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Race and the Prognostic Influence of p53 in Women with Breast Cancer

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Abstract

Background—Prior study suggests that p53 status behaves as an independent marker of prognosis in African American (AA) women with breast cancer. We investigate whether the influence of p53 is unique to AAs or is present in other race/ethnic groups, and how this compares with known prognostic factors.

Methods—Cox regression models [hazard ratios (HRs), 95% confidence intervals (CIs)] were used to select and evaluate factors prognostic for all-cause mortality in 331 AA and 203 non-AA consecutively treated women.

Results—Statistically significant baseline prognostic factors were as follows. For AAs: stage [(III/I) HR 5.57; 95% CI 3.08–10.09], grade [(higher/low) HR 1.55; 95% CI 1.14–2.11], estrogen receptor (ER)/progesterone receptor (PR) status [(+/+) HR 2.01; 95% CI 1.38–2.93], triple negative (ER–, PR–, HER2–) subtype [(+/–) HR 1.95; 95% CI 1.33–2.85], and p53 status [(+/–) HR 1.69; 95% CI 1.10–2.58]. For non-AAs: stage [HR 11.93; 95% CI 2.80–50.84], grade [HR 1.61; 95% CI 0.96–2.71], and ER/ PR status [HR 2.13; 95% CI 1.19–3.81]. There was a differential effect of race within p53 groups ($P = 0.05$) and in multivariate modeling p53-positive status remained an adverse prognostic factor in AAs only [HR 1.82; 95% CI 1.04–3.17]. Compared to non-AAs, 5-year unadjusted survival was worse for AAs overall (73.4% vs. 63.6%; $P = 0.032$), and also for AAs with p53-positive status (80.3% vs. 54.2%; $P = 0.016$), but not for AAs with p53-negative disease (68.4% vs. 67.9%; $P = 0.81$).

Conclusions—Among women with breast cancer of different race/ethnicity, an adverse prognostic effect as a result of p53 positivity was only observed in AA women.

In a prior report, we demonstrated that abnormal p53 immunohistochemical expression (IHC; with Pab 1801 antibody) or p53-positive (+) status, was associated with more aggressive tumor features, including high tumor grade of differentiation (grade), estrogen and progesterone receptor (ER/PR) negative (–) status, and basal subtype [i.e., ER–, PR–, HER2–, and cytokeratin (CK)5/6+ and/or HER1+ status]. It also behaved as an independent marker of poor prognosis in African American (AA) women of lower socioeconomic status (SES) with breast cancer.¹ It remains unclear, however, whether the prognostic influence of p53 status is unique to AA women or is present in other race/ethnic groups (non-AA), and how this relates to other factors thought to influence prognosis.

A cohort of women of different race/ethnicity and of lower SES, similarly treated for breast cancer at a public hospital, offers the opportunity to further explore the relationship between tumor biology and race while conditioning on a common socioeconomic environment. Hence, the rationale for this study is to evaluate and compare the influence and role of p53 status as a marker of prognosis and survival among AA and non-AA women of lower SES with breast cancer, accounting for the important influences of ER/PR-negative subtypes, including triple negative (TN; i.e., ER–, PR–, and HER2– status) and basal subtypes. Toward this end, the specific aims of the present study were: (1) to evaluate and compare relationships between p53 status and other tumor characteristics among AA and non-AA women, (2) to determine the prognostic value of p53 status within both subgroups, and (3) to compare between groups, the value of p53 status as a prognostic marker in relation to the inclusion of other commonly used prognostic factors.

MATERIALS AND METHODS

Selection and Description of Participants

The study sample is a historical cohort of 534 consecutively enrolled women with primary breast cancer aged 24–94 years; it represents the major race/ethnic groups presenting for diagnosis and treatment. A total of 331 patients were AA, and 203 were non-AA consisting of 115 Hispanic and 88 non-Hispanic white women. All were treated and followed at a large urban public hospital providing care to the medically uninsured in metropolitan Chicago between 01 Jan 2000 and 31 Dec 2005, and were patients of physicians participating in the National Cancer Institute supported Minority-Based Community Clinical Oncology Program (MBCCOP).

Technical Information

Newly diagnosed cases were reviewed at multidisciplinary conference and proceedings were recorded for management.² After approval by the local institutional review board (protocols 04-02 and 103-03), data were collected from available conference/medical records, including: demographics; medical history; social/family history; risk factors; clinicopathologic factors, including age, race, body mass index (BMI), tumor size, lymph node status, American Joint Committee on Cancer (AJCC) stage/ tumor, node, metastasis (TNM) classification, tumor grade, ER/PR and HER2 status; type of treatment (surgery,

radiation, chemo/endocrine therapy); and follow-up on breast carcinoma related recurrence and mortality. Women were recorded as having received chemo/endocrine therapy if they received any type of chemo/endocrine therapy. Race was determined by self-identification at initial patient visit and abstracted from medical records. Comorbid disease was defined as any history of diabetes, hypertension or cardiac disease. U.S. 2000 census ZIP Code Tabulation Area (ZCTA) data matched to patient address zip codes at diagnosis was used to develop surrogate markers for SES. These included poverty and education status (the reference point for ZCTA based poverty status was taken as less than or equal to a U.S. poverty mean of 9.2%, on the basis of national census data for the number of families living below the poverty level threshold in 1999).^{3,4}

