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*Research Article*

# Genes Associated with Prostate Cancer Are Differentially Expressed in African American and European American Men

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## Abstract

**Background:** Despite more aggressive screening across all demographics and gradual declines in mortality related to prostate cancer (PCa) in the United States, disparities among populations persist. A substantial proportion of African American men (AAM) have a higher overall incidence, earlier age of onset, increased proportion of clinically advanced disease, and increased bone metastases and mortality from PCa compared to European American men (EAM). Limited early evidence indicates that underlying causes for disparities may be observed in tumor-specific gene expression programs.

**Methods:** This study used microarray-based methods to measure expression levels for 517 genes that were previously associated with PCa in archived formalin-fixed paraffin embedded (FFPE) specimens; testing the hypothesis that gene expression features of functional consequence to cancer distinguish PCa from AAM and EAM. A *t* test was conducted comparing AAM to EAM expression levels for each probe on the array.

**Results:** Analysis of 639 tumor samples (270 AAM, 369 EAM) showed that 95 genes were overexpressed specifically in PCa from AAM relative to EAM and 132 were overexpressed in PCa from EAM relative to AAM. Furthermore, systems-level analyses highlight the relevant signaling pathways and functions associated with the EAM- or AAM-specific overexpressed gene sets, for example, inflammation and lipid metabolism.

**Conclusions:** Results here bring further understanding to the potential for molecular differences for PCa in AAM versus EAM.

**Impact:** The results support the notion that therapeutic benefits will be realized when targeted treatments are designed to acknowledge and address a greater spectrum of PCa subtypes and molecular distinctions. *Cancer Epidemiol Biomarkers Prev; 22(5); 891–7. ©2013 AACR.*

## Introduction

The incidence of prostate cancer (PCa) is 60% greater and the mortality rate is 2 to 3 times higher when comparing African American men (AAM) with European American men (EAM; ref. 1). It is likely that multiple factors contribute to these disparities but tumor-specific molecular and genome-based evidence is being increasingly reported. Wallace and colleagues examined known metastasis-promoting genes, including autocrine motility factor receptor, CXCR4, and matrix metalloproteinase 9 (MMP9) using microarray technology and found that these genes were more highly expressed in primary tumors from AAM than in tumors from EAM (2). These genes may be impacted by environmental factors, including diet, obesity, hypertension, and inflammation. and AAM have been reported to have a higher fat content diet (3), are more obese (higher BMI; ref. 4), and have a higher rate of hypertension than EAM (5). The mechanisms associated with obesity and hypertension includes release of inflammatory cytokines, release of reactive oxides and thus oxidative stress, and DNA damage and activation of NFkB. NFkB activates androgen receptor signaling and has been reported to cause PCa cell proliferation (6). In reports of metabolic syndrome EAM have a greater prevalence of Dyslipidemia than AAM that may be associated with PCa progression (7, 8).

Arrayed comparative genomic hybridization was previously used in a relatively small study to identify 27 chromosomal regions that were more commonly altered in AAM or EAM prostate tumors (9). Copy number changes in these 27 regions correlated with gene expression differences (9). More recently, DASL (*c*DNA-mediated *a*nnealing, *s*election, extension, and *l*igation) sample preparation and assay methods for microarray-based

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analysis was developed to analyze the expression of hundreds or thousands of genes in fragmented RNA such as that derived from archived formalin-fixed paraffin-embedded (FFPE) specimens. Sboner and colleagues successfully examined gene expression profiles in FFPE transurethral resections of prostate (TURP) samples utilizing DASL and microarray methods (10). They determined that expression profiles derived from analysis of 6,100 genes from 281 men could be divided into 2 extreme groups: men who died of PCa and men who survived more than 10 years without metastasis.

