Optimizing Health Among Ductal Carcinoma In Situ Survivors

By

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A Dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

(Epidemiology)

at the

UNIVERSITY OF WISCONSIN-MADISON

2017

Date of final oral examination: July 26th, 2017

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ABSTRACT

Women diagnosed with ductal carcinoma in situ (DCIS) are faced with the challenge of undergoing appropriate treatment. Assessment of recent trends in DCIS treatment, accounting for demographic factors is important in highlighting adherence to treatment guidelines. Effective surveillance following treatment is important, especially as newer technologies such as magnetic resonance imaging (MRI) have emerged, with limited knowledge about its use among DCIS survivors. Though less well described among DCIS survivors, cardiovascular health promotion strategies are important for improving long-term survival.

Recent trends in DCIS treatment using data from the National Cancer Database demonstrated plateauing of adjuvant radiation use after breast conserving surgery at approximately 70% after 2007. Postmastectomy reconstruction and contralateral mastectomy utilization rates increased over time and were inversely associated with increasing age, and varied according to ancestry/ethnicity and geographical region.

Breast MRI use among 1,103 DCIS survivors of the Wisconsin in situ cohort (WISC) was approximately 12% and demonstrated a positive association with a lifetime risk breast cancer risk ≥20%, increasing income and educational status. Compared to metropolitan residents, mean travel time to breast MRI facilities was significantly longer among non-metropolitan residents. Consequently, breast MRI access may be challenging for DCIS survivors residing in non-metropolitan areas.

The prevalence of the American Heart Association's (AHA) cardiovascular metrics and adverse events were assessed among DCIS survivors in the WISC and according to surgical treatment as well as adjuvant therapy use. Less than a third of DCIS survivors had ideal levels for diet (25%), total cholesterol (31%) and blood pressure (32%) metrics, with about 2% of women having ideal levels of all 7 AHA cardiovascular metrics. The prevalence of adverse

cardiovascular events was substantially lower with tamoxifen use, with no statistically significant difference observed upon exclusion of women with a history of stroke and stroke-like events. These findings highlight potential cardiovascular disease risk factors that may be challenging to modify among DCIS survivors.

Continued research and interventions are required to improve mastectomy utilization, facilitate appropriate breast MRI use including access, as well as the adoption of dietary habits and lifestyles that reduce cardiovascular disease risk following a DCIS diagnosis.

ACKNOWLEDGMENTS

During my PhD training I have been privileged to receive immense support, guidance and encouragement from various individuals whom I would like to acknowledge. First, I sincerely appreciate my advisor, Dr. Amy Trentham-Dietz for her outstanding advice and support. She guided me through the world of population-based cancer research, providing an enabling environment for the successful initiation, conduct and dissemination of research. Under her mentorship I learned grant writing and successfully secured a National Cancer Institute PA-15-322 diversity supplement award, that funded most of my PhD training. Amy patiently worked with me, encouraged me, and provided valuable feedback that molded this dissertation from inception to completion. I am greatly indebted to her for her extraordinary mentorship.

I would like to thank other members of my dissertation committee for generously giving their time and expertise. I am very grateful to Dr. Brian Sprague, for his guidance and support during my graduate studies. His work with the Vermont Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) center exposed me to screening and surveillance based research. In addition, his insightful comments were invaluable throughout the course of my dissertation. I would like to thank Dr. Caprice Greenberg for her insightful comments on clinical aspects of my dissertation, and Dr. Ronald Gangnon for his guidance and assistance regarding statistical analysis in this dissertation. I am greatly indebted to Dr. Corinne Engelman for her invaluable critique, advice and support throughout the course of this dissertation

I owe a special debt of gratitude to the employees and graduate students of the Cancer Epidemiology Studies group: John Hampton, Julie McGregor, Xiao Zhang, Patricia Jewett, Natalia Arroyo and Danielle Robertson. I regard them as the “Hidden Figures” behind my successful path through graduate school. Working in the background, they ensured that data management, grant administration and other research logistics went smoothly. They also provided professional and moral support throughout the course of my graduate studies. I particularly would like to thank John Hampton for his assistance in analyzing the various datasets I used in this dissertation. I would also like to acknowledge the contributions of Dr. Polly Newcomb to the Wisconsin in Situ Cohort study.

I am grateful to my family for their unconditional love and care which has carried me through the course of my graduate studies. I thank my parents and parents-in-law for their presence and spiritual support at challenging times of my graduate studies. The faithful support and encouragement of my wife (Yinka) and children (Soore and Damisayo) without which I would not have made it this far is highly appreciated. Their personal sacrifices on my behalf motivated me to stay the course and finish my PhD program on time. Finally, I thank my God, for his blessings, daily guidance and for seeing me through graduate school.

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CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

Ductal carcinoma in situ (DCIS) is a preinvasive breast cancer lesion accounting for about 20-25% of all breast cancer cases in the United States [1, 2]. Surgical excision with or without adjuvant radiation therapy is the mainstay of DCIS treatment. Supplemental surgical therapies include postmastectomy reconstruction and contralateral mastectomy. The goal is to provide appropriate treatment that lowers recurrence risk and prevents invasive breast cancer development, in line with treatment guidelines.

Following treatment, DCIS survivors still require active and effective surveillance. This is because they have a five-fold increase of being diagnosed with breast cancer compared to women in the general population [3]. Breast magnetic resonance imaging (MRI) is increasingly utilized among women with a personal history of breast cancer, with questions being raised about consideration of underlying breast cancer risk and equitable breast MRI access.

DCIS survivors are eventually more likely to die from cardiovascular disease than from breast cancer [4]. Adoption of healthy lifestyles among DCIS survivors is important for breast cancer and cardiovascular disease prevention even as adjuvant therapies may impact the occurrence of adverse cardiovascular events. [5, 6]. However, there is limited knowledge about the level of adoption of healthy lifestyles among DCIS survivors compared to women in the general population.

Hence, the life course of a woman following DCIS diagnosis can be complex and may result in variations in patterns of care and advanced imaging utilization. Additionally, the extent to which DCIS survivors adopt and maintain healthy lifestyles may influence their cardiovascular disease risk which increases as they grow older.

1.1 Surgical Treatments, Adjuvant Radiation and Supplemental Therapies

The introduction of widespread mammography screening in the 1980s, (Figure 1.1) has been strongly attributed to the concurrent rise in the detection of DCIS lesions [7-10]. For instance DCIS incidence increased over seven-fold from 1980 to 2007 (4.8 per 100,000 to 34.6 per 100,000 respectively) [11]. The incidence of DCIS also varies by ancestry/ ethnicity, with women of European ancestry having the highest incidence (26.6 per 100,000 women) in the US population [12]. Additionally, DCIS incidence increases with age, relatively rare among women 20-39 years (3.4 per 100,000 women) and highest among women 70-79 years (84.3 per 100,000 women) [12].

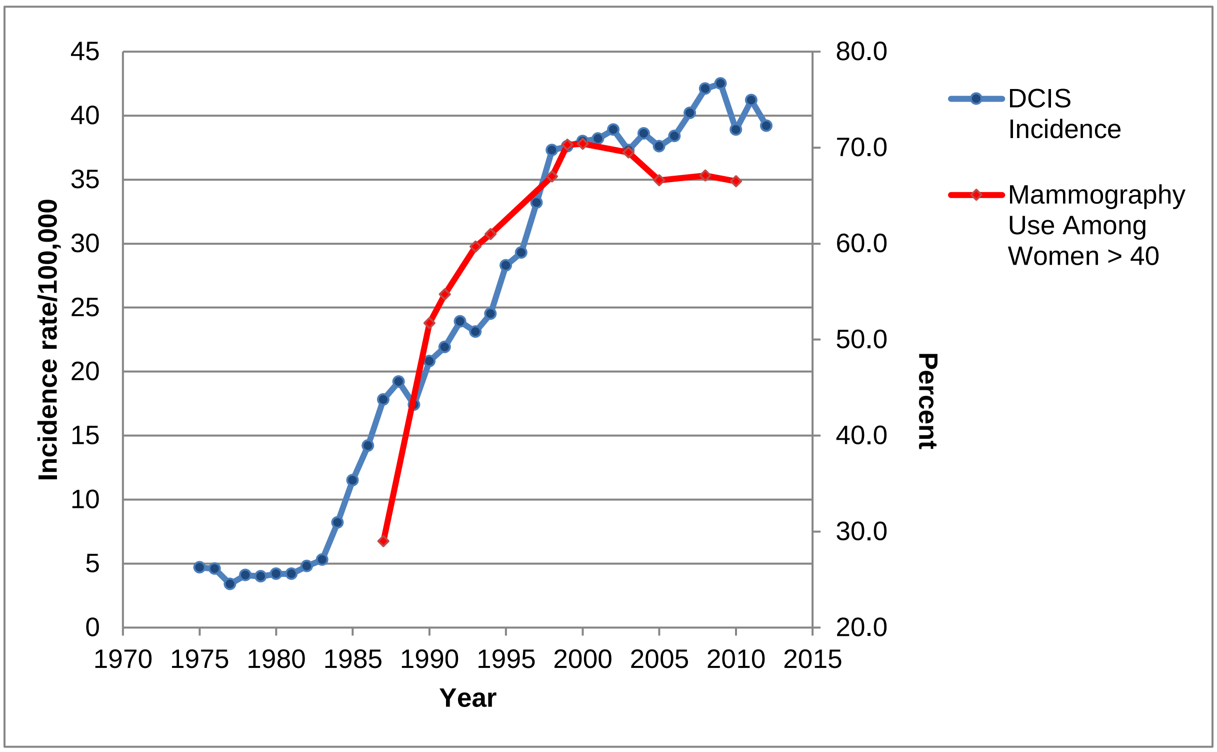


Figure 1.1. Age-adjusted DCIS incidence (Surveillance, Epidemiology, and End Results Program, 1975-2012) and age-adjusted proportion of women over 40 years reporting mammography use (National Health Interview Survey, 1987-2013).

Women diagnosed with DCIS undergo localized treatment by means of surgical excision with or without adjuvant radiation. The extent of surgical excision may vary from breast conserving surgery (lumpectomy or partial mastectomy) to complete removal of the breast (simple mastectomy). The overall goal of DCIS treatment is to deter recurrence and ultimately prevent progression to invasive breast cancer. DCIS treatment is continually evolving and reflects the impact of randomized clinical trials and evidence from other forms of published research [13-16].

Until about 3 decades ago, mastectomy was the standard treatment for DCIS, with evidence for treatment modification initially derived from randomized clinical trials on invasive breast cancer management. For instance, results from the NSABP B-06 trial comparing lumpectomy, lumpectomy with adjuvant radiation, and mastectomy for stage I and II invasive breast cancer treatment, lead to a paradigm shift from mastectomy for DCIS treatment, towards less aggressive breast conserving therapy [17, 18]. Current treatment guidelines recommend adjuvant radiation therapy following breast conserving surgery for DCIS as additional evidence from randomized DCIS treatment trials suggest that it lowered the risk of recurrence [19, 20]. The NSABP B-17 trial assessing the efficacy of adjuvant radiation therapy following breast conserving surgery among DCIS cases reported a significantly higher five-year event-free survival rate among women who received radiation therapy (84.4%) compared to those who did not (73.8%) [13]. However, adjuvant radiation therapy following breast conserving surgery for DCIS does not improve breast cancer specific or overall survival [21-23]. Some women as a preference may opt to forego radiation therapy following breast conserving surgery for DCIS. In addition to patient preference, situations in which radiation may be omitted following breast conserving surgery include complete low-grade tumor resection with wide negative margins, advancing age and comorbidity.

Adjuvant endocrine therapy may be indicated as part of DCIS treatment as about 60-75% of tumors express estrogen receptor (ER) and/or progesterone receptor (PR) [24, 25]. Tamoxifen is the most widely studied and recommended antiestrogen agent especially following breast conserving surgery [26-28].

Mastectomy may be a preferred DCIS treatment option, especially in cases of diffuse, multifocal disease; anticipated cosmetic breast deformity with breast conserving surgery; conditions that preclude radiation therapy such as pregnancy; and the presence of specific breast cancer mutation genes such as in *BRCA1/2* [29]. Although mastectomy has a lower rate of recurrence compared to breast conserving surgery with or without radiation, it does not improve breast cancer specific or overall survival. For instance, a 2015 analysis of over 100,000 women with primary DCIS tumors at diagnosis in the Surveillance, Epidemiology, and End Results (SEER) database observed similar 10-year breast cancer specific mortality between women treated with lumpectomy compared mastectomy (HR: 1.2; 95% CI 0.96-1.50) [30]. Since breast cancer specific survival does not vary by extent of surgical treatment, mastectomy may be an overly aggressive treatment option for many women diagnosed with DCIS. Therefore, achieving the right balance between DCIS treatment choice and the risk of recurrence can be a challenging decision for both patients and healthcare providers.

Following mastectomy, breast reconstruction may be a consideration for most women. Postmastectomy reconstruction allays concerns about body image and has been shown to positively impact self-esteem including the psychological and emotional functioning of women [31, 32]. The impact of postmastectomy reconstruction on quality of life was a key driver in the enactment of the Women's Health and Cancer Rights Act, mandating healthcare payer coverage for breast reconstruction following mastectomy [33]. In the US about 40% of women treated with mastectomy undergo breast reconstruction [34].

The utilization of contralateral mastectomy (i.e. surgical removal of the uninvolved breast), particularly among high-risk women, is controversial as current evidence does not clearly suggest any survival benefit for most breast cancer patients without deleterious *BRCA1/2* mutations [35]. Factors associated with contralateral risk reducing mastectomy utilization include younger age, family history, genetic predisposition, tumor size and grade.[36, 37] Although the Society for Surgical Oncology has specific indications for its use, current trends suggest that women utilizing contralateral risk reducing mastectomy for early stage breast cancer treatment fall short of these recommendations. [38, 39]

Previous studies have reported variations in the treatment of DCIS [40]. These variations have been observed in the utilization of both surgical treatment (breast conserving surgery and mastectomy) as well as supplemental therapies such as radiation treatment and breast reconstruction following mastectomy. For some women diagnosed with DCIS, these variations may result in under-treatment in some instances or overly aggressive therapy. Given the historical variation in DCIS treatment, it is unclear how demographic factors are related to recent treatment trends, even as clinical guidelines are continually evolving.

1.2 Posttreatment Breast Magnetic Resonance Imaging

Women with a personal history of DCIS have about five-fold increased risk of developing breast cancer compared to women with no breast cancer history [3, 22, 41]. Treatment type also impacts the risk of recurrence or second breast cancer development, with women undergoing mastectomy rarely developing ipsilateral breast cancer. Annual mammography is the main imaging modality recommended for surveillance among breast cancer survivors [42, 43]. Adherence to mammography surveillance in the first year posttreatment is almost 80% among DCIS survivors and decreases over time [44, 45]. Among DCIS survivors previously treated with breast conserving surgery, those that received adjuvant radiation therapy were more likely to adhere to annual mammography surveillance (OR: 1.28; 95% CI, 1.08-1.53) [45, 46]. Imaging surveillance is important for early detection of second breast cancer events (including recurrent lesions).

Breast MRI has emerged as an important supplementary imaging modality to mammography. Previous studies have demonstrated greater sensitivity of breast cancer detection for supplemental Breast MRI screening compared to mammography, among confirmed or suspected *BRCA1/2* mutation carriers [47-50]. In contrast, screening breast MRI specificity is lower (84-91%) compared to mammography (93-97%), leading to a higher false positive rate yielding benign lesions among confirmed or suspected BRCA mutation carriers [50]. Breast MRI is usually performed with contrast enhancement, which has the added advantage of better distinguishing fibrosis secondary to treatment from recurrent carcinoma and can detect recurrent disease at an earlier stage. Compared to mammography, breast MRI is more expensive and is only cost effective for screening among women with a high breast cancer risk [48]. According to Stout et al, the application of breast MRI has increased steadily since the early 2000s to 2010 [51]. Beyond screening among women with no prior history of breast cancer, breast cancer surveillance among women with a personal history of breast cancer (including DCIS survivors) is the next most frequent indication for breast MRI utilization. Apart from surveillance, there are other indications for breast MRI use among women with a personal history of breast cancer. These include: additional diagnostic workup, especially when clinical and mammographic findings are inconclusive; assessment of breast implants; and evaluation of the extent of recurrent breast cancer including multifocal disease [52].

The 2015 surveillance guidelines jointly sponsored by the American Cancer Society (ACS) and the American Society of Clinical Oncology recommend the use of breast MRI supplementary to mammography among certain group of breast cancer survivors [53]. These are women defined as having a high risk of breast cancer based on the 2007 ACS breast MRI guidelines [54]. Women at high risk of breast cancer are: known *BRCA* mutation carriers or untested women with affected first degree relatives; women with certain familial cancer syndromes (such as Li-Fraumeni syndrome) including first degree relatives; women with previous chest radiation between age 10 and 30 years and women with a lifetime breast cancer risk of at least 20-25 % as evaluated by breast cancer risk models that are largely dependent on family history [54]. Examples of breast cancer risk assessment models include Gail, Claus, BRCAPRO and Tyrer-Cuzick models [55-59]. Lifetime breast cancer risk is estimated from specific input variables which include age, prior breast biopsy including presence of atypia, age at menarche, age at first live birth, history of breast cancer in first-degree relatives, race and history of deleterious mutations such as the *BRCA1/2* genes.

Breast MRI surveillance among DCIS survivors is contentious with some researchers suggesting it may be beneficial to women with a personal history of breast cancer [60]. Previous studies characterizing breast MRI utilization in general have linked its use to some underlying breast cancer risk factors. For instance, Wernli et al noted that breast MRI utilization was more likely among younger, non-Hispanic white women, with a positive family history of breast cancer and with extremely dense breast tissue [61]. Younger age is an important risk factor for breast cancer recurrence among DCIS survivors. The 10-year recurrence rate among DCIS survivors decreases with increasing age from 27.3 % among women less than 40 years of age to 7.5 % for women 80 years and older [62]. Furthermore, breast MRI may be more valuable among young women with dense breasts in detecting mammographically occult breast cancers [63].

There are racial differences in the risk of second breast cancer events among DCIS survivors. For instance, African American women are more likely to develop ipsilateral (relative risk [RR] 1.46; 95% confidence interval [CI] 1.29–1.65) and contralateral breast cancer (RR 1.21; 95 % CI 1.08–1.36) compared to non-Hispanic white women [64]. Racial differences in breast MRI utilization have been reported with mixed results possibly due to differences in study population [61, 65]. However, there are no studies that have assessed breast MRI use among DCIS survivors according to race/ethnicity.

