IS THERE A DIFFERENCE IN COMPLETION RATE OF RADIATION TREATMENT IN AFRICAN AMERICAN AND CAUCASIAN WOMEN IN CLINICAL TRIALS?

by

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IS THERE A DIFFERENCE IN COMPLETION RATE OF RADIATION TREATMENT IN AFRICAN AMERICAN AND CAUCASIAN WOMEN IN CLINICAL TRIALS?

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University of Pittsburgh, 2009

Breast cancer is a disease that can affect all women. However, the rate at which this disease affects women varies by race and ethnicity.

When one analyzes incidence rates for a life threatening disease, a higher incidence rate for a certain group usually portends a higher death rate. However this is not necessarily true for breast cancer. In particular, when comparing incidence rates with their white counterparts, African American women have a lower incidence rate but a higher death rate.

The phenomenon of racial differences or health disparities among cancer patients has been established several times by studies primarily associated with differences in health care in the general population. However, within randomized clinical trials, one does not anticipate that disparities in health outcome would be evident as all patients receive treatment in accordance with standard treatment protocols. The purpose of this study is to test this premise by asking the question: Is there a difference in radiation treatment when comparing African American and Caucasian women who are treated in randomized clinical trials?

The study population includes patients from the National Surgical Adjuvant Breast and Bowel Project (NSABP) on various protocols (B15, B16, B18, B22, B23, B25, and B28). The

focus was on patients who received chemotherapy in the form of Adriamycin and cyclophosphamide (AC), alone or prior to other chemotherapy agents. AC was given as adjuvant in all of the protocols. There were 9,646 Caucasian patients and 1,040 African-American (AA) patients. Among these patients were 3,504 Caucasian patients and 377 AA patients who received radiation therapy according to protocol.

After adjusting for various potential confounders no evidence was found of a difference by race in total radiation therapy.

Public health importance: Randomized clinical trials provide important evidence for the choices of breast cancer treatment. The success of such trials in providing an environment where patients received a standardized treatment would be called into question if there were treatment differences by race in those trials. This study did not find evidence of racial disparity in radiation therapy in the NSABP breast cancer trials examined.

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1.0 INTRODUCTION

1.1 WHAT IS BREAST CANCER?

Although breast cancer is a disease that can affect all women, the rate at which this disease affects women varies by race and ethnicity.[i] According to the Center for Disease Control (CDC) in 2005, 186,467 women developed breast cancer and 41,116 died from the disease in the United States (CDC 2009).

Cancer occurs when a malignant tumor, an abnormal and uncontrollable growth, develops in the body tissue. Cancers are named based for the body tissue of origin. Thus, cancers that form in the breast tissue are labeled as breast cancer.

Malignant, or cancerous, breast tumors are capable of spreading to parts of the body beyond the breast (NCI 2009). Benign breast tumors are not life threatening and do not spread outside the breast (NCI 2009).

The cells in breast tissue may cycle between states of proliferation and quiescence. Uncontrolled cell growth does not occur when gene function is in equilibrium. When this balance is lost, uncontrolled and aberrant cell growth results. Along with abnormal growth, cancerous tumors can spread through lymphatic and vascular pathways to involve lymph nodes and other tissues in the body. This process is referred to as metastasis (NCI 2009).

Lymph nodes are small glands or organs that are connected by lymphatic vessels. Breast cancer cells can enter the small, vein-like lymphatic vessels and begin to grow (ACS 2009). When lymph nodes are affected by breast cancer they are labeled as "positive" and when the lymph nodes are not affected they are labeled as "negative". The number of lymph nodes positive or negative is very important in determining the appropriate treatment. Doctors usually characterize a patient's stage and prognosis, in part, based upon the number of either clinically or pathologically positive lymph nodes (NCI 2009).

Figure 1 is an image of normal breast cells. Each breast has several sections called lobes and each lobe has smaller sections called lobules (B). The cancer usually forms in the breast ducts that carry milk to the nipple, (D), and the lobules, (B), that make the milk (natural-disease-solutions.com 2009). The rest of the breast consists predominately of adipose tissue.

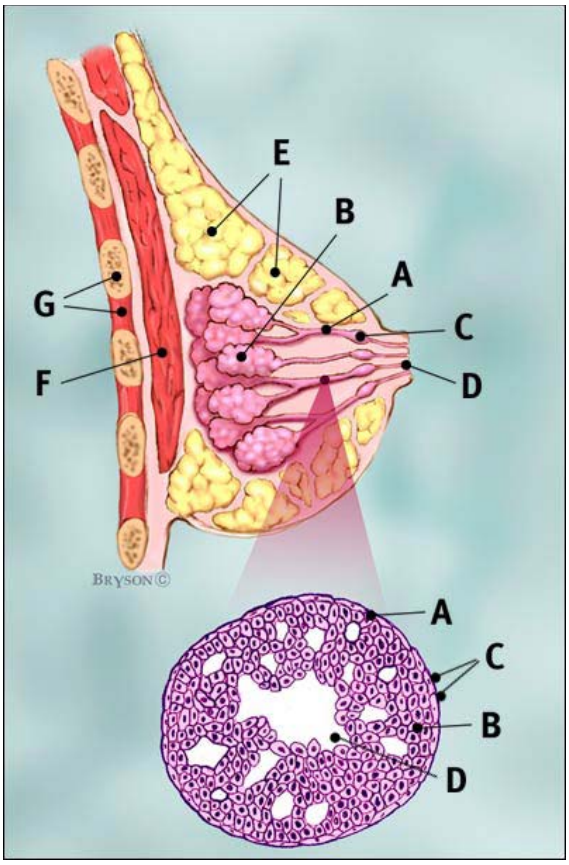

Figure 1. Normal Breast Tissue

Adapted from natural-disease-solutions.com 01/08/2009

Bill Montgomery

Breast profile:

A Ducts
B Lobules
C Dilated section of duct to hold milk
D Nipple
E Fat
F Pectoralis major muscle
G Chest wall/rib cage

Inset

A Normal duct cells
B Basement membrane
C Lumen (center of duct)

Breast cancer is made up of two main types, noninvasive and invasive and is usually classified by the kind of tissue in which the cancer starts and by the extent of its spread. Noninvasive breast cancer can be classified as ductal carcinoma in situ (DCIS), Figure 2, and lobular carcinoma in situ (LCIS) (NCI 2007). In DCIS, abnormal cells originate in the ducts and are confined to the milk ducts of the breast, accounting for 20 to 30 % of breast cancers. With LCIS, abnormal cells originate in the lobules and proliferate within milk-producing glands of the breast. Women with LCIS have a 30% chance of developing invasive breast cancer in the same or opposite breast during the subsequent 2-3 decades following the original diagnosis (Merck.com 2009). LCIS accounts for 1 to 2 percent of breast cancer. With both of these classifications, there are abnormal cells present but they have not invaded surrounding tissue. Even though the cells in the breast are not cancerous with carcinoma in situ, this is an indication that breast cancer may develop at a later time (Breastcancer.org 2009).

Figure 3 is an image of invasive breast cancer.

Breast cancer that begins in the ducts and spreads to nearby tissue is called invasive ductal carcinoma (IDC), which accounts for about 65 to 80 percent of all breast cancers (Merck.com 2009). IDC originates in the milk ducts invading the surrounding breast tissue by breaking through the wall of the ducts. Breast cancer that begins in the lobes and spreads to nearby tissue is called invasive lobular carcinoma (ILC) (BreastCancer.org 2009). ILC begins in the part of the breast that produces milk and spreads to other parts of the body by invading the surrounding breast tissue. This type of invasive breast cancer accounts for 10 to 15 percent of breast cancers (Merck.com 2009). Inflammatory breast cancer (IBC) is an uncommon type of invasive cancer that is fast-growing and often fatal. The cancer cells block the lymphatic vessels in the skin of the breast, causing the breast to appear inflamed, look swollen and red, and even

feel warm. This type of breast cancer usually spreads to the lymph nodes of the armpit. These axillary lymph nodes can feel like hard lumps but often no individual, discrete lump is felt in the breast because this cancer is dispersed throughout the entire breast itself. Inflammatory breast cancer accounts for about 1% of breast cancers (Merck.com 2009).