Histologic subtype was determined according to World Health Organization classification.^{5,6} Stage was defined by integrating data on tumor size, node status, and distant metastasis into the AJCC staging system that was in place at the time of ascertainment.^{7,8} Representative tumor blocks were selected for independent reference laboratory IHC for ER, PR and HER2 status. Hormone receptor status was defined as combined ER/PR status, and regarded as positive when either was positive (i.e., >5% nuclear staining). IHC score of 3+ was regarded as positive for HER2 overexpression, and specimens with scores of 1+ and 2+ had further assay with fluorescence in situ hybridization.⁹ CK 5/6 and HER1 IHC assays were performed in house as previously described.¹⁰ Pab 1801 is a mouse monoclonal antibody against amino acids 32–79 near the N-terminus of human p53, and was used in IHC at dilution of 1:600.¹¹ p53 status was scored on the Allred 0–8 system, with a score of 2 reported as positive (i.e., nuclear immunostaining score for accumulation of nonfunctional p53 protein).¹²

Statistical Methods

First, associations between p53 status and other patient/disease characteristics were examined. For continuous variables, the *t*-test was used to compare means. For categorical variables, the chi-square test of association was used to examine the significance of relationships [odds ratios (ORs) and 95% confidence intervals (CIs)]. Second, survival function estimates by race for groups with specific tumor marker status were generated using the Kaplan-Meier method with death from any cause considered an event, and were compared using the log rank test.¹³ Third, the Cox proportional hazards regression model was used to estimate hazard ratios (HRs) with 95% CIs for prognostic factors, first singly and then in multivariate models, with redundant factors being excluded from final models.¹³ Analyses were conducted using Stata statistical software, version 10 (StataCorp, College Station, TX), and all tests were two-sided.

Further details on construction and adjustment of multivariate models were as follows: age, comorbid disease, and BMI were included, particularly as AA women were more likely to be older, and have comorbid disease and higher BMI. In addition, chemo/endocrine therapy was included as adjustment for systemic treatment. As poverty and education status factors were developed from the same ZCTA data source, these factors were considered to have overlapping information, and either factor was included, but not both. Likewise for hormone receptor negative types, because TN and basal type definitions incorporate ER/PR-negative

status, these three factors were included in models individually (and as TN and basal types also include HER2 status, the same consideration applied). Hence, three final fully adjusted multivariate models are reported on the basis of factors currently thought to influence prognosis: model 1 includes TN status but excludes individual ER/PR and HER2 status, and also basal type; model 2 includes individual ER/PR and HER2 status but excludes TN and basal types; and model 3 includes basal type but excludes TN status and individual ER/PR and HER2 status.

RESULTS

Baseline characteristics by race are provided in Table 1. No statistically significant differences were noted between AAs and non-AAs at diagnosis regarding: education status, stage, grade, ER/PR status, TN phenotype, p53 status, or treatment with endocrine therapy, surgery, and radiotherapy. AAs were significantly older [mean age 56.6 vs. 50.9 years for non-AAs ($P < 0.001$)], with higher mean BMI [31.2 vs. 29.7 ($P = 0.026$)], and more likely to have: comorbid disease (OR 2.61; 95% CI 1.77–3.86), less favorable poverty status (OR 4.17; 95% CI 2.70–6.45), and tumors with basal subtype (OR 1.65; 95% CI 1.01–2.69). AAs were significantly less likely to have HER2+ tumors (OR 0.63; 95% CI 0.41–0.97), and there was no difference in use of trastuzumab therapy between groups, when examined according to HER2-positive status. There also was no difference between groups with respect to chemo-therapy use among women aged <50 years; however, AAs aged ≥ 50 years were significantly less likely to have received chemotherapy (OR 0.52; 95% CI 0.31–0.87), most likely as a result of greater comorbid disease. While the majority of cases with poverty status at or below the U.S. 1999 national census mean were non-AA, the majority of cases with poverty status worse/above the national census mean were AA (i.e., cases originated from ZCTAs where more families lived below the national poverty threshold when compared to the U.S. census mean). Further, all cases with poverty status worse than 300% above the U.S. census mean were AA (Fig. 1).

For AAs, as expected: p53+ tumors were statistically significantly more likely to be (1) poorly differentiated or high grade (OR 4.35; 95% CI 1.33–14.14), (2) ER/PR- (OR 2.56; 95% CI 1.49–4.35), and (3) TN (OR 2.67; 95% CI 1.55–4.59) and basal type (OR 3.39; 95% CI 1.86–6.19). For non-AAs, similar trends were observed: p53+ tumors were more likely to be high grade (OR 6.61; 95% CI 1.04–52.98), ER/PR- (OR 1.72; 95% CI 0.88–3.45), and TN (OR 1.53; 95% CI 0.75–3.12) and basal type (OR 1.79; 95% CI 0.73–4.43). Only the relationship with grade was statistically significant, however.