Underlying breast cancer risk increases 2-4 fold with increasing number of affected first-degree relative. Women diagnosed with in situ or early stage breast cancer have an increased risk of second primary breast cancer if they have a first-degree breast cancer family history [66, 67]. First-degree breast cancer family history may be suggestive of possible deleterious breast cancer mutations and thus confer high risk of breast cancer on affected relatives, prompting supplemental breast MRI utilization. Breast MRI use in community practice is more likely among women with a first-degree family of breast cancer [61]. However, there is limited knowledge about the relationship between family history and breast MRI utilization among DCIS survivors.

Primary DCIS tumor features such as tumor size and grade have been shown previously to be associated with disease-free survival albeit to varying extents. For instance, the SweDCIS trial found a lower risk of recurrence (HR: 0.43; 95% CI, 0.21–0.89) among women with tumor size <1 cm [68]. However, there was no significant relationship between tumor size and recurrence in the NASBP B-17 and B-24 trials (HR: 1.03; 95% CI, 0.73–1.44), though most cases (80%) in this analysis had tumor size less than 1cm [27]. Another study assessing DCIS grade and recurrence demonstrated a 60% increase in the risk of recurrence for high versus low grade DCIS [69]. Despite these findings, the relationship between tumor features at primary DCIS diagnosis and breast MRI utilization among DCIS survivors, is less described.

Socioeconomic factors especially increasing level of educational attainment and income have been positively linked to preventive services utilization [70-73]. Breast MRI does not have a wide distribution compared to mammography, probably due to the high cost of maintaining a breast MRI facility [74]. An assessment of differences in breast MRI use according to socio economic factors is important as it may highlight inequality in its distribution which may contribute to disparities in its use.

Geographic access to imaging facilities, measured as travel time from residence to closest facility varies by imaging modality. About 85% of women have ≤20 minutes travel time to a mammography or breast ultrasound facility compared to 70% of women who have ≤20 minutes to a breast MRI facility. [74] It is likely that proximal access to MRI facilities may influence breast MRI utilization pattern among DCIS survivors, with women living farther off less likely to utilize it. However, there are no previous studies assessing the relationship between geographic access and breast MRI utilization among women with a personal history of breast cancer in general or following a DCIS diagnosis.

Breast MRI facilities will expectedly be fewer and probably located in urban areas due to high equipment cost and specialized personnel training. Previously, among women undergoing breast cancer screening, it has been observed that women residing in rural areas have 4-8 times longer travel time to a breast imaging facility compared to women in urban areas [74]. Although these findings were observed among women undergoing breast cancer screening in general, not much is known about the relationship between rural/urban residence including proximity to a breast MRI facility and its utilization among DCIS survivors.

1.3 Cardiovascular Health and Disease among Ductal Carcinoma in Situ Survivors

The breast cancer specific mortality following DCIS diagnosis and treatment is very low and estimated to be about 3.3% at 20 years according to a 2015 SEER study [30]. Some experiences peculiar to DCIS survivors may increase their risk for cardiovascular disease and other chronic morbid conditions. Changes in health behavior such as diet and physical activity may occur following DCIS treatment with subsequent changes in weight and BMI. Studies have shown excess weight gain among women previously diagnosed with DCIS and early stage breast cancer beyond that attributable to aging [75, 76]. Among the preventable causes of death in the US, the top 4 (cardiovascular disease, cancer, chronic lower respiratory disease and cerebrovascular disease) are related to modifiable health behaviors [77-79]. Cardiovascular disease is the leading cause of death in the US with DCIS survivors more likely to die from cardiovascular disease within 20 years (13.2%; Confidence Interval [CI], 12.8-13.7) than from breast cancer (3.2%; 95% CI: 3.0-3.4) [4, 78]. In the United States, about one sixth of healthcare expenditure is on cardiovascular disease [80].

Lifestyle interventions targeting smoking cessation, dietary habits, physical activity and body mass index (BMI) management are important strategies for cardiovascular disease and cancer prevention [81-83]. Maintaining healthy levels of biological factors such as blood pressure, glucose and total cholesterol may decrease cardiovascular disease risk [84]. Together, the highlighted four health behaviors and three biological factors constitute the American Heart Association (AHA) cardiovascular metrics [84]. The AHA cardiovascular metrics also known as Life's Simple 7, were developed by the American Heart Association as a tool for assessing progress in attaining its year 2020 goal: the improvement of cardiovascular health of all Americans by 20% and reduction in cardiovascular disease (CVD) and stroke mortality by 20% [84]. The AHA cardiovascular metrics have been shown to be related to the incidence and survival for cardiovascular and other chronic diseases such as stroke, diabetes, chronic pulmonary and kidney diseases [85-91]. Previous research suggests less than 1% of the adult US population meet ideal conditions for all 7 cardiovascular metrics [92]. Long-term survivorship care is very important because DCIS survivors are increasingly at risk of developing chronic diseases as they grow older [93].

Though adjuvant radiation and endocrine therapies improve disease-free survival [28, 94], these therapies have adverse health effects and may increase the risk of cardiovascular disease [95-97]. Adjuvant radiation therapy following breast conserving surgery is associated with up to a threefold increased risk of cardiovascular disease depending on the extent of radiation treatment [98]. Cardiovascular disease risk varies with individual endocrine agents. Tamoxifen is the most widely studied and recommended antiestrogen agent following Localized treatment [26-28]. Previous studies have shown a reduced risk of ischemic heart disease associated with tamoxifen use with increased risk of thromboembolic events [99, 100]. Tamoxifen reduces total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, both of which are risk factors for ischemic heart disease [101-103]. Reports on cardiovascular disease risk in relation to aromatase inhibitor use has been mixed with a 2016 meta-analysis demonstrating no change in cardiovascular disease risk (RR: 1.01, 95% CI: 0.85-1.20) [95, 104, 105].

Studies comparing cardiovascular risk among women previously diagnosed with early stage breast cancer compared to similar women without a history of breast cancer have shown mixed results [99, 106]. However, among DCIS survivors, previous research suggests a reduced risk of cardiovascular mortality compared to the general population [5]. A limitation of previous studies characterizing cardiovascular disease burden according to DCIS history is the absence of cardiovascular disease risk factor measures [107]. Evaluating modifiable cardiovascular risk factors is important as they impact the development of adverse cardiovascular events, regardless of breast cancer history. Any observed differences in these factors may provide some insight to observed patterns of cardiovascular disease prevalence among DCIS survivors.

The presence of different treatment options for managing DCIS including the emergence of breast MRI with a better tumor detection rate than mammography presents a challenge in selecting appropriate treatment and breast imaging utilization, balancing benefits and harms. Furthermore, an understanding of the extent of adoption of cardiovascular health interventions among DCIS survivors is important including the impact of adjuvant therapies on cardiovascular disease prevalence.

CHAPTER TWO

SPECIFIC AIMS

Following DCIS diagnosis, there is the need to undergo appropriate treatment, breast imaging in accordance with guidelines and maintenance of healthy lifestyles that improve cardiovascular health. The purpose of this dissertation was to evaluate surgical treatment and adjuvant therapies' utilization, follow-up breast MRI use, as well as the extent of adoption of modifiable cardiovascular health interventions among women diagnosed with DCIS

The specific aims of this dissertation include:

1. Evaluate recent trends in DCIS treatment, according to demographic factors.

The use of surgery and radiation therapy in treating DCIS is directed by treatment guidelines and evidence from research. Differences in DCIS treatment utilization may result in under-treatment in some cases or overly aggressive surgical therapy for others. Recent patterns in DCIS treatment, postmastectomy reconstruction and contralateral mastectomy utilization were examined according to demographic factors.

Paper 1: *Emerging trends in surgical and adjuvant radiation therapies among women diagnosed with ductal carcinoma in situ*

Data for women diagnosed with DCIS between 1998 and 2011 (n = 416,232) in the National Cancer Data Base were assessed for trends in treatment patterns by age group, calendar year, ancestral/ethnic group and geographic region. The likelihood of receiving specific treatment modalities was analyzed using multivariable logistic regression.

2. Examine breast MRI utilization among DCIS survivors according to underlying breast cancer risk factors, socioeconomic status and geographic access.

DCIS survivors have a 3-5 fold increased risk of developing breast cancer and require imaging surveillance for early detection of second breast cancer events. Breast MRI utilization has been increasing in recent times, with no studies assessing its utilization and accessibility among DCIS survivors.

Paper 2: *Breast magnetic resonance utilization among ductal carcinoma in situ survivors*

Data from 1,103 women recruited between 1997 and 2006 into the Wisconsin in situ cohort and responding to the 2013 mailed survey questioning breast MRI use were analyzed. The likelihood of breast MRI utilization according to age at diagnosis, race, family history, lifetime breast cancer risk, tumor features and treatment type were evaluated using multivariable logistic regression models. Furthermore, the likelihood of breast MRI utilization according to educational attainment, household income, rural/urban residence and shortest travel time to a breast MRI facility were evaluated.

3. **Evaluate the prevalence of cardiovascular health interventions and adverse events among DCIS survivors.**

DCIS survivors are eventually more likely to die from cardiovascular disease than from breast cancer. Modifiable cardiovascular risk factors are important intervention targets for improving cardiovascular health and cancer prevention. The prevalence of the 7 American Heart association's (AHA) cardiovascular metrics (smoking, physical activity, body mass index, smoking, total cholesterol, blood pressure and fasting plasma glucose and adverse cardiovascular events was examined among DCIS survivors.

Paper 3: *Cardiovascular health status and adverse events among ductal carcinoma in situ survivors*

The age-adjusted prevalence of the 7 AHA cardiovascular metrics and adverse cardiovascular events were estimated using data from 1,014 DCIS survivors ≥40 years in the Wisconsin in situ cohort (WISC) responding to the 2015 mailed survey on health behavior, chronic diseases and breast health measures. The estimates from DCIS survivors were compared to that of women in the general US population using data from 5,930 women in the National Health and Nutritional Examination Survey (NHANES). Further, comparisons of each cardiovascular metric and adverse cardiovascular events were performed according to surgical treatment including adjuvant radiation and endocrine therapy utilization.

CHAPTER THREE

EMERGING TRENDS IN SURGICAL AND ADJUVANT RADIATION THERAPIES AMONG WOMEN DIAGNOSED WITH DUCTAL CARCINOMA IN SITU

Note: This chapter was published in the journal *Cancer*.

Citation: Shiyanbola OO, Sprague BL, Hampton JM, Dittus K, James TA, Herschorn S, Gangnon RE, Weaver DL, Trentham-Dietz A. *Emerging trends in surgical and adjuvant radiation therapies among women diagnosed with ductal carcinoma in situ*. *Cancer* 122(18):2810-2818, 2016.

Introduction

Ductal carcinoma in situ (DCIS) is a pre-invasive breast lesion, with one woman diagnosed with DCIS for every four women diagnosed with invasive breast cancer [1]. Prior to routine mammography, DCIS lesions accounted for less than 5% of breast cancer cases [108]. However, widespread screening mammography caused a rise in the detection of DCIS lesions [7]. The incidence of DCIS in the US increased from 1.87 per 100,000 women in 1973-1975 to 32.5 in 2004 [109].

Various treatment options to lower the risk of recurrence and prevent invasive breast cancer are available for patients with DCIS. The DCIS 5-year mortality rate is <2% [5]. Surgical excision with or without adjuvant therapy is the primary approach for DCIS treatment. Surgical options include breast conserving surgery (BCS) with or without radiotherapy, or mastectomy [108, 110]. Adjuvant tamoxifen may also be utilized, especially among women with estrogen receptor (ER) positive disease [26].

Variations in the utilization of treatment modalities for DCIS treatment likely result in under-treatment in some cases or overly aggressive surgical therapy for others [111, 112]. Avoidance of adjuvant radiation therapy following BCS may increase the utilization of mastectomy despite the lack of overall survival benefit [18, 113]. Geographic and temporal variations have been observed in the treatment of DCIS, with the Midwest and south-central states having higher rates of mastectomies compared to Northeastern states [111]. Breast reconstruction following mastectomy is associated with geographical/regional location, institutional practice pattern, age and race/ethnicity [111, 113].

The utilization of contralateral mastectomy (i.e. surgical removal of the uninvolved breast), particularly among high-risk women, is controversial. Factors associated with contralateral mastectomy include younger age, family history, genetic predisposition, tumor size and higher grade [36, 37].

Given the historical variation in treatment of DCIS, we sought to examine recent trends using the National Cancer Data Base (NCDB) including the association of demographic factors with local DCIS treatment.

Methods

Study Population

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Over 1500 cancer care institutions contribute data to the NCDB, including 70% of all newly diagnosed cancers in the United States. Further details about the NCDB have been reported elsewhere [114, 115]. We obtained data from the NCDB for women ≥20 years diagnosed with DCIS between 1998 and 2011. The study was approved by the University of Wisconsin-Madison institutional review board. Women diagnosed with DCIS were identified using International Classification of Diseases for Oncology third edition (behavior code 2 and morphology codes 8050, 8201, 8210, 8230, 8401, 8500, 8501, 8503, 8504, 8507, 8522, 8523, 8540 and 8543), and were coded as stage 0 according to the American Joint Committee on Cancer seventh edition guidelines [116, 117]. A total of 434,695 cases met these criteria. Patients with no treatment data (n= 4,248), who had an unspecified mastectomy type with no information on receipt of reconstruction or contralateral mastectomy (n=1,562), extended radical mastectomy (n=87) or did not receive any treatment (n=12,566) were excluded.

Variables of Interest

Treatments were categorized as BCS, BCS with radiation, and mastectomy (i.e. total mastectomy). Women undergoing mastectomy were sub-classified based on whether they received contralateral mastectomy and/or breast reconstruction. Ancestry/ethnicity was classified as Non-Hispanic European, Non-Hispanic African, Hispanic, and other. Region of residence was categorized as Northeast, Midwest, West and South. Facility type was classified into community cancer program, comprehensive community cancer program, academic/research program (including NCI-designated comprehensive cancer centers) and other. Treatment facilities were divided into patient volume tertiles based on the number of women treated for DCIS.

Statistical Analysis

We estimated the odds ratios (OR) and 95% confidence intervals (CI) of receiving adjuvant radiation therapy following BCS and the utilization of BCS (with or without radiation therapy) compared to mastectomy using multivariable logistic regression models. Additionally, we evaluated breast reconstruction following mastectomy and contralateral breast removal following therapeutic mastectomy. In all models, covariates included age of diagnosis, ancestry/ethnicity, year of diagnosis and geographic region. We also adjusted for comorbidity, health insurance, tumor size and grade, treatment facility and institutional volume. Two-sided *P*-values <0.05 were considered statistically significant. Interaction between ancestry/ethnicity and year of diagnosis were examined. Age-adjusted rates of surgeries following therapeutic mastectomy (i.e. breast reconstruction and contralateral risk-reducing mastectomy) by ancestral/ethnic groups were calculated using the 2000 U.S. standard million population [118]. Analyses were performed using SAS®, version 9.3.

Results

We identified 416,232 women diagnosed with DCIS between 1998 and 2011 (Table 3.1). Women in the 45-54 and 55-64 age groups accounted for most cases (over 26% each). Most cases (80.4%) were women of non-Hispanic European ancestry. About 60% of women had private health insurance; 46% were treated with adjuvant radiation therapy and 29% received adjuvant endocrine therapy.

BCS and Mastectomy

Women ≥45 years were more likely to undergo BCS (Table 3.2). Compared to 1998-1999, women diagnosed since 1999 were more likely to undergo BCS, peaking during 2006-2007 (OR, 1.23; 95% CI, 1.16-1.31) and subsequently declining. Ancestry/ethnicity was associated with BCS treatment, as women of African and Hispanic ancestry were more likely to undergo BCS. Surgery patterns changed over time according to ancestry/ethnicity with BCS rates for women of African ancestry being lowest in 1998, while women of European ancestry had the lowest rates in 2011 (data not shown). Women outside the Northeast had lower odds of undergoing BCS.

BCS with Adjuvant Radiation Therapy

Age was associated with the likelihood of undergoing adjuvant radiation therapy following BCS (Table 3.3). There was an increase in the proportion of women undergoing adjuvant radiation therapy following BCS from 58.5% in 1998-1999 to 70% during 2006-2011. Women of European ancestry were more likely to undergo adjuvant radiation therapy following BCS than other ancestral/ethnic groups. Women in the Midwest were more likely to receive adjuvant radiation therapy following BCS.

Breast Reconstruction following Mastectomy

Younger age at diagnosis was associated with undergoing breast reconstruction (Table 3.4). Women diagnosed in 2010-2011 were more likely to undergo reconstruction following mastectomy compared to women in 1998-1999 (OR, 3.57; 95% CI, 3.27-3.91). Breast reconstruction rates have been increasing among the three racial/ancestral groups with women of European ancestry having the highest rates (Figure 3.1A). Women in the Northeast were more likely to undergo breast reconstruction following mastectomy.

Contralateral Risk Reducing Mastectomy

Rates of contralateral risk reducing mastectomy decreased with increasing age at diagnosis (Table 3.4). Women diagnosed in 2010 were more likely to undergo contralateral mastectomy than women diagnosed in 1998-1999 (OR, 4.56; 95% CI, 4.09-5.08). The annual proportion of women undergoing contralateral mastectomy increased in all 3 racial/ancestral groups (Figure 3.1B). Women outside the Northeast were more likely to undergo contralateral mastectomy.

Discussion

In analyzing the patterns of care for DCIS among women using a large nationwide clinical database, we observed an increase in BCS among women diagnosed with DCIS between 1998 and 2005. This was followed by a decline in BCS through 2011, with a corresponding rise in mastectomy utilization. This is consistent with previous observations of increasing mastectomy rates among women with early stage breast cancer [119, 120]. Unlike previous studies which included small invasive node negative cancers and in situ cancer, we observed these findings specifically among DCIS patients.

Using the NCDB, we observed an increase in adjuvant radiation therapy utilization following BCS until 2007. BCS and adjuvant radiation treatment is beneficial in preventing localized ipsilateral breast cancer recurrence compared to BCS alone, with similar survival benefit to mastectomy [18, 121]. Although most women were treated with BCS and adjuvant radiation therapy (46%), the proportion of women undergoing adjuvant radiation therapy following BCS has plateaued at 70% after 2007. The increasing trend in the proportion of women undergoing adjuvant radiation therapy following DCIS diagnosis has been previously shown [111, 122]. However, our findings suggest adjuvant radiation therapy utilization may be at a saturation level. Not all women diagnosed with DCIS undergoing BCS are ideal candidates for adjuvant radiation therapy and women may have concerns regarding adverse effects of radiation. Social factors such as cultural beliefs, marital status and social support may be related to choice of undergoing radiation therapy following BCS.[123, 124] Although breast density is not a criterion for choice of surgical therapy, having a high breast density has been associated with an increased likelihood of undergoing mastectomy (including contralateral mastectomy) [125, 126]. Additionally, women living at an increased distance from a hospital with a radiotherapy facility were less likely to undergo BCS [127].

