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The Molecular Mechanisms Underlying Prostate Cancer, and the Incidence in Africa

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Abstract

Prostate cancer is the most frequently diagnosed cancer in men and the second leading cause of male death due to cancer in the developed countries. Studies have shown that initiation, development and metastasis of cancers are based on varieties of factors ranging from genetic conditions in which there are mutations in genes that control cell cycle and apoptosis, to production of aberrant proteins that are involved in cell signal transduction cascades and distorted functions due to gene mutation. The initiation of prostate cancer is due to mutation in genes that code for DNA repair enzymes leadingto the accumulation of DNA replication errors and onset of carcinogenesis and defective prostate metastasis. Understanding the key players in prostate cancer would provide insight into devising novel diagnostic and therapeutic approaches. The incidence of prostate cancer shows substantial global and regional/ racial variation, and among the African countries, incidence varied from East with highest incidence through south with intermediate and the West African region with least incidence rates. Difference in access to health care facilities, registry quality including completeness of case ascertainment and estimates of population at risk, screening practices, as well as lifestyle factors within the population among other factors are likely to be responsible for the observed variations.

Introduction

Prostate cancer is the most commonly occurring cancer, and the major cause of death due to cancer in men around the world (Attard*et al*., 2016: Mohler*et al.,* 2019). Results of the prostate

specific antigen (PSA) screening has shown that incidence of cancer varies from one country to another and is responsible for death rate 1-2% in men, and highest prevalence in the western worlds due to lifestyle (Schulz, *et al.*, 2003: Attard, *et al*., 2016). Cancer is a disease based on genetic alterations that leads to inactivation of tumor repressor genes and the activation of oncogenes. Cancer cells show a number of unique properties such as increased growth rate, loss of ability to differentiate, and the capacity to escape apoptosis and senescence which differentiate it from normal counterparts (Trapman, 2001). The differences between cancerous and normal cells are the reflection of genetic instability characterized by chromosomal aberrations such as chromosomal deletions, amplification and translocation seen in cancer cells, and most importantly mutation in some specific genes that are involved in cell cycle (Trapman, 2001). Manifestation of most cancers takes time due to the fact that, it is a result of progressive and cumulative alteration in various genes leading to some overlap of control in the cell cycle (Karayi& Markham, 2004). Development of most cancers are due to dominant function of oncogenes and recessive tumor suppressor genes (TSGs) (Schulz, *et al*., 2003), also, studies have shown that mutation in the genes encoding DNA repair enzymes can result in the accumulation of DNA replication errors leading to increased rate of cancer development (Schulz, *et al*, 2003): Karayi& Markham, 2004 & Zhang *et al*., 2017).

Studies of prostate cancer show the genetic causes of prostate cancer has not follow a standard scheme since Linkage analyses shows many chromosomal loci such as 1q24-1q25 (HPC1, 1q42-q43 (PCAP), Xq27-q28 (HPCX), 1q36 (CABP), 20q13 (HPC20), 17p11 (ELAC2) and 16q23, may harbor prostate cancer susceptible genes however, none of the loci have been fully verified, none of these genes has remained consistent in different prostate carcinoma population which confirms that there is a tremendous heterogeneity in prostate cancer predisposing factors (Schulz, *et al*., 2003: Kati and Tapio, 2004). In recent development however, comprehensive genomic profiling have identified the androgen receptor (AR) signaling pathway, the P13K pathway, the Ras/Raf/MEK/ERK pathways and the retinoblastoma protein (pRB) signaling pathway as the four major signaling pathways that are mostly altered in prostate cancer (Bakin*et al*., 2003: Pearson *et al*., 2009: Georgi*et al*., 2014: Lang *et al*., 2017). According to Aggarwal*et al*., (2019), mutation of p53 gene is highly implicated in the initiation, progression and metastasis of prostate cancer. It is eminent that understanding the mechanism of cancer development at the molecular level will provide means of designing novel tools for diagnosis,

prognosis and treatment and to some degree, provide preventive guide to the disease (Kati and Tapio, 2004).

