Conservatively Managed Breast Cancer in African American Women: Clinical and Cosmetic Outcomes

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Abstract

CONSERVATIVELY MANAGED BREAST CANCER IN AFRICAN AMERICAN WOMEN: CLINICAL AND COSMETIC OUTCOMES.
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Purpose: The purpose of this study was to evaluate the prognostic significance of race in breast cancer patients treated with lumpectomy and radiation therapy.

Methods and Materials: Between 1973 and 1997, 1737 patients were treated with lumpectomy and radiation therapy at our institution. All patient data including race, age, stage, pathology, treatment and outcome variables were entered into a computerized database. One hundred and one women were identified as African American and 1513 were identified as white. A small number (22) of patients of Asian, Hispanic or other ethnic backgrounds were eliminated from analysis. A detailed cosmetic analysis was performed on a selected subset of 20 African American patients and 20 white patients from the database. The two groups were intentionally matched by age, follow-up, adjuvant therapy, and breast size and asked to participate in a detailed cosmetic evaluation.

Results: As of September 2002, median follow-up was 14.5 years. African American patients presented with an earlier age of onset when compared to white patients (51.1 yrs African American vs 56.5 yrs white, $p<.001$). By age groups, 42.5% of African-American patients were over age 50 compared to 68.6% of white patients over age 50. African American patients presented with larger tumors (mean pathological size 1.87cm African American vs 1.57cm white, $p=.002$), and were more frequently ER negative (51% ER negative African American vs 37% ER negative white, $p=.02$). However, nodal status was similar in the two populations (24% node positive white vs 27% node positive

African-American, p=.56). Given the younger age and ER negativity, African American patients were more likely to receive adjuvant tamoxifen. Despite the earlier age of onset and larger tumor size, there were no significant differences between the African-American and white patients with respect to overall survival (82% African American vs 79% white) or cause specific survival at 10 years (88% African American vs 86% white). African American patients had a significantly lower breast relapse free rate at 10 years (81% African American vs 87% white, p=.026). Although this may be part in related to the younger age, a multivariate analysis including age, race, margin status, and treatment parameters revealed young age and African American race to be significantly associated with local relapse. With respect to overall cosmetic outcome and all specific cosmetic measures (edema, fibrosis, and pigmentation), African American patients fared poorer than white patients. Overall cosmesis was good to excellent in 55% of African Americans compared to 90% of whites (p=.014).

Conclusion: Despite a younger age of onset and larger tumor size, outcome in African American patients was similar to white patients with respect to overall and cause specific survival. The explanation for a slightly higher local relapse rate and poorer cosmetic result requires further investigation.

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Introduction

Breast cancer remains as the most commonly diagnosed malignant condition affecting women in the United States. According to the American Cancer Society, it is estimated that there were 203,500 new cases of breast cancer diagnosed in the United States in 2002 (1). Over the past 20 years, the incidence of breast cancer has steadily increased and it is currently estimated that one out of every eight women in the United States will develop this disease (2). However, the proportion of women diagnosed at earlier stages has also increased and accordingly there has been a resulting decline in breast cancer mortality since 1990 (1).

Amongst African American women, the incidence of breast cancer reflects national statistics and is the most commonly diagnosed cancer (3-5). However, the overall incidence of breast carcinoma is lower for African American women than for white women (3-5). While the incidence rate of breast cancer is about 13% lower in African-American women than in white women, the mortality rates from breast cancer are higher for all stages of breast cancer among African American women (6). In the early 1970's, African American and white women had almost comparable odds of dying from breast cancer (7). Yet, since 1980, mortality rates from breast cancer have fallen almost 15% for white women but have risen by 22% for African American women (7). Therefore, it is important to identify those variables including treatment modalities that correlate with improved or worsened outcomes in African American women.

One factor that has been correlated with the poorer prognosis for African American women is that they are more likely to be diagnosed with more advanced stage of disease (8). In examining data from the Surveillance Epidemiology and End Results

program, 29.1% of African American women present with Stage I breast cancer in comparison to 42.7% of white women; conversely, for Stage IV disease, the figures are 7.3% of African American women in comparison to 4.2% of white women (8). Therefore, some studies suggest that the later stage of diagnosis is the primary explanation for the worsened outcome of African American women (9). However, when controlling for the stage of diagnosis, research has demonstrated that the higher mortality from breast carcinoma remains for African American women and race continues to be an independent predictor of mortality (9, 10). Hence, another area that must be examined in the worsened outcome of African American women is the method of and response to treatment.

The conservative management of breast cancer with lumpectomy and radiation therapy has been consistently documented as the preferred standard of care for the majority of women with early stage breast cancer. Several prospective randomized trials, as well as retrospective series, have clearly demonstrated that patients conservatively treated with lumpectomy and radiation therapy consistently experience equivalent outcomes as do their counterparts treated with conventional mastectomy. These studies have shown equivalent disease-free survival, distant-disease free survival, and overall survival rates between early stage breast cancer patients treated with conservative management and those treated with mastectomy (11-19).

Therefore, according to the 2002 practice guidelines set forth by the National Comprehensive Cancer Network and the 1990 National Institute of Health Consensus Development Statement, breast conserving treatment or total mastectomy is the appropriate method for primary treatment for most women with stage I or stage II breast

cancer. However, Nattinger and colleagues found that although the use of breast conservation treatment has increased since the development of the 1990 NIH Consensus Statement, the proportion of women receiving inappropriate treatment (omission of radiation therapy or axillary dissection) increased from 10% in 1989 to 19% in 1995 (20). Furthermore, when Josyln looked at women in the National Cancer Institute's Surveillance, Epidemiology, and End Results program between 1988 and 1998, African American women were significantly more likely to receive breast conserving surgery in comparison to white women (6). However, among those women with early stage breast cancer who underwent breast conserving surgery, African American women were significantly less likely to receive radiation therapy following surgery. In analyses of therapeutic outcome, research demonstrates that the use of follow-up radiation after breast-conserving surgery decreases the extent of racial disparity in death rates by nearly fifty percent (6). Thus, research demonstrates that African American women are not receiving the standard of care, which would reduce the magnitude of the survival disparity.

