RESEARCH

Androgen metabolism genes in prostate cancer health disparities

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ABSTRACT

For men in the United States, prostate cancer is common, and newly diagnosed cases of prostate cancer outnumber those of all other cancer types. For prostate cancer, there are racial disparities between Caucasian Americans and African Americans. Androgens and androgen metabolism may be involved in these disparities as well as in the initiation and progression of prostate cancer. Here, we analyzed, in the Cancer Genome Atlas (TCGA) database, the mRNA expression of genes involved in androgen metabolism in prostate cancer based on the patient's race. The results revealed that expressions of *UGT2B15* and *CYP3A5* are higher but that *SRD5A2*, *CYP17A1*, *HSD3B2*, and *AKR1C3* are lower in African American prostate cancers than in those of Caucasian Americans. These genes may relate to the racial disparities associated with prostate cancer. However, the evidence require validation and functional analysis.

KEYWORDS: prostate cancer; racial disparity; androgen; metabolism; gene expression

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INTRODUCTION

According to the latest statistics provided by the American Cancer Society (ACS), there are 161,360 incident cases newly diagnosed with prostate cancer, accounting for 19% of all new cancer cases in 2017 and, for males, leading all other cancers (Siegel et al., 2017). The incidence varies with race. The rate for African American (AA) men is 198.4/100,000, higher than 114.8/100,000 for Caucasian American (CA) men. Although the racial disparities in prostate cancer are related to lifestyle, dietary, socioeconomic, and clinical factors, genetic factors are also substantial (Chang et al., 2014; Cooper and Page, 2014; Plata Bello and Concepcion Masip, 2014; Schaid, 2004; Singh et al., 2017). For most prostate cancers, which are generally androgen-sensitive, androgen withdrawal can produce initial regressions (Cooper and Page, 2014). Lower levels of intraprostatic androgens are associated with a lower incidence of prostate cancer (Cooper and Page, 2014). Androgen deprivation therapy, a common treatment, can block progression of metastatic prostate cancer (Welsh and Hentz, 2017; Yang et al., 2017; Young et al., 2017). Further, differences in androgen metabolism may relate to the racial disparities in this disease (Singh et al., 2017). Thus, for prostate cancer, androgen metabolism may be involved in racial disparities as well as in tumor imitation and progression.

For CA and AA men in the United States, there are differences in androgen levels. Serum testosterone levels of AA men (aged 31 to 50) are about 15% higher than those of CA men (Ellis and Nyborg, 1992; Singh et al., 2017). In prostate tissues of AA men, androgens, androstenedione, and sex hormone-binding globulin levels are greater than those in tissues of CA men (Singh et al., 2017). Likewise, for AA men, expression of the androgen receptor (AR) protein is 22% higher in benign prostate tissue and 81% higher in prostate cancer tissue relative to CA men (Gaston et al., 2003). These differences may contribute to racial disparities for prostate cancer. Other factors, such as age, body mass index, prostate specific antigen, and pathologic Gleason grade, may be involved in these disparities (Plata Bello and Concepcion Masip, 2014; Schaid, 2004). However, whether genes involved in androgen metabolism are primary factors for these racial disparities is not known. Therefore, with the Cancer Genome Atlas (TCGA) database, we conducted an expression analysis of genes involved in androgen metabolism in prostate cancer based on the patient's race. From the findings, we have presented a potential mechanism underlying androgen metabolism in racial disparities for prostate cancer.

RESULTS AND DISCUSSION

We analyzed the mRNA expression of 20 genes involved in androgen metabolism, including *AKR1C2*, *AKR1C3*, *CYP3A4*, *CYP3A5*, *CYP7B1*, *CYP11A1*, *CYP17A1*, *CYP19A1*, *HSD3B1*, *HSD3B2*, *HSD17B3*, *HSD17B6*, *HSD17B10*, *RDH5*, *RDH16*, *SRD5A1*, *SRD5A2*, *SRD5A3*, *UGT2B7*, and *UGT2B15*, by use of a web-portal UALCAN tool (Chandrashekar et al., 2017) for analyses of TCGA gene expression data in 52 normal prostate tissues, 147 CA prostate cancer tissues, and 6 AA prostate cancer tissues. For AA tissues, there were significantly higher expressions of 5 genes, including *HSD3B2* (cancer/normal fold change = 1.11; $p = 4.31 \times 10^{-2}$), *HSD17B3* (fold change = 3.22; $p = 1.11 \times 10^{-16}$), *HSD17B10* (fold change = 1.27; $p = 1.79 \times 10^{-12}$), *SRD5A1* (fold change = 1.27; $p = 4.02 \times 10^{-5}$), and *SRD5A3* (fold change = 1.14; $p = 2.58 \times 10^{-3}$), but significantly lower expressions of 9 genes, including *AKR1C2* (fold change = 0.32; $p = 9.42 \times 10^{-3}$), *CYP3A5* (fold change = 0.14; $p = 1.32 \times 10^{-3}$), *CYP11A1* (fold change = 0.21; $p = 3.85 \times 10^{-8}$), *CYP19A1* (fold change = 0.27; $p = 4.32 \times 10^{-2}$), *CYP7B1* (fold change = 0.52; $p = 2.20 \times 10^{-4}$), *HSD17B6* (fold change = 0.59; $p = 6.56 \times 10^{-4}$), *RDH5* (fold change = 0.50; $p = 5.76 \times 10^{-5}$), *SRD5A2* (fold change = 0.23; $p = 5.73 \times 10^{-10}$), and *UGT2B7* (fold change = 0.00; $p = 1.83 \times 10^{-2}$). Of note, expressions of *AKR1C3*, *CYP3A5*, *CYP17A1*,