In this review, the roles of mutant Androgen receptor (AR),Ras, NF-kB, BCL2, and P53 in cellular signaling pathways that brings about prostate cancer initiation, promotion, progression and metastasis are highlighted.

Nature of the Prostate gland

During fetal development, testosterone stimulates budding of the prostate epithelium from the urogenital sinus which subsequently produce growth factors like sonic hedgehog to activate the underlying mesenchyme (Schulz, *et al*., 2003). During the developmental stages there is increasing expression of androgen receptors (AR) and at maturation, androgen receptors appears in the secretory layer (schulz, *et al*., 2003).

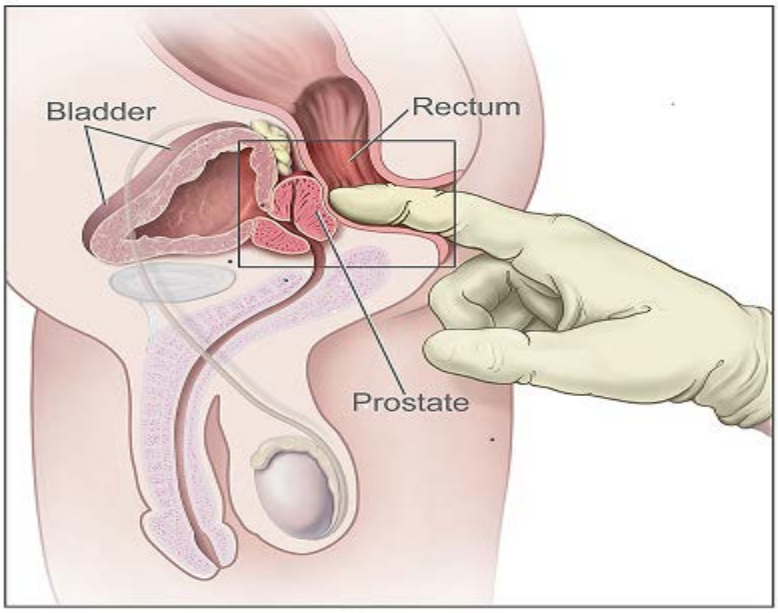

Figure 1 showing the position of the prostate gland. Source; e-medicine health.

Normal prostate gland in adult comprises of two glandular epithelial and fibromuscularstroma regions, which gradually renew itself in response to wearing and tearing (normal cell turn over), the glandular region is composed of large peripheral and small central zones which together made up to 95% of the gland (Schulz, *et al*., 2003). Most prostate cancers start from the peripheral zone and retain a glandular structure, classified as adenocarcinoma (Trapman, 2001).

Prostate cancer must be differentiated from benign prostate hyperplasia (BPH), which develop mainly from the peri-urethral stroma and glands of the transition zone. The earlier marker that best indicate prostate cancer is the prostatic intraepithelial neoplasia (PIN), revealed by histological studies, other markers includes androgen receptors (AR) and prostate specific antigen (PSA) (Schulz *et al*., 2003).

