OUTCOME DISPARITIES IN AFRICAN AMERICAN COMPARED WITH EUROPEAN AMERICAN WOMEN WITH ER+HER2- TUMORS TREATED WITHIN AN EQUAL-ACCESS HEALTH CARE SYSTEM

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Purpose: Breast cancer mortality rates are higher for African American women (AAW) than for any other ethnic group in the United States. Recent reports suggest that outcome disparities between AAW and European American women (EAW) are present in the ER+HER2- subtype. To improve our understanding, pathological characteristics, mortality and molecular profiles from women treated within an equal-access health care system were evaluated.

Procedures: All AAW (n=90) and EAW (n=308) with ER+HER2- tumors were identified. Gene expression profiles were generated from primary breast tumors from 57 AAW and 181 EAW. Pathological characteristics, survival and gene expression analysis were evaluated using chi-square analysis, log-rank tests and ANOVA.

Results: Tumors from AAW were significantly more likely to be PR-, Ki67+ and of higher grade. Tumor stage, size and lymph node status did not differ significantly, nor did mortality rates (P=.879). At the molecular level, genes PSPHL and CRYBB2P1 were expressed at significantly higher levels in tumor tissues as well as normal stroma and blood from AAW. Polymorphisms controlling expression of each gene were identified with minor allele frequencies differing significantly between populations but not between cases and controls within each population.

Conclusions: Survival disparities were not detected in patients with ER+HER2- tumors treated within an equal-access health care system and molecular differences in tumors were not causal. Thus, outcome disparities in AAW with ER+HER2- tumors are largely attributable to socioeconomic factors affecting access to screening and treatment, rather than reflecting underlying biological differences.

Keywords: Breast Cancer; African American; Luminal A; Disparities

INTRODUCTION

Although the overall incidence of breast cancer is lower in African American women (AAW) compared with European American women (EAW), the five-year survival rate for AAW is significantly lower than for EAW, and the age-adjusted mortality rate for AAW is the highest rate for any ethnic group studied. Outcome disparities may be attributable to social barriers such as access to timely and quality health care, mistrust of the health care system and racial profiling. In conjunction, tumors from AAW are more likely to have high-grade, hormone receptor negative and triple negative tumors compared with EAW; these characteristics are all associated with poor prognosis. Differences in tumor biology combined with differences in clinical care may combine to create “the perfect storm” for survival disparity.

Higher mortality rates have been detected for AAW when breast cancer was considered as a single disease; however, breast cancer is heterogeneous, and can be classified into subtypes based on expression of hormone receptor (HR) and HER2. Evaluation of survival within triple negative (HR-HER2-) tumors, characterized by poor prognosis and higher frequency in premenopausal AAW, failed to detect outcome differences between AAW and EAW. Data from the Carolina Breast Cancer Study also revealed no significant difference in survival between AAW and EAW with triple negative breast cancer; significant survival differences were, however, detected between AAW and EAW with estrogen receptor (ER) positive, HER2 negative tumors. Survival disparities in patients with ER+HER2- tumors have

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also been reported for AAW with stage II/III or p53- tumors diagnosed at 50-64 years.10,11 Evaluation of response to neoadjuvant therapy found that AAW with HR+ tumors had significantly inferior outcomes than EAW, including higher risk of recurrence and death, despite similar treatments and rates of pathologic response.12 These data suggest that survival disparities within the ER+HER2- subtype may be a contributing factor to the overall higher breast cancer mortality in AAW.

PSPHL was also differentially expressed in stromal tissues.13 The authors determined that expression of PSPHL and CRYBB2 could be used as a two-gene signature to discriminate specimens by ethnicity, not only in breast cancer but in prostate cancer as well.14 Gene expression profiling of 26 sets of breast tumors matched by grade, age and ER status revealed 23 differentially expressed genes, including PSPHL and CRYBB2; within the stromal specimens from patients without breast cancer, PSPHL and CRYBB2 were also overexpressed in tissues from AAW compared with EAW.15 Although these studies demonstrated that gene expression profiles differ in breast tumors from AAW compared with EAW, both studies included a heterogeneous mix of tumor subtypes and neither study demonstrated that these differences were associated with decreased survival. A recent study that classified tumors by intrinsic subtype, rather than using HR and HER2 status, identified six genes differentially expressed by ethnicity and also associated with survival, including PSPH and CRYBB2.16 In this study, PSPH and CRYBB2 were also differentially expressed in reduction mammoplasty specimens, and the authors concluded that these survival-associated genes are differentially expressed from the earliest stages of or precede malignancy.

