PROSTATE CANCER: COPING WITH THE MONSTER IN A THIRD WORLD SETTING

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It is my pleasure and honour to deliver this inaugural lecture to this audience, consisting of some of the finest minds in our country today, a quality for which our great university is known.

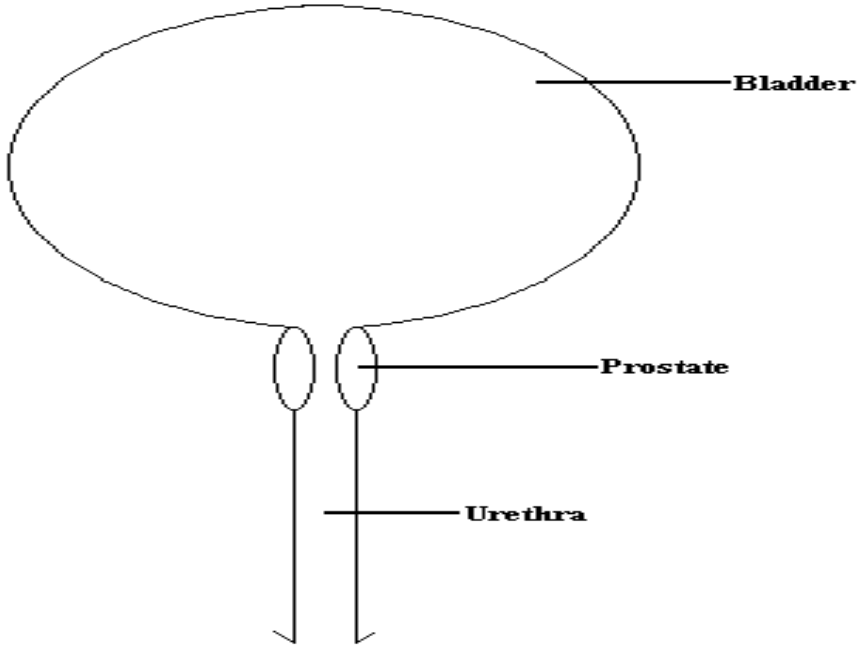
I have chosen to speak on prostate cancer for a lot of reasons as follows:

1. Gradually but surely, our population is ageing and therefore, we will begin to see a lot more of prostate cancers in the years ahead.
2. Following the advent of a powerful screening test for prostate cancer that has been available in Nigeria for over a decade, it is now possible to detect prostate cancer early and thus significantly improve outcome.
3. Cancer of the prostate affects the lives of every body, whether man or woman, directly or indirectly. For a woman, it can affect a father, uncle, husband, brother and even son. For a man, in addition to the above relations, we all are potential sufferers.
4. Most people, including some medical personnel, are ignorant of the CAUSE and the COURSE of the disease. As a result, most patients detected early do not wish to submit themselves to definitive therapy because of poor advise. Furthermore, routine medical examination is non-existent making early detection almost impossible.
5. Those that present themselves for initial treatment do not take their drugs religiously due to ignorance and follow-up visits are not kept to, thereafter, patients return only when the disease has advanced beyond therapy. Also, because of poverty, those who may wish to submit themselves to treatment may not afford the cost. To compound the problems, some essential facilities for the management eg. Radiotherapy, are not routinely available in this part of the country.
6. It is however a heart-warming news that researchers, both in Nigeria and abroad, have found certain drugs and food items which may help to delay the initiation, promotion or progression of prostate cancer. These will be highlighted.
7. Lastly, I want to use this forum to raise awareness about a key component of men's health – PROSTATE CANCER – so that we can attempt to uplift our gender issues the way our womenfolk have so admirably done.

What is the Prostate?

The prostate is a guava-shaped gland found only in the males, located below the neck of the bladder and through it, traverses the first part of the urethra (prostatic

urethra) *See figure below*. It contributes to the quality and quantity of the semen produced. It is the main source of the prostate specific antigen (PSA). Growth of the prostate is primarily governed by two hormones – the androgens and the oestrogens. The androgens cause it to proliferate while oestrogens cause it to degenerate. The delicate balance between these two hormones is thought to be the cause of some of the diseases of the prostate. Like other organs, the prostate is present at birth but undergoes a growth spurt at puberty under the influence of androgens mainly produced by the testes.



What Problems May Be Associated With the Prostate?

There are three common problems associated with the prostate in adult males:

- Prostatitis (inflammation of the prostate) which may be acute or chronic
- Benign Prostatic Hyperplasia (BPH)
- Cancer of the Prostate

When an adult male presents with an enlargement of the prostate, what is uppermost in the mind of the attending physician is to rule out cancer of the prostate, as the other two conditions are benign.

What is Cancer of the Prostate?

Cancer, I will simply define as uncontrolled/unregulated tissue growth, with a capacity for spread and debility of the host [1].