Since 2005, the proportion of women undergoing mastectomy following DCIS has increased, despite BCS with adjuvant radiation therapy generally being an appropriate and less extensive treatment option. Apart from concerns about the effects of radiation therapy, some women may be dissatisfied with their cosmetic outcome following BCS [128]. Breast reconstruction following mastectomy may be favored for cosmetic and psychological reasons [31, 129]. Legislative mandates such as the Women's Health and Cancer Rights Act (WHCRA) requiring coverage for breast reconstruction following mastectomy by most insurance plans may have influenced the increase. A recent study observed 2-to-4-fold increases in reconstruction following the enactment of the legislation [130].

Throughout the study period, women of European ancestry consistently had higher proportions undergoing breast reconstruction following mastectomy. However, women of African ancestry and Hispanic women showed an increasing trend in postmastectomy reconstruction, almost parallel to that observed among women of European ancestry. Lack of insurance coverage, lack of knowledge about postmastectomy reconstruction, cultural issues and socioeconomic status have been previously associated with observed differences in postmastectomy reconstruction by ancestry/ethnicity [131, 132].

We observed an increasing trend in the utilization of contralateral risk reducing mastectomy among women undergoing mastectomy and a more rapid rise among women of European ancestry compared to other racial/ancestral groups. This trend has been observed previously among woman <45 years of age diagnosed with early stage breast cancer [133]. Previous research has also shown similar prevalence of *BRCA1/2* mutations among breast cancer patients of European, African, and Hispanic ancestry [134]. Mammography screening rates appear to be higher among women of European ancestry [135, 136]. Ancestral/ethnic differences in screening may be lead to differences in diagnosis and treatment. Furthermore, previous research has shown that women of European ancestry are less likely to delegate treatment decisions to their physicians [137]. This may be related to higher educational attainment [138]. Women with higher levels of educational attainment have increased participation in surgical decision making and are more likely to undergo mastectomy [139, 140].

Breast cancer diagnosed in younger women is associated with a higher risk of recurrence following breast conserving surgery [141]. Undergoing lifelong surveillance may be disruptive and anxiety provoking for some. Hence, younger women may prefer to undergo mastectomy including the removal of the uninvolved breast. The decision to undergo mastectomy may be influenced by multifocal or widespread disease, positive margins, age, physician's preference, access to radiation facilities, fear of recurrence and insurance coverage [119, 120, 142]. For many women, bilateral mastectomy may be considered aggressive treatment given the generally low absolute risk of a future invasive carcinoma. There is no overall survival benefit for contralateral risk reducing mastectomy in early stage breast cancer among ER-negative patients [143]. Survival benefits seen in some studies may be due to selection bias [144]. Among *BRCA1/2* mutation carriers, contralateral mastectomy may confer a survival advantage [145]. The role of contralateral mastectomy is debatable. However, there is less contention regarding the relationship between mammography and increased DCIS incidence over time which may suggest aggressive treatment at times among women diagnosed with DCIS.

Geographical variations in the utilization of surgical treatments including postmastectomy reconstruction among women diagnosed with DCIS have been documented previously [111]. We observed persistent geographic variations in the utilization of DCIS treatment options. For instance, the Northeast had the greatest odds of undergoing breast conserving surgery and reconstruction following mastectomy, and the smallest odds of undergoing contralateral mastectomy. This may suggest a preference towards aesthetic preservation in the Northeast. Regional variations may reflect practice differences among institutions and available surgical expertise. This may partly explain the lower odds of undergoing breast conserving surgery (including adjuvant radiation therapy) in the South and West. Incidentally, these regions compared to the Northeast had the highest odds ratios of undergoing contralateral mastectomy. The presence of more surgeons with reconstruction expertise in treatment facilities is associated with increased utilization of these procedures following mastectomy [113].

The NCDB is a rich resource for examining patterns of DCIS treatment, but it does have limitations. Cancer cases are from only Commission on Cancer accredited hospitals. Hence, the NCDB may represent selected cases. However, selection bias may not be substantial as 70% of cancer cases in the US are captured by the NCDB, reporting data from diverse institutions such as large comprehensive cancer centers including smaller community cancer treatment facilities.

The absence of data on hormone receptor status and human epidermal growth factor receptor 2 (*HER2/neu*) for most patients and lack of information on some genetic markers such as *BRCA* gene status precluded the assessment of treatment variation according to DCIS molecular subtypes and genetic risk. Finally, we lacked information on patients' preferences and physician's characteristics including variations in the geographic distribution of reconstructive surgeons and radiation oncologists. However, our study findings corroborate findings from population based cancer registry data such as SEER [119, 120]. With the NCDB, we have been able to provide updated information regarding trends in local therapies for DCIS treatment with the discovery of some new findings.

In assessing patterns of care for women diagnosed with DCIS, substantial variation exists in all four major local treatment decisions. Significant differences between treatment types were observed according to ancestry/ethnicity and geographical region. There was increasing utilization of adjuvant radiation treatment following breast conserving surgery and breast reconstruction following mastectomy since 1998. These increases coincided with the introduction of policies and clinical guidelines that favored their utilization. The study period mostly encompassed the years prior to the passage of the Patient Protection and Affordable Care Act of 2010. It will be interesting to examine trends in DCIS treatment following the implementation of this legislation. Finally, the impact of treatment variation on cancer recurrence and progression to invasive cancer warrants further investigation.

Table 3.1. Characteristics of Women Diagnosed with Ductal Carcinoma in situ in the National Cancer Data Base, 1998-2011

Characteristic	N	%
Total	416,232	
Age group, y		
<45	47,567	11.4
45-54	108,907	26.2
55-64	109,767	26.4
65-74	89,712	21.5
≥75	60,285	14.5
Year of diagnosis		
1998-1999	48,002	11.5
2000-2001	54,101	13.0
2002-2003	56,418	13.5
2004-2005	56,421	13.6
2006-2007	61,994	14.9
2008-2009	70,605	17.0
2010-2011	68,691	16.5
Ancestry/ethnicity		
Non-Hispanic, European	334,757	80.4
Non-Hispanic, African	42,648	10.2
Hispanic	16,354	3.9
Other	22,473	5.4
Geographic region		
Northeast	103,564	25.0
Midwest	102,289	24.5
South	139,354	33.5
West	71,025	17.0
Health insurance		
Private	250,004	60.1
Government	151,069	36.3
Uninsured	6,173	1.5
Unknown	8,986	2.2
Primary treatment		
Breast conserving surgery without adjuvant radiation	95,076	22.8
Breast conserving surgery with adjuvant radiation	189,847	45.6
Mastectomy	131,309	31.5

Table 3.1, continued

Characteristic	N	%
Adjuvant endocrine therapy		
Yes	120,607	29.0
No	270,859	65.1
Unknown	24,766	5.9
Facility type		
Community cancer program	40,832	9.8
Comprehensive community cancer program	247,915	59.5
Academic/research program	118,025	28.4
Other specified types of cancer programs	9,460	2.3

Table 3.2. Demographics of Breast Conserving Surgery among Women Diagnosed with Ductal Carcinoma in situ, National Cancer Data Base, 1998-2011

Variable	Mastectomy (N= 131,309) Row %	BCS (N= 284,923) Row %	OR[a] (95% CI)
Age group, y			
<45	43.5	56.5	1
45-54	32.9	67.1	1.60 (1.54-1.65)
55-64	29.2	70.8	1.92 (1.85-1.99)
65-74	28.4	71.6	2.14 (2.05-2.23)
≥75	28.6	71.4	2.11 (2.02-2.21)
Year of diagnosis			
1998-1999	33.4	66.6	1
2000-2001	31.9	68.1	1.12 (1.08-1.16)
2002-2003	29.9	70.1	1.21 (1.15-1.26)
2004-2005	29.3	70.7	1.21 (1.13-1.29)
2006-2007	30.2	69.8	1.23 (1.16-1.31)
2008-2009	32.8	67.2	1.12 (1.05-1.19)
2010-2011	33.1	66.9	1.12 (1.05-1.20)
Ancestry/ethnicity			
Non-Hispanic, European	31.4	68.6	1
Non-Hispanic, African	32.2	67.8	1.05 (1.01-1.08)
Hispanic	31.6	68.4	1.14 (1.08-1.21)
Other	32.3	67.7	1.00 (0.94-1.06)
Geographic region			
Northeast	25.9	74.1	1
Midwest	31.7	68.3	0.75 (0.73-0.77)
South	35.2	64.8	0.64 (0.62-0.66)
West	32.4	67.6	0.70 (0.68-0.73)

[a] Adjusted for comorbidity index, health insurance, facility type, DCIS patient volume, tumor size and grade.

Test of interaction between year of diagnosis and ancestry/ethnicity: X^2=42.70, df=18, P< 0.01.

Table 3.3. Demographics of Radiation Treatment Following Breast Conserving Surgery for Ductal Carcinoma in situ, National Cancer Data Base, 1998-2011

Variable	BCS Only (N=95,076) Row %	BCS with Adjuvant Radiation (N=189,847) Row %	OR[a] (95% CI)
Age group, y			
<45	31.0	69.0	1
45-54	29.1	70.9	1.07 (1.04-1.11)
55-64	28.3	71.8	1.10 (1.07-1.14)
65-74	32.7	67.3	0.95 (0.92-0.98)
≥75	52.2	47.8	0.41 (0.39-0.43)
Year of diagnosis			
1998-1999	41.4	58.6	1
2000-2001	39.1	60.9	1.07 (1.04-1.11)
2002-2003	36.2	63.8	1.12 (1.08-1.16)
2004-2005	32.4	67.6	1.19 (1.13-1.25)
2006-2007	29.2	70.8	1.38 (1.31-1.46)
2008-2009	29.1	70.9	1.40 (1.32-1.47)
2010-2011	29.9	70.1	1.32 (1.25-1.39)
Ancestry/ethnicity			
Non-Hispanic, European	32.9	67.1	1
Non-Hispanic, African	34.2	65.8	0.92 (0.90-0.95)
Hispanic	36.8	63.2	0.86 (0.83-0.90)
Other	35.6	64.4	0.89 (0.86-0.93)
Geographic region			
Northeast	36.2	63.8	1
Midwest	25.8	74.2	1.62 (1.58-1.65)
South	35.0	65.0	0.99 (0.97-1.01)
West	36.9	63.1	0.83 (0.81-0.85)

[a] Adjusted for comorbidity index, health insurance, facility type, DCIS patient volume, tumor size and grade.

Test of interaction between year of diagnosis and ancestry/ethnicity: X^2=21.03, df=18, *P*= 0.28.

Table 3.4. Demographics of Reconstruction and Contralateral Risk Reduction Mastectomy among Women Diagnosed with Ductal Carcinoma in situ, National Cancer Data Base, 1998-2011

Variable	Mastectomy alone (N=87,130) Row %	Mastectomy with Reconstruction (N=44,179) Row %	OR[a] (95% CI)	Unilateral Mastectomy (N=104,970) Row %	Contralateral Mastectomy (N=26,339) Row %	OR[a] (95% CI)
Age group, y						
<45	45.5	54.5	1	67.1	32.9	1
45-54	52.0	48.0	0.75 (0.72-0.79)	73.6	26.4	0.67 (0.65-0.70)
55-64	66.0	34.0	0.42 (0.41-0.44)	80.3	19.7	0.45 (0.43-0.47)
65-74	83.9	16.1	0.24 (0.23-0.25)	88.8	11.2	0.29 (0.27-0.31)
≥75	95.9	4.1	0.06 (0.05-0.06)	94.8	5.2	0.13 (0.12-0.14)
Year of diagnosis						
1998-1999	78.7	21.3	1	91.4	8.6	1
2000-2001	74.5	25.5	1.31 (1.24-1.38)	88.4	11.6	1.43 (1.33-1.54)
2002-2003	72.9	27.1	1.40 (1.31-1.49)	85.0	15.0	1.85 (1.70-2.01)
2004-2005	69.9	30.1	1.57 (1.43-1.72)	82.0	18.0	2.12 (1.93-2.41)
2006-2007	64.5	35.5	2.04 (1.86-2.23)	77.3	22.7	2.95 (2.64-3.29)
2008-2009	58.5	41.5	2.76 (2.52-3.02)	72.8	27.2	3.79 (3.40-4.23)
2010-2011	53.6	46.4	3.57 (3.27-3.91)	69.7	30.3	4.56 (4.09-5.08)
Ancestry/ethnicity						
Non-Hispanic, European	65.5	34.5	1	78.5	21.5	1
Non-Hispanic, African	72.0	28.0	0.69 (0.66-0.72)	88.5	11.5	0.43 (0.41-0.45)
Hispanic	66.3	33.7	0.83 (0.78-0.89)	83.2	16.8	0.57 (0.53-0.62)
Other	68.0	32.0	0.66 (0.63-0.70)	82.9	17.1	0.56 (0.52-0.60)

Table 3.4, continued

Variable	Mastectomy alone (N=87,130) Row %	Mastectomy with Reconstruction (N=44,179) Row %	OR[a] (95% CI)	Unilateral Mastectomy (N=104,970) Row %	Contralateral Mastectomy (N=26,339) Row %	OR[a] (95% CI)
Geographic region						
Northeast	60.6	39.5	1	81.2	18.8	1
Midwest	66.0	34.0	0.88 (0.85-0.92)	80.6	19.5	1.14 (1.10-1.20)
South	68.5	31.5	0.81 (0.78-0.84)	80.0	20.0	1.29 (1.24-1.34)
West	69.0	31.0	0.72 (0.68-0.75)	77.4	22.6	1.49 (1.42-1.56)

[a] Adjusted for comorbidity index, health insurance, facility type, DCIS patient volume, tumor size and grade.
Reconstruction: Test of interaction between year of diagnosis and ancestry/ethnicity: X^2=25.90, df=18, P=0.10.
Contralateral risk reducing mastectomy: Test of interaction between year of diagnosis and ancestry/ethnicity: X^2=27.63, df=18, P=0.07.

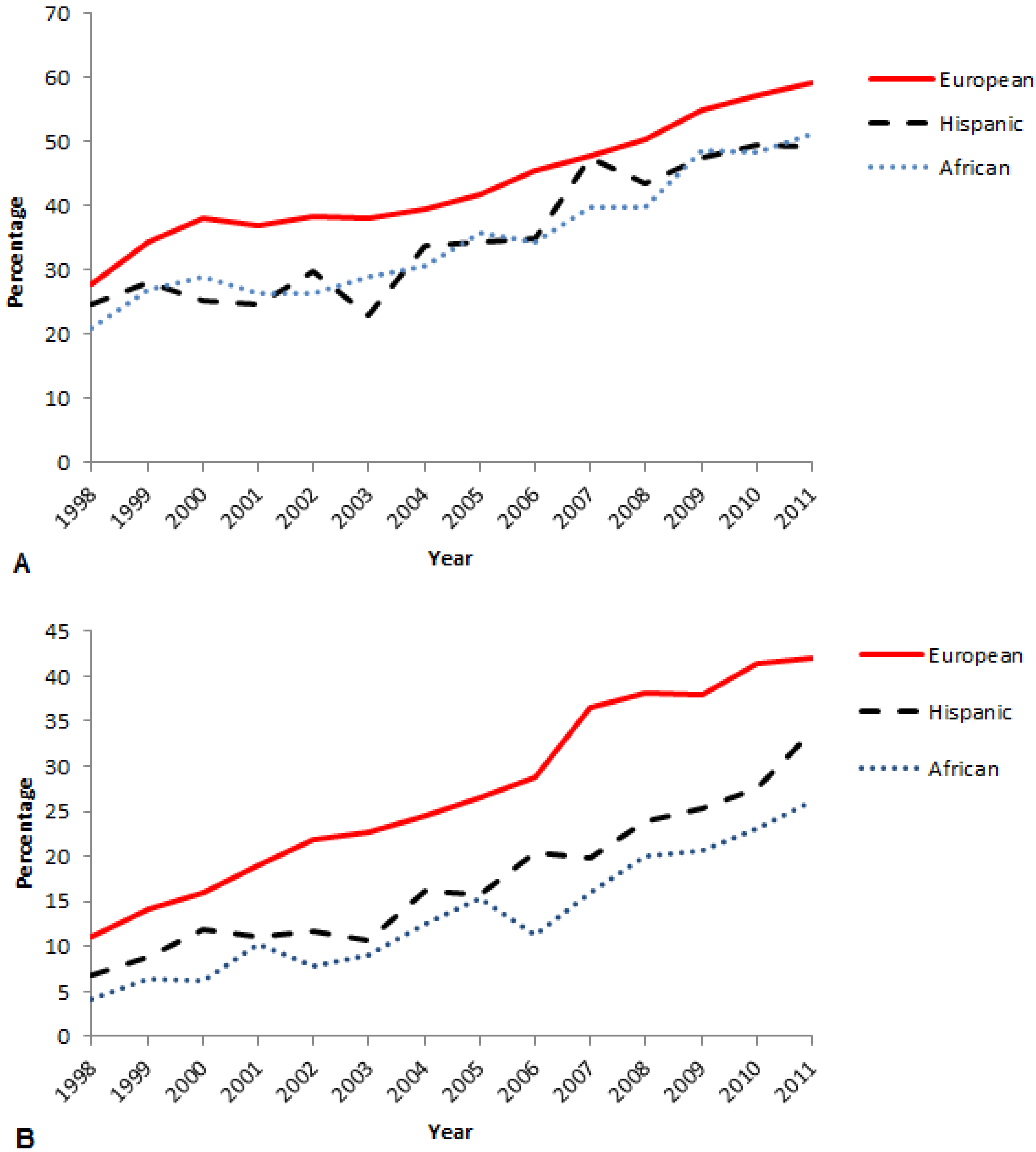


Figure 3.1. Age-adjusted annual proportion of patients undergoing (A) reconstruction and (B) risk reducing contralateral mastectomy among women with mastectomy for ductal carcinoma in situ according to European, African, and Hispanic ancestry, National Cancer Data Base, 1998-2011.

CHAPTER FOUR

BREAST MAGNETIC RESONANCE IMAGING UTILIZATION AMONG DUCTAL CARCINOMA IN SITU SURVIVORS

Introduction

Women with a personal history of ductal carcinoma in situ (DCIS) have a 3-5 fold increased risk of developing subsequent breast cancer events (DCIS and invasive breast cancer) compared to women in the general population [3, 41, 146]. Underlying breast cancer risk factors such as younger age and a positive family history of breast cancer have been shown previously to increase the likelihood of recurrence and development of contralateral breast cancer events among DCIS survivors [66, 67, 147, 148]. Primary DCIS tumor features such as higher tumor grade and larger tumor size as well as treatment choice such as breast conserving surgery without radiation may increase the risk of recurrence among DCIS survivors [13, 27, 149]. Hence, with the complex relationships between various breast cancer risk factors, DCIS survivors require adequate imaging surveillance as part of their follow-up care.