For the cohort as a whole, median follow-up time from diagnosis is 60.4 months. Overall, AA race was associated with statistically significantly greater mortality hazard [(AA/non-AA) HR 1.45; 95% CI 1.03–2.05], and 5-year unadjusted survival (Fig. 2a) was 63.6 and 73.4% for AAs and non-AAs, respectively ($P = 0.033$). The influence of specific tumor markers on unadjusted survival according to race was further examined (Fig. 2b–i) and it should be noted that overall AAs had relative mortality excesses of approximately 30–50% for all these factors, but outcomes in early follow-up years were similar and these differences did not achieve statistical significance. Specifically, for women with ER/PR+ tumors [(AA/non-AA) HR 1.42; 95% CI 0.86–2.36], and 5-year survival (Fig. 2b) was 72.2

and 79.9% respectively ($P = 0.17$); and for women with ER/PR- tumors [(AA/non-AA) HR 1.39; 95% CI 0.86–2.36], and 5-year survival (Fig. 2c) was 52.4 and 63.1% ($P = 0.167$). For women with tumors with non-TN type [(AA/non-AA) HR 1.32; 95% CI 0.85–2.05], and 5-year survival (Fig. 2d) was 69.4 and 77.0% ($P = 0.211$); and for women with TN type tumors [(AA/non-AA) HR 1.52; 95% CI 0.87–2.66], and 5-year survival (Fig. 2e) was 52.6 and 63.5% ($P = 0.137$). For women with tumors with luminal A/B [i.e., ER+ and/or PR+, HER2–; and ER+, and/or PR+, HER2+, status respectively] type [(AA/non-AA) HR 1.42; 95% CI 0.86–2.36], and 5-year survival (Fig. 2f) was 72.2 and 79.9% ($P = 0.17$); and for women with basal type tumors [(AA/non-AA) HR 1.64; 95% CI 0.75–3.59], and 5-year survival (Fig. 2g) was 52.9 and 64.4% ($P = 0.209$). For women with tumors with p53-status, AA race was not associated with any material excess in mortality hazard [(AA/non-AA) HR 1.06; 95% CI 0.68–1.65], and 5-year survival (Fig. 2h) was 67.9 and 68.4% ($P = 0.81$); however, for women with tumors with p53+ status, AA race was associated with significantly greater mortality hazard [(AA/non-AA) HR 2.33; 95% CI 1.45–4.73], and 5-year survival (Fig. 2i) was 54.2 and 80.3% ($P = 0.016$). A formal test via the Cox proportion hazards model confirmed a differential effect of race within p53 groups (race by p53 interaction, $P = 0.05$).

Because of evidence of a differential influence of race on survival by p53 status, subsequent modeling proceeded separately for AA and non-AA women. Univariate and multivariate Cox models for all-cause mortality by race are provided in Table 2. Univariate model effects for grade, ER/PR status, TN type, and basal type in non-AAs were of similar magnitude to that of AAs, and as anticipated, p53+ status was associated with poorer survival in AAs [(+/-) HR 1.69; 95% CI 1.10–2.58], but not in non-AAs ($P = 0.445$). Our first multivariate model included age, stage, grade, TN type, and p53 status, and adjustment for comorbid disease, BMI, poverty status, and systemic therapy (Table 2, model 1). For AAs, age at diagnosis ($P = 0.950$) and higher grade ($P = 0.531$) were not found to be independent predictors of survival. The HR for TN type was smaller than observed in univariate analysis and also not statistically significant [(+/-) HR 0.97; 95% CI 0.46–2.05]. However, higher stage at diagnosis [(III/I) HR 4.88; 95% CI 1.86–12.81; (IV/I) HR 9.84; 95% CI 3.31–29.25] and p53 status [(+/-) HR 1.82; 95% CI 1.04–3.17] were found to be independent predictors of survival. For non-AAs using this model, neither age ($P = 0.825$), grade ($P = 0.596$), TN type ($P = 0.430$) nor p53 status ($P = 0.431$) were found to be independent predictors of survival. However, as expected, higher stage was: [(III/I) HR 13.20; 95% CI 2.13–81.79; (IV/I) HR 84.17; 95% CI 10.51–673.9]. Our second multivariate model included age, stage, grade, individual ER/PR and HER2 status (instead of TN type), and p53 status, and similar adjustment factors as given above (Table 2, model 2). For AAs, once again, independent predictors of survival were higher stage [(III/I) HR 5.08; 95% CI 1.91–13.51; (IV/I) HR 10.24; 95% CI 3.37–31.08], and p53 status [HR 1.89; 95% CI 1.08–3.29]. For non-AAs, only higher stage [(III/I) HR 13.66; 95% CI 2.10–88.76; (IV/I) HR 77.65; 95% CI 9.39–642.5] remained as an independent predictor in the second model. Our third multivariate model included age, stage, grade, basal type (vs. luminal A/B, instead of TN status), and p53 status, and again similar adjustments as given above (Table 2, model 3). The overall results were similar to the models described above. For AAs, once more independent predictors of survival were higher stage [(III/I) HR 5.02; 95% CI 1.74–14.49; (IV/I) HR 9.28; 95% CI

2.64–32.55], and p53 status [HR 1.98; 95% CI 1.06–3.68], and for non-AAs, only higher stage remained as an independent predictor. In addition, the HR for basal type in AAs was smaller than observed in univariate analysis and also not statistically significant [(basal/luminal A & B) HR 1.36; 95% CI 0.53–3.51].

DISCUSSION

Our findings demonstrate that among a cohort of women of different race/ethnicity (AA vs. non-AA) and lower SES, consecutively and similarly treated for breast cancer at a single institution, the negative prognostic influence of p53+ disease was confined to AA women. Five-year unadjusted survival estimates for women with p53-negative disease were similar for AAs and non-AAs (67.9% vs. 68.4%, respectively; Fig. 2h); however, for women with p53+ disease, these estimates were far worse for AAs, with a 26.1% absolute decrease in 5-year survival (54.2% vs. 80.3%; Fig. 2i). In addition, survival models adjusting for other covariates confirm a differential adverse prognostic effect of p53 (test for race/ethnicity by p53 interaction, $P = 0.05$), as also illustrated by Kaplan-Meier survival estimates according to p53 status for AA ($P = 0.015$) and non-AA women ($P = 0.443$) shown in Fig. 3.