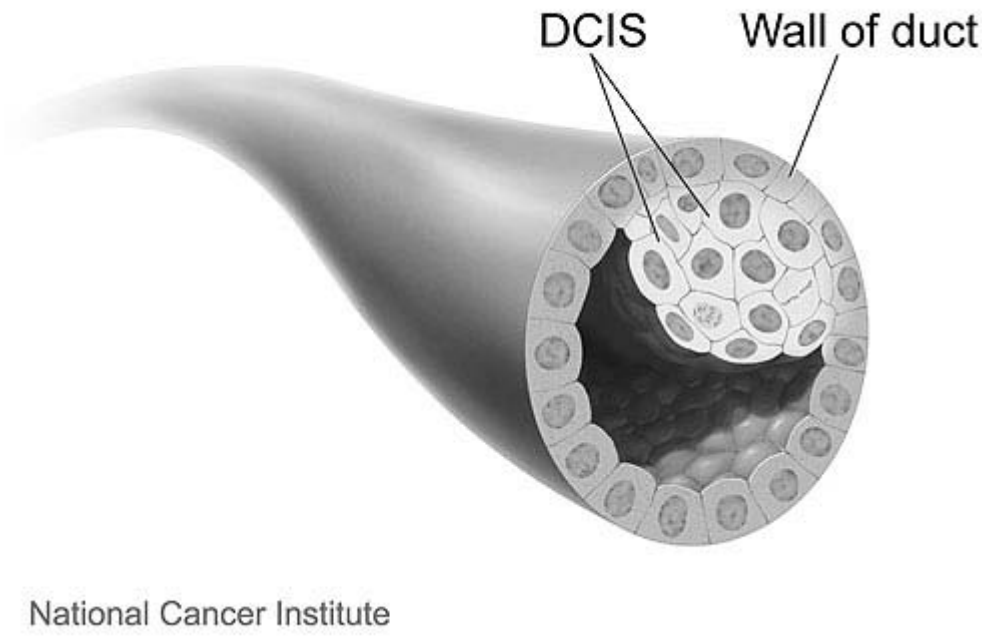

Figure 2. Ductal Carcinoma in situ (DCIS)

Adapted from NCI 01/08/2009

Don Bliss (artist)

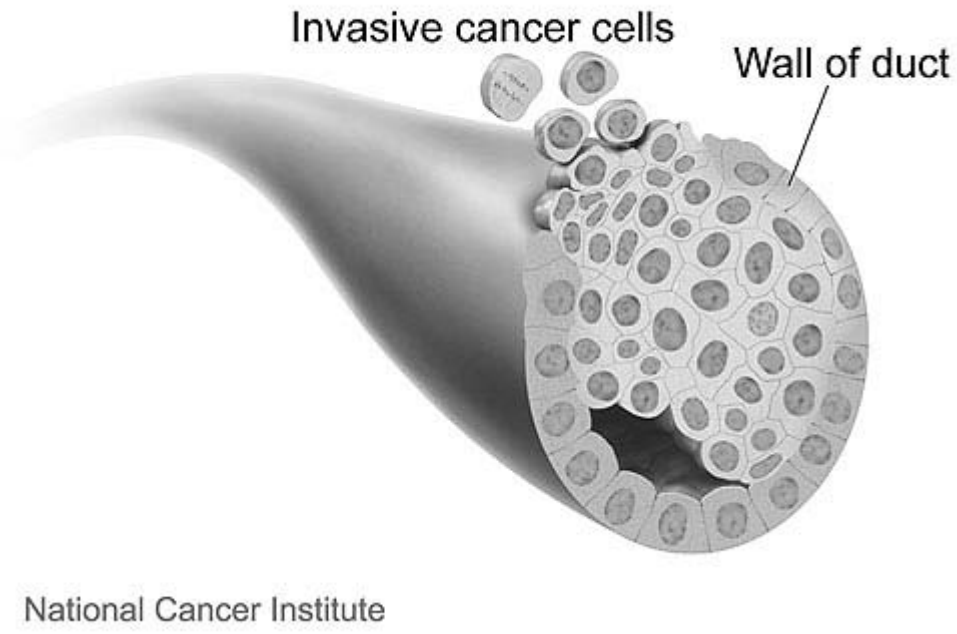

Figure 3. Invasive Breast Cancer

Adapted from NCI 01/08/2009
Don Bliss (artist)

1.2 INCIDENCE AND MORTALITY

When one analyzes incidence rates for a life threatening disease, a higher incidence rate for certain groups usually portends a higher death rate. However, this is not necessarily true for breast cancer.

In the United States, breast cancer mortality rates are increasing and there are significant survival differences for African-American women (Jotoi 2005, Shiao 1997). African-American women have lower incidence rates of breast cancer, but, compared to white women, they are known to have a higher breast cancer mortality rates (Jotoi 2005).

When comparing breast cancer incidence and mortality rates, African Americans have a higher incidence but a lower mortality rate. The incidence and mortality rates are 117.5 and 33.5 (per 100,000) for African American woman, 130.6 and 24.4 (per 100,000) for white women (Jemal 2009). This leads to African American women, for breast cancer alone, having an 11% lower incidence rate and a 37% higher death rate.[1]

During the years 1992 to 1998, white women had a higher incidence rate compared not only to black women also to other races as well. Death rates among African American women increased between the years of 1975 and 1991 annually and then declined in women 50 years of age or younger after 1991 (ACS 2009).

1.3 DIAGNOSIS AND PROGNOSIS

1.3.1 Treatment

After a woman is diagnosed with breast cancer, staging of the tumor is carried out to determine the disease extent and formulate an appropriate treatment plan. However, treatment algorithms may be complex because the different types of breast cancer differ greatly in growth rate,

[1] Per 100,000 population, age adjusted to the 2000 US standard population

tendency to spread, and response to treatment. In addition, individual practitioners may have different opinions about the most appropriate treatment for women with the same type of breast cancer. Treatment usually involves surgery and may include cytotoxic chemotherapy, radiation therapy, hormonal therapy, and/or novel targeted antiproliferative systemic therapy. Often, a combination of these treatments is used (NCI 2009). The different stages of breast cancer are localized non-invasive, localized invasive, regional invasive and distant invasive. The different stages can also be labeled using numbers I-IV, respectively. If the cancer has not progressed to stage I or higher, carcinoma in situ, stage 0 is a precancerous condition and surgery is the method used at this stage. If the cancer has progressed to stage higher then or I there are five types of treatment used: surgery, chemotherapy, hormone therapy, radiation therapy, and/or novel targeted antiproliferative systemic therapy (NCI 2009). These modalities are usually administered sequentially.

Surgical extirpation is the mainstay of treatment approaches for both invasive and non-invasive local and/or regional breast cancer. Surgery is used to remove the cancer from the breast as well as from the axillary lymph nodes. The lymph nodes are then examined for the presence of cancerous cells. There are several types of surgical procedures that can be performed depending upon the stage, including but not limited to lumpectomy, quadrectomy partial mastectomy, total mastectomy, modified radical mastectomy, and radical mastectomy (NCI 2009). A lumpectomy is a procedure that removes the tumor and a small amount of normal tissue around it. A partial mastectomy, or segmental mastectomy, removes part of the breast that contains cancer and some normal tissue around it as well. A total mastectomy is a procedure that removes the entire breast. A modified radical mastectomy is a procedure that not only removes the whole breast, but also axillary lymph nodes, the lining over the chest muscles and, from some

part of the chest wall muscles. A radical mastectomy is the last surgical procedure that removes the breast containing cancer, the chest wall muscles under the breast, and all of the lymph nodes under the arm (NCI 2009).

The second type of treatment discussed is cytotoxic chemotherapy. Chemotherapy is the use of medications to stop the growth of the cancerous cells by killing cancerous cells, usually by inducing abnormal cell division. Chemotherapy is administered orally or by injection into a vein or muscle. Some of the drugs given during chemotherapy are doxorubicin (also referred to as Adriamycin), cyclophosphamide, methotrexate, fluorouracil, and taxanes (NCI 2009).

The third type of treatment discussed is hormone therapy. Estrogen is a hormone that is produced by a woman's ovaries until menopause. After menopause, small amounts of estrogen are still made and may promote the growth of breast cancer cells. Signals are sent through receptors from estrogen telling estrogen-sensitive breast cancer cells to grow (ACS 2009).

