

Detection of Androgen Receptor Gene Polymorphism in Sudanese Patients of Prostate Cancer in Khartoum State

Abstract:

Background: Prostate cancer (PCa) is the most commonly diagnosed solid tumor among men. Genetic susceptibility had been proposed among the risk factors for the development of this cancer.

Aim: To investigate the effect of androgen receptor gene polymorphism in the susceptibility of prostate cancer among Sudanese patients.

Methods: This study was conducted in Khartoum State during the period from January 2019 to January 2021. The study population was selected as one hundred patients of prostate cancer who attended for routine follow-up of chemotherapy treatment. A total of 5 ml EDTA anti-coagulated venous blood samples were obtained from all participants. Prostate specific antigen (PSA) was measured by competitive chemiluminescence immunoassay. DNA extraction was performed for all samples by chemical method and genotyping was performed by PCR-RFLP method using *Eco147I* enzyme.

Results: The Androgen receptor genotype showed that wild (G/G) type was more frequent (89%) than heterozygous (G/A) type (11%), and allele G was more frequent (94.5%) than allele A (5.5%). The mean PSA level among prostate cancer patients was 18.71 ± 31.68 ng/ml. Comparison of the mean PSA levels

between different AR genotypes revealed no significant association between the genotype and the hormonal level (p . values > 0.05).

Conclusion: Androgen receptor gene polymorphism was detected in this study population as heterozygous type. Moreover; there was no significant association between AR genotype and serum PSA level.

Keywords: Androgen receptor (AR), Prostate cancer (PCa), PSA-Sudan

Introduction:

Prostate cancer is a major public health problem worldwide. Prostate cancer is estimated to be a major cancer of men in several sub-Saharan African countries, and African-Americans have higher rates of prostate cancer incidence and mortality compared to men of other ancestries, particularly in the younger age groups (Ahmed et al., 2017; Brawley, 1998; Delongchamps et al., 2007). Mortality rate is generally high in black population (Ahmed et al., 2017). Despite this, no published data are currently available for prostate cancer in the Sudan, and prostate cancer is not included in the major cancer series from Central Sudanese hospitals. This is most probably the consequence of multiple combined factors, including little attention to prostate cancer screening, lack of diagnostic facilities, scarce disease awareness, comparatively low life expectancy and young population structure. Yet, prostate cancer is considered the second among cancers in Sudan, with a high mortality rate (Ahmed et al., 2017).

The androgen receptor (AR) (NR3C4, nuclear receptor subfamily 3, group C, gene 4) belongs to the steroid hormone group of nuclear receptors with the estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptor (PR) and mineralocorticoid receptor (MR)(Nuclear Receptors Nomenclature Committee, 1999; Mangelsdorf et al., 1995; Tsai et al., 1994). The AR is a ligand-dependent transcription factor that controls the expression of specific genes. The binding of

the AR to its native ligands 5 α -dihydrotestosterone (DHT) and testosterone initiates male sexual development and differentiation.

Mutation of AR, especially mutations that result in a relaxation of AR ligand specificity, may contribute to the progression of prostate cancer and the failure of endocrine therapy by allowing AR transcriptional activation in response to antiandrogens or other endogenous hormones. Similarly, alterations in the relative expression of AR co-regulators have been found to occur with prostate cancer progression and may contribute to differences in AR ligand specificity or transcriptional activity. Prostate cancer progression is also associated with increased growth factor production and an altered response to growth factors by prostate cancer cells. The kinase signal transduction cascades initiated by mitogenic growth factors modulate the transcriptional activity of AR and the interaction between AR and AR coactivators. The inhibition of AR activity through mechanisms in addition to androgen ablation, such as modulation of signal transduction pathways, may delay prostate cancer progression (Heinlein and Chang, 2004).

The aim of the current study is to illustrate the etiological role of AR polymorphism in prostate cancer among Sudanese subjects.

