



Is Race a Prognostically Significant Factor in Survival Outcomes for Breast Cancer Among Caucasian and African-American Women?

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Abstract

Despite recent improvements in overall survival shared among patients of all races, disparities in breast cancer related survival between Caucasian and African-American women have widened due to disproportionate gains achieved by Caucasian women. The following review analyzes both early and contemporary literature for patterns in their findings of the extent to which clinical and socioeconomic drivers account for racially driven differences in outcome. The increased mortality rates for African-American patients relative to Caucasian counterparts are deconstructed into racial differences in prognostically significant variables. Both early and contemporary studies find that African-American patients present with high-risk clinical characteristics such as younger age, more advanced tumor stage, and unfavorable histology. Furthermore, census-tract data, and hospital records indicated African-American patients to be socioeconomically disadvantaged, and therefore prone to increased breast-cancer related mortality rates relative to Caucasian counterparts. Although minor differences in findings exist between early and recent literature, the overarching theme among studies focusing on data between 1946-1990 was the resolution of survival disparities by race after controlling for effects of racial discrepancies in a for mentioned parameters. Alternatively, following multivariate analyses adjusting for racial differences in clinical and socioeconomic variables, contemporary studies maintained persistent survival gaps between African American and Caucasian patients.

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Introduction

The disparities between African-American and Caucasian Breast Cancer patients with regards to overall survival have been widely studied for the past few decades. Data from 1955 to the present have conveyed a consistent theme of African-American women being at a survival disadvantage, ranging from 10-40% depending on the population and time period considered [1,2]. This disparity appears to persist despite an overall trend towards improvements in Breast Cancer related mortality, with 5-year survival rates increasing from 75.2% in 1975 to 90.6% in 2008 for women in the U.S. as a whole [2]. However, these survival gains were disproportionately seen among Caucasian patients [2]. Estimates for 5-year survival in African-American patients ranged from between 12-20% below that of Caucasians between 1951-1973, with this gap widening to 28% from 2004-2009 [2-4]. In light of these findings, multiple investigators have sought to address the question of whether or not race itself was a prognostic factor for Breast Cancer survival, and designed studies quantifying the impact of clinical and pathologic variables on outcomes. Previous studies have found clinical, and pathological Breast Cancer parameters such as age, stage at diagnosis, histological tumor characteristics, tumor subtype, and treatment were not only prognostically significant for survival, but also variable between African-Americans and Caucasians [5-9]. Furthermore, socio-economic criteria such as income, comorbidities, education level, and insurance status have also been observed as indicators for Breast Cancer-related mortality. Moreover, a marked delineation between socioeconomic status (SES) of African-American and Caucasian Breast Cancer patients has been identified consistently in the literature [6,10-14]. The majority of early literature, addressing subjects diagnosed with Breast Cancer between 1946 and 1990, found that racial survival disparities were not statistically significant after controlling for prognostic clinical, pathologic and socioeconomic parameters [1,3-6,10-12,15-27]. Of note these were studies incorporating smaller sample sizes with shorter periods of follow-up. More recent data from studies of patients diagnosed from 1961 to 2011 largely demonstrate persistent increased risk of death among African-American Breast Cancer patients even after adjusting for differences in variables closely associated with survival

rates [2,7-9,13,14,28-47]. The purpose of this review is to examine differences in Breast Cancer survival outcomes by race taking into consideration clinical, pathologic and socioeconomic factors.