HSD3B2, *SRD5A2*, and *UGT2B15* showed significant differences in prostate cancer tissues between CA men and AA men (Figure 1). Expressions of *CYP3A5* (fold change = 1.38; p = $4.32x10^{-2}$) and *UGT2B15* (fold change = 1.87; p = $4.32x10^{-2}$) in AA prostate cancers were higher than those for CA prostate cancers, but expressions of *AKR1C3* (fold change = 0.58; p = $4.32x10^{-2}$), *CYP17A1* (fold change = 0.50; p = $4.32x10^{-2}$), *HSD3B2* (fold change = 0.77; p = $4.32x10^{-2}$), and *SRD5A2* (fold change = 0.71; p = $4.32x10^{-2}$) were lower in AA prostate cancers than in CA prostate cancers (Figure 1).

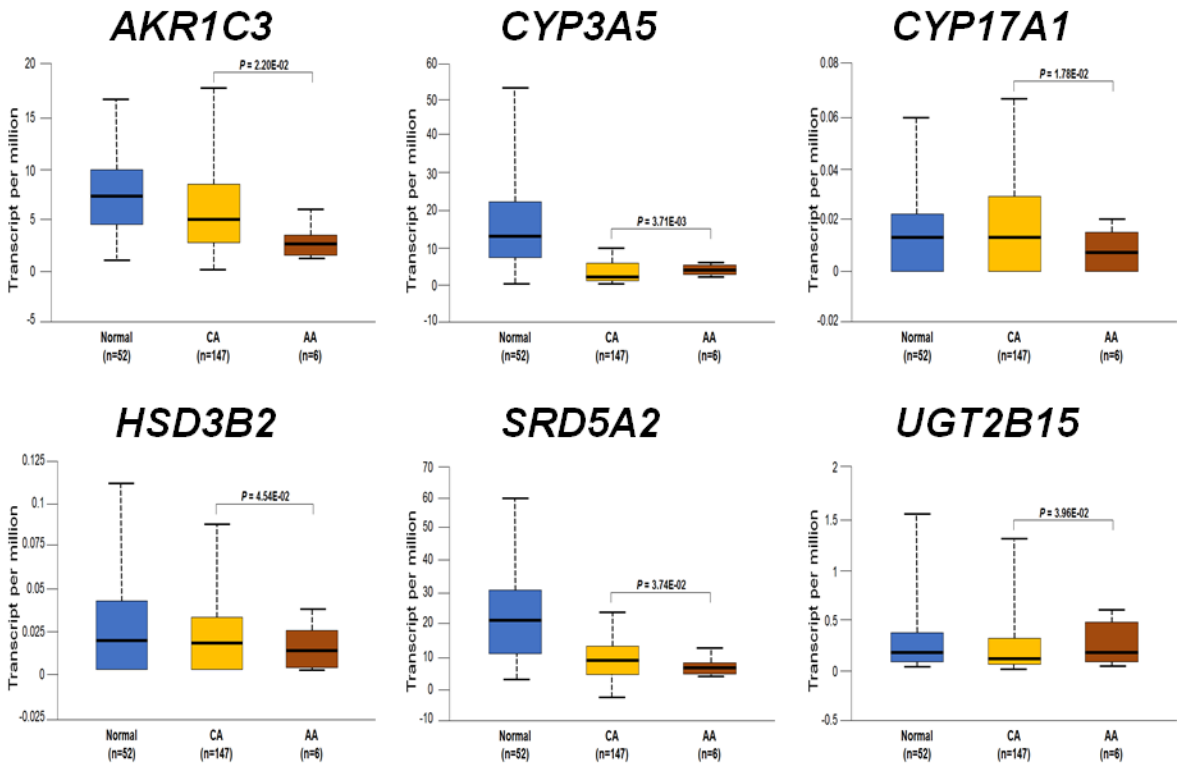

Figure 1. mRNA expression of genes involved in androgen metabolism in normal prostate tissues and prostate cancers based on the race of patients as determined with the TCGA database. CA, Caucasian American; AA, African American.

