Towards improving cervical cancer screening in Nigeria: A review of the basics of cervical neoplasm and cytology

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Abstract
Cervical cancer screening is the key to reducing the incidence and mortality of cervical cancer in developing countries. In the absence of a national screening program, healthcare givers in Nigeria are encouraged to routinely inform and screen eligible women. This review aims at equipping health workers for this task by re-educating them on the basics of the disease and its screening by cytology. Relevant texts and online databases including Pubmed, African Journal Online, and Google Scholar, were searched for relevant literature on the subject area. Persistent infection by a high-risk human papilloma virus, especially types 16 and 18, is necessary for the development of cervical cancer. The exfoliation of cells from the metaplastic squamous cells of transformation zone of the cervix is the basis of cervical cytology. Organized Pap screening reduces the incidence and mortality of cervical cancer, but screening protocols vary. Nevertheless, annual screening is not recommended except for high-risk women such as HIV-positive women. Abnormal Pap smear results are currently reported using either the Bethesda System or the British Society for Clinical Cytology classification, and colposcopy with or without biopsy are necessary when indicated. In conclusion, the use of cervical cytology to detect pre-cancerous lesions followed by an appropriate treatment when necessary is the key to reducing invasive cervical cancer. The task of provider-initiated counseling and testing for cervical cancer by health practitioners requires update on the current etio-pathology of cervical cancer, and its screening as reviewed.

Key words: Cervical cancer, control, cervical cytology, human papilloma virus, Nigeria

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Introduction
Cervical cancer is a preventable cancer of the female genital tract. It is still a leading cause of cancer death among women in areas where organized screening is not available.[1] The disease is caused by infection with persistent oncogenic human papilloma virus (HPV), which makes timely vaccination with HPV vaccine an effective primary prevention method. However, the cost of the vaccine makes it inaccessible in developing countries, thereby leaving secondary prevention through cervical cytology as the best alternative method of cervical cancer prevention; this is without prejudice to the cheaper visual screening methods [using acetic acid (VIA) or Lugol’s iodine (VILI)], currently being advocated for poor-resource settings. VIA and VILI involve the inspection of the cervix without magnification, after painting with dilute acetic acid or Lugol’s iodine respectively; abnormal cervical tissue turns white (VIA) or yellow (VILI).

Furthermore, an important strategy towards reduction of the incidence and mortality of cervical cancer is by increasing

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the screening rate of women that have not screened or those that screen infrequently.[6] Nevertheless, knowledge of the physio-anatomical changes of the cervix by health practitioners involved in reproductive health of women is very relevant, irrespective of the screening method being advocated. Because healthcare providers are encouraged to routinely inform and screen all eligible women for cervical cancer,[10] it becomes important to re-educate them on the basics of cervical neoplasm and cervical cytology. This review provides a concise discussion on the physiological changes in the cervical epithelium; association between HPV and cervical cancer; history, guidelines and reliability of Pap smear; and the classification of abnormal cervical cytology.

Materials and Methods

Literature search was both manual and electronic. Relevant texts were searched for information on the subject area. Online databases including Pubmed, African Journal Online, and Google Scholar were also searched using a combination of the key words. Related literatures were identified and studied, and relevant information retrieved. The information was further organized and presented in themes.

Cervical squamo-columnar junction

The cervix is the inferior one-third of the adult uterus and consists of the endocervix and ecto-cervix [Figure 1]. The latter projects and opens into the vagina, thereby making it accessible for inspection and sampling. Furthermore, the cervical canal is lined by columnar epithelium superiorly and squamous epithelium inferiorly – both epithelia meet at a dynamic point referred to as the squamo-columnar junction [point A in Figure 1]. The original squamo-columnar junction (SCJ) is the boundary between the original squamous epithelium covering the ectocervix and the columnar epithelium of the endocervix.[4] The position of this junction varies throughout the reproductive life of a woman [Figure 1]. In an estrogen-deficient state such as in pre-pubertal women, the junction lies well within the endocervical canal. During puberty, there is down-growth of the columnar epithelium below the external cervical os; thus, the SCJ lies on the ectocervix. However, this delicate columnar epithelium exposed to the lactobacilli-created acid environment of the vagina undergoes metaplasia to become squamous epithelium. As squamous metaplasia takes place, the original SCJ becomes the border between the metaplastic squamous epithelium and the original squamous epithelium [point A in Figure 1]. The superior border of the metaplastic epithelium becomes the new squamo-columnar junction (NSCJ) [point B in Figure 1]. The area between the original SCJ and the NSCJ of the cervix [i.e., in-between points A and B in Figure 1], where this continuous epithelial regeneration and remodeling take place is known as the transformation zone (TZ).[4,5]

