FACTORS CONTRIBUTING TO DISPARITIES IN EARLY BREAST CANCER TREATMENT

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ABSTRACT OF THE DISSERTATION

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by

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Specific Aims: This dissertation was conducted to examine the following specific aims among early breast cancer patients: 1) Racial differences in the use of pre-operative magnetic resonance imaging (MRI) and the role of pre-operative MRI on rates of re-operation and contralateral prophylactic mastectomy (CPM), and time to surgery; 2) Racial differences in elapsed time and sessions received during radiation therapy; and 3) Racial differences in chemotherapy dose modifications and role of neutropenia in this association.

Design, setting and subjects: Subjects were selected from the Breast Cancer Treatment Disparity Study which is an ongoing cohort study of African American (AA) and white subjects residing in eastern New Jersey who were newly diagnosed with early breast cancer between 2005 and 2010. Data were collected through a detailed review of medical records obtained from multiple health care providers of these participants.

Results: A significantly higher use of pre-operative MRI among whites versus AAs (58.3% vs. 39.7%, $p< 0.01$) was seen in the first study. Receipt of pre-operative MRI was associated with a non-significant lower rate of re-operation (RR= 0.76; 95% confidence interval [CI]: 0.54, 1.07), but a significantly higher rate of CPM (RR= 1.75; 95% CI: 1.04, 2.92) and a longer time to surgery (geometric mean= 40.5 days versus 27.6 days, $p< 0.01$). The second study revealed no differences between AA and white women in elapsed time and sessions received during standard radiation therapy following lumpectomy (median elapsed time= 48 days, % subjects with >49 days elapsed time= 36%, and mean sessions= 33, for both racial groups). In the third study, a significantly lower relative dose intensity (RDI) was delivered to AA subjects than white subjects (94.4% versus 100.0%, $p= 0.005$) during chemotherapy and the risk of >15% reduction in RDI was more than double (RR= 2.62; 95% CI: 1.40, 4.89) in AA women as compared to white women. White blood cell counts at initiation of chemotherapy and in subsequent cycles were similar between the races and were unable to account for differences in dose intensity between the two groups. Conclusion: The rapid rise in use of pre-operative MRI is a concern as no benefit of its use was observed in this study. We also conclude that once treatment is initiated AA women and white women were very similar in receipt of care delivered during radiation. However, this did not hold true for chemotherapy. AA women in comparison to white women were at more than two-fold risk of experiencing dose modifications during chemotherapy that was not explained by differences in their blood counts.

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true. My son Shray, who was born while working on my dissertation, has made this experience a lot more joyous and worthwhile.

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INTRODUCTION

Breast cancer epidemiology

Breast cancer is the most common type of cancer and the second leading cause of cancer death among women, accounting for 29% of cancer diagnoses and 14% of cancer deaths in the US women.[1] The American Cancer Society (ACS) estimated that among women, in 2012, approximately, 226,870 new cases of invasive breast cancer will be diagnosed and 39,510 deaths from breast cancer will occur.[1] On the basis of incidence and death rates from 2007-2009, the chance that a woman will develop breast cancer sometime during her lifetime is about 12.4% (i.e., 1 in 8 women), and the lifetime risk of dying from breast cancer is about 2.8% (i.e., 1 in 36 women).[2]

Female breast cancer rates have generally increased for incidence and decreased for mortality but have gone through periods of varying trends since 1975. The incidence stayed constant from 1975 to 1980 and then increased steeply by 4.0% per year from 1980 to 1987.[2] This rapid increase in incidence between 1980 and 1987 was largely due to increased detection of breast cancer through screening mammography and its ability to detect smaller size tumors.[3] This has resulted in a "stage-shift" towards detecting more early stage tumors and has also increased the sensitivity of detecting breast cancer among older women.[4,5] From 1987 to 1994 the incidence of female breast cancer remained relatively stable and then again increased by 1.7% per year from 1994 to 1999.[2] This slower increase in incidence during the second half of 1990s could be attributed to increase in mammography screening, increase in obesity rates and increased use of menopausal hormones.[3] Thereafter, a

period of sharp decline in incidence rate happened between 1999 and 2005 at the rate of 2.1% per year.[2] The decline occurred mostly between 2002 and 2003 and was more pronounced for white women, for ages 50 to 69, and for ER positive tumors.[6,7] This decline has been attributed to reduction in the use of hormone replacement therapy (HRT) after the results of Women's Health Initiative Study came out in 2002.[8,9] The incidence rates have again been constant between 2005 and 2009.[2] The decrease in use of HRT hasn't been large enough between 2005 and 2008, which may explain this recent stabilization of breast cancer incidence rates.[10] Other reasons may include improvement in sensitivity of mammography with reduced HRT use and stable rates of screening mammography since the year 2000.[11,12]

Mortality rates from breast cancer increased by 0.4% annually from 1975 to 1990 and then decreased annually by: 1.8% from 1990 to 1995, 3.2% from 1995 to 1998 and 1.9% from 1998 to 2009.[2] The decline in mortality from 1990 to 2007 has however been higher for women who were less than 50 years of age at diagnosis as compared to women who were 50 years or older at diagnosis.[2] Both improved methods of treatment and early detection have contributed to this decline in mortality.[13]

Breast cancer epidemiology by race

Trends in incidence and mortality of female breast cancer mask important racial differences that exist between African American (AA) and white women. Over the past three decades, age-adjusted breast cancer incidence rates have generally been 10% to 20% higher among whites as compared to AAs.[14] Among whites, incidence rate did not

change from 1975 to 1980, but then went through a period of sharp increase of 4.0% per year from 1980 to 1987.[2] Therefore, the rapid increase seen in overall incidence during this period was primarily occurring among white women in the US and is believed to be due to a significant increase in mammography uptake. From 1987 to 1994, the incidence again remained constant among whites, followed by an increase of 1.9% per year from 1994 to 1999.[2] Thereafter, incidence decreased by 2.3% per year from 1999 to 2004[2], primarily due to a significant reduction in the use of HRT among white women.[8,9]

Breast cancer incidence among AAs has followed a different trend as compared to whites. The incidence increased by 3.3% per year from 1978 to 1988 and then by 0.3% per year from 1992 to 2008 among AAs.[2] This stabilization of incidence among AAs could be attributed to decreased mammography screening rates and to reduced use of HRT.[15] The trends in incidence between the two racial groups however, reveal a different pattern by age at diagnosis and stage of disease. Under the age of 40 years, age-specific breast cancer incidence rates are higher for AA women as compared to whites; but after the age of 40, the rate is higher among white women than the AAs.[14] AA women are also more likely than white women to be diagnosed with large tumors and distant stage disease.[16]

Death rates from breast cancer were comparable between AAs and whites during 1970s. The trend between the two races started to diverge and disparity began widening in the early 1980s resulting in a higher mortality rate among AAs than among whites at all ages.[14] From 1975 to 1990 the age-adjusted death rate from breast cancer

increased by 0.3% per year among white women.[2] An increase in death rate also occurred among AAs during 1975 to 1992, but it was at a much higher rate of 1.5% per year.[2] Since early 1990s there has been a remarkable reduction in breast cancer mortality among both AAs and whites, but the decline is smaller among AA women as compared to white women. Among white females, the age-adjusted death rates declined by: 2.0% from 1990 to 1995, 3.4% from 1995 to 1998 and 2.0% from 1998 to 2009.[2] The decline in AA females has however been slower, i.e., at a rate of 1.4% from 1992 to 2009.[2] A later stage at diagnosis and poorer stage-specific survival among AA women with breast cancer are the possible reasons explaining this disparity in mortality between the two races.[15]

The reasons for these racial differences are myriad and yet none on its own can fully explain why there is such a difference between the two races. Possible predictors that have been associated with poor survival among AA women include biologic differences in the nature of the tumor, later stage at diagnosis, lower screening and poor access to health care, socio-economic differences, co-morbidities and disparity in receipt of treatment. [15,17-22]

Treatment of Breast Cancer

Through most of the 20th century, breast cancer was considered a local-regional disease. In the past 20 years, there has been a paradigm shift recognizing that breast cancer is a systemic disease which has changed the approach to its treatment.[23,24] Management of early breast cancer includes the treatment of local disease with surgery,

radiation therapy, or both; and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combination of these.[25] Clinical factors that influence treatment selection include age, menopausal status, comorbidities, clinical characteristics of the tumor, axillary lymph node status, hormone receptor status, and presence of metastatic disease.[25]

Pre-operative work-up and staging

Mammography and ultrasonography are standard imaging modalities used in routine clinical practice for diagnostic evaluation of positive breast cancer findings.[25] However, women who are newly diagnosed with breast cancer are at risk of harboring additional occult, ipsilateral or contralateral breast cancer that is undetected by mammography and ultrasonography. Additional occult foci of cancer have been seen in about 21% to 63% of affected breasts among newly diagnosed breast cancer patients who are originally felt to have a single and resectable tumor on clinical examination and conventional imaging.[26-30]

Magnetic resonance imaging (MRI) uses magnetic fields to produce detailed cross-sectional images of the body. The use of contrast enhanced material increases the sensitivity of MRI for detecting breast cancer in high-risk asymptomatic and symptomatic women.[31-34] A recent meta-analysis reported that MRI detected additional multifocal and multicentric disease in the affected breast that were not identified through conventional imaging in 16% women with breast cancer.[35] Factors such as tumor size, extent, location, grade, histology, and patient preference are considered when planning

the surgical management of suspected or biopsy proven breast cancer.[25] Based on these factors a choice is made between either a breast conserving surgery (BCS) or mastectomy. The advantage of high resolution imaging with MRI allows for a more accurate staging of disease. This is particularly important for patients who are being considered for BCS. For example, presence of multifocal or multicentric disease detected through MRI may change a course of surgical treatment from BCS to mastectomy; and presence of additional cancer foci in the opposing breast may result in contralateral mastectomy as well. Houssami *et al.* reported that pre-operative MRI resulted in alteration in surgical management in 7.8% to 33.3% of patients among women with proven or suspected breast cancer.[35] As a result there has been a recent increase in the use of MRI in pre-operative evaluation to identify synchronous cancers, multifocality and multicentricity, and contralateral disease.[36-39]

Recent ACS guidelines recommend MRI use only for screening women at high risk of breast cancer which includes women with a BRCA gene mutation, first degree relative of BRCA carrier, or a lifetime risk of ≥ 20% based on family history.[40] Lack of data from randomized controlled trials examining the impact of MRI on survival among breast cancer patients has limited its recommendation only for screening high risk patients. No guidelines have yet been established for use of MRI in the pre-operative setting or for surveillance of patients. Additional limitations associated with pre-operative MRI use include high false-positive rate and no reduction in recurrence rate.[35,37,41-43] The steep rise in adoption of MRI is therefore based on the assumption that its superior detection capability will reduce re-operation rates. However, only a few

studies have examined its impact on re-operation and have reported inconsistent results. Some have showed an advantage; whereas, most studies failed to show a benefit.[37,44-49] Other concerns associated with its use include overtreatment resulting from unnecessary surgeries and delay in receipt of definitive breast surgery resulting from the time taken to investigate MRI findings.[36,50-52] Particularly interesting is the recent albeit insufficient evidence suggesting a higher risk of contralateral prophylactic mastectomy (CPM) among patients receiving pre-operative MRI.

The first study in this dissertation examined the impact of pre-operative MRI on surgical outcomes of breast cancer. We specifically looked at the existence of racial difference in the use of pre-operative MRI and also examined the association between pre-operative MRI and re-operation, CPM, and time to surgery. Only recently, Sommer *et al.* reported that AAs were 25% less likely to receive a pre-operative MRI as compared to whites using the Surveillance Epidemiology and End Results-Medicare linked data.[39]

Breast conserving surgery plus radiation therapy

Randomized trials have established that for most women with early breast cancer, BCS with radiation therapy is an attractive alternative to mastectomy.[53-58] BCS is recommended as the preferable surgical treatment due to equivalent survival benefits along with preservation of breast tissue and potentially an improved quality of life in comparison to mastectomy.[59] However, there are marked racial/ethnic variations in the

use of BCS plus radiation therapy in the US and several studies have reported that AAs are less likely than whites to receive BCS.[60-63]

Radiation therapy is an integral part of BCS and has been recommended as an appropriate treatment for early-stage breast cancer.[64] Omission of radiation therapy after BCS is associated with increased risk of recurrence and mortality.[56,65] Women who underwent BCS and who did not receive radiation therapy have local recurrence rates of about 35% after 5 years.[56] Significant racial differences have also been reported on the receipt of radiation therapy following BCS. AA women who undergo BCS are less likely than white women to receive radiation therapy.[66-71]

Radiation therapy that follows BCS typically involves daily treatments (weekends excluded), for a period of 5 to 6 consecutive weeks.[25] The lengthy schedule of radiation therapy can be burdensome and pose practical challenges for some women. This can cause either early discontinuation of radiation therapy or gaps during therapy resulting in prolongation of treatment time. Incomplete radiation treatment defined as receiving less than the standard 25 sessions has been significantly associated with increased 3 year and 5 year hazard of breast cancer recurrence.[72] Non completion rates of 13% to 22% have been reported during radiation therapy with a higher likelihood of non-completion seen among AA women.[72,73]

The impact of prolongation of treatment time during radiation on the local failure rate has been studied extensively in a variety of tumors including, cancers of head and neck region, cervix and lung. [74-82] A median reduction of 14% in local control rate

resulting from one week of prolongation has been established for head and neck cancers.[82] In breast cancer patients, only one study has examined the impact of elapsed time on patient outcomes. Bese at al showed a reduction of 5% in 5-year local control rate attributed to greater than one week prolongation during radiation therapy in stage I to III breast cancer patients.[83,84] Additionally, only one study to date examined racial differences in elapsed time during radiation and it failed to show any differences between AA and white women.[85]

We therefore conducted the second study in this dissertation to investigate if racial differences exist in elapsed time and sessions received during radiation therapy. We hypothesized that AA women are more likely to experience a longer time in completing radiation therapy as compared to white women. We also investigated predictors of elapsed time and sessions received.

Adjuvant chemotherapy

In most patients of standard treatment does not stop with surgery. Though surgery may remove detectable early stage breast cancer, polychemotherapy as well as adjuvant hormonal therapy when indicated can remove undetected metastatic deposits that remain in the body.[86,87] Chemotherapy has been associated with a significant reduction in the odds of annual recurrence and death from breast cancer.[86,87] Although use of such therapies seems to be improving overall[20,88], their underuse still remains a problem among minority women[22,89]. Bickell *et al.* found that underuse rate of

appropriate adjuvant therapy was 34% among AA women as compared to 16% among white women.[22]

Patients receiving cytotoxic chemotherapy are at a high risk of being neutropenic due to its impaired effect on the hematopoietic system. This population is in fact more vulnerable to develop neutropenia of longer durations (i.e., > 1 week) along with serious infections.[90] Failure to return neutrophil count to a normal level during chemotherapy may result in dose alterations such as delay in starting chemotherapy cycles or reduction in chemotherapy dose levels.[91-93] Neutropenia therefore has been identified as a major dose-limiting toxicity of chemotherapy.

In the past decade, large clinical trials have provided some data showing that dose modifications during chemotherapy can reduce the benefit of survival and recurrence associated with chemotherapy.[94-96] Furthermore, studies suggest that chemotherapy use and dose intensity may differ between races and, in turn, contribute to differences in outcome.[89,97-101] AA women are offered chemotherapy at similar rates as white women but are more likely to have up-front dose reductions and to receive lower dose intensity once treatment is initiated.[98,101] It is also known that AA women exhibit a lower white blood cell (WBC) and acute neutrophil count (ANC) levels than their white counterparts (referred to as ethnic neutropenia).[102,103] However, it is unclear whether chemotherapy dose modification is more prevalent among AA than whites and if this difference is related to the lower WBC and ANC level of AAs at presentation.[98,101]

The third study in this dissertation therefore investigated racial differences in chemotherapy dose modifications and role of neutropenia in explaining this difference.

Organization of the thesis

The overall objective of this dissertation was to examine factors that contribute to racial differences in the treatment of early stage breast cancer. The first chapter compares the utilization of pre-operative MRI by race and evaluates the role of pre-operative MRI in the surgical management of early stage breast cancer. The next two chapters focus on race related disparities when patients undergo radiation therapy and chemotherapy for their breast cancer. Specific aims of the three chapters in this dissertation are as follows:

Manuscript 1:

1. Examine racial differences in the use of pre-operative MRI
2. Examine the role of pre-operative MRI on i) re-operation, ii) contralateral prophylactic mastectomy and iii) time to surgery

Manuscript 2:

1. Examine racial differences in elapsed time and mean number of sessions received between initiation and completion of radiation therapy
2. Identify socio-demographic and clinical predictors of prolonged elapsed time and sessions received during standard course of radiation therapy

Manuscript 3:

1. Examine racial differences in chemotherapy dose modifications and the role of neutropenia in chemotherapy dose modifications.

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THE ROLE OF PRE-OPERATIVE MRI IN THE MANAGEMENT OF EARLY STAGE BREAST CANCER

by

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ABSTRACT OF MANUSCRIPT 1 OF 3

THE ROLE OF PRE-OPERATIVE MAGNETIC RESONANCE IMGING IN THE MANAGEMENT OF EARLY STAGE BREAST CANCER

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ABSTRACT

Background and rationale: There are no evidence-based recommendations on the use of pre-operative magnetic resonance imaging (MRI) in management of early stage breast cancer. We examined the use of MRI by race in routine pre-operative work-up of early stage breast cancer patients. We also examined the role of pre-operative MRI on the rates of re-operation and contralateral prophylactic mastectomy (CPM), and time to surgery using a population-based study of New Jersey early stage breast cancer patients.