Additionally, while a high rate of disease free survival remains as an important factor in the continued used of lumpectomy and radiation therapy, the psychological impact of conservative management has also been recognized as an important endpoint in the evaluation of this modality of treatment. Studies have demonstrated that women who opted for lumpectomy plus radiation therapy were less likely to feel unattractive or sexually undesirable and were less likely to be ashamed of their breasts in comparison to women who received mastectomy (21, 22). Also, studies have shown that one of the primary reasons that an overwhelming majority of women opt for breast conservation

therapy is that they desire the preservation of an acceptable cosmetic appearance and want to avoid the negative feelings of disfigurement that they associate with mastectomy (21, 22). Therefore, the goal of treatment with lumpectomy and radiation therapy remains to use techniques of radiation therapy and surgery that will not only maximize disease free survival but will also optimize the likelihood of long term breast preservation with good cosmetic results and minimal complications. Thus, cosmetic outcome is also an important endpoint in the evaluation of lumpectomy and radiation therapy.

Much research has been done focusing on the cosmetic results following breast conservation surgery and radiotherapy for breast carcinoma. When Beadle and colleagues examined the cosmetic results for 239 breast cancer patients treated conservatively, they found that the rate of excellent or good cosmesis at 5 years was 86% (23). Similarly, researchers at the University of Pennsylvania found that for 1053 patients who were treated with breast-conservation therapy who did not receive chemotherapy 96% and 93% of patients had an excellent or good cosmetic result at 3 and 5 years, respectively (24).

While the majority of patients with breast cancer treated with conservative surgery and radiotherapy have acceptable cosmetic outcomes, clinical factors influencing cosmesis have been the focus of a great deal of research. The data are conflicting with regards to the impact of age on cosmetic outcome. Some researchers have seen no relationship between age and cosmesis while others have found that age at diagnosis >60 is associated with poorer cosmetic outcome (25-27). Similarly, differing results have been demonstrated regarding the relationship of tumor size and cosmesis. In some studies, tumor size has been found to influence cosmesis, with larger tumors being

associated with worsened cosmetic outcome, while other researchers have seen no such association (25-27). It is suggested that this difference may be related to the volume of breast tissue excised and/or the radiation doses given as a function of the size of the tumor (25). Furthermore, tumor location impacts the cosmetic outcome following breast conserving therapy. Tumors located in the upper-outer quadrant of the breast are more often associated with an excellent or good cosmetic result while tumors in the inner half of the breast particularly the lower inner quadrant are associated with worse cosmetic results (27, 28).

In addition, variations in surgical treatment have been found to have an impact on cosmesis following breast conserving treatment. One of the major contributors known to influence the cosmetic outcome is the extent of surgical excision. Many authors have shown that a poorer cosmetic outcome is associated with an increase in the amount of tissue excised (24, 29, 30). For patients with greater than $70cm^3$ excised, researchers found an associated decline in the cosmetic scores (24, 29). De la Rochfordiere and colleagues observed poorer cosmesis with resected tumor volume greater than $86cm^3$ and Taylor et al. noted a similar decline in cosmetic outcome with a tumor volume greater than 100 cm^3 (25, 30). Accordingly, the type of breast surgery is associated with cosmetic outcome. Patients undergoing an excisional biopsy have the highest rate of excellent cosmetic outcome, followed by those who receive a wide excision and those with quadrantectomy (25).

In addition to surgical technique, radiation treatment technique influences the cosmetic outcome in breast cancer patients. For instance, the number of radiation fields treated affects the cosmetic outcome in conservatively managed patients. As the number

of radiation fields increased, Taylor and colleagues noted declining cosmetic results with the best cosmetic results seen in patients who received tangential breast irradiation alone (25). No comment is made regarding the relationship between the number of fields and the size of the tumor or the extent of surgery. Also, increased radiation dose to the entire breast is associated with poorer cosmetic outcome. Several researchers have found that doses greater than 50 Gy to the entire breast correlates with a poorer cosmetic outcome (25, 31, 32). Research has yielded contrasting data regarding the influence on cosmetic outcome with the use or absence of boost. Some authors noted worsened cosmesis with boost (23, 28, 31) while others suggest that there is no difference in cosmetic score with or without boost (25). Again, the data is conflicting regarding the effect of the type of boost on cosmetic outcome. Some reports found no effect on cosmesis with differences in the type of boost (electron irradiation or interstitial implant) while others demonstrated poorer cosmesis with interstitial implants (25, 29-31). Additionally, daily fractionation with high dose per fraction (fraction size >2.5 Gy) leads to poorer cosmetic outcome in the form of greater fibrosis and breast retraction (24, 25, 32).

Despite the acceptance of lumpectomy and radiation therapy as standard therapy in early stage breast cancer and the consistently documented differences in African American and white patients, few studies have looked at the significance of race in the conservative management of breast cancer (3, 8, 33). Also, little work has been done examining any difference in the response to radiation therapy among the races. Therefore, the purpose of this study is to evaluate the prognostic significance of race in the clinical presentation, treatment, and outcome in breast cancer patients treated with

lumpectomy and radiation therapy. Also, this study seeks to examine the influence of race in cosmetic outcome following breast-conserving treatment.

Purpose

The purpose of this study is to evaluate the prognostic significance of race in the clinical presentation, treatment, and outcome in breast cancer patients treated with lumpectomy and radiation therapy. Also, this study seeks to examine the influence of race in cosmetic outcome following breast-conserving treatment.

Methods

The medical records of 1737 of women who were diagnosed with primary breast cancer and received subsequent treatment with lumpectomy and radiation therapy at Yale New Haven Hospital between the years of 1973 and 1997 were retrospectively reviewed and updated. For all patients, race was recorded. Only patients with stage I or stage II breast cancer or patients with ductal carcinoma in situ (DCIS) were included. Patients were routinely treated with a wide local excision of the tumor followed by external beam radiation therapy. The intact breast was typically irradiated with regional nodal irradiation delivered as clinically indicated at the discretion of the treating radiation oncologist. Radiation therapy employed standard techniques with 4 to 6 Mev photons, using a daily fraction size of 2.0 Gy to a total median dose of 46 Gy. An electron boost was routinely administered, resulting in a total tumor bed dose of 64 Gy. Adjuvant systemic cytotoxic chemotherapy and/or adjuvant hormonal therapy was employed as clinically indicated in accordance with standard practices during this time.

