

# Cervical Cancer Screening An Essential Component In Reducing The High Incidence Of Cervical Cancer In Nigeria. A Review Of The Current State Affairs

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## Abstract:

**Background:** Cervical cancer is the leading genital tract cancer and a leading cause of cancer related deaths in low and medium resource nations like Nigeria. The burden of cervical cancer is even more worrisome in light of its preventable nature. Many countries have successfully and significantly reduced its incidence using well defined national screening programs that utilize interval based cervical cytology screening, some have introduced co-testing with screening for high risk Human Papilloma Virus. Due to the various constraints affecting countries like Nigeria simpler techniques such as the use of visual inspection with acetic acid and/or visual inspection with Lugol's iodine have been used with satisfactory outcomes.

**Objective:** The aim of this article is to reacquaint local healthcare providers with the basics of the evolution of the disease and strategies that can greatly reduce the incidence and mortality associated with cervical cancer.

**Data source:** Electronic searches were done on Pubmed, Embase, Cochrane library, MEDLINE and Google scholar for relevant articles on the subject matter.

**Conclusion:** The need for reinforcement of, the grossly inadequate, currently available healthcare provider initiated cervical cytology with pap smear is obvious. This must be augmented with cervical health education, vaccination, visual inspection techniques, the see and treat approach and Human papilloma virus testing. Ultimately a national screening guideline needs to be implemented. All this will definitely reduce the unacceptably high incidence of cervical precancerous lesions and cancer.

**Keywords:** Cervical cancer, Cytology, Precancerous, Vaccine, Human papilloma virus, Nigeria.

## I. INTRODUCTION

Cervical cancer is a global disease with a disproportionately higher incidence and associated mortality (85% of cases and 87% of mortalities) occurring in low resource countries located in sub Saharan Africa, South-Central Asia, Central America and Melanesia. Globally, it is responsible for 275,000 deaths annually. There are 36.59 million Nigerians, aged 15 years and older, who are at risk of cervical cancer. In Nigeria, the national incidence of cervical cancer is 250/100,000.<sup>5</sup> A study in 2011 reported that cervical cancer was the leading cause of gynecological cancers in Northern Nigeria, accounting for 65.7% of all gynecological cancers. This high incidence was also observed in the Nigerian cities of Ibadan and Maiduguri with 62.7% and 72.6% respectively. The lowest incidence and mortality rates are seen in countries where cervical cancer screening is readily

available. The causal effect of the Human Papilloma virus (HPV) has been well elucidated in cervical cancer and its precursor lesions. Over 90% of cervical cancer specimens test positive for high risk HPV. One study showed 100% positivity to high risk HPV (hrHPV) in samples with abnormal cytology. The Human papilloma virus is sexually transmitted through intimate skin contact. The impact of population-based screening is evident in a marked reduction in the incidence of cervical cancer over the past 50 years in countries with established cytology-based screening programs. In Nigeria what currently exists is healthcare provider initiated cervical cancer screening programs that educate and encourage women to have cervical cytology. The Papanicolaou test is the commonest screening method employed in Nigeria at the moment. It is mainly offered at tertiary health care centres, expensive private health care institutions and research based facilities which are largely concentrated in the urban areas.

Those in the more rural areas who account for a significant proportion of the countries population have almost no access to any form of cervical cancer screening.

## II. THE CERVIX AND THE HUMAN PAPILLOMA VIRUS

Infection of the cervix with HPV has been shown to clear over the course of 6 to 24 months. The cervix which lies at the base of the uterus, constituting its lower third, and partly projects into the anterior aspect of the vagina. With regard to carcinogenesis, it can be viewed topologically as a 2-dimensional ring of epithelium. It has two parts; the ectocervix and the endocervix. It has an area of metaplasia that is quite dynamic. The ectocervix is lined by squamous epithelium and has a meeting point with the columnar epithelium, that lies superiorly lining the endocervical canal, at the squamocolumnar junction[SCJ]. This junction continues to change in position due to squamous metaplasia. The area between the original SCJ and the new SCJ (the junction of the superior border of the area of squamous metaplasia and the columnar epithelium) is termed the transformation zone. Figure 1 outlines these areas and how they change with age.