Methods: African American (AA) and white subjects who participated in the Breast Cancer Treatment Disparity Study and underwent breast surgery for newly diagnosed early stage breast cancer were studied. Re-operation was defined as re-excision following initial lumpectomy or mastectomy, or mastectomy following initial lumpectomy. CPM was defined as removal of the unaffected breast along with the affected breast. Time to surgery was calculated as number of days from diagnosis to initial surgery. Associations of pre-operative MRI with re-operation and CPM were examined using binomial regression models and with time to surgery using linear regression model.

Results: A total of 606 breast cancer patients were studied. Almost half of the study population (49.5%) received pre-operative MRI. Use of pre-operative MRI was more frequent among whites than AAs (58.3% vs. 39.7%, *p< 0.01*). Re-operation rates were similar between patients with (17.7%) and without (19.9%) pre-operative MRI (p>0.05). In contrast, rate of CPM was significantly higher in those with (15.7%) pre-operative MRI than those without (5.9%), p<0.001. After adjusting for potential confounders, receipt of pre-operative MRI was associated with a non-significant lower rate of re-operation (RR= 0.76; 95% confidence interval [CI]: 0.54, 1.07) and a significantly higher rate of CPM (RR= 1.75; 95% CI: 1.04, 2.92). Furthermore, patients with pre-operative MRI were more likely (geometric mean= 40.5 days; 95% CI: 37.0, 44.4) to experience a longer time from diagnosis to initial surgery than those without pre-operative MRI (geometric mean= 27.6 days; 95% CI: 25.5, 30.0).

Conclusions: Although whites in comparison to AAs were more likely to undergo pre-operative MRI, it did not affect the rate of re-operation; but was associated with a significantly higher rate of CPM and increased time to surgery. Physicians and patients should consider these findings when making decision on the use of pre-operative MRI.

THE ROLE OF PRE-OPERATIVE MAGNETIC RESONANCE IMGING IN THE MANAGEMENT OF EARLY STAGE BREAST CANCER

Introduction

Current guidelines recommend the use of bilateral mammography as the primary modality and breast ultrasonography if necessary to determine tumor extent pre-operatively and plan surgical treatment of early stage breast cancer.[1] There are however, no evidence-based recommendations on the use of magnetic resonance imaging (MRI) in the pre-operative setting. Despite the lack of evidence, use of pre-operative MRI has significantly increased in the past decade.[2-5] This is because MRI is a highly sensitive modality in detecting clinically occult breast tumors and in characterizing the extent of the disease.[6] Results from two meta-analyses have shown that MRI detected additional disease in the affected and contralateral breast that were not identified on conventional imaging in 16% and 9.3% of women with breast cancer, respectively.[6,7]

It is assumed that increased detection capability of MRI will result in wider excision and removal of additional disease, which will in turn lead to fewer positive margins and repeat operations.[8] On the other hand, its low specificity may have adverse consequences such as increase in contralateral prophylactic mastectomy (CPM) and increase in time to surgery without substantial benefit. The few studies that have examined the impact of pre-operative MRI on re-operation report inconsistent

results.[3,9-14] Similarly research that has investigated the role of pre-operative MRI on CPM rates and time to surgery is limited and is inconsistent in its findings.[2,15-19]

The growing use of MRI has been controversial because of the absence of data showing a survival advantage. MRI is more expensive than a mammogram and the additional procedures required to evaluate MRI findings also raise concerns about the costs associated with it.[20] The evidence available so far is insufficient to determine whether MRI should be included in the routine pre-operative work-up of patients with early stage breast cancer. We therefore conducted a population-based study to examine racial differences in the use of pre-operative MRI and to investigate the role of pre-operative MRI on i) re-operation, ii) CPM and iii) time to surgery.

Materials and Methods

Population based subject recruitment

Subjects who participated in the Women's Circle of Health Study (WCHS) and in the Breast Cancer Treatment Disparity Study (BCTDS) were included in the study. The WCHS is an ongoing multi-site case-control study of African American (AA) and white women conducted in New Jersey (NJ) and New York (NY). The general methodology of subject recruitment for the WCHS has been reported elsewhere.[21] The BCTDS is a matched retrospective cohort study that included only invasive breast cancer cases from the WCHS in NJ. Newly diagnosed histologically confirmed cases of invasive breast cancer with no prior history of cancer other than non-melanoma skin cancer were identified from all the major hospitals in seven counties of NJ (Bergen, Essex, Hudson, Mercer, Middlesex, Passaic, and Union) through rapid case ascertainment by the New Jersey State Cancer Registry staff.

All AA women who were 20 to 85 years of age and diagnosed with stage I, II, and $T_3N_1M_0$ breast cancer between 2005 and 2010 were included in the BCTDS. For each AA woman with breast cancer, a white woman within ± 5 years of age and who resided in the same county was randomly selected from the pool of potential white breast cancer patients. Cases that were ≤ 75 years of age and agreed to be contacted were then telephoned by WCHS research staff to schedule an in-person interview at home. During the home interview, trained WCHS interviewers administered questionnaires and collected body measurements and a saliva sample from each participant. At the end of the interview, they invited WCHS cases to participate in another study that examines

breast cancer treatment disparities (BCTDS). Women who were older than 75 years of age were not recruited in the WCHS study and were directly contacted by BCTDS staff to request their participation. A total of 626 cases agreed to participate and were included in the BCTDS (white= 329 and AA= 297). Subjects who did not undergo any breast excision after diagnosis were excluded from this analysis.

The study was approved by the institutional review boards at the University of Medicine and Dentistry of New Jersey and at the NJ State Department of Health and Senior Services.

Data collection

The participating subjects gave consent for the release of their medical records and also provided a list of the names and addresses of health care providers who were involved in their breast cancer care. These included the primary care physician, surgical oncologist, medical oncologist, radiation oncologist and the hospital where the surgery was performed. The providers were contacted to obtain records on initial diagnostic information, pathology reports, and detailed operative and adjuvant treatment reports. As most of the adjuvant treatment is provided in an outpatient setting, outpatient records were obtained from one year prior through one year after the initial diagnosis of breast cancer from each subject's health care provider. Trained personnel abstracted the medical records to collect information on patient socio-demographics, family history, clinical presentation of cancer, pre-operative investigations, surgical treatment, tumor characteristics, and adjuvant treatment. Information on selected

characteristics including race, education, and measured height and weight was obtained from the in-person interview conducted with the subjects during their participation in the WCHS which was also verified from medical records.

Study outcomes

In all cases the cancer was pathologically confirmed either by percutaneous biopsy (includes fine needle aspiration biopsy, core needle biopsy or vacuum-assisted biopsy) or surgical biopsy (includes excisional biopsy). Resection of breast tissue performed after the pathologic diagnosis of cancer was defined as the initial surgery and consisted of either lumpectomy or mastectomy. Re-operation was defined as at least one repeat breast operation done after initial surgery and included either a re-excision following initial lumpectomy or mastectomy, or mastectomy following initial lumpectomy. CPM was defined as removal of the unaffected breast at the same time with the affected breast. Time to surgery was calculated as the time interval in days from pathologic diagnosis of cancer to initial surgery. Subjects who received neo-adjuvant chemotherapy were excluded from the analysis of time to surgery.

Pre-operative MRI

Pre-operative MRI was defined differently for each of the study outcomes. To examine re-operation, MRI done before the initial surgery was considered pre-operative. To examine time from diagnosis to initial surgery, MRI done between diagnosis and

initial surgery was defined as pre-operative. To examine CPM, MRI administered any time before CPM or the final surgery was considered pre-operative.

Socio-demographic characteristics

Age at diagnosis was categorized into 10-year intervals including: <45 years, 45 to 54 years, 55 to 64 years, or older than 65 years. Education level was divided into less than college graduate or college graduate and above. Health coverage by a private insurance or non-private insurance (including, Medicaid, Medicare, and uninsured or self-pay) was determined. Body mass index was calculated in kg/m^2 and was categorized into underweight or normal (< 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), or obese (≥ 30.0 kg/m^2) using the Centers for Disease Control and Prevention classification system.

Pre-operative investigations and tumor characteristics

Family history of breast cancer was determined for each subject. It included both first degree and second degree relatives. Method of presentation that led to cancer suspicion was broadly classified into patient finding (including breast self-exam or skin changes), physician finding, or screening mammogram. Investigations done pre-operatively including mammogram, ultrasound, MRI, genotype testing, and method of diagnosis (percutaneous biopsy or surgical biopsy) were examined. Findings from the mammogram were summarized using the Breast Imaging Reporting and Data System (BIRADS) that classifies breast lesions into a category from 0 to 6 (0= incomplete, 1=

negative, 2= benign, 3= probably benign, 4= suspicious abnormality, 5= highly suspicious of malignancy, or 6= known biopsy proven malignancy). Some pre-operative tumor characteristics were determined from the biopsy results including, grade (well, moderately, or poorly differentiated), histology (infiltrating ductal carcinoma, infiltrating lobular carcinoma, other invasive carcinoma, or in-situ carcinoma) and presence of multifocality and/or multicentricity

Post-operative tumor characteristics

Tumor characteristics determined from the surgical pathology report were defined as post-operative characteristics. These included: initial surgery (lumpectomy or mastectomy), grade (well, moderately, or poorly differentiated), histology (invasive ductal carcinoma, invasive lobular carcinoma, or other invasive), size (≤1.0cm or >1.0cm), lymph node status (negative or positive), and multifocality and/or multicentricity (yes or no). Margin status at initial surgery was categorized into positive, negative, or close (defined as ≤ 1mm). The facility where breast surgery was received was classified into an accreditation category established by the American College of Surgeons. The categories included teaching hospital cancer program, NCI-designated comprehensive cancer program, community hospital cancer program and community hospital comprehensive cancer program. Facilities which were not identified in the database were categorized into a separate group as “other”.

Statistical analysis

Socio-demographics, pre-operative and post-operative clinical characteristics of the study subjects who received and did not receive a pre-operative MRI before initial surgery were summarized. Re-operation rate, CPM rate and time to surgery were compared by receipt of pre-operative MRI. Study outcomes were also compared within different levels of subject characteristics. Re-operation and CPM rates were reported as percentages and time to surgery was reported as geometric mean with 95% confidence interval (CI) due to its positively skewed distribution. Differences in the distribution of categorical and continuous variables were examined using chi-square test and analysis of variance, respectively.

Separate univariate and multivariate binomial regression models were utilized to examine the unadjusted and adjusted association between pre-operative MRI and re-operation and CPM. The multivariate model for re-operation was adjusted for age, race, education, insurance, body mass index, method of diagnosis, multifocality/multicentricity, and type of surgical facility. The multivariate model for CPM was adjusted for age, race, education, body mass index, family history of breast cancer, genotype testing, clinical presentation, and type of surgical facility. The associations were expressed using relative risk (RR) estimates with their corresponding 95% CI. Nonlinear programming (NLP) procedure in SAS was used to estimate the RR. Two additional sensitivity analyses were done. First, we examined the association between re-operation and pre-operative MRI separately among subjects where the cancer was diagnosed by percutaneous biopsy (excluded subjects diagnosed by surgical biopsy).

Second, the association between MRI administered any time before initial surgery was also examined with CPM.

Linear regression model using the general linear model (GLM) procedure in SAS was used to estimate geometric mean with 95% CI for time to surgery by pre-operative MRI after adjusting for age, race, education, insurance and type of initial surgery. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Use of pre-operative MRI

A total of 606 breast cancer subjects were included in the study. Of these, 49.5% (300/606) received pre-operative MRI before the initial surgery. As shown in Table 1, subjects receiving pre-operative MRI were more likely than those without, to be young, of white race, more educated, covered by private health insurance and normal in weight. Table 2 summarizes the pre-operative investigations and clinical characteristics of the study population. MRI was more commonly done among subjects who had a family history of breast cancer and had their cancer discovered by themselves or their physician rather than by mammography. Subjects with pre-operative MRI more commonly underwent diagnostic ultrasound and genotype testing and also were more frequently diagnosed by percutaneous biopsy versus surgical biopsy. No differences were seen in the receipt of diagnostic mammogram or in pre-operative tumor grade, histology and presence of multifocality and/or multicentricity between the two MRI groups. Post-operative tumor characteristics showed no differences in distributions of tumor grade and histology, tumor size and surgical margins by receipt of MRI (Table 3). On the other hand, MRI subjects more commonly had a positive lymph node and a multifocal and/or multicentric cancer detected on initial surgery. Use of pre-operative MRI did not vary by the facility type where the initial surgery was performed.

Study outcomes

Overall 18.8% (114/606) and 10.7% (65/606) subjects underwent re-operation and CPM, respectively (Table 4). No difference in the rate of re-operation was observed between MRI+ and MRI– groups (17.7% and 19.9%, respectively; p=0.4751). When subjects who had their cancer diagnosed through excisional biopsy were excluded, a lower rate of re-operation was seen for MRI+ group (18.8%) as compared to 24.6% for MRI– group, but the difference did not reach statistical significance. A significantly higher rate of CPM was observed for subjects receiving MRI before the final surgery in comparison to no MRI group (15.7% and 5.9%, respectively; p<0.0001). The rates of CPM did not change much when the alternate definition of pre-operative MRI was used (before the initial surgery). Geometric mean time from diagnosis to initial surgery was 36.6 days (95% CI: 33.9, 39.5) and 26.0 days (95% CI: 24.3, 27.8) for MRI+ and MRI– groups, respectively (p<0.0001).

Rates of re-operation and CPM, and time to surgery for different subject characteristics have been included in Table 5. Re-operation rates were significantly higher for subjects who had a higher body mass index, were diagnosed by percutaneous biopsy, had invasive histology other than ductal or lobular carcinoma, had positive or close margins on initial surgery, and received surgery in a community hospital. On the other hand, rates of CPM were significantly higher among subjects with younger age, white race, higher education level, private health insurance, lower body mass index, family history of breast cancer, patient finding the cancer, genotype testing, and multifocal and/or multicentric tumor. Time from diagnosis to initial surgery

was significantly longer for AA subjects and for those undergoing mastectomy as their initial surgery.

Table 6 provides unadjusted and adjusted estimates for the association between pre-operative MRI and study outcomes. Receipt of pre-operative MRI was not significantly associated with a reduction in re-operation rate, either in the unadjusted (RR= 0.89; 95% CI: 0.64, 1.23) or adjusted (RR= 0.76; 95% CI: 0.54, 1.07) models. Subjects receiving MRI before the final definite surgery had a substantially increased risk of undergoing CPM (RR = 2.90; 95% CI: 1.69, 4.99) of undergoing CPM. After adjusting for age, race, education, body mass index, family history, genotype testing, clinical presentation, and type of surgical facility the risk of undergoing CPM remained significantly elevated for the pre-operative MRI group (RR= 1.75; 95% CI: 1.04, 2.92). Results from the adjusted linear regression model showed that subjects who received a pre-operative MRI experienced a significantly longer time from diagnosis to initial surgery (geometric mean= 40.5 days; 95% CI: 37.0, 44.4) as compared to subjects who did not receive pre-operative MRI (geometric mean= 27.6 days; 95% CI: 25.5, 30.0). The results did not change much for the two sensitivity analyses models.

Discussion

In this study we examined the association of pre-operative MRI with re-operation, CPM and time to surgery among early stage breast cancer patients. Almost half of the study population received MRI during pre-operative evaluation and 18.8% and 10.7% underwent re-operation and CPM, respectively. No difference in re-operation rate was observed between subjects who received and did not receive pre-operative MRI whereas, after adjustment for confounders pre-operative MRI was associated with a 75% increased risk of CPM. MRI subjects also experienced a significantly longer delay from the time of diagnosis to receipt of initial breast surgery.

Use of MRI for pre-operative staging has gained worldwide popularity in planning surgical treatment of breast cancer primarily due to its proven superior accuracy in detecting additional disease in comparison to conventional imaging. However, it is argued that the additional cancers detected by MRI are prognostically irrelevant and may be sufficiently treated with adjuvant radiation and systemic therapy. There is no data available showing survival advantage associated with pre-operative MRI, which has added to the existing ambiguity. Additionally, a few studies that have examined its impact on decreasing breast cancer recurrence have failed to show any benefits.[3,22]

It is important to understand how surgical management of breast cancer patients is affected by use of MRI, given that no recommendations are established for its use in the pre-operative setting. The steep rise in the use of MRI seen in the past decade has been based on the assumption that its high sensitivity will reduce re-excision rates. If true, this can reduce both the cost and patient anxiety associated with repeat

operations. However, this assumption is not supported by most of the emerging data. Few single institution cohort studies examined differences in the re-excision rate by receipt of pre-operative MRI. The majority of them reported no differences in re-excision rates[3,9,10,12], although Mann et al reported a significantly lower rate of re-excision for the MRI+ group (9%) than for the no MRI group (27%).[11] Two recent European randomized trials evaluated the efficacy of pre-operative MRI among breast cancer patients. One of them reported that MRI was not significantly associated with a reduction in re-excision or mastectomy within 6 months of randomization (OR= 0.96; 95% CI: 0.75 to 1.24).[14] The second trial on the other hand, found a significant increase in re-excisions after BCS in the MRI group (34%) versus the control group (12%).[13] Rate of re-operation seen in our study is similar to these pre-existing reports and concurs with most of the available evidence that there is no benefit of pre-operative MRI on re-operation rates.

