Differences in gene-expression profiles in breast cancer between African and European-ancestry women

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Abstract

African American (AA) women have an excess breast cancer mortality than European American (EA) women. To investigate the contribution of tumor biology to this survival health disparity, we compared gene expression profiles in breast tumors using RNA sequencing data derived from 260 AA and 155 EA women who were prospectively enrolled in the Southern Community Cohort Study (SCCS) and developed breast cancer during follow-up. We identified 59 genes (54 protein-coding genes and 5 long intergenic non-coding RNAs) that were expressed differently between EA and AA at a stringent false discovery rate (FDR) < 0.01. A gene signature was derived with these 59 genes and externally validated using the publicly available Cancer Genome Atlas (TCGA) data from 180 AA and 838 EA breast cancer patients. Applying C-statistics, we found that this 59-gene signature has a high discriminative ability in distinguishing AA and EA breast cancer patients in the TCGA dataset (C-index = 0.81). These findings may provide new insight into tumor biological differences and the causes of the survival disparity between AA and EA breast cancer patients.

Introduction

Breast cancer is the most common cancer in women worldwide, with more than 2 million new cases diagnosed annually (1). Due to advances in early detection and improvements in treatment, breast cancer survival has increased substantially over the last three decades, particularly in developed countries where the 5-year survival rates for invasive breast cancer have reached 90% and higher (2). However, there is a significant racial disparity in breast cancer survival, with African American (AA) patients having a higher breast cancer mortality rate than European American (EA) patients. This disparity could be partially attributed to differences in breast cancer biology between AA and EA (3).

Several previous studies have profiled gene expression in breast cancer tissues to investigate possible distinct biological mechanisms and molecular pathways of breast carcinogenesis and prognosis between AA and EA women (4–8). A recent study analyzed racial differences in the expression levels of 200 genes, including 50 genes from the PAM50 panel, in breast cancer tissues collected from 495 AA and 478 EA patients included in the Carolina Breast Cancer Study (7). In another recent study, RNA sequencing (RNA-Seq) data generated from the breast cancer tissues of 154 AA and 774 EA breast cancer patients included in the Cancer Genome Atlas (TCGA) were analyzed (4). Both studies identified genes that were differentially expressed between AA and EA patients. However, none of these studies rigorously cross-validated their findings using an independent dataset, and thus some of the reported observations could be spurious due to type I errors.

In this study, we used RNA-Seq data generated from a large collection of breast tumors—from 260 AA and 155 EA patients from the Southern Community Cohort Study (SCCS)—to identify a gene signature that best differentiates between these two patient groups. We constructed a 59-genes signature using the SCCS data and externally validated this gene signature with...
used for coding gene and noncoding RNAs annotation in the human from aligned BAM files using HT-Seq-Count (12). The GENCODE v22 was human reference genome (hg38). RNA expression levels were determined following the mRNA analysis pipeline of TCGA GDC (https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/Expression_mRNA_Pipeline/).

- **TCGA data**
  - Breast cancer data from TCGA, which are publicly available from the NCI GDC data portal (https://portal.gdc.cancer.gov/), was used in this study as an independent validation set. We obtained the most updated clinical information from the TCGA Pan-Cancer Clinical Data Resource (18). HTSeq-FPKM data for TCGA breast cancer samples were downloaded as gene expression profiles and for further analysis, by using R package TCGAbiolinks (12,19). Principal component analyses were conducted using EIGENSTRAT bases on genotype data from TCGA samples (20). Using the 1000 Genomes Project data as reference (21), we used the first and second principal components of TCGA samples to determine race and kept those AA and EA samples for subsequent analyses.
  - TCGA RNA-Seq gene expression data were processed following the same transformation, normalization, and subtyping steps applied to the SCCS data. We used the TCGA breast cancer data as an external validation set for our race-differentiated gene signature identified from the SCCS.

- **Statistical analyses**
  - All statistical analyses were performed in R 3.6.1. Differences in demographic and clinicopathological characteristics between AA and EA patients were assessed with t-test or nonparametric Wilcoxon rank-sum test for continuous variables. Binary and categorical data were analyzed with chi-square test. Univariable overall survival analyses were conducted using Kaplan-Meier estimates and log-rank tests. The Cox proportional hazards were used for multivariable modeling.