Age, Stage, Histology

In efforts to examine the effect of race on breast-cancer survival investigators have examined the impact of age, tumor stage, and tumor histology. Several studies have found that patients presenting at a young age, with a high-grade tumor and advanced stage, were more likely to be at an increased risk of breast-cancer related mortality. Neale et al. [11] in a study of 10,778 women from 1973 to 1988 was able to show that Breast Cancer patients presenting with local disease <40 years of age had an increased relative risk of death from Breast Cancer as compared to those 40-54, 55-69, and >69 years of age. (HR 1.0 vs. 0.86 vs. 0.64 vs. 0.82; $p = 0.0281$). Furthermore, Du et al. [39] examining a cohort of 35,029 Breast Cancer patients from 1992-1999 reported an increase in the hazard ratio for mortality from 1.00 to 2.21 (1.88-2.61; $p=0.05$) to 4.02 (3.21 - 5.03; $p=.05$) in patients presenting with stage I, II, and IIIA Breast Cancer. Tumor grade was also similarly prognostic of mortality, with high-grade tumors much more likely to lead to death in comparison to low-grade tumors. HR =3.42 (2.63 - 4.44; $p=0.05$) vs. HR=1.00 ($p = 0.05$).

Many early as well as more contemporary studies found that African-American women tended to present with a Breast Cancer diagnosis at an earlier age compared to their Caucasian counterparts [1,4-6,11,15,16,18-20,22,26]. Although there were a few exceptions from studies that found no difference in age at presentation among African-Americans and Caucasians, they were underpowered and in the minority [13,37,39-41,43,44]. The findings of younger age at presentation among African-American patients was observed in high-powered studies utilizing a large sample size in both older and newer studies. Vernon et al. [6] found that in analyzing a sample of 1,983 Breast Cancer patients from 1949 to 1978, 5.1% more African-Americans were diagnosed under the age of 55 ($p<.001$).

With regards to stage, 6 of the early studies found no significant difference between Caucasians and African-Americans at initial diagnosis [3,4,22,23,26,27]. Dayal et al. [3] in a study of 903 patients between 1968 and 1977 found that African-American patients were diagnosed with local, regional, and distant disease at virtually indistinguishable relative frequencies compared to Caucasians. However, 13 studies utilizing more robust data sets have shown a tendency for African-American patients to present with disease at a more advanced stage than Caucasians [1,5,6,10-12,16,18-21,24,25]. In particular, Perkins et al. [12] looking at 3,382 patients at MD Anderson from 1958 - 1987 showed that 81.2% of Caucasian patients presented with localized disease as opposed to only 70.1% of African-American patients ($p<.001$). Natarajan et al. [24] obtained data on 27,355 patients from 565 U.S. hospitals diagnosed between 1965 and 1981, and found that 34.1% of African-Americans had tumors smaller than 2cm as opposed to 45.3% of Caucasians ($p<.0001$).

Contemporary studies mirror these findings as well, with a large body of evidence demonstrating marked differences in stage at presentation among African-Americans and Caucasians [2,7-9,13,14,28-30,34,36-47]. Li et al [34]. examining a population of 124,934 patients from 1992-1998, found that Caucasian compared to African-American patients tended to present with lower stage disease 50.4% vs. 35.4% stage I; 38.3% vs. 45.7% stage II; 6.8% vs. 11.0% stage III; 4.5% vs. 7.9% stage IV ($p<0.05$) respectively. Recent 2003-2014

data from SEER reports 53.8% of African-American Breast Cancer patients are diagnosed with localized disease as compared to 64.5% of Caucasians, while 35.2% and 8.6% of African-Americans have regional and distant involvement in contrast to 28.3% and 5.1% of Caucasians [48].

Although studies examining histological type found no significant racial differences, those focusing on histological grade often found that African-American patients tended to present with higher-grade tumors. Natarajan et al. [24] in a study of 27,355 patients found that African-Americans and Caucasians were diagnosed between 1965 and 1981 with a similar distribution of pathologic types heavily skewed towards ductal infiltrating tumors. However racially-based differences were outlined in regard to tumor grade. Warner et al. [7] in a study of 17,268 patients found that 64.6% of African-American patients were diagnosed with a high grade tumor as opposed to 43% of Caucasians ($p<.001$).