Furthermore, data have also suggested that pre-operative MRI may lead to overtreatment in the form of wider excisions and more mastectomies that may be unnecessary[2,4,6,12] Of particular interest is the recent rise in CPM rates in the United States that has been associated with MRI use. In their analysis using the Surveillance, Epidemiology and End Results (SEER) database Tuttle et al reported an increase in CPM rate from 1.8% in 1998 to 4.5% in 2003 among all surgically treated stage I, II and III breast cancer patients.[23] CPM rate of 10.7% seen in our study is higher as compared to the population-based numbers reported from SEER analysis.[23] However, some recent single institution based studies have reported CPM rates ranging between 5.3%

and 28.9%.[15-18] CPM is considered beneficial for patients who are at a high risk of developing bilateral breast cancer which includes subjects with young age at diagnosis, family history of breast cancer, lobular histology, multicentricity, previous radiation exposure, and *BRCA* gene mutation.[24-28] However, the majority of the women who choose to undergo CPM are not at a high risk of bilateral breast cancer.[16,17,29,30] A combination of both clinical and non-clinical factors has been associated with this increasing trend in CPM rates. Only a few studies have particularly examined the role of pre-operative MRI as a predictor of CPM and these have reported varying results.[15-18] Sorbero et al and King et al showed significantly increased risk of CPM associated with pre-operative MRI.[15,16] Whereas, two studies did not show any association between MRI and CPM.[17,18] Results from our analysis also show that pre-operative MRI was associated with a high risk of CPM after adjusting for the clinically relevant predictors, hence suggesting that performing an MRI may influence a patients' decision to elect for CPM.

We also found that subjects who received pre-operative MRI took a significantly longer time from diagnosis to initial surgical treatment. Geometric mean of time from diagnosis to initial surgery was 40.5 days and 27.6 days for MRI+ and MRI– groups, respectively ($p<0.05$) after controlling for differences due to age, race, education, insurance and type of initial surgery. Only two studies to date have examined the impact of pre-operative MRI on time to treatment. Bleicher et al reported a mean time of 56.9 days in the MRI group and 38.1 days in no MRI group (p=0.01) from diagnosis to operation and Hulvat et al reported a median time to surgical treatment of 43 days

versus 32 days in MRI+ and MRI- groups, respectively (p=0.054).[2,19] Our results are similar to what has been reported earlier, although previous studies only reported the unadjusted differences. The longer delay seen among the MRI group could be due to the additional tests and biopsies that are conducted to investigate the findings on the MRI. Although the difference seen between the two groups may not have much detrimental effect on treatment outcome, but the longer time taken to initiate surgery for MRI recipients likely contributing to patient anxiety and treatment dissatisfaction.

There were some potential limitations of our study. We did not examine whether the decision to undergo CPM was based on the findings of MRI or not. We also did not have data on the additional tests that may have been performed to investigate MRI findings and their influence on the surgical outcomes. The study however, utilizes the strength of detailed clinical information available in medical records such that confounding by indication is not a major issue in this analysis. Additionally, this is a population-based study that provides a stronger level of evidence on the impact of pre-operative MRI on surgical outcomes in contrast to most of the existing reports that are single institution based.

In conclusion, we found that despite its high sensitivity, pre-operative MRI did not offer any substantial benefits in the surgical management of breast cancer patients. The re-operation rates did not differ significantly by receipt of pre-operative MRI. Additionally, MRI had a significant influence on the decision-making process of undergoing a CPM and increasing the time to surgery. Patients need to be well

informed about the effectiveness of pre-operative MRI before the choice of surgery is made solely using the results from MRI.

Tables and Figures

Table 1. Socio-demographic characteristics, by receipt of pre-operative MRI

Socio-demographics, n (%)	MRI + (n= 300)	MRI – (n= 306)
Age at diagnosis, years		
< 45	67 (22.3)	52 (17.0)
45-54	109 (36.3)	74 (24.2)
55-64	88 (29.3)	111 (36.3)
≥ 65	36 (12.0)	69 (22.5)
Race		
White	186 (62.0)	133 (43.5)
AA	114 (38.0)	173 (56.5)
Education		
Below college	134 (44.7)	180 (58.8)
≥ College graduate	150 (50.0)	96 (31.4)
Unknown	16 (5.3)	30 (9.8)
Health insurance		
Non-private*	52 (17.3)	111 (36.3)
Private	244 (81.3)	189 (61.8)
Unknown	4 (1.3)	6 (2.0)
Body mass index		
Underweight and normal	121 (40.3)	85 (27.8)
Overweight	84 (28.0)	81 (26.5)
Obese	95 (31.7)	137 (44.8)
Unknown	0 (0.0)	3 (1.0)

Abbreviations: MRI= magnetic resonance imaging; AA= African American.
*Non-private insurance includes Medicare, Medicaid, no insurance, and charity care.

Table 2. Pre-operative clinical characteristics, investigations and tumor characteristics, by receipt of pre-operative MRI

Pre-operative characteristics n (%)	MRI + (n= 300)	MRI – (n= 306)
Family history of breast cancer		
Yes	133 (44.3)	117 (38.2)
No	167 (55.7)	189 (61.8)
Clinical presentation		
Patient finding	138 (46.0)	116 (37.9)
Physician finding	19 (6.3)	10 (3.3)
Screening mammography	142 (47.3)	180 (58.8)
Additional investigations		
Diagnostic mammogram	284 (94.7)	295 (96.4)
Diagnostic ultrasonography	255 (85.0)	228 (74.5)
Genotype testing	71 (23.7)	34 (11.1)
BIRADS category on mammography		
Incomplete	47 (15.7)	50 (16.3)
Negative	6 (2.0)	3 (1.0)
Benign	14 (4.7)	1 (0.3)
Probably benign	7 (2.3)	6 (2.0)
Suspicious abnormality	119 (39.7)	159 (52.0)
Highly suggestive of malignancy	86 (28.7)	74 (24.2)
Known biopsy proven malignancy	4 (1.3)	0 (0.0)
Not available	17 (5.7)	13 (4.2)
Method of diagnosis		
Percutaneous biopsy	266 (88.7)	231 (75.5)
Surgical biopsy	34 (11.3)	75 (24.5)
Pre-operative tumor grade		
Well differentiated	63 (21.0)	44 (14.4)
Moderately differentiated	87 (29.0)	105 (34.3)
Poorly differentiated	60 (20.0)	77 (25.2)
Unknown	90 (30.0)	80 (26.1)
Pre-operative tumor histology		
Invasive ductal carcinoma	220 (73.3)	224 (73.2)
Invasive lobular carcinoma	28 (9.3)	23 (7.5)
Other invasive	36 (12.0)	36 (11.8)
In-situ	16 (5.3)	23 (7.5)
Pre-operative multifocality/multicentricity		
Yes	26 (8.7)	22 (7.2)
No	274 (91.3)	284 (92.8)

Abbreviations: MRI= magnetic resonance imaging; BIRADS= breast imaging-reporting and data system.

Table 3. Tumor characteristics, by receipt of pre-operative MRI

Characteristics, n (%)	MRI + (n= 300)	MRI – (n= 306)
Initial surgery		
Lumpectomy	183 (61.0)	208 (68.0)
Mastectomy	117 (39.0)	98 (32.0)
Tumor grade		
Well differentiated	62 (20.7)	52 (17.0)
Moderately differentiated	116 (38.7)	132 (43.1)
Poorly differentiated	105 (35.0)	108 (35.3)
Unknown	17 (5.7)	14 (4.6)
Tumor histology		
Invasive ductal	244 (81.3)	248 (81.0)
Invasive lobular	33 (11.0)	30 (9.8)
Other invasive	23 (7.7)	28 (9.2)
Tumor size		
≤ 1.0cm	104 (34.7)	115 (37.6)
> 1.0cm	196 (65.3)	191 (62.4)
Lymph node status		
Negative	206 (68.7)	235 (76.8)
Positive	93 (31.0)	66 (21.6)
Unknown	1 (0.3)	5 (1.6)
Multifocality/multicentricity		
Yes	74 (24.7)	51 (16.7)
No	226 (75.3)	255 (83.3)
Margin status at initial surgery		
Positive	37 (12.3)	42 (13.7)
Close	57 (19.0)	42 (13.7)
Negative	205 (68.3)	222 (72.5)
Unknown	1 (0.3)	0 (0.0)
Type of surgical facility		
Community hospital cancer program	16 (5.3)	24 (7.8)
Community hospital comprehensive cancer program	90 (30.0)	95 (31.0)
NCI-designated comprehensive cancer program	16 (5.3)	21 (6.9)
Teaching hospital cancer program	156 (52.0)	142 (46.4)
Other	22 (7.3)	24 (7.8)

Abbreviations: MRI= magnetic resonance imaging.

Table 4. Re-operation rate, CPM rate, and time to surgery, by receipt of pre-operative MRI

Study Outcomes	Pre-operative MRI +	Pre-operative MRI –	*P-value*
Re-operation	*MRI done before initial surgery (all subjects)*		*0.475*
N	300	306	
Yes, %	17.7	19.9	
No, %	82.3	80.1	
Re-operation	*MRI done before initial surgery (among subjects diagnosed by percutaneous biopsy)*		*0.112*
N	266	232	
Yes, %	18.8	24.6	
No, %	81.2	75.4	
CPM	*MRI done before final surgery*		*<0.001*
N	311	295	
Yes, %	15.7	5.4	
No, %	84.2	94.6	
CPM	*MRI done before initial surgery*		*<0.001*
N	300	306	
Yes, %	15.7	5.9	
No, %	84.3	94.1	
Time to surgery, days	*MRI done after diagnosis and before initial surgery*		
N	242	329	
Mean (SD)	42.3 (23.5)	31.9 (23.8)	
Geometric mean (95% CI)	36.6 (33.9, 39.5)	26.0 (24.3, 27.8)	*<0.001*
Median	36.0	27.0	

Abbreviations: MRI=Magnetic resonance imaging; CPM=Contralateral prophylactic mastectomy; SD=Standard deviation

P-values were derived from chi-square test for proportions and analysis of variance for means

Table 5. Re-operation rate, CPM rate, and time to surgery, by subject characteristics

Characteristics	Re-operation rate, %	CPM rate, %	Time to surgery, geometric mean days (95% CI)
Age at diagnosis, years			
< 45	19.3	25.2	30.4 (26.9, 34.3)
45-54	18.6	13.1	30.9 (28.1, 34.0)
55-64	21.6	4.5	29.1 (26.6, 31.9)
≥ 65	13.3	1.9	30.0 (26.5, 34.0)
	p= 0.375	*p< 0.001*	*p= 0.839*
Race			
White	17.6	16.0	27.9 (26.0, 30.0)
AA	20.2	4.9	32.6 (30.2, 35.2)
	p= 0.404	*p< 0.001*	*p= 0.004*
Education			
Below college	19.1	9.2	30.3 (28.1, 32.6)
≥ College graduate	18.7	14.2	29.3 (26.9, 31.8)
Unknown	17.4	2.2	32.9 (27.4, 39.6)
	p=0.960		*p= 0.502*
Health insurance			
Non-private	17.8	3.1	32.6 (29.5, 36.1)
Private	19.6	13.9	29.2 (27.4, 31.1)
Unknown	0.0	0.0	26.9 (17.8, 40.8)
	p= 0.270	*p< 0.001*	*p= 0.158*
Body mass index			
Underweight and normal	11.7	18.9	29.5 (27.0, 32.3)
Overweight	21.8	8.5	30.0 (27.1, 33.1)
Obese	23.3	5.2	30.6 (28.1, 33.3)
Unknown	0.0	0.0	29.0 (14.1, 59.7)
	p= 0.009	*p< 0.001*	*p= 0.949*
Family history of breast cancer			
Yes	17.6	14.8	31.2 (28.8, 33.8)
No	19.7	7.9	29.2 (27.3, 31.3)
	p= 0.522	*p= 0.007*	*p= 0.226*
Clinical presentation			
Patient finding	15.4	15.0	29.2 (26.9, 31.8)
Physician finding	10.3	10.3	29.1 (23.1, 36.7)
Screening Mammography	22.4	7.5	30.7 (28.6, 33.0)
	p= 0.101	*p= 0.037*	*p= 0.650*
Genotype testing			
Done	18.1	35.2	33.3 (29.4, 37.8)
Not done	19.0	5.6	29.4 (7.8, 31.1)
	p= 0.836	*p< 0.001*	*p= 0.076*
Method of diagnosis			
Percutaneous biopsy	21.5	10.9	30.8 (29.0, 32.6)
Surgical biopsy	6.4	10.1	27.1 (24.0, 30.6)
	P< 0.001	*p= 0.813*	*p= 0.064*

Initial surgery			
Mastectomy	----	----	36.3 (33.3, 39.7)
Lumpectomy	----	----	27.3 (25.7, 29.1)
			p< 0.001
Tumor grade			
Well differentiated	19.3	7.9	31.3 (27.8, 35.2)
Moderately differentiated	16.1	11.3	29.3 (27.0, 31.8)
Poorly differentiated	20.7	11.7	30.1 (27.5, 33.0)
Unknown	25.8	9.7	30.8 (24.4, 38.9)
	p= 0.448	*p= 0.729*	*p= 0.830*
Histology			
Invasive ductal	17.3	11.0	30.4 (28.7, 32.2)
Invasive lobular	17.5	9.5	26.6 (22.6, 31.2)
Other Invasive	35.3	9.8	31.6 (26.4, 37.8)
	p= 0.007	*p= 0.917*	*p= 0.265*
Tumor size			
≤ 1.0cm	21.0	10.5	31.4 (28.8, 34.2)
> 1.0cm	17.6	10.9	29.3 (27.4, 31.3)
	p= 0.299	*p= 0.894*	*p= 0.197*
Lymph node status			
Negative	18.6	9.8	30.1 (28.3, 32.0)
Positive	20.1	13.8	29.8 (26.8, 33.2)
Unknown	0.0	0.0	29.9 (18.0, 49.9)
	p= 0.453	*p= 0.251*	*p= 0.989*
Margin status at initial surgery			
Positive	81.0	----	----
Close	36.4	----	----
Negative	3.0	----	----
	p< 0.001		
Multifocality/multicentricity			
Yes	24.8	16.8	----
No	17.3	9.1	----
	p= 0.055	*p= 0.014*	
Type of surgical facility			
Community hospital cancer program	50.0	0.0	29.6 (24.1, 36.3)
Community hospital comprehensive cancer program	16.2	9.2	29.3 (26.7, 32.2)
NCI-designated comprehensive cancer program	27.0	18.9	38.5 (31.1, 47.6)
Teaching hospital cancer program	13.8	12.1	30.4 (28.2, 32.7)
Other	28.3	10.9	25.8 (21.3, 31.3)
	p< 0.001	*p= 0.077*	*p= 0.139*

Abbreviations: CPM= contralateral prophylactic mastectomy; AA= African American; CI= confidence interval.
P-values were derived from chi-square test for proportions and analysis of variance for means

Table 6. Unadjusted and adjusted association between pre-operative MRI and study outcomes

Outcomes	Pre-operative MRI	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Re-operation	*MRI done before initial surgery*		
	Yes	0.89 (0.64, 1.23)	0.76 (0.54, 1.07)[†]
	No	Ref	Ref
Re-operation*	*MRI done before initial surgery*		
	Yes	0.77 (0.55, 1.07)	0.75 (0.53, 1.07)[†]
	No	Ref	Ref
CPM	*MRI done before final surgery*		
	Yes	2.90 (1.69, 4.99)	1.75 (1.04, 2.92)[‡]
	No	Ref	Ref
CPM**	*MRI done before initial surgery*		
	Yes	2.66 (1.58, 4.48)	1.62 (0.99, 2.65)[‡]
	No	Ref	Ref
		Unadjusted geometric mean (95% CI)	Adjusted geometric mean (95% CI)[¶]
Time to surgery, days	*MRI done after diagnosis and before initial surgery*		
	Yes	36.6 (33.9, 39.5)	40.5 (37.0, 44.4)
	No	26.0 (24.3, 27.8)	27.6 (25.5, 30.0)

Abbreviations: MRI=Magnetic resonance imaging; CPM=Contralateral prophylactic mastectomy; RR=Relative risk; CI=Confidence interval

[†]Adjusted for age, race, education, insurance, body mass index, method of diagnosis, multifocality/multicentricity and surgical facility

[‡]Adjusted for age, race, education, body mass index, family history of breast cancer, genotype testing, clinical presentation, and surgical facility

[¶]Adjusted for age, race, education, insurance, and type of initial surgery

*Sensitivity analysis model between re-operation and MRI restricted to subjects diagnosed by percutaneous biopsy

**Sensitivity analysis model between CPM and MRI where MRI done any time before initial surgery was considered pre-operative

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RACIAL DIFFERENCES IN ELAPSED TIME AND SESSIONS RECEIVED FOR BREAST CANCER RADIATION THERAPY

by

SHEENU CHANDWANI

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Written under the direction of

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ABSTRACT OF MANUSCRIPT 2 OF 3

RACIAL DIFFERENCES IN ELAPSED TIME AND SESSIONS RECEIVED FOR BREAST CANCER RADIATION THERAPY

Dissertation Director:

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ABSTRACT

Introduction: Prolongation of elapsed time for delivery of radiation therapy can negatively impact tumor control. We examined racial differences in elapsed time and sessions received during adjuvant radiation therapy in breast cancer patients.

Methods: African American (AA) and white subjects who participated in the Breast Cancer Treatment Disparity Study and received adjuvant radiation therapy following surgery for newly diagnosed early breast cancer were included. Data was collected through a retrospective review of medical records. The binomial regression model was used to examine the association between elapsed days > 49 days and race and additional predictors among lumpectomy subjects. Difference in mean number of sessions received was examined through the linear regression model.