The utilization of DASL assay methods, microarray scanning technology, and bioinformatic and statistical analyses of gene expression profiles in PCa from AAM and EAM allowed us to examine many genes across a relatively large sample size and understand the quantitative relationships among genes in each group. The results of analyses presented here show PCa-specific differential expression for particular genes comparing AAM or EAM. From subsequent systems-level analyses of differentially expressed genes we infer which signaling pathways are uniquely activated or overlapping in PCa from AAM or EAM. There have been many genes reported to be associated with PCa in general but they may not be directly important for the progression of disease or explain racial disparity. Our analyses and relevant discussion providing a literature-based functional context for our results contribute to a clearer understanding that a single gene acting alone is not responsible for PCa progression, mortality, or racial disparity. Thus, high-throughput methods to measure gene expression in archived specimens, such as DASL assays, and tailored bioinformatic and biostatistical analyses may identify key genes that impact aggressiveness, recurrence, mortality, and disparities. Furthermore, identified sets of genes may lead to development of gene expression signatures or profiles as markers and targets for individualized therapy.

## Materials and Methods

### Patient samples and gene expression analysis

Archived tumor samples from radical prostatectomy (639 FFPE blocks) from the Wayne State University (WSU, Detroit, MI) pathology core dated 1991 to 1996 were included in the study. Total RNA was isolated from FFPE specimens (5–8 10μ sections) at The Applied Genomics Technology Center (AGTC) at WSU using the High Pure RNA Paraffin kit (Roche). RNA quantity and quality were estimated using a NanoDrop 1000 spectrophotometer (Thermo Fisher) and by quantitative real-time reverse transcription (RT)-PCR using an ABI TaqMan assay for RPL13A (ABI). Further sample processing and gene expression profiling using a custom DASL assay were also done at the AGTC. The custom DASL assay was designed in partnership with product specialists and scientists at Illumina and microarrays were scanned using the BeadArray reader (Illumina Inc.). A total of 1,507 probes measured the expression of 517 genes in 639 tumor samples (270 AAM, 369 EAM) and 163 matched normal (control) samples (80 AAM, 83 EAM). The primary analysis to identify biological networks created from genes that are differentially expressed between AAM and EAM is run on the tumor samples, whereas a supplemental descriptive analysis employed to assess the relative importance of tumor status and race on expression uses both the tumor and control samples. Controls tissues were from normal adjacent tissue that had no discernible tumor upon pathology review. Genes were chosen for inclusion in the assay based on existing evidence from the literature and our own data for their importance to PCa, PCa aggressiveness, or cancer in general (see Supplementary Table 1 for a list of genes).

### Bioinformatic and statistical analyses

Data were exported from Illumina's Bead Studio software after conducting the needed quality control checks and uploaded into GeneSpring. The data were then quantile normalized and transformed to median baseline. Log base 2 transformation and quantile normalization was done to the raw probe-level intensity measurements for each assay to ensure that the distributions of intensity values were the same for all patients. A $t$ test using the Satterthwaite approximation of degrees of freedom was then conducted comparing the expression of AAM to EAM for each of the 517 PCa-linked genes represented in the array. Genes that were statistically significant at the 0.05 level were subsequently entered into Ingenuity Pathways Analysis software (Ingenuity Systems) to determine the most significantly enriched functions and pathways among the analyzed genes. A subset of 8 genes in the resulting functional networks and pathways were selected to verify the gene expression differences observed by DASL microarray via real time RT-PCR analysis using an Applied Biosystems 7900HT system and TaqMan probes (Life Technologies Inc.) on a subset of 16 AAM and 16 EAM specimens. The microarray data discussed in this publication have been deposited in NCBI's Gene Expression Omnibus and are accessible through accession number GSE41969 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE41969).

With 270 AAM and 369 EAM samples, the study has 90% power to detect a mean difference in log expression of 0.13 between the groups using a 2-sample $t$ test; assuming a Type I error rate of 0.05 and equal standard deviations of 0.50 for both races. We chose not to adjust for multiple tests because the gene selection component is just the first step for our main objective, which is to identify significant networks. If the analysis was too stringent in the first component, we may have missed the important networks. In some sense, the pathway analysis exercise could be viewed as a "validation" of the original single-gene analyses, used to produce our desired result: pathways of genes with differential gene expression between AAM and EAM. We desired to cast the proverbial "wide-net" to ensure not to miss any interesting networks.