A test is usually given, known as an estrogen receptor assay, to determine if the cancer cells have hormone receptors. After the test is administered, if breast cancer cells are found without receptors they are then labeled as estrogen-receptor negative or ER negative. If the cancer cells are found with receptors they are labeled as estrogen-receptor positive or ER positive. If estrogen receptors are present, hormone therapy is a usually a very good option (Breastcancer.org ACS 2009). These agents change the tumor microenvironment. Tamoxifen is an anti-estrogen drug given to patients with early stages of breast cancer and metastatic breast cancer. Tamoxifen is usually given for up to five years but can be taken for longer periods of time (Breastcancer.org 2009). Aromatase inhibitors, such as anastrazole, are given to stop the production of estrogen. They work by blocking the enzyme, aromatase, responsible for making estrogen in postmenopausal women (ACS 2009).

The fourth type of treatment discussed is targeted therapy at the human epidermal growth factor receptor 2 (HER2). HER2 is a gene that produces HER2 protein. It is found in normal breast cells and aids in their growth. In the presence of abnormally high amounts of HER2 genes, an "over expression" of the protein occurs. This "over expression" allows cancer cells to proliferate and divide more quickly. Cancer cells with this "over expression" are labeled as HER2 positive (HER2+) (Breastcancer.org 2009).

The last type of treatment to discuss is radiation therapy and its utilization is dependent on the type and stage of cancer. The two types of ionizing radiation therapy, external and internal, use high-energy x-rays (photons) or electrons. External beam radiation uses a machine known as a linac, an abbreviation for linear accelerator, to direct radiation toward the cancer. Internal radiation also known as brachytherapy uses a radioactive substance such as iridium-192 or iodine-125, sealed in needles, seeds, wires, or a catheter placed directly into or near the cancer (ACS 2009). Radiation therapy, which causes double-stranded DNA, breaks, preferentially in cancer cells that in G2/M phase of the cell cycle may take takes days or weeks to kill all the cancer cells. Radiation therapy is often administered in conjunction with other cancer treatments such as surgery and chemotherapy. Radiation can be given before, during, or after surgery or chemotherapy. If given before surgery it is used to shrink the size of the cancer. If given during surgery it is used so that it goes straight to the cancer without passing through the skin. If it is given after surgery, it is used to kill any cells that may remain. Also, chemotherapy can be given so that radiation therapy is more efficient. Radiation therapy is often administered after women have had a lumpectomy (NCI 2009). This paper will focus on radiation therapy.

1.4 STUDIES OF TREATMENT DIFFERENCES AND DIFFERENCES IN INCIDENCE AND MORTALITY RATES WHEN COMPARING AFRICAN AMERICAN AND WHITE WOMEN IN THE GENERAL POPULATION.

The National Institutes of Health (NIH) developed a definition of cancer health disparities: "Cancer health disparities are differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States." (NIH 2009) An example of a health disparity is noted in a retrospective, longitudinal cohort study among newly diagnosed breast cancer patients covered by the same health plan in south-eastern US (Short et al 2009). The cohort included patients from an administrative medical claims database between the years 1/2000 to 12/2004. The study found that African American women, at diagnosis, were significantly younger (p=.001) and had twice the rate of hypertension (p=<.001) when compared to white women (Short 2009). The analyses, after adjusting for age, geography according to RUCA, and SED, also showed that African American women were at an increased odds for being diagnosed with a later stage of cancer (OR=1.71; 95% CI, 1.09-2.67; p=0.02) (Short 2009).

Some factors that may contribute to the survival difference between African American and white women include lower quality of health care when accessible, a higher prevalence of coexisting conditions, and differences in tumor biology (Merck 2009). In addition, African American women are often diagnosed with more advanced stages of the disease than white women. Other proposed explanations that could account for this disparity include differences in treatment based on race, socioeconomic status (SES), sociocultural differences, unequal access to or provision of medical care, environmental factors, genetic factors and possibly biological factors (Hershman 2003).

According to Vona-Davis (2009) the average annual breast cancer mortality rate was 35.6 per 100,000 and 28.2 per 100,000 for African American women and white women, respectively. Even though the death rate has decreased during the years 1990 to 2000, the rate of mortality has only decreased 1.0% for African American women and 2.5% for white women per year (Vona-Davis 2009)

The phenomenon of racial difference or health disparity among cancer patients has been established in several studies. One proposed reason for this phenomenon is the low rate of screening, contributing to the late stage of diagnosis. In the study by Morris et al (2004) blacks, compared to whites, were diagnosed with breast cancer at a much younger age and at a more severe stage (Morris 2004). Another study by Li et al (2003) also found that in the US, black women have more advanced stages of breast cancer and have lower survival rates compared to non-Hispanic whites .

An association was also found between early termination of chemotherapy and racial disparities in breast cancer outcomes (Hershman 2003). The white blood cell count (WBC), which differs among racial groups, can also play an important role when determining treatment and the amount of treatment a patient can withstand. On average, African-American women have 25% - 40% lower WBC counts compared to European-American women (Hershman 2003). For patients undergoing adjuvant chemotherapy, if the WBC count falls below a predefined treatment threshold, a reduction in dose or treatment delay may occur (Hershman 2003). Other options, such as treatment termination or change in dose, can also occur.

The findings of Hershman and colleagues (Hershman 2003) support the conclusion of Mandelblatt et al (2005) in that it would be more cost-effective to make sure black women receive complete adjuvant therapy than to change or create a different screening program.

Ensuring completion could also reduce overall mortality (Hershman 2005). Hershman et al. found an overall statistically significant difference between African-American women and white women, with the length of treatment for newly diagnosed stage I and II breast cancer. In their study, African American women were treated for 19 weeks and white women were treated for 15 weeks, with a difference of 4 weeks ($p=0.03$). African American women were able to have longer treatment because of lower dose intensity (Hershman 2003). Chu et al (2003) established that African American women, when compared to white women, have more advanced-stage breast cancer and less early stage breast cancer. This in turn would give reason for African American women having lower survival rates.

Racial differences in treatment and standard of care could also be other factors in lower survival rates. For African American women and white women with the same disease stage and diagnosis, a randomized clinical trial was performed. The clinical trial showed that equal utilization of medical services leads to equal survival rates, while unequal survival rates based on the stage could indicate racial differences in treatment (Chu 2003). Other observations shown by Diehr et al (1989), observed a treatment difference when looking at radiation therapy in combination with radical/modified mastectomy. Black women were less likely to receive the therapy and were less likely to receive rehabilitation services after enduring mastectomy. They were referred less often for post mastectomy rehabilitation and were less likely to have progesterone receptor assay when compared to white patients. Blacks also significantly differed with respect to health insurance, hospital, and physician characteristics. Schneider et al (2002) found that black patients, relative to white patients, were less likely to be screened for breast cancer, (62.9% vs. 70.9%; $p<.001$) (Schnieder 2002).

The reason for giving cancer statistics for African Americans is to highlight areas where better prevention, early detection, and treatment can reduce their excessive affliction of suffering and death from breast cancer (Merck 2009).

2.0 RESEARCH QUESTION: IS THERE A DIFFERENCE IN THE DOSE, THE NUMBER OF DAYS OR INTENSITY OF RADIATION THERAPY BETWEEN AFRICAN AMERICAN AND CAUCASION WOMEN IN CLINICAL TRIALS?

There is compelling evidence documenting the differences of diagnosis, treatment, and death rates between African-American women and Caucasian women treated in the general population. In the randomized clinical trial setting, it is the premise that because all patients are treated by the same high-quality treatment protocol, all patients get equivalent quality of care. Several articles exist discussing racial health disparities in the general population and the treatment option of chemotherapy. Radiation therapy however, did not have such an extensive literature. As a result I wanted to further examine radiation treatment. The NSABP is a known clinical trial coorperative group that has established different standards in breast cancer treatment. The following question arises: Is there a difference in quality of radiation treatment between African American and Caucasian women in clinical trials? Quality of radiation treatment will be defined as dose (the amount of radiation therapy received), days (the number of radiation therapy days completed), and intensity (dose/days).