All patient data including race, age, T stage, hormone receptor status, nodal status, use of adjuvant chemotherapy and/or hormone therapy, method of detection, histology, margin status and treatment technique were analyzed. Patient outcomes were examined with respect to overall survival, cause specific survival, breast relapse free survival and distant relapse free survival. Patients were classified as African American (AA) or White. 101 women were identified as African American and 1614 were identified as White. A small number of patients (22) were eliminated from this study secondary to classification in racial groups that were neither African American nor White.

A detailed cosmetic assessment was performed on a subset of 40 patients coming in for follow-up visits during a 4-month period. For this analysis, 20 African-American women and 20 matched control white patients were recruited. Patients were matched in regards to age, use of chemotherapy, radiation technique (tangents vs. three field, use of boost), follow-up years, and size of breast (assessed as the separation between the medial and lateral field edges as measured at the time of radiation treatment) and were scored by physician assessment. The untreated breast was compared with the treated breast using a 4 point scale: 1=excellent, no difference between the two breasts; 2=good, slight difference between the two breasts; 3=fair, moderate difference between the two breasts; 4=poor, marked obvious difference between the two breasts. Each patient received a score of 0-3 on the basis of skin pigmentation, edema, and fibrosis (0-no difference, 1-mild, 2-moderate, 3-severe).

Statistical Analyses: All patient data including patient characteristics, clinical and treatment variables, and cosmetic analysis were entered into a computerized database. Tests for statistical significance between groups employed the chi-square test for categorical variables and the T-Test for continuous variables. Survival curves were calculated by the life table method, with differences between curves tested by the Mantel-Haenzel statistic.

Results

Patient Characteristics

Patient characteristics of the African American and white cohorts are summarized in Table 1. Median age at the time of original diagnosis for all patients was 56.0 years. The median age in the African American patients was 48.0 years compared with 57.0 years in the white patients ($p<.001$). When broken down by age groups, 8.9% of African American patients were under age 36 compared to 5.2% of white patients; 48.5% of African American patients were between 36-49 compared to 26.2% of white patients; 42.6% of African American patients were age 50 and over compared to 68.6% of white patients ($p<.001$).

There was no significant difference between the groups in terms of method of detection of the tumor (mammography vs. physical exam). 37% of African American patients and 36% of white patients were detected with mammography alone. Similarly, 39% of African American patients and 37% of white patients presented with tumors that were palpable on physical exam and detectable mammographically.

The average pathologic size of the tumor for African American patients was 1.89cm versus 1.57cm for white patients ($p=0.002$). Accordingly, there was a significant difference in the pathologic T-stage of the tumor; 62% of African American patients versus 77% of white patients were in the T1 stage; 24% of African American women compared to 14 % of white patients were T2. The incidence of ductal carcinoma in situ (DCIS) lesions was similar between the two groups (13% African American vs. 8.2% white). African American patients were significantly more likely than white patients to have tumors that were ER negative. 51% of African American patients versus 37% of

white patients were ER negative. There was no significant difference in progesterone receptor status between the two groups. There was also no significant difference between the two groups in the histology of the tumors with the majority of the cases reported as infiltrating ductal carcinoma. Despite the larger tumor size and T-stage of the African American group, there was not a statistically significant difference in terms of axillary nodal involvement (27%African American patients vs. 24% white patients were node positive). The African American women were more often found to have positive final surgical resection margins (11% for African Americans vs. 5% for whites, p =.03).

There was no significant difference between the two groups with respect to radiation technique, use of regional nodal irradiation, or the total radiation dose delivered to the tumor bed. While there was no significant difference in the rate at which patients in both groups received adjuvant systemic therapy, there was a significant difference in the type of adjuvant therapy received by the two groups. Specifically, 29% of African American patients received adjuvant chemotherapy in comparison to 22% of white patients (p=.07). 18% of African American patients received adjuvant hormone treatment compared to 27% of white patients (p=.04).

Long-term outcome

As of September 2002, the median follow-up from the date of original diagnosis was 14.5 years for all patients with follow-ups ranging from 2 to 24 years. There was no difference in clinical status of the two groups at the time of last follow up. For both the African American and white patients, survival with no evidence of disease was about 80% at time of last follow up. Similarly, 5% and 6% of African American and white patients respectively were alive with disease at last follow-up.

Overall survival, distant metastasis free survival (DMFS), cause specific survival (CSS), and breast relapse free survival (BRFS) as a function of race are depicted in Figures 1-4 respectively. As seen in Figure 1, there was no difference in overall 10-year survival in the African-American and white patients (82 $\pm$ 4% African American vs. 79 $\pm$ 1% white). During the first three years post-treatment, both African American and white patients experienced similar declines in the survival rates. However, between years 3 and 4, there was a drop of 10% in survival among African American patients, which contrasts with white patients in whom there was a continual gradual drop. Cause specific survival reflects a similar trend to that seen in overall survival (see Figure 3). Again, in terms of 10-year survival, there was no significant difference in cause specific outcome between the African American and the white patients. At 10 years, African American women had a survival rate of 88 $\pm$ 4% and white women had a survival rate of 86 $\pm$ 1%. But, during the time between years 3 and 4, there is a 7% drop in survival in African American patients, similar to the decline seen in overall survival. Figure 2 demonstrates that the distant metastasis free rate reflects similar outcomes in both groups (79 $\pm$ 5% African American vs. 82 $\pm$ 1% white).

In the BRFS curve (see Figure 4), the percentage of African Americans who were breast relapse free remained significantly lower than the percentage of white women from year three onward. A small but statistically significant difference in outcome is seen with respect to local relapse in the conservatively managed breast. At 10 years, the ipsilateral breast relapse free rate was 81 $\pm$ 5% in the African American patients compared to 87+/-1% in white patients (p=.026).