These data suggest the higher mortality rates in AAW with breast cancer may, in part, be driven by survival differences within the ER+/HER2- subtype and that these differences may be attributable to population-specific molecular differences within the tumor. The majority of these studies, however, utilized data from tumor registries or public databases where provision of clinical care was not integral to the study. In contrast, our project is a federally mandated breast cancer research program with both clinical and research arms. Patients have been enrolled since 2001 at a military hospital where equal-access health care is provided to all military personnel and dependents. In this study, we utilized these resources to determine whether survival disparities exist for female patients within a US Department of Defense clinical facility and how molecular differences may impact survival.

**Methods**

**Patient Enrollment**

Only patients with ER+HER2- tumors were eligible for this study. For enrollment, all patients met the following criteria: 1) adult aged > 18 years; 2) mentally competent and willing to provide informed consent; and 3) presenting to the breast centers with evidence of breast disease. Tissue and blood samples were collected with approval from the Human Use Committee and Institutional Review Board of Murtha Cancer Center. All patients enrolled voluntarily, agreed to participate and gave written informed consent. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national)
and with the Helsinki Declaration of 1975, as revised in 2000.

**Human Tissue Samples**

Tissue was collected from patients undergoing lumpectomy or mastectomy. Within 5-15 minutes of surgical removal, breast tissue was taken on crushed, wet ice to the pathology laboratory where a licensed pathologist or pathologists’ assistant performed routine pathology analyses. Diagnosis of every specimen was performed by a breast pathologist; staging was performed using guidelines defined by the AJCC Cancer Staging Manual seventh edition and grade assigned using the Nottingham Histologic Score. ER, PR, Ki67 and HER2 status were determined by immunohistochemistry analysis (MDR Global, Windber, PA); cases with HER2 scores = 2+ were evaluated by fluorescence in situ hybridization using the PathVysion HER-2 DNA Probe kit (Abbott Laboratories, Abbott Park, IL). Hormone receptor and HER2 status were defined using current ASCO/CAP guidelines. Ki67 positivity was defined as >20% stained cells. Patient status through 2015 was obtained by searching electronic health records.

**Gene Expression Data**

To generate gene expression data, patients with available frozen tumor specimens were identified. Tumor samples were laser microdissected and gene expression data were generated using HG U133A 2.0 arrays (Affymetrix, Santa Clara, Calif.) as previously described. Intrinsic subtype was assigned using the BreastPRS (Signal Genetics, New York, N.Y.). Ribonucleic acid (RNA) from a subset of 116 tumors, as well as from blood samples from 40 control patients, was reverse transcribed using the High-Capacity cDNA Reverse Transcription kit (Life Technologies, Grand Island, N.Y.) and qRT-PCR (real-time quantitative reverse transcription – polymerase chain reaction) was performed using commercial TaqMan gene expression assays Hs00166761_ml and Hs00417416_ml for CRYBB2 and CRYBB2P1 transcripts, respectively, and custom assays were designed for CRYBB2P1 transcripts ENST00000382734, ENS00000354451 and ENST00000509460. Amplification was performed in duplicate using TaqMan Universal PCR Master Mix (Life Technologies, Grand Island, N.Y.). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the endogenous control for normalization of all assays. Relative quantification of gene expression levels was determined using the Comparative Ct method.

**Analysis of CRYBB2P1 Polymorphisms**

Genomic DNA was isolated from blood clots of 1,512 cases and controls using the Gentra Clotspin and Puregene DNA purification kits (Qiagen Inc, Valencia, Calif.). Primers 5’CTCCAGCTTG-CAGATGACCT3’ and 5’AGCT-GTTTTCCTCCAGGAC3’ were designed to amplify ~500 bp of the 5’ untranslated region plus the transcription start site. PCR reactions were performed using 25 ng genomic DNA with standard cycling conditions. PCR products were sequenced using BigDye terminator v 3.1 cycle sequencing kits (Life Technologies, Grand Island, N.Y.) and run on a 3730xl DNA Analyzer (Life Technologies, Grand Island, N.Y.). Data were analyzed using Sequencer 4.10.1 (Gene Codes Corporation, Ann Arbor, Mich.).