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## Results

A description of the patients who contributed a tumor sample for this study is shown in Table 1, stratified by race. Categorized Gleason's grade was significantly different between the 2 groups ($P = 0.037$), with AAM having a higher prevalence of high Gleason's grade. The groups were defined and stratified as aggressive: Gleason's grades including 7(4 + 3), 8, 9, and 10 versus nonaggressive: Gleason's grade ≤7 (3 + 4). This stratification has been reported to result in different survival outcomes between AAM and EAM (11, 12). There were 227 genes of the 517 measured that were statistically significantly different between the races at the 0.05 level. Among these, 95 were overexpressed in PCa from AAM relative to EAM and 132 were overexpressed in PCa from EAM relative to AAM. Using a linear regression model to allow for the adjustment for covariates (age and Gleason's grade category) did not substantively change the results: 217 of the 227 genes were statistically significant and Kendall's $\iota$ correlation between the 2 sets of *P*-values was 0.914 The 2 sets of genes identified to be significantly more highly expressed in the context of PCa from either AAM or EAM were analyzed using Ingenuity Pathways Analysis software to identify shared and unique signaling pathways that were likely to be activated in each context. The functional interaction network derived from this analysis shows a high degree of inherent, functional interrelatedness for a subset of factors from the analyzed gene expression datasets (Fig. 1). Results suggest that AAM and EAM prostate tumors are distinguished at gene level with NFKB and inflammatory cytokines implicated in PCa from AAM; although a unique set of highly expressed genes in EAM are centered on TNF. However, edges (lines) linking members of both sets to P38MAPK, TNF and PI3K/AKT genes suggests that their associated pathways are operating to some extent in both EAM and AAM contexts. Furthermore, the network suggests multiple modalities that together can reinforce the upregulation and activation of bone morphogenetic protein 2 (BMP2) in tumors from AAM; thus, providing supporting evidence for the notion that tumor epithelial cells or stroma produce the factors that promote metastases. The data presented in the network graph also highlight results that the ETS-related gene (ERG)—a recognized oncogene for PCa—was found to be more highly expressed in PCa from EAM.

Boxplots of the expression of the genes measured by the DASL microarray assay that are represented in the functional interaction network (Fig. 1) are shown in Fig. 2. Individual genes that comprise the PI3K complex are also named. The expression of TNF was not statistically different between the races, but its inclusion in the network generated by Ingenuity Pathways Analysis is a consequence of the fact that TNF is an important hub to both networks of genes that are up- and downregulated in EAM versus AAM. Table 2 reports the mean expression ratio and the *t* test *P*-value of AAM versus EAM for the genes included in the functional network in Fig. 1 and box plots in Fig. 2. Employing real time RT-PCR analysis we proceeded to validate the expression level differences observed by microarray for a select set of key genes or hub genes in a subset of samples distributed evenly among AAM/EAM and aggressive/nonaggressive cases (Supplementary Table 2). The direction of the racial difference in expression as measured by real time RT-PCR resulted in 7 of 8 measured genes (including IL6, ALOX15 ERG, and AKT1) being in the same direction as the odds ratios from Table 2; evidence confirming our initial microarray-based findings.

A principal components analysis (PCA) of the expression of all 517 genes on all tumor and control samples yielded an interesting relationship as shown in Fig. 3. The objective of a PCA is to determine the orthogonal linear transformations of the input data (the gene expression profile in this implementation) such that the first principal component accounts for the most variability and subsequent components account for the most variability in the data given the effect of the preceding components. It is a tool used to investigate patterns of variability in a set of data. After plotting the first 2 principle components and labeling them according to race and tumor status, an interesting relationship emerges. The samples cluster together by tumor/control status and not by race, even though all of the control samples had a matched tumor sample included in the database. A couple of the tumor samples may be considered outliers, particularly on the PC1 scale; however, we determined to keep all of the samples in the analysis presented to better represent the potential patient population. A PCA analysis of only patients with both tumor and control tissue measured yielded a similar relationship (Supplementary Figure 1).

