediatric cancers

2. WORKING GROUP

Epidemiology & Biostatistics

Cancer Control

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3. BACKGROUND AND RATIONALE

Although childhood cancer survivors (CCSs) now enjoy living longer lives due to improved therapy, they face substantially increased risks of morbidity and mortality resulting from their cancer treatment. As this population grows in number (now estimated to be >350,000), the financial impact of their long-term care on limited resources (government programs and private healthcare insurers) becomes an urgent issue requiring as much scrutiny as treatment efficacy. Breast cancer (BC) is an unfortunate late consequence for women treated with chest radiation (≥20 Gy) for histologically distinct malignancies during childhood, adolescence or young adulthood (herein, referred to as *childhood cancers*). Their risk of developing BC is 13 to 55 times that of the general population. Women who receive lower doses of radiation are also at risk, as shown by the linear dose-response relationship for BC demonstrated by Inskip et al.,[1] and the elevated risk shown in women exposed to lower doses (10-19 Gy) of chest radiation.[2,3] The breast cancer is observed typically after a median latency of 25 years after radiation therapy and is diagnosed at an earlier age than in the general population (median of 32 to 35 years compared to 61)[4]. It is estimated that 12% to 20% of these survivors will develop BC by age 45 years. This incidence is similar to that in women with BRCA1 gene mutation, where by age 40 years, the cumulative incidence ranges from 10% to 19%. It is substantially higher than that in young women in the general population, where the incidence of

invasive breast cancer by age 45 years is 1%.[5] Long-term follow-up studies demonstrate an increasing risk with time since radiation exposure, with no evidence of a plateau.

BC screening can identify cancer at an earlier stage when prognosis is better and treatment cost is lower. Early detection is particularly important in this population because treatment options for BC may be limited due to prior therapy received for the primary cancer, which can lead to poorer outcome. Several BC screening guidelines exist currently for women at high risk, including the chest-irradiated childhood cancer cohort.[6] The Children's Oncology Group (COG) guidelines are risk-based, exposure-related follow-up guidelines for childhood cancer survivors (www.survivorshipguidelines.org). These guidelines include specific recommendations for women exposed to ≥20 Gy of chest radiation for the treatment of childhood cancers. The COG Guidelines recommend annual clinical breast examination starting at puberty until age 25 years, then every 6 months. Additionally, they recommend annual mammography and annual breast magnetic resonance imaging (MRI) as an adjunct beginning 8 years after radiation exposure or age 25, whichever is later. An upper age limit is not specified for screen termination in the COG Guidelines. Version 4.0 of the Guidelines (to appear) recommends healthcare providers to discuss the benefits and risks/harms of screening with patients who received 10-19 Gy of chest radiation or Total Body Irradiation alone. If screening is decided upon, the recommendation for patients who received ≥ 20 Gy should be followed.

Screening mammography has been shown to reduce BC mortality in women aged 39-69 years in the general population.[7] However, lower sensitivity of mammography in younger women, which may be related to their higher breast density, makes it less effective as a screening tool. MRI, on the other hand, is not affected by breast density and is more sensitive than mammography. As a result, MRI is presumed to be a more effective screening tool with the *potential* to reduce BC mortality in younger high risk women who are recommended to initiate screening at earlier ages because of earlier BC onset. To date, however, no empirical evidence exists that supports survival advantage of screening with MRI in any population[8]. Notably, the COG recommendations were developed by expert consensus in the absence of scientific evidence supporting their effectiveness. Following the COG recommendation for lifetime annual BC screening using both mammography and MRI could exact a high financial toll (MRI costs $1,000 to $2,000 or more, 10 times that of mammography) without a clear idea of the mortality benefits and cost-effectiveness of implementing MRI in addition to mammography. Higher sensitivity and lower specificity of MRI[9] can incur additional diagnostic cost in order to rule out false-positive results which may cause anxiety in patients.