Material and methods:

This study was done in Khartoum state during the period from January 2018 to January 2021. The study was approved by the research committee at the faculty of Medicine, El imam Elmahdi university. Informed consent were taken from each subject before enrollment in the study. A total of One hundred prostate cancer patients were included in this study. Patients had other form of malignancies were excluded. Venous blood (5 ml) were collected in EDTA tubes from all participants. Prostate specific antigen (PSA) were measured by competitive chemiluminescence

immunoassay. The remain of blood samples were kept at liquid nitrogen (AT - 20°C) until used for genotyping.

DNA was extracted by chemical method. Genotyping was performed by PCR-RFLP method using *Eco147I* enzyme at 37°C. PCR & digestion product were visualized on 1.5% agarose electrophoresis.

Data was analyzed by statistical package for social science (SPSS), version 16. Qualitative data was presented as mean and SD.

Results:

The Androgen receptor genotype showed that wild (G/G) type was more frequent (89%) than heterozygous (G/A) type (11%), and allele G (94.5%) was more frequent than allele A (5.5%).

Table 1: Distribution of Androgen receptor polymorphisms among prostate cancer patients

Genotype		Patient N(%)
Androgen receptor	G/G	89(89.0)
	G/A	11(11.0)
	allele G	189(94.5)
	allele A	11(5.5)

PSA assay revealed that, the mean value among prostate cancer patients was 18.71 ± 31.68 ng/ml. Comparison of the mean PSA levels between different AR genotypes revealed no significant association between the genotype and the hormonal level (p . values > 0.05) (Table 2).

Table 2: Comparison between hormonal parameters and Androgen receptor genotypes among prostate cancer patients

AR Genotype	PSA ng/ml (Mean \pm SD)	P-value
G/G	18.22 \pm 31.66	0.664
G/A	22.65 \pm 33.14	

Discussion:

Prostate cancer is the most common cancer in Sudanese men. Despite the substantial public health impact of prostate cancer little is known about its etiology. Risk factors for the development of prostate cancer are advanced age, familial predisposition and potentially ethnicity. The aim of this study was to explore the etiological role of AR polymorphism in prostate cancer among Sudanese subjects.

In the present study, the AR genotyping showed that wild (G/G) type was more frequent than heterozygous (G/A), and the G allele was more frequent than A allele. These figures differ from what had been observed in the study done by Andrea Gsur, *et al*, 2002, in which the AR (G/A) genotype was more frequent (40.0 %) followed by (A/A) type (30.5 %) and (G/G) type was 29.5% .

In the current study the mean results of PSA level is significantly increased in patients compared to control group (*p*. values = 0.000). This corresponding to study done by Andrea Gsur, *et al*. 2002, which showed statistically significant elevation of mean serum PSA levels in prostate cancer (30.8 ng/ml) when compared to control group (4.7 ng/ml) (*p*. value = 0.001).

Similarly, another study conducted in Omdurman and Soba teaching hospitals in Khartoum-Sudan by Akram H. Awadalla *et al*, 2012. Results showed significant elevation of mean PSA level in cases (23.04 \pm 32.26) ng/ml when compared with control group (1.23 \pm 0.89) ng/ml (*p*. value = 0.000) and could be used as useful

prognostic and screening markers for prostate cancer. Also agree with a study done by Zhiang Zhao 2010, who were found a significance difference in the mean of serum level of prostate specific antigen at cutoff of value 4ng/ml between the patients group (2.07 ± 1.12) and control group (0.88 ± 0.46) ng/ml ($P = 0.014$).

In another study done by Haala M. Gabra, *et al*, 2014, serum total PSA (42.6 ± 27.2 ng/ml) in the prostate cancer group was found to be higher than that in Benign prostatic hyperplasia group (7.8 ± 5.1 ng/ml) (p . value < 0.05).

Finally; in the current study, no statistically significant association between PSA level and AR genotype. This is in line with the study done by Andrea Gsur, *et al*. 2002, which showed no significant association between the PSA level with the AR genotype as the mean PSA level among patients with A/A genotype was (4.6 ng/ml) compared to patients with G/A genotype (4.7 ng/ml) and G/G genotype (4.8 ng/ml) with (p . value = 0.98).

Conclusion:

Androgen receptor gene polymorphism was detected in this study population as heterozygous type. Moreover; there was no significant association between AR genotype and serum PSA level.

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