Results: The study included 218 white and 190 AA cases with a completed course of adjuvant radiation therapy. The majority of lumpectomy patients (90.5%) and all mastectomy patients (100%) received standard external beam radiation therapy (EBRT). For both races, median elapsed time was 48 days and 41 days and median number of sessions received (with boost) was 33 and 28 during standard EBRT

following lumpectomy and mastectomy, respectively (all $p > 0.05$). Overall 10% cases received accelerated EBRT and accelerated partial breast irradiation following lumpectomy with median elapsed time of 21.5 days and 5.0 days, respectively with no differences seen by race. Proportion of subjects who took >49 days to complete standard EBRT post lumpectomy was 36.3% for whites and 36.4% for AAs ($p >0.05$). Low annual household income, high BMI level and receipt of care in a community-based radiation facility were identified as significant predictors of a protracted radiation course, i.e. > 49 days in the univariate analysis. In the adjusted model however, only type of radiation facility remained as the significant independent predictor of long elapsed time. Except for radiation facility no differences were seen in number of sessions received across all the predictors examined, both in the unadjusted and adjusted models. Conclusion: Although multiple studies have shown that AA are less likely to receive the recommended treatment for breast cancer, findings from this study indicate that once treatment was initiated both AA and white women were very similar in the pattern of care delivered during radiation.

RACIAL DIFFERENCES IN ELAPSED TIME AND SESSIONS RECEIVED FOR BREAST CANCER RADIATION THERAPY

Introduction

Several randomized trials have established that for most women with early-stage breast cancer, breast conserving surgery (BCS) followed by radiation therapy is an equivalent treatment alternative to mastectomy.[1-6] Radiation therapy is considered an integral part of BCS and its omission following BCS is associated with increased risk of recurrence and mortality.[5,7-11] The National Comprehensive Cancer Network (NCCN) recommends standard radiation therapy doses and schedules for patients undergoing BCS. The doses should be delivered without gaps (excluding weekends) in schedules of 5 days per week requiring 6.5 to 7.0 weeks for completion.[12] The lengthy schedule of radiation therapy can pose practical difficulties for treatment adherence. Additional factors such as machine breakdowns, national holidays and side-effects from treatment may also contribute to unplanned interruptions during radiation therapy.[13,14] This can result in either a prolongation of treatment time or discontinuation before the recommended regimen is completed.

Prolongation of treatment time in radiation therapy has been associated with a reduction in the local control rate for several tumor sites, including breast cancer.[15-23] A retrospective analysis of 853 breast cancer patients who completed postoperative radiation therapy showed that an interruption of greater than 7 days during radiation

treatment was associated with an average decrease of 5% and 8% in the 5-year locoregional control rate and overall survival rate, respectively.[13]

Multiple population-based studies have shown that African-American (AA) women are less likely than White women to undergo BCS[24-29] and receive adjuvant radiation therapy following BCS.[29-34] AA women experience longer delays in initiating adjuvant radiation therapy contributing to lower survival among these patients.[35-38] It has also been shown that once radiation therapy is initiated, AA patients are at a higher likelihood of not completing the recommended regimen.[39,40] However racial differences in radiation treatment time and number of sessions received during a radiation course have not been well studied. To our knowledge only one study to date has examined racial differences in elapsed time for radiation therapy and found no differences between AA and white patients.[41] We therefore studied racial differences in elapsed time and mean number of sessions received between initiation and completion of radiation therapy. We also examined additional socio-demographic and clinical predictors of elapsed time and sessions received during the course of standard radiation therapy.

Materials and Methods

Study population

The study population was selected from subjects who participated in the Breast Cancer Treatment Disparity Study (BCTDS) and the Women's Circle of Health Study (WCHS). WCHS is an ongoing multi-site case-control study designed to evaluate risk factors of breast cancer in AA and white women, and is conducted in New York (NY) and New Jersey (NJ). Details of subject selection and recruitment for the WCHS have been included elsewhere.[42] Only invasive breast cancer cases (stage I, II and $T_3N_1M_0$) that participated in the WCHS in NJ were considered for inclusion in the BCTDS. Subjects were between the ages of 20 and 85 years and had no prior history of cancer other than non-melanoma skin cancer. During recruitment each AA case was matched on age ± 5 years with a white case from the pool of potential participants. Cases were identified at all the major hospitals in eastern and central NJ by New Jersey State Cancer Registry staff through rapid case ascertainment. A total of 626 participants were included in the BCTDS between 2005 and 2010; of these, a subset of 411 cases who received adjuvant radiation therapy following breast surgery comprised the study population for this analysis.

Data collection

Data for the study was collected through review of medical records that were obtained from all the health care providers involved in each subject's breast cancer care. These included the primary care physician, surgical oncologist, medical

oncologist, radiation oncologist and the hospital where the surgery was performed. Records included initial diagnostic information, pathology reports, and detailed operative and radiation treatment reports. As most of the adjuvant treatment is provided in an outpatient setting, outpatient records were obtained from one year prior through one year after the initial diagnosis of breast cancer from each subject's health care provider. Trained personnel abstracted the records to collect information on patients' socio-demographics, clinical and tumor characteristics, and radiation treatment factors. Information on participants' race, marital status, education, income, menopausal status, and measured height and weight was primarily obtained from the WCHS and was also verified from medical records. Data collected from radiation records was reviewed by two radiation oncologists (Dr. Molly Gabel and Dr. Carl Nelson) for accuracy.

Patient factors

Socio-demographic characteristics of study population that were examined included age at diagnosis (<45, 45-54, 55-64, or ≥ 65), marital status (married/living as married, widowed/separated/divorced, or single/never married), education (below college or college graduate and above), annual household income (<$70,000 or ≥ 70,000), and insurance status (government, private, or no insurance).

Clinical factors

Body mass index was calculated in kg/m^2 and was categorized into underweight or normal (< 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), or obese (≥ 30.0 kg/m^2) using

the Centers for Disease Control and Prevention classification system. Comorbidities were summarized using a total score of selected comorbid conditions presenting in each participant. It was calculated by assigning a score of 1 to each of the following conditions including, cerebral vascular accident, congestive heart failure, diabetes mellitus, gastro-intestinal disease, hypertension, ischemic heart disease, malignancies, organic heart disease, peripheral vascular disease, primary arrhythmias or conduction problems, renal disease, respiratory problems, neurologic disorders, immunologic or connective tissue disorders, endocrine disorders (other than diabetes), and moderate to severe liver disease. Study subjects were classified into three levels of the comorbidity score: score of 0, score of 1, or score of ≥ 2. Menopausal status at the time of diagnosis was categorized into pre-menopausal, peri-menopausal, or post-menopausal.

Principal breast surgery was divided into lumpectomy or mastectomy. The final margin status at the end of the principal surgery was summarized as positive, negative, or close (defined as ≤ 1mm). Distribution of tumor stage (I, IIA, IIB, or IIIA), tumor grade (well differentiated, moderately differentiated, or poorly differentiated) and Estrogen receptor (ER)/Progesterone receptor (PR) status (one positive, both positive, or both negative) was also examined. Receipt of adjuvant chemotherapy and hormonal therapy was examined separately for subjects with ER positive or PR positive receptor status versus subjects with ER negative and PR negative receptor status.

Radiation treatment factors

Lumpectomy patients received radiation to whole breast or partial breast, and mastectomy patients received radiation to the chest wall. In addition to whole breast or chest wall, some patients also received radiation to one or more regional lymphatic site (supraclavicular area, infraclavicular area, axilla, or internal mammary lymph nodes). Radiation region was therefore classified into partial breast, whole breast alone, or whole breast with regional lymphatics for lumpectomy patients; and chest wall alone or chest wall with regional lymphatics for mastectomy patients. Receipt of a boost or supplemental dose of radiation to whole breast or chest wall was also examined.

Fractionation schedules summarizing the dose per session required to deliver the total dose were categorized into three schedules consistent with common Unites States practice patterns. They were broadly divided into standard external beam radiation therapy (EBRT), accelerated EBRT, or accelerated partial breast irradiation (APBI). Elapsed time was defined as the total number of calendar days (including weekends) between start date and end date of the entire radiation therapy course. Total number of sessions administered was also examined for each fractionation schedule, with or without boost (if applicable).

Radiation treatment was delivered at 43 different facilities throughout New Jersey. These facilities were broadly classified into the Commission on Cancer accreditation categories established by the American College of Surgeons. Facilities were primarily divided into teaching hospital cancer program, NCI-designated comprehensive cancer program, community hospital cancer program and community hospital comprehensive cancer program. Information on 3 free standing facilities was

not available in the Commission on Cancer database and these were assigned a separate category.

Statistical Analysis

Summary statistics stratified by race (AA vs. white) were calculated for socio-demographics, clinical characteristics, and tumor characteristics of the study population. Radiation therapy characteristics were stratified by both race (AA vs. white) and principal surgery (lumpectomy vs. mastectomy). Due to expected differences in the delivery of the different types of fractionation schedules, total sessions and elapsed time were examined separately for each schedule. Total number of sessions delivered for each schedule with or without boost was summarized on a continuous scale using median and range. Elapsed time was examined both on continuous (median and range) and categorical scales. Standard EBRT requires delivery of 45-50 Gy to whole breast or chest wall given in 1.8-2.0 Gy/fx followed by 10-16 Gy boost dose using 2.0 Gy/fx. This totals to approximately 30 to 33 sessions with boost that requires 6.5 to 7 weeks for completion.[12] Multiple cut-off values were examined for standard EBRT elapsed time including 45 days (6.5 weeks) to 49 days (7 weeks), and 56 days (8 weeks). Accelerated EBRT usually requires delivery of 21 fractions with boost taking approximately 4 weeks for completion; hence a 28-day cut-off was examined for these patients.[12] A 7 day cut-off was used for patients receiving APBI which is administered for a total of 10 fractions delivered twice per day.[12] Univariate differences by race were

examined using the chi-square test for proportions, t-test for means, and Wilcoxon two-sample test for medians.

The binomial regression model was used to examine the risk associated with >49 days of elapsed time and linear regression model was used to examine differences in mean number of total sessions received (with boost), by race and additional socio-demographic and clinical predictors. These models were restricted to lumpectomy subjects who received standard EBRT radiation therapy (n=322). Due to inherent differences in the various fractionation schedules they were not examined together. In addition, small sample sizes for accelerated EBRT and APBI did not allow for their separate examination in the statistical models. Mastectomy patients were also excluded from the statistical models. Additional predictors examined included age, education, annual household income, primary health insurance, marital status, body mass index, comorbidity score, tumor stage, and type of radiation facility. Unadjusted relative risks (RR) with 95% confidence interval (CI) were estimated to compare the risk of elapsed time >49 days between AA and white women and between different levels of additional predictors. Similarly, mean number of sessions administered were reported for different categories of race and the additional predictors. The independent effect of the additional predictors on both outcomes was also examined by adjusting for all them together in the models. All analysis was conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient and clinical factors

The study included 411 early breast cancer cases (White=219 and AA=192) who received radiation therapy following surgery. Socio-demographic characteristics of the study population are shown in Table 1. A higher proportion of white women were diagnosed between the ages of 45 to 54 years and over 65 years; whereas more AA women were diagnosed at 55 to 64 years of age. The proportion of white subjects with at least a college degree and annual household income of $70,000 or more was approximately twofold compared to AA subjects. Private health insurance coverage was more common among white subjects as compared to AA subjects. White women were more likely to be married or living as married and AA women were more likely to be single or never married. The distribution of clinical and tumor characteristics by race are shown in Table 2. AAs were more likely to be overweight and obese, and have a higher comorbidity score compared to whites. More than half of the women in each group were post-menopausal with no significant differences observed by race. AA subjects were more likely to be diagnosed with stage II and $T_3N_1M_0$ breast cancer; whereas white subjects were more commonly diagnosed with stage I breast cancer. A higher prevalence of poorly differentiated and receptor negative tumors was seen among AAs and a higher prevalence of well differentiated and receptor positive tumors was seen for whites. There were no differences in the type of surgery and adjuvant treatment received by race. The majority of the study population underwent lumpectomy as compared to mastectomy (87% vs. 13%).

Radiation treatment factors

Radiation therapy records were unavailable for 2 subjects, and only 1 subject did not complete radiation therapy. These subjects were excluded and data from remaining 408 subjects was used to summarize radiation therapy factors by surgery and race (Table 3). Therefore, everyone included in the analysis of radiation treatment factors had completed their course of recommended radiation treatment. No racial differences were observed in the radiation modality or technique factors examined. Lumpectomy subjects most commonly received radiation to whole breast alone (white= 87.1% and AA= 87.7%; p> 0.05), followed by whole breast with regional lymphatics (whites= 5.2% and AA= 8.0%; p> 0.05) and partial breast (white= 7.8% and AA= 4.3%; p> 0.05). On the other hand, subjects who underwent mastectomy were more likely to receive radiation to chest wall with regional lymphatics (white= 76.0% and AA= 77.8%; p> 0.05) followed by chest wall alone (white= 24.0% and AA= 22.2%; p> 0.05). A boost dose was administered to almost all the subjects receiving radiation to whole breast post lumpectomy (white= 98.3% and AA= 98.1%; p> 0.05); whereas, it was given to only 24.0% whites and 37.0% AAs receiving chest wall radiation post mastectomy.

Most of the study population underwent standard EBRT (lumpectomy= 90.6%; mastectomy= 100%). It was administered to deliver an average of 46.8 Gy (range= 41.4-59.4 Gy) given in 1.8-2.0 Gy/fx to whole breast (among lumpectomy subjects) followed by a boost dose of 1.4 Gy (range= 7.0-20.0 Gy) given in 2.0 Gy/fx (range= 1.6-5.0/fx) to the tumor bed. For mastectomy subjects, standard EBRT delivered an average of 50.4 Gy (range= 46.0-54.0 Gy) to chest wall plus boost of 10.0 Gy (range=

10.0-16.0 Gy) to tumor bed using 1.8-2.0 Gy/fx (including boost). Median number of fractions delivered with boost was 33 for whole breast and 28 for chest wall.

Accelerated EBRT and APBI were utilized following lumpectomy in approximately 10% of the patients. Several common fractionation schedules were used to deliver accelerated EBRT. Two-thirds of the accelerated EBRT patients (8/12) received a dose of 42.4 Gy (range= 42.4-42.7 Gy) at 2.66 Gy/ fx to the whole breast followed by a boost dose of 10.0 Gy (range= 8.0-10.0 Gy) at 2.0 Gy/fx to the tumor bed. It was administered over a median of 21 total fractions. APBI was administered using brachytherapy in 10 fractions of 3.4 Gy each in five days to 22 subjects.

No significant differences were seen between white and AA subjects in the type of radiation facility where treatment was received. Both groups most commonly received radiation treatment in a teaching hospital cancer program followed by a community hospital comprehensive cancer program. Overall median elapsed time required to complete different fractionation schedules was also similar between the two groups and had median times of 48 days, 41 days, 29.5 days, and 5 days for standard EBRT post lumpectomy, standard EBRT post mastectomy, accelerated EBRT and APBI, respectively. More than one-third subjects (white=36.3% and AA=36.0; $p>0.05$) receiving the standard course of EBRT following lumpectomy took longer than 7 weeks to complete their radiation course. On the other hand, 12.0% white and 11.1% AA subjects receiving standard EBRT following mastectomy took greater than 7 weeks' time to complete their radiation course.

While examining different cut-off days for elapsed time among standard EBRT lumpectomy subjects (Figure 1), a higher proportion of AA subjects took >45 days, >46 days, > 47 days and > 48 days to complete radiation therapy (although not statistically significant). However, the difference disappeared when a standard cut-off of >49 days was used (White= 36.3%; AA= 36.4%).

Results from the unadjusted and adjusted binomial regression models for elapsed time >49 days are presented in Table 4. No difference was observed between AA and white subjects in their risk of having a longer elapsed time. However, for both races low education level, low annual household income, high body mass index and receipt of care in a community-based radiation facility were identified as significant predictors of a protracted radiation course. Less than college education was associated with RR= 1.42 (95% CI: 1.03, 1.97) as compared to patients with at least a college degree. Annual household income ≤$ 70,000 was associated with RR= 1.61 (95% CI: 1.15, 2.25) in comparison to annual household income >$70,000. Overweight and obese subjects were associated with RR= 1.65 (95% CI: 1.07, 2.56) and RR=1.74 (95% CI: 1.15, 2.63), respectively as compared to subjects who were normal or underweight. Radiation treatment received at a community-based facility (includes community hospital cancer program, community hospital comprehensive cancer program and free standing) was associated with RR= 1.56 (95% CI: 1.17, 2.09) versus a teaching facility (includes NCI-designated comprehensive cancer program and teaching hospital cancer program).

When all the socio-demographic and clinical predictors were adjusted together, only type of radiation facility was independently associated with a longer elapsed time. Radiation treatment received at a community-based facility was associated with an adjusted RR= 1.66 (95% CI: 1.17, 2.25) for completing radiation in more than 7 weeks in comparison to a teaching facility.

AA and white subjects were also similar in the mean number of sessions they received during a standard course of radiation (mean=33). Differences were neither observed across the levels of different predictors in either the unadjusted or adjusted models except for type of radiation facility (Table 5). However, although statistically significant, the difference in mean sessions observed between teaching and community-based facilities was less than 1 day and probably is not of clinical relevance.

Discussion

In this study we investigated predictors of elapsed time and sessions received during a completed course of adjuvant radiation therapy in early stage breast cancer patients, with a primary focus on race. For both races, standard EBRT had been the most frequently administered fractionation schedule. A higher utilization of APBI was seen among whites, although it did not reach statistical significance. No differences were seen between AA and white women in the elapsed time (median=48 days) and sessions received (median= 33) during the standard EBRT course following lumpectomy. 36.2% subjects took greater than 7 weeks to complete the standard course of radiation. Examination of additional sociodemographic and clinical factors showed that low education, low annual household income, high BMI level, and treatment in a community-based radiation facility were associated with longer elapsed time. However, only type of facility was independently significant after adjusting for the effect of other predictors. Except for type of radiation facility no differences were seen in number of sessions received across all the predictors examined.