Current guidelines primarily recommend annual mammography for imaging surveillance among DCIS survivors [42, 43]. However, supplementary breast magnetic resonance imaging (MRI) may be indicated among DCIS survivors determined to be at high risk of breast cancer according to the American Cancer Society (ACS) guidelines. These include women ≥20% lifetime risk of developing breast cancer based on breast cancer risk models and *BRCA* mutation carriers [53, 54]. Among women with confirmed/suspected *BRCA1/2* mutations, screening breast MRI has been shown to be more sensitive [47, 150, 151]. However, breast MRI is expensive, and with a lower specificity (84-91%) compared to mammography (93-97%), breast MRI has a higher false positive rate for malignant breast lesions [50].

Previous studies describing breast MRI utilization have shown a rising trend in its use especially since 2000, with surveillance being the second most common indication after screening [51, 61]. With a lower false positive rate among women with a personal history of breast cancer (12.3%) compared to women with genetic/familial predisposition (21.6%), some researchers have suggested that breast MRI be routinely considered as a supplement to mammography among breast cancer survivors [60]. However, there is limited knowledge regarding factors related to breast MRI use among women with a personal history of breast cancer especially DCIS survivors. Additionally, socioeconomic status and travel burden to treatment facilities, impact preventive services utilization [72, 73, 152].

Our study sought to assess factors related to breast MRI utilization among DCIS survivors using data derived from participants in the Wisconsin in Situ Cohort (WISC) study. Specifically, we evaluated breast MRI use in relation to underlying breast cancer risk factors such as age, race and first-degree family history, lifetime breast cancer risk at diagnosis, prognostic primary DCIS features such as tumor grade and size, as well as treatment type. Additionally, we assessed breast MRI utilization in relation to socioeconomic factors such as education and income as well as geographic access to breast MRI facilities.

Methods

Study Population

The WISC study is a cohort of women with a first primary DCIS diagnosis reported to the Wisconsin Cancer Reporting System from 1997 to 2006. Details of the WISC study can be found elsewhere [153]. Briefly, women between ages 20-74 years were eligible for enrollment in the WISC study if they had a known date of diagnosis and a listed telephone number. A total of 1,925 women were recruited into the WISC study with 838 women initially enrolled for a case-control study from 1997-2001 and a further 1,087 women recruited between 2002-2006 [154, 155]. Participants provided verbal consent prior to enrollment and the study protocol was approved by the University of Wisconsin-Madison Health Sciences Human Subjects Committee. Participants completed telephone interviews at baseline during 1997-2006 and were approached for biennial follow-ups beginning in 2003 through 2010. Subsequent surveys during 2013-2015 were in the form of mailed questionnaires. In 2013, mailed surveys were sent to 1,608 DCIS survivors and completed by 1,180 women for a response rate of 73.4%. WISC participants that did not return a completed survey were either deceased (n=14), unable to complete survey due to illness (n=7), refused further participation (n=156), or could not be contacted due to change in residential address (n=251).

Data Collection

On average, the baseline interview was conducted at about 1.3 years following primary DCIS diagnosis. Data on sociodemographic factors, breast health, reproductive history, mammography use and general well-being were self-reported at baseline and follow-up. Pathology data including tumor size, grade and date of primary DCIS diagnosis were provided by the Wisconsin Cancer Reporting System, with WISC participants self-reporting treatment information. Follow-up surveys queried any new DCIS or invasive breast cancer diagnosis. Additionally, WISC participants provided written consent for the collection of pathology reports of subsequent DCIS or invasive breast diagnoses from their health care providers.

Baseline data for our analysis included age at diagnosis, race, age at menarche, primary DCIS tumor features (DCIS grade and size), prior benign breast biopsies, primary DCIS surgical treatment as well as adjuvant radiation and endocrine therapy. Breast cancer family history was defined as self-reported breast cancer diagnosis in a mother, sister or daughter. Second breast cancer events (i.e. any DCIS or invasive breast cancer) were obtained from follow-up surveys and available pathology reports for consenting participants. Finally, we retrieved breast MRI utilization, socioeconomic and residential location data from the 2013 follow-up survey. For the 2013 survey, WISC participants provided information on breast MRI utilization in the past 4 years (Appendix A).

Lifetime Breast Cancer Risk

According to the 2007 ACS criteria, supplementary breast MRI screening is indicated for: known BRCA mutation carriers or untested women with affected first degree relatives; women and first-degree relatives with certain familial cancer syndromes; and women with ≥20% lifetime breast cancer risk using risk prediction models that are heavily reliant on family history [58, 59]. For our analysis, we used the National Cancer Institute (NCI) Breast Cancer Risk Assessment tool (BCRAT) to estimate the lifetime breast cancer risk for each women at their age of primary DCIS diagnosis (https://www.cancer.gov/bcrisktool/) [55]. Input variables for estimating lifetime breast cancer risk included current age (age at primary DCIS diagnosis), race, number of first-degree relatives (mother, daughter or sister) diagnosed with breast cancer, age at menarche, number of previous biopsies including atypical hyperplasia manifestation. The BCRAT is not recommended for breast cancer risk calculation among DCIS survivors. However, its application in this study was to determine a woman's eligibility for supplemental breast MRI surveillance which is inferred from the 2007 ACS eligibility criteria for breast MRI screening [53, 54]. Additionally, Lifetime breast cancer risk was determined using age at primary DCIS diagnosis as this was the last age WISC cohort participants were breast cancer free.

Geographic Access

Geographic access to breast MRI facilities was evaluated based on the rural/urban residence of WISC participants and the travel time to the nearest breast MRI facility. In determining the rural/urban residence of each WISC participant, we used their residential census tract data to derive their primary Rural-Urban Commuting Area (RUCA) codes and subsequently classified them as residing in metropolitan (codes 1-3) and non-metropolitan areas (codes 7-10) [156, 157]. Using the American College of Radiology (ACR) accredited facility search website (http://www.acraccreditation.org/accredited-facility-search), we retrieved the addresses of the 45 ACR breast MRI facilities located in Wisconsin. We geocoded the residential addresses of

WISC participants and the breast MRI facilities to street-level latitude and longitude point locations using ArcGIS version 10 (Environmental System Research Institute, Redlands, CA). An origin-destination matrix was created by calculating the shortest travel time in minutes between each WISC participant's address and all breast MRI facilities, using the ArcGIS Network Analyst Extension and its associated network dataset. In indicating the nearest breast MRI facility for each WISC participant, we selected the shortest travel time of all calculated travel times per participant.

Statistical Analysis

For our analysis, we utilized data from 1,103 out of 1,180 DCIS survivors that completed the 2013 survey, excluding 47 participants who had double mastectomy following primary DCIS diagnosis and 30 women that did not provide information on breast MRI utilization. Period of diagnosis was classified into 2 groups (1997-2001 and 2002-2006). Our Statistical analysis was performed using Stata/SE 14 Software (StataCorp LP, College Station, TX). Summary statistics were produced for sociodemographic and other analytic variables. Missing values for breast cancer family history, primary DCIS tumor size, grade and treatment type as well as household income were estimated using multiple imputation with chained equations over ten iterations (Appendix B) [158]. Pooled estimates were derived from the analysis of the imputed datasets using methods previously described [159].

In comparing mean shortest travel times to breast MRI facilities by rural/urban residence and education attainment according to residential location, we performed t-tests assuming equal variance. Additionally, we evaluated differences in mean shortest travel times by household income according to rural/urban residence using a one-way analysis of variance (ANOVA) test. We estimated the odds ratios (ORs) and 95% confidence interval (CIs) of undergoing breast MRI utilization among WISC participants using multivariable logistic regression models. The first model evaluated the likelihood of undergoing breast MRI utilization according to breast cancer risk factor profile (age, race/ethnicity, family history and lifetime breast cancer risk), period of diagnosis, primary DCIS tumor features (grade and size) and treatment type. The second model assessed the likelihood of undergoing breast MRI utilization according to socioeconomic factors (education and household income) and geographic access (rural/urban residence and travel time), adjusting for age, race and period of diagnosis and lifetime breast cancer risk. Travel time was dichotomized using 15 minutes as the cutoff mark because the median travel time to a breast MRI facility among WISC participants was 14.0 minutes. Due to the high correlation between travel time and rural/urban residence ($\rho = 0.7$, $P < 0.01$), we mutually excluded either variable in our second logistic regression model.

Both regression models were assessed with and without individuals with second breast events (n=136) since women with a second diagnosis may systematically use MRI differently than women with a single diagnosis. Additionally, in the first model, we tested interactions between age and family history as well as age and treatment. All statistical tests were considered significant at $P < 0.05$ level.

Results

Table 4.1 illustrates select characteristics of DCIS survivors in the WISC study. Most women at primary DCIS diagnosis were at least 50 years old (71.0%), non-Hispanic white (95.8%), without a family history of breast cancer (78.9%) and had <20% lifetime breast cancer risk (92.7%). About a third of DCIS survivors had ipsilateral mastectomy for primary DCIS treatment with 12.3% of them developing second breast events. Most women resided in a metropolitan area (77.2%), with only 3 (6.7%) of the 45 accredited breast MRI facilities in Wisconsin located in non-metropolitan areas (Figure 4.1). Women residing in metropolitan areas on average had about 35 minutes shorter mean travel time to a breast MRI facility compared to women living in non-metropolitan areas (Figure 4.2). Additionally, for each residential category, women with at least a college degree had a significantly shorter mean travel time to a breast MRI facility compared to women with less than a college degree.

Underlying Breast Cancer Risk factors, Tumor Features and Treatment

The likelihood of breast MRI utilization was greater among women <50 years compared to older women, persisting after the exclusion of women with second breast events (OR, 2.26; 95% CI, 1.42-3.60) as shown in Table 4.2. Similarly, DCIS survivors with race/ethnicity other than non-Hispanic white (OR, 3.01; 95% CI, 1.34-6.78) and with a ≥20% lifetime risk of breast cancer (OR, 2.35; 95% CI, 1.01-5.47) had a greater likelihood of breast MRI utilization compared to non-Hispanic White women and those with <20% lifetime risk of breast cancer respectively. However, there was no statistically significant difference in the likelihood of breast MRI use according to breast cancer family history of breast cancer, primary DCIS tumor size and grade. DCIS survivors having a more recent diagnosis period (2002-2006) were more likely to undergo breast MRI assessment compared to women diagnosed earlier (OR, 1.77; 95% CI, 1.06-2.94, excluding women with second breast events). Compared to those treated with breast conserving surgery alone, women who received adjuvant radiation were 18% less likely to use breast MRI, with the likelihood 40% less among women treated with ipsilateral mastectomy. Though risk estimates for underlying risk factors differed with and without the inclusion of women with second breast events, confidence intervals were greater than the null value in both models apart from lifetime breast cancer risk.

Socioeconomic Factors and Geographic Access

Breast MRI use was more common with increasing level of household income, with findings persisting after excluding women with second breast events. Women with household income >$100,000, compared to those with income ≤ $50,000, were 2.4 times more likely to use breast MRI, as shown in Table 4.3. Similarly, women with at least a college degree compared to those who did not attain a college degree were more likely to utilize breast MRI (OR, 1.74; 95% CI, 1.07-2.82). There was no significant increase in the likelihood of breast MRI use according to rural/urban residence and travel time to a breast MRI facility.

Discussion

Unlike previous studies assessing women undergoing screening regardless of breast cancer history, our study is the first to report on breast MRI use among DCIS survivors. As previously reported in the US female population [65], the extent of breast MRI utilization was low (less than 10%) in our cohort of DCIS survivors. This is not unusual, since these women typically require annual mammography surveillance, with a few women requiring supplementary breast MRI as recommended by the 2007 ACS criteria. Additionally, these cohort of DCIS survivors being diagnosed prior to the introduction of the ACS breast MRI criteria, would have been undergoing long-term mammography surveillance. In our study, we have shown that underlying breast cancer risk factors, specifically age and race, were related to breast MRI use among DCIS survivors.

Similar to previous findings [61] , DCIS survivors with a young age at diagnosis were more likely to utilize breast MRI. This observation may be a reflection of the higher rate of recurrence and mortality among younger women long-term [30, 109]. Hence, women diagnosed with DCIS at a younger age may prefer to undergo supplemental breast MRI for prompt detection of any new breast cancer events. Additionally, breast MRI may be particularly beneficial to young women with dense breasts for detecting new breast cancers which may be mammographically occult [63].

Wernli et al noted that most women undergoing breast MRI were non-Hispanic white women (85.3%) and were more likely to undergo breast MRI compared to other racial/ethnic groups [61]. However, in our cohort of DCIS survivors we observed a greater likelihood of breast MRI utilization for other racial/ethnic groups compared to non-Hispanic white women.

Differences in study population may partly explain this observation, with Wernli et al assessing breast MRI use among women (regardless of breast cancer history) undergoing breast imaging in community-based facilities compared to our analysis of DCIS survivors in Wisconsin. Additionally, we had a lower subsample of 46 women that were other than non-Hispanic white, which may limit the extent to which we can analyze the relationship between breast MRI use and race/ethnicity. Though not statistically significant, we observed a lower likelihood of undergoing breast MRI utilization with increasing extent of surgery. Recent reports have shown an increasing trend in both unilateral and bilateral mastectomy utilization following a DCIS diagnosis, with its use more likely among non-Hispanic white women [38, 160]. This has implications for future surveillance measures, since women treated with bilateral mastectomy do not require imaging surveillance [53, 161]. As highlighted earlier, limited sample sizes by race/ethnicity in our DCIS cohort prevented examination of race and primary DCIS treatment jointly in relation to breast MRI use.

Previous reports have highlighted the increasing use of breast MRI among women with a personal history of breast cancer since 2000 [51]. With increasing breast MRI utilization and growing evidence of its efficacy over time, an increasing number of women following DCIS diagnosis and treatment might be expected to use this imaging modality. This may partly explain our observed increase in likelihood of breast MRI utilization associated with more recent period of DCIS diagnosis. Women diagnosed with in situ or early stage breast cancer have an increased risk of second primary breast cancer if they have a first-degree breast cancer family history [66, 67]. However, we did not observe an increased likelihood of breast MRI use among women with a positive family history of breast cancer. We demonstrated an increased likelihood of breast MRI use among women with ≥20% lifetime breast cancer risk at primary DCIS diagnosis. These contrasting findings linking breast MRI utilization to lifetime breast cancer risk but not family history may suggest more reliance on risk assessment tools among DCIS survivors in determining breast MRI use in line with ACS recommendations [54]. However, as seen in previous studies, most WISC participants undergoing breast MRI (90%) do not meet the ACS criteria [51, 61].

Mammography use is an important determinant of DCIS diagnosis. Researchers have suggested that DCIS survivors have increased health-seeking behavior than women in the general population [107, 162]. Socioeconomic factors especially increasing level of educational attainment and income have also been related to preventive services utilization [70-73], and were associated with breast MRI use in our cohort of DCIS survivors. In comparison to mammography, breast MRI equipment, staffing and maintenance is more expensive. With about 80% of the US population residing in urban areas [163], breast MRI facilities may preferentially be located in areas of high population concentration. Breast MRI use was unrelated to rural/urban residence in our study. However, the 35-minute longer mean travel time to breast MRI facilities for non-metropolitan compared to metropolitan residents highlights the potential travel burden faced by rural residents in accessing breast MRI.

The increase in DCIS diagnosis and treatment associated with widespread mammography screening has resulted in a large number of survivors who require imaging surveillance. The WISC study has provided the unique opportunity to study breast MRI utilization among DCIS survivors. To the best of our knowledge, this is the first population-based study to examine breast MRI use among DCIS survivors based on underlying breast cancer risk, primary DCIS features and treatment, socioeconomic status and geographic access. However, there are some limitations to the current analysis. Though data collection was consistent and reliable over the years in the WISC study, some covariates had missing values, requiring multiple imputation for efficient use of available data and generation of unbiased pooled estimates. The absence of genetic information such as *BRCA1/2* career status limited our ability to explore other possible indications for breast MRI use based on ACS criteria. However, deleterious *BRCA1/2* mutations are generally rare. Breast MRI was self-reported with no access to medical records. These limited our ability to rule out breast MRI use beyond surveillance particularly for the assessment of breast implants. Though the ACS recommends the use of risk prediction models largely dependent on family history such as the BRCAPRO and Tyrer-Cuzick models [57, 59], the BCRAT was the most suitable risk prediction model we could apply with the data we had available. Finally, our study population was predominantly non-Hispanic white, similar to the racial population distribution in Wisconsin (87.6% non-Hispanic white).

The emergence of breast MRI has seen a surge over time in its use for screening, surveillance and other investigative indications. However, breast MRI use among DCIS survivors is low, more likely among younger women, and not dependent on primary DCIS tumor features and treatment. Though breast MRI use is more likely among DCIS survivors with ≥20% lifetime breast cancer risk, most women reporting its use do not meet the ACS breast MRI screening criteria. Increasing socioeconomic status was related to breast MRI utilization, requiring further investigation on the appropriate use of this expensive imaging modality including equitable access. Differences in mean travel time between a woman’s residence and breast MRI facilities, according to rural/urban residence highlights potential challenges encountered with accessing breast MRI and require further investigation. Additional longitudinal studies among DCIS survivors are also required to assess the effect of breast MRI utilization on disease-specific and overall survival.

Table 4.1. Select Characteristics of Primary Ductal Carcinoma in Situ Survivors in the Wisconsin in Situ Cohort (2013)

Characteristic	N	Col %
Total	1,103	
Age at diagnosis, y		
≥50	783	71.0
<50	320	29.0
Period of diagnosis		
1997-2001	418	37.9
2002-2006	685	62.1
Race/ethnicity		
Non-Hispanic White	1057	95.8
Other	46	4.2
First degree family history of breast cancer		
No	870	78.9
Yes	233	21.1
Lifetime breast cancer risk		
<20	1,023	92.7
≥20	80	7.3
Education		
< College degree	725	65.7
College degree or higher	378	34.3
Income		
≤ $50,000	529	47.9
$50,001-$100,000	384	34.9
> $100,000	190	17.2
Health insurance		
Private	1,016	92.1
Medicare	60	5.4
Medicaid	7	0.6
Other	20	1.8
Primary DCIS treatment		
Ipsilateral mastectomy	336	30.3
BCS		
With radiation	634	57.7
Without radiation	133	12.0
Adjuvant endocrine Therapy		
No	564	51.1
Yes	539	48.9

Table 4.1 contd.