In earlier studies after adjusting for age, stage and histology there was no racially-driven difference in survival [18,20,25]. Dansey et al. [18] incorporating 2,033 subjects found that after adjusting for age and race, the relative risk of African-Americans to encounter Breast Cancer-related mortality compared to Caucasians dropped from 2.4 to 1.23 ($p=.074$). However more contemporary studies have found that multivariate analysis adjusting for differences in age and stage was unable to fully account for racially delineated survival discrepancies [36,45]. Roetzheim et al. [25] in a study of 11,113 patients found a hazard ratio of 1.39 (1.16-1.66; $p<.001$), dropping from 1.67 (1.39-2.00; $p<.001$) after adjusting for stage at diagnosis. Additionally, Warner et al. [7] in a study of 17,268 Breast Cancer patients found that even after adjusting for age, African-Americans still remained at greater risk of death with a HR of 2.01 (1.70-2.38; $p=0.05$). The persistence of disparities despite adjustments for age, and stage illustrated a need to account for potential drivers of disparities not included in the aforementioned analysis, such as hormone receptor status.

Estrogen Receptor Status

Investigators have sought to quantify the impact of incorporating differences in hormone-receptor status, namely estrogen receptor (ER) status into multivariate analyses. The literature has ubiquitously illustrated the increased risk of death in Breast Cancer patients carrying ER - tumors [14,19,36]. Iqbal et al. [14] in analyzing a sample size of 452,215 Breast Cancer patients diagnosed between 2004 and 2011 found that subjects with ER+ tumors had a HR of 0.31 (0.29-0.34; $p<.001$) of Breast Cancer-related death compared to an HR of 1 (reference; $p<.001$) in subjects with ER- disease. In regards to this particular variable, there were marked differences between early and recent literature. From our literature search, only 6 studies looking at samples of patients diagnosed between 1946 and 1990 presented data on the relative frequency of ER+ and ER- tumors of African-American and Caucasian Breast Cancer patients. The dearth of such studies reflects the lack of ubiquitous testing for ER status prior to 1977. Gordon et al. [19] in examining a population of 1,392 from 1974-1985, found that 32.4% of African-Americans carried ER- tumors compared with only 21.7% of Caucasians ($p<.001$).

All 16 contemporary studies offering data on ER status were in agreement with previous findings asserting African-American patients presented more frequently with ER- disease [7-9,13,14,28,29,34-40,43,44]. Studies such as that carried out by Grann et al. [35]

examining 205,736 patients diagnosed between 1990 and 2000, finding 27.1% of African-American and only 19.1% of Caucasian patients had tumors characterized as ER- exemplified a definitive discrepancy based on a statistically robust data set ($p < .0001$).

Adjustments for the propensity of African-American patients to present with ER- disease in multivariate analysis failed to eliminate increased risk of mortality in the African-American population. Elledge et al. [29] looking at a sample size of 6,778 subjects from 31 different institutions concluded that after controlling for the greater proportion of African-American patients harboring advanced stage, and ER- tumors, African-American patients remained subject to an increased relative risk ratio for death of 1.2 (1.1-1.4; $p = 0.004$) as compared to Caucasian patients. Although consideration of differences between the two groups in terms of these two prognostically significant variables resulted in a reduction of statistically significant increased risk of death for African-American patients from $p < .0001$ to $p = 0.004$, the increased risk of breast-cancer related death was still evident. The persistence of increased odds of death among African-Americans from Breast Cancer subsequent to controlling for ER status necessitated consideration of other clinically relevant parameters.