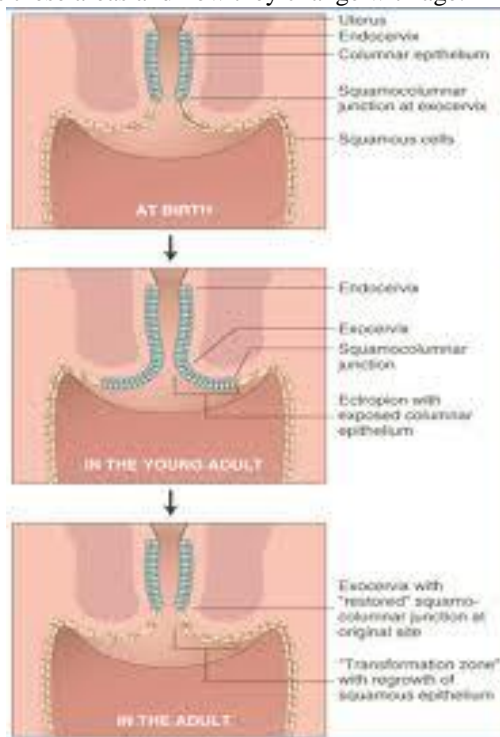


Figure 1: The dynamic SCJ and the transformation zone

The transformation zone contains the area of squamous metaplasia which is the site of most neoplastic change. The Human Papilloma virus has over a hundred subtypes of which over 40 are sexually transmitted. Persistent, long term HPV infection is the central causal agent.

Fifty years ago, for squamous histology, the cervical cellular abnormalities viewed as the precursors of cervical cancer were termed mild, moderate, or severe dysplasia; severe dysplasia was distinguished from the more severe diagnosis of carcinoma *in situ*. Richart in the 1960s, proposed the concept of intraepithelial neoplasia. CIN3 encompassed

severe dysplasia and carcinoma *in situ*, CIN2 replaced moderate dysplasia, and CIN1 later came to include both the microscopic evidence of HPV infection (koilocytotic atypia) and mild dysplasia. The severity of the diagnosis was based on the degree of replacement of the normal stratified epithelium with mitotically active basal-like epithelium ( $\leq 1/3$  = CIN1,  $\leq 2/3$  = CIN2,  $> 2/3$  = CIN3). CIN was viewed as a stepwise progression, with a high probability of transition from the more minor to more serious cancer precursors.

Over time, CIN1 was found to be a poorly reproducible and insensitive histologic diagnosis of acute and mostly transient HPV infection. CIN2 was reconsidered as a heterogeneous borderline category between acute HPV infection and the more likely cancer precursor lesions (CIN3). The risk factor profiles and HPV genotype distributions in CIN2 and CIN3 are different, and CIN2 is more likely to regress spontaneously compared to CIN3, but current clinical management of CIN2 and CIN3 diagnoses is very similar. The histologic nomenclature did not formally change, however, to a 2-stage system (low-grade lesion reflecting acute HPV infection, high-grade lesion representing cancer precursor to be treated) until the Lower Anogenital Squamous Terminology (LAST) conference in 2012. The LAST nomenclature relies on p16 staining to triage CIN2; p16 is a biomarker of disruption by HPV of the Rb pathway. CIN2 that is p16-positive is combined with CIN3 to form high-grade squamous intraepithelial lesion (HSIL), representing the immediate precursor to cervical cancer. CIN2 negative for p16 is combined with CIN1 to form low-grade squamous intraepithelial lesion (LSIL), representing the histologic sign of HPV infection.

Of crucial importance are the high risk subtypes that have been clearly implicated in carcinogenesis. The carcinogenic types of HPV are genetically related and found in several species of the alpha HPV genus. The established carcinogenic types (high risk HPV) include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The most important HPV subtype is 16, which is responsible for only 20% of infections but which causes 40% of high grade squamous intraepithelial lesions (HSIL) and half of the cases of cervical cancer. The next most important subtype is 18 and it is also preferentially responsible for adenocarcinoma. However subtype 18 is underrepresented in cancer precursors compared with its importance in cervical cancer. Jointly subtypes 16 and 18 account for 70% of cervical cancers. Viral genomic variation, when it comes to etiology, is so important that even subtle variations within viral types (called viral variants) influence risk of progression and invasion.