3.0 METHODS

3.1 PATIENT/DATA SOURCE

The study samples were breast cancer patients enrolled in several randomized clinical trials performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP). Table 1 lists these protocols and identifies the treatments that were used in these trials. Tables 2 and 3 list the numbers of patients by protocol and race and the number of patients by type of treatment and race, respectively.

For the purpose of this paper, not all arms of treatment will be used. The focus will be on women who received chemotherapy in the form of Adriamycin and cyclophosphamide (AC), alone or prior to other chemotherapy agents. There were 9,646 Caucasian women and 1,040 African American (AA) women. Women who qualified for radiation therapy according to the protocol were women who had lumpectomy surgery and completed 4 cycles of AC chemotherapy. Forty women were also recommended for RT for reasons that were unknown, even though they had mastectomy surgery. This information was not available. These women were excluded from the final analysis because they did not follow the recommended RT protocol. Among these patients were 3,305 Caucasian women and 377 African American women receiving radiation therapy per protocol and were analyzed.

This paper will compare African American and Caucasian women with respect to total radiation received, duration of radiation treatment, and intensity of the radiation treatment.

All analysis was done in SAS 9.2.

4.0 ANALYSIS

4.1 LOGISTIC REGRESSION

Logistic regression was used as the method of analysis. The independent, or predictor variables that were assessed included race, age, number of positive nodes, the number of AC cycles completed (which ranged from 1), pathologic tumor size, and protocol. The dependent, or outcome, variables that were used included three measures of radiation therapy: 1) dose (the total amount of radiation therapy administered); 2) days (the number of radiation therapy days completed); and 3) dose intensity (dose/days). As race was the main focus of this analysis, the approach for each of the three outcome measures of radiation therapy was to first assess the association between race and outcome without adjustment for any potential confounder variables. The second step was to construct a model that included all significant independent factors, and then add race to this model to test if there was a difference by race in radiation dosing. This approach provided a control for any possible confounders. The multivariate model was constructed using a forward stepwise process. Chi-squared tests were used to assess each variable's model inclusion with an alpha of 0.05 as the criterion for entry and removal. Once the multivariate model was identified, race was added and tested for statistical significance.

Race, number of positive nodes, number of cycles of AC, and protocol were categorical variables, while age and tumor size were continuous variables. Race was coded 0 for Caucasian

and 1 for African American. Number of positive nodes was coded 0 for 0 positive nodes, 1 for 1-3 positive nodes, 2 for 4-9 positive nodes, and 3 for 10+ positive nodes. Cycle was coded 0 for less than four cycles of AC and 1 for received all four cycles of AC. Protocol was coded 15, 16, 18, 22, 23, 25, and 28 corresponding to the cancer protocol. The outcome variables for this analysis were originally continuous in nature (Figures 6-10); due to the non-normality of their distributions I chose to dichotomize the outcomes and use regression models for binary response data. Binary response model were used where the response (days, dose, or intensity) was a dichotomous variable that would equal 0 if the woman received less than the targeted radiation therapy and 1 if the woman receive greater than or equal to the targeted radiation therapy. Days equaled 0 for less than 35 days of RT and 1 for greater than or equal to 35 days of RT. Dose equaled 0 for less than 5,000 rads[2] and 1 for greater than or equal to 5,000 rads. Intensity equaled 0 for 142.86 rads/days and 1 for greater than or equal to 142.86 rads/days. These numbers were chosen based on the targeted or recommended RT according to the protocol.

The logistic model has the form $$logit(p) = log\left(\frac{p}{1-p}\right) = \alpha + \beta' x$$

Where α is the intercept parameter and β is the vector of slope parameters. The βs provide information about the relationships of the independent variables to the dependent variables. The estimates of the population coefficients are $\hat{\alpha}$ and $\hat{\beta}$. Maximum likelihood estimation is used to make the estimates. This technique of maximum likelihood finds the value of the parameter that is most likely to have produced the observed sample data. *P* is the probability of a success, or in this analysis the probability of receiving the recommended amount radiation therapy.

[2] The term "rads" that is used it similar to"centigray" or "cGy"

Odds ratios were obtained to quantify the relationship between the predictors and the outcomes. An odds is the probability that some event will occur divided by the probability that the same event will not occur. Odds (E) = $\frac{P(E)}{P(\bar{E})} = \frac{P(E)}{1-P(E)}$ Here E is the probability that some event will occur and $\bar{E}$ is the probability that same even will not occur. An odds ratio is the ratio of two odds. When comparing two groups the Odds Ratio = $\frac{\mathbf{odds(Ea)}}{\mathbf{odds(Eb)}} = \frac{(P(Ea)/1-P(Ea))}{(P(Eb)/1-P(Eb))} = \frac{P(Ea)*[1-P(Eb)]}{P(Eb)*[1-P(Ea)]}$. Where a and b are two groups thus Ea is the probability that some event will occur in group a and Eb is the probability that some even will occur in group b. An odds ratio that is not statistically different than one indicates that the odds are the same in both groups therefore concluding that the two groups do not differ. An odds ratio that is greater than one indicates that the odds of the event occurring in group A is greater than the odds of the event occurring in group B.

5.0 RESULTS

African American and Caucasian women were analyzed to see if there was a difference in the number of days of radiation therapy completed, the target radiation dose, and the treatment intensity.

Tables 2 and 3 describe the number of African American and Caucasian women were in each protocol and treatment respectively.

Completeness was defined as completing the recommended number of days according to the radiation protocol (35 days). The majority of women completed all recommended days, 327(86.7%) among AA patients and 3,101(88.3%) among Caucasian patients. Tables 4-10 are comparisons of patients and tumor characteristics.

The 3 radiation doses (dose, days, and intensity) were originally continuous in nature; the data was highly concentrated around the mean compared to that of a normal distribution, due to lower variations within observations (Figures 6-11). Due to the leptokurtic distributions I choose to dichotomize the doses. Zero was given if a patient had less than the recommended dose and a one if the patient received greater than or equal to the recommended dose.

Several models were run to assess the completeness of radiation treatment when comparing African American and Caucasian women. Data were from the NSABP clinical trials conducted during the years of 1984 to 1998. The majority of the women [404 AA women (38.9%) and 3,474 Caucasian (36.2%)] were between the ages of 40 and 49 (Table 4). The

majority of women had between 1 to 3 positive nodes, [507 AA women (49.1%) and 5,211 Caucasian women (54.4%)] (Table 5). The most common range of tumor size was 1.0 - 2.0 cm for Caucasian women [2,263 women (32.7%)], whereas the most common tumor size was greater than or equal to 4.0 cm for African American women [232 women (31.5%)] (Table 6).The majority of women completed all four cycles of AC [9,269 Caucasian women (96.4%) and 992 AA women (95.5%)] (Table 7). The majority of the women completed the recommended dose [331 AA women (87.7%) and 3,183 Caucasian women (90.8%)] (Table 8), the recommended number of days [327 AA women (86.7%) and 3,101 Caucasian women (88.3%)] (Table 9), and therefore led to the majority of women receiving the appropriate intensity [296 AA women (78.5%) and 2,860 Caucasian women (81.4%)] (Table 10).