For both AA and non-AA women with p53+ tumors, similar rates of immunoreactivity (28.1 and 29.7% respectively) and trends of association were observed, and these tumors tended to be of high grade, and of ER/PR-negative, TN, and basal subtype. A recent report by Baker et al. utilizing microarray gene-chip assay for p53 mutations in women with breast cancer has also described similar trends.¹⁴ Further, although our non-AA cohort has a small size, no difference in p53 immunoreactivity was found between the three individual races that constitute our cohort (chi-square test, $P = 0.373$), and when analyzed as separate subsets, neither Hispanics nor non-Hispanic whites with p53+ disease were found to have worse survival (log rank test, $P = 0.142$ and $P = 0.519$ respectively). A prior large study which evaluated p53 immunoreactivity in 1016 AA, 777 Hispanic and 4885 white women with breast cancer, also utilized the Pab 1801 antibody which is used in the current study, and demonstrated similar rates of prevalence in all 3 subsets (i.e., 45, 46 and 49% respectively).¹¹ However, this study also used a second antibody, Pab 240, which could account for the difference in observed p53 IHC prevalence when compared to the current study. Jones et al. performed a smaller IHC study using the DO7 antibody and reported p53 prevalence of 25 and 7% respectively in 145 AA and 177 white women with breast cancer.¹⁵ However, these results are inconsistent with our prior experience with this antibody, where we reported IHC prevalence of 37 and 32% in 81 AA and 32 non-AA women, respectively.¹⁶ In addition, Morris et al. reported p53 IHC prevalence of 19.4 and 13.1% respectively in 55 AA and 255 white women in another breast cancer study; however, the authors did not specify which antibody clone was used.¹⁷ Hence, reported p53 IHC prevalence (using a variety of antibody clones) has a wide range in the context of studies among women with breast cancer of different race/ethnicity: for AAs, approximately 19–45%, whereas for non-AAs (i.e., Hispanics and non-Hispanic whites), about 7–49%. Lai et al. reported on 64 white Hispanic and 167 white non-Hispanic women using PCR amplification of exons 5–8 for p53 mutation analysis and found that the gene mutation rate was far lower in white Hispanics than in white non-Hispanics (51.6% vs. 70.7%, $P = 0.01$); however, analyses of mutation type, location, and multiplicity also failed to show

statistically significant differences between the two groups.¹⁸ We acknowledge that there are substantial methodological differences between these reports and the current study regarding p53 assay (including that Hispanic women in the current study did not provide information on subethnicity); however, prevalence rates in the current report (28.6% overall) appear to be similar to a more recent report in 246 white women with breast cancer, where mutations were identified in 26% of tumors overall.¹⁴ Importantly, although this latter study by Baker et al. was not an investigation of prevalence among women of different race/ethnicity and was performed in the U.K., a p53 microarray gene chip was used to comprehensively probe exons 2–11, and the mutation prevalence is lower than reported above by Lai et al.

Because other well-known prognostic markers are already in use, we sought to determine the significance and context for appropriate clinical application of p53 status as a tumor marker among our cohort.^{1,19–22} Hence, we examined survival estimates by race/ethnicity for several biologic marker types currently in common use based on a combination of ER, PR and HER2 markers, including ER/PR positive and negative, non-TN and TN, and luminal A/B and basal types. Survival estimates were marginally worse for AA women irrespective of the aforementioned types, suggesting that risk associated with these types is not race specific. Further, the observed statistically significantly greater age, higher BMI, and increased comorbidity at diagnosis in AA women were factors that would be expected to contribute to lower survival estimates. In addition, several multivariate models were created to include these biologic markers and adjust for relevant factors including systemic treatment, and consistently, p53 status performed as a marker of independent prognosis in AA women with HRs ranging between 1.82 and 1.98, with all *P* values <0.05 (Table 2). However, p53 status was not found to predict prognosis in non-AA women in any model. In addition, it is also important to note that neither TN nor basal type performed as an independent prognostic marker in any multivariate model for AA women which included p53 status.

The relationship between race, tumor biology, and SES is complex and a conceptual framework is outlined in Fig. 4.^{23,24} Baker et al. suggest that p53 mutation in breast cancer may be associated with socioeconomic deprivation and may provide a molecular basis for understanding poorer outcome in women from impoverished communities.¹⁴ In the United States, lower SES is more common among minorities including AA and Hispanic women.^{3,25} Further, compared to the luminal A type, the more aggressive basal type has been reported to be more prevalent among premenopausal AA women and more often is associated with *TP53* mutations.^{1,21,26,27} The TN phenotype, which is considered a less accurate clinical proxy for basal type (i.e., approximately 80–90% are basal-like type), has also been reported to be more prevalent among AA and Hispanic women and may be associated with lower SES.^{21,28–30} In the report from Baker et al., p53 mutations were found to be most common (10/17 or 58.8%) in white women within the lowest decile of the poverty index and these women had far worse overall survival; however, neither p53 nor TN status were independent markers of poorer prognosis in Cox multivariate models, and this latter finding is largely consistent with results in non-AA women in the current study.¹⁴ Importantly, unlike Baker et al., we found that women with poverty and education status worse than the U.S. national census means, did not have higher likelihood of having p53+

status (respectively, OR 1.02; 95% CI 0.61–1.70 and OR 1.24; 95% CI 0.68–2.27). Possible explanations for the observed difference between studies include dissimilar methods for p53 assay (microarray gene chip vs. IHC) and measures of SES (Carstairs index vs. ZCTA data), and also probable unknown factors.³¹ Furthermore, unlike Baker et al., we chose not to perform analysis at the extremes of our measures for SES because we found important differences between AA and non-AA women in our sample (i.e., all cases from ZCTAs where poverty status was greater than 300% above the U.S. poverty mean were AA; Fig. 2).