**Statistics**

Clinicopathological variables were evaluated by chi-square analysis. Survival analysis was performed using R (v3.1.1) statistical software. Kaplan-Meier survival estimates were calculated for AAW and EAW. For breast cancer-specific survival, all alive with disease (AWD), no evidence of disease (NED) and death from other causes (DOC) statuses were censored. For overall survival, all AWD and NED were censored. A Log-Rank test was performed to test homogeneity of the survival estimates across AAW and EAW. A P of .05 was used to determine significance. To identify differentially expressed genes, microarray data were imported into Partek® Genomics Suite™ 6.6 (Partek, Inc, St. Louis, Mo.) as CEL files using default parameters. Raw data were preprocessed, including background correction, normalization and summarization using robust multi-array average (RMA) analysis and expression data log2 transformed. Differential expression analysis for the tumor specimens was performed using ANOVA with a False-Discovery Rate (FDR) <.05, 2-fold change
defining differential expression.

To determine whether samples within each population were in Hardy-Weinberg equilibrium (HWE), the Hardy-Weinberg equilibrium calculator including analysis for ascertainment bias tool (http://www.oeye.org/software/hwe-mr-calc.shtml) was used. Allele and genotype frequencies were compared between AAW and EAW with or without breast cancer, and by disease status within each population using chi-square analysis (http://www.physics.csbsju.edu/stats/contingency_NROW_NCOLUMN_form.html).

**RESULTS**

Between 2001 and 2013, 398 women (AAW = 90, EAW = 308) were diagnosed with ER+HER2-breast tumors. Average age at diagnosis was significantly lower (*P* = .031) in AAW (mean = 57.9 years, range 33-85 years) compared with EAW (mean = 61.3 years, range 30-97 years). While tumor stage, size and lymph node status did not differ between populations, AAW were significantly more likely to have poorly differentiated tumors with negative PR status and ki67>20% (Table 1). Although all tumors were considered ER+ using ASCO/CAP guidelines, AAW were significantly more likely to have tumors with low (1%-9%) ER staining. Rates of recurrence (4% and 2%) and progression (7% and 4%) did not differ significantly between populations (Table 1). The inclusion of covariates including age at diagnosis, tumor grade, PR and Ki67 status did not significantly contribute to survival differences between populations.

To determine whether survival disparities may be attributable to intrinsic subtypes, frequency of subtype within ER+HER2- tumors were evaluated. Microarray data were available from 57 AAW and 181 EAW; intrinsic subtypes were more likely to be luminal B (17%) or basal-like (10%) in AAW compared with EAW (8% and 5%, respectively). To determine whether tumors differed at the transcriptome level, gene expression profiles from ER+HER2- tumors were compared and 10 differentially expressed genes, including PSPHL and CRYBB2//CRYBB2P1, were detected (Table 2). Of note, eight of these genes overlapped with the 13 genes detected when luminal A gene expression profiles were compared between AAW and EAW.

Previous work demonstrated that expression differences in
PSPHL within tumor epithelium is not causal but rather represents population stratification attributable to a polymorphism on chromosome 7p. Because expression of PSPHL and CRYBB2 has been described as an effective two-gene signature for classifying patients by ancestry and more recently, that higher expression of these genes is associated with poor survival, we further investigated the source of expression level differences of probe 206777_s_at.

While probe 206777_s_at is homologous to both CRYBB2 and CRYBB2P1, probe 206778_at, specific to CRYBB2, was not differentially expressed between populations in tumor, stroma or blood in our study, nor were qRT-PCR results using Hs00166761_m1; thus CRYBB2 is not driving the differential expression detected with probe 20677_s_at. In contrast, CRYBB2P1 assay Hs00417416_m1 demonstrated significantly higher