When we link up these, we immediately see that prostate cancer is an uncontrolled/unregulated growth of cells of the prostate gland with a capacity for spread, debility and ultimately death of the patient.

To help to appreciate the size of the problem, let us review some facts [2-6]:

- Prostate cancer is the leading cancer diagnosis and the second most common cause of cancer-related death in USA.
- Incidence is 50% greater in blacks than in whites
- It is relatively uncommon in the orientals
- In USA (a multiracial society), the incidence for black population is 249/100,000 males; for whites, it is 182/100,000; for Hispanics 104,000/100,000; and for Asians, 82/100,000.
- In China, the incidence is <2/100,000 males
- In Jamaica, which has the world's highest incidence, it is 304/100,000 males
- In Lagos, hospital incidence is 127/100,000 males
- In Enugu, hospital incidence is 192/100,000 males

To appreciate the problems more in our environment, a study carried out at the University of Nigeria Teaching Hospital, Enugu on urological cancers showed that over a 13 years period, Urethral cancers – 8 new cases; Bladder cancers- 103 new cases; Ureteric cancers – 7 new cases; Kidney cancers – 74 new cases; for Prostate Cancers, 847 new cases were diagnosed over a period of just ten years [3, 7-10]**.**

What are the Risk Factors for Prostate Cancer?

These are factors that confer a higher probability of developing prostate cancer on an individual. They are as follows [2, 11-13]:

1. Sex: Since the prostate gland is only present in the males, one has to be a man to develop prostate cancer, as compared to breast cancer for example which though much commoner in women, can and does occur in men!! The chance of a man acquiring prostate cancer during his lifetime is 15%.
2. Age: "Since ageing seems to be the only available way to live long …" - Espirit Auber, it is important that while we emphasize the virtues of healthy living and longevity, we should emphasize that *prostate cancer is largely a disease of the elderly*. "Elderly" usually defined as those over the age of 65 years, though, prostate cancer can start much earlier!
3. Genetic influences: Men with one first degree male relative with prostate cancer have a 2-fold risk of developing prostate cancer, whereas men with two or three affected first degree relatives have 5-10 fold risk. About !0% of prostate cancer cases are believed to be inherited. These cancers are known for early onset <55 years, and aggressive biological behaviour.
4. Diet: A diet high in fat is a major risk factor for developing prostate cancer.
5. Hormonal factors: Androgen (mainly testosterone) is necessary for the growth of the prostate and also for development of prostate cancer. Males castrated before puberty (Eunuchs) do not develop prostate cancer.
6. Race: Prostate cancer is 50% greater in African American men than Caucasians and relatively uncommon in Asians.

7. Country of Residence: This may be affected by diet and other environmental factors. When the incidences in Chinese living in China and those living in USA are compared, this factor will be better appreciated.
8. Chemical Factors: Workers in the rubber, fertilizer and textile industries have increased rates of prostate cancer. So also are men who are continuously exposed to cadmium – a known antagonist of zinc. Here, selenium may have a protective effect.
9. Sexually Transmitted Diseases (STDs): Some viruses eg. Human Papilloma Virus (HPV) which are sexually transmitted have been shown to be associated with prostate cancer.

Presentation of Prostate Cancer

It is important to distinguish two modes of presentation of prostate cancer that actually constitute a consortium:

- Histological Prostate cancer that is often detected as a result of screening
- Clinical Prostate cancer that often comes to light because the patient has developed symptoms of the disease.

From the foregoing, it is evident that screen-detected prostate cancer is likely to be of a low stage and therefore, easier to treat, and attended by better prognosis, while the converse holds for the clinical prostate cancer.

Screening for Prostate cancer

Introduction of this procedure now begs the question of whether to screen or not to screen, and when detection is made, what to do about it.

There is no doubt that screening is the way to go if we are to pick up cancers early, given the propensity of the negro to develop this ailment, and the weak social security of our healthcare system that does not readily provide adequate care for the patient with advanced malignancy.

How then should we screen?

In our country today, I believe the best way is to take a good clinical history and examine our patients well especially doing a digital rectal examination! Thirty percent (30%) of prostate cancers can be detected in this manner by a well trained and proficient clinician. This figure is increased considerably by adding PSA estimation (discussed below)

Prostate Specific Antigen (PSA) Estimation

This is a blood test that assesses PSA, a product of the prostate that is elevated in cancer, but also, other conditions of the prostate. The discovery of this assay revolutionalized the diagnosis of prostate cancer in developed countries, but opened a plethora of problems in Nigeria:

- Lack of standardization of lab methods

- Use of fake or sub-standard kits
- Poor understanding by some clinicians of the limitations of the test in detecting prostate cancer
- The availability of internet, that treasure trove of information that often produces the “instant doctor syndrome” and untold anxiety in patients and relations
- The widely held belief that an elevated PSA is equal to cancer and therefore **a death sentence**
- Lack of confidentiality in the handling of lab reports, such that patients are given results “because they paid for them anyway” and told that his PSA level is high or low, without the requisite follow-up explanation that should encompass all the intricacies involved.