Hence, although the majority of the women in our cohort are regarded as being of lower SES (i.e., only 12.1% AAs and 36.5% non-AAs came from ZCTAs where the poverty status was less than or equal to the U.S. poverty mean), and for women with p53+ disease, AA women were significantly more likely to be in the lowest SES groups [i.e., (>300%/ U.S. poverty mean) OR 8.89; 95% CI 2.11–36.52; $P = 0.002$], we are unable to conclude that p53 abnormalities in breast cancer were specifically associated with lower SES.

There are several limitations to our study. First, we recognize our relatively small sample size and a median follow-up of only 60 months. Second, false positive and negative results are common when using IHC, which is reported to be approximately 85% accurate for predicting *TP53* status.³² However, p53 gene alterations, whether assayed by molecular methods or IHC, have been associated with poorer outcome among patients with breast cancer and resistance to systemic therapy.^{33–37} In addition, we did not perform p53 mutation analysis in the current study and are therefore unable to enumerate the specific types of mutations in women in our sample. We previously reported on a subset of 48 AA women (included in the current study) who had fresh frozen tissue available, on which sequencing of exons 2–11 was performed for evaluation of p53 mutations, and found that transversions were more common, and that non-CpG G:C to A:T and A:T to G:C transitions demonstrated similar frequency.³⁸ However, other reports detailing mutations in these women have suggested variable results.^{39–41} Although when these reports are considered together, they suggest that important race differences may exist regarding p53 mutations, and also that increased mortality among a subgroup of AA women may contribute to the enigma of race-based survival disparity, further study detailing types of mutations involved is needed.¹ Third, data on specific treatment regimens were unavailable, and important qualitative differences might exist; however, use of standardized protocols reduced the likelihood that treatment variations would confound results, and women treated by practitioners other than MBCCOP physicians were excluded. And although compliance with recommended treatment was not specifically measured, a standard compliance protocol for adherence to treatment and follow-up was in place as a component of MBCCOP quality assurance. Further, Cox models included covariates to adjust for the effects of systemic treatment. Fourth, our cohort included some women with stage IV and clinically important comorbid disease who did not have surgery. However, further analysis excluding women who did not have surgery did not alter our results. Fifth, we also acknowledge that use of ZCTA-based SES surrogates are more likely to represent cross-sectional SES at the point of diagnosis, rather than actual SES.

We conclude that among women of different race/ethnicity with breast cancer, the negative prognostic influence of p53 status was confined to AA women, and a differential adverse

prognostic effect was evident for AA women with p53+ disease. Further, in multivariate models, p53 status consistently performed as a marker of independent prognosis in AAs, while other commonly used biologic markers on the basis of ER/PR-negative subtype, did not. Our findings thus support the targeted inclusion of p53 status as a tumor marker when characterizing potential prognosis in this patient subgroup, and also further research on factors which predispose development of *TP53* mutations in breast cancer and characterization of specific mutations involved.

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REFERENCES

1. Dookeran KA, Dignam JJ, Ferrer K, et al. p53 as a marker of prognosis in African-American women with breast cancer. *Ann Surg Oncol*. 2010; 17:1398–405. [PubMed: 20049641]
2. Commission on Cancer of the American College of Surgeons. [25 Sep 2008] Cancer Program Standards. 2004. <http://www.facs.org/cancer/coc/cocprogramstandards.pdf>.
3. U.S. Census Bureau. Poverty. [14 Dec 2010] Census 2000 brief. 1999. <http://www.census.gov/prod/2003pubs/c2kbr-19.pdf>.
4. Tehranifar P, Neugut AI, Phelan JC, et al. Medical advances and racial/ethnic disparities in cancer survival. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:2701. [PubMed: 19789367]
5. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histo-pathology*. 1991; 19:403–10.
6. Tavassoli, FA.; Devilee, P. Pathology and genetics of tumours of the breast and female genital organs. IARC; Lyon: 2003.
7. Fleming, ID.; Cooper, JS.; Hensen, DE., editors. AJCC cancer staging manual. 5th ed.. Lippincott-Raven; Philadelphia: 1997.
8. Greene, FL.; Page, DL.; Fleming, ID., editors. AJCC cancer staging manual. 6th ed.. Springer; New York: 2002.
9. Porter PL, Lund MJ, Lin MG, et al. Racial differences in the expression of cell cycle-regulatory proteins in breast carcinoma. *Cancer*. 2004; 100:2533–42. [PubMed: 15197793]
10. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res*. 2004; 10:5367–74. [PubMed: 15328174]
11. Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. *J Natl Cancer Inst*. 1994; 86:705–12. [PubMed: 7908990]
12. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol*. 1998; 11:155–68. [PubMed: 9504686]
13. Klein, JP.; Moeschberger, ML. Survival analysis: techniques for censored and truncated data. Springer; New York: 2003.
14. Baker L, Quinlan PR, Patten N, et al. p53 mutation, deprivation and poor prognosis in primary breast cancer. *Br J Cancer*. 2010; 102:719–26. [PubMed: 20104224]
15. Jones BA, Kasl SV, Howe CL, et al. African-American/white differences in breast carcinoma: p53 alterations and other tumor characteristics. *Cancer*. 2004; 101:1293–301. [PubMed: 15368321]
16. Dookeran, KA.; Gao, X.; Ferrer, K., et al. Evaluation of p53 immunoreactivity in African-American patients with breast cancer.. Proceedings of the American Association for Cancer Research (94th Annual Meeting; Washington, DC. July 11–14 2003; 2003. p. 295

17. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients. *Cancer*. 2007; 110:876–84. [PubMed: 17620276]
18. Lai H, Lai S, Ma F, Meng L, Trapido E. Prevalence and spectrum of p53 mutations in white Hispanic and non-Hispanic women with breast cancer. *Breast Cancer Res Treat*. 2003; 81:53–60. [PubMed: 14531497]
19. Greenberg S, Rugo HS. Challenging clinical scenarios: treatment of patients with triple-negative or basal-like metastatic breast cancer. *Clin Breast Cancer*. 2010; 10:20–9.
20. Millar EKA, Graham PH, O'Toole SA, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-bio-marker panel. *J Clin Oncol*. 2009; 27:4701–8. [PubMed: 19720911]
21. Peppercorn J, Perou CM, Carey LA. Molecular subtypes in breast cancer evaluation and management: divide and conquer. *Cancer Invest*. 2008; 26:1–10. [PubMed: 18181038]
22. Voduc KD, Cheang MCU, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol*. 2010; 28:1684–91. [PubMed: 20194857]
23. Komenaka IK, Martinez ME, Pennington RE, et al. Race and ethnicity and breast cancer outcomes in an underinsured population. *J Natl Cancer Inst*. 2010; 102:1178. [PubMed: 20574040]
24. Dunn BK, Agurs-Collins T, Browne D, Lubet R, Johnson KA. Health disparities in breast cancer: biology meets socioeconomic status. *Breast Cancer Res Treat*. 2010; 121:281–92. [PubMed: 20437200]
25. DeNavas-Walt, C.; Proctor, BD.; Lee, CH. U.S. Census Bureau. Current population reports. U.S. Government Printing Office; Washington: 2006. Income, poverty, and health insurance coverage in the United States: 2005.; p. 60-231.
26. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006; 295:2492–502. [PubMed: 16757721]
27. Dookeran K, Gao X, Wang Y, et al. Basal subtype predicts poorer prognosis in younger, but not older, African-American women with breast cancer. *AACR meeting abstracts*, No. 2510. Apr 14.2007
28. Cheang MCU, Voduc D, Bajdik C, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. *Clin Cancer Res*. 2008; 14:1368. [PubMed: 18316557]
29. Lund MJ, Butler EN, Hair BY, et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes. *Cancer*. 2010; 116:2549–59. [PubMed: 20336785]
30. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. *Cancer*. 2007; 109:1721–8. [PubMed: 17387718]
31. Carstairs, V.; Morris, R. Deprivation and health in Scotland. Aberdeen University Press; Aberdeen: 1991.
32. Oliveira AM, Fletcher JA, Ross JS. Tumor suppressor genes in breast cancer: the gatekeepers and the caretakers. *Pathol Patterns Rev*. 2005; 124:16–28.
33. Allred DC, Clark GM, Elledge R, et al. Association of p53 protein expression with tumor cell proliferation rate and clinical outcome in node-negative breast cancer. *J Natl Cancer Inst*. 1993; 85:200–6. [PubMed: 8423624]
34. Bergh J, Norberg T, Sjogren S, Lindgren A, Holmberg L, Coplete J. Sequencing of the p53 gene provides prognostic information in breast cancer patients, particularly in relation to adjuvant systemic therapy and radiotherapy. *Nat Med*. 1995; 1:1029–34. [PubMed: 7489358]
35. Harris LN, Broadwater G, Lin NU, et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. *Breast Cancer Res*. 2006; 8(6):R66. [PubMed: 17129383]
36. Kandioler-Eckersberger D, Ludwig C, Rudas M, et al. TP53 mutation and p53 overexpression for prediction of response to neoadjuvant treatment in breast cancer patients. *Clin Cancer Res*. 2000; 6:50–6. [PubMed: 10656431]

37. Thor AD, Moore DH, Edgerton SM, et al. Accumulation of p53 tumor suppressor gene protein: an independent marker of prognosis in breast cancers. *J Natl Cancer Inst.* 1992; 84:845–55. [PubMed: 1317462]
38. Dookeran KA, Gao X, Wang Y, et al. p53 gene mutations in African-American women with breast cancer. *Breast Cancer Res Treat.* 2006; 100(Suppl. 1):S145.
39. Blaszyk H, Vaughn CB, Hartmann A, et al. Novel pattern of p53 gene mutations in an American black cohort with high mortality from breast cancer. *Lancet.* 1994; 343(8907):1195–7. [PubMed: 7909871]
40. Shiao YH, Chen VW, Scheer WD, Wu XC, Correa P. Racial disparity in the association of p53 gene alterations with breast cancer survival. *Cancer Res.* 1995; 55:1485–90. [PubMed: 7882357]
41. Shiao YH, Chen VW, Wu XC, et al. Racial comparison of p53 alterations in breast cancer: difference in prognostic value. *In Vivo.* 1996; 10:169–73. [PubMed: 8744796]

FIG. 1.

