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TOPIC:

A WOMAN EXPLORING THE PECULIAR DISEASES OF WOMANHOOD: MY ODYSSEY AS AN ACADEMIC PATHOLOGIST

By
PROFESSOR ADEKUNBIOLA AINA FEHINTOLA BANJO

A WOMAN EXPLORING THE PECULIAR DISEASES OF WOMANHOOD: MY ODYSSEY AS AN ACADEMIC PATHOLOGIST

An Inaugural Lecture Delivered at the University of Lagos Main Auditorium on Wednesday, 6th May, 2015

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DEDICATION

This lecture is dedicated to the memory of my late husband, Dr Taiwo Okundolapo Banjo, and the women, both known and unknown, who have suffered from the scourge of female cancers.

PROTOCOL

The Vice –Chancellor,
The Deputy Vice –Chancellors, (Academic and Administration),
The Registrar and Secretary to the Governing Council and Senate,
The Provost, College of Medicine, Idi-Araba,
The Dean, Faculty of Basic Medical Sciences,
Deans of other Faculties,
Members of Senate, University of Lagos,
Distinguished Ladies and Gentlemen.

INTRODUCTION

Mr. Vice-Chancellor Sir, distinguished ladies and gentlemen, it is a great privilege to stand before you today to give this lecture, , marking my inauguration as a Professor of Anatomic Pathology at my Alma Mater, the University of Lagos, the University of First Choice and the Nation's Pride.

This event is the culmination of a most serendipitous harmonisation of occurrences strewn over a period of about five decades. I marvel at how all these events, like pieces of a jigsaw puzzle, have come to fit nicely into the story being told today. God alone, the Father of our Lord, Jesus Christ, deserves all the glory and the accolades. I welcome you all to the 6th inaugural lecture of the University of Lagos for the year 2015.

Womanhood as defined by the Merriam-Webster dictionary is the state of being a woman i.e. when a girl reaches puberty, starts menstruating, develops breasts and is mature enough to become a wife and a mother. All these processes are associated with growth and cyclical proliferation of parts of the body. The inherent risk of some of the changes predisposes to neoplasm or tumours which can or may not be cancerous. "Diseases of womanhood" are mentioned in the title of this inaugural lecture because women's health, gender-specific diseases of women and the prevention of these diseases have been the focus of my specialist interest and research, and also to acknowledge the toll of various diseases upon women,

majority of which are preventable. Michelle Obama states that, "Women in particular need to keep an eye on their physical and mental health, because if we're scurrying to and from appointments and errands, we don't have a lot of time to take care of ourselves. We need to do a better job of putting ourselves higher on our own 'to-do' list." It is my hope that this statement by Michelle Obama would resound deeply with all the women seated here today as they listen to this lecture and that they would learn to put themselves higher up on their to-do lists.

Before we delve into the main theme of the lecture, I think it is appropriate that we take a brief look at the discipline of Pathology and its crucial role in the practice of Medicine.

What is Pathology?

The term pathology is used broadly to refer to the study of diseases in general, and the body's response to them. It includes a number of distinct but inter-related medical specialties that diagnose diseases mostly through the analysis of tissues, cells and body fluid samples. These specialties are Clinical Chemistry or Chemical Pathology, Medical Microbiology and Parasitology, Haematology and blood transfusion and *Anatomic Pathology*, my field of specialisation. The new emerging field of Molecular Pathology traverses all of the fields listed above and I have found it most useful for my some of research. A medical or veterinary doctor with postgraduate training and certification in pathology is called a pathologist.

The practice of pathology dates back to ancient times, but the broad field of Pathology developed significantly as a medical specialty during the 19th century. It evolved, not out of sheer curiosity but, primarily out of the need to improve the effectiveness of the physician in combating the diseases of humans and other living forms. Clinical Pathology or Laboratory medicine has become recognised as an integral field of Medicine with the evolution and development of new diagnostic investigations and tests, over the last 100 years . As observed by Tonellato et al,[1] "The discipline of Pathology

has served a central role in the detection, classification, and interpretation of cellular, biochemical, molecular, and microbiological markers of disease to guide treating physicians in the care and management of patients."

The Pathologist's Role in the Management of Diseases

At this juncture, I would like to enumerate 10 major steps involved in the evaluation of a patient for disease. These steps include:

1. The patient's presenting complaint (including the identification of the chief or the central complaint).
2. The history of the present illness.
3. Other relevant clinical history including a review of the systems, the past medical history, the family history, the social history, etc.
4. Complete and thorough clinical examination.
5. Categorisation of Disease (Generation of differential diagnoses).
6. Requisition of relevant clinical investigations.
7. The generation of a working diagnosis or a definitive diagnosis and an interim or definitive management plan.
8. Treatment.
9. The prescription of prognosis.
10. The follow-up of patients.

The pathologist is usually not involved in steps 1-3; however with increasing contact with patients than would first be imagined, pathologists are now frequently found in the wards or in the operating room, on consultations and seeing patients before some procedures are carried out or carrying out procedures. The expert contributions of a pathologist may be sought for Step 5 if an unusual case is involved, or confounding factors are found during history taking and clinical examination. For this reason, the pathologist is sometimes referred to as the doctor of doctors as he may be the umpire with the final word when a difficult case is encountered.

The pathologist is involved, to varying degrees, in the categorisation of disease, the process by which the diagnosis

is obtained, the generation of a treatment plan and prescription of prognosis.

In oncology or cancer centres in developed nations, patients are commenced on treatment as guided by joint decisions made at Multidisciplinary team (MDT) meetings with the pathologist and other experts from various relevant fields in attendance. These other experts include haematologists, medical oncologists, radiation Oncologists/ radiotherapists, radiologists, surgical or gynaecologic oncologists, general surgeons, cancer care nurses, allied health professionals (such as nutritionists, occupational therapists, physiotherapists, psychotherapists, speech therapists and social Workers) as well as General Medical Practitioners (GPs). Each member of the multidisciplinary team (MDT) provides specialised knowledge and skills, and they all collaborate together to make treatment recommendations that ensure quality patient care while maintaining to the greatest extent the physical, mental and psychosocial wellbeing of the patient who becomes diagnosed with a terminal illness such as cancer.

The duties and the responsibilities of a pathologist

There are 3 broad areas of practice within Anatomic pathology. These include Autopsy Pathology, Surgical pathology and Cytopathology.

Autopsy pathology involves the study of post-mortem specimens in order to determine the cause of death. It could be hospital autopsy or medico-legal autopsy. Knowing the cause of death not only provides information for health planners, it is also useful to the family for closure.

Surgical pathology involves the examination of histopathological slides made from processing tissues that have been surgically removed from the body. These slides are studied and the pathologist helps to determine if the lesion is cancer or not. If it is not cancer, is it a non-cancerous growth, an infection or an inflammatory lesion?

Cytopathology includes fine needle aspiration and the examination of exfoliated cells shed naturally into body fluids, (urine, sputum, abdominal fluid collections) or exfoliated artificially (e.g. Cervical scrapings, bronchial brushings etc.) or touch imprint of the surface of the tumour Fine needle aspiration involves the use of a fine needle, gauge 23 or less, (smaller than the 21 gauge that is used to give injections) to obtain samples from swellings in the body, with or without the addition of ultrasound guidance. The sample obtained is stained with Giemsa or Pap stains and the features of individual cells are studied.

In providing the various services offered by the pathologist, it is important to ensure accurate and timely reports for all the cases he is consulted on. For this purpose, appropriate quality control and quality assurance programs must be put into place. Quality control is defined as a system for verifying and maintaining a desired level of quality in an individual test or process. Quality control activities span the testing process from the moment of specimen collection until the time the physician receives the report. Quality assurance (QA) is defined by the College of American Pathologists as "systematic monitoring of quality control results and quality practice parameters to assure that all systems are functioning in a manner appropriate to excellence in health care delivery".

Pathologists have a crucial role in public health, contributing towards the prevention and the control of certain diseases and reducing the public health burden from such diseases by identifying those at risk. This role is best exemplified by the detection of pre-cancerous lesions that precede invasive cancer of the cervix.

Practice of Pathology

Mr. Vice-Chancellor Sir, before I proceed into my area of specialised interest and research focus, I would like to highlight the roles I have played as a lecturer and a consultant pathologist in the department of Anatomic and Molecular Pathology at the College of Medicine, University of Lagos and the Lagos University Teaching Hospital, over the last 23 years,

and my contributions to the development of Pathology in general.

Since I qualified as an anatomic pathologist in 1992, I have worked as a lecturer at the College of Medicine of the University of Lagos and as an honorary consultant pathologist at the Lagos University Teaching Hospital. During this period, I was instrumental to the establishment of a Fine Needle Aspiration Cytology (FNAC) clinic in the department. Several years later, during my sabbatical leave at Olabisi Onabanjo University Teaching Hospital (OSUTH), I also spear-headed the establishment of similar services at the Department of Morbid Anatomy and Histopathology.

The FNAC clinic in LUTH started in 1998 shortly after my return from my Master's degree programme in Clinical Cytopathologyat St. Mary's Hospital, University of London, England where I trained under the tutelage of Prof Dulcie Colman.

Fine Needle Aspiration Cytology (FNAC) is the technique in which cells are aspirated from a palpable lesion and examined under the microscope[2]. It is an affordable and minimally-invasive technique for harvesting cells which are then examined for diagnostic purposes. In experienced hands, it is safe and highly accurate. Since the establishment of the Fine needle aspiration cytology clinic nearly 18 years ago, over 10, 000 FNAC samples obtained from various organs have been examined by pathologists at our department. An 8 year analysis of the sites from which FNAC samples were obtained revealed that a total of 3,479 FNAC samples were performed between 2007 and 2014. The highest numbers of samples were obtained from the breast, the thyroid gland and lymph nodes from different regions; 61.4% of these samples came from the breast, 19.3% from the thyroid gland, and 8.7% from the lymph node.