Only two studies to date have reported elapsed time for radiation therapy among breast cancer patients. A mean duration of 49.5 days from first to last radiation treatment was reported among 297 Washington State Medicaid enrollees who started radiation therapy.[14] A chart review of early stage breast cancer patients treated at the Yale University School of Medicine reported median elapsed time of 45 days for completing radiotherapy with no differences seen between AA and white patients.[41] In the present analysis, median elapsed time of 48 days was observed which is consistent

with the previous reports. However, none of these studies investigated any additional predictors of elapsed time.

The number of fractions or treatment sessions received during radiation therapy has most frequently been used to identify patients who fail to complete the expected course of radiation. Using SEER-Medicare linked data set, Srokowski et al found that 13% subjects did not complete a standard course of radiation therapy, defined as receipt of at least 25 radiation sessions.[40] They demonstrated that black race, mastectomy, hospitalization during radiation treatment, earlier year of diagnosis and residence in rural areas were independently associated a higher risk of not completing the recommended radiation therapy. In their study Ramsey et al used a cut-off of 30 and 33 sessions for patients not receiving chemotherapy and receiving chemotherapy, respectively. Using this definition they reported a 22% non completion rate for radiotherapy.[14] However, none of the clinical and socio-demographic factors were identified as significant predictors of non completion in the adjusted model.[14] Although in the current study we only included patients who completed a minimum number of recommended sessions (i.e., 25), we did not find any racial differences.

Several patient-related and treatment facility related factors have been reported as common reasons for unplanned interruptions during radiation.[13,14] This is the first study however to identify factors associated with elapsed time and sessions received during breast cancer irradiation. Although multiple studies have shown that AA are less likely to receive the recommended treatment for breast cancer[43-48], findings from this study indicate that once treatment was initiated both AA and white women were very

similar in the pattern of care delivered during radiation. Among other predictors examined, we found that lower income and education levels were significantly associated with a longer than 7 weeks elapsed time. Patients who are economically disadvantaged often have to overcome additional challenges, including those related to cost of care, dependent care, and daily travel to the radiation facility. Low income level and barriers like long travel distance to radiation facility have been shown to influence the receipt of postoperative breast irradiation.[49-54] Patients with a lower education level may be less knowledgeable about treatment compliance and may not be proactive in adhering to the recommended regimen. As a result they miss radiation sessions resulting in an overall prolongation of treatment time.

High BMI level was another patient factor associated with long elapsed time. Patients with a high BMI are more likely to experience dose inhomogeneity to the treated breast.[55,56] This may result in higher radiation doses delivered to certain regions of the breast, causing a more severe skin reaction. As a result the treating radiation oncologist may interrupt the therapy in order to allow adequate time for healing. In the adjusted model however no patient factor was identified as independent predictor of elapsed time. Radiation treatment delivered in community-based facility was associated with both a long elapsed time and high number of radiation sessions after adjusting for additional predictors. This may represent disparities in the health care delivery system level.

Our study had some potential limitations. We did not examine the number and reasons of interruptions that resulted in prolongation of treatment time. A delay of more

than a week in completing radiation therapy has been previously associated with a negative impact on breast cancer outcomes.[13] Due to sample size limitations we were unable to examine factors that were responsible for more than 1 week delay. The study however is population-based and is one of the first ones to report the current pattern of care among patients receiving breast cancer radiation therapy using data from comprehensive medical records review.

Currently recommended radiation schedules incorporate weekend breaks and any additional prolongation carries a significant potential of negatively impacting the benefit of therapy. Reduction in local control rate due to prolongation of radiotherapy has been studied extensively in a variety of tumors including, cancers of head and neck region, cervix and lung. [15-23] A median reduction of 14% in local control rate resulting from one week of prolongation has been established for head and neck cancers.[15] There are however, only two reports by Bese at al showing a reduction of 5% in 5-year local control rate if the radiation treatment is prolonged for more than a week in stage I to III breast cancer patients.[13,57] Due to lack of sufficient evidence in slow growing tumors like breast cancer a safe minimum for prolongation has not been established. Nevertheless, it is important to identify patients who have experienced a gap during their course of radiotherapy proactively so that changes can be made in their treatment schedule to compensate for the prolongation.[58] This highlights the need of future studies that examine the impact of elapsed time during breast cancer irradiation on patient outcomes.

Tables and Figures

Table 1. Socio-demographics of patients receiving adjuvant radiation therapy, by race

Socio-demographics, n (%)	White (n=219)	AA (n=192)
Age at diagnosis, years		
< 45	33 (15.1)	35 (18.2)
45-54	71 (32.4)	48 (25.0)
55-64	66 (30.1)	79 (41.1)
≥ 65	49 (22.4)	30 (15.6)
Marital status		
Married or living as married	142 (64.8)	72 (37.5)
Widowed/Separated/Divorced	52 (23.7)	55 (28.6)
Single/Never married	16 (7.3)	47 (24.5)
Unknown	9 (4.1)	18 (9.4)
Education		
Less than high school	4 (1.8)	21 (10.9)
High school or GED graduate	38 (17.4)	53 (27.6)
Technical/vocational school or some college	49 (22.4)	48 (25.0)
College graduate or above	119 (54.3)	52 (27.1)
Unknown	9 (4.1)	18 (9.4)
Annual household income		
< $35,000	18 (8.2)	60 (31.3)
$35,000 - $69,999	40 (18.3)	53 (27.6)
≥ $70,000	133 (60.7)	49 (25.5)
Unknown	28 (12.8)	30 (15.6)
Primary health insurance		
Medicaid	4 (1.8)	10 (5.2)
Medicare	39 (17.8)	36 (18.8)
Private insurance	166 (75.8)	123 (64.1)
No insurance or self-pay	5 (2.3)	17 (8.9)
Unknown	5 (2.3)	6 (3.1)

Abbreviations: AA= African American

Table 2. Clinical and tumor characteristics of patients receiving adjuvant radiation therapy, by race

Clinical and tumor characteristics, n (%)	White (n=219)	AA (n=192)
Body mass index		
Underweight or normal weight	92 (42.0)	28 (14.6)
Overweight	61 (27.9)	70 (36.5)
Obese	66 (30.1)	93 (48.4)
Unknown	0 (0.0)	1 (0.5
Comorbidity score		
0	50 (22.8)	27 (14.1)
1	71 (32.4)	46 (24.0)
≥ 2	98 (44.7)	119 (62.0)
Principal surgery		
Lumpectomy	193 (88.1)	164 (85.4)
Mastectomy	26 (11.9)	28 (14.6)
Margin status		
Positive	9 (4.1)	8 (4.2)
Close	24 (11.0)	26 (13.5)
Negative	186 (84.9)	158 (82.3)
AJCC tumor stage		
Stage I	143 (65.3)	94 (49.0)
Stage II or above	75 (34.2)	95 (49.5)
Unknown	1 (0.5)	3 (1.6)
Tumor grade		
Well differentiated	61 (27.9)	22 (11.5)
Moderately differentiated	88 (40.2)	80 (41.7)
Poorly differentiated	62 (28.3)	82 (42.7)
Unknown	8 (3.7)	8 (4.2)
ER/PR status		
Only one positive (ER + or PR +)	20 (9.1)	29 (15.1)
Both positive (ER + and PR +)	166 (75.8)	105 (54.7)
Both negative (ER - and PR -)	33 (15.1)	57 (29.7)
Unknown	0 (0.0)	1 (0.5)
ER positive or PR positive	White (n=186)	AA (n=134)
Hormonal therapy alone	109 (58.6)	59 (44.0)
Hormonal therapy plus chemotherapy	70 (37.6)	61 (45.5)
Chemotherapy alone	5 (2.7)	7 (5.2)
No therapy	2 (1.1)	7 (5.2)
ER negative and PR negative	White (n=33)	AA (n=57)
Hormonal therapy alone	0 (0.0)	1 (1.8)
Hormonal therapy plus chemotherapy	1 (3.0)	1 (1.8)
Chemotherapy alone	29 (87.9)	48 (84.2)
No therapy	3 (9.1)	7 (12.3)

Abbreviations: AA= African American; AJCC= American joint committee on cancer; ER= Estrogen receptor; PR= Progesterone receptor

Table 3. Radiation therapy characteristics, by principal surgery and race

Radiation therapy characteristics	Lumpectomy		Mastectomy	
	Whites (n=193)	AA (n=163)	Whites (n=25)	AA (n=27)
Radiation region, n (%)				
Whole breast alone	168 (87.1)	143 (87.7)	-	-
Whole breast with regional lymphatics	10 (5.2)	13 (8.0)	-	-
Partial Breast	15 (7.8)	7 (4.3)	-	-
Chest wall alone	-	-	6 (24.0)	6 (22.2)
Chest wall with regional lymphatics	-	-	19 (76.0)	21 (77.8)
Boost received, n (%)				
Whole breast	175 (98.3)	153 (98.1)	-	-
Chest wall	-	-	6 (24.0)	10 (37.0)
Fractionation schedule, n (%)				
Standard EBRT	171 (88.6)	151 (92.6)	25 (100.0)	27 (100.0)
Accelerated EBRT	7 (3.6)	5 (3.1)	-	-
APBI	15 (7.8)	7 (4.3)	-	-
Radiation sessions, median (range)				
Standard EBRT without boost	26 (23 to 30)	26 (23 to 33)	28 (25 to 30)	28 (23 to 28)
Standard EBRT with boost	33 (25 to 38)	33 (28 to 38)	28 (25 to 33)	28 (23 to 36)
Accelerated EBRT without boost	16 (15 to 19)	16 (11 to 16)	-	-
Accelerated EBRT with boost	21 (15 to 23)	20 (15 to 21)	-	-
Partial Breast Brachytherapy	10 (10 to 10)	10 (10 to 10)	-	-
Type of radiation facility, n (%)				
Community hospital cancer program	11 (5.7)	19 (11.7)	2 (8.0)	3 (11.1)
Community hospital comprehensive cancer program	66 (34.2)	49 (30.1)	3 (12.0)	8 (29.6)
NCI-designated comprehensive cancer program	11 (5.7)	13 (8.0)	2 (8.0)	1 (3.7)
Teaching hospital cancer program	97 (50.3)	77 (47.2)	16 (64.0)	15 (55.6)
Free standing	8 (4.2)	5 (3.1)	2 (8.0)	0 (0.0)
Elapsed days by fractionation schedule				
Standard EBRT	White (n=171)	AA (n=151)	White (n=26)	AA (n=27)
Elapsed days, median (range)	48 (33 to 80)	48 (38 to 81)	42 (38 to 53)	41 (34 to 55)
> 49 days, n (%)	62 (36.3)	55 (36.0)	3 (12.0)	3 (11.1)

Accelerated EBRT	White (n=7)	AA (n=5)	-	-
Elapsed days, median (range)	29 (21 to 34)	30 (22 to 33)	-	-
> 28 days, n (%)	5 (71.4)	3 (60.0)	-	-
APBI	White (n=15)	AA (n=7)	-	-
Elapsed days, median (range)	5.0 (3 to 7)	5.0 (5 to 7)	-	-
> 7 days, n (%)	0 (0.0)	0 (0.0)	-	-

Abbreviations: AA= African American; EBRT= External beam radiation therapy; APBI= Accelerated partial breast irradiation
Regional lymphatics includes: supraclavicular lymph nodes, infraclavicular lymph node, internal mammary lymph nodes or axilla
P-values were derived from t-test for mean, Wilcoxon two-sample test for median, and chi-square test for proportion.
No statistically significant differences were seen by race at the p-value of 0.05.

Figure 1. Elapsed days for completing radiation therapy, by race

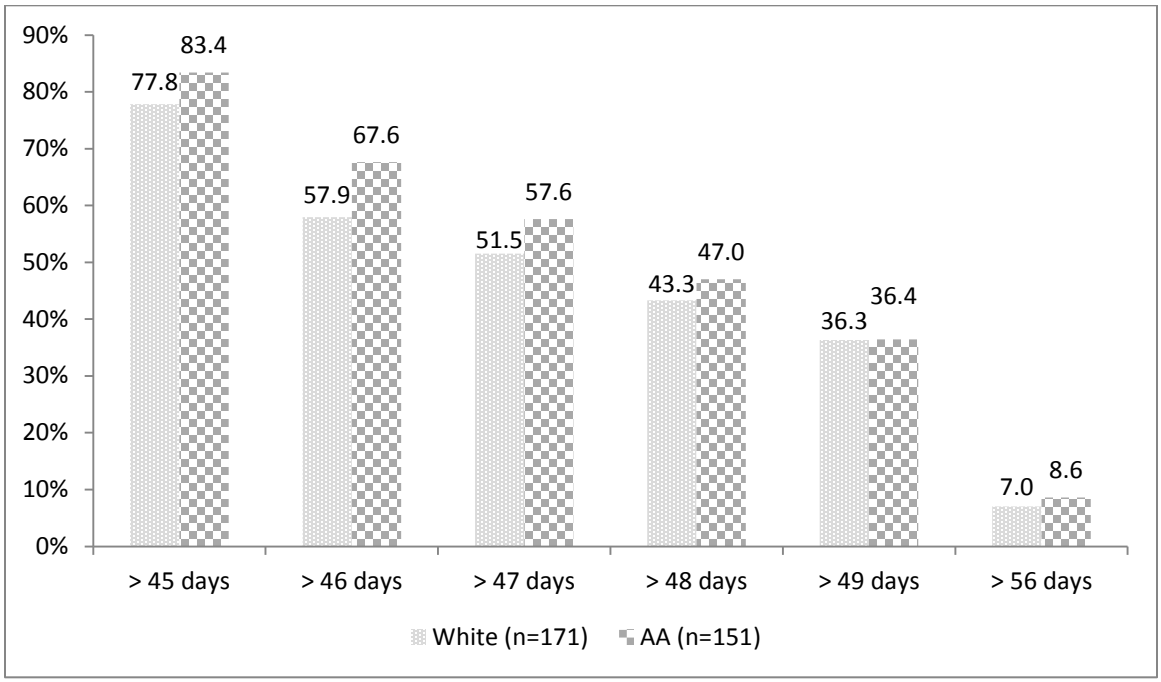

Table 4. Relative risk for completing adjuvant radiation therapy in > 49 days

Characteristics	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Race		
AA	1.00 (0.75, 1.34)	-
White	Ref	
Age at diagnosis, years		
Less than 45	Ref	Ref
45-54	1.27 (0.76, 2.12)	1.47 (0.82, 2.62)
55-64	1.39 (0.85, 2.28)	1.41 (0.79, 2.49)
65 and older	1.12 (0.64, 1.98)	0.83 (0.37, 1.85)
Education		
Below college	1.42 (1.03, 1.97)*	1.01 (0.68, 1.50)
College graduate and above	Ref	Ref
Unknown	1.59 (0.96, 2.65)	-
Annual household income		
< $70,000	1.61 (1.15, 2.25)*	1.47 (0.96, 2.25)
≥ $70,000	Ref	
Unknown	1.37 (0.88, 2.12)	-
Primary health insurance		
Private insurance	Ref	Ref
Non-private insurance	1.12 (0.82, 1.54)	1.20 (0.77, 1.88)
Unknown	1.14 (0.52, 2.49)	-
Marital status		
Married or Living as married	Ref	Ref
Widowed/Separated/Divorced	1.00 (0.70, 1.44)	1.20 (0.76, 1.88)
Single/Never married	1.21 (0.82, 1.80)	0.95 (0.65, 1.38)
Unknown	1.33 (0.82, 2.16)	-
Body mass index		
Underweight and Normal	Ref	Ref
Overweight	1.65 (1.07, 2.56)	1.42 (0.88, 2.29)
Obese	1.74 (1.15, 2.63)	1.56 (0.99, 2.47)
Comorbidity score		
0	Ref	Ref
1	0.97 (0.61, 1.53)	1.08 (0.69, 1.71)
≥ 2	1.19 (0.80, 1.77)	0.81 (0.48, 1.36)
AJCC tumor stage		
Stage I	Ref	Ref
Stage II or above	1.06 (0.79, 1.43)	0.88 (0.64, 1.22)
Unknown	1.41 (0.35, 5.71)	-
Radiation facility		
Teaching-based	Ref	Ref
Community-based	1.56 (1.17, 2.09)*	1.66 (1.17, 2.35)*

Abbreviations: RR= Relative risk; AA= African American; AJCC= American joint committee on cancer

*p-value< 0.05

Table 5. Mean number of sessions received during standard EBRT

Characteristics	Unadjusted mean sessions (95% CI)	Adjusted mean sessions (95% CI)
Race		
AA	33.0 (32.8, 33.3)	-
White	33.0 (32.8, 33.3)	
Age at diagnosis, years		
Less than 45	32.8 (32.4, 33.2)	32.2 (32.7, 33.2)
45-54	33.0 (32.6, 33.3)	32.5 (32.9, 33.2)
55-64	33.2 (32.9, 33.5)	32.7 (33.1, 33.5)
65 and older	33.0 (32.6, 33.4)	32.4 (32.9, 33.5)
Education		
Below college	33.1 (32.9, 33.4)	32.6 (32.9, 33.2)
College graduate and above	32.8 (32.5, 33.1)	32.6 (32.9, 33.2)
Unknown	33.6 (33.0, 34.2)	
Annual household income		
< $70,000	33.1 (32.8, 33.3)	32.7 (33.0, 33.3)
≥ $70,000	32.9 (32.7, 33.2)	32.4 (32.8, 33.2)
Unknown	33.2 (32.7, 33.6)	
Primary health insurance		
Private insurance	33.0 (32.6, 33.3)	32.4 (32.8, 33.3)
Non-private insurance	33.0 (32.8, 33.3)	32.7 (33.0, 33.3)
Unknown	33.1 (32.1, 34.1)	
Marital status		
Married or Living as married	33.1 (32.8, 33.3)	32.8 (33.1, 33.4)
Widowed/Separated/Divorced	32.9 (32.6, 33.3)	32.6 (33.0, 33.3)
Single/Never married	32.7 (32.3, 33.2)	32.2 (32.7, 33.1)
Unknown	33.6 (33.0, 34.2)	
Body mass index		
Underweight and Normal	32.7 (32.4, 33.1)	32.4 (32.7, 33.1)
Overweight	33.2 (32.9, 33.5)	32.7 (33.1, 33.4)
Obese	33.1 (32.8, 33.3)	32.6 (32.9, 33.3)
Comorbidity score		
0	32.9 (32.5, 33.3)	32.6 (33.0, 33.4)
1	33.0 (32.7, 33.3)	32.5 (32.9, 33.3)
≥ 2	33.1 (32.8, 33.3)	32.5 (32.9, 33.2)
AJCC tumor stage		
Stage I	33.0 (32.8, 33.2)	32.6 (32.9, 33.2)
Stage II or above	33.0 (32.8, 33.3)	32.6 (32.9, 33.3)
Unknown	32.0 (29.8, 34.2)	
Radiation facility*		
Teaching-based	32.7 (32.5, 32.9)	32.3 (32.6, 32.8)
Community-based	33.4 (33.2, 33.7)	32.9 (33.3, 33.6)

Abbreviations: AA= African American; AJCC=American joint committee on cancer
*p-value<0.05

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ROLE OF NEUTROPENIA IN CHEMOTHERAPY MODIFICATIONS BY RACE IN EARLY BREAST CANCER TREATMENT

by

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ABSTRACT OF MANUSCRIPT 3 OF 3

ROLE OF NEUTROPENIA IN CHEMOTHERAPY MODIFICATIONS BY RACE IN EARLY BREAST CANCER TREATMENT

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ABSTRACT

Introduction: African American (AA) women in comparison to white women are more likely to not receive optimal care or discontinue treatment early for their breast cancer. We examined differences in chemotherapy dose modifications by race and the role of neutropenia in explaining these differences.

