

C.3 Specific Aim 1: To estimate the long-term adverse effects and quality of life impacts of the most commonly used breast cancer chemotherapy regimens.

C.3.1 Literature Search

The research team will conduct a series of systematic reviews to estimate the rates of long-term adverse effects of commonly used adjuvant chemotherapy regimens for breast cancer. As shown in the search protocol 1 in Appendix A, the series of systematic reviews will address five categories of chemotherapy-related adverse events: 1) cardiac toxicity, 2) ovarian failure, 3) secondary malignancies, 4) neurotoxicity, and 5) cognitive dysfunction.

Chemotherapy agents commonly used in the US for breast cancer adjuvant therapy will be included: anthracyclines (doxorubicin, epirubicin), cyclophosphamide, and taxanes. Because these agents are used in combination, we will search for literature on outcomes from combined regimens. The English language literature will be comprehensively searched in Medline, Embase, the Cochrane library and Web of Science for the period of 1975 to current. In addition, references of relevant identified studies will be hand searched for additional studies, and experts in the field will be consulted to ensure we have comprehensively identified the relevant literature. The search phrases for each condition are listed in Table A1, Appendix A.

C.3.2 Inclusion/Exclusion Criteria

Study populations will include women of all ages with breast cancer of stages I–IIIA, all LN and endocrine receptor status, and receiving adjuvant chemotherapy agents listed above. Because we are searching for evidence of long-term adverse effects, which are often not reported in randomized trials, study designs will include randomized controlled trials (RCT), observational cohort studies, and case control studies.^{143, 144} Included studies must report a minimum of 12 months of follow-up and loss to follow-up less than 30%. Studies will be stratified by study type (RCT, cohort, case-control) and by long-term adjuvant therapy-related adverse effects (cardiac, ovarian failure, neuropathies, cognitive dysfunction, and secondary malignancies). Studies that have incomplete reporting of outcomes, as well as case reports, case series, and interim studies with data included in a later report, or otherwise do not meet the criteria listed above will be excluded.

C.3.3 Data Collection

Eligible articles identified via the search strategies detailed above will be screened independently by two members of the research team. Relevant titles will be selected for abstract review, and full papers of relevant abstracts will be reviewed independently by two members of the research team. Papers meeting inclusion criteria will be indexed by keywords in EndNote X4 (© 2010 Thompson ISI ResearchSoft). Key data elements will be abstracted by Dr. Melnikow, a graduate researcher, and Mr. Yang, with consultation and review by Dr. Ganz. Abstracted data will include identifying data (first author, year of publication), population characteristics (N, mean age, range), study setting (country, university based, community based), study type (RCT, cohort, case control), inclusion and exclusion criteria, study population source, characteristics, follow-up duration, loss to follow-up, chemotherapy regimen, covariates, and outcomes. Study quality assessment scores will be assigned based on pre-established criteria depending on study design. Data from our analysis of cohort studies (see Section X.X below) will be included in the systematic review and considered for meta-analysis. In both the literature review and analysis of existing cohort studies we will examine our findings for evidence of disparities in treatment or outcomes based on race-ethnicity, socio-economic status, insurance status, or other measures of access to care. Data will be entered in an Excel database. A draft data abstraction form and quality assessment criteria are attached in Appendix A.

C.3.4 Analysis

After the studies have been reviewed and abstracted, and the collection is determined to be qualitatively homogeneous, standard meta-analytic techniques will be used to estimate pooled incidence rates (per patient-year) for each category of chemotherapy-related long-term adverse event.⁶⁴ The study-level relationship between baseline risk, treatment choice, and adverse event incidence will be explored. Random effects models will be used to allow for the estimation of between-study variation. Quantitative heterogeneity will be examined using I^2 statistics and subgroup analysis. Publication bias will be examined using L'Abbe plots and

funnel plots. If possible, meta-regression will be used to model study-level incidence rates and study-level characteristics to explain sources of heterogeneity, especially heterogeneity with respect to baseline risk and treatment choice.¹⁴⁵ We will also assess the feasibility of conducting an individual participant data meta-analysis.⁶⁴ When feasible, we will calculate pooled estimates of incidence rates. These will be applied to the cost effectiveness model (Aim 2). If pooling is not possible due to qualitative heterogeneity, we will highlight rate estimates from the highest quality studies for application to the model. Findings from the systematic reviews will be submitted for publication, and will provide a needed resource summarizing current research and key gaps in this field.