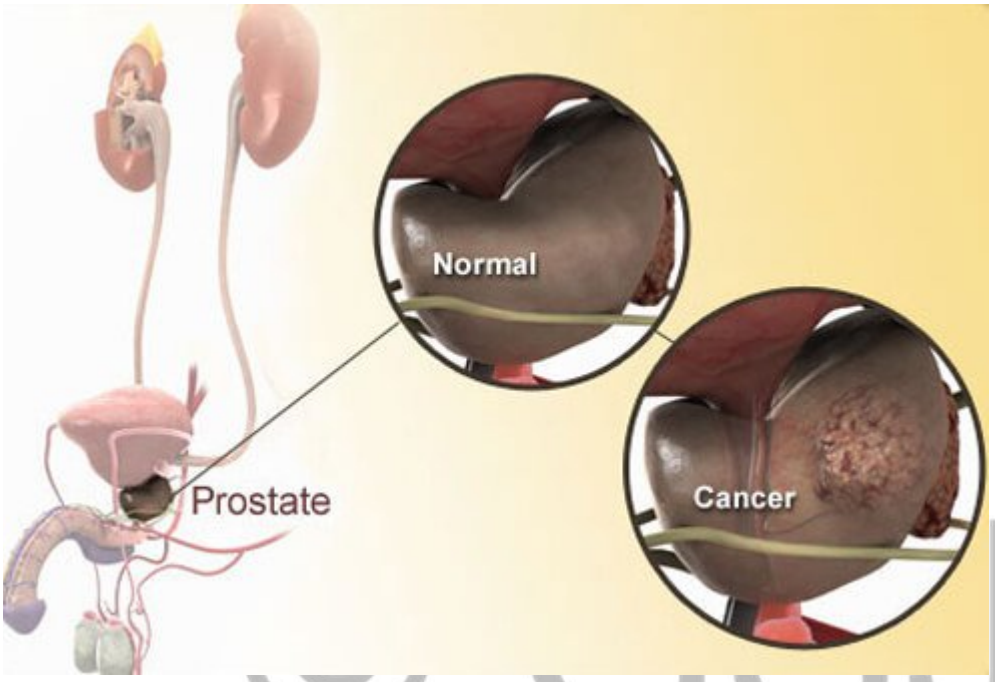

Figure 2 Picture of a normal and cancerous prostate; Source; e-medicine health.

While many prostate cancers maintain a very slow growth rate, about a third become locally invasive, spreading beyond their zones, or proliferating to local lymph nodes and different organs such as bones and liver (Schulz *et al*., 2003). About 60-70% of prostatic cancers occur in the peripheral zone, 10-20% in the transition zone and 4-10% of the cancer originate from central zone.

The initiation of prostate cancer proceeds unnoticed due to the fact that mutation in genes that code for DNA repair enzymes can result in the accumulation of DNA replication errors leading to the silent onset of carcinogenesis and defective prostate metastasis, suppressor genes increase the metastatic potentials of prostate cancer as it develop (Karayi& Markham, 2004).

Androgen receptor (AR) and Prostate cancer

Androgens are male sex hormones produced in the testes which play key roles in the prenatal gender differentiation, favoring the formation of external genital organ during fetal life and

development of male sexual characteristics in puberty as well as establishment of adult sexual functions (Wilson, 1999: Berenbaum&Beltz, 2016: Takayama, 2018).

The two major androgens, testosterone and dihydrotestosterone exert their effects by binding and activating androgen receptor (AR) which brings about regulation of gene expression (Heinlein & Chang, 2004). The normal development, maintenance and functioning of the prostate requires androgens which act through the androgen receptor (AR) (Foley *et al.,* 2004; Heinlein & Chang, 2004: Berenbaum&Beltz, 2016). Testosterone having synthesized in the testes, is transported to the target tissue, activated to a more potent dihydrotestosterone by 5α-reductase thereby inducing transcriptional activation of androgen receptors, regulated by other co-regulators and phosphorylation (Heinlein & Chang, 2004).