Tomosynthesis, also known as 3-dimensional digital (3D) mammography, in combination with 2-dimensional digital (2D) mammography, was approved by the FDA for BC screening. A recent report based on the data from 13 breast centers showed that, compared to 2D mammography alone, the combination (2D/3D) procedure has a higher invasive BC detection rate (4.1 vs. 2.9 per 1000 screens, p<.001), lower recall rate (91 vs. 107 per 1000 screens, p<.001), and similar in-situ cancer detection rate (1.4 per 1000 screens for both methods).[10] The positive predictive value (PPV) for recall and biopsy (% of recalls and biopsies that resulted in BC diagnosis) were also higher for 2D/3D compared with 2D (6.4% vs. 4.3% for PPV Recall; 19.3% vs. 18.1% for PPV Biopsy, both p<.001). However, the biopsy rate was also higher (p=.004) for 2D/3D (1.93%) compared to 2D alone (1.81%). These results suggest potentially superior sensitivity and specificity of 2D/3D compared to 2D alone. Even if the sensitivity of 2D is maintained with the addition of 3D, a lower false-positive rate for 2D/3D could reduce unnecessary diagnostic workup and the accompanying emotional stress. Given that the screening recall rates of 2D/3D mammography are lower, particularly for those younger than 50 years and those with dense breasts, the cost-effectiveness of the 2D/3D mammography merits examination in chest-irradiated childhood cancer survivors.

Although the current COG Guidelines do not specify the type of mammography to be used, given that 2D mammography has replaced screen-film mammography in over 90% of the US market,[11] and since 2D mammography has been shown to be more sensitive for detecting BC in younger women and in those with denser breasts compared to film-screen mammography,[12] it is appropriate to consider 2D as the mammographic screening technology of choice for chest-irradiated female childhood cancer survivors. Thus, we specifically address 2D mammography in this proposal.

Since a randomized controlled trial is not feasible in this limited population and the long time needed to obtain mortality results will make the findings outdated with advances in screening technology, the proposed study will employ a computer simulation approach using Markov decision models to evaluate the clinical effectiveness (reduction in BC mortality and gain in life-expectancy) and the cost-effectiveness (defined in the next paragraph) of the COG screening guidelines for women exposed to chest radiation at age 21 or younger. While the focus will be on those exposed to ≥ 20 Gy of chest radiation, we will also consider women exposed to 10-19 Gy in light of the recent findings.[2] A 4-health state model (No BC, asymptomatic BC, clinically overt BC, death due to BC or death due to other causes) will be constructed using Markov models. The life-histories of female childhood cancer survivors treated with chest-irradiation will be simulated under the no screening condition (natural history of breast cancer development) and under various BC screening strategies to compute the lifetime health care costs and life expectancies.

Cost-effectiveness of a screening strategy will be evaluated by using an index called the incremental cost-effectiveness ratio (ICER). ICER is the difference in healthcare costs between two screening strategies divided by the difference in their quality-adjusted life-expectancies (QALE). It is the additional cost per extra quality-adjusted life-year (QALY) gained from the more effective screening strategy compared to the less effective option. QALY takes into account the length as well as the quality of life; one QALY is a year of life lived in perfect health. A screening strategy is considered to be more cost-effective than an alternative strategy if its ICER relative to the alternative is lower than a threshold. The threshold value often used is $100,000 per QALY.

QALY is affected by the sensitivity and specificity of the screening procedures. While these estimates are available for 2D mammography and MRI (see **Section 5d, Screening test characteristics**), their estimates for the 2D/3D procedure and the cost are presently unavailable. The specific CPT (Current Procedure Terminology) code is expected in early 2015. Lacking the necessary information for conducting cost-effectiveness analysis, we will instead perform a variant called the threshold analysis. Cost-effectiveness analysis can be applied to existing (or established) programs (mammography, MRI) as well as to emerging programs (2D/3D mammography) in what is called a threshold analysis or "what if" studies, before good data are available.[13] We will examine the 2D/3D procedure as exploratory, and conduct threshold analysis by varying the magnitude of its sensitivity and specificity (and the cost, depending on its availability). It may be reasonable to assume that sensitivity and specificity are at least as good as that of 2D mammography, and increase their levels by increments. This will result in varying effectiveness (e.g. QALY) of screening. Various levels of sensitivity and specificity will be assumed to conduct threshold analysis to determine the effects that are necessary for the screening to achieve the acceptable standards of cost-effectiveness (e.g. $100,000 per QALY compared to an alternative strategy, e.g. 2D alone).