Treatment

Variability in treatment received was thought to play a role in the increased relative risk of death in African-American patients. Eley et al. [10] in examining a sample of 1,130 subjects from 3 sites found that the HR of Breast Cancer related mortality among African-American compared to whites dropped from 2.2 (1.7-2.9; $p = 0.05$) to 1.9 (1.5-2.6; $p = 0.05$) after accounting for differences in treatment in the survival analysis. Also, El-Tamer et al. [2] in a study of 1,745 patients showed that adjusting for stage, and surgery type led to a drop in relative risk of mortality of African-Americans compared to Caucasians from 1.27 (1.05-1.55, $p = 0.05$) to 1.04 (0.86-1.27; $p = 0.05$). The findings of previous studies imply a role for treatment discrepancies contributing to the existence of differential survival statistics among African-Americans and Caucasians. Early studies found no significant differences in treatment protocols administered between the races. Heimann et al. [20] showed that in a population of 1,518 patients treated at University of Chicago between 1946 and 1987 there was inadequate data to substantiate statistically significant differences in adjuvant treatment (radiotherapy, chemotherapy, hormonal therapy) between African-American and Caucasian patients. However, the same group found a statistically significant difference in type of surgery, with Caucasians tending to be treated more frequently with radical mastectomy than African-American ($p < 0.01$). Of note this was standard of care during this period. In subsequent periods as breast conservation was increasingly being used in the treatment of Breast Cancer, Muss et al. [23] found that Caucasians tended to be treated more heavily with breast conserving surgery ($p = 0.004$). Later studies by both Hershman et al. [37] and Hershman et al. [40] looking at separate populations diagnosed between 1989-2004 found no differences in the chemotherapeutic drug regimen administered to African-Americans and Caucasians, however they did find that African-American patients were more likely to have a premature discontinuation or delay in their treatment. Furthermore, Vernon et al. [6] focused on a subset of 3,061 women who had recorded their initial Breast Cancer symptoms diagnosed with Breast Cancer between 1949 and 1978, reporting that among Caucasians < 3 month delay, 3-6 month delay, and > 6 month delay in

receiving initial treatment was 55.4%, 18.7%, and 25.9%, compared to 36.2%, 26.3%, and 37.5% among African-Americans ($p < 0.001$).

It becomes important to note that these findings consisted of univariate analyses, and after controlling for stage at presentation, a factor commonly regarded as significantly disparate between the two groups, differences in treatment often became negligible. In a study by Franzini et al. [42] examining 1,332 patients from 1987 to 1991, treatment differences between African-American and Caucasians in terms of incorporation of RT, chemotherapy and/or hormonal therapy with surgery became statistically insignificant when categorized by stage. African-American patients with local disease had an odds ratio compared to Caucasians of receiving surgery and chemotherapy of 1.34 (0.63-2.85; $p = 0.05$), while African-Americans with nodal involvement had an odds ratio of 0.88 (0.42-1.81; $p = 0.05$), and African-Americans with extended and nodal involvement had an odds ratio of 1.63 (0.77-3.46; $p = 0.05$), all showing non-significant differences in comparison with Caucasians. Due to the nature of the disease, it was highly likely that treatment decisions were guided by the diagnosed stage, implicating a correlation between the two variables. Both early and contemporary literature attributed a sizable component of racial survival disparities into the cumulative effects of differences in age, stage, histology, ER status, and treatment. Gregorio et al. [4], in a study of 185 patients diagnosed between 1957-1965, found that race did not have a significant effect on survival subsequent to controlling for age, stage, and treatment delays ($p = 0.84$). Howard et al. [21], Pierce et al. [26] and Roach et al. [43] drawing from 246, 697, and 1,572 patients diagnosed between 1972 and 1996 arrived at similar results. The limitation of these studies was their small sample size (average $n = 675$), derived solely from 1 to 3 institutions. In contrast, Li et al. [34] in a multi-institutional study of 124,934 patients between 1992 and 1998 found that African-American patients remained at a greater risk of mortality HR=1.5 (1.4-1.6, $p = 0.05$) of mortality even after adjusting for age, stage, treatment and ER status. Based on a robust data set, disparities in age, stage, histology, ER status, and treatment were unable to fully account for racially-directed survival disparities.