The process of metaplasia can be disrupted, leading to disordered squamous epithelium. The metaplastic squamous epithelium in the TZ is the critical site for the development of the cervical neoplasia. Exfoliation of cells from this zone is the basis for cervical cytology.[6]

Human papilloma virus and cervical neoplasia

HPV is the name of a group of epitheliotrophic DNA viruses that includes more than 100 different strains or subtypes involved in human disease. They are numbered according to their discovery. About 30 of these are sexually transmitted and are primarily transmitted to the genital tract through skin-to-skin contact.[7] On the basis of both epidemiologic and phylogenetic classification, the 30 genital HPV types are classified into high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), possibly high-risk (26, 53, and 66), and low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).[8] They infect the basal cells of the stratified squamous epithelium as well as the metaplastic cells of the transformation zone of the cervix. Depending on the HPV genotype and the host/virus interaction, there can be asymptomatic infection, clinical manifestations of genital warts, or cervical dysplastic changes.[9] The low-risk HPV types are associated with condylomas, which are benign lesions, while the high-risk types have been solidly demonstrated as the cause of the cervical cancer and its immediate precursors (severe dysplasia and carcinoma in situ).[10-12] HPV’s are found in over 85%–90% of all precancerous and invasive cervical lesions, and most of the behavioral and sexual risk factors for cervical cancer become statistically insignificant as independent variables after adjusting for HPV infection.[9] The most frequent types detected, in decreasing order of frequency, were 16, 18, 45, 31, 33, 52, 58, and 35.[9] However, HPV 16 and 18 are responsible for 70% of cervical cancers, with trivial differences among countries, and for over 60% of cervical intraepithelial neoplasia (CIN) 2/3 lesions worldwide.[13,14] This may explain why the HPV vaccines in current use contain antigens for both HPV 16 and 18.

Figure 1: The human cervix at different reproductive periods[4]
HPV infection can be transient or persistent. It is persistent when the presence of the viral DNA can be assessed by polymerase chain reaction after six months’ interval. Persistence of oncogenic HPV viruses is required for the cellular changes associated with cervical dysplasia; however, most HPV infections are unnoticed and resolve spontaneously within 24 months. Persistent HPV infection plays the causal role in the development of cervical cancer and its precursors by integrating into the host’s cellular genome and interfering with the essential regulatory mechanism of cellular growth, DNA repair, and immunological escape, thus permitting uncontrolled cellular proliferation. A cell-mediated immune response is required for HPV containment and lesion regression; therefore, people with cell-mediated immune dysfunction such as HIV/AIDS have higher rates of HPV infection and are more likely to manifest large, multifocal, and dysplastic lesions. Furthermore, cigarette smoking among HIV-infected women significantly increases the prevalence and incidence of HPV infection, alters the natural history of the infection (HPV), as well as increases the risk of cervical disease.

Papanicolaou (Pap) smear

The fact that cervical cancer develops slowly from its precursor lesions makes it a suitable disease for screening. The Pap test is a complex system of laboratory and clinical procedures, which has been widely used globally in the diagnosis of pre-malignant lesions and cancer 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. Afterwards, in 1947, a Canadian gynecologist, Ernest J. Ayre, 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 contain cells from the squamous epithelium of vaginal portion of the cervix, the transformation zone, and the endocervix. To obtain a better sample from the latter, 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 combined with the conventional Ayre spatula, the number of inadequate smears is reduced and hence the false negative rate. Fine cotton wool stick can also be used to collect endocervical cell samples but the results are less satisfactory. The Pap test requires fixing of the cervical scraping on a glass slide followed by staining with Papanicolaou staining and manual analysis under the microscope.