Poverty status distribution of breast cancer cases by race. ZCTA-based poverty means for cases were compared to the 1999 U.S. national census mean. The reference point for poverty status was taken as 1999 U.S. census poverty mean of 9.2%, reflecting the number of families living below the poverty threshold nationally.^{3,4}

FIG. 2. Unadjusted Kaplan–Meier survival curve estimates according to race. **a** All cases, **b** ER/PR-positive status, **c** ER/PR-negative status, **d** non-TN type, **e** TN type, **f** luminal A/B type, **g** basal type, **h** p53-negative status and **i** p53-positive status

FIG. 3. Kaplan–Meier survival curve estimates according to p53 status. **a** Non-AA and **b** AA

FIG. 4.
Conceptual framework of the complex relationship of race, tumor biology, and SES

TABLE 1

Patient, tumor, and treatment characteristics by race

Characteristic	Subcharacteristic	Non-AA n (%)	AA n (%)	OR	95% CI	P
Age	<50 (ref)	97 (47.8)	101 (30.5)			
	50	106 (52.2)	230 (69.5)	2.08	1.45–2.99	0.0001
Comorbid disease ^a	No (ref)	95 (56.9)	97 (33.6)			
	Yes	72 (43.1)	192 (66.4)	2.61	1.77–3.86	<0.0001
Poverty status	1999 U.S. mean (9.2%) (ref)	74 (36.5)	40 (12.1)			
	>U.S. census mean	129 (63.5)	291 (87.9)	4.17	2.70–6.45	<0.0001
Education status ^b	1999 U.S. mean (80.4%) (ref)	39 (19.2)	48 (14.5)			
	<U.S. census mean	164 (80.8)	283 (85.5)	1.40	0.88–2.23	0.1525
Stage	1 (ref)	41 (20.2)	94 (28.4)			
	2	102 (50.3)	150 (45.3)	0.64	0.41–1.00	0.05
	3	47 (23.2)	64 (19.3)	0.59	0.35–1.00	0.051
	4	13 (6.4)	23 (7.0)	0.77	0.40–1.65	0.51
Grade	1 (ref)	18 (9.0)	33 (10.1)			
	2	68 (33.8)	104 (31.8)	0.83	0.44–1.59	0.585
	3	115 (57.2)	190 (58.1)	0.90	0.49–1.66	0.742
ER/PR status	Negative (ref)	78 (38.8)	135 (41.3)			
	Positive	123 (61.2)	192 (58.7)	0.90	0.63–1.29	0.573
HER2	Negative (ref)	149 (74.9)	268 (82.5)			
	Positive	50 (25.1)	57 (17.5)	0.63	0.41–0.97	0.037
TN type ^c	Negative (ref)	147 (73.1)	222 (67.9)			
	Positive	54 (26.9)	105 (32.1)	1.29	0.87–1.90	0.202
Basal subtype ^d	Luminal A/B (ref)	123 (81.5)	192 (72.7)			
	Basal	28 (18.5)	72 (27.3)	1.65	1.01–2.69	0.045
p53	Negative (ref)	111 (70.3)	200 (71.9)			
	Positive	47 (29.7)	78 (28.1)	0.92	0.60–1.41	0.708
Endocrine therapy, overall	No (ref)	93 (45.8)	164 (49.6)			
	Yes	110 (54.2)	167 (50.4)	0.86	0.61–1.22	0.402
Endocrine therapy, provided to ER/PR+ patients	No (ref)	19 (15.6)	40 (20.83)			
	Yes	104 (84.6)	152 (79.2)	0.69	0.38–1.26	0.232
Surgery	No (ref)	27 (13.3)	45 (13.6)			
	Yes	176 (86.7)	286 (86.4)	0.98	0.59–1.62	0.923
Radiation therapy	No (ref)	68 (33.5)	135 (40.8)			
	Yes	135 (66.5)	196 (59.2)	0.73	0.51–1.05	0.092
Chemotherapy age < 50 year	No (ref)	15 (15.5)	10 (9.9)			
	Yes	82 (84.5)	91 (90.1)	1.66	0.72–3.84	0.239
Chemotherapy age ≥ 50 year	No (ref)	25 (23.6)	86 (37.4)			
	Yes	81 (76.4)	144 (62.6)	0.52	0.31–0.87	0.012
Trastuzumab	No (ref)	181 (89.2)	314 (94.9)			

Characteristic	Subcharacteristic	Non-AA <i>n</i> (%)	AA <i>n</i> (%)	OR	95% CI	<i>P</i>
Trastuzumab, provided to HER2+ patients	Yes	22 (10.8)	17 (5.1)	0.45	0.23–0.85	0.014
	No (ref)	32 (64.0)	42 (73.7)			
	Yes	18 (36.0)	15 (26.3)	0.64	0.28–1.44	0.279