- **Gene signature development and validation**
  - Using data from the SCCS, we identified genes that were differentially expressed between AA and EA breast cancer patients using linear regression models, adjusting for age at diagnosis, PAM50 subtypes, tumor, nodes, and metastases stages, probabilistic estimation of expression residuals factors, and batch effect. A false discovery rate (FDR) of 0.01 was employed to account for multiple testing. Penalized logistic regression with ridge regularization was used to reduce the prediction variance and overcome the potential problem of multicollinearity by shrinking the model coefficients when building the race-differentiated gene expression signature (22). Cross-validation was used for the tuning parameter selection.
  - To externally validate this gene signature derived from the SCCS, we used data from TCGA. The identified gene signature was fitted to the TCGA gene expression data to predict patient race (AA versus EA). Ridge regression was used instead of lasso or elastic net because the purpose was to validate the gene signature post model finalization; therefore no further variable selection should be performed at this step. The gene signature was then evaluated in terms of both discrimination and calibration. The C-statistic was calculated to assess the predictive accuracy of the entire signature in discriminating AA and EA breast cancer in this external validation set. Calibration of the gene signature was assessed graphically in a calibration graph by plotting the observed outcomes against the predicted probabilities.

- **Survival analyses**
  - The race-differentiated genes identified above were assessed for their associations with breast cancer survival in the SCCS. Allowing for retesting of correlated genes, we used elastic net penalized Cox regression to identify a subset of the race-differentiated genes that were prognostic of breast cancer survival, adjusting for clinical variables, including age at diagnosis, stage, race, ER, PR, and HER2. Variable selection was achieved through elastic net-penalized partial likelihood, where both mixing and overall shrinkage tuning parameters are simultaneously cross-validated.

- **Results**

### Study samples

The demographic and clinical characteristics are summarized separately for SCCS and TCGA patients in Table 1. A total of 415 SCCS female participants (260 AA and 155 EA) with breast cancer were included in the study. The median follow-up period in the SCCS was 132 months (range, 7–177 months). AA cases...
were diagnosed at a younger age than EA cases in both the SCCS ($P = 0.029$) and TCGA ($P = 0.007$). Using the PAM50 classifier, more AA patients were classified as basal-like and HER2-enriched breast cancer subtypes than EA patients (basal-like: 25.8% versus 20.6% in the SCCS, 37.2% versus 14.3% in TCGA; HER2-enriched: 11.2% versus 7.7% in the SCCS, 12.2% versus 8.9% in TCGA). Fewer AA patients were classified as luminal A and luminal B breast cancer subtypes than EA patients (luminal A: 43.1% versus 50.3% in the SCCS, 24.8% versus 32.2% in TCGA; luminal B: 13.8% versus 15.5% in the SCCS, 15.5% versus 11.2% in TCGA). More AA patients were classified as triple negative breast cancer (TNBC) subtype than EA patients (18.1% versus 13.5% in the SCCS; 18.3% versus 8.7% in TCGA). These differences were statistically significant in TCGA but not in the SCCS.

Race-differentiated gene signature in breast cancer tumor tissues

We identified 19,065 genes (16,586 protein-coding and 2,479 lincRNAs) that were expressed in over half of the SCCS samples. Of these, 2001 (10.5%) were differentially expressed in EA and AA at a nominal $P$ value < 0.05, among which 59 genes (54 protein-coding genes and 5 lincRNAs) reached an FDR-adjusted $P$ value < 0.01 (Table 2). Of these 59 genes, 31 genes expressed significantly higher in AA than EA women, while the remaining 28 genes expressed significantly higher in EA than AA women. The top three differentially expressed genes which expressed higher in AA were TAS2R43 (OMIM 612668), NUTM2F (no OMIM ID), and PWP2 (OMIM 601475), while the top three differentially expressed genes which expressed higher in EA were PM20D1 (OMIM 617124), BIRC7 (OMIM 605737), and LOC102724159 (ENSG00000275464, no OMIM). Hierarchical clustering of this gene set shows a good performance of the enrichment for both race and different subtypes (Figure 1). All 59 of these genes were included in constructing the race-differentiated gene signature.

Penalized logistic regression model with ridge regularization was implemented to shrink the coefficients in order to reduce the variance in prediction.