Table 1: Most Common Sites for Fine Needle Aspiration Cytology and their Frequency (2007-2014).

Nature of specimen	Total number	Percentage
Breast	2203	61.4%
Thyroid	691	19.3%
Lymph node	311	8.7%
Salivary gland	162	4.5%
Soft tissue	112	3.1%
Liver	110	3.0%
Total	**3479**	**100%**

It is important to note here, that carcinoma of the breast is currently the most common malignant disease of women worldwide as well as in Nigeria[34] . The Triple Test, consisting of clinical Examination, radiological examination and FNAC has been found useful for the triage of patients with breast lump[5].The Triple Test is almost 100% accurate in the diagnosis of palpable breast lesions when all three elements are concordant. Cost analysis showed that elimination of confirmatory open biopsy in such cases and also in cases in which the fine-needle aspiration and one other element of the test had a suspicious or malignant result, saved a lot of money, compared to the triple test followed by routine confirmatory open biopsy[6].

Some of my efforts have been directed towards the establishment of a one-stop breast clinic at LUTH where clinical, radiologic and pathologic evaluation would be offered sequentially at a single clinic visit. Patients with palpable breast lumps are examined by the clinician, offered radiological investigations and they go on to have fine needle aspiration within a few hours. This would go a long way in helping to allay the fears and the anxiety of patients who may have to wait several days between one and the next of these investigative components of the triple test. The patient receives immediate feedback about the nature of the breast lump and is told the lump is benign, suspicious or malignant. Those with benign lesions are reassured and priority given to the management of those with suspicious or malignant lesions. FNAC can also be therapeutic when used to aspirate fluid from

breast in cystic disease, the most common cause of breast lumps.

Mr. Vice-Chancellor Sir, it is with great delight that I inform you and the rest of my audience today that, with sponsorship provided by Run for Cure, a Non-governmental organisation (NGO) with a focus on breast cancers, a team consisting of a pathologist, a surgeon and a radiologist have been sent to India for specialised training in preparation for the establishment of a one-stop breast clinic in LUTH.

Auditing, Continuing Medical Education and Quality Assurance

Clinical audit is part of the continuous quality improvement process and one of the key elements of clinical governance. Clinical governance is a systematic approach to maintaining and improving the quality of patient care within a health system. Clinical governance became important in health care after the Bristol heart scandal in 1995, during which anaesthetist Dr Stephen Bolsin exposed the high mortality rate for paediatric cardiac surgery at the Bristol Royal Infirmary. In the United Kingdom, clinical governance is defined as a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish." (NHS Executive, 1998)[7]

It rest on seven (7) pillars, namely:

1. Clinical Effectiveness
2. Clinical Audit
3. Risk Management
4. Education and training
5. Information management
6. Openness
7. Clinical Research

I will take you through some of my research work in the area of clinical audit for improving and maintaining the quality of

patient care within our health system, specifically in the practice of autopsy pathology.

Medical Audit

Medical audit can be defined as a detailed review and evaluation of selected clinical records by qualified professional personnel for evaluating quality of medical care with the aim of identifying areas for improvement and implementing change[8]. The main objective of medical audit in pathology as identified by Batstone is to improve quality both of the service provided and the quality of life for the patient rather than dealing with professional standards[9]. He also noted that it involved peer review of practice and could serve as an educational tool. He recognised that it is based on measurable standards which if not met, served as effective tools for change of attitude either within individuals or the organisation.

Medical audit is essential in assessing the efficacy of health care delivery system.

The use of autopsy services for medical audit is largely unrecognised and greatly under-utilized in this environment. It is looked upon indifferently by the clinicians and superstitiously by the public.

A ten-year audit of maternal deaths at the Lagos University Teaching Hospital was carried out to determine the causes of death and the frequency of death as seen at autopsy[10].The study included 445 women who died from pregnancy-related conditions. The cause of death was classified as direct or indirect. **Direct obstetric deaths** are those resulting from obstetric complications of the pregnancy, labour and the puerperium, from inappropriate intervention or treatment, omissions, or from a chain of events resulting from any of the above. **Indirect obstetric deaths** are those resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy. The findings showed that in 81% of the autopsies performed, deaths were due to direct causes **(Table 2)**. The three leading

causes were obstetric haemorrhage (25.61%), genital sepsis (19.68%) and pregnancy-induced hypertension (16.71%). The most common indirect cause was anaemia accounting for 70% of cases. The causes of obstetric haemorrhage include ruptured uterus (38.89%), ectopic pregnancy (18.95%) and retained placental/ products of conception (10.52%) **(Table 3)**.

Table 2: CAUSES OF MATERNAL DEATHS

		Number	Percentage
A	**DIRECT CAUSES**		
	Obstetric Haemorrhage	95	(25.61)
	Genital Sepsis	73	(19.68)
	Pregnancy Induced Hypertension	62	(16.71)
		51	(13.75)
	Abortion Complications	13	(3.50)
	Perioperative Complications	5	(1.35)
	Complications of Obstructed Labour (other than ruptured uterus)	1	(0.27)
	Acute Uterine Inversion with DC		
B	**INDIRECT CAUSES**		
	Anaemia	26	(7.01)
	Infections (non-genital tract)	22	(5.93)
	Hepatocellular Failure/Acute Hepatic	6	(1.62)
		5	(1.35)
	Intracranial Haemorrhages	3	(0.81)
	Aspiration pneumonitis	3	(0.81)
	Hypertensive Cardiovascular Disease	6	(1.62)
	Others		
	i. Chronic Ischaemic Heart Disease		
	ii. Acute-on-chronic Cor Pulmonale		
	iii. Bleeding Oesophageal Varies	**371**	**(100.00)**
	iv. Splenic Vein Rupture		
	v. Cerebral Malaria		

	vi. Diabetic Ketocidosis **Total**		

Table 3: CAUSES OF OBSTETRIC HAEMORRHAGE

Causes	Number	Percentage
Ruptured Uterus	37	(38.95)
Ectopic Tubal Pregnancy	18	(18.85)
Retained Placenta/Product of Conception	10	(10.52)
Post-operative Haemorrhage	10	(10.52)
Abruption Placentae	7	(7.37)
Genital Tract Laceration	7	(7.37)
Primary Post-Partum Heamorrhage	4	(4.21)
Placenta Praevia	1	(1.05)
Unspecified APH*	1	(1.05)
Total	95	(100.00)
*APH = Antepartum haemorrhage		

This study was carried out when the Late Prof Olikoye Ransome-Kuti was the Federal Minister of Health in Nigeria. Prof Ransome-Kuti made it compulsory for all maternal deaths to be autopsied to ascertain the cause of death in order for appropriate interventions to be made. Since that time, both the Federal Government of Nigeria and the Lagos State Government have gone on to establish blood transfusion services, making safe blood more readily available to manage postpartum haemorrhage, the most common cause of maternal deaths in addition to putting other strategies in place. Medical audit is not only useful for improvement of patient care; it can also be used to provide data for policy formulation and improvement of the society's well-being.

Observing the high rates of deaths from Road traffic Accidents in Benin, studies were designed to determine the patterns of morbidity and mortality amongst drivers involved in Road traffic Accidents (RTA) in Benin[11], as well as on Nigeria

motorcycle riders and their passengers[12]. Both studies were carried out between August 2003 and September 2004 and are quite illuminating.

The autopsy study carried out on drivers involved in Road traffic accidents in Benin-City showed that the drivers of mini-buses were the largest group involved (33.3%), followed by car drivers (27.9%)[10]. It is pertinent to note that commercial drivers accounted for about 61.2% of drivers. Majority of the drivers did not hold valid driver's licences and 25.1% died from severe injuries involving the head, deaths that could have been prevented by the use of seat belts. Alcohol abuse was also found to play a significant role in these accidents.

It is well documented that most of the buses in use were imported second-hand vehicles with questionable roadworthiness, carrying more than the recommended number of passengers and driven by over-speeding drivers. The drivers should have been counselled that there is more money to be paid on the formula one race track than attempting to get to their next destination by 'air'!

The second study sought to evaluate patterns of morbidity and mortality among bike-riders and pillion-seat passengers involved in road traffic accidents. A total of fifty-one (51) bike-riders and pillion-seat passengers, involved in road traffic accidents and enrolled into the study, were brought to the Accident and Emergency unit of either the University of Benin Teaching Hospital (UBTH) or the State Specialist Hospital in Benin. The injured patients were examined, resuscitated and managed while the dead ones were autopsied.

Findings showed that the 51 cases of accidents involving bike-riders and pillion-seat or passengers accidents represented 18% of the total accidents recorded. In 68.6% of the cases, motorbike riders/pillion-seat passengers were hit by cars, 13.5% were hit by articulated vehicles, 13.5% of cases were hit by buses, and 3.9% fell off the bikes following attacks of epilepsy and sustained secondary injuries. Males were more in number with a male to female ratio of 2.5: 1. It was also

observed that none of the motorbike riders or their passengers had crash helmets on at the time of the accidents. The most common cause of death among these autopsies was intracranial haemorrhage which could have been prevented by the use of crash helmets. Even though we had always previously known this anecdotally, we can now scientifically conclude that, for a fact, most bike-riders and their pillion-seat passengers are hit by cars, presumably because the "Okada riders", as they are popularly known in these parts, lack any form of training and have little or no knowledge about the highway code and other information relevant to road users.