To make sense of it all, let me explain what PSA is, the causes of PSA elevation and its relationship with prostate cancer [14-16]:
PSA is a substance produced by normal and cancerous epithelial cells of the prostate. It is a 33 KDa serine protease (a kallikrein) and its gene is KLK3 which encodes for hK3 (PSA). The kallikrein genes KLK1 to KLK15 cluster in a 300 kb region on chromosome 19q 13.4. HK2 and HK3 expression is highly restricted to the prostate gland in males and thus makes them useful tumour markers in prostatic diseases.
PSA is produced in a ‘pre-pro form’ with chymotrypsin-like substrate specificity. Its substrates includes the gel-forming proteins in freshly ejaculated semen – seminoglobulin1 (sg1) and seminoglobulin2 (sg2), synthesized and secreted by the seminal vesicles and the prostate resulting in the immediate formation of a loosely connected gel structure that entraps spermatozoa. Sg1 and sg2 are the major structural proteins in the gel and the enzymatically active PSA in the seminal fluid proteolytically cleaves the trosyl and glutaminyl peptide bonds to generate soluble fragments of sg1 and sg2. These sg1 and sg2 cleavage sites have been used to generate specific substrate for measuring PSA enzymatic activity.

It should be noted however that for ultimate diagnosis of prostate cancer, a tissue specimen of the prostate has to be sent for histological diagnosia.

Historically, while very high PSA levels (> 10 ng/ml) have been associated with histological diagnosis of prostate cancer, ranges of 4-10 ng/ml are associated with lower rates of positive histology (< 25%).

Overall, PSA testing is associated with an average lead time of 5-6 years for prostate cancer detection, using 4ng/ml as the threshold for normal. However, it should be noted that PSA levels are normally affected by certain factors – androgen levels, prostate volume, race and age.

Based on the above variations and realization that PSA is organ specific and not tissue specific, investigations have begun to evaluate forms of PSA in serum, in a bid to improve the specificity of PSA assay. These include:

- PSA-ACT (Alpha 1 antichymotrypsin), a form of PSA that is bound to an inhibitor and circulates in the plasma as such
- fPSA (free PSA), which circulates in plasma unbound
- PSA-A2M (Alpha 2 macroglobulin), another complexed form that is not detectable using standard assays.

Antibodies have been developed to measure free and complexed PSA fractions in the serum. It has been determined that with a free PSA of 25% or less of the total, it would be possible to prediuct 95% of cancers and avoid 20% of unnecessary biopsies. With this finding, came the acceptance that there are two basic molecular forms of PSA in plasma [17-19]:

- Complexed PSA
- Free PSA (unbound)

65-95% of PSA in the serum is PSA-ACT and this is the predominant form in serum of men with normal prostates, BPH and prostate cancer.. The remainder consists of free PSA which forms 5-35% and of course PSA-A2M. A small amount of PSA is found complexed with alpha-1-protease inhibitor AP1 (PSA-AP1). PSA-A2M and PSA-AP1 are not routinely measured even though assay methods are now available.
Thus, total PSA = fPSA + PSA-ACT +PSA-2AM +PSA-AP1

Attempts at fine-tuning the specificity of PSA for prostate cancer diagnosis have led to other concepts viz:

- PSA velocity: This factor is the rate of rise of PSA over a 12 month period. Above 0.75 ng/ml/year increases the chances of prostate cancer
- PSA Density: Serum PSA divided by the volume of the prostate. Above 0.15 ng/ml^3 increases the chances of prostate cancer
- Age-Specific PSA: This relates PSA level to age. The lower the age and the higher the PSA, the higher is the risk of prostate cancer
- Percentage (%) Free PSA: Free PSA divided by total PSA multiplied by 100 ie fPSA/TPSA x 100. <25% increases the chances of prostate cancer.

Having discussed at some length, we may now begin to see that though it is an undoubtedly important tool (tumour marker), its interpretation requires a high level of training and complete understanding of the issues I have alluded to. At this juncture it is also very important to mention other causes of PSA elevation apart from prostate cancer and some of these are commoner than cancer of the prostate:

- Benign Prostatic Hyperplasia (BPH): This is a benign tumour of the prostate that produces elevation of the PSA and has some symptom overlap with prostate cancer.
- Prostatitis: This is an inflammation of the prostate and may be acute or chronic. It is benign, non-fatal and treatable.
- Prostatic Manipulations: A typical case is digital rectal examination (DRE) that is so often done for assessment of men.
- Prostate Biopsy: Trauma to the prostate does occur during this procedure and can cause transient elevation of the PSA.