**Table 1.** Descriptive statistics of the samples under study

| Variable | AAM ($n = 270$) | EAM ($n = 369$) | *P*-value |
|---|---|---|---|
| Age | 62.76 (6.35) | 61.74 (6.82) | 0.054 |

| Variable | Levels | AAM ($n = 270$) | EAM ($n = 369$) | *P*-value |
|---|---|---|---|---|
| Gleason's grade | | | | 0.177 |
| | ≤6 | 92 (0.34) | 139 (0.38) | |
| | 7 (3 + 4) | 77 (0.29) | 122 (0.33) | |
| | 7 (4 + 3) | 60 (0.22) | 61 (0.17) | |
| | ≥8 | 41 (0.15) | 47 (0.13) | |
| Gleason's grade categorized | | | | 0.030 |
| | Nonaggressive | 169 (0.63) | 261 (0.71) | |
| | Aggressive | 101 (0.37) | 108 (0.29) | |

NOTE: Age is described as mean and *SD*, whereas the Gleason's grade variables are presented as number of observations and percentage. The *P*-values in the table are a result of a test of the difference between races using a *t*-test for age and a $\chi^2$ test for the Gleason's grade variables.

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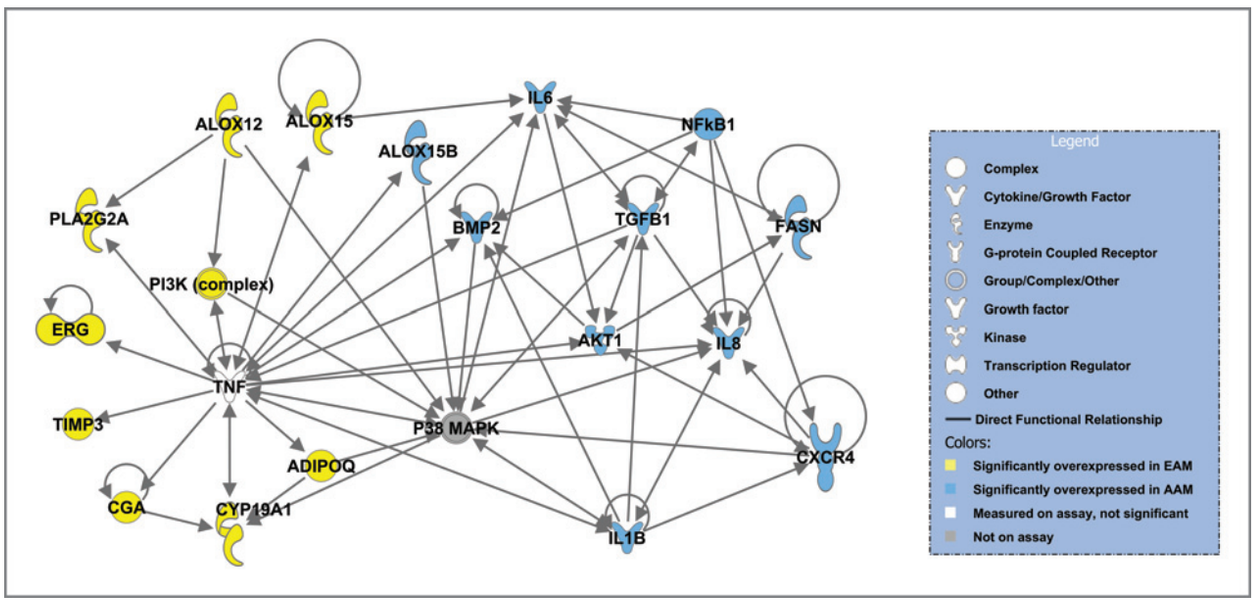


**Figure 1.** Functional Interaction Network from analysis of genes upregulated in prostate tumors from AAM or EAM. The network derived from Ingenuity Pathways analysis shows a high degree of inherent, functional interrelatedness for a subset of factors from the analyzed gene expression datasets (AAM blue, EAM yellow). Results suggest that AAM and EAM prostate tumors are distinguished at gene level with NFKB and inflammatory cytokine factors primarily upregulated in PCa from AAM; EAM-upregulated genes are centered on TNF. Edges (lines) linking members of both sets to P38MAPK, TNF, and PI3K/AKT genes suggests that the associated pathways are operating to some extent in both EAM and AAM contexts.