Cosmetic Analysis

In the cosmetic analysis, patients were matched in terms of age, radiation technique, use of chemotherapy, follow-up years, time from diagnosis to treatment, and size of the breast. Thus, as expected, no significant difference was seen in these variables between the two populations. However, for all of the measured cosmesis endpoints, a significant difference is observed between the two populations. The cosmetic analysis is summarized in Table 2. For edema, 65% of African American patients were judged to have either moderate or severe reactions in comparison to 20% of white patients ($p=.015$). Similarly, in 80% of African American patients versus 15% of white patients, there was observed a moderate to severe amount of pigmentation in the treated breast compared to the untreated breast ($p<.001$). Of note, no white patients were judged to have a severe degree of pigmentation. Furthermore, the degree of fibrosis seen in African American patients was observed to be either moderate or severe in 80% of patients in contrast to the white patients in which only 30% were considered to have had a moderate to severe fibrotic response ($p=.005$). These variables are all reflected in the overall score. 90% of white patients were judged to have an excellent or good overall cosmetic result in comparison to 55% of African Americans ($p=.04$).

Discussion

This study examined the relationship between race and clinical characteristics and clinical outcome following treatment with lumpectomy and radiation therapy. The results from this study support the well-documented statistics showing that African American women present at a younger age (3, 5, 8). Even though the African American patients tended to be younger at time of initial presentation and to be detected by routine screening mammogram at an equivalent rate, this study demonstrated that they were more likely to present with more advanced disease, which again supports national data. The African American women had larger primary tumors as measured by T-stage and mean pathologic size, reflecting a more aggressive pathology in spite of similar histology. However, axillary nodal status was similar in the African American and white patients in this study.

Indeed, several studies have regularly documented poorer outcomes of African American women with breast carcinoma. Lyman et al. found in their study that African American women suffering from breast cancer have a greater risk of recurrence, shorter overall survival, and shorter survival after relapse than did white women (34). Similarly, when Joslyn and West looked at women in the SEER program from 1988-1992, they found that the African American women experienced lower survival compared with white women (6).

However, this study found equivalent survival rates both at 10 years and at the time of last follow-up for both patient populations. This difference in survival is presumably due to the use of an appropriate treatment regimen for the African American women treated at this institution. While the African American and white patients

received adjuvant therapy at an equal rate, there was a difference in the type of adjuvant treatment that each group tended to receive. African American patients were more likely to have received adjuvant chemotherapy while white patients were more likely to have received adjuvant tamoxifen. This difference in treatment modality is appropriate given the different clinical presentation of the two groups. African Americans presented with larger, estrogen receptor negative tumors, thus they were more likely to require chemotherapy.

Analysis of the ipsilateral breast relapse revealed that African American women were more likely to have a local relapse. While this supports the findings from other studies demonstrating that African American women with breast cancer have a greater risk of recurrence when compared with similarly treated and staged white women (34, 35), there is limited information regarding the risk of local-regional relapse in African-American women. In one study, Connor et al. found a statistically significant difference in the actuarial tumor recurrence rate in African American and white patients (35). They observed a 13% 5-year risk of local relapse in African-American patients compared to a 4% risk in whites (p=.075). However, they also noted that this difference in recurrence no longer maintained its significance when patients with skin or soft tissue recurrence overlying the breast were excluded (35). Although no significant difference in local relapse was observed, Pierce et al. noted a higher rate of regional relapses in a cohort of conservatively managed African American breast cancer patients (33). Specifically, the regional relapse rate as a first component of failure was 16% for blacks compared to 4% for whites. While collectively these data, along with the observations from the present

study, suggest a more aggressive local-regional behavior of the tumors in African-American women, further studies are clearly needed.

Given the younger age of presentation in the African American women, the decreased BRFS of African Americans is also consistent with studies reported in the literature demonstrating that young age is associated with an increased incidence of local relapse (18, 36-41). Thus, the higher recurrence rate in African American women may be attributable their younger age. The association of young age and local relapse is not well understood. Also, of note is that the margin status was more frequently positive in the African American patients; a positive margin has a known association with a higher local recurrence rate. However, in a multivariate model, taking into account all known risk factors for local relapse, including age, race, margin status, use of adjuvant therapy and radiation dose, both young age and African American race maintained statistical significance with respect to ipsilateral breast relapse. Potentially, the higher local recurrence rate may be related to the hormonal environment or a molecular marker or some other mechanism associated with African American race or young age that has yet to be elucidated.

Some studies have looked at diet and nutritional factors to understand the advanced presentation of breast cancer in African American women. Research has documented that African American women are at greater risk for obesity. Furthermore, research suggests that obesity is not only a risk factor for breast cancer but may be related to a more advanced stage of disease, potentially due to the effect of increased estrogen that occurs from the presence of a greater number of fat cells (42, 43). Thus, the higher

prevalence of severe obesity among black women may play an important role in explaining their advanced stage at diagnosis of breast cancer.

Furthermore, research has also focused on some of the recently identified genetic and molecular markers associated with breast tumor biology (44, 45). Recent studies have focused on contributions of BRCA1 and BRCA2 mutations among African Americans. Data suggest that African-American patients with breast cancer may carry some unique BRCA1 gene mutations (46-48). Research has also looked at variations of p53 mutations among African American women. Blaszyk et al. detected differences in the pattern of acquired p53 mutations in African American women with breast cancer compared with white women (49). Therefore, differences in molecular and genetic markers as a function of ethnic and racial groups is an area of investigation that may lead to further insights regarding the observed differences in clinical behavior and outcome (44, 45).