We will estimate the age-specific BC incidence devoid of screening effects, i.e. breast cancers that would be detected by clinical exams/signs only, using the general population data when screening was not common and the radiation risk model for BC estimated by Preston et al.[14] Non-BC mortality will be estimated from the chest-irradiated female CCSS cohort. These probabilities and other parameters (described in **section 5d**) will be used as inputs in Markov models to simulate the life

histories of chest-irradiated female CCSs under no screening and under various screening strategies.

4. SPECIFIC AIMS

Aim 1:
Examine the cost-effectiveness (CE) of annual clinical breast examination starting at puberty (age 12) until age 25, then every 6 months (CBE strategy).

***Aim 2*:**
Examine the CE of annual 2-dimensional digital (2D) mammography only strategy, beginning 8 years after diagnosis of childhood cancer but no earlier than age 25, combined with the CBE strategy (COG recommendation, without MRI as adjunct).

Exploratory Aim 2a:
Examine the CE of annual 2D mammography combined with breast tomosynthesis (3D mammography) strategy, beginning 8 years after diagnosis of childhood cancer but no earlier than age 25, combined with the CBE strategy (COG recommendation, adding 3D mammography, without MRI as adjunct)

Aim 3:
Examine the CE of annual MRI only strategy, beginning 8 years after diagnosis of childhood cancer but no earlier than age 25, combined with the CBE strategy (COG recommendations, without mammography).

Aim 4:
Examine the CE of a contemporaneous annual 2D mammography and MRI strategy, beginning 8 years after diagnosis of childhood cancer but no earlier than age 25, combined with the CBE strategy (full COG recommendation).

Exploratory Aim 4a:
Examine the CE of a contemporaneous annual 2D mammography combined with 3D mammography and MRI strategy, beginning 8 years after diagnosis of childhood cancer but no earlier than age 25, combined with the CBE strategy (full COG recommendation, modified by the addition of 3D mammography)

5. ANALYSIS FRAMEWORK

a. Outcome(s) of interest:

Vital status (alive, dead, lost)
Date of vital status
Cause of death
Date of breast cancer (BC) diagnosis (the earlier date if bilateral BC)
Laterality of BC

b. Subject population:

Female CCSS baseline cohort from the first questionnaire exposed to any chest radiation for their primary cancer

Although the current COG guidelines focus on women exposed to at least 20 Gy of chest radiation, we will also evaluate the cost-effectiveness of the screening strategies when applied to women exposed to lower doses (10 to 19 Gy) in whom elevated risk of BC has been demonstrated recently.

c. Exploratory variables:

Birth date
Race/Ethnicity
Education
Type of first cancer
Date of first cancer diagnosis
Estimated regional breast doses (for all available breast sites) received from the primary cancer treatment used for the GWAS analysis
Estimated dose to the breast cancer tumor site in breast cancer patients and their matched controls in the case-control study of breast cancer (Inskip et al., JCO 2009)
Pelvic radiation therapy for primary cancer (Y/N, dose if available)
Chemotherapy data
- Use of alkylating agent and dose
- Use anthracycline and dose

History of ever have had mammography (Y/N)
Date of breast cancer (BC) diagnosis, including DCIS
Laterality of BC
Estrogen Receptor (ER) status (if available)
Data of subsequent BC dx (if available), including date of dx, laterality of BC
Age at menarche
Menopause (y/n); if yes, age at menopause
Age at first pregnancy
Breast cancer in first degree relatives and their age of onset

d. Components of cost-effectiveness analysis:

Markov model simulation: One million chest-irradiated female CCSs will be simulated whose distribution will reflect that of the chest-irradiated female CCSS cohort in terms of age at diagnosis and chest radiation dose. They will be followed from 5 years after primary cancer diagnosis until death, during which they will transition from one health state to another (No BC, asymptomatic BC, clinically presented BC, death due to BC or death due to other causes). The Markov model will be used to portray their recursive transitions through discrete health states while accumulating life-years, QALYs, and treatment-related costs. We will also calculate the mean age at diagnosis, the number of false positive cases, the distribution of the BC stage at diagnosis, and the sensitivity of each screening strategy. We will model the natural history of BC and superimpose onto it the effects of screening and treatment. Life expectancy and lifetime healthcare cost of the cohort with and without screening will be calculated and compared to determine the gain in QALYs and the ICER associated with the different screening strategies relative to no screening and to the less effective screening strategy.