Socioeconomic Status

The most common components of Socioeconomic status (SES) are census-tract derived measures of income, education, insurance status, and comorbidities, while less common factors included marital status, nutrition, home value, and family size. SES as a significant independent predictor of breast-cancer related mortality has been demonstrated in both early and current papers. Ansell et al. [15] looking at 1,270 patients between 1973 and 1986 showed an increased risk of death for those making <\$20,000 in income HR=1.46 (1.23-1.69; $p = 0.05$) compared to patients >\$20,000. Roetzheim et al. [31] in a multi-institutional study of 11,113 patients from 1994-1997 also showed the propensity of patients insured under Medicaid or those who lacked insurance to experience poorer survival rates than those covered by private insurers, with relative risk of mortality of 1.58 (1.18-2.11; $p = 0.002$).

In studies of populations diagnosed between 1946 and 1990 the majority found that African-American patients were significantly disadvantaged in relation to Caucasians in regards to SES. Census-tract measures revealed that African-American patients earned less income, were more inclined to be enrolled in Medicaid or be uninsured, underwent less years of formal education, and were more likely to have female-headed households and utilize public housing

assistance than their Caucasian counterparts [1,3,4,10,16,19]. An overview of later studies of patients diagnosed from 1961-2011 demonstrated similar findings [2,7-9,13,14,28,30,31,37-39,41,42,44].

In addition to economic challenges, African-American patients were also at a disadvantage from having higher numbers of high-risk preexisting health conditions unrelated to Breast Cancer. Coates et al. [5] drawing from a population of 1,960 between 1975 and 1984 showed that African-American patients were more likely to have a higher BMI and lower levels of serum albumin and hemoglobin ($p < 0.05$), conditions which were demonstrated in a univariate analysis to be correlated with a higher risk for mortality ($p < 0.001$). In a more recent investigation focusing on 588 patients between 1994 and 1997, Du et al. [39] found that African-Americans suffered from diabetes ($p < 0.001$), hypertension ($p < 0.001$), and heart disease/CVA ($p = 0.027$) in higher proportions than Caucasians at diagnosis.

The following survival analysis takes into account the disadvantages of African-American patients at presentation in regards to age, stage, histology, ER-status, treatment, and SES. The prognostic significance of each of these variables considered independently had been identified in the literature, and African-American clinical and socioeconomic features at presentation have consistently placed this group in the high-risk category. A majority of early studies were able to successfully deconstruct racial survival disparities into differences in the parameters mentioned above. Eley et al. [10] in looking at a sample size of 1,130 in the metropolitan region of Atlanta, Los Angeles, San Francisco, and New Orleans from 1985 to 1990 found that the elevated hazard ratio of mortality of African-Americans as compared to Caucasians at face-value, $HR = 2.2$ ($1.7 - 2.9$; $p < 0.05$) dropped to non-significant levels $HR = 1.3$ ($0.9 - 1.8$; $p < 0.05$) after controlling for the effects of differential age, stage, histology, ER status, treatment, and SES between African-Americans and Caucasians at presentation. In a stepwise Cox proportional hazards stepwise regression model, Gordon et al. [19] showed that in a multi-institutional sample size of 1,392 diagnosed between 1974 -1985, race was a significant predictor of survival even after adjustment for age, stage, and ER status ($p = 0.01$), but ceased to be of prognostic value subsequent to controlling for SES ($p = 0.43$). A minority of contemporary research was also able to resolve race-driven survival disparities. Du et al. [39] focusing on a small sample size of 588 between 1994 and 1997 was able to reduce relative risk from 1.56 ($1.09-2.25$; $p < 0.05$) to 1.06 ($.64-1.75$; $p < 0.05$) subsequent to adjusting multivariable Cox proportional hazard regression for age, stage, ER-status, and comorbidities.