Table 1. Protocols and Randomized Treatments in NSABP Protocols that Included African American Women

NSABP Protocol Number	Treatment Arms in the Protocol
B-15	AC ***vs.*** AC →CMF ***vs.*** CMF
B-16	TAM ***vs.*** ACT ***vs.*** PAFT
B-18	POST-OP AC ***vs.*** PRE-OP AC
B-22	AC ***vs.*** AC ***vs.*** AC
B-23	CMF+Placebo ***vs.*** CMF+T ***vs.*** AC+Placebo ***vs.*** AC+T
B-25	AC+G ***vs.*** AC+G ***vs.*** AC+G
B-28	AC ***vs.*** AC->TX

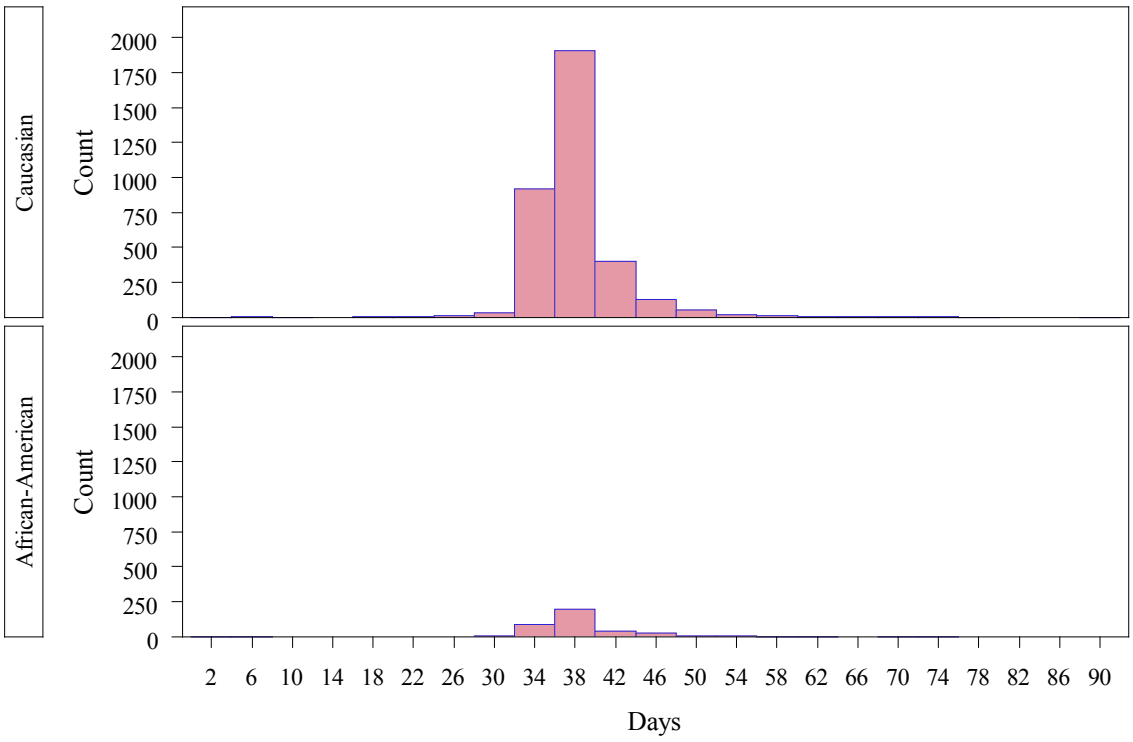

Figure 4. Plot comparing the count of patients by number of days of radiation therapy completed for African American and Caucasian women

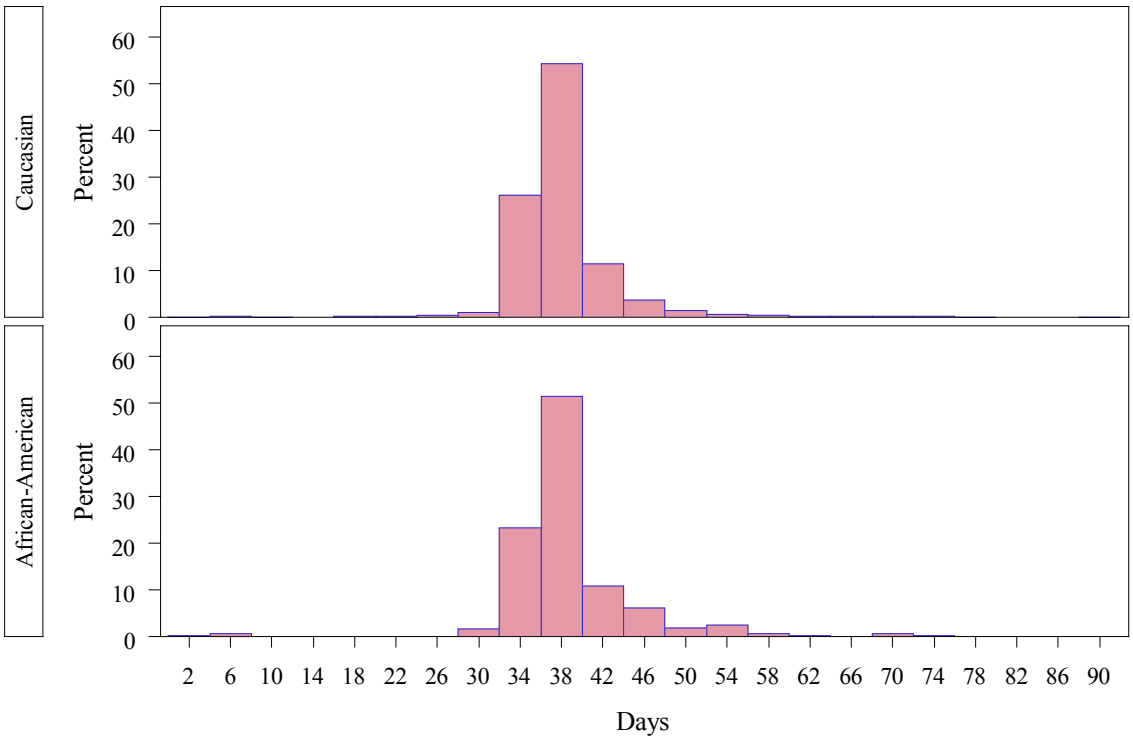

Figure 5. Plot comparing the percent of total days of radiation therapy completed for African American and Caucasian women

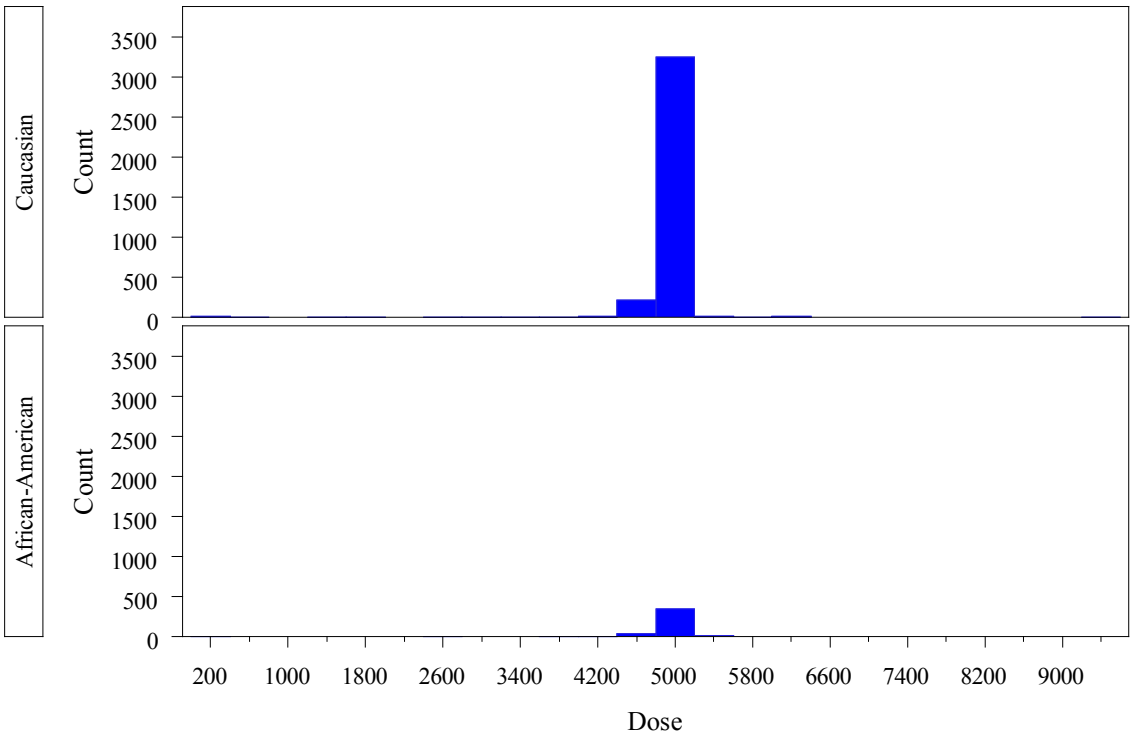

Figure 6. Plot comparing count of patients by the total dose of radiation therapy given for African American and Caucasian women