Methods: Subjects were selected from the Breast Cancer Treatment Disparity Study comprising of AA and white women diagnosed with early breast cancer between 2005 and 2010. Subjects who received chemotherapy for their primary breast cancer were included. Detailed data on chemotherapy administration was abstracted from the medical charts of the patients. Chemotherapy dose modification was defined using relative dose intensity (RDI) for the entire course of therapy as well for each cycle delivered. White blood cell (WBC) level at initiation of each cycle was examined. Linear regression and binomial regression models were utilized to examine racial differences in mean RDI delivered and risk of >15% reduction in RDI during the course of chemotherapy.

Results: Mean RDI delivered per subject was 94.4% for AAs and 100.0% for whites (mean difference= -5.62%, $p= 0.005$). After adjusting for mean WBC level across chemotherapy the difference between AA versus white was -5.29% ($p= 0.009$). Unadjusted risk of >15% reduction in RDI was 2.62 times (95% CI: 1.40, 4.89) in AA women as compared to white women; and it changed to 2.50 (95% CI: 1.33, 4.70) after adjusting for overall mean WBC level. When RDI delivered per cycle was examined, the mean unadjusted difference between AAs and whites was -8.27% ($p< 0.001$). This changed to a mean difference of -7.92% ($p< 0.001$) after adjusting for per cycle mean WBC level.

Conclusions: WBC levels did not explain the significant dose reduction experienced by AA women in comparison to white women during receipt of chemotherapy for early breast cancer. This highlights the need of investigating other toxicities or patient and physician related factors that may be responsible for explaining such a difference in pattern of care delivered by race.

ROLE OF NEUTROPENIA IN CHEMOTHERAPY MODIFICATIONS BY RACE IN EARLY BREAST CANCER TREATMENT

Introduction

Long-term benefits of polychemotherapy on survival among early breast cancer patients have been established in several randomized trials.[1,2] However, in real practice, patients seldom receive 100% of the projected chemotherapy dose. Significance of measuring dose intensity delivered during chemotherapy was first established by Hryniuk *et al*.[3-5] Thereafter, large clinical trials have shown a negative impact on disease-free and overall survival among patients who experience dose reductions or delays during chemotherapy.[6-8] Patients undergoing cytotoxic chemotherapy are at a high risk of neutropenia due to its deleterious effect on the hematopoietic system. Risk of neutropenia also increases with cytotoxic dose.[8] Failure to return neutrophil count to a normal level during chemotherapy may result in dose alterations such as delay in starting chemotherapy cycles or reduction in chemotherapy dose levels.[9-11] Neutropenia therefore has been identified as a major dose-limiting toxicity of chemotherapy

AA women in general are predisposed to significantly lower white blood cell (WBC) and acute neutrophil count (ANC) levels than their white counterparts (called ethnic neutropenia).[12,13] Similar differences by race have also been seen in women with breast cancer.[14,15] Although there has been an increase in the use of adjuvant chemotherapy for all stages of breast cancer[16], recent studies on racial differences in

breast cancer treatment have shown that AA women are more likely to receive reduced doses of chemotherapy and reduced number of chemotherapy cycles, and experience dose delays in initiating subsequent cycles. [14,15,17,18] However, it is unclear whether these racial differences in chemotherapy administration can be explained by differences in their blood counts.[15,17] We examined racial differences in chemotherapy dose modifications and the possible role of neutropenia in this association among participants in the Breast Cancer Treatment Disparity Study.

Materials and Methods

Study population

Subjects who participated in the Breast Cancer Treatment Disparity Study (BCTDS) and the Women's Circle of Health Study (WCHS) comprised the target population for the study. The WCHS is an ongoing case-control study of AA and white women conducted in New Jersey (NJ) and New York (NY). The BCTDS is a cohort study that included only invasive breast cancer cases recruited from NJ in the WCHS. Details on subject selection and subject recruitment for the WCHS has been reported previously[19], and for the BCTDS has been described in manuscript 1 of this dissertation. Briefly, the BCTDS is comprised of AA and white women with the following inclusion criteria: diagnosed with stage I, II and $T_3N_1M_0$ breast cancer between 2005 and 2010, matched 1:1 on age (± 5 years), between the ages of 20 and 85 years at diagnosis, and no prior history of cancer other than non-melanoma skin cancer. Eligible subjects were New Jersey (NJ) residents and were identified at all the major hospitals in eastern and central NJ by New Jersey State Cancer Registry staff through rapid case ascertainment. From a total of 626 participants included in the BCTDS, subjects who received chemotherapy for their breast cancer treatment were included in this analysis.

Data Collection

All the consenting participants provided a list of names and addresses of the health care providers involved in their breast cancer treatment. The providers were contacted to obtain medical records on initial diagnostic information, surgical pathology

reports, and adjuvant treatment reports. As most of the chemotherapy is administered in an outpatient setting, detailed outpatient chemotherapy records were obtained from the treating oncologist for patients undergoing chemotherapy. Trained personnel abstracted the records to collect information on patient socio-demographics, clinical and tumor characteristics, and chemotherapy characteristics. Information on participants' race, education, income, and measured height and weight was obtained from the WCHS and was also verified from the medical records.

Chemotherapy records were scrutinized in detail to collect the following cycle-specific information: type of regimen, drug names and total dose administered, patient weight, dates of administration, complete blood counts (CBCs) at the beginning of each cycle, use of granulocyte colony stimulating factors (G-CSF) and associated adverse events. A total of 356 subjects received chemotherapy for their breast cancer treatment. Of these, 22 cases were excluded because they received a combination of neoadjuvant and adjuvant chemotherapy (n=7) or there was a change in their chemotherapy regimen (n=15). Additionally, 38 subjects were excluded due to missing information on chemotherapy details such drug names, dosage or dates of administration. There were 8 subjects who received combinations of chemotherapy agents that departed significantly from standard of care and they were excluded as well. After applying these exclusions, a total of 288 cases who received either neoadjuvant or adjuvant chemotherapy (corresponding to 2063 chemotherapy cycles) with complete information on dose were included in the analysis.

Relative dose intensity per subject

The primary outcome of the study, chemotherapy dose modification was measured using relative dose intensity (RDI). Hryniuk *et al* in 1984 defined dose intensity of a chemotherapy regimen as the amount of drug delivered per unit time. When expressed as a fraction of the corresponding dose intensity of a standard regimen, it is called RDI.[3,4] RDI captures modifications in chemotherapy that occur either due to delay in administration or reduction in dose. Its calculation is based on the assumption that all drugs in a regimen have equivalent activity against breast cancer. Several research studies have thereafter used RDI to measure dose intensity and it has become widely accepted.[10,17,20,21] In our study we calculated RDI using the same method as proposed by Hryniuk; however, in addition to computing it for the overall chemotherapy course for each subject, we also calculated it for every cycle of chemotherapy administered. The steps outlined below were followed to calculate RDI per subject:

Step 1: Calculate actual dose intensity in mg/day for each drug in a regimen.

$$\text{Actual dose intensity} = \frac{\text{Total dose delivered (mg)}}{\text{Total time taken (days)}}$$

$$\text{Actual dose intensity} = \frac{\sum_{i=1}^{n} \text{Total dose (mg) delivered}}{\sum \text{Day 1 of cycle 1 to last day of cycle n}}$$

where,

i,…..,n= cycle number

n= total number of cycles received

The last day of last cycle is usually not recorded in medical charts. To handle this, average time taken (in days) per cycle was computed for each subject. This value was added to day 1 of the last cycle in order to obtain the last day of last cycle.[22]

Step 2: Calculate expected dose intensity in mg/day for each drug in a regimen.

$$\text{Expected dose intensity} = \frac{\text{Expected total dose (mg)}}{\text{Expected total time (days)}}$$

$$\text{Expected dose intensity} = \frac{\sum_{i=1}^{N}\left(\text{Reference dose in mg/m}^2 \times \text{BSA}_i\right)}{\text{Reference cycle duration (days)} \times N}$$

where,

i,…..,N= cycle number

N= total number of reference cycles

BSA= Body surface area in mg/m^2

The National Cancer Comprehensive Network (NCCN) guidelines were primarily used to obtain reference values for chemotherapy dose and schedule for most of the regimens administered to the study population.[23] There were however, a few regimens that were not included in NCCN recommendations and were mostly administered as a part of an ongoing clinical trial. For these drug combinations, the schedule followed in their respective clinical trial was used as reference. A list of the different chemotherapy regimens included in the analysis and their reference dose and schedule has been provided in the table below.

Regimen	**Reference dose**	**Reference schedule**
Dose-dense AC→ paclitaxel[23]:		
Doxorubicin+ Cyclophosphamide Followed by Paclitaxel	i) Doxorubicin 60 mg/m^2 IV day 1 ii) Cyclophosphamide 600 mg/m^2 IV day 1 Followed by iii) Paclitaxel 175 mg/m^2 IV day 1	Every 14 days for 4 cycles Every 14 days for 4 cycles

AC→ paclitaxel[23]:		
Doxorubicin+	i) Doxorubicin 60 mg/m^2 IV day 1	Every 21 days for
Cyclophosphamide	ii) Cyclophosphamide 600 mg/m^2 IV day 1	4 cycles
Followed by	Followed by	
Paclitaxel	iii) Paclitaxel 80 mg/m^2 IV day 1	Every 7 days for 12 cycles
AC[23]:		
Doxorubicin+	i) Doxorubicin 60 mg/m^2 IV day 1	Every 21 days for
Cyclophosphamide	ii) Cyclophosphamide 600 mg/m^2 IV day 1	4 cycles
TAC[23]:		
Docetaxel+	i) Docetaxel 75 mg/m^2 IV day 1	Every 21 days for
Doxorubcin+	ii) Doxorubicin 50 mg/m^2 IV day 1	6 cycles
Cyclophospahmide	iii) Cyclophosphamide 500 mg/m^2 IV day 1	
AC→ docetaxel[23]:		
Doxorubicin+	i) Doxorubicin 60 mg/m^2 IV day 1	Every 21 days for
Cyclophosphamide	ii) Cyclophosphamide 600 mg/m^2 IV day 1	4 cycles
Followed by	Followed by	
Docetaxel	iii) Docetaxel 100 mg/m^2 IV day 1	Every 21 days for 4 cycles
AC→ albumin-bound paclitaxel[24]:		
Doxorubicin+	i) Doxorubicin 60 mg/m^2 IV day 1	Every 14 days for
Cyclophosphamide	ii) Cyclophosphamide 600 mg/m^2 IV day 1	4 cycles
Followed by	Followed by	
Albumin-bound Paclitaxel	iii) Albumin-bound Paclitaxel 260 mg/m^2 IV day 1	Every 14 days for 4 cycles
CEF[25]:		
Cyclophosphamide+	i) Cyclophosphamide 500 mg/m^2 IV day 1	Every 21 days for
Epirubicin+	ii) Epirubicin 100 mg/m^2 IV day 1	6 cycles
5-Fluorouracil	iii) 5-Fluorouracil 500 mg/m^2 IV day 1	
CE→ T[26]:		
Cyclophosphamide+	i) Cyclophosphamide 600 mg/m^2 IV day 1	Every 21 days for
Epirubicin	ii) Epirubicin 90 mg/m^2 IV day 1	4 cycles
Followed by	Followed by	
Docetaxel	iii) Docetaxel 100 mg/m^2 IV day 1	Every 21 days for 4 cycles
TC[23]:		
Docetaxel+	i) Docetaxel 75 mg/m^2 IV day 1	Every 21 days for
Cyclophosphamide	ii) Cyclophosphamide 600 mg/m^2 IV day 1	4 cycles
CMF[27]:		
Cyclophosphamide+	i) Cyclophosphamide 600 mg/m^2 IV day 1	Every 21 days for
Methotrexate+	ii) Methotrexate 40 mg/m^2 IV day 1	6 or 8 cycles
5-Fluorouracil	iii) 5-Fluorouracil 600 mg/m^2 IV day 1	

T-carboplatin[23]:		
Docetaxel+ Carboplatin	i) Docetaxel 75 mg/m^2 IV day 1 ii) Carboplatin AUC 6 IV day 1	Every 21 days for 6 cycles
Paclitaxel[28]:		
Paclitaxel	i) Paclitaxel 175 mg/m^2 IV day 1	Every 14 days for 4 or 6 cycles

Body surface area (BSA) for each cycle was calculated through Mosteller formula[29] using patient weight recorded in each cycle and patient height obtained from the in-person interview. In situations where patient weight was missing for a cycle, preceding cycles' weight was carried forward to impute missing weight information. This occurred for 10.9% of the total cycles administered (white= 12.9%; AA= 8.6%). Information on cycles that were not given was also incorporated in the calculation of expected dose intensity. Subjects where a schedule of chemotherapy was not completed (i.e., n<N), BSA from the last cycle received was carried forward to compute the reference dose for missing cycles. For example, if a subject only received 2 out of the 4 recommended cycles of a regimen, cycle 2 BSA was used to calculate a reference dose for cycles 3 and 4.

Step 3: Calculate RDI for each drug in a regimen.

$$\text{RDI} = \frac{\text{Actual dose intensity}}{\text{Expected dose intensity}} \times 100\%$$

Step 4: Calculate RDI for a regimen by taking an average of each drug's RDI that comprise the regimen.

Relative dose intensity per cycle

Similar to the steps outlined above, RDI was also computed on a per cycle basis as follows:

Step 1: Calculate actual dose intensity in mg/day per cycle for each drug in a regimen.

$$\text{Actual dose intensity}_i = \frac{\text{Total dose}_i \text{ (mg)}}{\text{Day 1 to last day of cycle}_i \text{ (days)}}$$

The last day of a cycle was considered as the day before the next cycle begins.

Step 2: Calculate expected dose intensity in mg/day per cycle for each drug in a regimen.

$$\text{Expected dose intensity}_i = \frac{\text{Reference dose in mg/m}^2 \times \text{BSA}_i}{\text{Reference cycle duration (days)}}$$

Step 3: Calculate RDI per cycle for each drug in a regimen.

$$\text{RDI}_i = \frac{\text{Actual dose intensity}_i}{\text{Expected dose intensity}_i} \times 100\%$$

Step 4: Calculate RDI per cycle for a regimen by taking an average of each drug's RDI_i that comprise the regimen.

While RDI calculated on a subject level accounted for incomplete chemotherapy regimen, the RDI_i per cycle was calculated only for the cycles that were delivered during therapy.

WBC and ANC level

WBC and ANC levels (per cubic millimeter) recorded at the initiation of each cycle of chemotherapy were examined. Information on the WBC level was available for 89.9% of total cycles included in the study (white=92.7% and AA= 86.7%); whereas, ANC levels were available only for 46.6% of total cycles (white= 46.9% and AA=

46.3%). Due to a high proportion of missing ANC information, WBC level was primarily utilized in this analysis as a surrogate for neutropenia. An occurrence of a neutropenic event, if recorded in the charts and use of G-CSF was also examined.

Patient Factors

Age at diagnosis was categorized into 10-year intervals including: <45 years, 45 to 54 years, 55 to 64 years, or older than 65 years. Highest education level of the study subjects was divided into below college or college graduate and above. Participants were divided into 3 groups of annual household income which included, < $35,000, $35,000 to $69,999, or ≥ $70,000. Primary health insurance coverage of the study population included Medicaid, Medicare, private insurance, or uninsured or self-pay.