Peculiar Issues in Nigeria

As I mentioned earlier, in Nigeria, we are far from the utopian picture painted elsewhere regarding the detection of prostate cancer despite the large burden of disease in our population. The advent of PSA estimation in Nigeria in the 90's was followed by many problems which we, as Urological surgeons have had to evolve ingenious strategies to control. These include:

- Lack of standardization of lab methods: With a primary economic intent, many persons, often unqualified, soon mount little and large signs announcing the availability of PSA testing 'within'. The unwary are often attracted and I am often confronted with patients who come with lab results with outrageously high PSA reading and told they have prostate cancer, based solely on a poorly done PSA, with great toll taken on their psyche, business and family life. After full assessment confirming that the diagnosis is wrong (which happens in a sizeable proportion), it often requires long periods of counseling, to 'delete' the wrong information and 'reformat' the patient as it were!!
- Faking/Counterfeiting is a phenomenon that is still with us though the valiant campaign of one of our own Professor Dora Akunyili, has greatly raised awareness and caused some reduction. The outright faking of kits, poor storage and the attendant degradation, with poor results are all too common. Again, I and my colleagues have had to determine where standards are maintained and proficient and qualified staff are present, and use them in order to check this menace.
- We have also had to deal with the half information dispersed by some health workers to patients that sets them on a cyclical pilgrimage to hospitals, clinics, etc until fortune's wind blows them into an institution where things are done correctly. Sadly however, this is often not before the patient's meager resources have been depleted.

At this juncture ladies and gentlemen, let me emphasize the fact that prostate cancer is rife in Nigeria and the daily pick up rate of new cases is increasing. 80-90% of our patients present with very advanced disease and severe complications, with death occurring about 1-3 years after presentation, after a painful and resource

consuming period that puts families in the red financially and brings on a lot of grave social implications. Taking this fact into consideration, let me recommend, though some may say prematurely or alarmist, that every Nigerian man over the age of 40 years, should get an annual check-up by a urologist because a:

- We are black and our race is a known risk factor
- Our diet is rapidly being westernized even in the rural areas with a high consumption of fats and a paucity of fruits and vegetables that supply the much needed antioxidants that are known to prevent the cancer.

How do I know I have it? Warning Signals!!!

A Chinese proverb has it that if one sends an adolescent on a mission to capture a rare animal, one must also tell the person in no uncertain terms how to recognize it when he sees it. Here, we speak of clinical features ie. Symptoms and signs of prostate cancer. Symptoms are changes noticed by the patient, while signs are usually elicited by the surgeon on examination of the patient.

In broad categories, patients are classified as:

- Asymptomatic: Here, there are absolutely no changes or abnormalities noticed by the patient but cancer is discovered in the course of a routine assessment.
- Local Symptoms: These are symptoms referable to an organ. These are Lower Urinary Tract Symptoms (LUTS) highlighted below.
- Metastatic Symptoms: Here, the hallmark of malignancy has shown ie. Spread of cancer cells to adjacent structures and distant sites such as bones, lymphatics and solid organs like the liver. Unfortunately, it is at this stage that we see most of our patients in this part of the world!! And why? We need to look further than the bible "My people perish for lack of knowledge''
- General Presentation of Cancer: Weight loss, weakness sleeplessness etc.

Lower Urinary Tract Symptoms (LUTS) are commonly seen in cancer of the prostate though not exclusively, as Benign Prostatic Hyperplasia and Prostatitis present in much similar way. These symptoms include:

- Frequency of urination – diurnal and nocturnal
- Urgency
- Hesitancy
- Poor Urinary Stream
- Intermittency
- Straining
- Dysuria
- Haematuria
- Pyuria
- Terminal Dribbling

- Feeling of Incomplete Emptying

Associated with LUTS may be:

- Weight Loss
- Urinary Tract Infection
- Acute or Chronic Urinary Retention
- Perineal and/or Suprapubic pains from local or nerve infiltration
- Low Back pain
- Chronic Constipation
- Anaemia
- Obstructive Nephropathy (Renal Impairment)
- Cerebral Metastasis (Headache, nausea and vomiting)
- Lower limb swelling

Signs: These are findings on examination:

- Distended Bladder
- Oedema of the Lower Limbs
- Exquisite Spine Tenderness
- Skin or Skull Nodules
- A Hard, Craggy and Irregular prostate with nodules

Note: Symptoms and signs above may singly or in clusters suggest a possible diagnosis of prostate cancer and as we can see, many of the symptoms are by no means specific for prostate cancer.

What else could it be? Differential Diagnosis

- BPH
- Chronic Prostatitis
- Skeletal Metatstases from other primary tumours.