The key assumption we make is that earlier diagnosis from screening results in a stage shift of BC which affords better prognosis than the prognosis of the later-occurring non-screen-detected BC. No assumption is made regarding the tumor growth process.

Natural history of breast cancer: The cost-effectiveness analysis will be based on modeling the underlying natural history of BC which is assumed to be a progressive disease.[15,16] The model consists of 4 discrete health states: 1) no BC (or underlying condition is undetectable by screening); 2) asymptomatic BC (detectable by screening); 3) symptomatic presentation of BC (clinical diagnosis); 4) death due to BC or non-BC cause. BC is assumed to progress from less severe to more severe disease stage: Ductal Carcinoma-in-Situ (DCIS) → local (non-lymph node-involved) BC → regional (lymph node-involved) BC → distant (metastatic) disease. DCIS is a noninvasive BC in which abnormal cells are found in the lining of a breast duct. We assume that it can progress to invasive BC. A woman in any health states could die of non-BC causes.

The natural incidence of BC is ideally estimated using the data from the un-screened chest-irradiated female CCSS cohort. However, whether adequate data exist for this purpose is not known. The original cohort included about 1600 female chest-irradiated survivors (including those who received TBI) of whom 122 developed BC as of 2001.[1] Assuming about 50% to never have had mammographic screening[4], there would be about 800 survivors available for estimating the natural history. It is likely that less than 50% of the 122 BC cases had been among this group of women who never had screening. Moreover, only about 50% of the chest-irradiated female cohort was over 40 years of age at the 2007 follow-up, with 59 years as the oldest possible age for a survivor. Thus, not only might there not be sufficient data to obtain a reliable estimate of the natural incidence rate of BC, but no data are available in the CCSS to estimate the lifetime natural incidence of BC devoid of screening effects.

Therefore, we will estimate the natural incidence of BC without the effects of screening in the chest-irradiated female CCS cohort by using the general population rates and the excess absolute risk (EAR) model for radiation risk: $\lambda + \varepsilon(d, \mathbf{X})$, where λ is the population BC rate and $\varepsilon(d, \mathbf{X})$ is the excess risk that depends on radiation dose (d) and other risk factors ($\mathbf{X}$).

Population BC rates will be estimated using the US Surveillance, Epidemiology and End Results (SEER) database from the pre-screen period (1975-1979). These data have been used by the NCI-sponsored Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to estimate the trends of BC incidence during the period when screening was not common in the general population for their study of the impact of mammography and adjuvant therapy on the BC mortality rate in the US between 1975 and 2000.[17] We will use the same data, stratifying the background rates by age and race.

For the excess rate attributed to radiation, we will use the BC risk model estimated by Preston et al[14] for the chest-irradiated females in the general population:

$$\text{EAR/10,000 WY} = \begin{cases} 10 \bullet d \bullet \exp[-0.5(agex-25)] \bullet (age/50)^{3.5} & \text{for attained age} \le 50y \\ 10 \bullet d \bullet \exp[-0.5(agex-25)] \bullet (age/50) & \text{for attained age} > 50y \end{cases}$$

where agex is age at radiation exposure, d is chest radiation dose, and WY denotes woman-year. To account for effect modification such as that from radiation exposure to the ovaries, pregnancy history, and premature menopause, we will adjust the radiation risk according to the relative risks reported in the literature.[18] For chest radiation doses, we will use the average doses estimated for each of the four quadrants of the left and right breasts calculated for the GWAS study. If the dose estimates vary markedly by quadrant and/or breast, we will follow each woman by breast and regions of the breast for the development of BC. To account for the 8 locations in the breasts being monitored, we will adjust the probabilities of BC development by weighting them by the prevalence of the tumor locations reported in the general population which is similar to that reported in Hodgkin's Lymphoma survivors.[5]

Although the CCSS data will not be used for estimating the natural incidence of BC in the simulation study, we will use the data to help validate and calibrate the above model as necessary.