On the contrary, later studies generally concluded that race was a prognostically significant variable even after adjusting for clinical and socioeconomic differences. Crowe et al. [44] looking at a sample of 2,325 from multiple sites was able to quantify a decrease in risk of death among African-Americans from $HR = 2.24$ ($1.56 - 3.24$, $p < 0.001$) to $HR = 1.76$ ($1.16 - 2.66$, $p = 0.008$) after adjusting for age, stage, ER status and SES, however, the statistical significance of the elevated hazard ratio remained. Furthermore, Ooi et al. [13] in a multi-institutional study of 229,594 patients similarly discovered that subsequent to adjusting for age, stage, ER status, treatment and SES, the increased HR of African-Americans to Breast Cancer-specific mortality dropped from 2.4 ($2.3-2.5$; $p < 0.05$) to 1.5 ($1.4-1.6$; $p < 0.05$) but disparities were still evident at a statistically significant level. Other investigators discovered similar effects after controlling for different variations of the factors mentioned throughout this review

[7,8,13,14,31,32,35,37,40,44,47].

In recent literature, the average sample size of studies with multivariate analysis for known prognostic factors demonstrating survival disparities between African-Americans and Caucasians was $n = 71,528$. Studies showing no difference after controlling for clinical and SES variables looked at a much smaller population set on average $n = 2,013$, and consisted of investigations carried out focused on single or only a few institutions.

Discussion

Upon controlling for prognostically significant differences between African-Americans and Caucasians, the prevailing theme in early studies was that there was no significant differences in racially driven survival disparities, while recently published work was characterized by the persistence of these differences following multivariate analyses. Earlier studies did not account for ER status differences [3,18,20], as testing did not become prevalent until the late 1970's. Moreover, the average sample size was much smaller in early studies, and comprised of data from a single, or a small collection of institutions, potentially leading to resolution of disparities in a sample unrepresentative of the general population [4,21,27]. Sources also indicated that although survival rates for Breast Cancer patients have been on an overall upwards trend since the early 1970's, the gains were disproportionately distributed among Caucasians [2,48].

Recent studies, which drew from a robust set of data representative of multiple institutions and large population sizes compared to early literature, were unable to be completely resolve racial disparities in Breast Cancer survival [14,34,35]. However, these contemporary investigations also had several limitations. The small number of actual deaths having occurred due to Breast Cancer in light of recent advances in adjuvant treatment warranted extrapolation of mortality events, compromising the true extent of racially-driven differences in mortality [9]. Also, as contemporary studies incorporated a broader scope of race and ethnicities, often incorporating Hispanics, Asians, and Native Americans in their analysis, misclassification of subjects was a potential source of error [29]. Among newer investigations, a survival difference between African-Americans and Caucasians despite adjusting for clinical and socioeconomic variables was observed in certain subgroups of Breast Cancer patients but not overall. Lund et al. [38] found that after adjusting for differences in age, histology, SES, stage, and treatment, within the triple-negative subtype, African-Americans remained at higher risk of mortality, while survival differences among all subtypes did not persist. Curtis et al. [9] also found within stage II/III Breast Cancer patients, an increased probability of death among African-Americans could not be resolved after controlling for similar clinical and socioeconomic factors, however, within the overall sample the disparity failed to persist.

Both early and contemporary literature utilized socioeconomic data points from the census-tract level. Although this had been cited as a weakness due to potential for deviation from socioeconomic realities at the individual level, census-tract data had produced strong correlations with prognosis in univariate models [8,14,15,19]. Overall, the failure of highly powered studies to amend racially driven Breast Cancer survival disparities suggests presence of genetic drivers yet to be clearly elucidated. Although differences in risk factors such as stage and ER-status at presentation may be influenced by socioeconomic disadvantages culminating in suboptimal health choices, medical

screening and medical treatment, the simultaneous role of genetics is beginning to be explored. Elledge et al. [29] investigated expression of the p53 tumor suppressor gene between African-Americans and Caucasian Breast Cancer patients, and although they found no significant differences by race ($p=0.31$), this is only one of many oncogenes purported to have a role in predisposition of patients to highly aggressive forms of Breast Cancer. Elucidation of such high-impact genetic factors may empower future studies to fully rectify the increased mortality risk among African-American patients.

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