The Bible says that the fear of the Lord is the beginning of wisdom. I, Kunbi Banjo would like to add that "the fear of motorbikes, popularly known as Okada, is the beginning of wisdom." A popular Nollywood movie, Akoto Olokada, which refers to crash helmets in English, has not helped matters in that it depicts motorbike riders who would place a charm on helmets, their passengers becoming zombies to be used for money rituals. If you are afraid of coming under the influence of a charm and you frequently use the okada as a means of transportation, my advice is that you buy your own crash helmet and carry it along with you at all times.

These findings reiterate the need for enforcement of legislation on the use of seat belts, helmets as well as safe driving and regulations on the consumption of alcohol.

Atubu A[13] in a Paper titled, "Determinants of road traffic accident occurrences in Lagos State" identified the following as strategies for prevention of road traffic accidents in Nigeria: constant training of drivers to ensure that they operate vehicles safely and comply with traffic regulations at all times; understudying countries such as the US and the UK with better traffic management systems; rationalising the use of traffic police check-points and adequate funding for the Federal Road Safety Corps of Nigeria.

On November 1st, 2013, the Lagos State government commenced the registration of public transport operators (bus

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Some of the issues addressed in the book include proper fixation of the tissues, an important prerequisite for immunohistochemical testing. Immunohistochemical testing for hormone receptors, (estrogen and progesterone) as well HER2/ neu (an oncogene or cancer promoting gene whose amplification or overexpression has been shown to play an important role in the development and progression of certain aggressive types of breast cancer) is used to guide the choice of treatment for breast cancers. It is well known that management of breast cancers should be individualised.

Continuing Medical Education and Quality Assurance in Histopathology

It is no longer acceptable for any doctor to remain in practice following the attainment of professional qualification without periodically participating in continuing medical education programs. This is because most of the knowledge acquired during training tends to become out-dated within a short period. In line with this, the Medical and Dental Council of Nigeria (MDCN) introduced participation in Continuing Medical Education program as a prerequisite for annual registration of all practicing doctors. While legislation is good for the purpose of enforcing compliance, doctors should recognise that it is their professional duty and responsibility to remain up-to-date in their specific areas of specialisation and in the field of Medicine, in general.

In Anatomic Pathology, continuing medical education is also an integral part of Quality Assurance. It includes processes taken to generate an accurate histopathology report and to enable easy retrieval and review (if needed) over a defined time period[16]. The processes involved could be divided into 3 aspects: pre-analytical, analytical and post analytical processes.

However, unlike in other disciplines of laboratory medicine, assessment of analytical aspects in histopathology is not easy given the subjectivity of the reports. Various modes of internal audits have been described and recommended, each with their advantages and disadvantages[17].

The following general recommendations were made to improve quality assurance in India, a resource-limited country, which may be applicable for use in Nigeria [15]:

1. For departments with more than one pathologist:
    a. Intradepartmental consultation (review of selected cases by colleagues)
    b. Comparison with other reports (frozen/cytology/histopathology)
    c. Random case review (blinded second review for previously reported cases that are randomly selected)
        i. By the same person (to check for precision)
        ii. By a different person (to check for accuracy)
2. Hierarchical form of reporting (slides are first reported by a junior colleague such as a trainee pathologist or resident doctor)
3. Intra- and interdepartmental conferences (clinicopathological conference (CPC)/clinical rounds)
2. For laboratories run by a single pathologist:
   Pathologists must be strongly discouraged from practicing in isolation. In the rare situation where a laboratory has to be run by a single pathologist, quality may be maintained by implementing the following:
    a. Random blinded review of reported cases (to check for precision)
    b. External consultations (this is required more regularly than when there are more pathologists on the team)
    c. Review by experts
    d. Participation in Continued Medical Education (CME) programs

A brilliant Nigerian pathologist, Dr. Uche Igbokwe, came up with the idea of the first indigenous Diagnostic External Quality Assurance (EQA) Programme for Nigeria as his own contribution to the development of Pathology in the country. Even though Dr. Igbokwe now practices Pathology in the United Kingdom, he had previously trained as a pathologist at the University of Benin Teaching Hospital, during which time he was sent to the Lagos University Teaching Hospital as a

supernumerary and I was opportune to have supervised his training. The idea was eagerly received and we ran with it. The program was run informally for a few years, and was formally launched in 2011. Since then, I have served as the Director of this program, and several local and international Nigerian Pathologists as well as a Ghanaian Pathologist have volunteered their services and served as facilitators/ resource persons for the workshops which hold twice a year, in May and November, in 3-4 centres across Nigeria. The Pathologists include Drs. Uche Igbokwe, Olorunda Rotimi, Tunde Diegbe, Adetola Daramola, Abideen Oluwasola, Kwame Ado-Poku, Rtd. Gen Yawale Iliyasu, Late Professor EEU Akang, and Prof Fatimah Abdulkareem. This Diagnostic EQA scheme has contributed significantly towards professional development and quality improvement among Nigerian pathologists. Before this EQA scheme was launched, though well established in some countries, such schemes were hitherto non-existent in Nigeria. In 2013, a presentation reviewing the program which, by then, had been running for 2 years, was presented at the Biennial congress of the International Academic of Pathology which held in South Africa[18].

The first workshop following the establishment of the EQA scheme held in May 2011. A practical demonstration and detailed explanation was provided about the concept of Diagnostic Histopathology EQA. Subsequently, slide sets (each consisting of 24 cases) were circulated around various centres across the country with a provision for confidential online responses to be sent in via the dedicated website for the EQA scheme. Even though most of the 60 participants in each workshop series had reviewed the slides, only 23 of them eventually submitted responses to circulation 001 (November 2011) and 16 to circulation 002 (May 2012).

Participants' reasons for not submitting responses include problems with the circulation of slide sets, internet access problems, aversion to being 'examined' and 'laziness' in the absence of any compulsion or regulatory requirement.

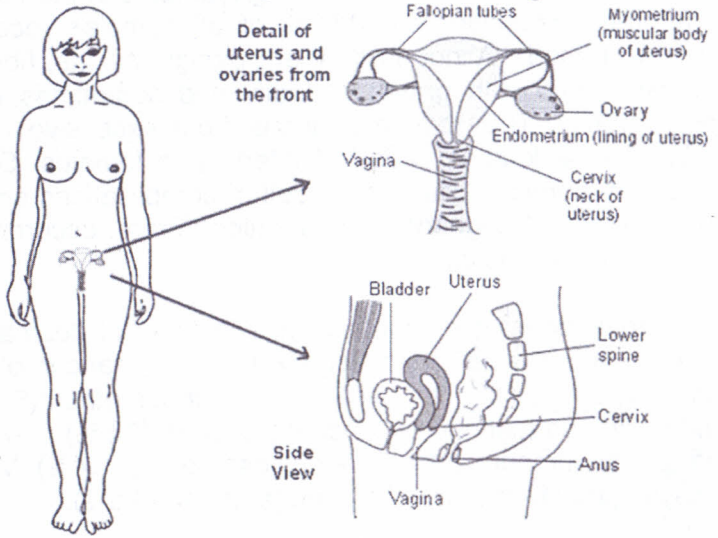
From the observations, it can be concluded that significant difficulties need overcoming in establishing a diagnostic histopathology EQA scheme in the absence of regulatory compulsion. The educational aspect seems to be popular and needs to be emphasized over performance assessment.

My Journey through the study of Pathology of the Female Genital Tract

As a trainee pathologist or resident doctor in pathology, I observed the relatively high frequency of samples received from women among the biopsies registered at the Department of Anatomic and Molecular Pathology. This prompted me to carry out a study on the morphologic patterns of tumours and tumour-like lesions of the female genital tract, seen over a 6 year period, for my thesis[19].

The female genital tract comprises of the womb (the body is known as the uterus and the neck as the cervix), the fallopian tubes, the ovaries, the vagina and the vulva **(Figure 1).**

Figure 1: Schematic Diagram of the female genital tract



A total of 2,238 cases were seen, majority of which were from the body of the uterus, (47.6%), the neck of the womb, (24.4%), and the ovaries (14.4%). Other sites include the

fallopian tubes, vulva and vagina which accounted for 10.5, 1.7 and 1.5% respectively. Majority of the tumours were benign with a benign to malignant ratio of 2.2: 1.

Table 6: Site Distribution and Frequency of Tumours and Tumour- Like Lesions of the Female Genital Tract

Sites	Percentage
Uterus,(body of the womb)	47.6%
Cervix,(neck of the womb)	24.4%
Ovaries	14.2%
Fallopian tubes	10.5%
Vulva	1.7%
Vagina	1.6%
Total	**100**

Although the body of the uterus had the highest percentage of tumours, majority were benign and mainly leiomyomas, commonly known as uterine fibroids. Other benign lesions seen include ectopic gestations, endometrial hyperplasia and benign ovarian teratoma.

Fibroids were the most common benign tumours in the female genital tract accounting for 32.9% of all samples received during the period. Although they are benign lesions, fibroids were associated with grave morbidity and sometimes even some mortality. They cause anaemia from excessive blood loss and are a leading cause of infertility in females. Some deaths from fibroids occur as a result of complications arising from treatment. Malignant transformation is rare, occurring in less than 1.0% of the cases.

The 10 commonest malignant tumours in order of decreasing frequency are, cancer of the cervix (72%) , cancer of the ovary (6.8%), cancer of the endometrium(5.4%), choriocarcinoma,(cancer of placenta tissue) (3.8%), Mixed mesodermal tumours(2.1%), Leiomyosarcoma(1.4%) Vulva (1.4%), vagina (1.4%) and immature teratoma (0.6%).