The samples did not cluster by race when a PCA analysis of only tumor samples was conducted. This implies that the entire dataset of 517 genes, patients are more similar by their tumor/control attribute than by race.

## Discussion

We examined RNA expression of genes already identified to be associated with PCa among men who underwent radical prostatectomy to identify upregulated genes

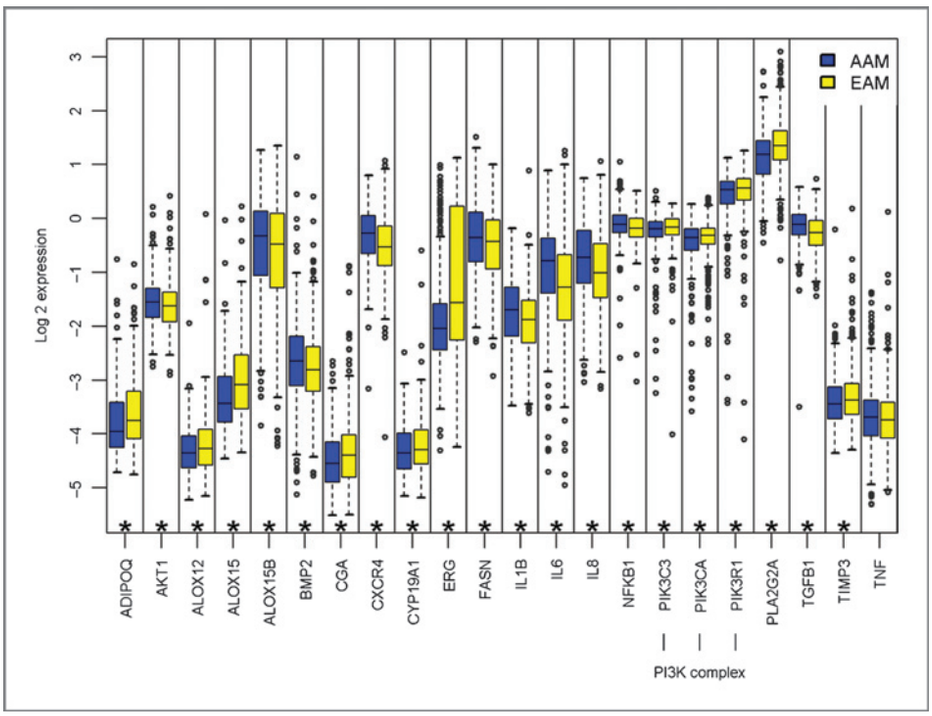


**Figure 2.** Boxplots of the log base 2 expression levels for genes mapped to the functional interaction network. The genes identified in the functional interaction network in Fig. 1 were stratified by race and the individual genes measured by the DASL assay identified as the PI3K complex genes are named. The stars at the bottom of the graph indicate statistically significant differences between races. As TNF is a central hub in the network, it is included in the graph even though it is not statistically significant.

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**Table 2.** Mean expression ratio of EAM as compared to AAM for the functionally linked genes from the network in Fig. 1