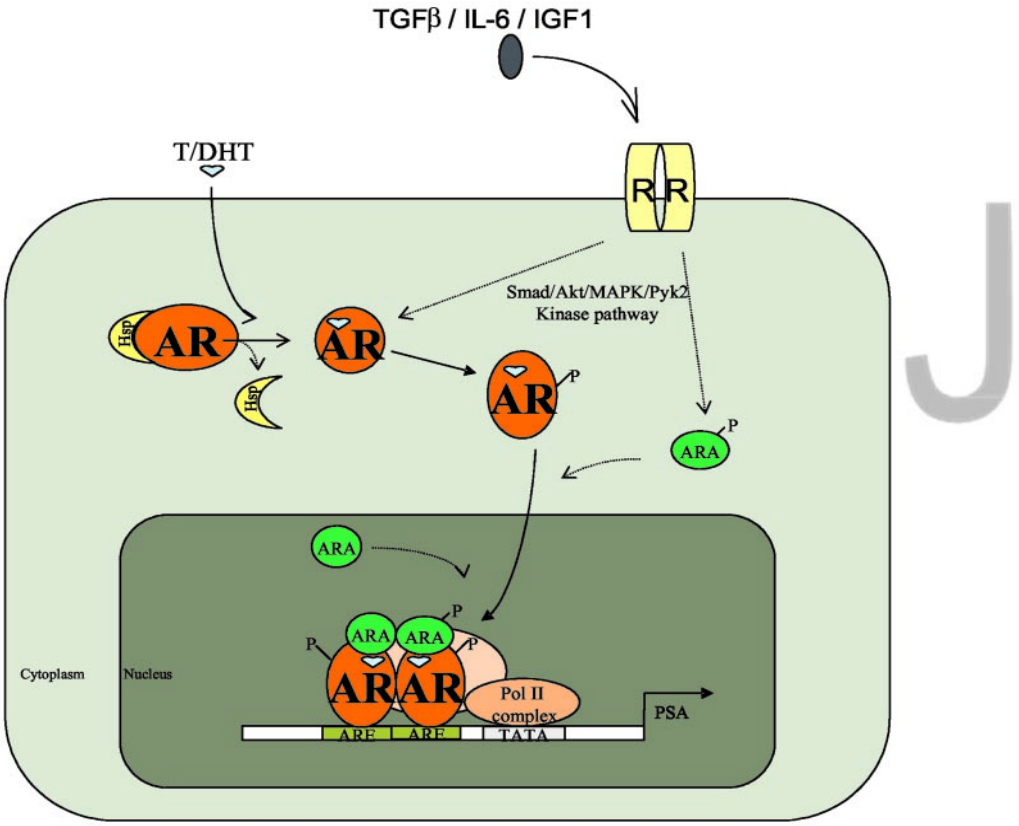

Figure 3.Showing Androgen- AR action in the prostate. Source:Heinlein & Chang (2004)

However, mutation and alteration in the expression of androgen receptor (AR) and related proteins are highly implicated in the development of prostate cancer (Foley *et al.,* 2004: Heinlein & Chang, 2004: Zhou *et al.,* 2015). C reported that clinical and experimental evidences showed that prostate cancer progression occur due to alterations in the normal androgen pathways by dysregulating AR activity via signal transduction cascades, alteration in the

expression of AR coregulators and mutation in AR receptors. Most of the androgen receptor (AR) mutations identified in prostate cancers are point mutation in which a single codon is substituted with resultant single amino acid replacement (Heinlein & Chang, 2004). These mutation are mainly localized to the androgen receptor (AR) ligand binding domain (LBD), occurrence of such mutations (point mutation) could result in increasing the number of ligands capable of inducing androgen receptor transactivation (Heinlein & Chang, 2004). There are two basic functional consequences of AR mutations, 1) to enable the antiandrogens to function as androgen receptor agonists, and 2) allow androgen receptor transcription by the adrenal androgen dehydroepiandrosterone (DHEA) and androstendiol (Heinlein & Chang, 2004). The above mentioned types of mutation and several others have been isolated in single tumors from prostate cancer patients (Heinlein & Chang, 2004).

Ras and Prostate cancer

Ras is an enzyme linked cytoplasmic 21kDa protein (cell receptor), a superfamily of monomeric GTPases which relay signals from receptor tyrosine kinase (RTKs) to the nucleus that brings about the regulation of cell proliferation and differentiation.Rasprotein is positively regulated by Guanine nucleotideexchange factors (GEF).Rasis located in the inner surface of the plasma membrane where, upon activation by incoming signal, it activates other components of the pathway which “turn on” the gene transcription of proteins that are responsible for cell growth, differentiation and survival (Junxia*et al*., 2010: Gurung&Bhattacharjee, 2015).