Other risk factors that have been identified in cervical cancer are; sexual debut at an early age, multiple sexual partners, cigarette smoking and long term use of combined oral contraceptives.

## III. SCREENING TECHNIQUES

The commonest is the Pap test/smear. The Pap test is a complex system of laboratory and clinical procedures, which has been widely used globally in the diagnosis of precancerous and cancerous lesions of the cervix. It is a secondary

prevention method, aimed at identifying the precancerous lesions that need follow-up and/or treatment. It was named after George N. Papanicolaou who first discovered that cervical cancer cells might be observed in human vaginal smears made from exfoliated cells collected from the posterior fornix of vagina. Later, a Canadian gynecologist, Ernest J. Ayre, in 1947 documented an easier and more efficient method of using a wooden spatula to obtain smears directly from the cervix. The sample for Pap test should ideally pick up cells from the squamous epithelium of vaginal extension of the cervix, the transformation zone, as well as the endocervix. In order to enhance sample collection, the Ayre spatula was modified into extended tip spatulas such as Aylesbury; cytobrush and other endocervical brushes were also introduced. Their shapes enable them to be inserted deeper into the endocervix. The cytobrush should not be used alone, and when used in conjunction with the conventional Ayre spatula, the number of inadequate smears is decreased and hence the false negative rate. The Pap test requires fixing of the cervical scraping on a glass slide followed by Papanicolaou staining and manual analysis under the microscope. It has a sensitivity of only 51% and false negative rate of 5-10%.

Liquid based cytology (LBC), represents the first advance in nearly 50 years in cervical cancer screening technology. The ThinPrep® Pap test (Hologic, Inc, Marlborough, MA) was the first of this new methodology to gain approval from the US Food and Drug Administration (FDA) for use in cervical cancer screening. This test provides clinicians a more sensitive and specific methodology with which to diagnose cervical dysplasia. Subsequently, the SurePath® Pap test (Becton, Dickinson and Company, Franklin Lakes, NJ) was approved. Today, LBC accounts for over 90% of the Pap tests performed in the United States. The approved liquid based cytology (LBC) products by FDA claim a 65-percent increased detection rate of high grade squamous intraepithelial lesions (HSIL) compared with conventional smears, as well as decreased unsatisfactory sample rates. Evidence shows that liquid based preparation is more sensitive and accurate for the detection of both squamous and glandular lesions of the cervix. Studies of the accuracy of liquid based preparations report sensitivity of 61-66% and specificity of 82-91%.

Visual inspection with acetic acid and visual inspection with Lugol's iodine have been shown to be effective screening techniques that were initially designed for resource limited nations like Nigeria. One study demonstrated the sensitivity and specificity of VIA and VILI to detect CIN 2+ lesions were 82.6% and 86.5% for VIA, 87.2% and 84.7% for VILI respectively. This is however in sharp contrast to studies showing a low specificity compared to cytology and a high rate of false positives. Entities such as inflammation, cervical condyloma and leukoplakia can give false positive results of VIA test. These visual methods are not expensive and do not require prolonged training of personnel. The inspection of the cervix following the application of 3 – 5% acetic acid produces aceto-whitening in undifferentiated cells producing a positive VIA or in the absence of obvious aceto-whitening it is a negative VIA. Inspection with Lugol's iodine is positive in the presence of yellow areas with poor iodine uptake. A study done in India showed that these techniques in the hands of

health workers (who had just 1 year of training in cytotechnology) yielded significant reduction in the risk of developing cervical cancer.

HPV testing, this can be done using: Digene Hybrid Capture 2 High-Risk HPV DNA Test, APTIMA HPV Assay, Cervista HPV 16/18, or Cervista HPV HR test. Its use in Nigeria is very sparse. Co-testing using cytology plus HPV testing is a method that is gaining popularity.

The use of certain biomarkers as possible screening tests are being investigated, for example the use of p16, a cyclin-dependent kinase-4 inhibitor. It is expressed in a limited range of normal tissues and tumors and has been identified as a biomarker for HPV transforming infections. Its use has been initiated because, over time, p16 accumulates in the nucleus and can be detected by immunostaining. It however has a place in the current histological designation of CIN lesions as already mentioned. Another biomarker of interest; hrHPV E6/E7 oncogenes which are highly expressed in parabasal cells of high-grade CIN and interact with p53 and pRB, respectively. In this way, they interfere with cell cycle control. As a consequence, uncontrolled proliferation and chromosomal instability occur, resulting in additional (epi) genetic changes. Therefore, detection of elevated E6/E7 mRNA levels in cervical smears has been suggested to be an attractive biomarker. These biomarkers currently have no place in cervical cancer screening as it relates to Nigeria.