One important factor that this study was unable to control for was socioeconomic factors which are well known to affect the use of screening tools, delay the time of diagnosis, and inhibit the use of treatment services. When socioeconomic status is considered, some studies suggest that racial differences in clinical characteristics and outcomes of breast cancer patients dramatically decline in significance (3, 5). However, these same studies also indicate that while there was a decline in the significance of racial disparities when there was rigorous control for socioeconomic factors, racial differences in breast cancer survival still existed. Furthermore, it is important to keep in mind that there is a strong association between socioeconomic status and race in the United States whereby African Americans and other racial minorities are overrepresented in the lower

socioeconomic strata. Also, even among women with comparable income levels and access to care, there is still underutilization of screening services among African American women (4). Therefore, it is too simplistic to attempt to attribute the racial variations in the study population to socioeconomic factors alone. Furthermore, it should be noted that in our selected population the percentage of breast cancers detected by screening mammography was similar among the African American and white populations.

In addition to clinical characteristics and long-term outcome, cosmetic result also remains as an important endpoint in the evaluation of conservative management of breast cancer in African American patients. Thus, this study also focused on the association between race and cosmetic outcome in conservative management of breast cancer. The results of this study demonstrated that African American patients did significantly worse on all of the cosmetic endpoints (fibrosis, pigmentation, skin edema, and overall cosmetic appearance) in comparison to white patients. These results support the findings from previous studies demonstrating significantly fewer African American women having an excellent-to-good cosmetic result (25, 33).

Several factors have been associated with a worse cosmetic outcome and have been proposed to explain the difference seen in African American and white patients. For instance, the size of the tumor dictates the amount of tissue removed, with larger tumors requiring more generous excisions, leading to more asymmetry and thus poorer cosmetic outcome (29, 50). Also, adjuvant chemotherapy has been associated with poorer cosmetic outcome (25, 29, 33, 51, 52). Thus, it could be assumed that since African American patients were more likely to have larger tumors that required the use of

adjuvant chemotherapy, they were more likely to experience a worsened cosmetic outcome. However, the patients in this study were well matched in terms of those factors documented to affect the cosmetic outcome (tumor size and treatment method) and the patients were also additionally matched for size of breast and age. Even when controlling for those factors associated with worsened cosmetic outcome, the African American women still had a poorer cosmetic outcome. Thus, a broader understanding is needed in order to elucidate the biological factors associated with the less-than-acceptable cosmetic result in African Americans women. Why do the African Americans exhibit a more intense response to the radiation therapy? Or, is it potentially the combination of chemotherapy and radiation therapy that produces such an intense response in the African American patients?

It is known that hypertrophic scars and keloids are fibrous tissue outgrowths that occur because of an exaggerated wound healing response of the skin following injury (53, 54). This results in an excessive deposition of extracellular matrix, especially collagen. Evidence suggests that keloid scar formation may be mediated, in part, by deranged growth factor activity, including that of transforming growth factor (TGF) beta1. Research has shown increased expression of TGF-beta1 and TGF-beta2 ligands and TGF beta receptors in keloid fibroblasts when compared with normal human dermal fibroblasts (NHDFs), suggesting that TGF-beta may be important in promoting fibrosis in keloid pathogenesis (53, 54). This role of increased expression of TGF beta and its receptors in keloid fibrosis may extend itself to explaining the radiation-induced fibrosis seen in African American patients treated with lumpectomy and radiation therapy. There

may potentially be increased expression of TGF beta or other growth factors following radiation therapy that may result in the increased fibrotic response.

Furthermore, recent studies suggest that women who are heterozygous for the ATM gene mutation may have an enhanced radiosensitivity and thus may be at greater risk for radiation-induced normal tissue toxicity (55). Mutations in both copies of the ATM gene result in the rare autosomal recessive condition ataxia-telangiectasia (AT). In the general population, 1% of people express a single mutated copy of the ATM gene, and while they do not exhibit classic symptoms of AT, they may possess an increased sensitivity to radiation because of differences in ATM protein function or transcription levels. Iannuzi and colleagues found that female breast cancer patients who possess heterozygous ATM mutations were at increased risk for subcutaneous late tissue effects following radiation therapy (55). They suggest that possession of an ATM mutation, especially two ATM mutations if they are on opposite chromosomes, may be a relative contraindication to standard breast conserving therapy. The incidence of ATM mutations in African American women and the role of ATM mutations in African American women suffering from breast cancer are unknown (55). Hence, a potential explanation for the poorer cosmesis of African American women is that they may be more likely to be heterozygotes for the ATM gene and may be at increased risk for radiation induced injury from conventional doses.

Of note, while the overall cosmetic outcome was more often judged to be fair to poor by physician evaluation among the African American patients, when questioned, the majority of the patients expressed satisfaction with the outcome. This disagreement between physician and patient evaluation of cosmetic outcome was seen in the study by

Taylor et al., in which patients were more likely than physicians to score their cosmetic result as excellent/good (25). In the majority of cases, the cosmetic outcome was judged as acceptable by the patient. Our observations were similar to this study.

In summary, the current study provides support for studies showing that African American women present at a younger age and with a more advanced and aggressive disease than white women. The results from this study are further strengthened by its extensive long-term follow-up. However, in contrast to many studies, we were able to demonstrate equivalent overall survival between African American and white patients. This is presumably due to the use of an appropriate treatment regimen. African American women were more likely to receive adjuvant chemotherapy than white women, but this goes along with the more advanced presentation of the African American women. Therefore, as our study shows, with the appropriate treatment there is significant potential for an improved clinical outcome. However, as this study also demonstrates, additional work needs to be done to understand the progression of disease in African American women and to reach out to the African American community to encourage both mammography at an earlier age and regular physical exams.

Furthermore, this study also shows that African American women experience a worse cosmetic outcome following lumpectomy and radiation therapy. The reason for this poorer outcome is not well understood. There may be a potential role of growth factors such as TGF-beta or genetic mutations such as in the ATM gene. Therefore, more molecular, biological, and clinical cancer research is needed to evaluate the earlier onset, more advanced presentation of disease and poorer cosmetic outcome for breast cancer in conservatively managed African American women.