Although Pearson *et al*., (2009) and Lang *et al*., (2017) reported that mutation in Ras genes are relatively uncommon in prostate cancer, however, wild-type Ras can be chronically activated by autocrine and paracrine growth factor stimulation. Activation of small GTPase such as Ras and Arf1 is found to be a critical component of the signaling pathways for most of the receptors shown to be upregulated in advance prostate cancer (Pearson *et al*., 2009: Lang *et al*., 2017). The activatingmutation of Ras mostly affects the GTPase activity of Ras leading to accumulation of Ras-bound GTP, as a result, this can cause hyperactivation of other downstream effector proteins leading to constitutive abnormal signaling inside the cancer cell even in the absence of incoming regular signal (Bakin*et al*., 2003:Gurung&Bhattacharjee, 2015). Oncogenic Ras are normally activated by missense point mutation at codon 12, 13 or 61, mutant Ras protein do not function correctly as GTPases by maintaining their activated GTP bound state, resulting in

transmittingpersistent signaling and subsequent irregular cell proliferation (Karayi& Markham, 2004: Junxia, *et al*., 2010: Gurung&Bhattacharjee, 2015).

NF-κB and Prostate cancer

Nuclear factor kappa-B (NF-κB) is a family of transcription factors that regulate the expression of genes involved in immune and inflammatory responses, cell growth, differentiation and apoptosis (Suh&Rabson, 2004). NF-κB are made of homo or hetero-dimers having sub-units p65 (rel A) and another sub-unit as p50 (rel C) or (rel B). The dimers are kept inactive in the cytoplasm bound to inhibitor family member IkB, it is activated and released by phosphorylation and cleavage/degradation of the IkB ubiquitin proteasome pathway, the freed NF-κB move into the nucleus and bind to DNA, and bring about the control of wide range of genes (Sylvia, *et al*., 2011). Activation of NF-kB involves induction of its nuclear localization and transcriptional activation potential leading to the expression of a large number of target gene (Suh&Rabson, 2004).This brings about the regulation of the expression of many cytokines and chemokines, angiogenic factors such as vascular endothelial growth factors (VEGF), interleukins (IL-8), type IV collagenases, MMP-2 and MMP-9.(Ismail, *et al*., 2004).These factors are essential for angiogenesis as well as cancer cell motility, invasiveness and metastasis (Ismail, *et al*., 2004).NF-κB may promote cell growth and proliferation in prostate cancer by regulating the expression of some other factors like MYC, cyclin D-1, interleukin-6 (IL-6) since they are equally essential in tumor cell motility, invasiveness and metastasis(Ismail, *et al*., 2004). Other NF-κBcan target genes which codes for proteins with anti-apoptotic activities thereby promoting cell survival (Ismail, *et al*., 2004). In cancer, mutation in NF-κBgenes as well as other gene products of NF-κB are reported to be associated with pro-proliferative and anti-apoptotic activities that could lead to development, progression and resistance to therapy of non-lymphoid tumor cells(Ismail *et al*., 2004; Suh&Rabson, 2004: Porkka&Visacorpi, 2004).

In studies by Ismail *et al*., (2004) results shows that NF-κB nuclear localization and activation was up-regulated in tumor cells as well as in the surrounding lymphocytes of metastatic lymph node of prostate cancer patients. Also, NF-κB have been shown to regulate the expression of an important marker for prostate cancer progression, prostate specific antigen (PSA). Suh&Rabson, (2004) also reported that series of studies from different laboratories have shown

NF-κB activities has been constitutively activated in many prostate cancer cell lines as well as prostate carcinoma xenografts.

Bcl2 and prostate cancer

B- cell lymphoma 2 (Bcl-2) is a regulatory protein usually localized to the outer membrane of the mitochondria, which play a role in regulating apoptosis by either inducing cell death, pro-apoptosis or cell survival, anti-apoptosis (Li *et al*., 2016). This process is mediated via the mitochondrial or intrinsic pathway, the activation process begins with the leakage of cytochrome c into the cytoplasm where it brings about caspase 9 activation and subsequent initiation of the caspase cascade which are responsible for the final executionary steps of the apoptosis (Chaudhari, *et al*., 1999; Correia, *et al*., 2015).