It is well recognized that Pap test reduces the incidence and mortality of cervical cancer. It diminishes the risk of progression of a precancerous lesion to cancer, and should only be carried out in asymptomatic women. The level of protection for women aged 35–64 years is about 93.5% for annual screening, 83.5% for screening every 5 years, and 64% for screening every 10 years. Furthermore, it is estimated that organized screening can reduce cervical cancer deaths by 70% or more, prevent not only the loss of large numbers of life years but also the morbidity and costs of treating advanced disease, and in many cases, preserve fertility when it might otherwise be lost. Nevertheless, there has not been a universal agreement as to the age at initiation or cessation of Pap smear as well as the intervals for repeat screening. The World Health Organization (WHO) recommended a 5-year screening interval for women over 50 years and a 3-year interval for those within the age group of 25–49 years if the resources are available. It did not recommend annual screening at any age; and for women above 65 years, screening is not necessary provided the last two previous smears were negative. Though, the WHO recommended that organized cervical cytology programs should not include women less than 25 years of age in their target populations, the American College of Obstetricians and Gynecologists (ACOG) protocol indicates that cervical cytology should begin for every woman by age 21 years, irrespective of HPV vaccination status. Afterwards, she should continue with 2-yearly screening until the age of 29 years. From the age of 30 years, screening interval could be increased to 3 years for women who had three consecutive negative cervical cytology tests. However, cervical cancer screening should stop at age 65 or 70 years among women who have three or more negative cytology results in a row and no abnormal test results in the past. With respect to cost analysis, it has been shown that the 3-yearly cervical cytology screening is the most cost-effective strategy for women with prior normal results.

On the other hand, high-risk women such as the HIV-positive, immunosuppressed, and those exposed to diethylstilbestrol, should be screened more frequently. For HIV-positive women in particular, twice yearly Pap smear is recommended in the first year after diagnosis, and if the results are normal, screening should continue annually afterwards.

Pap test is generally very specific (86%–100%) but has varied sensitivity of 30%–80%. It has an apparently high false negative rate of up to 50% for invasive carcinoma and 28% for pre-invasive lesions, which are contributed mainly by sampling error and screening error. Other causes of error include interpretative error and exfoliative potential of the lesion; for instance, false negative smear have been reported in as many as 40%–50% of patients with invasive cervical cancer, which emphasizes that it is a screening procedure for detecting precursor lesions and not a diagnostic method for cervical cancer. Though serial Pap testing improves sensitivity, and diminishes impact of false negativity,
automated techniques have been developed to supplement manual screening and further improve accuracy. These techniques are the Pap-net system and the thin-prep system. The former is a computer-assisted slide reader used for re-screening the manually diagnosed negative smears.[32] The thin-prep system is a liquid-based alternative to the conventional slide Pap smear preparation, where the collection device is rinsed in a tube of preservative solution and sent to the laboratory. The specimen is centrifuged and then removed and suspended in a diluent and a smear is then made on the slide. These new techniques, although effective,[33] increase the cost of screening. Therefore, since false negative smears contribute only a small fraction to the incidence of cervical carcinoma, resources, especially in resource poor countries, should be spent to increase the screening of the population by conventional Pap smear.[31]

Most importantly, despite the recognized importance of regular Pap smear, it cannot be effective if the people who need it, especially women at high risk, are neither aware of it nor convinced that they need it.[6] Unfortunately, the awareness of cervical cytology by women alone might not translate to its increased use, therefore, the need for an additional motivation for women.[3]

Furthermore, in addition to the prevailing low awareness of cervical cancer and Pap test among the women population as well as lack of priority on the disease prevention by policy makers, other impediments to the uptake of the cervical cytology include poor health consciousness, inadequate spread of health centers with Pap screening facilities, poor referral system, and lack of a national screening program.[14,33]