Table 7: Showing the 10 most common malignancies of the Female Genital Tract

Tumour type	Frequency (%)
Cancer of the cervix (Neck of the womb)	72 %
Cancer of the ovary	6.8%
Cancer of the Endometrium (Lining of the womb)	5.4%
Choriocarcinoma (Cancer of placental tissue)	3.8%
Mixed Mullerian Tumour (Mixed Tumour of the endometrium)	2.1%
Leiomyosarcoma (malignant Leiomyoma or Fibroid)	1.4%
Cancer of the vulva	1.4%
Cancer of the vagina	1.4%
Immature Teratoma (malignant germ cell tumour of the ovary)	0.6%

Similar findings were obtained in a review of female gynaecological tumours at the Olabisi Onabanjo University Teaching Hospital, Sagamu and Usman Dan Fodio University in Sokoto where cervix carcinoma was the most common[2021]. However Choriocarcinoma was the second most common malignancy in Sokoto in contrast to findings from Lagos and Sagamu where ovarian malignancies were the second most common.

Female genital tract neoplasms were not limited to adults only. A review of paediatric gynaecological neoplasms seen at LUTH between 1985 and 1990 showed that they accounted for 1% of gynaecological neoplasms[22]. In contrast to the findings in adults, the most common site was the ovary and the most common lesion was mature cystic teratoma, a benign germ cell tumour with components derived from the three germ cell layers, and characterised by the presence of skin and its appendages, hairs, bone, brain tissue etc. Other tumours seen in this age group were granulosa cell tumour (with patients presenting clinically with precocious puberty) and embryonal rhabdomyosarcoma, a specific subtype of malignant tumour of

skeletal muscle. In this age group, this tumour can also be observed in the walls of hollow, mucosa-lined structures such as the nasopharynx, the common bile duct, urinary bladder of infants and young children or the vagina in females is commonly seen.

Table 8: Tumour Type, Site and Frequency of Paediatric Gynaecological Malignancies (1985-1990)

Tumour type and site	Frequency (%)
Benign Neoplasm	
Benign Cystic Teratoma,(Ovary)	90.1%
Granulosa Cell Tumour,(Ovary)	9. 9%
Malignant Neoplasm	
Dysgerminoma,(Ovary)	50%
Burkitt's lymphoma,(Ovary)	25%
Embyronal Rhabdomyosarcoma,(Vagina)	25%

The most common malignancy of the body of the uterus was endometrial carcinoma. It accounted for 40.5% of malignancies and occurred in patients with age ranging from 32 to 86 years. Majority of the tumours were of the endometriod type. Endometrial carcinomas have been found to be associated with obesity, hypertension, low parity, oestrogen producing tumours of ovary, use of exogenous oestrogens as well as the use of tamoxifen for the treatment of breast cancer.

Tamoxifen is an anti-oestrogen drug with weak estrogenic properties that is known to cause endometrial hyperplasia, a precursor lesion for endometrial carcinoma. The first reported case of endometrial carcinoma following treatment for breast carcinoma in Nigeria was described in a 52 year old in Sagamu[23]. This occurred during the era when women were given Tamoxifen anecdotally before testing for hormone and HER/neu was widely available in Nigeria. On testing her breast sample, it was found to be hormone receptors negative, meaning she would not have benefitted from the treatment. This prompted a study to determine the hormone receptor status for breast cancers in Shagamu. [24] All histopathologically diagnosed tissue samples from the department of

Histopathology of the Olabisi Onabanjo University Teaching Hospital, Sagamu seen from January 2003 to December 2004 were examined and graded using the Elston and Ellis Modification of the Scarff-Bloom –Richardson grading system and stained for their oestrogen/progesterone receptor status. Forty-seven cases of breast carcinoma were seen during the period under study. Of these, 44 (93.7%) were invasive ductal carcinoma, with majority being poorly differentiated. Their ages ranged from 25-75 years with majority in the age group 40-59 years. The mean age was 47.3 years. Of the 27 cases that had their ERPR status analysed, 21 cases (77.8%) were ERPR negative, while only 3 (11.1%) were ERPR positive. This study shows that there is a predominance of high grade invasive ductal carcinomas that are likely to be ERPR negative, suggesting a biologically aggressive form of breast cancer in Nigeria with the possibility of poor response to hormonal therapy.

It is important that all patients receiving tamoxifen for the treatment of breast cancer are followed up routinely by the gynaecologist. The recommended follow up regimen for postmenopausal breast cancer patients intending to have treatment with tamoxifen includes a two-step evaluation: pre-treatment to classify those at risk of developing endometrial pathologies and on-going evaluation to ensure early diagnosis.[25]

Although thought to be rare, Mixed Mullerian Tumours of the uterine corpus are highly aggressive tumours of the endometrium with unusually large numbers seen over a 5-year period in LUTH[26]. It occurred most commonly between the 6th and 7th decades and the mean age of presentation was 62.2 years. In contrast to findings reported in literature, all the patients were parous with average parity of 3.9 children. Associated findings included hypertension (33%) and Diabetes mellitus (15%). In all the cases, death occurred within 6 months of diagnosis. The most common type was the heterologous type, (containing tissues that are not normally seen in the uterus) accounting for 66.7% of the cases.

Gestational trophoblastic Disease (GTD)

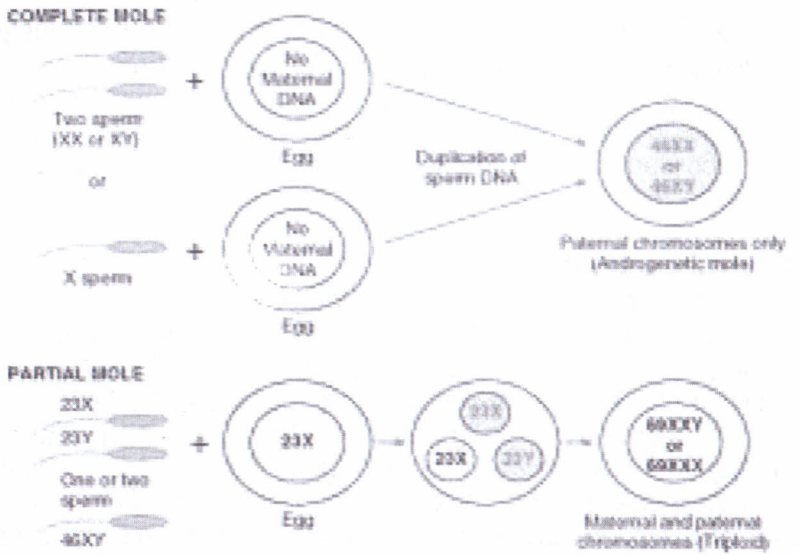
Gestational Trophoblastic Disease (GTD) is common in Nigerian women occurring mainly in the reproductive years. This is a group of diseases, including tumours (hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumour) and tumour-like lesions (exaggerated placental site, placental site nodule) that are related to trophoblastic proliferation. The trophoblast of the embryo develops into the placenta. Hydatidiform mole or molar pregnancy is benign; PSTT is usually benign but may be malignant; invasive mole and choriocarcinoma are malignant.

In a ten year review of Gestational Trophoblastic Disease in Benin, a frequency of 1:252 deliveries was observed[27]. Hydatidiform mole was found to be most prevalent (87.5%) while choriocarcinoma accounted for 12.5%. There are two types of hydatidiform moles: the Complete and the Partial.

Partial Molar Pregnancy: The partial mole is characterized by the presence of an abnormal placenta and some foetal development. Partial moles result from fertilization of an egg with two sperms. In these moles the karyotype is triploid or even occasionally tetraploid. Foetal parts are usually present. The risk of development of choriocarcinoma is low.

Complete Molar Pregnancy: There is an abnormal placenta but no foetus. The complete mole results from fertilization of an empty egg i.e. without the genetic material - all the genetic material derived completely from the father. In 90% of the cases, it results from the reduplication of the father's genes. The Karyotype is diploid, that is, they have the normal numbers of chromosomes. Patients have 2.5% risk of subsequent choriocarcinoma.

Figure 2: schematic Representation of the Pathogenesis of Hydatidifrom Mole



Choriocarcinoma: The prevalence of choriocarcinoma varies amongst populations. In the study from Lagos, it is the 4th most common malignant lesion, while in Sokoto, it is the 2nd most common[4]. It is important to note that when the correct diagnosis is made early, choriocarcinoma respond well to chemotherapy and is therefore curable. However, if detected late, they are highly aggressive, metastasizing widely and causing death from massive haemorrhage.

A case of metastatic choriocarcinoma to the small bowel presenting with upper gastrointestinal haemorrhage was reported in a young lady that had previously undergone uterine evacuation for a supposed miscarriage[28]; the sample obtained was however not submitted for histopathological examination. Death in this case could have been prevented if her sample had been subjected to histological examination, and appropriate treatment given.

Mr. Vice-Chancellor Sir, ladies and gentlemen, I use this opportunity to inform you and the public that all tissue samples

removed from the body must be subjected to histopathology examination for a definitive diagnosis to be made.

Choriocarcinomas have been known to occur spontaneously, following a normal pregnancy, a miscarriage or complicating a molar pregnancy most especially following the complete type. Progression from benign to malignant trophoblastic tumour was recorded in 17% of cases in a study reported by Agboola et al[29].

Cervical Carcinoma

Ladies and gentlemen, early in my journey in pathology as you can see, I was captivated by the peculiar malignant diseases of women, and more importantly, by the most depressing statistics of the consequences of the diseases. We see them when they are advanced and beyond mitigation, only palliation but then in a few cases. The gloom could have been lifted with the knowledge that we could screen healthy women to detect and treat the precursors and early forms of the diseases as you would see in my latter pre-occupation. Before I discuss that, I will like to explore with you - Cervical Cancer: the queen of cancerous diseases of womanhood.