AKR1C3 is associated with a reduction of androstenedione and lower (Mostaghel and Nelson, 2008) production of testosterone and dihydrotestosterone (DHT) (Yepuru et al., 2013). Higher expression of *AKR1C3* enhances survival of prostate cancer cells and formation of endothelial cell tubes, and is positively correlated with a higher Gleason score (Dozmorov et al., 2010). However, there were lower expressions of *AKR1C3* in AA prostate cancers than in CA prostate cancers, which suggests a contradictory function of *AKR1C3* in racial disparities between AA and CA men.

CYP3A5, which is involved in hydroxylation of testosterone and dehydroepiandrosterone (Zeigler-Johnson et al., 2013), enhances growth of prostate cancer cells through facilitating the nuclear translocation of AR (Mitra and Goodman, 2015). The higher expression *CYP3A5* in AA men may be associated with higher AR levels and a higher risk of prostate cancer (Singh et al., 2017). As shown here, there were higher expression levels

of *CYP3A5* in AA prostate cancers compared with CA prostate cancers, supporting the previous observation and hypothesis.

In the gonads and adrenals, CYP17A1 is involved in various pathways of androgen biosynthesis (Bremmer et al., 2014). Although greater expression of *CYP17A1* appears to correlate with higher stages and shorter relapse-free times in prostate cancer (Bremmer et al., 2014; Gomez et al., 2015; Salvi et al., 2016), expression of the *CYP17A1* gene was lower in primary prostate cancers than in normal prostate tissue and was lower in AA prostate cancers than in CA prostate cancers. Although, for AA men, a dysfunction of *CYP17A1* may affect the susceptibility to prostate cancer, the present data do not support the concept that *CYP17A1* is a regulator for racial disparities between AA men and CA men.

HSD3B2 is involved in catalyzing androstendione and DHT metabolites (Simard et al., 1996). Higher expression of *HSD3B2* accelerates the degradation of DHT metabolites and leads to lower DHT levels (Simard et al., 1996). However, the relationship between high DHT levels and prostate cancer risk is controversial. For CA men and AA men, there are no significant differences in DHT levels in sera and tissues (Singh et al., 2017). The present data also showed higher expression of *HSD3B2* in AA prostate cancers compared with CA prostate cancers, results that are inconsistent with racial disparities between AA and CA men.

SRD5A2 is responsible for the conversion of testosterone into DHT (Fang et al., 2017). Genetic analyses suggest that there are *SRD5A2* TA repeat alleles in AA men at high risk for prostate cancer but not in CA men (Singh et al., 2017), indicating that genetic variants of *SRD5A2* may be associated with racial disparities. Variants of the enzyme may enhance the activity and result in higher levels of DHT, leading to cancer progression. However, higher expression of *SRD5A2* appears to be inconsistent with higher levels of DHT (Singh et al., 2017). The present data showed that expression of *SRD5A2* was lower in AA prostate cancers compared with those of CAs, which does not support a role of *SRD5A2* in the racial disparities between AA men and CA men.

In the androgen biosynthesis pathway, *UGT2B15* is a regulator for androstenedione glucuronidate (Gauthier-Landry et al., 2015). High androstenedione levels may require more glucuronosyltransferases encoded by *UGT2B15* (Singh et al., 2017). Of note, there are higher androstenedione levels in normal prostate tissues and greater expression of *UGT2B15* in AA prostate cancers than in those of CAs (Singh et al., 2017). As shown here, there was higher expression of *UGT2B15* in AA prostate cancers compared with CA prostate cancers, supporting a function of *UGT2B15* in racial disparities of prostate cancers.

Since prostate cancer is a pathophysiologic disease involving a variety of genetic factors (Chang et al., 2014; Cooper and Page, 2014), the change of a single gene may be insufficient to produce racial disparities. Further, the functions of genes in racial disparities in prostate cancer are associated with mRNA and protein expression. Moreover, the AA cohort of prostate cancers in this TCGA database includes only six cases, which limits the statistical power to detect significant differences in our analysis. Therefore, a larger sample cohort is needed to establish the relationship between the genes and racial disparities in prostate cancer.

In summary, in the United States, the incidences of prostate cancer are different for CA and AA men. Genes, such as *CYP3A5* and *UGT2B15*, which are involved in androgen metabolism, appear to be associated with racial disparities between AA and CA prostate cancers. Due to a limitation of sample size, however, the results need to be validated in further studies.

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Conflict of interest statement

The author has declared that no competing or conflict of interests exist. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

WL performed the analyses. RL and LW wrote the manuscript.

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