Table 2. Genes differentially expressed between ER+HER2- tumors from AAW and EAW

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<tr>
<th>Gene symbol</th>
<th>Accession number</th>
<th>Gene name</th>
<th>Probe ID</th>
<th>P</th>
<th>Fold-change (AAW/EAW)</th>
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<td>crystallin, beta B2 /// crystallin, beta B2 pseudogene 1</td>
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<td>immunoglobulin heavy constant gamma 1 (G1m marker) /// immunoglobulin heavy constant ga</td>
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a. Probes also differentially expressed when comparing luminal A tumors. Genes differentially expressed only in luminal A tumors include COL2A1 (213492_at), CPB1 (205509_at), NKAIN1 (219438_at), SCN1A (210383_at) and UGT2B28 (211682_x_at).
gene expression levels in tumors from AAW \((P<.00003, 5\text{-fold difference})\). Paradoxically, probe 222048_at, located within exon 6 of CRYBB2P1, demonstrated 1.5-fold lower levels in tumor and stroma tissues from AAW. Use of custom TaqMan expression assays for each of the four CRYBB2P1 transcripts in the Ensembl database revealed that expression levels of transcripts ENST00000354451 and ENST00000509460 were not significantly different between populations; ENST00000415709 was expressed 16-fold higher in tumors from AAW compared with EAW \((P<0.0005)\) and ENST00000415709 was expressed 8.7-fold lower \((P<0.00005)\), suggesting that in AAW, ENST00000415709 is expressed at the expense of ENST00000382734 (Figure 2).

Two polymorphisms in the 5’ UTR, rs576585 representing a T/C polymorphism and rs58348884 representing a 9 bp insertion/deletion polymorphism located at the predicted transcription start site, were genotyped. rs576585 was not significantly associated with expression differences; however, the presence of the deletion allele (del/del or del/ins) of rs58348884 was associated with 5.9-fold decreased expression of ENST00000382734 and 33.4-fold increased expression of ENST00000415709. Similar results were observed in blood specimens with the deletion associated with 2.2-fold decreased expression of the major transcript and 24.6-fold increased expression of the minor transcript. Genotype frequencies for rs58348884 were in HWE for all populations. Minor (deletion) alleles differed significantly between EAW and AAW cases (.09 and .55, respectively) and controls (.07 and .62, respectively) but not between cases and controls within a single population. In addition, the deletion allele was not associated with age at diagnosis, tumor stage, size or grade, ER, HER2, lymph node status or breast-cancer specific survival. Thus, gene expression differences in CRYBB2P1, as with PSPHL, reflect population stratification and are not associated with tumorigenesis or outcome disparities.

**Discussion**

The original report of survival disparities in AAW with ER+HER2-tumors was surprising as these tumors have been associated with favorable prognoses. Identification of factors contributing to this disparity, such as differences in tumor biology, response to treatment and provision of health care, may provide new avenues to improve survival in AAW. Detection of survival differences between AAW and EAW with
ER+HER2- tumors has largely been in studies from tumor registries where access to and quality of clinical care are not standard. In contrast, no significant difference in survival was detected in our study in which all patients were treated within an equal-access health care system.

Accessibility of health care can have a significant effect on disease outcomes. In our patients, no differences in stage at diagnosis, tumor size or lymph node status, all factors affected by the chronology of the tumor, were detected. AAW with stage II or III ER+/HER2- tumors were found to have less favorable outcomes than EAW, and, in the general population, AAW are more likely to be diagnosed at a later stage, which has been attributed to less frequent and longer intervals between screening and delays between diagnosis and treatment. Within the military health care system, however, receipt of surveillance mammography did not differ significantly between non-Hispanic Whites and minority populations, which may account for the >50% of AAW diagnosed with stage I tumors.

Classification of tumors based only on the expression of ER and HER2 status may fail to detect pathological differences contributing to less favorable survival of AAW. The use of four biomarkers: ER, PR, HER2 and Ki67, has been used to classify IHC-defined ER+/HER2- tumors into luminal A or luminal B, based on low or high expression of Ki67. The current St. Gallen consensus classification of ER+/HER2- tumors in surrogate subtypes includes both Ki67 and PR status. Using these criteria, 19% of ER+/HER2- tumors from AAW would be classified as luminal B compared with 6% from EAW, which is similar to what was found when gene expression based intrinsic subtypes were assigned. Thus, survival disparities within patients with ER+/HER2- may reflect a significantly higher frequency of luminal B tumors, which have a significantly lower 10-year survival estimate (54.4%) compared with luminal A tumors (70%). Together, these data suggest that if using an IHC-based system to assign surrogate subtypes, at a minimum, Ki67 should be included to discriminate luminal A from luminal B tumors.