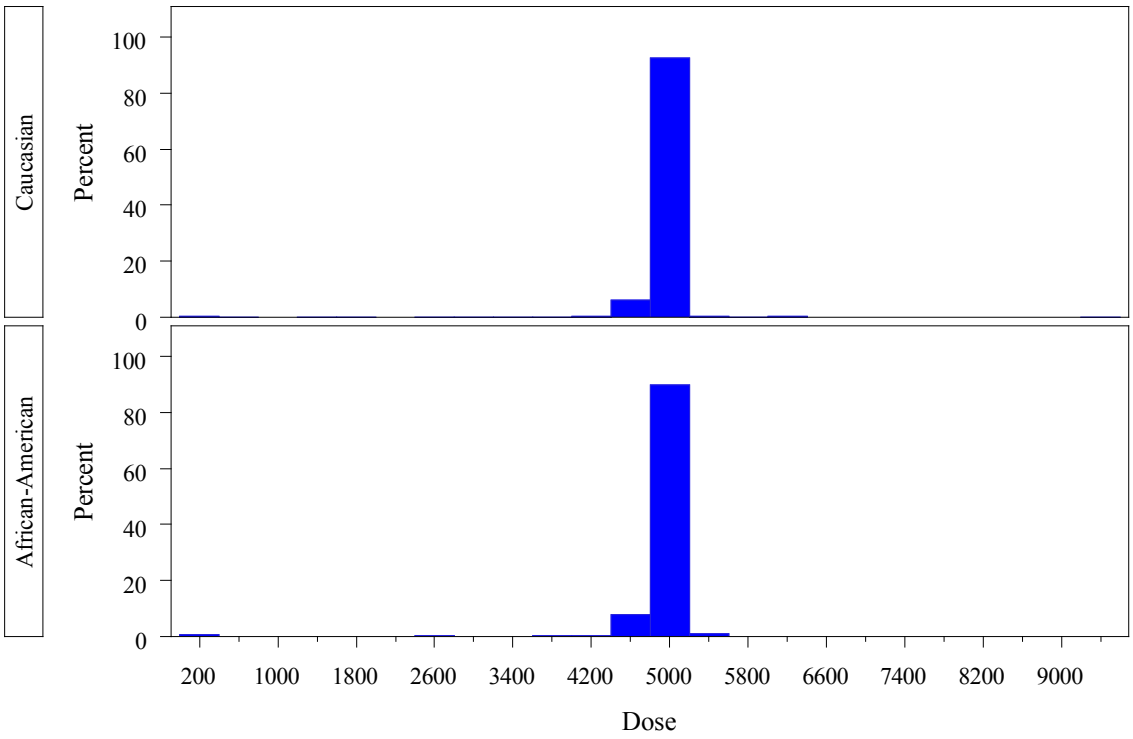

Figure 7. Plot comparing the percent of patients by total dose of radiation therapy given for African American and Caucasian women

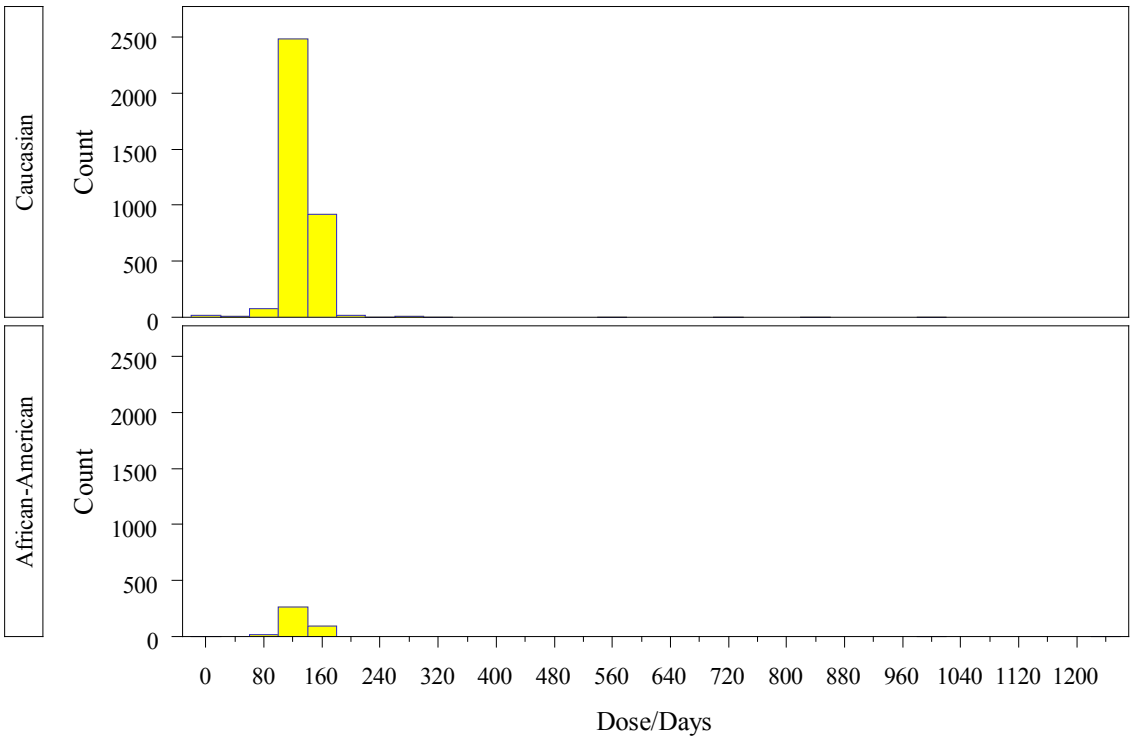

Figure 8. Plot comparing the count of patients by dose intensity of radiation therapy for African American and Caucasian women

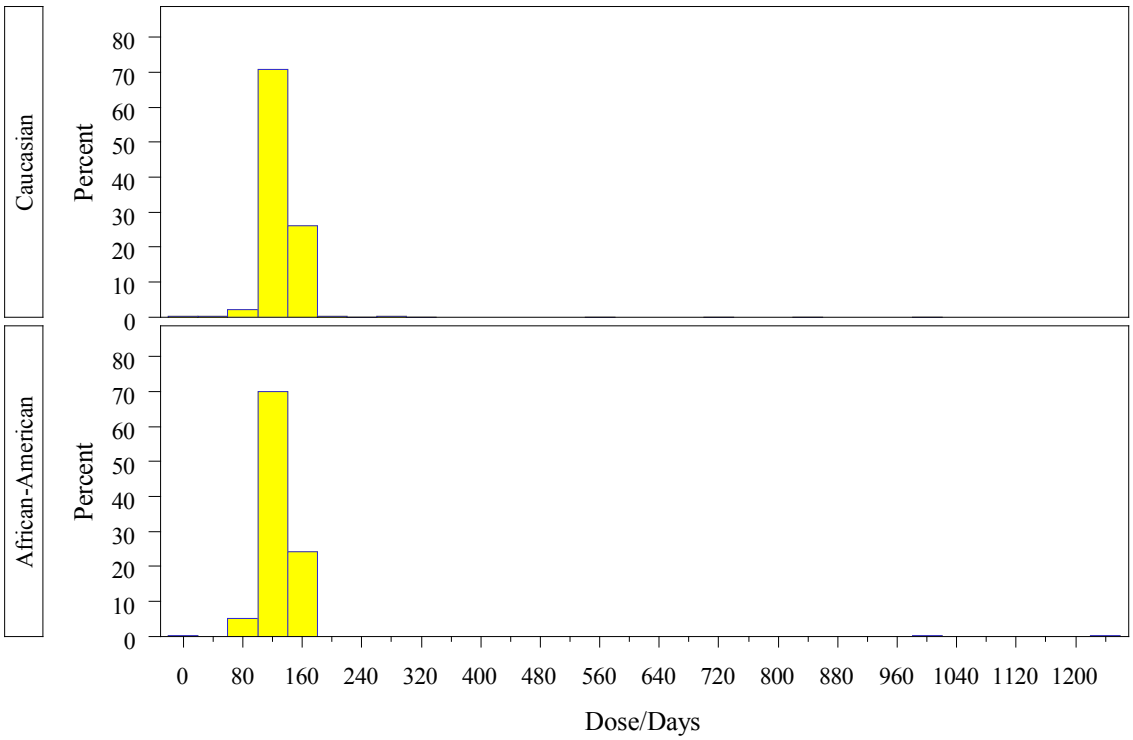

Figure 9. Plot comparing the percent of patients by dose intensity for African American and Caucasian women