Characteristic	N	Col %
Second breast events		
No	967	87.7
Yes	136	12.3
Rural-Urban Residence		
Metropolitan (RUCA codes 1–3)	851	77.2
Non-Metropolitan (RUCA codes 4–10)	252	22.8
Travel Time to Breast MRI Facility, min		
≤15	586	53.1
>15	517	46.9
Breast MRI in past 4 years		
None	972	88.1
≤2	98	8.9
3-6	33	3.0

Abbreviations: BCS, breast conserving surgery; MRI, Magnetic resonance imaging; RUCA, Rural-Urban Commuting Area.

Table 4.2. Odds Ratios for Breast MRI Utilization according to Breast Cancer Risk Factors, Primary DCIS Tumor Features and Treatment in the Wisconsin in Situ Cohort (2013)

Characteristic	Breast MRI Utilization			Breast MRI Utilization (excluding second breast events)		
	No (n=972), Row %	Yes (n=131), Row %	Adjusted[a] OR (95% CI)	No (n=875), Row %	Yes (n=92), Row %	Adjusted[b] OR (95% CI)
Age Group, y						
≥50	90.9	9.1	1	92.4	7.6	1
<50	81.3	18.7	2.42 (1.63-3.60)	85.4	14.6	2.26 (1.42-3.60)
Race/ethnicity						
Non-Hispanic White	88.6	11.4	1	91.0	9.0	1
Other	78.3	21.7	2.26 (1.04-4.91)	78.0	22.0	3.01 (1.34-6.78)
Lifetime breast cancer risk, %						
<20	88.4	11.6	1	90.9	9.1	1
≥20	85.0	15.0	1.49 (0.69-3.21)	84.4	15.6	2.35 (1.01-5.47)
Period of diagnosis						
1997-2001	89.7	10.3	1	92.6	7.4	1
2002-2006	87.2	12.8	1.60 (1.04-2.44)	89.3	10.7	1.77 (1.06-2.94)
Family history of breast cancer						
No	88.2	11.8	1	90.8	9.2	1
Yes	89.0	11.0	0.87 (0.50-1.51)	90.5	9.5	0.84 (0.46-1.56)
Tumor grade						
Well	86.7	13.3	1	89.4	10.6	1
Moderate	88.8	11.2	0.76 (0.42-1.38)	91.8	8.2	0.81 (0.39-1.66)
Poor/ Undifferentiated	88.7	11.3	0.91 (0.50-1.64)	89.3	10.7	1.19 (0.65-2.16)
Tumor size, cm						
≤1	86.0	14.0	1	89.6	10.4	1
1-2	88.2	11.8	0.77 (0.40-1.46)	91.7	8.3	0.76 (0.36-1.59)
>2	86.8	13.2	1.10 (0.39-3.12)	89.5	10.5	1.19 (0.40-3.55)

Table 4.2, contd.

Characteristic	Breast MRI Utilization			Breast MRI Utilization (excluding second breast events)		
	No (n=972), Row %	Yes (n=131), Row %	Adjusted[a] OR (95% CI)	No (n=875), Row %	Yes (n=92), Row %	Adjusted[b] OR (95% CI)
Primary DCIS treatment						
BCS alone	85.2	14.8	1	88.2	11.8	1
BCS + radiation	87.3	12.7	1.06 (0.59-1.91)	90.3	9.7	0.82 (0.40-1.66)
Ipsilateral mastectomy	91.0	9.0	0.62 (0.29-1.32)	91.4	8.6	0.60 (0.25-1.43)

Abbreviations: MRI, Magnetic resonance imaging; BCS, Breast conserving surgery; DCIS, Ductal Carcinoma in Situ; OR, odds ratio; CI, confidence interval.

[a] Model mutually adjusted for age, race, period of diagnosis, family history of breast cancer, projected lifetime breast cancer risk, primary DCIS tumor grade, size, treatment and second breast events (OR, 3.90; 95% CI, 2.43-6.19). Test for interactions between age and family history, T statistic = 1.04, *P*=0.30; age and treatment T statistic =0.16 , *P*=0.87.

[b] Model mutually adjusted for age, race, period of diagnosis, family history of breast cancer, projected lifetime breast cancer risk, primary DCIS tumor grade, size, treatment. Test for interactions between age and family history T statistic =0.94, P=0.30; age and treatment T statistic = 0.23, P=0.89.

Table 4.3. Odds Ratios for Breast MRI Utilization According to Socioeconomic Characteristics and Geographic Access in the Wisconsin in Situ Cohort (2013)

Characteristic	Breast MRI Utilization			Breast MRI Utilization (excluding second breast events)		
	No (n=972), Row %	Yes (n=131), Row %	Adjusted[a] OR (95% CI)	No (n=875), Row %	Yes (n=92), Row %	Adjusted[b] OR (95% CI)
Income						
≤ $50,000	91.9	8.1	1	93.8	6.2	1
$50,001-$100,000	89.2	10.8	1.09 (0.65-1.83)	91.6	8.4	1.10 (0.60-2.02)
> $100,000	75.4	24.6	2.54 (1.45-4.43)	79.6	20.4	2.41 (1.27-4.58)
Education						
< College degree	90.6	9.4	1	93.2	6.8	1
College degree or higher	83.3	16.7	1.52 (1.00-2.32)	85.3	14.7	1.74 (1.07-2.82)
Rural-Urban Residence						
Metropolitan (RUCA codes 1–3)	87.3	12.7	1	89.9	10.1	1
Non-Metropolitan (RUCA codes 4–10)	90.9	9.1	0.83 (0.50-1.37)	92.4	7.6	0.84 (0.48-1.49)
Travel Time to Breast MRI Facility, min						
≤15	86.3	13.7	1	89.1	10.9	1
>15	90.1	9.8	0.82 (0.55-1.22)	92.1	7.9	0.84 (0.53-1.33)

Abbreviations: MRI, magnetic resonance imaging; OR, odds ratio; CI, confidence interval; RUCA, Rural-Urban Commuting Area Codes.

[a] model includes age, race, period of diagnosis, lifetime breast cancer risk, second breast events, income and education.

[b] model includes age, race, period of diagnosis, lifetime breast cancer risk, income and education.

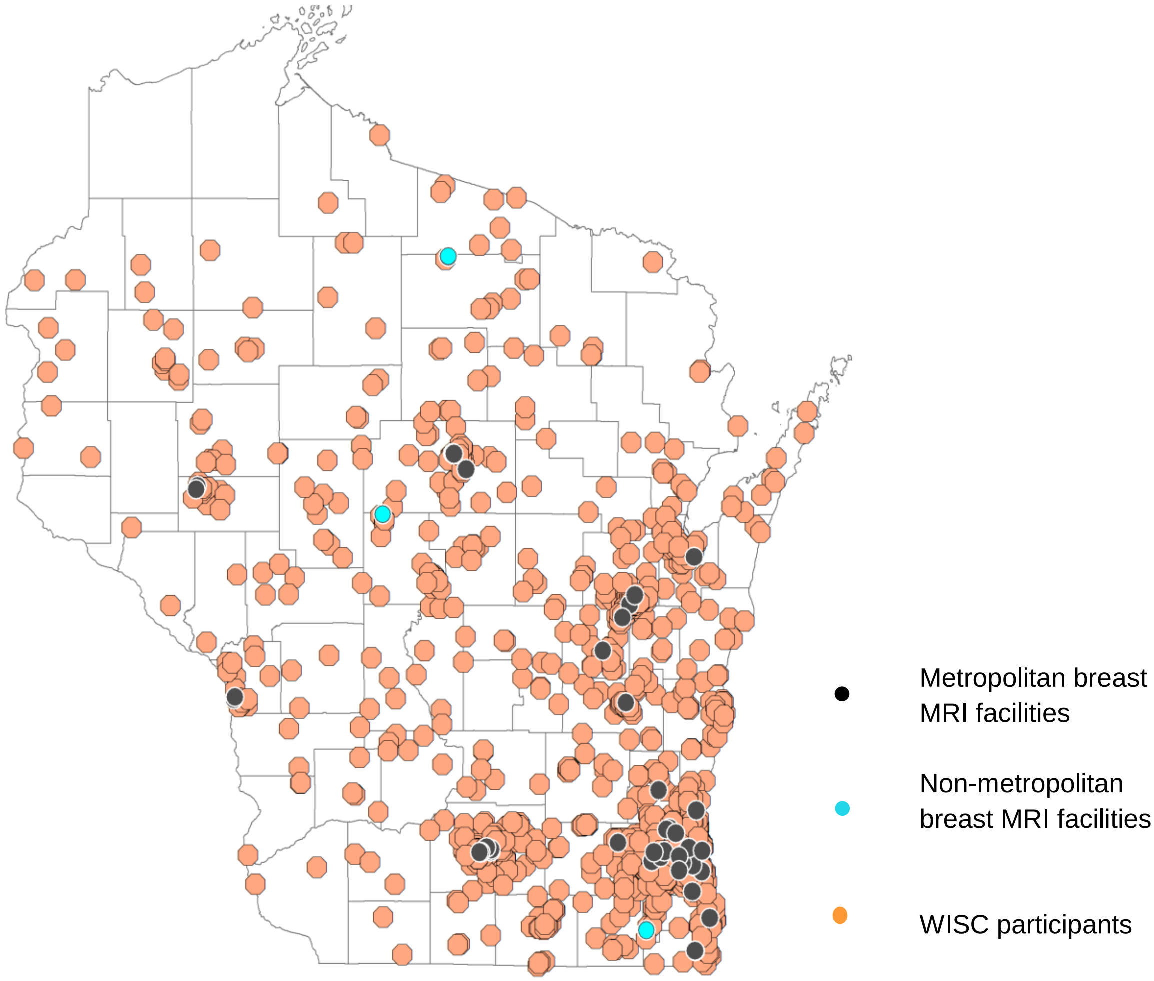
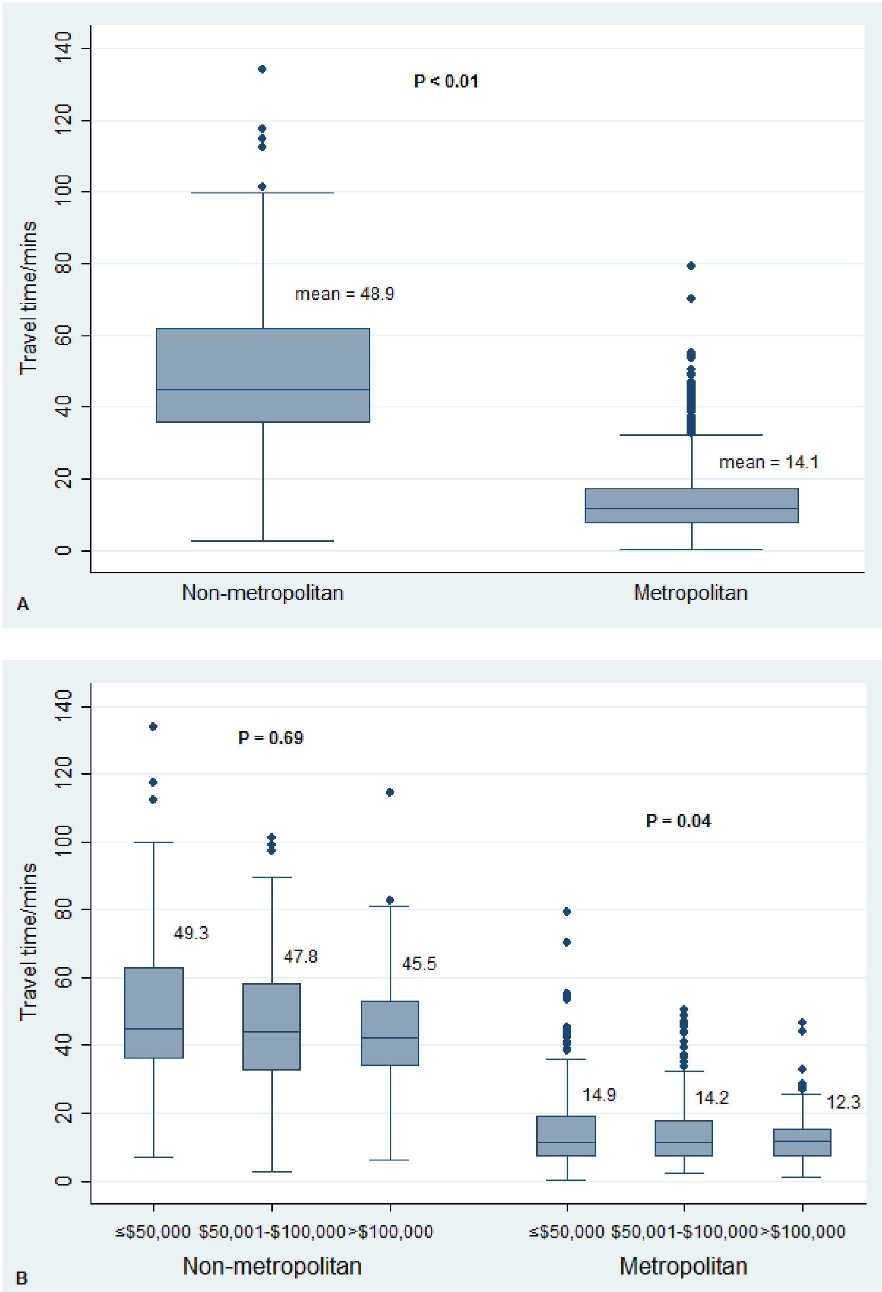


Figure 4.1. Geographical distribution of breast MRI facilities and women in the Wisconsin in situ cohort (2013).
Note: due to privacy concerns, geographic masking was applied to residential geocodes of Wisconsin in situ cohort participants.



Travel time/mins
0
20
40
60
80
100
120
140
P < 0.01
mean = 48.9
mean = 14.1
Non-metropolitan
Metropolitan
A
Travel time/mins
P = 0.69
P = 0.04
49.3
47.8
45.5
14.9
14.2
12.3
≤$50,000 $50,001-$100,000 >$100,000
Non-metropolitan
≤$50,000 $50,001-$100,000 >$100,000
Metropolitan
B

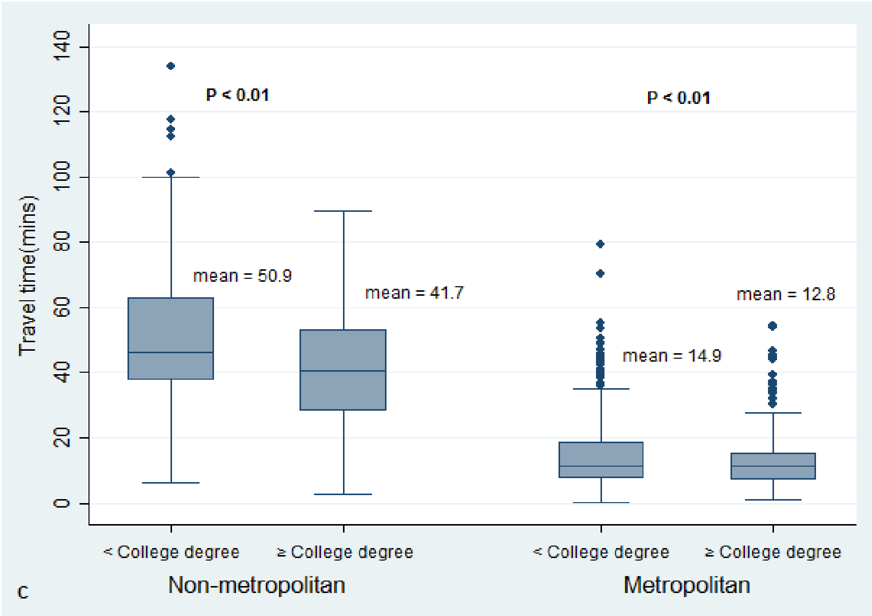


Figure 4.2. Boxplots showing mean travel time by (A) rural/urban residence and according to (B) household income as well as (C) education for each rural/urban residence category in the Wisconsin in situ cohort (2013).

P values derived from *T tests* except (B) which is derived from ANOVA.

Upper whisker = largest value; lower whisker = smallest value; top of box = 75th percentile; bottom of box = 25th percentile; horizontal line = median; diamond dots = outliers.

CHAPTER FIVE

CARDIOVASCULAR HEALTH METRICS AND ADVERSE EVENTS AMONG DUCTAL CARCINOMA IN SITU SURVIVORS

Introduction

Breast cancer-specific mortality following primary ductal carcinoma in situ (DCIS) diagnosis is low, with a recent Surveillance, Epidemiology, and End Results Program (SEER) report indicating about 3.3% at 20 years [30]. Improvements in breast cancer mortality over the past four decades have been largely attributed to widespread mammography screening for early tumor detection, including advances in surgical treatment and adjuvant therapies [164-166].

Cardiovascular disease is the leading cause of death in the US with DCIS survivors more likely to die from cardiovascular disease within 20 years (13.2%; Confidence Interval [CI], 12.8-13.7) than from breast cancer (3.2%; 95% CI: 3.0-3.4) [4, 78]. Lifestyle interventions targeting smoking cessation, dietary habits, physical activity and body mass index (BMI) management are important strategies for cardiovascular disease and cancer prevention [81-83]. Maintaining healthy levels of biological factors such as blood pressure, glucose and total cholesterol may decrease cardiovascular disease risk [84]. Together, the highlighted four health behaviors and three biological factors constitute the American Heart Association (AHA) Life's Simple 7 cardiovascular health metrics [84]. Previous research suggests less than 1% of the adult US population meet ideal conditions for all 7 cardiovascular metrics [92].

Though adjuvant radiation and endocrine therapies improve disease-free survival [28, 94], they do have adverse health effects and may increase the risk of cardiovascular disease [95-97]. Hence, the prevalence of adverse cardiovascular events may differ between DCIS survivors and women in the general population. However, previous studies characterizing cardiovascular disease burden according to DCIS history do not account for cardiovascular disease risk factors [107]. Evaluating modifiable cardiovascular risk factors is important as they impact the development of adverse cardiovascular events, regardless of breast cancer history. Using the Wisconsin In Situ Cohort and the National Health and Nutrition Examination Survey, we assessed and compared the prevalence of cardiovascular health metrics including adverse cardiovascular events between DCIS survivors and women in the US population. Additionally, we evaluated the prevalence of cardiovascular metrics and adverse cardiovascular events among DCIS survivors according to surgical treatment and receipt of adjuvant radiation and endocrine therapies.