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TABLE 1: Patient Characteristics

	African American	White	p Value
N=1614	101	1514	
Age Years (Mean)	51.0	56.5	<.001
age<36	9 (8.9%)	79 (5.2%)	
36-49	49 (48.5%)	396 (26.2%)	
age≥50	43 (42.6%)	1038 (68.6%)	<.001
Follow-up (Mean)	13.4 yrs	14.7 yrs	
Tumor Size (cm)	1.89cm	1.57cm	.002
T-Stage			<.001
T1	62 (61.6%)	1157 (78.7%)	
T2	25 (24.62%)	217 (14.54%)	
DCIS	13 (12.6%)	123 (8.2%)	
Method of Detection			.84
PE alone	16 (16.0%)	235 (15.7%)	
MG alone	37 (37.3%)	545 (36.3%)	
PE-MG positive	39 (39.4%)	558 (37.2%)	
PE-MG negative	7 (7.0%)	161 (10.7%)	
Adjuvant Treatment			
adj chemotherapy	30 (29.7%)	332 (22%)	.07
adj hormone	18 (17.8%)	405 (27%)	.043
ER Status			.02
positive	38 (49.33%)	669 (62.6%)	
negative	39 (50.6%)	399 (37.4%)	
PR Status			.40
positive	32 (46.3%)	462 (51.6%)	
negative	37 (53.6%)	434 (48.4%)	
Node Status			.55
positive	20 (27%)	230 (24%)	
negative	54 (73%)	728 (76%)	
Clinical Status			.51
alive, WD	11 (10.8%)	93 (6.2%)	
alive, NED	77 (75.5%)	1174 (77.7%)	
dead, WD	9 (8.8%)	142 (9.4%)	
dead, NED	5 (4.9%)	96 (6.4%)	

TABLE 2: Cosmetic Analysis

	African American	White	p Value
N=40	20	20	
Separation (cm)	23.69	22.34	
Edema			.015
0	1 (5%)	0 (0%)	
1	6 (30%)	16 (80%)	
2	11 (55%)	3 (15%)	
3	2 (10%)	1 (5%)	
Pigmentation			.001
0	0 (0%)	7 (35%)	
1	4 (20%)	10 (50%)	
2	14 (70%)	3 (15%)	
3	2 (10%)	0 (0%)	
Fibrosis			.005
0	1 (5%)	0 (0%)	
1	3 (15%)	14 (70%)	
2	11 (55%)	1 (5%)	
3	5 (25%)	1 (5%)	
Overall			.043
1	0 (0%)	4 (20%)	
1.5	1 (5%)	4 (20%)	
2	10 (50%)	10 (50%)	
2.5	3 (15%)	0 (0%)	
3	5 (25%)	1 (5%)	
3.5	1 (5%)	1 (5%)	

Figure Legends

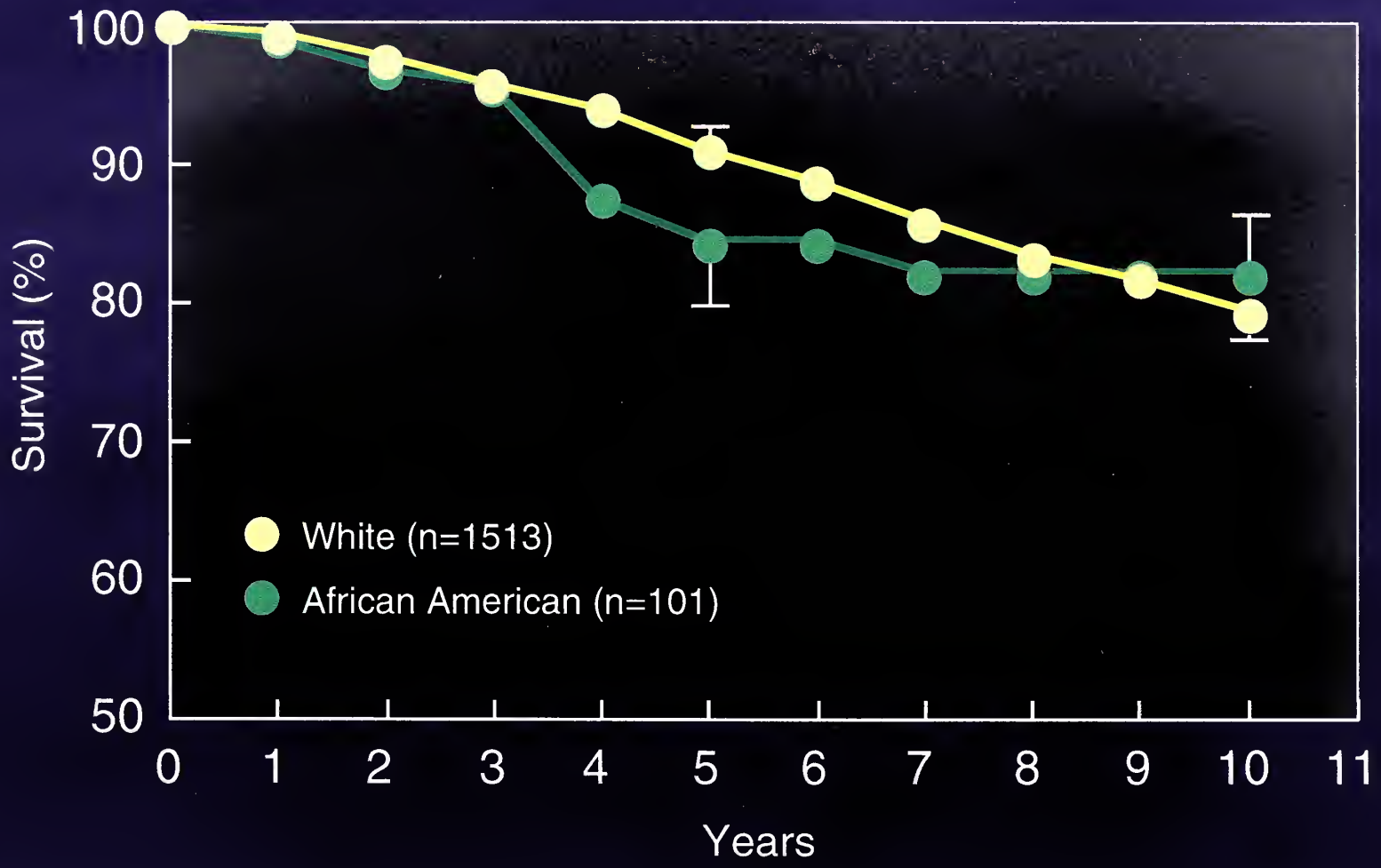
Figure 1: Overall survival by race.