In the simulation, each woman's BC diagnosis (symptomatic presentation) is stochastically simulated based on the above model. Women developing BC at a given age will have the disease stage assigned randomly according to the age-specific distribution seen in the general population in the period before screening became widespread (SEER data before 1979). The ER status will also be assigned according to its distribution in SEER which started collecting such data in 1990. Treatment will be assigned randomly according to the current pattern of care prescribed by disease stage and ER status. Women can die of BC or of causes other than BC. For each woman pre-destined to develop BC, we will estimate her pre-clinical sojourn time, i.e. the time between the (unobservable) onset of asymptomatic BC and (observed) symptomatic BC, assuming an exponential distribution with age-dependent mean.[19,20] Estimation of the mean dwell time in each BC stage will be performed using the method described in Mandelblatt et al.[21]

Breast cancer incidence under screening: The chance that the asymptomatic BC is detected by screening during the lead-time (time period during the pre-clinical sojourn time between the date of screening and the time when BC would have presented clinically without screening) depends on the sensitivity and specificity of the screening modalities used. At the time when the BC is detected by screening, the age-specific marginal distribution of the BC stage is determined using the SEER data for the period 1995 and later when screening was widespread (~73% or more had ever received mammography).[22] Using the marginal distribution of the BC stage, the dwell time estimates, the lead time and the BC stage assigned at the time of natural symptomatic presentation of BC, the Bayes theorem can be used to calculate the distribution of the BC stage for the screen-detected BC conditional on the BC stage that was assigned for the naturally occurring non-screen-detected symptomatic BC. A specific BC stage at screening will be assigned by sampling from the conditional BC stage distribution. Survival benefit from screening is achieved when the stage at the time of screening corresponds to an earlier stage than that would have been without screening.

The use of the general population rates in the CCSs is reasonable because the observed stage, histologic features, and hormone receptor status of secondary BC in CCSs appear to be similar to those in the general population.[23-26]

Non-breast cancer mortality rates: Since non-BC mortality may be affected by increasing uptake of mammography over time in the female survivors, we will first examine the effects of time period before and after when mammography became prevalent in CCSs. Cook et al[27] indicated that prior to their study in 1990, no reports had appeared of BCs detected by mammography in female Hodgkin disease survivors. Their report raised the awareness in radiologists of the association between radiation and BC development in these patients and the benefit of mammography for screening and diagnosing BC. Hence, it could be reasonably assumed that mammography was rare in these patients in 1990 and earlier. Among the approximate 1600 female chest-irradiated CCSS participants (described in **Section 5d, Natural history of breast cancer**), 266 non-BC deaths occurred in 1990 or earlier and 443 occurred after 1990. Thus there appears to be an adequate number of non-BC deaths in both periods. To examine the time-associated change, we will consider several strategies. First, a piece-wise exponential Poisson regression model will be fitted for non-BC mortality by attained age, adjusted for covariates such as age at radiation exposure, chest radiation dose, anthracycline dose, and education. We will then include a period effect (1990 or earlier vs. after 1990) to test if non-BC mortality varied significantly between the two periods. The period effect variable will also be categorized (e.g. 1974-1980, 1981-1990, 1990-1995, 1996-2000, etc) to examine its effects in more detail.

If no period difference is evident, the entire CCSS follow-up data could be used to estimate the non-BC mortality. Since only about 50% of the female chest-irradiated CCSS cohort were followed past age 40 years in 2007, to estimate the life-time non-BC mortality rate we will extrapolate the risk by using the rates estimated near the end of the CCSS follow-up (at around age 50 years), compare them to the general population rates available from the National Center for Health Statistics for the corresponding follow-up years to estimate the relative risk (RR). We will then assume a multiplicative model and multiply the RR by the general population rates for non-BC mortality for age >50 years to use as non-BC mortality rate in the chest-irradiated cohort.