Investigations

These are tests that are carried out with the aim of:

- Confirming Diagnosis
- Assessing Extent of the Disease
- Assessing Patient's fitness
- Planning Treatment Strategies

These tests are:

- Routine Investigations: Urine – Urinalysis & Microscopy, culture and sensitivity;
  Blood- Full Blood Count, Liver Function Tests, Urea, Electrolytes and Creatinine estimation
- Specific Investigations

- Acid Phosphatase
- PSA
- Skeletal Survey and Chest X-Rays
- Bone Scanning
- Prostatic Biopsy/Aspiration Cytology
- Lymphangiography
- CT Scanning and MRI
- Ultrasound – Transabdominal and TRUS
- Pelvic Lymphadenectomy
- Antibody Radiolabelled Scintigraphy (CYT-351)
- Endoscopy

Clinical Presentation in Enugu Study (N-847) [3, 20]

Raised ESR	847(100%)
Abnormal DRE	788(93%)
Irritative Bladder Symptoms	748(88.3%)
Weight Loss	722 (85.2%)
Dysuria	508 (60%)
Haematuria	485 (57.3%)
Metastatic Symptoms and Signs	407(48.1%)
Chronic Constipation	359(42.4%)
Urinary Retention	295 (34.8)
Renal Impairment	102(12.0%)
Incidental Finding	31(3.7%)

On completion of clinical assessment and investigations, a process known as 'staging' is done to stratify the disease into 4 possible categories in increasing degree of severity viz:

- Stage A - Incidental Cancer
- Stage B - Organ Confined Disease
- Stage C - Local Metastasis
- Stage D - Distant Metastasis

Stages Found in Enugu Study. (N-847) [3]

Stage A -	21(2.5%)
Stage B -	78 (9.2%)
Stage C -	242 (28.6%)
Stage D -	506 (59.7%)

Prognosis (outcome) naturally worsens as the stage of the disease goes higher and is usually given in terms of 5 years survival figures. Let me quickly add that this is

not because of a general 5 year ultimatum!!, but because generally, most people that survive cancer for 5 years are regarded as cured.
The 5 year survival figures are:

- Stage A - Normal
- Stage B - 75%
- Stage C - 60%
- Stage D - 30%

Note: In addition to the staging discussed above, the aggressiveness of the tumour cells as measured by cell differentiation (Grade of the Tumour) must be ascertained by Gleason's scoring system. The lesser the differentiation, the higher is the score and consequently, the worse is the prognosis.

On completion of the processes, a point is reached where the surgeon must now decide on the most appropriate method of treatment and advise his patient appropriately. The decision is individualized and there is no "one size fits all' approach to it. It must be preceded by a thorough explanation of the side effects, problems and expected benefits to the patient and culminate in the obtaining of an informed written consent before proceeding. Treatment option embarked upon depends on the following:

- Stage and Grade of the Tumour
- Age and General Condition of the patient
- Acceptance by the patient
- Affordability by the patient
- Availability of the Treatment
- Competence of the attending physician.

Treatment Options

1. Curative Surgery - Radical Prostatectomy
2. Curative Radiotherapy - External Beam; Interstitial Irradiation with ^{125}I, ^{198}Au.
3. Palliative Therapy [21-23]

-Hormonal Manipulations

- Bilateral Orchidectomy
- Oestrogen Therapy
- Progestational Agents
- LH-RH Analogues
- Anti-androgens

-Palliative Surgery

- TURP
- Cystostomy
- Nephrostomy

- Uretero-neo-cystostomy
- Colostomy
- Bone Fixation
- Laminectomy etc.

-Palliative Radiotherapy

Patient Re-Assessment [24]

- PSA
- General Quality of Life
- General Examination for Possible Metastases
- Other Biochemical Assays
- Haematological Assessment and Radiological if necessary
- Time to Progression
- Prostatic Biopsy

Note:

Radical prostatectomy is done for screen detected cancers which are confined to the prostate and the aim here is complete cure. It entails surgical removal of the prostate gland, seminal vesicles and the anastomosis of the bladder to the urethra. This is the commonest form of treatment in developed countries because they deal mostly with early stage tumours. Though our experience has been to find predominantly late diseases, I am glad to say that through counseling and education, we have detected a number of early stage tumours and successfully performed radical prostatectomy in my unit at the University of Nigeria Teaching Hospital with excellent results. Some of the worries associated with this procedure include incontinence, and erectile dysfunction. I am however glad to tell you that the incidence in our patients is very much lower than that quoted in western literatures.

Radiotherapy either by external beam or interstitial irradiation imparts ionizing radiation to the tissues, achieving cellular death, and may be used in place of radical prostatectomy. Associated problems include radiation proctitis and cystitis and the lack of a pathological specimen to complete the staging process.

Endocrine therapy: As earlier pointed out, androgen has a key role in embryogenic prostate and also in prostate growth and development spurt noticed at puberty. Most cancers of the prostate are therefore promoted to growth by testosterone leading to the concept of Androgen Sensitivity (AS) and Androgen Insensitivity (AI). Most cells in the prostate are androgen sensitive. This fact is used as a basis for endocrine therapy which is the mainstay for treatment of advanced cancer of the prostate which makes up the main bulk of our patients. Removal of androgen influence on the prostate in an AS tumour leads to a dramatic regression of tumour size and massive improvement in symptoms such as anaemia, pain and perhaps, most importantly, it can in some cases be used to reverse paraplegia occurring as a result of spinal cord compression by tumour

deposits. The utility of this salutary effect is probably better seen than told and has in my experience, converted hopelessness to a state of near normality, with the patient capable of clear thoughts, pain free, and above all, free to perform his personal functions of bathing, using the toilet etc. It also eases the **collective suffering** imposed on the family by malignancy. Unfortunately, changes occur at the cellular level that lead to the dominance of the AI cells thus creating clinically a relapse with the return of all the earlier symptoms. This is **Hormone Refractory Prostate Cancer** (HRPC).