The release of cytochrome c from the mitochondria into the cytosol is controlled by members of the Bcl2 protein family which include three (3) sub families that differ in structure and function;

i) pro-apoptotic effector proteins Bax and Bak which mediate mitochondrial outer membrane permeabilization (MOMP)
ii) anti-apoptotic family members including Bcl-2, Bcl-W, Mcl-1 and A1 which antagonizes MOMP
iii) Pro-apoptotic BH3 only proteins which promotes apoptosis either by directly binding Bax and Bak to form oligomers, or indirectly by neutralizing anti-apoptotic family members.

When the balance between these Bcl-2 family members points towards apoptosis, Bax and Bak will oligomerize to cause permeability to the mitochondrial outer membrane and release of cytochrome c, pro-caspase 9 and many other mitochondrial intermembrane space proteins (Correia*et al*., 2015) , leading apoptosis.

The apoptotic pathway is beneficial not only to normal cell growth and development, but also establish barrier towards cancer cells development, therefore genetic aberrations in Bcl-2 genes may cause dysfunction in the apoptotic pathway via overexpression of Bcl-2. High levels of Bcl-2 will bind Bax and prevent translocation from mitochondrial outer membrane, thereby inhibiting apoptosis by decreasing the release of cytochrome c and pro-caspase 9 from the

outer mitochondrial membrane (Correia*et al*., 2015), and finally cause the inactivation of the caspase cascades resulting in survival of cancer cells. Schulz et al., (2003) reported that growth factors not only stimulate cell proliferation, but also decrease apoptosis, for instance, fibroblast growth factor 7 (FGF-7) which is produced by prostatic mesenchymal cells , decreases apoptosis and promote cell survival in prostate cancer cells, this is probably by increasing Bcl-2 expression.