If a period difference is detected, we will further explore the interactions of the period effect with other covariates in the model to estimate a fuller model. The effects of attained age and other covariates on non-BC mortality can then be estimated for the period before and after the time when mammography became prevalent in the CCSs, by utilizing the information present in the entire CCSS follow-up data while accounting for period effects.

Another strategy that will be considered is the use of the data only through 1990, although this will limit the length of follow-up. We will compare the consistency of the results from this approach with those of the full-modeling approach. The data truncated to 1990 may also be used to calibrate the estimated fuller model. In either case, the lifetime risk of non-BC mortality will be estimated by extrapolation using the US general population rates as described previously. The extrapolated rates will depend on the RRs assumed. We will compare the RR estimates that result from the full-modeling approach and the truncated-data approach.

It will not be possible to know the most effective strategy for estimating the non-BC mortality rates until the actual data are examined using these methods.

Screening test characteristics: Age-specific sensitivity and specificity of CBE, mammography, and MRI will be obtained from the literature. CBE: Most data on CBE come from women over 40 years of age. A general review of the literature estimated the CBE sensitivity to be 54% and specificity to be 94%.[28] Using the data from the National Breast and Cervical Cancer Early Detection Program, Bobo et al [29] reported an overall sensitivity of 59% and specificity of 93%, consistent with the general review. A decreasing trend with increasing age in sensitivity and an increasing trend with increasing age in specificity were observed also. In women under 40 years of age, sensitivity, specificity, and positive predictive value (PPV) were 88%, 86% and 1.4%, respectively.[29] We will use age-specific estimates for ages 30 and above. The sensitivity and specificity of CBE for women less than 30 years of age will be adjusted by extrapolating the age trends reported in Bobo et al. Mammography: A prospective study of the chest-irradiated female Hodgkin Lymphoma patients by Ng et al.[30] and a retrospective study of chest-irradiated female mostly Hodgkin Lymphoma patients by Freitas et al.[9] showed the sensitivity of 2D mammography to be 68%-69% (95% CI: 60%-78%; 43%-87%) and specificity to be 93%-98% (95% CI: 90%-96%; 93%-99%). Another retrospective study of female chest-irradiated mostly Hodgkin Lymphoma patients who underwent mammography of unspecified type (Sung et al.[31]) showed the sensitivity and specificity to be 67% (95% CI: 30%-92%) and 93% (95% CI: 85%-98%), respectively, similar to estimates based on 2D mammography. MRI: Freitas et al.[9] estimated the sensitivity of MRI to be higher (92%, 95% CI: 86%-97%) than that of mammography (69%, 95% CI: 60%-78%), similar to results seen in BRCA survivors. On the other hand, Sung et al.[31] and Ng et al.[30] found the sensitivity of MRI (67% in both studies) to be no different from that of mammography (67% and 68%).[30,31] MRI+mammography: The prospective study by Ng et al.[30] estimated the sensitivity of MRI combined with 2D mammography to be 94% (95% CI: 71%-99%) with a specificity of 90% (87%-93%). Under the MRI + mammography strategy, we will use the combined test performance estimates as well as

consider the evidence from each modality independently, i.e. a positive finding from mammography or MRI will be counted as positive screen indication. Since CBE is included under all imaging-based strategies, the overall sensitivity and false-positive rates of each strategy will be determined by considering the rates for CBE independently from the rates for mammography or MRI or mammography + MRI.

In the proposed study, the following values will be used for sensitivity/specificity in the base case: 1) 2D mammography: 68%/93%; 2) MRI: 68%/67%; 3) 2D mammography+MRI: 94%/90%. Sensitivity analysis (described later) will consider ranges based on the 95% confidence intervals.

For the exploratory aims involving 2D/3D, we will assume the sensitivity and specificity to be at least as good as those of 2D mammography and vary them by increments.