At this stage, we face perhaps the greatest challenge in prostate cancer care with all the known agents being of modest effect and patient slowly but surely succumbs to the cancer. The mainstay of management at this stage is a multidisciplinary approach to palliation. Key personnel include the urologist, oncologist, orthopaedic surgeon, neurosurgeon, pain specialist, nurses, physiotherapist, psychologist, priest, spouse, friends, colleagues, etc. Each of these has key and deep contributions to make as the patient's problems at this stage are multiple and deep. It is of the greatest importance to realize that the primary goal at all times is to maintain the patient's dignity and well-being and to assist him have a peaceful transition.

Chemoprevention of Prostate Cancer

This is defined as the administration of dietary supplements, micronutrients, biologic agents, drugs etc. to prevent or delay the initiation, promotion or progression of prostate cancer [25].

1***. Hormonal Therapies*** [26-30]:

- Anti-androgens
- Finesteride
- Estrogens

2***. Phyto-oestrogens ie. Plant Oestrogens*** [31]

- Soy proteins - genistein
- Isoflavanoids
- Ligans - enterolactone, enterodiol

All these prevent prostate cancer by lowering 5-α-reductase activity; by increasing the serum levels of sex hormone binding globulin; or by lowering the serum level of free testosterone; and by decreasing the enzymatic activities of both tyrosine-specific protein kinase and P450 aromatase. They may also adversely affect angiogenesis and function as anti-oxidants.

3. ***Micronutrients/Anti-oxidants*** [32]

- Selenium
- Vitamin E

These combat reactive oxygen species (ROS)

4. ***Carotenoids*** [33,34]

Naturally occurring compounds that contain beta carotene (the precursor of vitamin A) and lycopene, found in

- Carrots
- Green leafy vegetables
- Tomato-based products
- Water melon

Actions include anti-oxidant effect and enhanced apoptosis.

5. Retinoids [33,34]

These are metabolites and synthetic analogues of vitamin A. Modes of action are similar to carotenoids.

6. ***Vitamin D and Analogues*** [35, 36]

- Inhibits cellular proliferation and limits cellular invasiveness in prostate cancer.
- Interacts with the androgen receptor, up-regulates it, and leads to decreased cellular proliferation.

7. ***Non-steroidal Anti-inflammatory Drugs (NSAIDS)*** [37-39]

There is evidence that cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) expression is higher in the prostate than in any other organ and that prostate cancers show selective over-expression of COX-2. NSAIDS block the conversion of arachidonic acid to a variety of products including prostaglandins by inhibiting COX and lipoxygenase enzymes. These enzymes lead to production of eicosanoids which are believed to have important role in the biology of prostate cancer by increasing cellular proliferation, cellular invasion, neoangiogenesis, metastasis rate and hormonal responsiveness. NSAIDS act by

- Direct inhibition of eicosanoid formation
- Indirect inhibition of eicosanoid by inhibiting expression of enzymes involved in eicosanoid synthesis
- Interfering with the function of cyclic guanosine monophosphate phosphodiesterase and activation of apoptosis associated caspases.

8. ***Farnestyl Protein Transferase Inhibitors (FPTI)*** [40, 41]

Eg. Perillyl alcohol (POH), a monoterpene isolated from the oils of several plants including *lavendin,peppermint,spearmint,cherries and celery seeds.*

- Ras proteins play a central role in signal transduction pathways that are important in oncogenesis. FPTI prevent the plasma membrane localization and activation of Ras thereby disconnecting the signals between the plasma membrane and the downstream nuclear effectors. This interferes with cellular growth and proliferation of the prostate cancer.

<u>In our Environment here:</u> Some researchers in our environment [42] have demonstrated that the diet supplements indicated below could be effective in the prevention and management of prostate problems in Nigerian population:

- Coconut (Cocos nucifera)
- Garlic (Allium sativum L.) / Onions (Allium cepa L.)

- Soymilk (Glycine max (L) Merr)
- Tomatoes (Lycopersicum esculentum)
- Bitterleaf extract (Vernonia amygdalina)
- Multi-vitamin/mineral supplement made up of Vitamin E(400 IU); Selenium (50 mcg); Vitamin C (250 mg); B-Complex; Multivitamin/multimineral with lutein.

It must however be noted that some of the components above eg. Coconuts contain oils that have been shown to be harmful to the cardiovascular system if consumed in large quantities as prescribed in the work.