BMI was calculated in kg/m^2 and was categorized into underweight or normal (< 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), or obese (≥ 30.0 kg/m^2) using the Centers for Disease Control and Prevention (CDC) classification system. Comorbidities were summarized using a total score of selected comorbid conditions presenting in an individual. It was calculated by assigning a score of 1 to each of the following conditions including, cerebral vascular accident, congestive heart failure, diabetes mellitus, gastro-intestinal disease, hypertension, ischemic heart disease, malignancies, organic heart disease, peripheral vascular disease, primary arrhythmias or conduction problems, renal disease, respiratory problems, neurologic disorders, immunologic or connective tissue disorders, endocrine disorders (other than diabetes), and moderate to

severe liver disease. Study subjects were classified into three levels of the comorbidity score: score of 0, score of 1, or score of ≥ 2.

Tumor Characteristics

Distribution of tumor stage (I or ≥ II), tumor grade (well differentiated, moderately differentiated, or poorly differentiated), histology (favorable or unfavorable), tumor size (≤ 0.5cm, > 0.5cm to ≤ 1.0cm, > 1.0cm to ≤ 2.0cm, or > 2.0cm), and lymph node status (negative or positive) was examined. Information on receptor status of the tumor including Estrogen receptor (ER)/Progesterone receptor (PR) status (one positive, both positive, or both negative), Human Epidermal Growth Factor Receptor 2 (HER2) status (positive or negative), and triple negative status was also examined.

Statistical Analysis

Socio-demographics and tumor characteristics stratified by race were summarized for the study population. We first examined racial differences in WBC levels at time of diagnosis and at cycle 1. Differences in WBC levels, occurrence of neutropenic event and use of G-CSF were then examined across all cycles. The Common Terminology Criteria for Adverse Events (CTCAE) provided by National Cancer Institute was used to classify severity levels of neutropenia (Appendix).[30] Differences in type of chemotherapy received (neo-adjuvant versus adjuvant), type of regimen received, and completion of recommended chemotherapy cycles was examined between the two racial groups. Racial differences in mean RDI delivered and

proportion of subjects receiving <85% and >100% RDI were examined, both on a subject level and cycle level. Receipt of <85% was defined as low dose intensity when examined on a categorical scale due to its significant association with survival in previous studies.[8]

While examining differences on a per cycle basis, information from cycles 1 through 8 was used. This is because all the regimens included in the study were delivered for 8 cycles or less, except for AC → paclitaxel which is usually administered for 16 cycles. Therefore, information from cycles 9 or above was contributed by only one type of regimen and therefore these cycles also had a relatively small size as compared to other cycles. Statistical differences between the two racial groups were determined using t-test for means and chi-square test for proportions on a subject level. Whereas, differences on a cycle level were examined using repeated measure analysis for means and generalized estimating equations for proportions.

The association between race and RDI was examined in three different ways: linear regression to determine mean difference in RDI delivered per subject, binomial regression to determine risk associated with <85% RDI delivered per subject and repeated measures analysis to determine mean difference in RDI delivered per cycle . Three different models were established within each method of analysis: unadjusted model, model adjusted for WBC and model adjusted for G-CSF use. The repeated measure analysis provided the advantage of examining the role of WBC or G-CSF use over time (i.e., by cycles). All analysis was conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

A total of 145 white cases and 143 AA cases who received chemotherapy were included in the study. White females who received chemotherapy were more likely to have young age at diagnosis, high education level, private health insurance coverage, normal weight and low comorbidities in comparison to AA cases (Table 1). While examining tumor characteristics of subjects undergoing chemotherapy (Table 2), a higher proportion of AA subjects versus white subjects presented with larger tumor size, higher stage and grade, and receptor negative tumor. Both the groups were similar with respect to tumor histology and lymph node status.

As seen in Table 3, white subjects had a higher mean WBC level at the time of diagnosis as compared to AA subjects (7.1×10^9/L versus 6.4×10^9/L, *p= 0.018*). However, at the start of chemotherapy (i.e. at cycle 1) WBC levels were similar between the two groups (white= 7.6×10^9/L; AA= 7.6×10^9/L, *p= 0.873*). While comparing mean WBC level across all cycles, again no difference was observed between white and AA subjects (white= 8.9×10^9/L; AA= 8.9×10^9/L, *p= 0.913*). Additionally, when examined on a categorical scale, a grade 2 or higher level of severity of neutropenia, defined as WBC $< 3.0\times10^9$/L was observed for less than 2% cycles, with no differences seen by race (white= 1.7%; AA= 1.9%, *p= 0.838)*. Neutropenic events explicitly recorded in medical charts, occurred in only in 3.5% cycles for white cases and 4.2% cycles for AA cases (*p=0.544).* A high use of G-CSF was seen in the study population although it was similar between whites and AAs (69.5% versus 71.4%, *p= 0.669*).

Mean WBC level and G-CSF use comparing the two racial groups for each cycle has been shown in Figure 1 and Figure 2, respectively. There was an overall increase in WBC level from cycle 1 to cycle 8 ($p< 0.001$); however, the trend was very similar among white and AA subjects for each cycle ($p= 0.913$). Similarly, although there was a difference in use of G-CSF between cycles, the trend was very similar for whites and AAs ($p= 0.822$).

Racial differences in chemotherapy characteristics and RDI are shown in Table 4. The majority of study subjects received adjuvant chemotherapy (white= 93.1%, AA= 91.6%) and the remaining received neoadjuvant chemotherapy (white= 6.9%, AA= 8.4%) with no differences seen by race. Commonly administered regimens were dose-dense AC→ paclitaxel (white= 32.4%, AA= 25.2%), AC→ paclitaxel (white= 13.1%, AA= 9.8%), AC (white= 12.4%, AA= 11.9%) and TC (white= 17.2%, AA= 23.1%). Receipt of anthracycline-based regimen (contain doxorubicin or epirubicin) was similar between white and AA subjects (69.7% and 67.1%, respectively). Of those who received anthracycline-based regimen, taxanes (docetaxel or paclitaxel) were added in 80.2% white subjects and 82.3% AA subjects. A higher proportion of AA subjects (10.5%) did not complete recommended number of cycles in comparison to white subjects (5.5%), although not statistically significant ($p= 0.120$).

As shown in Table 4, significantly higher mean RDI was delivered during the course of chemotherapy for white subjects in comparison to AA subjects (100.0% versus 94.4%, $p= 0.005$). Proportion of subjects who experienced a >15% reduction in RDI was more than twice for the AA group versus the white group (21.7% versus 8.3%,

p= 0.001). Furthermore, 33.1% whites received >100% RDI compared to only 20.3% AAs (*p= 0.014)*.

While comparing RDI delivered per cycle, AA subjects also had a lower mean RDI per cycle (92.7 versus 99.9, *p<0.001*), a higher proportion of cycles with <85% RDI (24.6% versus 9.1%, *p<0.001*) and lower proportion of cycles with >100% RDI (17.1% versus 32.0%, *p<0.001*), in comparison to white subjects. While examining differences in mean RDI delivered per cycle by race (Figure 3), it was systematically lower for AA versus white subjects (*p< 0.001*).

Results from the unadjusted and adjusted models between race and RDI delivered per subject are shown in Table 5. Results from the unadjusted model showed that mean RDI delivered during chemotherapy was 5.62% lower for AAs versus whites (95% CI: -9.51, -1.73). After adjusting for mean WBC level per subject (model 2) and G-CSF use at the start of chemotherapy (model 3), the mean difference in RDI% between AAs versus whites was -5.29 (95% CI: -9.27, -1.32) and -5.69 (95% CI: -9.57, -1.81), respectively. When RDI delivered per subject was examined on a categorical scale AAs were also associated with a significantly higher risk of receiving <85% RDI during the course of chemotherapy, both in the unadjusted and the adjusted models. The relative risk (RR) comparing AA versus whites were 2.62 (95% CI: 1.40, 4.89) in model 1 (unadjusted model), 2.50 (95% CI: 1.33, 4.70) in model 2 (adjusted for mean WBC level per subject) and 2.63 (95% CI: 1.41, 4.92) in model 3 (adjusted for G-CSF use in cycle 1). All the adjusted models were tested for interaction and they were not found to be significant.

Table 6 shows results from the repeated measures analysis examining racial differences in mean RDI delivered per cycle. AAs received a significantly lower mean RDI% per cycle as compared to white subjects (difference= -8.27; 95% CI: -11.87, -4.67). The difference remained significantly higher after adjusting for mean WBC per cycle (difference AA versus white = -7.92; 95% CI: -11.61, -4.24). In model 3, interaction between race and G-CSF was statistically significant ($p< 0.001$) and the association was therefore, estimated separately by G-CSF use. Difference between AA and whites was much higher when G-SCF was used (difference= -10.03; 95% CI: -13.91, -6.15) versus when G-CSF was not used (difference= -3.45; 95% CI: -8.08, 1.18). Change in mean RDI% delivered per cycle by race and G-CSF use has been shown in Figure 4.

Discussion

In this study we examined differences in delivery of chemotherapy between AA and white subjects with early breast cancer and role of neutropenia in explaining these differences. We found that AA women were significantly more likely to receive a reduced RDI during chemotherapy as compared to white women. However, WBC levels did not explain these differences. In fact, both the groups were very similar in their WBC levels at the start of chemotherapy as well as across the cycles delivered.

There has been an increase in the use of adjuvant chemotherapy for all stages of breast cancer[16], but AA women are more likely to experience delays in initiating chemotherapy as compared to their white counterparts.[20,31] Recent evidence has also suggested that once chemotherapy is started AAs are more likely to discontinue treatment early, receive reduced doses or experience dose delays.[14,15,17,18] Only two of these studies have however used a robust measure like RDI to define chemotherapy modifications. Griggs et al[17] reported a significantly lower mean RDI among AAs versus whites (76% and 81%, respectively; $p= 0.01$); whereas, Hershman et al[20] failed to see any differences between the two groups (AA= 87% and white=86%). Although RDI delivered during chemotherapy was relatively higher for our study population than that reported previously, AAs received a significantly lower mean RDI (94% versus 100%) and were 2.62 times more likely to experience greater than 15% reductions in RDI as compared to white subjects.

Neutropenia has been identified as one of the strongest predictors of dose reductions and dose delays during chemotherapy.[8-11] Since AA women in general have

lower WBC and ANC levels than white women, we hypothesized that differences in their blood counts will explain the differences in dose reductions seen during chemotherapy.[12-15] However, after adjusting for mean WBC level during chemotherapy the association between RDI and race stayed the same. In order to investigate this in more details, we also computed RDI for every cycle of chemotherapy delivered. This allowed us to examine the impact of changing WBC level on RDI per cycle. However, mean WBC per cycle was also similar between the two groups. As a result, when adjustment for WBC level per cycle was done, no significant change in the association between race and mean RDI per cycle was seen.

In our study, the occurrence of neutropenia was very low. A grade 2 or higher severity of neutropenia was seen in less than 2% cycles and it was not different between AAs and whites. A possible reason for such a low occurrence of neutropenia could be the high use of G-CSF seen in this population (approximately two-third of total cycles). G-CSFs are given to stimulate the production of WBC in the bone marrow which helps reduce severity and duration of neutropenia in cancer patients.[32] A high prophylactic use of G-CSF could have masked the difference in neutropenia between the two groups. Therefore, we also investigated the association between race and RDI after adjusting for G-CSF use. No significant change in the association was seen after adjusting for G-CSF use in cycle 1 in the subject-level model. When G-CSF use per cycle was adjusted for in the cycle-level analysis a significant interaction between race and G-CSF was seen. The mean difference in RDI delivered per cycle was larger in cycles where G-CSF was administered as compared to the cycles where G-CSF was

not administered. Although across both levels of G-CSF use, AAs received a lower RDI than whites.

The effect of neutropenia was examined using WBC levels instead of ANC levels, which was a major limitation in the study. Use of the ANC is a more accurate way of measuring neutropenia but due to high proportion of missing information on ANC levels, it was not used in the analysis. However, we were the first ones to examine RDI not only at a subject level but also at the cycle level. Most of the previous studies have examined either time delay or dose reduction on a cycle level, but not RDI on a cycle level.

Evidence from clinical trials has suggested that a reduction in dose intensity delivered during chemotherapy can have a significant negative impact on survival.[6-8] Future research that examines the role of other toxicities or possible patient or physician related factors in explaining the existing disparity in receipt of chemotherapy between AA and white women with breast cancer is warranted.

Tables and Figures

Table 1. Socio-demographics and clinical characteristics of subjects receiving chemotherapy, by race

Characteristics, n (%)	White (n=145)	AA (n=143)
Age at diagnosis, years		
< 45	39 (26.9)	34 (23.8)
45-54	62 (42.8)	46 (32.2)
55-64	32 (22.1)	55 (38.5)
≥ 65	12 (8.3)	8 (5.6)
Education		
Below college	57 (39.3)	95 (66.4)
College graduate and above	86 (59.3)	37 (25.9)
Unknown	2 (1.4)	11 (7.7)
Annual household income		
< $35,000	8 (5.5)	43 (30.1)
$35,000 - $69,999	20 (13.8)	39 (27.3)
≥ $70,000	104 (71.7)	36 (25.2)
Unknown	13 (9.0)	25 (17.5)
Primary health insurance		
Medicaid	3 (2.1)	7 (4.9)
Medicare	8 (5.5)	12 (8.4)
Private insurance	128 (88.3)	101 (70.6)
No insurance or self-pay	6 (4.1)	20 (14.0)
Unknown	0 (0.0)	3 (2.1)
Body mass index		
Underweight or normal weight	78 (53.8)	23 (16.1)
Overweight	33 (22.8)	44 (30.8)
Obese	33 (22.8)	76 (53.1)
Unknown	1 (0.7)	0 (0.0)
Comorbidity score		
0	51 (35.2)	22 (15.4)
1	42 (29.0)	41 (28.7)
≥ 2	52 (35.9)	80 (55.9)

Abbreviations: AA=African American
P-values were derived from chi-square test for proportions

Table 2. Tumor characteristics of subjects receiving chemotherapy, by race

Tumor Characteristics, n (%)	White (n=145)	AA (n=143)
AJCC tumor stage		
Stage I	62 (42.8)	40 (28.0)
Stage II or above	83 (57.2)	102 (71.3)
Unknown	0 (0.0)	1 (0.7)
Tumor grade		
Well differentiated	18 (12.4)	3 (2.1)
Moderately differentiated	64 (44.1)	50 (35.0)
Poorly differentiated	59 (40.7)	85 (59.4)
Unknown	4 (2.8)	5 (3.5)
Histology		
Unfavorable	143 (98.6)	142 (99.3)
Favorable	2 (1.4)	1 (0.7)
Tumor size		
≤ 0.5cm	8 (5.5)	7 (4.9)
> 0.5cm to ≤ 1.0cm	21 (14.5)	11 (7.7)
> 1.0cm to ≤ 2.0cm	69 (47.6)	44 (30.8)
> 2.0cm	47 (32.4)	81 (56.6)
Lymph node status		
Negative	85 (58.6)	86 (60.1)
Positive	60 (41.4)	57 (39.9)
ER/PR status		
Only one positive (ER + or PR +)	11 (7.6)	19 (13.3)
Both positive (ER + and PR +)	98 (67.6)	66 (46.2)
Both negative (ER - and PR -)	36 (24.8)	56 (39.2)
Unknown	0 (0.0)	2 (1.4)
HER2 status		
Positive	34 (23.4)	37 (25.9)
Negative	111 (76.6)	103 (72)
Unknown	0 (0.0)	3 (2.1)
Triple negative status		
Yes	23 (15.9)	41 (28.7)
No	122 (84.1)	99 (69.2)
Unknown	0 (0.0)	3 (2.1)

Abbreviations: AA=African American; AJCC=American joint committee on cancer; ER=Estrogen receptor; PR=Progesterone receptor; HER2=Human epidermal growth factor receptor 2

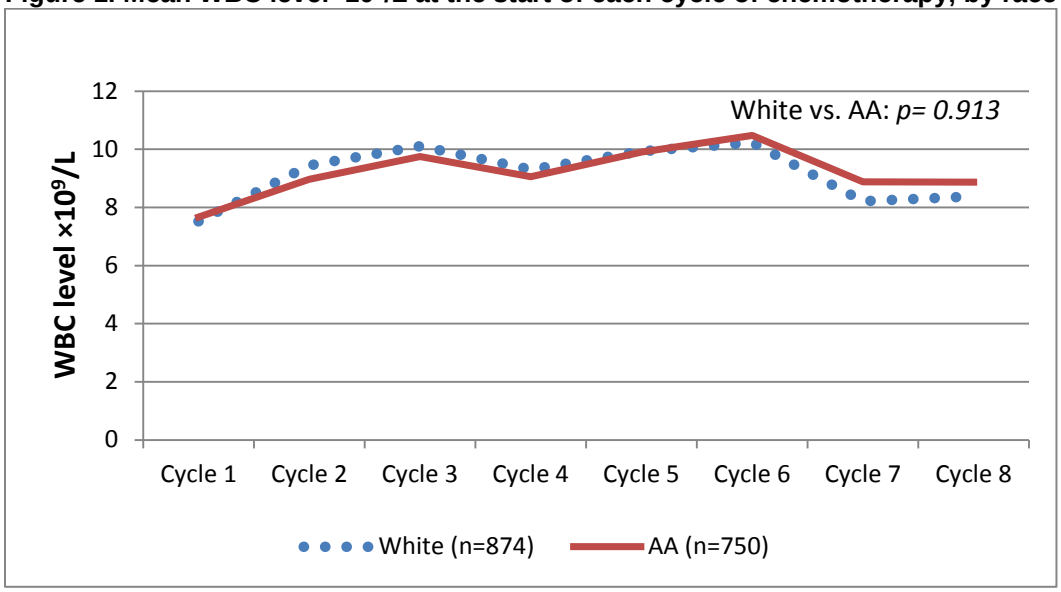
P-values were derived from chi-square test for proportions