Figure 2: Cause-specific survival by race.

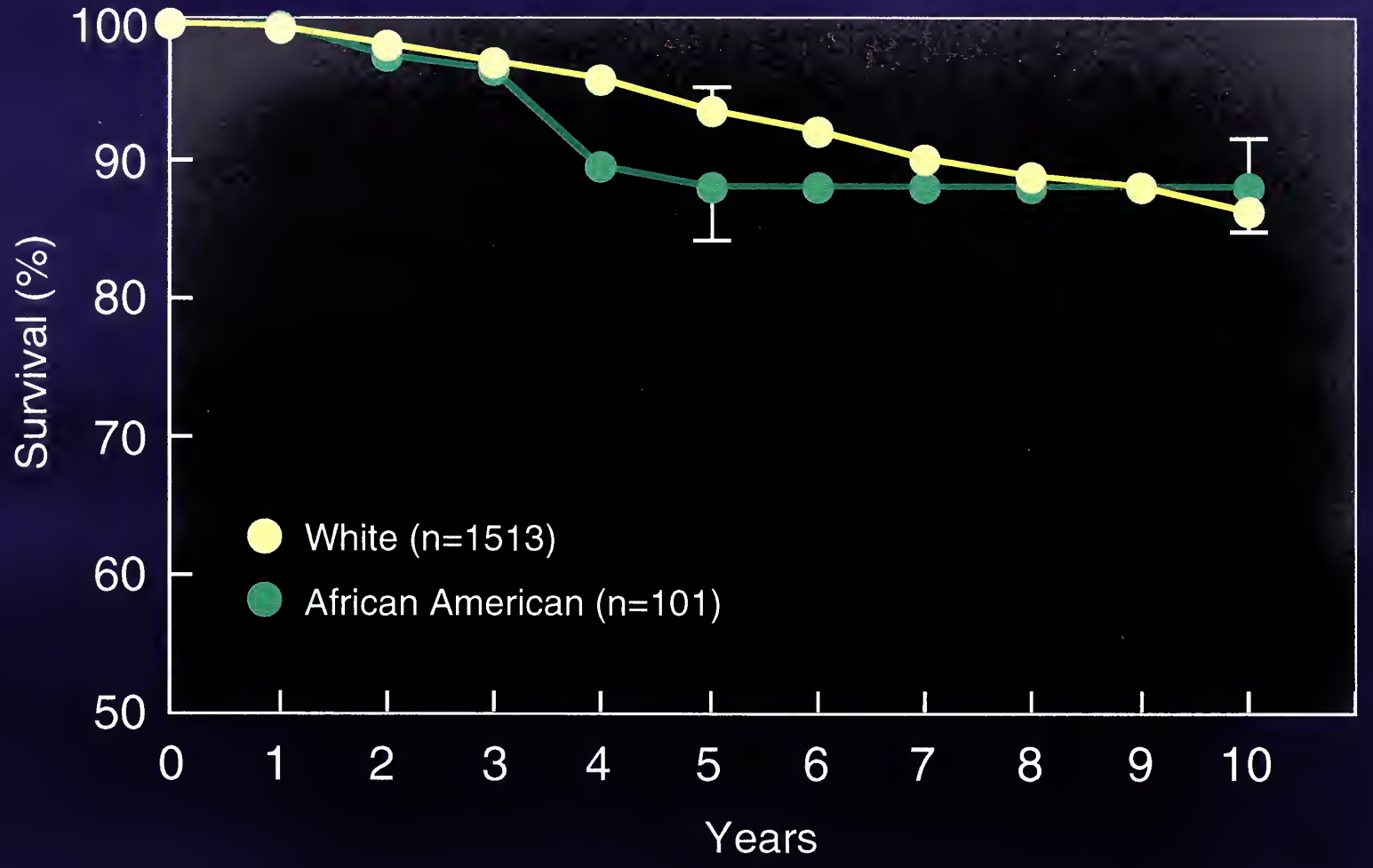
Figure 3: Distant metastasis free survival by race.

Figure 4: Breast relapse free survival.