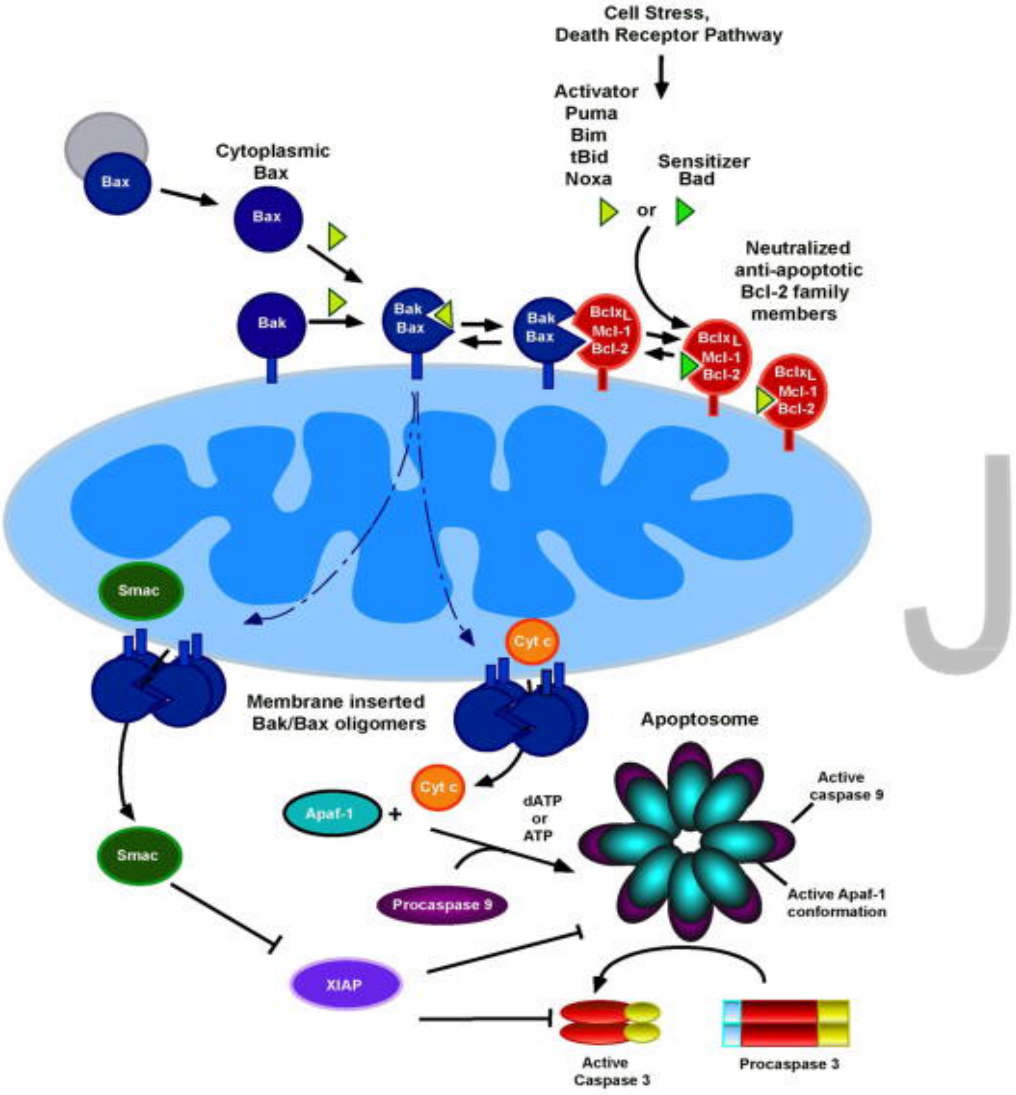

Figure 4The mitochondrial intrinsic pathway. Source; Correia, et al., (2015).

P53 and Prostate cancer

P53 proteins are tumor suppressor proteins that play a vital role in controllingcell cycle progression, maintaining genomic stability and inhibition of angiogenesis (Rivlin, *et a*l., 2011: Aggarwal*et al*., 2019).The mechanisms of its anticancer role may include the activation of DNA repair proteins when DNA sustains damage, arrest of growth by holding the cell cycle at G1/S

check points when DNA damage is noticed (if held for long time, the cell's DNA repair system will have time to fix the damage and allow the cell to continue life cycle). P53 can also initiate apoptosis if DNA damage prove irreparable (Rivlin, *et al*., 2011).

In normal cells, DNA damage or other stresses are the signatures for the activation of P53 pathway(Mraz, *et al*., 2009). Upon activation by its negative regulator mdm2, P53 induces cell cycle arrest either to allow the repair and survival of the cell, or apoptosis to discard the damaged cell, activated P53 bind to DNA (transcription factor) and activate the expression of several genes that brings about DNA repair, when damaged (Mraz, *et al*., 2009).

However, in prostate cancer, mutant p53 impairs the activation of ataxia telangiectasia mutated (ATM) after DNA double strand breaks (DSBs) damage by inhibiting its recruitment to the site of DNA damage and induce genetic instability (Foley *et al.,* 2004: Aggarwal*et al.,* 2019). Majority of mutations are missense that are localized to six hotspot residues of p53, which affects either the structural integrity or the DNA binding domain. This effect causes loss of contact with the consensus DNA binding sequence which results in loss of wild type p53 tumor suppressive activity (Aggarwal*et al*., 2019). Aberrantp53 genes may produce mutant p53 proteins which will cause the accumulation of cells with damaged DNA, resulting in cancer, mutant p53 not only lose their tumor suppressive effects, but also acquire some additional capacities that enhance cells with growth and survival advantages (Rivlin, *et al*., 2011).