Diagnostic work-up: After a positive screen result from CBE, diagnostic work-up will include mammography ± biopsy and/or 6-month follow-up. Diagnostic work-up after positive mammographic screening will include additional mammographic view and/or ultrasound, with or without biopsy and/or 6-month follow-up. Diagnostic work-up of positive MRI result will include additional ultrasound and/or mammography with or without biopsy and/or 6-month follow-up. Diagnostic work-up after a positive indication from the combined (MRI + mammography) strategy will depend on the modality that triggered the work-up. If both modalities showed positive screen result, the diagnostic work-up based on MRI will be followed. Probabilities for the work-up procedures will be obtained from published literature for women at high familial risk for BC.[32,33]

Treatments: Treatment for BC/DCIS will give consideration to prior chemotherapy and radiotherapy received for childhood cancer. We will use treatment frequencies reported for chest-irradiated cohort[34-36] to adjust the frequencies seen in the general population (SEER database) to determine the relative frequencies of various treatments by BC stage and ER status in the chest-irradiated cohort. The management of DCIS will include either simple mastectomy with or without breast reconstruction, or lumpectomy with or without radiotherapy. Management of local and regional BC will include modified radical mastectomy with or without reconstruction, or lumpectomy with lymph node dissection with or without radiation therapy, both with or without adjuvant chemotherapy, and with or without hormonal therapy. Management of distant BC will include hormone therapy and/or systemic chemotherapy. The percentage receiving radiotherapy will be lower than for BC patients in the general population because of prior radiotherapy. Treatment options will primarily affect costs associated with treatment of BC at different stages.

Breast-cancer-specific survival after breast cancer: A review of available studies showed that as in the general population, survival in chest-irradiated female CCSs appears to be associated with age and disease stage at diagnosis.[5] However, a large study comparing BC tumor characteristics in 298 Hodgkin Lymphoma (HL) survivors with 405,223 de novo BC survivors in SEER showed that HL survivors were significantly more likely to have ER-negative and PR-negative BC, and that HL survivors with localized BC were significantly more likely to have poorly differentiated cancer.[37] The hazard ratio (HR) of BC-death (adjusted for age and year of BC diagnosis, HL status, ER and PR status, radiotherapy for BC, sociodemographic status, race) in HL survivors with localized BC was 2.0 (p=.002, 95% CI: 1.3-3.1) and in HL survivors with regional/distant BC 1.3 (p=.15, 95% CI: 0.9-1.9). Limited treatment option (less frequent use of anthracycline and radiotherapy),[36-38] greater prevalence of contralateral BC, and patient susceptibility were suggested as possible explanations for the increased HR for BC deaths in HL survivors with localized BC. We will use the BC-survival rates estimated from the

SEER data stratified on age and stage at detection for women with regional/distant BC, and adjust the HR of BC-death by twice for women with localized BC.

Quality-adjusted life-Years: Effectiveness is ideally measured in terms of both the quantity as well as the quality of life gained from the use of the intervention. The most commonly used measure of effectiveness is the quality-adjusted life year (QALY) which weighs the quantity of life by the quality of that life. Quality of life is quantified by preference scores, ranging from 0 for death to 1 for perfect health, obtained using health related quality of life (HRQL) measures for various health states. The Panel on Cost-Effectiveness in Health and Medicine recommends that these scores be derived from a representative sample of people within society, rather than patients.[13] These scores have been obtained from over 15,000 adults aged 18 and over who responded to year 2000 Medical Expenditure Panel Survey.[39] Using these data, Stout et al[40] calculated the age-specific mean preference scores for women age 30 years or older, and assigned preference scores by BC stage assuming weights relative to healthy women (90% for DCIS and local BC, 75% for regional BC, and 60% for distant BC). We will use these preference scores for ages ≥ 30 years, and use values appropriately inflated for younger women according to preference scores calculated for those <30 years of age.[39] We will adjust the HRQL scores to account for lower levels found in childhood cancer survivors compared to those without cancer.[41] We will assume that a reduction in HRQL lasts for 2 years after BC diagnosis and returns to the healthy state after that time.[40] However, the possibility that recovery may take longer in childhood cancer survivors will be examined in sensitivity analysis.