C.3.5 Analysis of Data from Existing Studies.

We will use patient-level data from long-term follow-up of breast cancer cohort studies to inform the conditional state transition probability inputs and to validate outputs of the Markov models developed in Aim 2. Through her own NIH funded research, collaboration with other investigators, and affiliation with the NSABP, Dr. Ganz has access to a number of cross-sectional and longitudinal cohort studies that can provide patient reported outcomes related to persistent symptoms and health outcomes (e.g., fatigue, physical dysfunction, comorbid conditions) that are associated with chemotherapy exposure in the treatment of ESBC. The available studies are listed in Table 1. All of these cohort studies have extensive databases with information on additional health outcomes that have not previously been examined and will be mined for further information to be used in the proposed studies. Letters of support regarding access to data from these studies are attached.

C.3.6 Analytic Plan existing patient-level datasets and sample size considerations

The primary goal of the statistical analyses of the available patient-level observational data is to complement the meta-analysis by estimating treatment effect parameters and Markov-model state transition probabilities to inform the specification of inputs into the cost effectiveness models in Aim 2. To account transparently¹⁴⁶ in Aim 2 for important sources of confounding bias arising especially from the nonrandom allocation of treatment combinations, selection effects arising from non-response and mortality, and the potential unavailability of important covariates, we will produce a panel of parameter estimates based on alternative statistical models and assumptions for observational studies.^{147, 148} These will include preference-based instrumental variable methods¹⁴⁹ and propensity score methods.¹⁵⁰⁻¹⁵² We will combine them with subject-matter expertise from study investigators on the potential direction and relative size of confounding biases for purposes of encoding plausible distributions for Markov model inputs¹⁵³. Subject matter expertise will also be used to encode causal models¹⁵⁴⁻¹⁵⁶ to identify the appropriate use of measured covariates¹⁵⁷⁻¹⁵⁹. In order to minimize controllable sources of confounding bias, we will employ restriction of the dataset (i.e. to more homogeneous subgroups)¹⁶⁰ and choose parsimonious sets of measured covariates for inclusion in regression models.¹⁶¹⁻¹⁶⁷ Validation of the statistical regression models in Aim 1 and the cost effectiveness models in Aim 2 will include both internal (i.e., cross-validation) and external data sets. Statistical model complexity for adverse event outcomes will be limited to no fewer than 10 events / degree of freedom to enhance external validity.¹⁶¹

Table 1. Cohorts Available for Risk-prediction Model of Adjuvant Chemotherapy Long Term Adverse Effects

Study; PI	Study design	Baseline/Follow up	Refs
UCLA-Georgetown Women's Health Study; Ganz	<ul style="list-style-type: none"> Cohort: Breast cancer survivors (Los Angeles, Washington DC); Sample 1, n=863; sample 2, n=1,094 at baseline, 817 at follow-up survey Measures: RAND SF-36, CES-D; DAS, BCPT, WSFQ, CARES 	<ul style="list-style-type: none"> Baseline: 1–5 years post diagnosis Follow-up: 5 years after first survey 	3, 7, 190, 91
Moving Beyond Breast Cancer; Ganz	<ul style="list-style-type: none"> Cohort: Breast cancer patients identified ≤1 month after surgery (Lost Angeles, Washington DC, Kansas); N=558 Measures: RAND SF-36, Ladder of Life Scale, CES-D, RDAS, BCPT 	<ul style="list-style-type: none"> Base line: End of primary treatment Follow up: 2, 6, 12 months after baseline survey (stratified by chemotherapy exposure) 	1, 2, 1
UCLA Mind Body Study (R01);	<ul style="list-style-type: none"> Cohort: Breast cancer patients after primary treatment and prior to starting endocrine therapy; N=190 	<ul style="list-style-type: none"> Baseline: end of primary treatment Follow up: 	169, 1