External validation in TCGA

We validated our 59-gene signature by fitting the model to the independent TCGA gene expression data to predict patient race (AA versus EA). The gene signature was then evaluated in terms of both discrimination and calibration. The concordance statistic (C-statistic, equal to the area under the receiver operating characteristic curve, AUC) was computed to evaluate overall prediction accuracy. At the external validation in TCGA breast cancer data, the C-statistic for the 59-gene signature was 0.81, indicating high discriminative ability of the gene signature to distinguish between AA and EA breast cancer patients. Calibration is the degree of correspondence between the estimated probability produced by the gene signature and the actual observed probability. The calibration curve of the gene signature was constructed with TCGA data and shown in Supplementary Figure 1.
### Table 2. The set of 59 genes found to be significantly differential expressed in the SCCS at FDR-adjusted P value < 0.01

| ENSEMBL ID         | Gene symbol | P value (SCCS) | FDR (SCCS) | P value (TCGA) |
|--------------------|-------------|----------------|------------|----------------|
| ENSG00000255374    | TAS2R43     | <0.001         | <0.001     | <0.001         |
| ENSG00000130950    | NUTM2F      | <0.001         | <0.001     | <0.001         |
| ENSG00000241945    | PW2P        | <0.001         | <0.001     | <0.001         |
| ENSG00000259604    | Lnc-ALDH1A3-1 | <0.001   | 0.005      | <0.001         |
| ENSG00000160221    | GATD3A      | <0.001         | <0.001     | <0.001         |
| ENSG00000176681    | LRRC37A     | <0.001         | <0.001     | <0.001         |
| ENSG00000134184    | SIK1        | <0.001         | 0.001      | <0.001         |
| ENSG00000261701    | HPR         | <0.001         | 0.008      | <0.001         |
| ENSG00000158488    | CD1E        | <0.001         | <0.001     | <0.001         |
| ENSG00000196436    | NIP1BP1     | <0.001         | <0.001     | <0.001         |
| ENSG00000173678    | SPDY3EB     | <0.001         | <0.001     | <0.001         |
| ENSG00000224635    | AL391095.1  | <0.001         | <0.001     | <0.001         |
| ENSG00000106113    | CRHR2       | <0.001         | 0.004      | <0.001         |
| ENSG00000105499    | PLA2G4C     | <0.001         | <0.001     | <0.001         |
| ENSG00000204147    | ASAH2B      | <0.001         | 0.002      | <0.001         |
| ENSG00000197822    | OCLN        | <0.001         | 0.008      | <0.001         |
| ENSG00000197728    | RPS26       | <0.001         | <0.001     | <0.001         |
| ENSG00000168255    | POLK2J3     | <0.001         | <0.001     | <0.001         |
| ENSG00000203666    | EFCA8B      | <0.001         | 0.003      | <0.001         |
| ENSG00000106686    | SPAT16L     | <0.001         | <0.001     | <0.001         |
| ENSG00000152689    | RASGRP3     | <0.001         | 0.008      | <0.001         |
| ENSG00000178295    | GEN1        | <0.001         | <0.001     | <0.001         |
| ENSG00000215908    | CROCCP2     | <0.001         | <0.001     | <0.001         |
| ENSG00000154237    | LRRK1       | <0.001         | 0.001      | <0.001         |
| ENSG00000026950    | BTN3A1      | <0.001         | 0.007      | <0.001         |
| ENSG00000149292    | TTC12       | <0.001         | 0.004      | <0.001         |
| ENSG00000198060    | MARCH5      | <0.001         | 0.004      | <0.001         |
| ENSG00000154096    | THY1        | <0.001         | <0.001     | <0.001         |
| ENSG00000111671    | SPRS2       | <0.001         | 0.008      | <0.001         |
| ENSG00000135723    | FHOD1       | <0.001         | 0.004      | <0.001         |
| ENSG00000150477    | KIAA1328    | <0.001         | 0.009      | <0.001         |
| ENSG00000231389    | HLA-DPA1    | <0.001         | 0.008      | <0.001         |
| ENSG00000131669    | NIH1        | <0.001         | 0.009      | <0.001         |
| ENSG00000181481    | RNFI35      | <0.001         | 0.009      | <0.001         |
| ENSG00000203747    | FCGR3A      | <0.001         | 0.002      | <0.001         |
| ENSG00000144026    | ZNFS14      | <0.001         | 0.001      | <0.001         |
| ENSG00000186468    | RPS23       | <0.001         | <0.001     | <0.001         |
| ENSG00000175745    | NRRF1       | <0.001         | 0.009      | <0.001         |
| ENSG00000171503    | ETTFDH      | <0.001         | 0.002      | <0.001         |
| ENSG00000068654    | POLR1A      | <0.001         | <0.001     | <0.001         |
| ENSG00000185684    | EP400P1     | <0.001         | <0.001     | <0.001         |
| ENSG00000279457    | WASH5P      | <0.001         | 0.004      | <0.001         |
| ENSG00000280670    | CCDC163     | <0.001         | 0.008      | <0.001         |
| ENSG00000149089    | APPIP       | <0.001         | <0.001     | <0.001         |
| ENSG00000273136    | NBPF26      | <0.001         | <0.001     | <0.001         |
| ENSG000001402063   | SORD        | <0.001         | <0.001     | <0.001         |
| ENSG00000277203    | F8A1        | <0.001         | <0.001     | <0.001         |
| ENSG00000223865    | HLA-DPB1    | <0.001         | <0.001     | <0.001         |
| ENSG00000280071    | GATD3B      | <0.001         | <0.001     | <0.001         |
| ENSG00000019169    | MARCO       | <0.001         | <0.001     | <0.001         |
| ENSG00000262202    | Lnc-GRAP-3  | <0.001         | <0.001     | <0.001         |
| ENSG00000132207    | SLX1A       | <0.001         | <0.001     | <0.001         |
| ENSG00000215374    | FAM66B      | <0.001         | 0.001      | <0.001         |
| ENSG00000016402    | IL20RA      | <0.001         | <0.001     | <0.001         |
| ENSG00000170160    | CCDC144A    | <0.001         | 0.005      | <0.001         |
| ENSG00000275464    | LOC102724159| <0.001         | <0.001     | <0.001         |
| ENSG00000101197    | BIRC7       | <0.001         | 0.008      | <0.001         |
| ENSG00000162877    | PM20D1      | <0.001         | <0.001     | <0.001         |
available at Carcinogenesis Online. The Brier score measures disagreement between the observed outcome and a prediction and is the mean squared error ranging from 0 to 1, where the lower Brier score indicates the better calibration of the predictions. The Brier score of our 59-gene signature was 0.064, indicating high reliability and prediction accuracy of the gene signature to distinguish between AA and EA breast cancer patients.