Methods

Data Sources

We analyzed data derived from 2 sources: the Wisconsin in Situ Cohort (WISC) study and the National Health and Nutrition Examination Survey (NHANES). Details of the WISC study have been reported previously [153]. Briefly, the WISC study is a cohort of women with a primary DCIS diagnosis reported to the mandatory Wisconsin Cancer Reporting System between 1997-2006. Women between the ages of 20-74 years were eligible for WISC study enrolment if they had a known date of DCIS diagnosis and a listed telephone number. At baseline, 1,925 women were recruited with 838 women initially enrolled for a case-control study from 1997-2001 and 1,087 additional women recruited between 2002-2006 [154]. Participants provided verbal consent and the study was approved by the University of Wisconsin-Madison Health Sciences Human Subjects Committee. Baseline and initial follow-up interviews were conducted via telephone. However, from 2013 participants completed mailed surveys with the most recent recontact occurring in 2015. In addition to questions on sociodemographic factors, breast health, general wellbeing and comorbid conditions, the 2015 survey also inquired about modifiable cardiovascular risk factors. Of the 1,282 DCIS survivors recontacted in 2015, 1,014 women responded for a response rate of 79.1%.

The National Health and Nutrition Examination Survey (NHANES) is a series of nationally representative cross-sectional studies designed to evaluate the health and nutritional status of adults and children in the US. Since 1999, the NHANES has been conducted in 2-year cycles using a stratified, multistage probability sampling strategy for selecting a nationally representative sample of the non-institutionalized US population. NHANES was approved by the National Center for Statistics Research Ethics Review Board with written consent obtained from adult participants. Sociodemographic, health behavior, nutritional and comorbidity data were collected during interviews while anthropometric measurements were taken during physical examination sessions. Biospecimens were collected among selected participants and tested for biologic factors such total cholesterol and fasting plasma glucose. Further details of the NHANES can be found elsewhere [167, 168]. In our study, we utilized the 2009-2014 survey years (n=30,468), restricting our analysis to women ≥40 years (n=5,971) with at least one complete AHA cardiovascular metric (n=5,930).

Variables of Interest

For both studies, we retrieved data on demographic characteristics (age, race/ethnicity, educational attainment and household income) and the seven AHA cardiovascular metrics (smoking, physical activity, diet, BMI, blood pressure, blood glucose and total cholesterol). The AHA cardiovascular metrics also known as Life’s Simple 7, were developed by the American Heart Association as a tool for assessing progress in attaining its year 2020 goal: the improvement of cardiovascular health of all Americans by 20% and reduction in cardiovascular disease (CVD) and stroke mortality by 20% [84]. Each metric is defined over a spectrum in line with the AHA 2020 strategic goals and categorized as ideal, intermediate or poor (Table 5.1).

The four health behavior components were calculated from self-reported data in both studies, except BMI, which was derived from weight and height measurements taken during the examination session among NHANES participants. The AHA dietary component score is based on the attainment of 5 specific food consumption goals: ≥ 4.5 cups per day of fruits and vegetables, ≥ two 3.5-oz servings per week of fish, ≥ three 1-oz servings per day of whole grains, < 1500 mg per day of sodium, and < 450 kcal per week of sugar-sweetened beverages. In the WISC cohort, the dietary score was derived from data on the intake of the five specified food groups and their quantities typically consumed. NHANES participants completed two 24-hour dietary recalls from which the usual consumption of the five food groups were determined using the US Department of Agriculture Center for Nutrition Policy and Promotion's MyPyramid Equivalents methodology [169, 170]. In both studies, the physical activity component was derived from participants' response to the weekly frequency, duration and intensity of physical activities. Similarly, the smoking component was determined from self-reported smoking status including duration of smoking cessation.

The three biologic factors were derived from self-reported data in the WISC cohort (Appendix C) and from physical measurements/blood test results in the NHANES. In analyzing blood pressure data among NHANES participants, we calculated the average of three measurements taken during the physical examination session. Fasting plasma glucose data was available for a randomly selected subsample who had been previously instructed to fast before their physical examination. The prevalence of major cardiovascular events in both studies, was determined using self-reported data on the occurrence of the following conditions: heart failure, coronary heart disease, angina, heart attack and stroke.

In the WISC cohort, we retrieved self-reported breast cancer treatment data, categorizing surgical treatment as breast conserving surgery and mastectomy. Additionally, participants were categorized based on receipt of adjuvant radiation and endocrine therapies following primary DCIS diagnosis or subsequent breast cancer events.

Statistical Analysis

Statistical analyses were performed using Stata/SE 14 Software (StataCorp LP, College Station, TX) and SAS version 9.4 (SAS institute, Cary, NC). Among WISC participants, missing values for cardiovascular covariates were estimated using multiple imputation with chained equations over ten iterations, with pooled estimates determined using methods previously described [159]. We conducted a sensitivity analysis among WISC participants, performing chi-square comparisons of demographic characteristics according to the occurrence of missing data for 3 cardiovascular health metrics >10% missing values (blood pressure, fasting blood glucose and total cholesterol). Additionally, we compared between original and imputed data, the cardiovascular metrics distribution.

We utilized SAS survey procedures to analyze the NHANES sample, accounting for its complex multistage probability sampling design [167]. The sample weights were determined by dividing the survey sample weight by the number of combined surveys and subsequently utilized for calculating our prevalence estimates and 95% confidence intervals (CI). In both study samples, we estimated the proportions of demographic variables. We estimated the age-standardized prevalence of each cardiovascular metric by categories (poor, intermediate and ideal) and compared the distribution of the number of ideal levels of cardiovascular metrics (from 0 to 7) in both study samples. Age-adjustment was performed using the direct method to the standard 2000 US population [171]. Due to sampling differences in the NHANES interview, examination and biospecimen collection sessions, prevalence estimates of individual cardiovascular metrics were determined using recommended sampling weights [168], and available data on the specific cardiovascular metric. However, only women with complete information for all seven cardiovascular health metrics were included for prevalence estimates of the number of ideal cardiovascular metrics (0 to 7), applying the appropriate sampling weight. Additionally, we estimated the age-adjusted prevalence of adverse cardiovascular events in both study populations.

Among WISC participants, we performed chi-square comparisons of the proportions of women with ideal status for each cardiovascular health metric according to surgical treatment type including receipt of adjuvant radiation and endocrine therapies. In addition, we conducted chi-square comparisons of the prevalence of adverse cardiovascular events according to surgical treatment type, receipt of adjuvant radiation and endocrine therapies, controlling for time since diagnosis. Since, tamoxifen is contraindicated among women with a prior history of blood clots in the veins and lungs, or with stroke and stroke-like events [172], the prevalence of stroke will expectedly be lower among women using tamoxifen compared to those who don't. Hence, further comparison of adverse cardiovascular events excluding stroke and stroke-like events according to tamoxifen use was performed.

Results

Demographic Characteristics

The demographic characteristics of the WISC and NHANES participants are shown in Table 5.2. On average WISC participants were about 10 years older than NHANES participants, with women in the former most frequently 70 years and older (44.6%) compared to the NHANES who are mostly between 40-59 years (57.6%). Additionally, both study populations were composed mainly of non-Hispanic white women, with WISC participants having a higher proportion of women with a college degree or higher (35.6%) compared to NHANES participants (28.9%). A higher proportion of women in the NHANES had an annual household income of $100,000 or more (22.3%) compared to WISC participants (15.1%).

WISC Treatment Characteristics

Most WISC participants had breast-conserving surgery following their primary DCIS diagnosis (63.3%) with 56.9% having undergone adjuvant radiation therapy as shown in Table 5.3. Almost half of the WISC participants (48.9%) had received adjuvant endocrine therapy following their DCIS diagnosis, mainly tamoxifen (41.6%) with 12.8% having developed a second breast event (ipsilateral and contralateral in situ or invasive breast cancer following primary DCIS diagnosis). Women between 60-69 years were the largest proportion of WISC participants reporting ever use of tamoxifen (Appendix D). Among all DCIS treatment categories, women undergoing breast conserving surgery with adjuvant radiation therapy had the largest proportion reporting receipt of adjuvant tamoxifen therapy (48.6%) as shown in Table 5.4.

Prevalence of Cardiovascular Health Factors and Adverse Events

There was a high prevalence of self-reported ideal smoking status in the WISC (89.1%) and NHANES (89.0%) as shown in Table 5.5, with current smoking as the second most frequently reported smoking status in the WISC (8.3%) and NHANES (9.6%). Ideal physical activity was the most prevalent physical activity category in both study groups, with the WISC population having a higher prevalence (61.8%) compared to the NHANES (42.3%). Ideal BMI was most frequently reported in the WISC (41.2%) compared to women in NHANES who exhibited poor

BMI as the largest observed proportion (38.1%). In both study populations, the least prevalent ideal cardiovascular metric was healthy diet score, with a lower prevalence observed in the NHANES (1.5%) compared to the WISC (25.6%). WISC participants demonstrated a higher prevalence of ideal levels of total cholesterol (31.2%), blood pressure (32.0%) and fasting plasma glucose (48.8%) compared to women in the NHANES (25.3%, 17.4% and 40.5% respectively).

The distribution of the number of ideal levels of cardiovascular metric in the WISC and NHANES is shown in Figure 5.1. A larger proportion of women in the NHANES (94.1%) had ≤3 number of ideal levels of cardiovascular metrics compared to the WISC (78.2%). WISC participants (21.8%) compared to NHANES (5.9%) most frequently had 4 or more number of ideal levels of cardiovascular health metrics. Compared to the WISC (2.5%), the NHANES had a lower proportion of women (<0.1%) with ideal levels in all 7 cardiovascular health metrics. Women in the WISC, had a lower prevalence (8.8%) of self-reported adverse cardiovascular events (heart failure, coronary heart disease, angina, heart attack and stroke) compared to NHANES (10.7%) (Table 5.5).

Ideal Cardiovascular Metrics and adverse cardiovascular events by DCIS Surgical Treatment and Adjuvant Therapies

The most frequent ideal cardiovascular metric by DCIS surgical treatment and adjuvant therapies was ideal smoking (>90%) and the least frequent ideal cardiovascular metric was ideal blood pressure (Tables 5.6 and 5.7). Comparisons of ideal cardiovascular metrics according to surgical treatment type and receipt of adjuvant radiation and endocrine therapy (including tamoxifen use) were similar. An exception was ideal BMI according to DCIS surgical treatment type, with a lower proportion of women undergoing breast conserving surgery (34.3%)

compared to mastectomy (41.9%). There was no substantial difference in the prevalence of adverse cardiovascular events according to surgical treatment and adjuvant radiation utilization (Figure 5.2). However, receipt of adjuvant endocrine therapy (9.2%) particularly tamoxifen (8.4%) was associated with a significantly lower prevalence of adverse cardiovascular events compared to non-receipt (15.4%), after controlling for time since diagnosis. However, following the exclusion of women with stroke and stroke-like events, there was no statistically significant difference in the prevalence of adverse cardiovascular events according to tamoxifen use.

Sensitivity Analysis

Women with missing blood pressure, fasting plasma glucose and total cholesterol values were more likely to be older (50.6%, 47.3% and 49.6% respectively) compared to women with known data (41.8%, 37.6% and 49.6% respectively) as shown in Appendix E. Additionally, women with missing blood pressure (47.1%), fasting plasma glucose (41.0%) and total cholesterol data (40.7%) most frequently had an educational attainment of high school diploma or less. Differences in cardiovascular metric prevalence estimates between original and imputed data were less than 4% except for ideal (5.5%) and intermediate (9.1%) total cholesterol including intermediate fasting plasma glucose levels (4.1%) as shown in Appendix F. Age-standardized cardiovascular metric estimates were fairly similar between original (87.9%) and imputed WISC data (89.1%) for ideal smoking and adverse cardiovascular events (original: 7.9%, imputed: 8.8%).

Discussion

In assessing the AHA cardiovascular metrics among DCIS survivors ≥40 years, there was a greater proportion of WISC participants with ideal levels for each cardiovascular metric compared to similar women in the US population. These findings suggest that DCIS survivors more often adopt healthy lifestyle interventions compared to the general female population. There are some possible explanations for these findings. Mammography use is an important determinant of DCIS diagnosis [173]. Certain factors such as increasing educational attainment and race/ethnicity (non-Hispanic white) are associated with greater mammography use and DCIS diagnosis [174, 175]. Previous reports have shown that high education attainment and being non-Hispanic white is associated with increased likelihood of ideal levels for the different cardiovascular health metrics [85, 176]. Over 90% of the WISC population was composed of non-Hispanic white women compared to about 70% observed in the NHANES, with a larger proportion having at least a college degree or higher in the WISC compared to the NHANES. Additionally, researchers have suggested that women diagnosed with DCIS might be more health-conscious compared to women in the general population [107]. Although we could not ascertain the time of adoption of healthy lifestyle interventions, our comparative study is probably the first to demonstrate a better cardiovascular health profile among DCIS survivors compared to the general population using the AHA cardiovascular metrics.

About one quarter of WISC participants had an ideal healthy diet score, the lowest proportion observed for all 7 ideal cardiovascular metrics. Dietary habits influence other cardiovascular risk factors including BMI, blood pressure and total cholesterol. Hence, with the ongoing obesity epidemic vulnerable populations such as cancer survivors are increasingly recognized as requiring early intervention. Diet as a modifiable cardiovascular risk factor is increasingly become a focus for public health interventions. However, dietary interventions can be challenging with Crichton et al. reporting a 50% attrition rate in their 12-month dietary intervention study [177]. It is possible that DCIS survivors, while undergoing recommended follow-up care [178], are encouraged earlier and continually to adopt and maintain healthy lifestyles (including dietary habits) compared to women in the general population. This could account for the observed greater prevalence of ideal cardiovascular metrics including healthy diet score in the WISC compared to the NHANES. Women in the WISC were on average 10 years older than women in the NHANES and previous research has shown that healthy diet scores improve with increasing age [92]. Alternatively, differences in ideal healthy diet score prevalence may be related to each sample's study design, with food frequency questionnaires in the WISC favoring long-term assessment of usual intake compared to 24-hr dietary recalls in the NHANES favoring short-term dietary assessments [179, 180].

The WISC compared to the NHANES had a larger proportion of women with ≥4 ideal cardiovascular metrics. Additionally, WISC participants had a lower prevalence of adverse cardiovascular events compared to women in the NHANES. Increasing number of ideal levels of cardiovascular metrics is associated with a decreased risk from cardiovascular morbidity and mortality [85, 181, 182]. Our findings are in line with a recent Dutch study demonstrating a lower risk of dying from cardiovascular disease (standardized mortality ratio= 0.77; 95% CI: 0.67-0.89) among DCIS survivors compared to the general population [107]. Additionally, DCIS survivors may routinely seek other disease prevention strategies apart from cancer prevention, leading to early identification of adverse cardiovascular event precursors with subsequent adoption of lifestyle interventions.

Comparisons of ideal cardiovascular metrics according to surgical treatment type including adjuvant radiation and endocrine therapy utilization were mostly similar suggesting lifestyle interventions are not related to treatment choice following DCIS diagnosis. Additionally, recent reports have shown no increased risk for cardiovascular disease following adjuvant radiation utilization among DCIS survivors even as newer techniques minimize cardiac radiation exposure [107, 183]. Tamoxifen is the most widely studied adjuvant endocrine agent for breast cancer treatment. Tamoxifen reduces total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, both of which are risk factors for ischemic heart disease [101-103]. Reports on cardiovascular disease risk in relation to aromatase inhibitor use has been mixed with a 2016 meta-analysis demonstrated no change in cardiovascular disease risk (RR: 1.01, 95% CI: 0.85-1.20) [95, 104, 105]. Initially, we observed a substantial decrease in the prevalence of adverse cardiovascular events with tamoxifen therapy. This appeared to be consistent with previous reports demonstrating reduced risk of coronary heart disease associated with tamoxifen use [99, 100]. However, tamoxifen increases the risk of thromboembolic events including stroke, and is contraindicated among women with a previous history of venous or lung blood clots, stroke and stroke like events [172, 184]. Consequently, the occurrence of stroke among tamoxifen users will expectedly be lower compared to non-tamoxifen users. However, the exclusion of DCIS survivors with a previous history of stroke and stroke-like events in our analysis revealed similar prevalence estimates for adverse cardiovascular events. Due to the cross-sectional nature of our study, we are limited in our ability to assess causality in the association between tamoxifen and adverse cardiovascular events. However, these findings are important as they highlight the importance of separately evaluating the effect of tamoxifen therapy on heart disease and cerebrovascular disease.

Despite our novel findings, our study has some limitations. The WISC and NHANES had different data collection methods with WISC participants completing self-administered questionnaires compared to NHANES participants having 3 separate data collection methods (interview, physical examination and biospecimen collection). Data for fasting blood glucose, total cholesterol, blood pressure and BMI in the WISC cohort were self-reported. However, previous studies have shown that most self-reported blood pressure measurements were similar to actual tested readings [185], with the reliability of fasting plasma glucose readings estimated to be about 92% [186]. Hence, we anticipate that the WISC cardiovascular metric estimates derived from self-reported data reflect actual measurements and test results that would have been produced following data collection. The occurrence of missing data particularly for blood pressure, fasting plasma glucose and total cholesterol was a challenge in the WISC and as previously reported [187], occurred more frequently with increasing age. Multiple imputation of missing values was performed for efficient use of available data and generation of unbiased pooled estimates. Though cardiovascular disease prevalence in both study samples was entirely self-reported, previous research has shown substantial agreement between self-report chronic disease (including stroke and myocardial infarction) and medical record data (kappa 0.71-0.80) [188]. Despite these limitations, our study is unique as it assesses the prevalence of modifiable cardiovascular disease risk factors (often missing in similar studies) including adverse cardiovascular events among DCIS survivors compared to women in the general population. Additionally, it also assesses any differences in cardiovascular health profile of DCIS survivors by extent of surgical treatment and adjuvant therapy utilization.

In conclusion, our analysis of the AHA cardiovascular metrics among DCIS survivors in the WISC, demonstrated less than a third of women had ideal levels for diet, total cholesterol and blood pressure metrics, with about 2% of women having ideal levels of all 7 metrics. Additionally, the prevalence of adverse cardiovascular events among DCIS survivors in the WISC while lower than women in the US population did not differ according to surgical treatment as well as adjuvant radiation and endocrine therapy utilization. These findings demonstrate the need for DCIS survivors to increase their adoption and maintenance of health dietary and other lifestyle interventions as cardiovascular disease is the leading cause of mortality among them. Our study describes differences in cardiovascular health profile between DCIS survivors and women in the general US population. Future prospective studies are required to quantify the cardiovascular disease risk differences based on a prior DCIS diagnosis while accounting for modifiable lifestyle interventions including the use of adjuvant radiation and endocrine therapy.