Table 3. WBC level (10^9/L), neutropenic event and G-CSF use during chemotherapy, by race

Total subjects	White (n=145)	AA (n=143)	*P-value*
WBC at diagnosis			
N subjects	136	133	
Mean (SD)	7.1 (2.3)	6.4 (2.4)	*0.018*
WBC at cycle 1			
N subjects	139	124	
Mean (SD)	7.6 (3.6)	7.6 (3.9)	*0.873*
Total cycles	**White (n=1099)**	**AA (n=964)**	
WBC for all cycles			
N cycles	1016	833	
Mean (SE)	8.9 (0.34)	8.9 (0.35)	*0.913*
% cycles < 3.0×10^9/L	1.7	1.9	*0.838*
Neutropenic event, %	3.5	4.2	*0.544*
G-CSF use, %	69.5	71.4	*0.669*

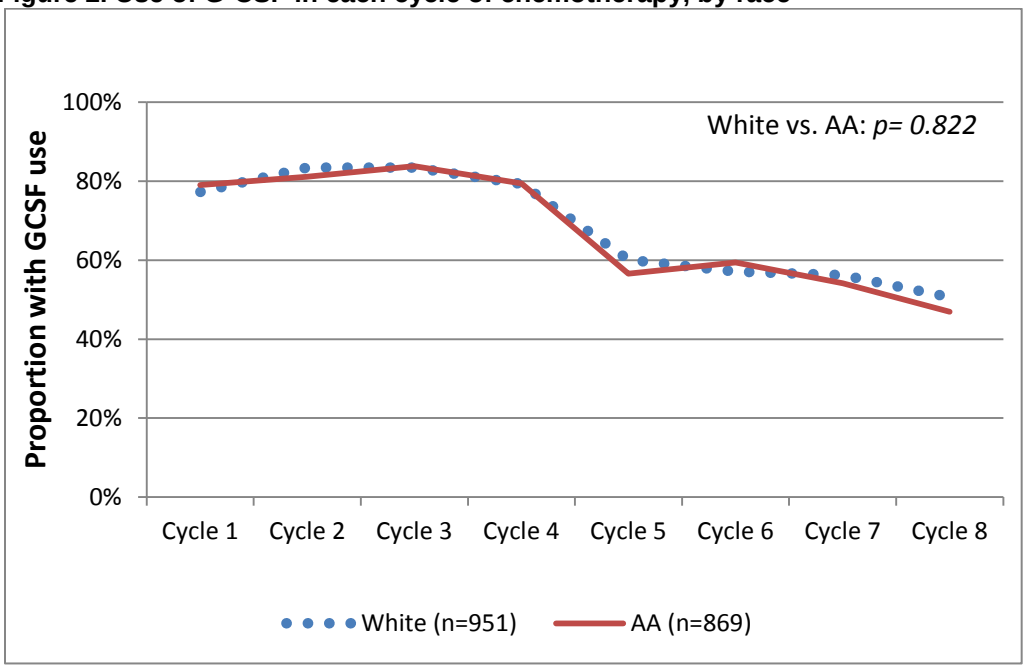
Abbreviations: AA=African American; WBC=White blood cells; SD=Standard deviation; SE=Standard error; G-CSF=Granulocyte-colony stimulator factor
P-values were derived from t-test for means, chi-square test for proportions, repeated measures model for mean per cycle and generalized estimating equations for proportion per cycle.

Figure 1. Mean WBC level×10^9/L at the start of each cycle of chemotherapy, by race



Abbreviations: WBC=White blood cell; AA=African American

Figure 2. Use of G-CSF in each cycle of chemotherapy, by race



Abbreviations: G-CSF=Granulocyte colony stimulating factor; AA=African American

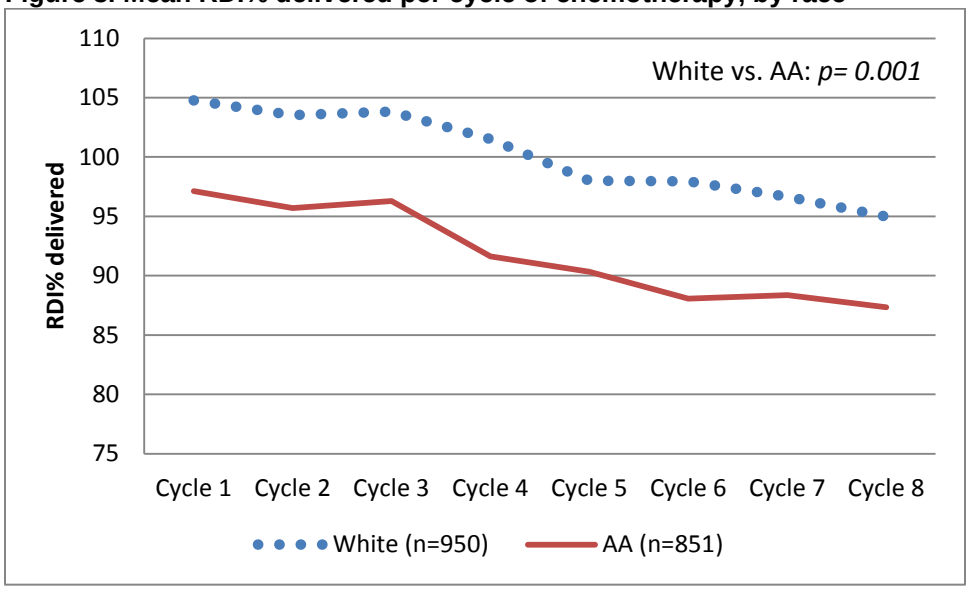
Table 4. Chemotherapy characteristics and RDI delivered, by race

Characteristics	White (n= 145)	AA (n=143)	*P-value*
Chemotherapy type, n (%)			*0.633*
Adjuvant	135 (93.1)	131 (91.6)	
Neoadjuvant	10 (6.9)	12 (8.4)	
Chemotherapy regimen, n (%)			
Dose-dense AC⟶ paclitaxel	47 (32.4)	36 (25.2)	
AC⟶ paclitaxel	19 (13.1)	14 (9.8)	
AC	18 (12.4)	17 (11.9)	
TAC	8 (5.5)	13 (9.1)	
AC⟶ docetaxel	6 (4.1)	13 (9.1)	
AC⟶ albumin-bound paclitaxel	1 (0.7)	2 (1.4)	
CEF	2 (1.4)	0 (0.0)	
CE⟶ T	0 (0.0)	1 (0.7)	
TC	25 (17.2)	33 (23.1)	
CMF	14 (9.7)	3 (2.1)	
T-carboplatin	3 (2.1)	10 (6.7)	
Paclitaxel	2 (1.4)	1 (0.7)	
Chemotherapy completed, n (%)			*0.120*
Yes	137 (94.5)	128 (89.5)	
No	8 (5.5)	15 (10.5)	
RDI% per subject			
Mean (SD)	100.0 (15.6)	94.4 (17.9)	*0.005*
< 85%, n (%)	12 (8.3)	31 (21.7)	*0.001*
> 100%, n (%)	48 (33.1)	29 (20.3)	*0.014*
RDI% per cycle	N= 1095	N= 946	
Mean (SE)	99.9 (1.2)	92.7 (1.2)	*<0.001*
< 85%	9.1%	24.6%	*<0.001*
> 100%	32.0%	17.1%	*<0.001*

Abbreviations: AA=African American; RDI=Relative dose intensity; SD=Standard deviation; IQR=Interquartile range; SE=Standard error

P-values were derived from t-test for means, chi-square test for proportions, repeated measures model for mean per cycle and generalized estimating equations for proportion per cycle.

Figure 3. Mean RDI% delivered per cycle of chemotherapy, by race



Abbreviations: RDI=Relative dose intensity; AA=African American

Table 5. Unadjusted and adjusted association between race and RDI delivered per subject

Model	Mean difference in RDI (95% CI)	Relative risk of RDI< 85% (95% CI)
MODEL 1		
Race		
AA vs. White	-5.62 (-9.51, -1.73)	2.62 (1.40, 4.89)
MODEL 2		
Race		
AA vs. White	-5.29 (-9.27, -1.32)	2.50 (1.33, 4.70)
Mean WBC level		
Every 1000 cell decrease	-0.27 (-0.76, 0.21)	1.02 (0.95, 1.09)
MODEL 3		
Race		
AA vs. White	-5.69 (-9.57, -1.81)	2.63 (1.41, 4.92)
G-CSF use at cycle 1		
Yes vs. No	3.90 (-0.83, 8.56)	0.88 (0.47, 1.67)

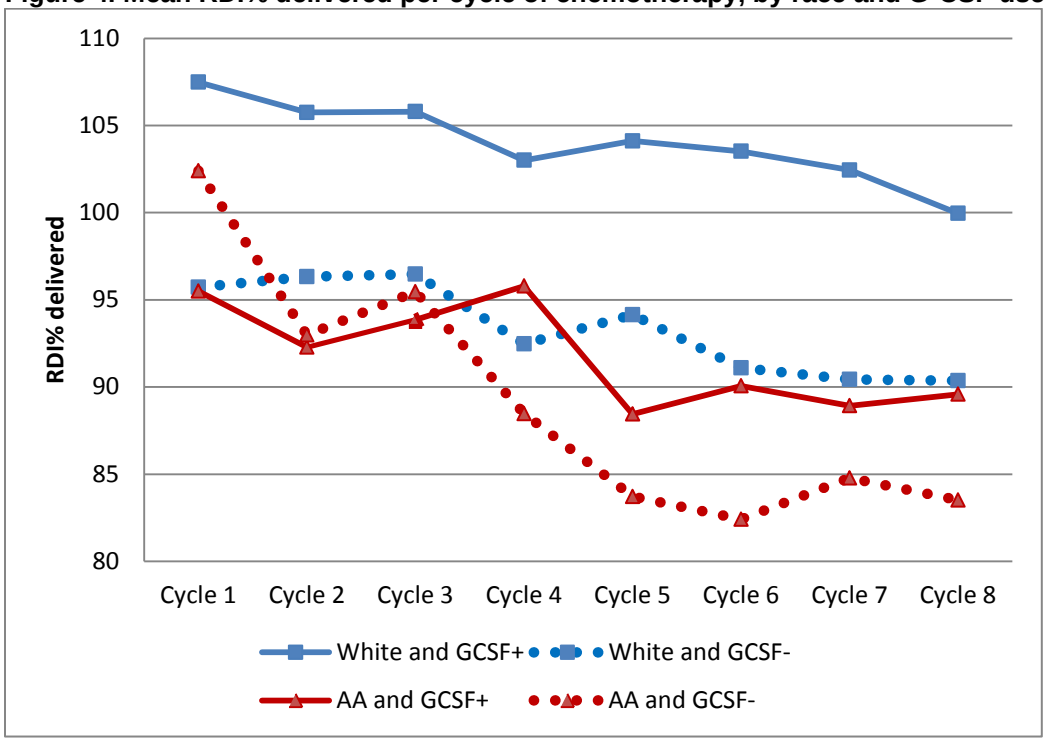
Abbreviations: RDI=Relative dose intensity; CI=Confidence interval; AA=African American; WBC=White blood cell; G-CSF=Granulocyte-colony stimulating factor

Table 6. Unadjusted and adjusted association between race and RDI delivered per cycle

Model	Mean difference in RDI per cycle (95% CI)
MODEL 1	
Race	
AA vs. White	-8.27 (-11.87, -4.67)
MODEL 2	
Race	
AA vs. White	-7.92 (-11.61, -4.24)
Mean WBC level	
Every 1000 cell decrease	-0.33 (-0.49, -0.17)
MODEL 3	
AA vs. White (among G-CSF+)	-10.03 (-13.91, -6.15)
AA vs. White (among G-CSF-)	-3.45 (-8.08, 1.18)

Abbreviations: RDI=Relative dose intensity; CI=Confidence interval; AA=African American; WBC=White blood cell; G-CSF=Granulocyte-colony stimulating factor

Figure 4. Mean RDI% delivered per cycle of chemotherapy, by race and G-CSF use



Abbreviations: RDI=Relative dose intensity; G-CSF=Granulocyte colony stimulating factor; AA=African American

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CONCLUSION

This dissertation examined the following research questions among early stage breast cancer patients 1) Racial differences in the use of pre-operative MRI and the role of pre-operative MRI on rates of re-operation and CPM, and time to surgery; 2) Racial differences in elapsed time and sessions received during radiation therapy; and 3) Racial differences in chemotherapy dose modifications and role of neutropenia in this association.

In the first chapter we demonstrated that although use of pre-operative MRI was significantly higher among white patients in comparison to AAs, it did not offer substantial benefits on surgical management of breast cancer. Despite the higher sensitivity of MRI in detecting tumor extent in comparison to conventional imaging, re-operation rates did not differ significantly between pre-operative MRI recipients and non-recipients. Furthermore, an approximately two-fold higher risk of undergoing CPM was seen among MRI subjects as compared to those who did not receive MRI after controlling for potential confounders. Adjusted time from diagnosis to initial breast surgery was also significantly longer for MRI subjects. The disproportionate use of MRI may result in different outcomes in different populations. The significant influence of MRI in the decision making process of undergoing a CPM that may be unnecessary, or a delay in receiving breast surgery raise particular concern in the absence of survival benefits associated with it.

The next two chapters in this dissertation assessed race related disparities during receipt of radiation therapy and chemotherapy administered for treatment of early

stage breast cancer. There is extensive evidence showing that AA women are less likely to receive optimal treatment for breast cancer as compared to their white counterparts. Additionally, among women to receive recommended treatment, AAs experience longer delays in initiating treatment. These racial differences are shown to exist within almost all the treatment modalities of breast cancer including surgery, radiation therapy, and adjuvant systemic treatment. However, research is limited in examining whether differences by race also prevail in the pattern of care delivered once treatments are initiated.

It has been established in fast growing cancers like head and neck, lung and cervix that prolongation of treatment time during radiation therapy negatively impacts patient outcomes. Recently, a study by Bese *et al* also showed a significant reduction in local control rate for breast cancer due to an interruption in radiation treatment that is greater than one week. In chapter 2, while examining differences in elapsed time and sessions received during a standard course of radiation therapy, we were unable to find any differences between AAs and whites. For both races, median elapsed time was 48 days and 41 days and median number of sessions received (with boost) was 33 and 28 during a standard radiation course following lumpectomy and mastectomy, respectively (all $p > 0.05$). Additionally, proportion of subjects taking longer than 49 days to complete the standard course of radiation following lumpectomy was also similar between the two groups (AA= 36.3% and white= 36.4%). Among other predictors of elapsed time examined, low household income, high BMI level, and receipt of care at a community-based radiation facility were associated with a protracted radiation course;

but only type of radiation facility was identified as an independent predictor. Given current treatment recommendations, it does not require more than 7 weeks to complete a standard course of radiation therapy (including weekend breaks); however, more than one-third of our study population took longer than the expected time. Due to limited research, a safe minimum for prolongation during radiation therapy among breast cancer patients has not yet been established. Nevertheless, it is important to identify subjects who experience a gap or interruption in their treatment so that changes can be made to compensate for prolongation and reduce the chances of negatively impacting treatment outcomes.

In chapter 3 of this dissertation we investigated racial differences in dose modifications experienced during delivery of chemotherapy among early breast cancer patients. Since AA women in general have lower WBC and ANC levels than white women, we also postulated that if racial differences exist in chemotherapy dose modifications, most of it can be explained by differences in their blood counts. We utilized RDI to define chemotherapy dose modifications as it has been previously associated with survival among breast cancer patients. Overall, AA women received a significantly lower mean RDI as compared to white women (AA= 94.4% and white= 100.0%, *p= 0.005*). Risk of experiencing a >15% reduction in RDI was more than twice among AAs versus whites (RR= 2.62, 95% CI: 1.40, 4.89). However, no significant differences were seen either in their mean WBC level at the beginning of chemotherapy (i.e., at cycle 1) nor in their mean WBC level across all cycles. As a result, when adjusted for the mean WBC level, no significant change in the association was

observed, and AA continued to have a high risk of dose reduction. We also investigated differences in RDI delivered in every cycle in order to incorporate time varying differences in WBC level within the analysis. However, similar to what was observed on a subject level, no change in the association between RDI per cycle and race occurred after adjusting for WBC level at every cycle. A very high use of GCSF was observed in the study population. GSCFs are used to stimulate the production of WBC from bone marrow because of which it could have masked the differences due to neutropenia. We therefore, also examined the association under study by adjusting for GCSF use instead of WBC levels. However, no change was seen in the risk estimates at the subject level analysis. In the cycle level analysis we observed a different association by use of GCSF. The difference in RDI delivered by race was much higher when GCSF were used as compared to when GCSF were not used. Although across both the levels of GCSF use, AAs continued to receive a reduced RDI per cycle.

The studies conducted as a part of this dissertation takes advantage of detailed clinical and treatment information available in medical records of patients diagnosed with early stage breast cancer. Such kind of information therefore allowed us to conduct studies to understand differences in pattern of care delivered during receipt of various treatment modalities. This was also a population-based cohort study that added to the strength of these investigations.

APPENDIX: Common Toxicity Criteria by National Cancer Institute

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Febrile Neutropenia			ANC<1000/mm3 with a single temperature of > 38.3^{0C} or a sustained temperature of ≥ 38^{0C} for > 1 hour	Life threatening consequences; urgent intervention indicated	Death
Neutrophil count decreased	1500 - <LLN*	1000 - < 1500	500 - <1000	<500	-
White blood cell count decreased	3000 - <LLN*	2000 - <3000	1000 - <2000	<1000	-

Source: CTCAE 4.03- June 14, 2010: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

*LLN- An abbreviation for Lower Limit of Normal, usually in reference to laboratory values.

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