**Survival analysis**

Using the Cox proportional hazards regression model, adjusting for age at diagnosis, subtype, ER, PR, HER2, and stage, we investigated the association of each gene from our 59 race-differentiated genes with overall survival (Supplementary Table 1, available at Carcinogenesis Online) among both AA and EA women. Using a P value of 0.10 as the tentative threshold for a significant association in the SCCS, we found that 10 of the 59 genes were associated with overall survival in AA but not in EA, while 7 genes were associated with overall survival in EA but not in AA. None of these genes were significantly associated with breast cancer survival after adjusting for multiple comparisons.

**Race-differentiated gene signature by breast cancer subtypes**

We investigated differentially expressed genes between AA and EA patients by three different breast cancer subtypes: (i) basal-like breast cancer subtype; (ii) luminal breast cancer subtype; and (iii) TNBC subtype. The analysis strategy was the same as the overall breast cancer patients. Among those breast cancer patients with both basal-like and TNBC subtypes, no gene reached an FDR-adjusted P value < 0.05. Within the patients with luminal breast cancer subtype, 1847 (9.7%) were differentially expressed in EA and AA at a nominal P value < 0.05, among which 40 genes (36 protein-coding genes and 4 lincRNAs) reached an FDR-adjusted P value < 0.01 (Supplementary Table 2, available at Carcinogenesis Online). Twenty-sevent of these 40 genes were in the overall 59 race-differentiated genes. We built a luminal-subtype-specific race-differentiated gene signature with these 40 genes by penalized logistic regression model with ridge regularization and externally validated with TCGA data. At the external validation in TCGA luminal breast cancer data, the C-statistic for the 40-gene signature was 0.80 and the Brier score was 0.21.

**Discussion**

In this study, we investigated differentially expressed genes between AA and EA breast cancer patients by using RNA-Seq data from the SCCS and using TCGA data for validation. For the first time, a race-differentiated gene signature was constructed and validated externally to predict breast cancer patient race. Moreover, we performed survival analyses to explore the association between gene expression and overall survival.