Data from our study suggest that, although patterns of gene expression in ER+HER2- tumors differ between AAW and EAW, the two genes with the most significant fold-changes are not causal but rather reflect an artifact of genetic ancestry. In the work of D’Arcy et al, PSPH and CRYBB2 were found to be: 1) differentially expressed between AAW and EAW; and, 2) associated with survival differences based on probes A_23_P251984 and A_23_P40574. Probe A_23_P251984 (PSPH) is identical to PSPHL at 57/60 bp, and multiple studies demonstrated that when qRT-PCR probes specific to either PSPH or PSPHL assayed, expression level differences between AAW and EAW are only detected for PSPHL. In a similar manner, probe A_23_P40574 (CRYBB2) also demonstrates homology to CRYBB2P1 and validation with qRT-PCR assays specific to each gene demonstrated that the expression between AAW and EAW differences were attributable to CRYBB2P1. D’Arcy et al suggested that because higher expression levels of probes A_23_P251984 and A_23_P40574 are detected in both tumor and normal breast specimens from AAW compared with EAW, these gene expression differences are present from the earliest stages of tumor development. In contrast, differential expression of probes for PSPHL and CRYBB2P1 have also been found in non-tumor tissues including blood and optic nerve heads, suggesting that expression level differences are systemic and not related to tumorigenesis.

In addition to difficulties linking differential expression of probes to the correct genes, both PSPHL and CRYBB2P1 are genes with unknown functions. PSPH is involved in the synthesis of L-serine, but PSPHL does not encode a functional protein and was classified by NCBI as a pseudogene in 2014 (http://www.ncbi.nlm.nih.gov/nuccore/NG_009001.2).
CRYBB2 is a structural protein of the eye lens while CRYBB2P1 has also been reported to be a pseudogene. Recent studies have demonstrated that pseudogenes, including CRYBB2P1, may function as competing endogenous RNA, which may contribute to tumorigenesis by altering gene expression profiles, however, our data demonstrate that expression of PSPHL and CRYBB2P1 transcripts in tissue and blood do not differ by disease status.

Our study has several strengths and limitations. To our knowledge, this is the first study to evaluate survival differences in patients with ER+HER2- tumors within an equal-access health care system. In addition, this study, with both clinical and research arms, is a prospective study, enrolling patients undergoing treatment from study physicians at the time of diagnosis. Thus, survival disparities related to disparate access to clinical care is minimized. In addition, we believe that our gene expression analysis included the most patient samples to date. Our study was limited to the length of follow-up across all samples. ER+HER2- tumors are characterized by longer times to recurrence, thus with an average follow-up of 8 years, we may not detect survival disparities that occur >5 years after diagnosis. In addition, treatment information was not available for these patients; thus, possible treatment differences that may have improved survival of AAW cannot be determined. Finally, these data may reflect enrollment bias: patients who do not appear emotionally or mentally capable of enrolling in a research protocol at the time of diagnosis are not approached and not every invited patient elects to participate. Thus, this group of women with ER+HER2- may be more likely to have fewer co-morbidities, to engage in routine screening, or to be compliant with treatment.

These data have important implications for future research. Although gene expression differences have been detected, if these differences reflect population stratification and are not clinically meaningful, as with PSPHL and CRYBB2P1, development of population-specific targeted treatments will not be necessary and resources can be devoted to strategies that reduce social barriers associated with survival disparities, such as increasing the number of minority patients with insurance, improving patient education and physician communication, and providing patient navigators.

In the state of Delaware, a number of intervention steps were implemented to decrease health disparities in African Americans with colon cancer; the interventions resulted in screening rates equal to those of European Americans, a decrease of late stage diagnoses, and a concomitant 42% decrease in patient mortality, eliminating survival disparities between populations. Future research should determine how this model can be adapted to breast cancer and how it can be implemented at a national level to help eradicate survival disparities in patients with breast cancer.

CONCLUSION

AAW patients with ER+HER2-breast cancer in our study did not have significantly different survival rates than EAW. This lack of survival disparity may be attributable to provision of clinical care within a military health care system where screening and treatment are provided at no costs to all eligible individuals, thus reducing the impact that impaired access to health care has on breast cancer outcomes. These findings, in conjunction with gene expression differences attributable to population artifact rather than causation, suggests that survival disparities detected in the general population may be reduced by changing health care access and delivery across the United States.

CONFLICT OF INTEREST
No conflicts of interest to report.

AUTHOR CONTRIBUTIONS
Research concept and design: Shriver, Ellsworth; Acquisition of data: Freeman, Ellsworth; Data analysis and interpretation: Costantino, Freeman, Shriver, Ellsworth; Manuscript draft: Costantino, Ellsworth; Statistical expertise: Costantino; Acquisition of funding: Shriver; Administrative: Freeman, Shriver; Supervision: Shriver, Ellsworth

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