With over 528,000 new cases every year, cervical cancer is the fourth most common cancer affecting women worldwide, coming after breast, colorectal, and lung cancers[30]. It is the most common malignancy of the female genital tract in Nigeria[4] . Majority of the cases occur in the developing world where it is associated with a high mortality[31]. The incidence of cervical cancer in the developed world has declined sharply as a result of well-organised screening programs utilising the Pap smear[32].

Hippocrates made the statement, "Declare the past, diagnose the present, and foretell the future." For no other disease is this statement more of an apt description than cervical cancer. I would like to digress slightly to give a brief history of cervical cancer, the past; the present and my research in cervical cancer and try to foretell its future.

Aretaeus of Cappadocia, a celebrated ancient Greek physician, gave one of the earliest descriptions of cervical cancer. He described it as superficial and deep ulcers which later infiltrate the uterus[33].

In 1842, Rigoni-Stern, a surgeon and an epidemiologist observed the rarity of cervical cancer in nuns compared to prostitutes[34]. This observation earned him the title of the Father of epidemiology.

Prof Han Hinselmann (1884-1945) invented the colposcope in 1925[35]. This tool revolutionised the follow-up and the treatment of cervical cancer and its precursor lesions.

Dr. Walter Schiller (1887 – 1960) invented the Schiller test, a simple test which uses iodine to differentiate between normal and abnormal areas of the cervix[36] . Because of the lack of glycogen in abnormal cervical tissue, the test is negative in precancerous cervix and positive in normal cervix. This test helps in the identification and diagnosis of cervical cancer in the pre-invasive stage and in the early invasive stage. Thus, the Schiller (Lugol's Iodine) test is a definite aid in locating the optimal site for cervical biopsy. Schiller advocated that cancer detection should be an integral part of every gynaecological examination. This method is still in use today and in conjunction with acetic acid staining; it is widely used for screening in resource poor countries[37].

The Pap test, which has revolutionised cervical screening and early detection of cervical cancer, was invented by Dr. George Papanicolaou (1883-1962)[38]. He observed that by examining smears from the vaginal vaults of women, he was able to pick up abnormal cells which later progressed to cancer.

Other notable events in screening for cervical cancer and its early detection include the development of the Ayre's spatula which allowed scrapings to be taken from both the ecto and the endocervix[39] .

Dr. Meig recognised that early diagnosis is the key to cure for cervical cancer (Meig's theory)[40]. She noted that both the doctor and the patient should pay attention to the symptoms especially vaginal discharge of more than 6 months' duration. She also recognised that surgery or radiation has the 2nd key to cure. She sought to know the cause of cervical cancer and advocated for early detection of this disease stating that "Propaganda surpasses its harm".

The First Screening in USA was organised by the American Society for Control of Cancer and National Cancer Institute (NCI) grant with the setting up of two clinics for screening between 1940 and 1943. This heralded the establishment of screening centres worldwide, and today in countries with organised screening for cervical cancer, the incidence has decreased drastically and it is no longer one of the four leading cancers among women. In the US, cervical cancer deaths decreased by approximately 74% in the last 50 years, largely due to widespread Pap smear screening[41].

Awareness of Cervical Cancer and Screening amongst Women in our Environment

Knowing that cervical cancer is a potentially curable cancer, with declining rates in the developed countries, stimulated the interest to find out why it was still ravaging Nigerian women.

A study was carried out to determine the level of awareness about cervical cancer and cervical cancer screening among women attending a primary health care facility in Lagos[42]. In the study, 500 women attending a primary health care clinic in a high-density and socioeconomically-deprived area of Lagos were interviewed to assess their awareness about cervical cancer screening. The ages of the women ranged from 16 to 49 years and the mean age was 25.64 years. Most of the women were uneducated with only 31% and 3.4% having completed secondary school and post-secondary education respectively. Most of the women were aware of breast cancer (80.7%) but only 3.4% had any knowledge of cervical cancer. None of those that were aware of cervical cancer had any knowledge that it could be prevented by screening. This study demonstrated poor knowledge about cervical cancer and

cervical cancer screening. Similar studies have been carried out by various authors in different parts of the country who also observed the low awareness among women about cervical cancer and screening with only very few women being able to identify the cause, the risk factors and the symptoms of cervical cancer[4344]. A lack of awareness was also identified as a barrier to uptake of cervical screening. Wright et al[45] in their study observed an increase in knowledge of women about cervical cancer and its associated risk factors following education and concluded that apparent efforts must be put in place by all stakeholders in reaching women at risk of cervical cancer through well-organised educational campaigns using culturally sensitive information, education and communication. It is pertinent to state at this point that if cervical cancer is to be controlled in the country, every effort must be made to enhance the knowledge of women about cervical cancer and to eradicate all barriers preventing the women from utilising screening services.

The Human Papillomavirus: Natural History and Causation of cancer

Human Papillomaviruses (HPV) are small (50-55 nm in diameter), non-enveloped, double-stranded DNA viruses which primarily infect epithelial cells of the skin and mucous membranes[46]

In 1976, Hausen found HPV in cervical cancer and genital warts. HPV 16 and 18 were recognised in cervical carcinoma in 1983 and 1984 respectively[47]. For his work, he was awarded the Nobel Prize for Medicine in 2008.

Over 200 types of HPV have been identified of which 40 types infect the genitals of males and females. Genital infection with the human Papillomavirus is estimated to be the most common sexually transmitted disease in the United States[48]. Its prevalence varies from country to country and amongst different groups. The prevalence amongst American Indians is 21.5% while in Athens, Greece, the prevalence was found to be 60% in a population based study. [4950]Amongst the Afro Caribbeans of Tobago, [51] a prevalence of 6% was obtained,

while In Ibadan, Nigeria the prevalence was found to be 26.3%.[52]

Human Papillomavirus is a sexually transmitted disease. Over 40 strains have been shown to infect the genital area and spread by skin to skin contact during sex.[53] The genital infections are categorised by their association with cervical cancer. Types 6 and 11, categorised as low risk, are associated with genital warts and benign cellular changes in the cervix, while types 16 and 18 are responsible for about 70% of cervical cancer.

Contact with HPV typically occurs during the first few years of sexual activity amongst adolescents or those in their early twenties[54]. Majority of infections clear up within two years, with more than 70% clearing up in the first year.[55] The highest prevalence of HPV is in women aged 20 to 24 years, and it decreases with age[56]. The decrease with age is attributed to acquired immunity from past exposure[55].This finding is in contrast to that of Thomas et al who found the prevalence to be high not only in young women but also in middle and old age in Nigerian females[52]. Dunne et al. in their study also reported a non-significant drop in HPV prevalence from age 24 to 59 years [55].

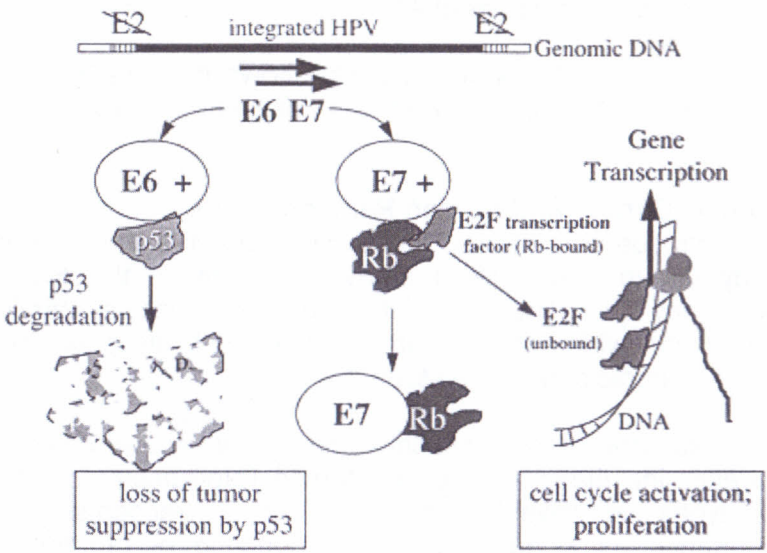
Many factors have been associated with persistent infection and these include older age, presence of high risk types, infection with multiple HPV types, and immune suppression.[55] Abnormalities caused by low grade infections usually resolve on their own with less than 1% progressing to cancer, while high grade lesions regress much less and progress more often without treatment[57].

In addition to viral persistence, other factors have been found necessary for cancer development. These include long term use of oral contraceptives, high number of live births, and co-infection with other STIs such as chlamydia, herpes simplex virus 2, cigarette smoking and diet.[58,59,60]

How does the Human Papillomavirus cause Cancer?

Most women become infected with the virus at the commencement of sexual activities and their immune system is able to clear the virus, usually within 2 years. In women with weak immune systems, the virus becomes integrated into their genes, interact with growth regulating proteins, promoting uncontrolled growth and "immortalisation" of the cells lining the cervix. The viral genes involved are called E6 and E7[61].

Figure 3: Schematic representation of E6 and E7 activities in cervical cells[62]



E6 from high-risk HPV binds tumour suppressor protein p53 and causes its rapid proteolytic degradation. The p53 protein normally suppresses cell proliferation by arresting growth of cells with damaged DNA in the G1 phase of the cell cycle, thus removing them from the cell cycle. Therefore, with less p53, the cells cannot suppress uncontrolled cell growth. Also it has been observed that some women have increased risk of cervical because of some genetic alterations in their p53.