In total, we identified 59 genes that showed significant differences in their expression levels between AA and EA breast cancer at an FDR-adjusted P value < 0.01. The results described in our study were quite consistent with previous studies. For example, 19 of 59 differentially expressed genes identified in our study were also differentially expressed at an FDR-adjusted P value of < 0.05 in Huo’s study (4).

Within the 59 race-differentiated genes, we found that several genes play a critical role in the immune system, such as IL20RA, MARCO, BTN3A1, HLA-DPA1 and HLA-DPB1. Some genes

![Hierarchical clustering of 59 genes significantly differentially expressed between AA and EA patients after adjusting for age at diagnosis, PAM50 subtypes, tumor, nodes, and metastases stages, probabilistic estimation of expression residuals factors and batch effects for both the SCCS and TCGA.](image-url)
were related to the prognosis of breast cancer, such as SORD and FAM3A. SORD is a key enzyme in the polyol pathway and plays an important role in the development of diabetic complications (23). SORD is usually used as the measurement of epithelial-to-mesenchymal transition suppression. Polyol pathways represent a molecular link between glucose metabolism and cancer differentiation. The overexpression of SORD may cause poor prognoses of cancer (24). FAM3A belongs to a family of cytokines containing four genes (FAM3A, FAM3B, FAM3C and FAM3D) that are mainly expressed in highly proliferative tissue, and it has been suggested that it plays a core role in cell proliferation, and functions as an activator of the ERK1/2 and p38MAPK signaling pathways (25,26). Interestingly, PWP2 which was more highly expressed in AA and LOC102724159 which was more highly expressed in EA are paralogous genes. Among the genes that were strongly upregulated with overall survival in both the SCCS and TCGA data, SPSB2 regulated protein degradation by acting as adaptors for ubiquitin ligases (27).

Our study focused on the discovery of the biological basis behind the race/ethnic difference between AA and EA breast cancer patients instead of the discovery of specific genes and as the cumulative effect of multiple genes rather than a single gene effect determines cancer phenotypes, a combination of race-differentiated genes may simultaneously contribute to the biological difference of racial disparity in breast cancer. We performed a Gene Ontology (GO) biological processes enrichment analysis with the 59 race-differentiated genes (Supplementary Table 3, available at Carcinogenesis Online) using WebGestalt (28). Forty-three GO terms were enriched at nominal P-value < 0.05 and most of these GO terms focus on endonuclease activity, endodeoxyribonuclease activity and antigen binding (Supplementary Figure 2, available at Carcinogenesis Online). Endonuclease activity may affect the base excision repair (BER) pathway (29), which was reported different between AA and EA (30).

There are two limitations in the present study. First, our RNA-Seq data in the SCCS were generated from FFPE samples, and thus, gene expression in some genes, particularly those with low expression levels, may not be reliably measured due to the processing and storage of FFPE samples (31,32). The second limitation is that only overall survival data were collected in the SCCS.

Conclusion

In this study, we analyzed racial differences in gene expression using RNA-Seq data generated from breast cancer samples included in the SCCS. We identified 59 that were differentially expressed in AA and EA breast cancer samples included in the SCCS. A gene signature constructed using these genes was externally validated using TCGA data yielding a C-statistic of 0.81 and the Brier score of 0.064. These findings provide insight into the biological differences in tumors and the survival disparity between AA and EA breast cancer patients.

Supplementary material

Supplementary data are available at Carcinogenesis online.

Supplementary Figure 1. Calibration plot of the 59-gene signature model with TCGA data to diagnose lack of fit. A calibration curve describes the relationship between predicted values (x-axis) and the truth (y-axis). The solid curve is for the fitted logistic regression model, and the dotted curve is its loess smoother. The diagonal line represents the line of perfect calibration. If the smoother lies close to the diagonal, the model is well calibrated. The smoother shows a slight deviation from the diagonal line. The Brier score of the gene signature was 0.064, indicating high reliability and prediction accuracy of the gene signature to distinguish between AA and EA breast cancer patients.

Supplementary Figure 2. Bar chart for enrichment ratios of 43 GO terms which were enriched at nominal P-value < 0.05 from 59 race-differentiated genes.

Supplementary Table 1. Association of selected genes with overall survival among breast cancer patients

Supplementary Table 2. The set of 40 genes found to be significantly differentially expressed between AA and EA in the Luminal subtype breast cancer patients of SCCS at an FDR-adjusted P value < 0.01.

Supplementary Table 3. Gene Ontology biological processes enrichment results with the 59 race-differentiated genes

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