Incidence of Prostate cancer in Africa

Globally, prostate cancer (PC) is rated second most occurring cancer in men (Abbasi-Kangevari*et al*., 2022) and sixth leading cause of death due to cancer among men with over 1.4 millioncases in 2020 (Ramaliba*et al*., 2022) and estimated 300, 000 deaths in 2012 (Adeloye*et al*., 2016).PC is ranked among top ten causes of disability adjusted life years (DALYs) in men of older age in 2019, with smoking as the singleassociated risk factor as distinguished by the Global Burden of Disease (GBD) study in2019 (Abbasi-Kangevari*et al*., 2022). PC has substantial variation in trends of incidence and death, this is attributed to regional population-based difference in risk factors, access to medical care and desperate screening and diagnosis approaches across different health care systems (Abbasi-Kangevari*et al*., 2022). Prostate cancer incidence varied by 189 fold across 186 countries, with age standardized incidence rate ranging widely from 1.0 per 100, 000 in Bhutan to as high as 181.9 per 100, 000 in Guadeloupe in 2018

(Ramaliba*et al*., 2022). Recently, research showed that Lithuania in Europe had the highest incidence rates of 128.9 per 100, 000 followed by Central and Southern America with 122.3 per 100, 000 (Ramaliba*et al*., 2022).

In sub Saharan Africa, Institute of Health Metrics and Evaluation (IHME) estimated that disability adjusted life years (DALYs) due to prostate cancer has increased from 100, 200 in 1999 to 219, 700 in 2010 and deaths increased from 5,600 to 12, 300 over the same period. In another report, the incidence and mortality rates from PC in Africa were 23.2 and 17.0 per 100, 000 respectively (Adeloye*et al*., 2016). While this is relatively lower than the figures reported in some other parts of the world, current argument among researchers is that African men suffer disproportionately from PC compared to many other regions (Chu*et al*., 2011; Adeloye*et al*., 2016). In fact, evidence shows that mortality rates due to PC is are generally higher in predominantly black African population compare to other races, and this variation is also observed in the pattern of PC incidence between northern and sub Saharan African region, with incidence and mortality rates 10.6 and 7.0 per 100, 000 for northern Africa, and average rate 34.3 and 22.1 per 100, 000 respectively for sub Saharan Africa. (Adeloye*et al*., 2016).PC shows surprising racial differences among different populations around the world with some countries having incidence rates that are 60 to 100 times higher than others (Hinata& Fujisawa, 2022). Incidence of PC is typically low in Asian men with age adjusted incidences ranging from 2-10 per 100, 000 men, in the northern Europe incidence is generally high whereas the African American men have the highest global incidence and mortality rates (Hinata& Fujisawa, 2022). Among the African countries, incidence range from 20 in Gambia (1997- 1998) to 3,432 (1989-1992) per 100, 000 in south African blacks. Incidence varied substantially by region in africa, with rates highest in the East (10.7-38.1) per 100, 000 man years, intermediate in the South (14.3-21.8) and lowest in the West (4.7-19.8). Incidence rates among US blacks were considerably higher, about 40 times those in Africa (195.3) in US blacks during 1993-1997 and(4.7) in Gambia during 1997-1998 (Chu*et al*., 2011). Reason for the large variation in incidence among African countries and the observed East-West disparity is not clearly understood, however, it likely due to differences in access to health care facilities, registry quality including completeness of case ascertainment and estimates of population at risk, screening practices, as well as lifestyle factors within the population (Chu*et al*., 2011).

Conclusion

Prostate cancer is found to be underlain by numerous genetic factors which may include gene mutations and expression of defective proteins associated with regulation of gene expression and cell cycle regulation, mutation in genes and expression of mutant proteins associated with cell signal transduction, age, lifestyle, epigenetics, chemical and infectious agents.There is usually an alteration in some normal signal transduction pathways during prostate cancer development, progression and proliferation. Cancer cells take advantage of other normal cellular mechanisms like NF-kB pathway to develop and proliferate, understanding these key cellular processes could minimize the associated deaths due to prostate cancer by paving ways in devising novel approaches towards tumor diagnosis, development of therapeuticand preventive measures against the disease. The incidence of prostate cancer shows substantial global and regional/ racial variation, and among the African countries, incidence variedfrom East with highest incidence through south with intermediate andthe West African region with least incidence rates. Difference in access to health care facilities, registry quality including completeness of case ascertainment and estimates of population at risk, screening practices, as well as lifestyle factors within the population among other factors are likely to be responsible for the observed variations.

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