Table 2. Number of Patients by Protocol by and Race

NSABP Protocol Number	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
B-15	1254	88.40%	164	11.50%	1418	100.00%
B-16	351	93.60%	24	6.40%	375	100.00%
B-18 (post-op)	573	88.00%	78	11.90%	651	100.00%
B-22	1901	90.30%	204	9.60%	2105	100.00%
B-23	739	84.00%	140	15.90%	879	100.00%
B-25	2143	91.70%	192	8.20%	2335	100.00%
B-28	2647	91.80%	236	8.10%	2883	100.00%
Total	9608	90.20%	1038	9.70%	10646	100.00%

Table 3. Number of Patients by Type of Treatment and Race

Type of Treatment	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
ACx4	626	88.20%	83	11.70%	709	100.00%
ACx4 ->CMFx3	628	88.50%	81	11.40%	709	100.00%
AC+TAM	351	93.60%	24	6.40%	375	100.00%
AC+TAM if >=50 yrs	573	88.00%	78	11.90%	651	100.00%
AC(C=600x4)	658	91.10%	64	8.80%	722	100.00%
AC(C=1200x2)	616	89.40%	73	10.50%	689	100.00%
AC(C=1200x4)	1342	91.30%	127	8.60%	1469	100.00%
ACx4+TAM	1693	90.20%	183	9.70%	1876	100.00%
ACx4+Placebo	369	83.60%	72	16.30%	441	100.00%
AC(C=2400x2)	701	90.40%	74	9.50%	775	100.00%
AC(C=2400x4)	727	92.60%	58	7.30%	785	100.00%
ACx4->TAX+TAM	1324	91.60%	121	8.30%	1445	100.00%
Total	9608	90.20%	1038	9.70%	10646	100.00%

Table 4. Number of Patients by Age and Race

Age (Years)	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
<30	156	1.60%	26	2.50%	182	1.70%
30-39	1533	15.90%	227	21.80%	1760	16.50%
40-49	3474	36.10%	404	38.90%	3878	36.40%
50-59	2773	28.80%	261	25.10%	3034	28.40%
60-69	1499	15.60%	103	9.90%	1602	15.00%
>=70	173	1.80%	17	1.60%	190	1.70%
Total	9608	100.00%	1038	100.00%	10646	100.00%

Table 5. Number of Patients by Number of Positive Nodes and Race

Number of Positive Nodes	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
None	974	10.10%	160	15.50%	1134	10.60%
1-3	5211	54.40%	507	49.10%	5718	53.90%
4-9	2486	25.90%	271	26.20%	2757	25.90%
10	902	9.40%	94	9.10%	996	9.30%
Total	9573	100.00%	1032	100.00%	10605	100.00%

Table 6. Number of Patients by Pathologic Tumor Size and Race

Tumor Size (cm)	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
<1.0	322	4.60%	16	2.10%	338	4.40%
1.0<-2.0	2262	32.70%	201	27.30%	2463	32.10%
2.0<-3.0	1814	26.20%	187	25.40%	2001	26.10%
3.0<-4.0	765	11.00%	100	13.50%	865	11.30%
>=4.0	1753	25.30%	232	31.50%	1985	25.90%
Total	6916	100.00%	736	100.00%	7652	100.00%

Table 7. Number of Patients by Last Cycle of Radiation Therapy Completed and Race

Last Cycle Of Radiation Completed	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
Cycle 1	83	8%	12	1.10%	95	8%
Cycle 2	94	9%	11	1.00%	105	9%
Cycle 3	163	1.60%	23	2.20%	186	1.70%
Cycle 4	9268	96.40%	992	95.50%	10260	96.30%
Total	9608	100.00%	1038	100.00%	10646	100.00%

Table 8. Number of Patients by Radiation Dose and Race

Radiation Dose (rads)	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
< 5000	322	9.10%	46	12.20%	368	9.40%
≥ 5000	3183	90.80%	331	87.70%	3514	90.50%
Total	3505	100.00%	377	100.00%	3882	100.00%

Table 9. Number of Patients by Days of Radiation Therapy Completed by Race

Days of Radiation Therapy	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
< 35	408	11.60%	50	13.20%	458	11.70%
≥ 35	3101	88.30%	327	86.70%	3428	88.20%
Total	3509	100.00%	377	100.00%	3886	100.00%

Table 10. Number of Patients by Radiation Dose Intensity and Race

Radiation Dose Intensity (rads/day)	Caucasian		African-American		Total	
	N	Pct	N	Pct	N	Pct
< 142.86	644	18.50%	81	21.40%	731	18.80%
≥ 142.86	2860	81.40%	296	78.50%	3156	81.10%
Total	3504	100.00%	377	100.00%	3881	100.00%

Table 11 describes the results of the univariate analysis for the outcome radiation dose. Race was borderline significant (p=0.06, OR=0.73; 95% CI=0.52-1.01), positive nodes was a significant predictor (p=0.04), and protocol was a highly significant (p=<.001) predictor of dose. Protocol was the only significant predictor after the forward selection (p= <.0001) (Table 12). Because this paper is focusing on comparing African American women and Caucasian women, race was added to the model after the forward selection process was applied to other significant variables (Table 13).

Table 14 shows the univariate analysis for the number of days of radiation therapy. Protocol was the only significant predictor for the number of days of radiation therapy (p=0.01). Therefore after the forward selection, protocol was the only significant predictor (p=0.01) (Table 15). Table 16 describes the final multivariate model with race (p=0.51) and protocol (p=0.01).

Table 17 shows the results of the univariate analysis for radiation dose intensity. Protocol was the only highly significant predictors for intensity (p=<.0001). Table 18 shows the

results after the forward selection for intensity. Protocol was the only highly significant predictor of dose intensity (p=<.0001). Table 19 describes the final multivariate model for radiation dose intensity. Protocol remained significant (p=<.0001). Race was not a significant predictor of intensity (p=.25).

Table 11. Results of Univariate Analysis for Radiation Dose

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-Square
Race 1 vs. 0	0.728	0.524	1.011	0.0582
Age	1.002	0.991	1.013	0.7544
Pos. Nodes 1 vs. 0	0.629	0.449	0.883	0.0398
Pos. Nodes 2 vs. 0	0.664	0.45	0.98	
Pos. Nodes 3 vs. 0	0.899	0.489	1.656	
Pathologic Tumor Size	1.114	0.996	1.246	0.0579
AC cycle 1 vs. 0	1.361	0.736	2.514	0.3257
Protocol 16 vs. 15	1.581	0.598	4.18	<.0001
Protocol 18 vs. 15	3.264	1.621	6.575	
Protocol 22 vs. 15	1.063	0.658	1.719	
Protocol 23 vs. 15	0.982	0.6	1.605	
Protocol 25 vs. 15	0.972	0.628	1.504	
Protocol 28 vs. 15	0.592	0.398	0.881	

Table 12. Results of Forward Selection for Radiation Dose

Odds Ratio Estimates				
Variables Assessed	**Point Estimate**	**95% Wald Confidence Limits**		**p-value for Chi-square**
Protocol 16 vs. 15	1.356	0.502	3.658	<.0001
Protocol 18 vs. 15	3.354	1.585	7.095	
Protocol 22 vs. 15	1.001	0.595	1.686	
Protocol 23 vs. 15	0.925	0.545	1.572	
Protocol 25 vs. 15	0.929	0.577	1.497	
Protocol 28 vs. 15	0.558	0.359	0.866	

Table 13. Results from Final Multivariate Model for Radiation Dose

Odds Ratio Estimates				
Variables Assessed	**Point Estimate**	**95% Wald Confidence Limits**		p-value for Chi-square
Race 1 vs. 0	0.732	0.524	1.021	0.0664
Protocol 16 vs. 15	1.595	0.603	4.218	<.0001
Protocol 18 vs. 15	3.289	1.632	6.625	
Protocol 22 vs. 15	1.083	0.669	1.751	
Protocol 23 vs. 15	1.024	0.624	1.679	
Protocol 25 vs. 15	0.985	0.636	1.524	
Protocol 28 vs. 15	0.6	0.403	0.893	