Ganz	<ul style="list-style-type: none"> • Measures: Cognitive function, NP testing, comorbid conditions, meds (on adjuvant endocrine therapy) <ul style="list-style-type: none"> ◦ Substudy: PET imaging 	<ul style="list-style-type: none"> – 6 & 12 month (NP testing, questionnaires, comorbid conditions, meds) – Annual cohort follow-up by survey – Currently at 4-years follow up 	
Life After Cancer Epidemiology (LACE); Caan	<ul style="list-style-type: none"> • Cohort: ESBC survivors (KPNCAL and UCR); N~2300 • Measures: Late cardiac effects, comorbid conditions, medications, physical disability, weight gain 	<ul style="list-style-type: none"> • Baseline: 2-years post diagnosis • Follow up: semi-annual 5-years; annual >5 years 	171-173
NSABP B-31	<ul style="list-style-type: none"> • Cohort: Patients with LN+/HER2+ breast cancer; N=2700 (projected; ACT vs AC-T + trastuzumab) • Measures (primary): Cardiotoxicity, DFS, OS 	<ul style="list-style-type: none"> • Follow up: 5-years; annually thereafter • Currently 5–8 years post randomization collecting repeat cardiac function, SF-36, symptoms • Data expected within 12 months 	175, 176
	•	•	
NSABP B-30	<ul style="list-style-type: none"> • Cohort: Patients with LN+ breast cancer; N=5351 (AC ± T) • Measures (secondary): AEs, QOL, amenorrhea 	<ul style="list-style-type: none"> • Follow up: 5 years after chemotherapy (24 months for QOL/menstrual history) 	95, 98
NSABP B-36	<ul style="list-style-type: none"> • Cohort: Patients with LN- breast cancer; N=2700 (projected; 4 x AC vs 6 x FEC) • Measures (secondary): AEs, QOL, amenorrhea, cardiac function study at baseline and 1 year in 400 patients 	<ul style="list-style-type: none"> • Follow up: 5 years after chemotherapy (36 months for QOL and amenorrhea) • First interim analyses expected < 2 yrs 	177
NSABP B-47	<ul style="list-style-type: none"> • Cohort: Patients with HER2-low breast cancer; N=3260 (adjuvant chemotherapy ± trastuzumab) • Measures (secondary): AEs, incl. menstrual history; comorbid conditions, concomitant medications, weight gain 	<ul style="list-style-type: none"> • Follow-up; all at regular intervals 	178

Abbreviations: AC(T), doxorubicin + cyclophosphamide (+ paclitaxel); FEC, fluorouracil, epirubicin, and cyclophosphamide; AEs, adverse events; BCPT, Breast cancer Prevention Trial symptom checklist; DFS, disease free survival; Kaiser Permanente California Registry; OS, overall survival; PET, positron emission tomography; QOL, Quality of life; RAND SF-36, RAND 36-item health survey; RDAS, Revised Dyadic Adjustment Scale; UCR, Utah Cancer Registry; WSFQ, Watts Sexual function Questionnaire

Power calculations that incorporate cautious design effect adjustments for use of analysis weights^{179, 180} and a varying number of model degrees of freedom¹⁸¹ indicate that when the analysis dataset consists of at least 800 observations (as we anticipate for most analyses), it will yield greater than 80% power to detect when parsimonious models have good discrimination (Area Under the Curve Statistics > 0.70) under two-sided testing of the no-discrimination null hypothesis (alpha=5%) for events with incidence proportions as low as 5%.^{182, 183} Variables available in the long-term survivor cohort studies^{5,89} contain demographics, including ethnicity and marital status; employment status and occupation; income at both time points; baseline cancer treatments (surgery, reconstruction, radiation, chemotherapy, endocrine therapy, or chemotherapy–yes/no); comorbid conditions; follow-up outcomes; BMI—height and weight; interval cancer recurrence and new cancers at follow-up; ongoing additional cancer therapy (at follow-up); and QOL measured with multiple scales, including SF-36; symptoms; and sexual health and functioning.