| Gene | Mean EAM relative to AAM expression | *P*-value |
|---|---|---|
| ADIPOQ | 1.12 | 0.002 |
| AKT1 | 0.94 | 0.026 |
| ALOX12 | 1.09 | 0.003 |
| ALOX15 | 1.24 | <0.001 |
| ALOX15B | 0.88 | 0.022 |
| BMP2 | 0.91 | 0.030 |
| CGA | 1.12 | 0.001 |
| CXCR4 | 0.87 | <0.001 |
| CYP19A1 | 1.06 | 0.029 |
| ERG | 1.62 | <0.001 |
| FASN | 0.90 | 0.009 |
| IL1B | 0.89 | 0.001 |
| IL6 | 0.78 | <0.001 |
| IL8 | 0.84 | <0.001 |
| NFKB1 | 0.96 | 0.048 |
| PIK3C3 | 1.05 | 0.033 |
| PIK3CA | 1.08 | 0.004 |
| PIK3R1 | 1.07 | 0.018 |
| PLA2G2A | 1.16 | <0.001 |
| TGFB1 | 0.91 | <0.001 |
| TIMP3 | 1.07 | 0.017 |
| TNF | 0.97 | 0.445 |

NOTE: The *t* test *P*-value testing the difference in expression between races is included in the table. Individual genes measured on the assay that were associated with the PI3K complex are named in the table.

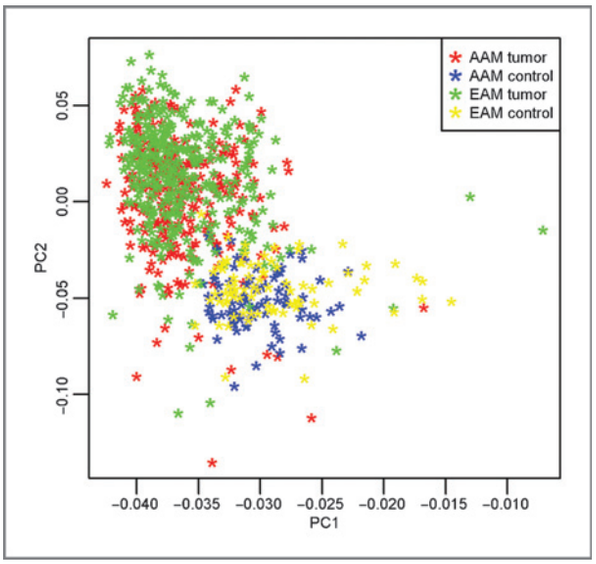


Figure 3. Plot of the first 2 principal components, computed from all 517 genes on 639 tumor samples (270 AAM, 369 EAM) and 165 control samples (82 AAM, 83 EAM). Although all of the control samples had a matching tumor sample and thus are expected to be highly correlated with the respective tumor sample, the samples clustered by tumor/control status, regardless of race. This implies that the expression profile of the tumor samples is similar across races and different than the profile of the control samples, which are also similar across races.

and associated functional gene networks and signaling pathways that may contribute to PCa progression in a racially diverse population. We used bioinformatic and statistical approaches to arrive at differentially expressed genes comparing PCa from AAM and EAM. Ingenuity Pathways Analysis software, which draws on an extensive curated knowledge-base was used to examine the interaction of genes and to identify key genes, or hub genes, in signaling pathways and networks comprising the significantly overexpressed genes in PCa from AAM or EAM. Hub genes are those that interact with several nodes or satellite genes; in addition, the hub genes we discovered from network analyses are known to functionally interact with each other, for example, NFKB, BMP2, TNF, and PI3K.

The analyses and results herein, by nature of the discovered genes and their known functions, suggest how a patient's diet and lifestyle intersect with gene expression and tumor progression. IL6, IL8, IL1B, CXCR4, and FASN show significantly higher expression levels in PCa from AAM, whereas ALOX15 is more highly expressed in aggressive PCa from EAM. The increased expression of FASN in PCa specimens from AAM may be a very important factor to explain the disproportionate mortality among AAM compared to EAM. Nguyen and colleagues report that *FASN* germline polymorphisms are significantly associated with risk of lethal PCa. Significant interactions of BMI with *FASN* polymorphisms and FASN tumor expression suggest FASN is a potential link between obesity and poor PCa outcome and raise the possibility that FASN inhibition could reduce PCa-specific mortality, particularly in overweight men (13). IL6, IL8, and IL1B are inflammatory cytokines linked to PCa (14, 15), whereas ALOX15 is associated with lipid metabolism and PCa (16). The differential expression of these genes are consistent with presentation of metabolic syndrome in that inflammatory cytokines are associated with hypertension and obesity, both of which are more prevalent among AAM compared to EAM; moreover, dyslipidemia is more prevalent among EAM than AAM (7). Yet evidence points to an overlap for inflammatory and lipid metabolism pathways, the functional interaction network in Fig. 1 maps empirical evidence that ALOX15 interacts with and regulates IL6 function (16). Thus, from the analyses reported here IL6 seems to be of particular importance in PCa for men of African descent, and possibly European descent as well.