Table 14. Results of Univariate Analysis for Days of Radiation Therapy

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-Square
Race 1 vs. 0	0.86	0.628	1.179	0.3497
AGE	1.006	0.996	1.016	0.2487
Pos. Nodes 1 vs. 0	0.815	0.612	1.084	0.3786
Pos. Nodes 2 vs. 0	0.901	0.642	1.265	
Pos. Nodes 3 vs. 0	0.705	0.439	1.133	
Pathologic Tumor Size	1.018	0.925	1.119	0.7209
Last AC cycle 1 vs. 0	0.755	0.378	1.509	0.4262
Protocol 16 vs. 15	1.07	0.479	2.388	0.0124
Protocol 18 vs. 15	1.339	0.803	2.23	
Protocol 22 vs. 15	0.69	0.45	1.056	
Protocol 23 vs. 15	0.73	0.468	1.139	
Protocol 25 vs. 15	0.803	0.536	1.203	
Protocol 28 vs. 15	0.653	0.447	0.954	

Table 15.Results of Forward Selection for Days of Radiation Therapy

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-square
Protocol 16 vs. 15	1.011	0.424	2.413	0.0072
Protocol 18 vs. 15	1.191	0.69	2.058	
Protocol 22 vs. 15	0.597	0.373	0.955	
Protocol 23 vs. 15	0.666	0.409	1.086	
Protocol 25 vs. 15	0.722	0.461	1.132	
Protocol 28 vs. 15	0.588	0.384	0.9	

Table 16. Results from Final Multivariate Model for Radiation Days

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-square
Race 1 vs. 0	0.899	0.655	1.234	0.5102
Protocol 16 vs. 15	1.073	0.48	2.394	0.0135
Protocol 18 vs. 15	1.342	0.805	2.236	
Protocol 22 vs. 15	0.694	0.453	1.063	
Protocol 23 vs. 15	0.74	0.474	1.157	
Protocol 25 vs. 15	0.806	0.538	1.208	
Protocol 28 vs. 15	0.656	0.449	0.958	

Table 17.Results of Univariate Analysis for Radiation Dose Intensity

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-Square
Race 1 vs. 0	0.831	0.64	1.077	0.1617
Age	1.005	0.996	1.013	0.2617
Pos. Nodes 1 vs. 0	0.744	0.586	0.944	0.1099
Pos. Nodes 2 vs. 0	0.812	0.614	1.074	
Pos. Nodes 3 vs. 0	0.791	0.524	1.196	
Pathologic Tumor Size	1.049	0.968	1.136	0.2442
Last AC cycle 1 vs. 0	0.85	0.494	1.461	0.5557
Protocol 16 vs. 15	1.5	0.711	3.164	<.0001
Protocol 18 vs. 15	1.671	1.068	2.615	
Protocol 22 vs. 15	0.714	0.497	1.025	
Protocol 23 vs. 15	0.694	0.478	1.008	
Protocol 25 vs. 15	0.763	0.543	1.07	
Protocol 28 vs. 15	0.521	0.38	0.714	

Table 18. Results of Forward Selection for Radiation Dose Intensity

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-square
Protocol 16 vs. 15	1.444	0.65	3.21	<.0001
Protocol 18 vs. 15	1.588	0.987	2.555	
Protocol 22 vs. 15	0.651	0.439	0.965	
Protocol 23 vs. 15	0.655	0.437	0.982	
Protocol 25 vs. 15	0.716	0.494	1.038	
Protocol 28 vs. 15	0.485	0.342	0.689	

Table 19. Results from Final Multivariate Model for Radiation Dose intensity

Odds Ratio Estimates				
Variables Assessed	Point Estimate	95% Wald Confidence Limits		p-value for Chi-square
Race 1 vs. 0	0.857	0.658	1.115	0.2496
Protocol 16 vs. 15	1.506	0.714	3.178	<.0001
Protocol 18 vs. 15	1.677	1.072	2.624	
Protocol 22 vs. 15	0.72	0.501	1.034	
Protocol 23 vs. 15	0.708	0.487	1.029	
Protocol 25 vs. 15	0.767	0.546	1.077	
Protocol 28 vs. 15	0.524	0.382	0.719	

6.0 DISCUSSION

As defined by the NIH,"Cancer health disparities are differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States" (NIH 2009). Examples of this disparity have been noted in many studies and apply to the general population. After examining health disparities, the question arose as to whether breast cancer health disparities and radiation treatment disparities exist within randomized clinical trials.

The majority of women in the NSABP clinical trials examined completed the recommended number of days [327 AA women (86.7%) and, 3,101 Caucasian women (88.3%)], the recommended dose [321 AA women (84.7%) and 183 Caucasian women (90.8%)], thus the majority of women completed the recommended dose intensity [327 AA women (86.7%) and 3,101 Caucasian women (88.3%)]. Even though the majority of women completed the recommended radiation therapy African American women received slightly less therapy but not at a significant level.

After adjustment for treatment protocol, race was not a significant predictor of radiation dose, duration (days), or intensity in the NSABP clinical trials examined.

Breast cancer health disparities, in the general population, were mentioned previously. Some factors that may contribute to this disparity are survival difference including lower quality of health care when accessible, a higher prevalence of coexisting conditions, differences in treatment based on race such as early termination of chemotherapy, SES, sociocultural differences, and unequal access to or provision of medical care. Clinical trials, however, are not random samples and may not provide an accurate representation of the total population because of the type of environment they provide. Participants voluntarily join clinical trials for various reasons such as compensation, age, gender, or exposure. There are strict guidelines and enrollment criteria which may restrict or prohibit certain individuals from participating. Population health disparities in unequal access to or provision of medical care and cost may have been eliminated from these clinical trials because of the qualifications and/or restrictions to participate. This may be a possible reason the majority of the women both African American and Caucasian completed the recommended radiation therapy.

7.0 CONCLUSION

In conclusion, within the NSABP breast treatment trials examined, the amount of radiation therapy provided did not differ significantly between African American and Caucasian women. When using three separate measure of radiation therapy dosing, the majority of women completed the recommended radiation therapy and there was no association between race and radiation received.

Public health importance: Randomized clinical trials provide important evidence for the choices of breast cancer treatment. The success of such trials in providing an environment where patients received a standardized treatment would be called into question if there were treatment differences by race in those trials. This study did not find evidence of racial disparity in radiation therapy in the NSABP breast cancer trials examined.

APPENDIX

EXAMPLE SAS CODE

```
proc logistic data = logistic descending ;
class afr_am /  param=ref ref=first;  /*use param=reference because have
different
levels of the class variables*/
model n_brads = afr_am  /  lackfit rsq outroc=roc clparm=wald clodds=wald
scale=none
pprob=0.5 ctable nodummyprint nologscale nocheck aggregate ; /*influence
iplots ;    */
/*output out p=hat xbeta=xbeta pred=predict lower=lcl upper=ucl; */
output out = mod1 p=y_hat  RESDEV=resdev RESCHI=reschi lower=lcl upper=ucl ;
/*ods output ParameterEstimates =mod1;*/
title 'Model  - Race only. outcome=dose';
run;

proc logistic data = logistic descending outest=betas covout;
class afr_am pos_nodes last_crs /param=ref ref=first;
model n_brads = afr_am pos_nodes mpsiz age last_crs/lackfit rsq outroc=roc1
clparm=wald clodds=wald scale=none pprob=0.5 ctable nodummyprint nologscale
nocheck
aggregate SELECTION=F SLENTRY=0.05  DETAILS/*influence iplots */;
/*out p=hat xbeta=xbeta pred=predict lower=lcl upper=ucl; */
output out = mod1L p=y_hat RESDEV=resdev RESCHI=reschi lower=lcl upper=ucl;
/*ods output ParameterEstimates =mod1l;*/
title 'Model  - FOWARD SELECTION ALL. outcome=dose';
run;.
```

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[1] The term “race” and “ethnicity” are limited biological constructs and for the purpose of this thesis these terms are synonymous