OR odds ratio, *ref* reference

^a Any history of diabetes, hypertension, or heart disease

^b High school education or higher

^c Negative for ER, PR, and HER2

^d Negative for ER, PR, and HER2, and positive for CK 5/6 and/or HER1

TABLE 2

Univariate and multivariate Cox models for all-cause mortality by race

Factor	AA			Non-AA		
	HR	95% CI	P	HR	95% CI	P
<i>Univariate</i>						
Age (per year)	1.00	0.99–1.02	0.791	1.00	0.97–1.03	0.897
Comorbid disease (yes/no)	0.92	0.60–1.41	0.704	1.68	0.87–3.24	0.123
BMI (30/<30)	0.96	0.62–1.48	0.852	1.10	0.58–2.10	0.772
Poverty status (>1999 U.S. mean/ mean)	1.53	0.77–3.02	0.223	1.18	0.64–2.17	0.588
Education status (<1999 U.S. mean/ mean)	2.10	1.06–4.14	0.033	0.99	0.48–2.05	0.982
Stage *						
II/I	1.99	1.14–3.48	0.016	2.65	0.60–11.74	0.200
III/I	5.57	3.08–10.09	<0.001	11.93	2.80–50.84	0.001
IV/I	10.34	5.26–20.36	<0.001	37.31	7.93–175.4	<0.001
Grade (higher/low)	1.55	1.14–2.11	0.005	1.61	0.96–2.70	0.072
ER/PR (-/+)	2.01	1.38–2.93	<0.001	2.13	1.19–3.81	0.010
TN (+/-)	1.95	1.33–2.85	0.001	1.72	0.95–3.14	0.075
Basal subtype (basal/luminal A/B)	1.99	1.27–3.12	0.003	1.84	0.81–4.16	0.143
p53 (+/-)	1.69	1.10–2.58	0.016	0.76	0.37–1.55	0.445
Hormone therapy (yes/no)	0.48	0.33–0.70	<0.001	0.45	0.25–0.81	0.008
Chemotherapy (yes/no)	1.09	0.71–1.67	0.692	1.04	0.44–2.46	0.922
<i>Multivariate model 1</i>						
Age (per year)	1.00	0.97–1.03	0.950	1.01	0.96–1.05	0.825
Comorbid disease (yes/no)	1.13	0.60–2.13	0.708	1.01	0.35–2.88	0.984
BMI (30/<30)	1.04	0.60–1.80	0.880	0.77	0.31–1.95	0.585
Poverty status (>1999 U.S. mean/ mean)	0.93	0.36–2.39	0.884	1.22	0.50–2.97	0.663
Stage						
II/I	1.56	0.66–3.66	0.311	2.30	0.32–16.51	0.408
III/I	4.88	1.86–12.81	0.001	13.20	2.13–81.79	0.006
IV/I	9.84	3.31–29.25	<0.001	84.17	10.51–673.9	<0.001
Grade (higher/low)	1.17	0.72–1.90	0.531	0.79	0.33–1.91	0.596
TN (+/-)	0.97	0.46–2.05	0.940	1.61	0.49–5.28	0.430
p53 (+/-)	1.82	1.04–3.17	0.035	0.66	0.24–1.84	0.431
Hormone therapy (yes/no)	0.82	0.41–1.65	0.578	0.52	0.18–1.51	0.226
Chemotherapy (yes/no)	0.80	0.32–2.03	0.643	0.34	0.07–1.70	0.189
<i>Multivariate model 2</i>						
Age (per year)	1.00	0.97–1.03	0.925	1.00	0.95–1.05	0.994
Comorbid disease (yes/no)	1.08	0.58–2.04	0.806	1.09	0.38–3.18	0.868
BMI (30/<30)	1.10	0.63–1.91	0.740	0.77	0.30–1.99	0.593
Poverty level (> 1999 U.S. mean/ mean)	0.88	0.34–2.25	0.785	1.23	0.49–3.09	0.668
Stage						
II/I	1.54	0.65–3.67	0.330	2.51	0.34–18.83	0.370

Factor	AA			Non-AA		
	HR	95% CI	P	HR	95% CI	P
III/I	5.08	1.91–13.51	0.001	13.66	2.10–88.76	0.006
IV/I	10.24	3.37–31.08	<0.001	77.65	9.39–642.5	<0.001
Grade (higher/low)	1.06	0.64–1.75	0.821	0.81	0.34–1.97	0.649
ER/PR (–/+)	1.43	0.57–3.60	0.442	1.62	0.35–7.39	0.535
HER2 (+/–)	1.37	0.74–2.54	0.313	0.57	0.19–1.67	0.304
p53 (+/–)	1.89	1.08–3.29	0.026	0.52	0.17–1.57	0.244
Hormone therapy (yes/no)	1.05	0.44–2.52	0.908	0.61	0.14–2.68	0.511
Chemotherapy (yes/no)	0.77	0.30–1.97	0.585	0.32	0.06–1.65	0.172
<i>Multivariate model 3</i>						
Age (per year)	1.00	0.96–1.03	0.845	1.00	0.94–1.06	0.989
Comorbid disease (yes/no)	0.89	0.44–1.77	0.733	0.69	0.19–2.43	0.558
BMI (30/<30)	1.41	0.80–2.59	0.266	0.92	0.29–2.92	0.894
Poverty status (>1999 U.S. mean/ mean)	0.77	0.29–2.02	0.594	1.31	0.47–3.68	0.611
Stage						
II/I	1.62	0.63–4.16	0.312	2.99	0.20–44.51	0.427
III/I	5.02	1.74–14.49	0.003	29.64	2.47–355.4	0.007
IV/I	9.28	2.64–32.55	<0.001	147.81	7.46–2929	0.001
Grade (higher/low)	1.22	0.71–2.10	0.475	0.55	0.18–1.65	0.286
Basal subtype (basal/luminal A/B)	1.36	0.53–3.51	0.519	1.67	0.27–10.30	0.580
p53 (+/–)	1.98	1.06–3.68	0.031	0.65	0.20–2.13	0.479
Hormone therapy (yes/no)	1.19	0.48–2.91	0.710	0.39	0.08–1.92	0.245
Chemotherapy (yes/no)	0.76	0.27–2.19	0.613	0.43	0.06–2.96	0.393

* Effect estimates for high stage are highly variable due to small numbers of cases; however, other parameterizations for stage such as combining stages III and IV into one category do not materially influence the effect estimate for p53