Table 5.1. American Heart Association's Definition for Each Cardiovascular Health Metric by Ideal, Intermediate and Poor Categories

Cardiovascular Health Metric	Category	Criteria
Smoking	Ideal	Never or quit >12 months
	Intermediate	Former <12 months
	Poor	Current
Body mass index	Ideal	<25 kg/m2
	Intermediate	25–29.9 kg/m2
	Poor	>30 kg/m2
Healthy diet score[a]	Ideal	4–5 components
	Intermediate	2–3 components
	Poor	0–1 components
Total cholesterol	Ideal	<200 mg/dl without treatment
	Intermediate	200-239 mg/dl or treated to goal
	Poor	>240 mg/dl
Blood pressure	Ideal	<120/<80 mm Hg without treatment
	Intermediate	SBP 120–139 mm Hg or DBP 80–89 mm Hg or treated to goal
	Poor	SBP >140 or DBP >90 mm Hg
Fasting serum sugar	Ideal	<100 mg/dl, without treatment
	Intermediate	100–125 mg/dl or treated to goal
	Poor	>126 mg/dl
Physical activity	Ideal	50 min/wk moderate intensity or 75 min/wk vigorous intensity or combination
	Intermediate	1–149 min/wk moderate intensity or 1–74 min/wk vigorous intensity or 1–149 min/wk moderate + vigorous
	Poor	None

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Healthy diet score components: fruits and vegetables ≥4.5 cups per day; fish ≥ two 3.5-oz servings per week; whole grains ≥ three 1-oz servings per day; sodium < 1500 mg per day; sugar-sweetened beverages ≤450 calories per week.
Adapted from Lloyd-Jones et al [84].

Tables 5.2. Select Characteristics of Ductal Carcinoma in Situ Survivors (WISC, 2015) and US Women (NHANES, 2009-2014) ≥ 40 years

Characteristic	WISC		NHANES[a]	
	N = 1,014	Prevalence, % (95% CI)	N = 5,930	Prevalence, % (95% CI)
Age mean (95% CI), y		69.1 (68.6-69.6)		58.0 (57.6-58.4)
Age Group, y				
40-59	139	13.7 (11.7-16.0)	3,030	57.9 (56.4-59.4)
60-69	424	41.8 (38.8-44.9)	1,409	21.3 (20.0-22.7)
≥70	451	44.5 (41.5-47.6)	1,491	20.8 (19.5-22.1)
Race				
Non-Hispanic White	975	96.2 (94.8-97.2)	2,604	71.1 (67.1-75.1)
Other	39	3.8 (2.8-5.2)	3,326	28.9 (24.9-32.9)
Education				
≤ High school degree	371	36.6 (33.7-39.6)	2,931	39.8 (37.0-42.7)
Some college	281	27.7 (25.0-30.6)	1,718	31.4 (29.6-33.2)
College or higher	362	35.7 (32.8-38.7)	1,281	28.8 (26.1-31.5)
Household Income				
< $15,000	57	5.6 (4.4-7.2)	951	10.5 (9.0-12.0)
$15,000 - $100,000	659	65.0 (62.0-67.9)	3,728	62.6 (60.0-65.1)
> $100,000	152	15.0 (12.9-17.3)	861	22.3 (19.6-25.0)
Other/Unknown	146	14.4 (12.4-16.7)	390	4.6 (4.1 – 5.2)

Abbreviation: WISC, Wisconsin in Situ Cohort; NHANES, National Health and Nutritional Examination Survey.

[a]Estimates are weighted to reflect the NHANES study design.

Table 5.3. Treatment characteristics of Ductal Carcinoma in Situ survivors in the Wisconsin in Situ Cohort (2015)

Treatment	N = 1,014	Prevalence %
Surgery		
Mastectomy	338	33.3
Breast Conserving Surgery	642	63.3
Other/Unknown	34	3.4
[a]Radiation Therapy		
No	420	41.4
Yes	577	56.9
Unknown	17	1.7
[b]Endocrine Therapy		
No	502	49.5
Yes		
Tamoxifen	422	41.6
Other	74	7.3
Unknown	16	1.6
Second breast event		
No	884	87.2
Yes	130	12.8

[a]Includes receipt of adjuvant radiation therapy following primary DCIS diagnosis and second breast events.
[b]Includes ever use of tamoxifen, raloxifen and aromatase inhibitors regardless of primary DCIS diagnosis.

Table 5.4. Primary Ductal Carcinoma in Situ Treatment and Adjuvant Endocrine Therapy Utilization among Women in the Wisconsin in Situ Cohort (2015)

Adjuvant[a] Endocrine Therapy	Primary Ductal Carcinoma in Situ Treatment			
	Breast Conserving Surgery alone (n=103), Col %	Breast Conserving Surgery with Radiation (n=539) , Col %	Mastectomy (n=338) , Col %	Total (n=980), Col %
Tamoxifen	42 (40.8)	262 (48.6)	109 (32.2)	413 (42.1)
Other Endocrine Therapy	7 (6.8)	42 (7.8)	22 (6.5)	71 (7.3)
None	49 (47.6)	235 (43.6)	204 (70.4)	488 (49.8)
Missing	5 (4.8)	0	3 (0.9)	8 (0.8)

[a]Includes ever use of endocrine agents regardless of primary Ductal Carcinoma in Situ diagnosis.
Note: 34 women had missing primary ductal carcinoma in situ treatment information.

Table 5.5. Prevalence of Cardiovascular Metrics and Adverse Events Among Ductal Carcinoma In Situ Survivors (WISC, 2015) and US Women ≥40 years (NHANES, 2009-2014)

Cardiovascular Metric	WISC		NHANES	
	N	Prevalence[a,b] % (95% CI)	N	Prevalence[a], % (95% CI)
Smoking Status				
Ideal	904	89.1 (85.3-92.9)	4,917	89.0 (87.5 – 90.4)
Intermediate	26	2.6 (0.6-4.6)	99	1.4 (1.0– 1.9)
Poor	84	8.3 (5.0-11.6)	914	9.6 (8.3 – 11.0)
Physical activity				
Ideal	627	61.8 (56.7-67.0)	2,198	42.3 (40.2 – 44.4)
Intermediate	331	32.7 (27.6-37.6)	1,612	25.1 (23.7 – 26.5)
Poor	56	5.5 (3.3-7.7)	2,117	32.6 (30.5 – 34.9)
Body Mass Index (kg/m^2)				
Ideal	418	41.2 (35.9-46.5)	1,535	30.2 (28.2-32.1)
Intermediate	296	29.2 (24.4-34.0)	1,682	31.7 (30.0-33.4)
Poor	300	29.6 (24.8-34.4)	2,462	38.1 (35.5-40.8)
Healthy Diet				
Ideal	260	25.6 (20.9-30.3)	80	1.5 (1.0-1.9)
Intermediate	660	65.1 (60.1-70.2)	2,340	46.3 (43.6-49.0)
Poor	94	9.3 (6.3-12.2)	2,421	52.3 (49.5-55.0)
Total Serum Cholesterol				
Ideal	316	31.2 (22.4-40.0)	1,734	25.3 (23.1-27.6)
Intermediate	578	57.0 (50.0-64.0)	2,748	57.2 (54.8-59.5)
Poor	120	11.8 (4.2-19.4)	910	17.5 (16.0-19.0)
Blood Pressure				
Ideal	324	32.0 (26.1-37.9)	1,513	17.4 (15.7 – 19.0)
Intermediate	581	57.3 (51.4-63.1)	2,685	50.6 (48.2 – 53.0)
Poor	109	10.7 (6.6-14.9)	1,301	32.0 (29.8 – 34.2)
Fasting Blood Glucose				
Ideal	495	48.8 (40.9-56.6)	1,170	40.5 (37.6–43.4)
Intermediate	383	37.8 (31.6-43.9)	1,018	46.2 (43.1– 49.4)
Poor	136	13.5 (7.0-20.0)	336	13.3 (10.8–15.8)
Adverse Cardiovascular Events				
Yes	125	8.8 (6.3-11.4)	785	10.7 (9.7-11.7)
No	881	91.2 (88.6-93.7)	5,158	89.3 (88.3-90.3)

Abbreviation: WISC, Wisconsin in Situ Cohort; NHANES, National Health and Nutritional Examination Survey.

[a] Estimates are age-standardized using the direct method to the 2000 US population.

[b] Estimates were determined following multiple imputation of missing data except cardiovascular disease prevalence.

Table 5.6. Prevalence of Ideal Cardiovascular Health Metrics According to Surgical Treatment including Adjuvant Endocrine and Radiation Therapy Utilization following Ductal Carcinoma in Situ Diagnosis (WISC, 2015)

Ideal Cardiovascular Health Metric		Surgery			Radiation Therapy			Endocrine Therapy		
		Breast Conserving Surgery n=642 (Col %)	Mastectomy n=338 (Col %)	P value[a]	Yes n=577 (Col %)	No n=420 (Col %)	P value[a]	Yes n=496 (Col %)	No n=502 (Col %)	P value[a]
Smoking Status	Yes	93.2	95.4	0.18	93.5	94.6	0.95	94.7	93.3	0.42
	No	6.8	4.6		6.5	5.4		5.3	6.7	
Physical activity	Yes	56.4	58.0	0.56	55.9	58.4	0.58	56.0	57.9	0.38
	No	43.6	42.0		44.1	41.6		44.0	42.1	
Body Mass Index (kg/m^2)	Yes	34.3	41.9	0.02	34.9	39.6	0.40	36.6	37.2	0.81
	No	65.7	58.1		65.1	60.4		63.4	62.8	
Healthy Diet	Yes	25.0	27.7	0.31	25.6	26.4	0.26	26.3	25.5	0.81
	No	75.0	72.3		74.4	73.6		73.7	74.5	
Total Serum Cholesterol	Yes	25.2	26.1	0.64	24.9	26.4	0.26	23.3	27.7	0.84
	No	74.8	73.9		75.1	73.6		76.7	72.3	
Blood Pressure	Yes	20.8	22.8	0.52	20.8	22.6	0.23	21.4	21.6	0.31
	No	79.2	77.2		79.2	77.4		78.6	78.4	
Fasting Plasma Glucose	Yes	45.5	48.4	0.28	45.3	48.3	0.48	46.1	47.0	0.76
	No	54.5	51.6		54.7	51.7		53.9	53.0	

Abbreviation: WISC, Wisconsin in Situ Cohort.

[a]P values are derived from pooled likelihood ratio chi-square tests and adjusted for age and time since diagnosis.

Table 5.7. Prevalence of ideal Cardiovascular Health Metrics according to Tamoxifen Therapy following Ductal Carcinoma in Situ Diagnosis (WISC, 2015)

Ideal Cardiovascular Health Metric		Tamoxifen Therapy		
		Yes n=496 (Col %)	No n=502 (Col %)	P value[a]
Smoking Status	Yes	94.7	93.3	0.42
	No	5.3	6.7	
Physical activity	Yes	56.0	57.9	0.38
	No	44.0	42.1	
Body Mass Index (kg/m^2)	Yes	36.6	37.2	0.81
	No	63.4	62.8	
Healthy Diet	Yes	26.3	25.5	0.81
	No	73.7	74.5	
Total Serum Cholesterol	Yes	23.3	27.7	0.84
	No	76.7	72.3	
Blood Pressure	Yes	21.4	21.6	0.31
	No	78.6	78.4	
Fasting Plasma Glucose	Yes	46.1	47.0	0.76
	No	53.9	53.0	

Abbreviation: WISC, Wisconsin in Situ Cohort.
[a]P values derived from pooled chi-square tests and adjusted for age and time since diagnosis.

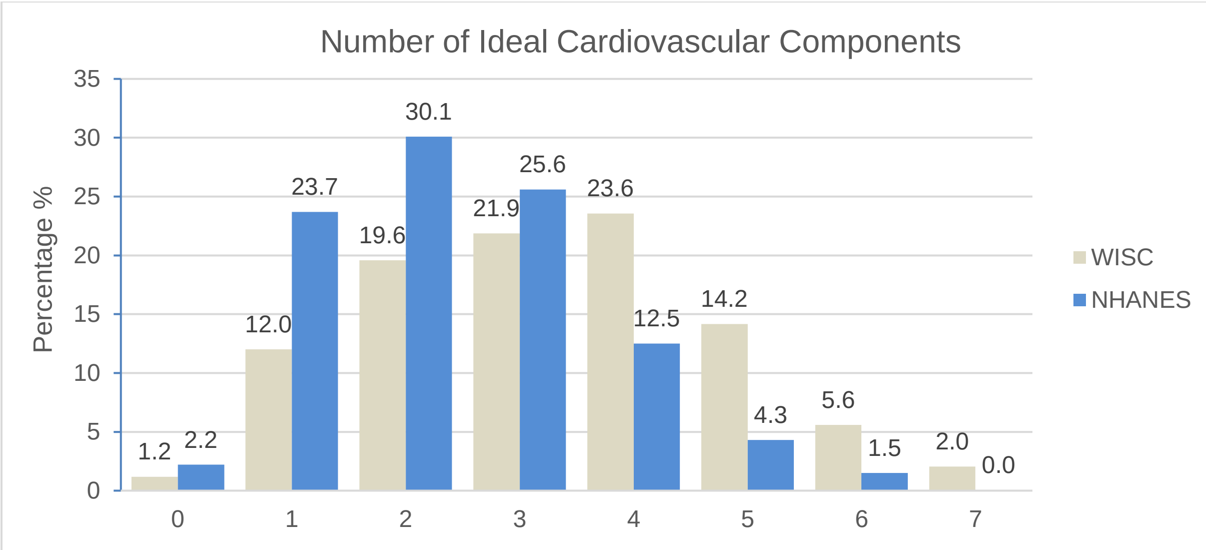


Figure 5.1. Number of ideal cardiovascular health components among ductal carcinoma in situ survivors (Wisconsin In Situ Cohort, 2015) and US women ≥ 40 (National Health and Nutrition Examination Surveys, 2009-2014). Estimates are age-adjusted by direct method to the 2000 US population.

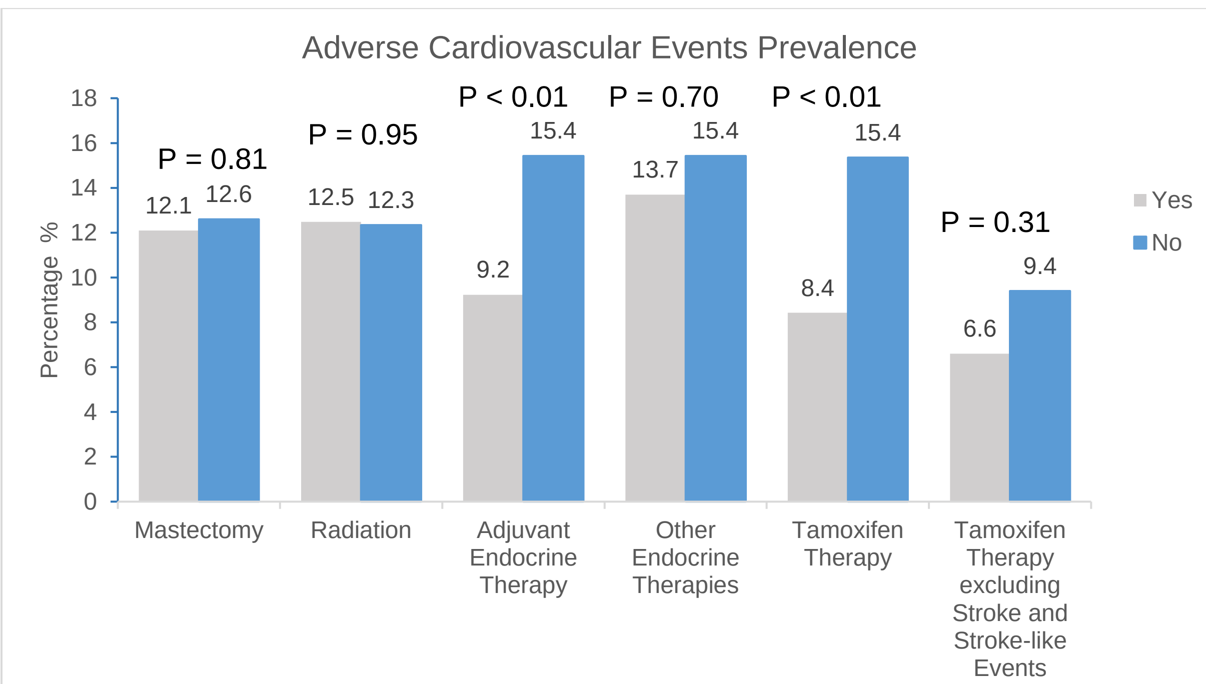


Figure 5.2. Prevalence of adverse cardiovascular events among ductal carcinoma in situ survivors (Wisconsin in Situ Cohort, 2015) according to surgical treatment, adjuvant radiation and endocrine therapy utilization. P values are derived from likelihood-ratio chi-square tests and adjusted for age and time since diagnosis.

CHAPTER SIX

CONCLUSION

6.1 Summary

The purpose of this dissertation was to evaluate specific experiences that impact disease-free and overall survival following a DCIS diagnosis. Specifically, this dissertation sought to assess trends in DCIS treatment and supplemental therapies' utilization. Furthermore, we examined breast MRI utilization according to underlying breast cancer risk factors, tumor features, socioeconomic factors and geographic access. Finally, we assessed the prevalence of cardiovascular health interventions and adverse events among DCIS survivors.

In evaluating recent treatment trends among 416,232 women following DCIS diagnosis between 1998 and 2011, breast conserving surgery was the most frequently utilized surgical treatment. However, adjuvant radiation use following breast conserving surgery stabilized at about 70% since 2007, suggesting adjuvant radiation therapy utilization may be at a saturation level. There was an increasing trend in postmastectomy reconstruction in general and according to ancestry/ethnicity with non-Hispanic white women having the highest rates. However, post-mastectomy reconstruction was inversely related to age, with women ≥75 years 94% less likely to undergo postmastectomy reconstruction compared to women <45 years. The rate of contralateral risk reducing mastectomy following DCIS diagnosis increased over time, and its utilization was less likely with increasing age. There were geographical variations in surgical treatment and adjuvant therapy utilization with women outside the Northeast having lower odds of undergoing breast conserving surgery and more likely to undergo contralateral mastectomy.

Breast MRI utilization among a cohort of 1,103 DCIS survivors was low (11.9%), with women <50 years 2.3 times more likely to undergo breast MRI compared to women 50 years. Breast MRI utilization was 2.4 times more likely among women with ≥20% lifetime breast cancer risk in line with ACS breast MRI recommendation guidelines. However, there was no association between breast MRI utilization and first-degree breast cancer family history, primary DCIS tumor features and surgery type. Increasing level of household income and education were associated with the increased likelihood of breast MRI utilization. Non-metropolitan residents had an additional 35-minute mean shortest travel time to breast MRI facilities compared to metropolitan residents, highlighting the potential travel burden faced by rural residents in accessing breast MRI.