E7 from high-risk HPV forms a complex with another human tumour suppressor gene, the retinoblastoma protein (pRB), and disrupts its binding to a transcriptional factor, E2F-1. The freed E2F-1 then stimulates DNA synthesis and uncontrolled cell growth E7 also inactivates the other CDKIs p21 and p27. E7 proteins from high-risk HPV types (types 16, 18, and 31) also bind and presumably activate cyclins E and A.

Of note, E6 and E7 protein from high-risk HPV types has a higher affinity for p53 and pRB than does E7 from low-risk HPV types. HPV-16 E6 and E7 together can also collectively cause cellular genetic instability.

From the above it has clearly been shown that the HPV is a definite carcinogenic virus and was designated so by WHO in 1996.

Cervical Cancer and Human Papillomavirus

The Retrospective International Survey and HPV Time Trends Study Group undertook a study to determine the Human Papillomavirus genotype distribution in invasive cervical cancer worldwide and our team of interested investigators was invited to participate in the study.[63]

A retrospective cross-sectional worldwide study was designed to determine the distribution of human Papillomavirus (HPV) genotypes in invasive cervical cancer recognising its importance as a guide to the introduction of prophylactic vaccines. It aimed to provide novel and comprehensive data about the worldwide genotype distribution in patients with invasive cervical cancer.

Paraffin-embedded samples of histologically confirmed cases of invasive cervical cancer were collected from 38 countries in Europe, North America, central South America, Africa, Asia, and Oceania. The inclusion criterion was the pathological confirmation of a primary invasive cervical cancer of epithelial origin in the tissue sample selected for analysis of HPV DNA. HPV detection was done by use of PCR with SPF-10 broad-spectrum primers followed by DNA enzyme immunoassay and

genotyping with a reverse hybridisation line probe assay. Also, sequence analysis was done to characterise HPV-positive samples with unknown HPV types.

Of the 10,575 cases of invasive cervical cancer included in the study, 85% were positive for HPV DNA. The most common HPV types were 16, 18, 31, 33, 35, 45, 52 and 58 with HPV types 16 and 18 detected in 71% of the invasive cervical cancers and HPV types 16, 18 and 45 detected in 94% of the cervical adenocarcinomas. One per cent of the HPVs were unknown and later identified by sequence analysis as 26, 30, 61, 67, 69, 82. Women with invasive cervical cancers related to HPV types 16, 18, or 45 were found to present at a younger mean age than did those with other HPV types. It is on record that this study is the largest assessment of HPV genotypes to date.

Further analysis of the samples from Nigeria revealed that of the 187 samples that were considered appropriate for HPV detection after histological evaluation, 160 (85.6%) were positive for HPV DNA[64]. The five most common types identified as single types among HPV positive cases were HPV16 (46.9%), HPV18 (19.4%), HPV45 (11.9%), HPV35 (5.0%) and HPV31 (3.1%). Others were HPV33, 39, 51, 52, 56, 58, 59, 66 and 68. HPV16 and 18 in single/multiple infections accounted for 69.4% of the samples. Multiple infections were detected in 4.4%. All the adenosquamous and neuroendocrine carcinomas tested positive for HPV, while 86.1% and 66.7% of the squamous cell and the adenocarcinomas were positive respectively.

Table 8: Detection of HPV/DNA in invasive cervical cancer cases from Nigeria, by age, at diagnosis and histopathological information

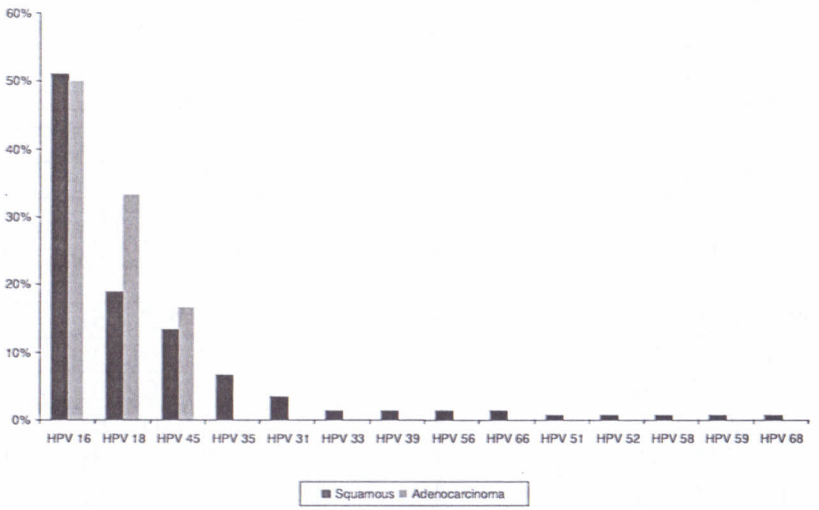
	Analysed cases [n]	HPV Positive cases [n]	HPV Detection [% (95% CI)]
Age (years)			
≤39	13	14	92.9 (79.4-100)
40-49	26	32	81.3 (67.7-94.8)
50-59	45	53	84.9 (75.3-94.5)
≥60	50	56	89.3 (81.2-97.4)
Miss4ing information	26	32	81.3 (67.7-94.8)
Histological type			
Squamous cell carcinoma	149	173	86.1 (81.0-91.3)
Adenocarcinoma	6	9	66.7 (35.9-97.5)
Adenosquamous carcinoma	2	2	100 (-)
Other types (neuroendocrine)	3	3	100 (-)

Table 9: Distribution of HPV types in invasive cervical cancer specimens from Nigeria

	HPV-type specific positive cases [n]	HPV-type specific relative contribution (n=160) [% (95% CI)]
Single types	***151***	*94.4 (90.8-97.9)*
HPV 16	75	46.9 (39.1-54.6)

HPV 18	31	19.4 (13.3-25.5)
HPV 45	19	11.9 (6.9-16.9)
HPV 35	8	5.0 (1.6-8.4)
HPV 31	5	3.1 (0.4-5.8)
HPV 33	2	1.3 (0.0-3.0)
HPV 39	2	1.3 (0.0-3.0)
HPV 56	2	1.3 (0.0-3.0)
HPV 66	2	1.3 (0.0-3.0)
HPV 51	1	0.6 (0.0-1.8)
HPV 52	1	0.6 (0.0-1.8)
HPV 58	1	0.6 (0.0-1.8)
HPV 59	1	0.6 (0.0-1.8)
HPV 68	1	0.6 (0.0-1.8)
Multiple types	***7***	***4.4 (1.2-7.5)***
HPV 16&45	2	1.3 (0.0-3.0)
HPV 16&18	1	0.6 (0.0-1.8)
HPV 16&35	1	0.6 (0.0-1.8)
HPV 16&51	1	0.6 (0.0-1.8)
HPV 35&45	1	0.6 (0.0-1.8)
HPV 35&51	1	0.6 (0.0-1.8)
Type X (uncharacterized type)	***2***	***1.3 (0.0-3.0)***
Potential vaccine impact of vaccinated types		
HPV16, 18, 16&18	107	66.9 (59.6-74.2)
HPV16, 18, 16&18, 16&45, 16&35, 16&51	111	69.4 (62.2-76.5)

Figure 4: Distribution of HPV types by histological diagnosis (squamous cell carcinoma and adenocarcinoma) in invasive cervical cancer specimens from Nigeria



**HPV single and multiple infections are counted.*

The above results are in consonance with reports from all other parts of the world that HPV 16 and 18 accounts for almost 70% of cervical cancers, supporting the data that effective vaccination against these 2 types will reduce the cervical burden in South-West Nigeria.

It is important to note that a third of invasive cancers are not associated with HPV16/18 indicating that screening for cervical neoplasia should be maintained after prophylactic vaccination against these types.

Apart from the number of virus identified in the studies above, a study was carried out to identify rare and possibly carcinogenic human Papillomavirus genotypes as single infections in invasive cervical cancer not detected in the earlier studies[65].

Further analyses were carried out on 331 HPV-positive invasive cervical carcinomas (ICCs) whose genotype remained unidentified by the HPV SPF10 PCR-DEIA-LiPA25. HPV26, 30, 61, 67, 68, 69, 73 and 82, and rare variants of HPV16, 18, 26, 30, 34, 39, 56, 67, 68, 69, 82 and 91 that were infrequently or never detected in ICC, were demonstrated in the samples by a novel sequence methodology, using multiple selected short regions in L1.

The identified genotypes were found to have close phylogenetic relationship with established carcinogenic HPVs and have been classified as possibly carcinogenic by IARC. The identified possibly carcinogenic types were detected only in squamous cell carcinomas, which were often keratinizing and diagnosed at a relatively higher mean age (55.3 years) than those associated with established carcinogenic types (50.9 years).

Mr. Vice-Chancellor Sir, since this study, Gardasil 9 (6, 11, 16, 18, 31, 33, 45, 52, and 58) has been introduced to protect against more strains of the virus, in particular those that are associated with cancers of the vulva, vagina, penis, anus and throat[66]. It should however be noted that this vaccine has potential to only protect against about 90% of viruses causing cervical cancer, therefore routine screening is recommended even for those that have been vaccinated. Also, the American Cancer Society recommends that there is no need for re-vaccination of those already given the Gardasil.

Human Papillomavirus and other Genital Cancers

With samples supplied by 183 collaborators from all over the world, the Retrospective International Survey and HPV Time Trends Study Group histologically confirmed Vulva Intraepithelial Neoplasm(VIN) and Invasive Vulva Carcinoma[6768](IVC) from 39 countries were examined for the presence of HPV and p16(INK4a) by immunohistochemistry. Invasive carcinoma was considered HPV driven if both HPV-DNA and p16 (INK4a) over-expression were observed simultaneously.