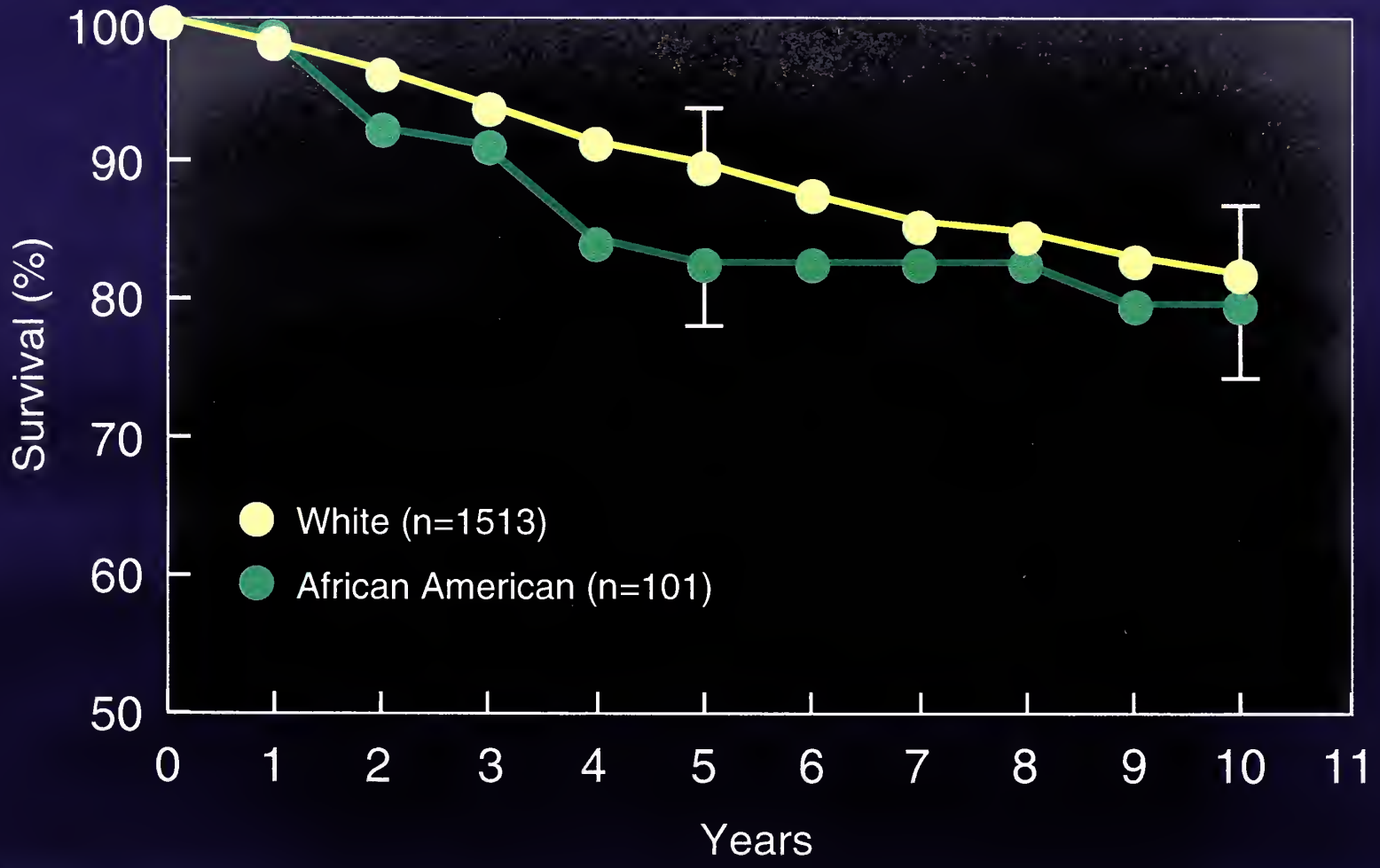
Overall Survival



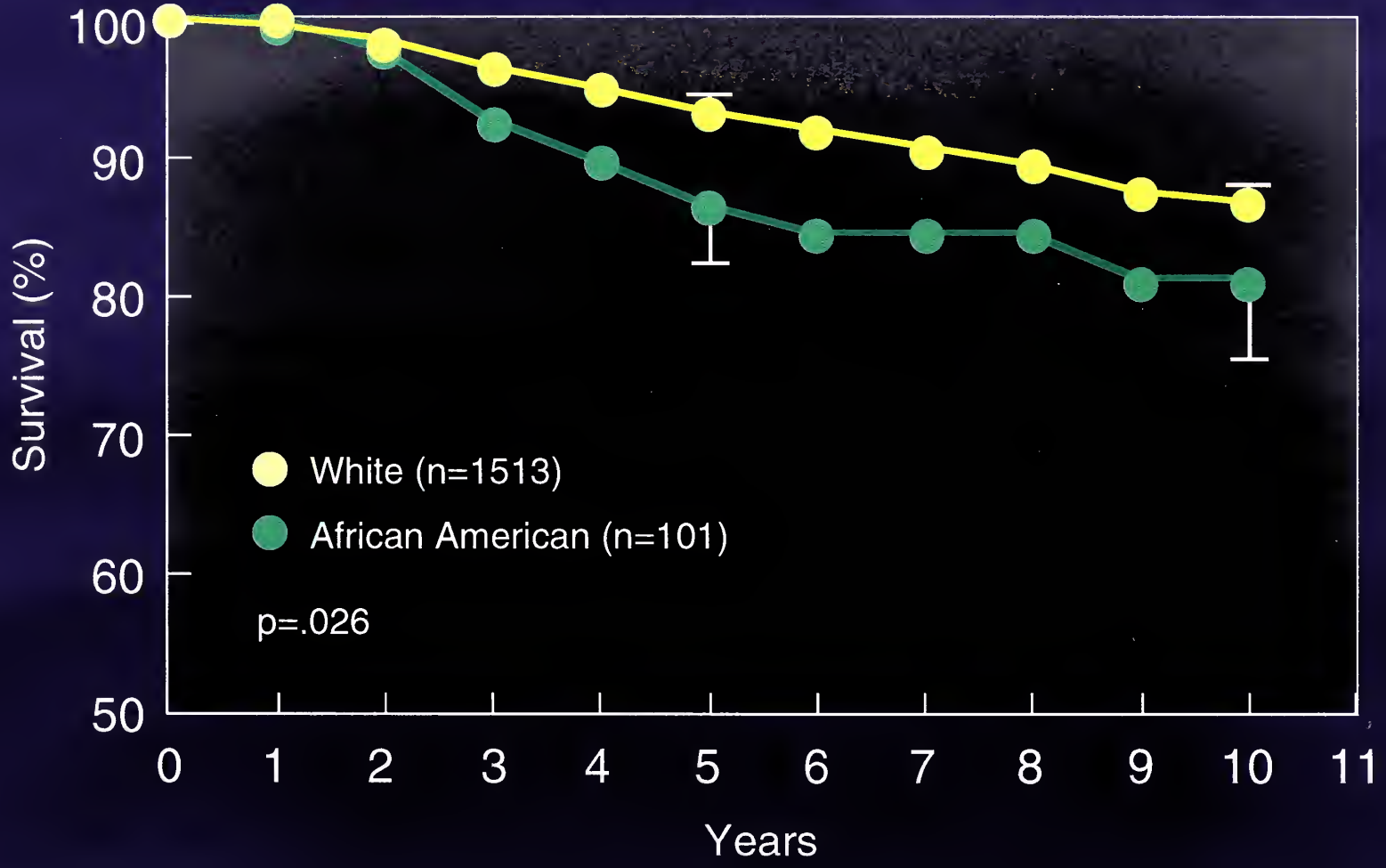
Cause-specific Survival



Distant Relapse-free Survival



Breast Relapse-free Survival



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