Our assessment of the American Heart Association cardiovascular metrics among DCIS survivors demonstrated higher proportions of ideal cardiovascular metrics among DCIS survivors compared to women in the general US population. However, less than a third of DCIS survivors had ideal levels for diet (25%), total cholesterol (31%) and blood pressure (32%) metrics, with about 2% of women having ideal levels of all 7 AHA cardiovascular metrics. There was a lower prevalence of adverse cardiovascular events among DCIS survivors compared to women in the general population. However, the prevalence of ideal cardiovascular metrics and adverse cardiovascular events among DCIS survivors, did not substantially vary according to surgical treatment as well as adjuvant radiation and endocrine therapy use. These findings suggest that DCIS survivors have a better cardiovascular health profile compared to women in the general population but require improvement in the adoption of healthy dietary habits and lifestyles that decrease cardiovascular disease risk.

6.2 Strengths and Limitations

The strengths and limitations of each dissertation aim have been previously discussed in the relevant chapter but a broader perspective involving the dissertation as a whole is provided in this section. The NCDB is the largest cancer data resource in the US, with data derived from hospital based registries, making it suitable for assessing patterns of breast cancer care. The

WISC is a population-based prospective study of DCIS survivors with consistent data collection on breast health and surveillance, health behaviors and chronic disease, making it suitable for studying breast MRI use and cardiovascular health status among DCIS survivors. A nationally representative data resource such as NHANES, with standardized data collection methods provided an opportunity to study modifiable health behaviors and adverse cardiovascular events.

Selection bias was a potential threat to the validity of our study results. For instance, only cases from Commission on Cancer accredited hospitals are reported in the NCDB, which may represent select cases. However, treatment facilities reporting data in the NCDB are diverse, ranging from academic facilities to community-based cancer centers. Additionally, more than 70% of new cancer cases covering all geographic regions, in the US are reported in the NCDB. Follow-up surveys in the WISC have been ongoing since initial enrolment, with dropouts occurring over the years for various reasons ranging from relocation, and death, to refusing further participation. Selection bias is a potential concern particularly if participants with severe comorbid conditions are more likely to drop out over time leaving more healthy participants within the cohort. This could result in a better cardiovascular health profile among DCIS survivors. However, WISC follow-up survey participation has been fairly consistent with response rates in both 2013 and 2015 almost 80%. Additionally, the racial/ethnic composition and the distribution of socioeconomic factors (household income and education) at diagnosis and at the most recent 2015 follow-up survey are fairly comparable allaying selection bias concerns.

In assessing treatment trends and breast MRI utilization among DCIS survivors, potential confounders were adjusted for in our regression models. However, there is the possibility of residual confounding particularly for factors that we lacked data such as hormone receptor and BRCA mutation status. In comparing the cardiovascular health profile of DCIS survivors and women in the general US population, we used the direct standardization method to age-adjust both study populations. Unfortunately, a limitation of direct standardization is the inability to control for other confounders that impact the distribution of cardiovascular metrics and adverse cardiovascular events. In utilizing cross-sectional data, temporality between cardiovascular metrics and the development of adverse cardiovascular events could not be ascertained among DCIS survivors and women in the general population. However, we anticipate future studies will address temporality of cardiovascular metrics, DCIS treatment including adjuvant therapy and adverse cardiovascular events.

Our assessment of adverse cardiovascular metrics and disease prevalence was based on self-reported data. This could lead to underreporting of socially undesirable health behaviors and conditions resulting in misclassification of cardiovascular metrics and adverse cardiovascular events. However, this might be minimal in our study with cardiovascular metrics such as smoking having similar distributions among DCIS survivors and women in the general population. Furthermore, the selected adverse cardiovascular events (heart failure, coronary heart disease, angina, heart attack and stroke) were derived from questions that were similar in description in the WISC and NHANES questionnaires to minimize misclassification.

6.3 Future Directions

In examining treatment trends, breast MRI utilization and cardiovascular health profile of women following DCIS diagnosis, study findings have provided some insight into areas for future work. Apart from demographic and geographic factors, patient-level factors such as patient’s preference including the presence of deleterious mutations are important in determining treatment choice. According to NCCN guidelines, genetic mutations such as *BRCA1/2* conferring a high risk of breast cancer are important considerations for contralateral risk reducing mastectomy. Hence, prospective studies assessing treatment utilization should incorporate data regarding patient's preference and deleterious genetic mutation status. Additionally, incorporating other markers such as mammographic density is important even as legislations are raising breast cancer risk awareness in relation to breast density. Over-diagnosis of DCIS is of concern with estimates suggesting that between 0-55% of DCIS tumors would not progress to invasive breast cancer [189-193]. Hence, prospective studies assessing the impact of treatment variation on cancer recurrence and progression to invasive cancer are needed.

Despite a greater likelihood of breast MRI use among DCIS survivors with ≥20% lifetime breast cancer risk, a limitation of breast MRI utilization studies is the lack of data on genetic mutations that confer high risk of breast cancer in line with ACS breast MRI criteria. Incorporating data on deleterious breast cancer mutations in future prospective studies, may provide insight on breast MRI use beyond lifetime breast cancer risk measures. Additionally, breast MRI is an expensive technology and despite its diagnostic advantage over mammography, breast MRI has no established survival advantage among women with a personal history of breast cancer. There is the need for prospective multicenter studies assessing breast cancer-specific and overall survival in relation to breast MRI use among DCIS survivors. These studies should assess other factors that may influence breast MRI use such as breast density among young women, who have an increased risk of second breast cancer events that may otherwise be difficult to detect on mammography. The positive association between socioeconomic status and mean travel time to breast MRI facilities also requires further investigation. Future studies should address breast MRI decision making among DCIS survivors and healthcare providers including the possibility of physician induced demand.

In comparing cardiovascular health status between DCIS survivors and women in the general population, DCIS survivors demonstrated a better cardiovascular health profile.

However, future population-based studies are required to determine cardiovascular disease risk according to DCIS diagnosis, in relation to the American Heart Association's cardiovascular metrics. Despite similarities in cardiovascular metrics, the prevalence of adverse cardiovascular events was observed to be substantially lower with tamoxifen use. Sample size limitations prevented further assessment of adverse cardiovascular events for other endocrine agents beyond tamoxifen or in combination. Results from studies assessing the cardiovascular effects of endocrine agents have been mixed [105, 194, 195], and do not account for modifiable cardiovascular risk factors such as smoking, BMI and physical activity. In proposing future studies among DCIS survivors examining the relationship between individual or combined adjuvant endocrine agents and cardiovascular disease development and mortality, consideration of modifiable cardiovascular risk factors should be a priority.

6.4 Implications and Conclusions

The findings reported in this dissertation have highlighted the extent of diffusion of evidence-based knowledge about the appropriate treatment of women following DCIS diagnosis. Variations observed in DCIS treatment and adjuvant therapy utilization according to age, ancestry/ethnicity and geographic region highlight possible differences in individual preferences and institutional patterns of care. The differences in DCIS treatment particularly in postmastectomy reconstruction and contralateral mastectomy utilization requires targeted effort at improving the harmonization of recommended treatment, with the hope of achieving optimized care. Expanded research effort is also needed in improving DCIS treatment decision making leading to appropriate treatment selection.

The low level of breast MRI utilization among DCIS survivors and the increased likelihood of breast MRI use among women with ≥20% lifetime breast cancer risk seems optimistic. However, about 90% of DCIS survivors undergoing breast MRI have a lifetime breast cancer risk <20%, which is of concern. The identification of a positive association between younger age (<50) at primary DCIS diagnosis and breast MRI use, may be explained by the increased risk of recurrence and breast cancer mortality among young women. Breast MRI compared to mammography may be more reliable in detecting second breast events among younger women with dense breast tissue. However, due to lack of information on breast density, its association with breast MRI was not assessed and would require further investigation. Increasing level of socioeconomic factors especially educational attainment and income positively impact preventive services utilization, and were associated with breast MRI use among women in the WISC. Furthermore, the potential travel burden experienced by non-metropolitan residents in accessing breast MRI highlights the unequal geographical distribution of breast MRI facilities. There is the need to develop and implement strategies ensuring equitable distribution of breast MRI facilities regardless of area of residence.

DCIS survivors in general had better cardiovascular metrics and a lower prevalence of adverse cardiovascular events compared to women in the general population. However, The low proportion of DCIS survivors with ideal levels of diet, total cholesterol and blood pressure demonstrate the need for these women to increase their adoption of modifiable health interventions. The observed similar prevalence of adverse cardiovascular events with or without adjuvant radiation therapy suggest that cardiac radiation exposure may be minimal in recent times, allaying fears relating to adjuvant radiation therapy use. Additionally, the absence of a statistically significant difference in the prevalence of adverse cardiovascular events with endocrine therapy in general and specifically with tamoxifen therapy suggests these agents may not impact cardiovascular disease prevalence.

Women diagnosed with DCIS are faced with complex treatment options and follow-up imaging surveillance choices aimed at preventing recurrence as well as early identification of second breast events. Adoption of healthy lifestyle interventions among DCIS survivors is important in lowering the risk of both breast cancer and cardiovascular disease. This dissertation contributes to the growing literature body on DCIS treatment and survivorship care, with results highlighting possible areas for further investigation.

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APPENDIX A
Breast Magnetic Resonance Imaging Assessment Section in Questionnaire

3. Did your most recent diagnosis occur within the last 4 years?

❑ No

❑ Yes ➡ 3a. How was your most recent carcinoma in situ, breast cancer or recurrence discovered?

❑ By you or your partner

❑ Routine screening or surveillance mammography

❑ Physician or other health care professional

❑ Unrelated medical procedure (x-ray for pneumonia, bone scan)

❑ Other. Please describe:____

3b. Was this detected in your left, right, or both breasts?

❑ Left only ❑ Right only ❑ Both

4. How many mammograms have you had within the past 4 years?

❑ None

❑ 1

❑ 2

❑ 3

❑ 4 or more

5. Have you had an MRI (magnetic resonance image) of your breasts within the past 4 years?

❑ No

❑ Yes ➡ 5a. How many have you had?

❑ 1

❑ 2

❑ 3

❑ 4 or more

APPENDIX B

Analytic Variables with Missing Data in the Wisconsin in Situ Cohort (2013)

Characteristic	N=1,103	Col %
Income		
≤ $100,000	788	71.4
> $100,000	175	15.9
Unknown	140	12.7
First degree family history of breast cancer		
No	825	74.8
Yes	228	20.7
Unknown	50	4.5
Tumor size, cm		
≤1	321	29.1
1-2	129	11.7
>2	85	7.7
Unknown	568	51.5
Tumor grade		
Well	180	16.3
Moderate	268	24.3
Poor/ Undifferentiated	291	26.4
Unknown	364	33.0
Mammography use in past 4 years		
None	59	5.4
1-4	917	83.1
>4	124	11.2
Unknown	3	0.3
Primary DCIS treatment		
Ipsilateral mastectomy	323	29.3
BCS		
With radiation	615	11.6
Without radiation	128	55.7
Other/Unknown	37	3.4

APPENDIX C

Cardiovascular Metric Assessment Section in Questionnaire

This section asks about HEALTH INFORMATION, PHYSICAL ACTIVITY and DIET.

29. How much physical activity do you get in a week? (You can include both moderate and vigorous activity levels. All types of activity count, such as gardening, walking briskly or bicycling.)

_____ minutes of moderate activity

A person doing moderate-intensity aerobic activity can usually talk, but not sing, during the activity. For example: walking briskly (3 miles per hour but not race-walking), water aerobics, bicycling slower than 10 miles per hour, tennis (doubles), ballroom dancing, general gardening, active-play video games.

_____ minutes of vigorous activity

A person doing vigorous-intensity activity usually cannot say more than a few words without pausing for a breath. For example: race-walking, jogging or running, swimming laps, tennis (singles), aerobic dancing, bicycling 10 miles per hour or faster, jumping rope, heavy gardening (continuous digging or hoeing, with heart rate increases), hiking uphill or with a heavy backpack.

30. How much fruit do you eat in an average day?
______ cups of fruit
Any fruit or 100% fruit juice counts as part of the fruit group. Fruits may be fresh, canned, frozen,
or dried, and may be whole, cut-up, or pureed. 1 cup serving of fruit is the same as:

1 large orange or banana	1 small wedge watermelon
1 small apple	1 large wedge cantaloupe
1 medium pear or grapefruit	2 large or 3 medium plums
8 large strawberries	½ cup raisins
15 grapes	

31. How many vegetables do you eat in an average day?
______ cups of vegetables
Any vegetable or 100% vegetable juice counts as a member of the vegetable group. Vegetables may be raw or cooked; fresh, frozen, canned, or dried/dehydrated; and may be whole, cut-up, or mashed. 1 cup serving of vegetables is the same as:

1 large bell pepper or ear of corn	1 medium potato or large sweet potato
1 cup cooked greens	2 cups raw greens (lettuce, spinach, etc.)
2 medium carrots or 12 baby carrots	2 large stalks of celery

32. Do you eat 2 servings or more of fish weekly? A serving of fish is 3.5 ounces, approximately the same size as a deck of cards.
❑ No ❑ Yes

33. Do you eat 3 ounces or more of whole grains daily? Whole grains include all whole grain products and whole grains used as ingredients.
❑ No ❑ Yes

34. Do you drink less than 36 ounces (450 calories) of beverages with added sugar weekly? Added sugars are the sugars and syrups added to foods and beverages in processing or preparation.

❑ No ❑ Yes

35. Do you eat 1,500 mg of sodium or less daily? If you don't track your daily sodium intake by reading the food label, to answer "Yes" you should do at least 2 of the following:

Avoid eating prepackaged processed food or eat low-sodium versions.
Avoid eating out or ask for low-sodium preparation.
Cook at home without adding salt.

❑ No ❑ Yes

36. Do you take medication to lower your blood pressure?

❑ No ❑ Yes

37. What is your systolic blood pressure? (Top or first number)

_____ mm Hg ❑ I don't know

38. What is your diastolic blood pressure? (Bottom or second number)

_____ mm Hg ❑ I don't know

39. Do you take medication to lower your cholesterol?

❑ No ❑ Yes

40. What is your blood cholesterol? (Total cholesterol)

_____ mg/dL ❑ I don't know this number

41. Do you take medicine to lower your blood sugar?

❑ No ❑ Yes

42. What is your blood sugar? (Fasting blood sugar)

33. _____ mg/dL ❑ I don't know this number

APPENDIX D

Select Demographic Characteristics According to Tamoxifen Use of Ductal Carcinoma in Situ Survivors in the Wisconsin in Situ Cohort (2015)

Variable	Tamoxifen Therapy		
	Yes n=422 (Col %)	No n=502 (Col %)	P value[a]
Age Group			0.01
40-59	60 (14.2)	75 (14.9)	
60-69	202 (47.9)	192 (38.3)	
≥70	160 (37.9)	235 (46.8)	
Insurance Status			0.80
Private	45 (10.7)	49 (9.8)	
Government	366 (86.7)	437 (87.1)	
Other	11 (2.6)	16 (9.9)	

[a]Derived from Pearson chi-square tests.

APPENDIX E

Demographic Characteristics of 1,014 DCIS survivors According to Missing Cardiovascular Metric (WISC, 2015)

Characteristic	Blood Pressure[a]			Fasting Plasma Glucose[a]			Total Cholesterol[a]		
	Known (n=304) N (%)	Missing (n=710) N (%)	P value[b]	Known (n=295) N (%)	Missing (n=719) N (%)	P value[b]	Known (n=375) N (%)	Missing (n=639) N (%)	P value[b]
Age Group, y			0.02			0.01			<0.01
40-59	98 (13.8)	41 (13.5)		40 (13.6)	99 (13.8)		52 (13.9)	87 (13.6)	
60-69	315 (44.4)	109 (35.9)		144 (48.8)	280 (38.9)		189 (50.4)	235 (36.8)	
≥70	297 (41.8)	154 (50.6)		111 (37.6)	340 (47.3)		134 (35.7)	317 (49.6)	
Education			<0.01			<0.01			<0.01
≤ High school degree	228 (32.1)	143 (47.1)		76 (25.8)	295 (41.0)		111 (29.6)	260 (40.7)	
Some college	218 (30.7)	63 (20.7)		97 (32.9)	184 (25.6)		108 (28.8)	173 (27.1)	
College or higher	264 (37.2)	98 (32.2)		122 (41.3)	240 (33.4)		134 (41.6)	206 (32.2)	
Income			<0.01			0.05			<0.01
< $15,000	32 (4.5)	25 (8.2)		9 (3.1)	48 (6.7)		12 (3.2)	45 (7.0)	
$15,000 - $100,000	245 (34.5)	111 (36.5)		100 (33.9)	256 (35.6)		120 (32.0)	236 (36.9)	
> $100,000	346 (48.7)	109 (35.9)		147 (49.8)	308 (42.8)		195 (52.0)	260 (40.7)	
Other/Unknown	87 (12.3)	59 (19.4)		39 (13.2)	107 (14.9)		48 (12.8)	98 (15.3)	

Abbreviation: DCIS, Ductal Carcinoma in Situ; WISC, Wisconsin in Situ Cohort.

[a]Cardiovascular metrics with >10% missing data.

[b]Derived from Pearson chi-square tests.

APPENDIX F

Cardiovascular Metrics Distribution Comparing Original and Imputed Data from 1,014 DCIS survivors (WISC, 2015)

Cardiovascular Health Metric	Original	Imputed	Prevalence Difference
	Prevalence (Col %)	Prevalence (Col %)	
Smoking Status	n=982	Imputed=32	
Ideal	92.9	94.0	1.1
Intermediate	2.3	1.2	1.1
Poor	4.8	4.8	0
Physical activity	n=927	Imputed=87	
Ideal	53.2	56.9	3.7
Intermediate	39	36.2	2.8
Poor	7.7	6.9	0.8
Body Mass Index (kg/m^2)	n=974	Imputed=40	
Ideal	37.2	36.9	0.3
Intermediate	31.2	30.9	0.3
Poor	31.6	32.2	0.6
Healthy Diet	n=935	Imputed=79	
Ideal	26.2	25.9	0.3
Intermediate	62.7	63.2	0.5
Poor	11.1	10.9	0.2
Total Serum Cholesterol	n=375	Imputed=639	
Ideal	20.0	25.5	5.5
Intermediate	73.3	64.2	9.1
Poor	6.7	10.3	3.6
Blood Pressure	n=710	Imputed=304	
Ideal	20.8	21.5	0.7
Intermediate	66.8	66.4	0.4
Poor	12.4	12.1	0.3
Fasting Blood Glucose	n=295	Imputed=719	
Ideal	45.7	46.6	0.9
Intermediate	44.1	40.0	4.1
Poor	10.2	13.5	3.3

Abbreviation: DCIS, Ductal Carcinoma in Situ; WISC, Wisconsin in Situ Cohort.