#### IV. BETHESDA CLASSIFICATION

This is used for the interpretation of Pap smear/ liquid based cytology. The Bethesda system was developed in 1988, revised in 2001 and updated in 2008. It helps standardize terms in reference to cytology reporting. It recognizes the following:

Atypical Squamous Cells (ASC) of “undetermined significance” and “can not exclude high grade lesion”, referred to as ASC – US and ACS-H respectively. A cytological report of ASC-US warrants either of the following 3 options; 1) Repeat pap smear in 6 or 12 months. 2) HPV testing. 3) Immediate colposcopy.

Low grade squamous intraepithelial lesion (LSIL) which is equivalent to CIN I on histology.

High grade squamous intraepithelial lesion (HSIL) which is equivalent to CIN II & CIN III.

#### V. HPV VACCINES

There are 3 of them that are currently available; Cervarix, Gardasil and Gardasil 9. Their role is in primary prevention. Cervarix (bivalent vaccine) is effective against HPV 16 & 18. Gardasil (quadrivalent vaccine) is effective against HPV 6, 11, 16 & 18. Gardasil 9 (nonavalent vaccine) is effective against HPV 6, 11, 16, 18, 31, 33, 45, 52 & 58. It is recommended that they be given to all females at 11 – 12 years of age routinely, as well as girls and women age 13 – 26 years who have not been vaccinated (catch-up population), it can be given as early as 9 years of age.

## VI. THE CHALLENGES OF CERVICAL CANCER SCREENING

In Nigeria the challenges are far reaching and include; a lack of awareness of cervical cancer screening and poor uptake of available screening methods. A study done in Onitsha (Southeast Nigeria) showed that only 35.6% of respondents were aware of this test, while just 1.78% had done a pap test. The level of awareness of cervical cancer screening in other areas were 52.8% in Owerri, 69.8% in Ilorin, 70% in Ibadan. Other factors include inadequate health care and public health infrastructure, competing health priorities, and persistent poverty prevent large-scale cervical cancer prevention programs from gaining traction. At the moment only an estimated 5% of women in Sub-Saharan Africa have ever been screened. High rates of HIV infection in the region further escalate cervical cancer incidence through an increased risk for Human Papillomavirus (HPV) infection (the central causal agents) and possibly an accelerated progression of cervical neoplasia. Growing anti-retroviral use in recent years is extending lifespans for HIV-infected women, without a clear benefit for cervical cancer outcomes. This increases the number of women living longer with excess cervical cancer risk. The absence of a clearly defined national screening program in Nigeria is another obvious pitfall. In the USA where cervical cancer has been on the decline for the past few decades due directly to screening using cervical cytology, the American College of Obstetricians and Gynecologists (ACOG) protocol clearly spells out the entry point, frequency and the end point for screening. It points out that cervical cytology should begin for every woman by age 21 years, irrespective of HPV vaccination status. Afterward, she should continue with 3 yearly screening until the age of 29 years. From the age of 30 years, cotesting with HPV testing should be done 5 yearly till age 65 years, however the screening interval of 3 years with cytology alone for women who are between 30 – 65 years is still acceptable. Cervical cancer screening should stop at age 65 years among women who have three or more negative cytology results in a row and no abnormal test results in the past.

## VII. CONCLUSION

There is an urgent need to proactively scale up existing cervical cancer screening techniques and provide vaccines in Nigeria. The centres with existing facilities must educate women on cervical health awareness and the need to have cervical screening at specified regular intervals. The incorporation of visual inspection methods at the level of the rural/semi-urban areas can be done with good results using trained health workers as seen in India. In addition HPV testing should be included as an option or in the form of co-testing. The burden still lies with the federal government to ensure wide spread sensitization, accessibility/affordability and obviously outline a national cervical cancer screening protocol.

Competing interests: None.

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