It is previously reported that high levels of IL6 correlate significantly with higher PCa Gleason scores and that IL6 signaling impacts androgen receptor signaling through mediators STAT3, MAPK kinase, and PI-3 kinase/Akt pathways (15, 17, 18). Also, according to our results Akt

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expression is significantly increased in PCa from AAM. Increased AKT function can alternatively upregulate androgen receptor signaling indirectly via activation of NFkB (19, 20). The PI3 kinase/Akt pathway is a very important pathway in PCa and is involved in many pathway cross-talk interactions. PI3 kinase/Akt is upregulated with insulin resistance and hyperinsulinemia in diabetic and obese men (21). AKT is phosphorylated by angiotensin II signaling and thus activated in hypertensive men, and AAM have a higher prevalence of hypertension than EAM (22). Thus, results here show higher expression of AKT in PCa from AAM and support a prediction that prostate tumor AKT signaling is highest among hypertensive AAM.

Results showing the upregulation of BMP2 and CXCR4 in tumors from AAM suggest how tumors and tumor stroma may support metastases in these patients. Literature supports a role for BMP2 in PCa bone metastases (23); and CXCR4 is a chemokine receptor shown to be a key regulator of metastasis of PCa cells (24). Furthermore, CXCR4 overexpression is associated with aggressive and therapy-resistant disease in patients and CXCR4 is reported to be more highly expressed among AAM than EAM (2). In contrast, results of our study showed increased ERG expression in tumors from EAM versus AAM. ERG plays a role in metastasis by overexpression of osteopontin, which is an extracellular matrix glycophosphoprotein that plays a crucial role in tissue remodeling, inflammation, tumor growth, angiogenesis, and metastasis (25). The gene-level result from the current analysis coincides with results from a recently published study that detected ERG protein, where ERG-positive prostate tumors were significantly greater in EAM compared to AAM (26).

The outcomes of this work support the conclusion that differential gene expression and inferred biological pathway activation point to molecular differences underlying PCa in AAM and PCa in EAM. Functional pathways that seem to be predominantly functioning in either AAM, that is signaling linked to inflammatory cytokines, or EAM, that is signaling associated with ALOX15 and ERG, are known to activate androgen receptor signaling and bone metastasis and may contribute greatly to PCa outcomes disparities. In addition, these data suggest an opportunity for different biologic markers and targeted therapy options for AAM and EAM.

## Disclosure of Potential Conflicts of Interest

R.B. Everson is employed (other than primary affiliation; e.g., consulting) as a Deputy Director for Cancer Prevention and Control in the University of Connecticut Health Center. C.N. Giroux is employed as a Health Science Administrator/ Scientific Review Officer in NIH. No potential conflicts of interest were disclosed by the other authors.

## Authors' Contributions

**Conception and design:** I.J. Powell, C.H. Bock, R.B. Everson, C.N. Giroux, A.G. Schwartz
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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** I.J. Powell, S. Land, J. Ruterbusch, M. Herawi, R.B. Everson, A.G. Schwartz
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** I.J. Powell, G. Dyson, S. Lenk, C.N. Giroux, A. Bollig-Fischer
**Writing, review, and/or revision of the manuscript:** G. Dyson, C. H. Bock, S. Lenk, R.B. Everson, C.N. Giroux, A.G. Schwartz, A. Bollig-Fischer
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** I.J. Powell, G. Dyson, J. Ruterbusch, R. B Everson, A. Bollig-Fischer
**Study supervision:** I.J. Powell, R.B. Everson, A.G. Schwartz

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