HPV-DNA was detected in 86.7% and 28.6% of the cases respectively and 25.1% of the invasive carcinomas were positive for both HPV-DNA and p16 (INK4a). IVC cases were largely keratinizing squamous cell carcinoma. The overall prevalence of HPV related invasive carcinoma cases were highest in younger women with squamous cell carcinoma with warty or basaloid features being more likely to be HPV and p16 (INK4a) positive. HPV 16 was the commonest type (72.5%) followed by HPV 33 (6.5%) and HPV 18 (4.6%).

Cervical Cancer and Screening

Anorlu[69] et al, while studying the cervical cancer screening practices of 503 general practitioners in two urban and two rural areas of Lagos state, noted that only 11.9% of the doctors had ever informed their patients about cervical cancer screening. It was observed that female doctors were more likely to offer screening than their male counterparts. Also, although 17.8% had facilities for Pap smears taking, only 5.4% screened their patients. Majority of those offering screening only did it selectively in 77.8% and routinely in (22.2%) of cases. It can therefore be concluded that only 1.2% of doctors offered routine screening. However, while routine screening was not being practiced, majority of doctors would do Pap smears for patients with post-coital bleeding and post-menopausal bleeding. The study thus concluded that cervical cancer screening practices and services in Lagos is inadequate and was no different from other parts of Nigeria and sub-Saharan Africa. It recommended that cervical cancer should be accorded the same attention as HIV, malaria, TB and childhood immunizations.

While doctors are not routinely screening patients in Lagos, a study was carried out to determine reasons behind non-uptake of cervical cancer screening by women who are aware of cervical cancer screening in southeast Nigeria[70].

In the study, a total of 3,712 women, attending gynaecologic clinics of 3 health institutions in Enugu, Nigeria, were interviewed by means of a questionnaire to determine those who were aware of cervical cancer screening and their bio-

demographic characteristics. The level of knowledge of cervical cancer screening of women who had been screened previously was compared with those of women who had no previous screening. Reasons for non-uptake of cervical cancer screening as well as potential reasons for undertaking cervical cancer screening were also extracted. Of these respondents, 55.2% were aware of cervical cancer screening; however only 19.0% of those who were aware of cervical cancer screening had undergone a previous screen. The study revealed that women in southern Nigeria do not go for cervical cancer screening because of poor understanding of cervical cancer prevention, feeling of violation of the privacy of their genitals, and poor health-seeking behaviour and recommends that there is a need to modify current policy approaches to cervical cancer prevention in Nigeria such that it addresses the privacy violation fears and poor health-seeking behaviour of the Nigerian woman.

Various authors have demonstrate the suitability of self-sampling to detect the presence of high risk HPV[71][72].There is an on-going collaboration with researchers in Ile-Ife to determine acceptability of self-sampling as well as detection of high risk HPV through self-sampling. If acceptable and found suitable, self-sampling would have addressed the issue of violation of privacy.

Methods of Screening for Cervical Cancer

The incidence of cervical cancer has reduced drastically through the organisation of Pap (conventional or liquid based Cytology) smear based routine services in developed countries.[73] [74] It involves early detection by screening of asymptomatic sexually active women between the ages of 25 to 65 years and by prompt treatment of all abnormalities. This has been difficult to do in less developed countries as a result of the lack financial capability required to provide the necessary infrastructure, manpower as well as a lack of political will.

Recognising this, various cheaper alternatives for cervical cancer screening have been recommended for use in resource

poor settings; one of the most popular is the Visual Inspection with acetic Acid (VIA)[75]. Various studies have advocated and supported the use of VIA in screening of women and the 'See and Treat' approach for women who are VIA positive has been adopted by WHO for use in resource poor settings[76 77]. The 'See and Treat' approach, using Visual Inspection with Acetic acid, is being advocated as a tool for routine screening for cervical cancer in Nigeria.

Background Information about VIA

VIA is a strategy proposed by the World Health Organisation (WHO) in 1985 as an alternative approach in developing countries where a meaningful coverage of all at-risk women by cervical cytology (Pap smear test) would not have been possible for decades to come. Unaided visual inspection of the cervix is referred to as 'downstaging' by the WHO. Variations on this theme include the Visual Inspection of the cervix after treatment with Acetic Acid solution (3-5% acetic acid,) otherwise known as VIA or after coating it with Lugol's Iodine (Visual Inspection with Lugol's Iodine, VILI). Abnormal areas turn white with acetic acid and brown with iodine, thus helping these areas to show up more clearly and be easily differentiated from surrounding normal areas.

At present, in the developing world, 80-85% of women with cervical cancer present to the treatment centres at advanced stages, when treatment no matter how sophisticated, fails to improve survival time.

The objective of the 'downstaging' approach is to improve the stage distribution of cervical cancer at the time of diagnosis with the aim of improving prognosis[78 79]. The results of the study by Basu et al[80] on the use of down -staging as a primary screening modality for cervical cancer showed sensitivities of 48.9% and 31.9%, respectively and specificities of 75.8% and 93.3%, respectively of low- and high-threshold downstaging to detect high-grade precursors and invasive cancers and concluded that downstaging is not suitable as an independent primary screening modality for cervical neoplasia. Other

authors have however shown significant reduction in the mortality from cervical cancer with screening using VIA[81].

VIA is a sub-optimal approach in comparison to the cervical cytological screening (Pap smear test). It is relevant in areas where there is a heavy load of prevalent cancer and screening by cervical cytology is not yet feasible but adequate treatment facilities are available. VIA is not expected to decrease the incidence of invasive cancer, but would decrease morbidity and mortality from the disease through detection at early stages [80].

Some noteworthy shortcomings of VIA include the following:

Specificity and sensitivity: The diagnostic accuracy of a test is measured by its specificity and sensitivity. The sensitivity of a test is its ability to identify true positives while the specificity of a test is its ability to identify true negatives. Hence, ideally, a sensitive test for a disease is one which is able to detect every case in which the disease is truly present and a specific test is one which adjudges as negative every case which does not have the disease. Such an ideal test does not exist. Although the sensitivity is comparable to that of cytology, VIA has low specificity[76]. It is also known that VIA is not able to identify cervical I lesions which are located high up in the cervix. VIA is even less sensitive for the detection of CIN (precancerous lesions). The aim in screening for cervical cancer is to be able to identify precancerous lesions and treat them appropriately so that their progression into cancer can be halted.

Women with precancerous lesions may be given a clean bill of health and gain a false sense of security and fail to seek any interventional methods until they develop cancer and cannot be helped significantly. These are called false negative cases. Inadequate health education about the benefits and limitations of VIA has led some women to believe that once they are told their VIA report is normal on one occasion, they are no longer at risk of developing cervical cancer.

Where women who do not have precancerous lesions may also be said to be positive for these lesions, unnecessary costs are incurred in follow up and treatment in addition to anxiety created in the patient. Such cases are called false-positive cases and are known to occur when benign tumours or infections cause redness, surface irregularities or distortions and or abnormal discharge.

If screening is done solely by the use of VIA which fails to identify so many positive cases, it then means that any estimation or documentation of the incidence and prevalence of CIN and the burden of cervical cancer related disease in Nigeria will be far from accurate. These details are important for documentation for the purposes of budget and planning and for the communication of any needs for assistance to international aid organisations. For it to be effective, it must be organised and community-based.

Recognising the poor specificity and high sensitivity for VIA as well as its high false-positive rates and the risk of overtreatment, a study was carried out to determine the histopathological findings in Acetic Acid Test (AAT) positive women.[82] .

Biopsies taken from the cervix of AAT positive females received in 4 laboratories in Lagos formed the materials for this study. The slides from these laboratories were retrieved and reviewed. The cases where classified as Normal, Benign, Cervical Intraepithelial Neoplasia (CIN), Invasive Squamous Cell Carcinoma and others. 116 cases were available for review. Thirteen were found to be unsatisfactory and excluded from the final analysis.

Of the 103 cases evaluated, majority 87 (84.5%) were benign with chronic cervicitis predominating 65 (61%). There were a total of 15 (14.7%) cases of CIN, of which, CIN I, II and III were 4 (3.9%), 3 (3.0%) and 8 (7.8%) respectively. Only 1 (1%) case of invasive squmaous cell carcinoma was seen. Other findings, 8(7.8%), were cervical polyp and squamous metaplasia. 16 (15.5%) showed normal cervical epithelium.

Table 10: Showing Histopathological Findings IN AAT positive Cervical Biopsy

Histopathological Diagnosis	Numbers (%)
Cervicitis	63(61%)
Normal Epithelium	16, (15.5%)
CINIII	8 (7.8%)
CIN I	4 (3.9%)
CIN2	3(3.0%)
Invasive SCC	1(1%)
Others	8(7.8%)
Total	**100%**

This study confirms the high rate of false-positive results with VIA, which will lead to overtreatment if a 'see and treat' policy is applied. It is recommended that it should only be used for mass screening of underserved rural populations and or in combination with other tests.

Screening with HPV

I was awarded a grant to undertake some work on the prevalence of HPV in our community by the Central Research Committee. This afforded me the opportunity to equip a lab for molecular studies and carry out research in HPV in collaboration with other researchers.

A prospective cross-sectional observational study was carried out to determine the prevalence of HPV in women attending a well woman clinic in Ile –Ife.[83] Cervical samples were collected from 118 consenting women visiting the clinic during the study period. Conventional Pap smear was obtained and smear results were classified using Bethesda classification, 2001.
HPV DNA was detected using the hybribio 21 HPV Geno array test kit which uses Polymerase Chain Reaction (PCR), amplification and flow through hybridization.