It is hoped that in near future, a good number of males will be able to protect themselves from the devastating effects of the cancer of the prostate.
On this perhaps optimistic note, I wish to end this discussion on this very important but unrecognized killer of men in our country, by giving a way forward to make things better:

Recommendations

1. That every member of this distinguished audience departs from this venue as an educator of sort on this disease, by adding on to what he/she has heard from **Reliable Source** and carrying the message of awareness of men's health especially prostate cancer to your spouse, siblings, co-workers etc., and by so doing, create a tidal wave of information that can only **bring us good.**

2. That every man should take an interest in his health issues which is the primary asset of any individual without which possessions and status suddenly become lack luster and vain. Get an annual physical if over 40 including PSA and urologic assessment, by a proficient physician.

3. That we eat healthy foods, reduce our consumption of saturated fats, and increase lycopene and other anti-oxidant intake.

4. That we use criteria such as quality control in choosing laboratories and not proximity, glowing neon signs or perhaps adverts on megaphones mounted on cars in motor-parks.

5. That we borrow a leaf from our womenfolk and use gatherings such as town union meetings, social clubs,professional associations, etc. to entrench, enlighten and generally promote awareness of our health so that we stop having the too often made comment by patients that "***Doctor, I have never been sick for one day in my whole life and look at me now!!"***

Finally, I want to use this opportunity to inform you that the University of Nigeria Teaching Hospital has benefited greatly from the on-going re-equipping of teaching hospitals and this has placed us in a much better position to screen, diagnose and treat effectively all stages of this ailment in our *backyard* and spare our people unnecessary and often liquidating trips abroad!!

Thank you immensely for your time.

REFERENCES

1. http://www.cancer.gov/. Accessed on March 19, 2007.
2. Bono AV. The global state of prostate cancer: epidemiology and screening in the second millennium. *BJUI* 2004; **94(suppl. 2):** 1-2.
3. Aghaji AE, Odoemene CA. Prostate cancer after prostatectomy for benign prostatic hyperplasia in Nigeria. *East African Medical Journal* 2000; **7(12):** 1-5.
4. Osegbe DN. Prostae cancer in Nigerians: Facts and non-facts. *J Urol* 1997; **157:** 1340-1343.
5. White RWD, Deitch AD, Jackson AG et al. Racial differences in clinically localized prostate cancers of black and white men. *J Urol* 1998; **59:** 1979-1983.
6. Glover FE Jr., Coffey DS, Douglas LL et al. The epidemiology of prostate cancer in Jamaica. *J Urol* 1998; **159:** 1984-1987.
7. Aghaji AE, Onoyona AU. Urethral cancers in Enugu, Nigeria. *Lagos Journal of Surgery* 1999; **2**: 15-19.
8. Aghaji AE, Mbonu OO. Bladder tumours in Enugu, Nigeria. *British Journal of Urology* 1989; **63:** 399-402.
9. Aghaji AE, Mbonu OO. Cancer of the ureter in a negro population. *Journal of the Royal College of Surgeons of Edinburgh* 1991; **36:** 306-308.
10. Aghaji AE, Odoemene C. Renal cell carcinoma in Enugu. *West African Journal of Medicine* 2000; **19:** 254-258.
11. Adami HO, Kuper H, Andersson SO, Bergstrom R, Dillner J. Prostate cancer risk and serological evidence of human papilloma virus infection: a population based, case control study. *Cancer Epidemiol Biomarkers Prev.* 2003; **12:** 872-875.
12. Key T. Risk factors for prostate cancer. *Cancer Surv* 1995; **23:** 63-77.
13. Anwar K, Nakakuki K, Shiraishi T, Naiki H, Vatani R, Inuzuka M. Presence of Ras oncogen mutations and Human Papilloma virus DNA in human prostate carcinomas. *Cancer Res* 1992; **52:** 5991-5996.
14. Catalona WJ, Smith DS, Ratliff TL et al. Measurement of prostate specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; **324:** 1156-1161.