Costs: We will include all direct medical costs associated with the procedures described under Diagnostic Work-up and Treatments. Costs will be derived from Medicare reimbursement rates.[42] Costs of CBE will include physician time and facility costs. Costs of mammography screening will include cost of bilateral initial screen 2-D mammography, diagnostic mammography, ultrasound, biopsy, radiologist and pathologist time, and facility cost. Costs of MRI screening will include initial bilateral screening MRI, diagnostic (unilateral) MRI, biopsy, radiologist and pathologist time, and facility cost. Treatment costs will include costs of mastectomy with reconstruction, lumpectomy, radiation therapy, adjuvant chemotherapy, hormonal therapy, and patient time lost from work. Metastatic BC treatment and follow-up annual surveillance costs will be included; the frequency will depend on diagnostic stage of BC and ER status. Management costs for recurrent and contralateral BC will be included in the cost of treating the first BC based on probability of their occurrence dependent on stage of first BC.

Costs due to patient time lost from work will be included in all strategies. Time costs result from the time spent by survivors while receiving screening, medical intervention, or treatment. When the survivors are minors, the time spent by caregivers for accompanying them to these procedures (screening) is considered. For example, 0.25 day of time cost could be involved for a clinical breast exam; 0.25 day for a bilateral screening mammography; 0.5 day for bilateral screening MRI; and 2 days for mammogram- or MRI-guided surgical biopsy. Time costs are determined by multiplying the time spent in these procedures by the mean (or median) wage of the individuals involved (caregiver or adult survivor). The mean/median income of the US general population is usually used.

A study showed the unemployment rate to be rather high in the CCSS: 11.9% were not in the labor force, 7.4% were unemployed for health-related reasons, and 4.7% were seeking work.[43] Female survivors were more likely to be not employed than male survivors (20% vs. 5%). One might argue that the time costs derived from the general population may be too high, which could contribute to an inflated ICER (i.e. screening is less cost-effective than it actually is). However, time costs are relatively low compared to other costs. Also, it is not possible to foresee the interplay between the use of inflated time costs, the potential increase in quality-adjusted life years due to BC averted from screening, and the potential decrease in the quality-

adjusted life years resulting from deaths due to competing causes. We acknowledge this limitation, and will consider examining the effects of varying time-costs (higher, lower) on ICER in sensitivity analysis.

Costs will be adjusted to 2014 U.S. dollars using the Consumer Price Index. Future medical costs are assumed to be averted with screening, but a greater societal value is usually placed on present savings as opposed to future gains. Therefore, all future benefits calculated will be discounted at an annual 3% rate.

Sensitivity analysis: Because input parameters for cost-effectiveness analysis could come from the literature, expert opinion, estimated from secondary data analysis, and extrapolated using secondary data sources, uncertainty is introduced into the results. The robustness of the findings and degree to which the study results are sensitive to the input parameters will be assessed by sensitivity analysis. One-way and two-way sensitivity analyses will be conducted to examine the effects of changes in one or two factors on ICER. Factors to be varied include sensitivity and specificity of CBE, mammography, and MRI, BC incidence and non-BC mortality rates, costs of screening, and ages for undergoing screening. The range of plausible rates and costs obtained from the literature, hypothesized values based on expert opinion, and confidence bounds of estimates obtained from secondary data analysis will be used as range of values to vary in sensitivity analysis.

e. Examples of specific tables and figures:

Table. Effectiveness and cost-effectiveness of the COG screening strategies for breast cancer in female chest-irradiated childhood cancer survivors

Screen strategy	Cost	Incremental cost	Life years	Quality-adjusted Life years	Incremental cost effectiveness ratio
No clinical breast exam, mammography, or MRI (no screen)		--			--
Clinical Breast examination only (Aim 1)					
COG recommendation, without MRI as adjunct (Aim 2)					
COG recommendation using 2D/3D mammography, without MRI as adjunct (Exploratory Aim 2a)					
COG recommendation, without mammography (Aim 3)					
Full COG recommendation (Aim 4)					
Full COG recommendation, using 2D/3D mammography (Exploratory Aim 4a)					

6. SPECIAL CONSIDERATIONS

The CCSS Statistical Center will provide the data. F.L. Wong will conduct the statistical analyses with input and review by the collaborators listed in the **WORKING GROUP**.

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