The mean age of the participants was 42.9 years (SD ± 10.9). A total of nine different HR-HPV types were identified with an overall HPV prevalence of 21.6%. The predominant HR-HPV types were HPV 16, 53, 18 and 52. In all, 41.7% of the infections involved more than one HPV type. Unlike in most

populations studied so far, HPV prevalence was high, not only among young women, but also in middle and old age. It was also observed that the prevalence of HR-HPV increases with parity.

This study shows that HPV 53 is the second most common type after HPV 16 in Ile- Ife. The high prevalence of HR-HPV in all age groups may be a distinctive feature of the population of the women where HPV transmission continues into the middle age and cervical cancer incidence is very high as also noted by Thomas et al.[52]

As a screening tool, Dillner et al recommend HPV Testing for primary screening, stating that it offers better long term predictive value for CIN 3 (or worse) than cytology alone[84] while Maryrand et al [85]also observed that HPV screening followed by Pap triage results in fewer referrals for colposcopy that did either test alone .

Sankaranrarayanan et al[86] carried out a Randomised trial of 131,746 women in rural India between the ages of 30 and 59 years. Women were randomly assigned to undergo screening by HPV testing (34,126 women), cytologic testing (32,058), or VIA (34,074) or to receive standard care (31,488 control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment. He found that, using HPV testing to screen for cervical cancer alone, there were 127 cases 34 deaths; Pap testing alone: 152 cases 54 deaths; Visual Inspection alone: 157 cases 56 deaths; and Counselling only:118 cases 64 deaths. From his study, he concluded that a single round of HPV testing was associated with a significant reduction in the number of deaths from cervical cancer in low resource settings and therefore recommends HPV for screening in resource limited countries. However the challenge is the cost of setting up HPV testing laboratories as well as time to get the results. The findings of Sankaranrarayanan et al were also corroborated by the work of Ajenifuja et al[87] that also confirmed VIA has not been reproducible nor was it sensitive

compared to cytology and HPV testing. They concluded that if 'see and treat' approach is adopted, it may lead to overtreatment and under treatment with dire consequences.

A study was carried out in Lagos to compare Visual Inspection with Acetic Acid, Liquid-Based Cytology and HPV-DNA Testing[88]. Out of the 208 screened, 199 (95.7%) were normal on VIA while 9 (4.3%) were screen positive. The LBC was abnormal in 13 (6.3%) cases comprising of 11 ASCUS and 2 HSIL that were VIA negative. HPV result comprised of 184 (88.5%) negative, 15 (7.2%) high-risk positive, 3 (1.4%) high- and low-risk positive, 5 (2.4%) low-risk positive and 1 (0.5%) HPV risk undetermined case. The 2 cases that were HSIL and hrHPV positive were confirmed by histology as CIN 3. There was no significant correlation between VIA and HPV ($p = 0.874$) while LBC and HPV showed statistically significant correlation ($p < 0.001$) .

It was concluded that LBC is more sensitive and specific than VIA in screening for precancerous cervical lesion and when combined with HPV testing, the sensitivity approaches 100%.

Human Immunodeficiency Virus (HIV), Cervical Abnormalities and HPV

Mr. Vice-Chancellor Sir, cervical cancer has been identified as one of the AIDS defining diseases and there are over four million people living with HIV/AIDS in Nigeria. To document the association in Lagos, a study was designed to determine the prevalence of abnormal cervical smear in Nigerian women who are HIV positive[89].

Cervical smears were taken from 233 HIV positive women and 235 HIV negative women who attended the HIV clinic and the family planning clinic respectively of the Lagos University Teaching Hospital during the period January-April 2004.

The findings showed that the prevalence of squamous intraepithelial lesion (SIL) was higher in those who were HIV positive than in those who were HIV negative, 10.9% vs. 4.3%. However, there was no significant difference in the prevalence of inflammatory smears in the two groups.

These findings were supported by another study carried out to determine the prevalence of and types of abnormal smears in HIV positive women as well comparing their frequencies with the CD4 counts[90]. The study documented the higher prevalence of abnormal smears in HIV positive women compared to HIV negative women as well as a relationship with the CD4 counts.

A cross sectional study of HIV positive women attending a large HIV treatment centre in Lagos, Nigeria carried out to assess the willingness and acceptability of cervical cancer screening among HIV positive showed a high level of awareness of cervical cancer in (56.2%) of the participants, although previous cervical cancer screening was low: 9.4%. Findings from the study showed that HIV positive women were willing to be screen for cervical cancer; however, the cost of the test (35.2%) and religious denial (14.0%) were identified some of the barriers to testing[91].

Mr. Vice-Chancellor Sir, various studies have alluded to the high prevalence of HPV amongst HIV positive women and that they are more likely to be infected with high risk HPV with the risk of progressing to cancer[92] [93] [94]. It has also been suggested that HIV may play a role in the underlying HPV18 and HPV45's contribution to cervical cancer.[95]

Since there is a paucity of data regarding the prevalence of sexually transmitted HPV infection among HIV positive women in Nigeria, a study was designed to determine the prevalence of high risk HPV among HIV positive and negative women in LUTH, Lagos, Nigeria and to relate HPV genotypes in the study population to commercially available HPV vaccine types that would be or not be appropriate for implementation of vaccination programs in Lagos State[96]. Screening was done using the Hybribio 21 HPV genoarray kit for the genotyping of HPV from samples obtained from 98 HIV positive and 97 HIV negative women. Data was analysed using Epi info 3.5.6.

Findings showed that the prevalence of HPV among HIV positive women was 44.9% while the prevalence of HPV among the HIV negative women was 11%. The prevalence of high risk types was 37.5% amongst the HIV positive women and the commonest high risk types seen were types 31, 52, 53 and 35. The commonest high risk types seen in HIV negative women were types 18, 16, 52 and 56.

From our findings of a high prevalence of cervical abnormalities and high risk HPV amongst HIV positive women as well as the willingness of the women to be screened for cervical cancer, it is recommended that reproductive health service is integrated into existing HIV programmes. Studies should also be carried out to determine the efficacy of existent HPV vaccines on this group of patients.
Mr. Vice-Chancellor Sir, having dealt extensively on cervical cancer, the story will not be complete without a mention of penile cancers.

Knowing that cervical cancer is caused by a sexually transmitted virus, we sought to determine and document the prevalence, age distribution, site and histologic types of penile carcinoma at the Lagos University Teaching Hospital Idi-Araba over a 20 year period[97].

All cases of the penile carcinoma recorded in the surgical pathology register of the Department of Morbid Anatomy, the Cancer Registry and the Medical Records Department of the Lagos University Teaching Hospital over a twenty year period were reviewed. Information extracted included the age, site of lesion, and histopathologic type. The histopathology slides were re-examined to confirm the diagnosis and to grade the lesion. The data was analysed using simple statistical methods.

The findings showed that there were only 7 cases of carcinoma of the penis accounting for 1.9% of malignant lesions of the male genital tract in LUTH, 3 (42.85%) of which were on the shaft of the penis. The ages of the patients ranged from 42-79 years with a mean of 52.2 years; majority (42.92)

of the cases were in the 5th decade. All the cases were well differentiated squamous cell carcinomas. It was difficult to comment on mortality because most of the cases were lost to follow-up.

It can therefore be concluded that while cervical cancer is very common, carcinoma of the penis is rare and the rarity may be attributed to the practice of neonatal male circumcision in Nigeria as suggested by other authors[98].

Before I go on to my recommendations, I would like to leave this quote by Roseanne Barr for the women in the audience. "The thing women have yet to learn is nobody gives you power. You just take it".

I hope we would all take the power to have control over our minds, our health, and our wellbeing. Please present yourselves for cervical screening!

The Way Forward

Mr. Vice -chancellor sir, going forward from where we are, I have asked myself the following question: what would I like to see done to aid our modest on-going efforts in this field so that the burden of these peculiar diseases on the Nigerian woman may be reduced?

First, my most burning desire is to see the establishment of an organised cervical cancer screening program available to all women in Nigeria without discrimination between the services offered to urban and rural women. This should be cytology and or HPV based and integrated into the National Health Insurance Scheme (NHIS).

I quite grant that this may not be achievable in the short term but it is possible now to institute efforts between the various Ministries of Health and Women's Affairs to develop well thought health education policies to educate women about preventive health issues in general and female specific cancer prevention strategies. This I believe may lead to improved health seeking habits of women.

Further studies are needed to determine the role of other markers such as p16inka for viral integration and viral oncogenes in screening.

The national policy recommending the 'See and Treat' approach to cervical cancer screening should be reviewed and all efforts made to assess the role of combined cytology and HPV testing for cervical cancer.

Cervical cancer screening should be integrated as part of the follow-up for HIV positive women and the role of vaccination in this group of women should be evaluated.

Whereas, Vaccination against HPV is a potentially useful strategy for prevention, and it should be made readily available and affordable, however, in my opinion, it is pertinent to state here again that women should continue going for the Pap smear test even after vaccination because the vaccines currently available in Nigeria protect against about only 70% of the cervical cancer-causing viruses.

The role of External Quality Assurance Schemes in delivery of quality anatomic pathology services should be recognised and incorporated into the Continuing Medical Education CME requirements for annual registration of practicing pathologists. Sub specialisation should be encouraged in anatomic pathology and tertiary hospitals should be adequately funded so that they are able to compete at the international level.

Mr. Vice Chancellor Sir, it is to the achievement of these ends that I intend to devote the rest of my days as an academic hospital pathologist, harnessing the opportunities devolved to me as a professor in this great citadel of learning.

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Ladies and gentlemen, I thank you for accompanying me through my journey in Pathology; thank you for your attention. God bless you all. God bless Nigeria.

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