15. Lundwall A, Lilja H. Molecular cloning of human prostate specific antigen with cDNA. *FEBS Lett* 1987; **214:** 317-322.
16. Rittenhouse HG, Finlay JA, Micolajezyk SD, Parton AW. Human kallikrein 2 (hK2) and prostate specific antigen (PSA): two closely related, but distinct kallikreins in the prostate. *Crit Rev Clin Lab Sci* 1998; **35:** 275-368.
17. Lilja H, Christenssen A, Dahlen U et al. Prostate specific antigen in serum occurs predominantly in complex with alpha-1-antichymotrypsin. *Clin Chem* 1991; **37:** 1618-1628.
18. Stenman UH, Leinonen J, Althan H, Ranniko H, Tuhkanen K, Alfthan O. A complex between prostate specific antigen and alpha-1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostate cancer: assay of complex improves clinical sensitivity for cancer. *Cancer Res*1991; **51:** 222-226.
19. Christenssen A, Laurell CB, Lilja H. Enzymatic activity of prostate specific antigen and its reaction with extracellular serine proteinase inhibitors. *Eur J Biochem* 1990; **194:** 755-763.
20. Magulike NO, Aghaji AE, Chuka-Okosa CM, Eze BI. Prostatic carcinoma metastatic to the orbit presenting primarily as proptosis. *Journal of College of Medicine* 2002; **7:** 3-4.
21. Aghaji AE. Uretero-neo-cystostomy in the management of lower ureteric obstruction by carcinoma of the prostate. *Nigerian Journal of Surgery* 1998; **5:** 55-59.
22. Aghaji AE. Dexamethasone in the management of acute lower ureteric obstruction by carcinoma of the prostate. *Journal of College of Medicine* 2001; **6:** 66-69.
23. Aghaji AE, Ohaju-Obodo JO, Osegbe DN, Mbibu HN, Maitama H. Therapeutic benefits of maximum androgen blockade and tolerability of bicalutamide in patients with advanced prostate cancer. *Journal of College of Medicine* 2004; **9(2):** 72-76.
24. Aghaji AE, Ohaju-Obodo JO, Osegbe DN, Mbibu HN, Maitama H. Prognostic significance of prostate specific antigen (PSA) rate of change in patients with advanced prostate cancer. *Journal of College of Medicine* 2005; **10(1):** 53-57.
25. Liberman R, Bermejo C, Greenwald P et al. Progress in prostate cancer chemoprevention: modulators of promotion and progression. *Urology* 2001; **58(6):** 835-842.
26. Andriole G, Lieber M, Smith J et al. Treatment with finesteride following radical prostatectomy for prostate cancer. *Urology* 1995; **45(3):** 491-497.
27. Cote RJ, Skinner EC, Salem CE et al. The effect of finesteride on the prostate gland in men with elevated seum prostate specific antigen levels. *Br J Cancer* 1998; **78(3):** 413-418.

28. Steiner MS, Raghow S, Neubauer BL. Selective oestrogen receptor modulators for chemoprevention of prostate cancer. *Urology* 2001; **57(4 suppl. 1):** 68-72.
29. Krege JH, Hodgin JB, Couse JF et al. Generation and reproductive phenotypes of mice lacking oestrogen receptor beta. *Proc Natl Acad Sci USA* 1998; 95(26): 15677-15682.
30. Bonkhoff H, Fixemer T, Hunsickler I et al. Estrogen receptor expression in prostate cancer and pre-malignant prostate lesions. *Am J Pathol* 1999; **155(2):** 641-647.
31. Messina MJ, Morton MS, Griffiths K. Diet and its preventive role in prostatic disease. *Eur Urol* 1999; **35(5-6):** 377-387.
32. Fleshner NF, Kukuk O. Antioxidant dietary supplements: rationale and current status as chemopreventive agents for prostate cancer. *Urology* 2001; **57(4 suppl. 1):** 90-94.
33. Kotake-Nara E, Kushiro M, Zhang H et al. Carotenoids affect proliferation of human prostate cancer cells. *J Nutr.* 2001; **131(12):** 3303-3306.
34. Lu QY, Hung JC, Herber D et al. Inverse associations between plasma lycopene and other other carotenoids, and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2001; **10(7):** 749-756.
35. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor in prostate cancer? (Hypothesis). *Anticancer Res.* 1990; **10(5A):** 1307-1311.
36. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for protective effect of ultraviolet radiation. *Cancer* 1992; **70(12):** 2861-2869.
37. Tjarodrawinata RR, Dahiya R, Hughes-Fulford M. Induction of cyclo-oxygenase-2 mRNA by prostaglandin E2 in human prostate carcinoma cells. *Br J Cancer.* 1997; **75(8):** 1111-1118.
38. Gupta S, Srivastava M, Ahmed N et al. Over-expression of cyclo-oxygenase-2 in human prostate adenocarcinoma. *Prostate* 2000; **42(1):** 73-78.
39. Lupulescu A. Prostaglandins, their inhibitors and cancer. *Prostaglandin Leukot Essent Fatty Acids* 1996; **54(2):** 83-94.
40. Gibbs JB, Kohl NE, Koblan KS et al. Farnestyl transferase inhibitors and anti-Ras therapy. *Breast Cancer Res Treat.* 1996; **38(1):** 75-83.
41. Hudes GR, Szarko CE, Adams A. Phase 1 pharmacokinetic trial of perillyl alcohol (NSC 641066) in patients with refractory solid malignancies. *Clin Cancer Res.* 2002; **6(8):** 3071-3080.
42. Elom SO, Obidoa O. Effect of intervention with dietary supplements on the prostate specific antigen (PSA) levels of prostate patients in a Nigerian population irrespective of the sequence of the intervention. *J Sci Eng Tech.* 2007; **14(3):** 7523-7531.