Classification of abnormal cervical cytology
The oldest classification is the Papanicolaou classification, which classified smears into classes I to V in order of worsening cellular atypia. It is no longer favored because it does not reflect the current understanding of CIN and there is no equivalent in diagnostic histopathological terminology.[6]

In 1969, the World Health Organization proposed the term dysplasia, graded as mild, moderate, and severe, and the term carcinoma in situ to denote the pre-invasive lesions of cervix.[36] These terms are widely used all over the world for both cytological and histological diagnosis. However, there are no internationally agreed criteria for the grading.[6]

Currently, there are two systems in use for cytology reporting, one is from the British Society for Clinical Cytology,[17] and the other from the United States (The Bethesda System).[38]

Bethesda classification
In 1998, the National Cancer Institute (NCI) workshop held in Bethesda, Maryland, resulted in the development of the Bethesda system for cytological reporting. This was later revised to give the Bethesda system 2001.[38] This classification has a wider use, which may be related to the fact that it provides a uniform and well-defined diagnostic terminology that facilitates unambiguous communication between the laboratory and the clinician.[39]

The revised system divided the premalignant squamous lesions into three categories thus:[38]

i. Atypical squamous intraepithelial cells (ASC)
ii. Low-grade squamous intraepithelial lesions (LSIL)
iii. High-grade squamous intraepithelial lesions (HSIL)

The ASC is categorized into those of undetermined significance (ASC-US) and those in which a high-grade lesion cannot be excluded (ASC-H). In ASC-US, the squamous cells do not look completely normal but the meaning of the cell changes is not certain. In ASC-H also, the cells appear abnormal but the meaning is uncertain; however, the risk of being precancerous lesion is higher than ASC-US. LGSIL includes cytological changes consistent with HPV changes called koilocytic atypia or mild dysplasia, and it corresponds to CIN I. On the other hand, the HGSIL is characterized by more severe abnormalities in the size and shape of cervical squamous cells and are more likely to progress to cancer. It denotes the cytological findings corresponding to CIN II and CIN III (Table 1).

The British society for clinical cytology classification
Abnormal cytology is classified into mild, moderate, and severe dyskaryosis, and are equivalent to histological diagnosis of CIN I (mild dysplasia), CIN II (moderate dysplasia), and CIN III (severe dysplasia) respectively. Mild dyskaryosis is equivalent to LGSIL while moderate and severe dyskaryosis correspond to HGSIL. The term borderline is taken to be equivalent to ASCUS (Table 1).

Cervical intraepithelial neoplasia
The CIN is a concept introduced in 1967 to embrace all grades of dysplasia and carcinoma in situ under a single disease heading.[40] The nomenclature conveys accurately the morphological unity and malignant potential of all cervical intraepithelial neoplastic lesions if left untreated.[6]

It means the disordered growth and development of the epithelial of the cervix, and the diagnosis is based on histological sections. It is graded as I, II, and III, which are equivalent to the mild, moderate, and severe dysplasia respectively (Table 1). The grading is based on the proportion of the epithelium occupied by the dysplastic cells. In CIN I, the disordered growth involves the lower third of the epithelial lining. Abnormal maturation of two-thirds of the cervical epithelium is called CIN II, while CIN III encompasses more than two-thirds of the epithelial lining.[14]

The epidemiological risk factors in CIN and cervical cancer include multiple sexual partners, early onset of sexual activity, HPV infection, lower genital tract neoplasia, history...
of STDs, cigarette smoking, immunodeficiency, multiparity, and long-term oral contraceptive pill use.\cite{14}

The need for appropriate interpretation of abnormal Pap result and appropriate referral of patients by health workers for optimal follow-up cannot be overemphasized. Generally, all women with ASC or LGSIL should have a repeat screening after 6 months and should be referred for colposcopy if the lesion is progressive [Table 1]. However, all cases of HGSIL should have colposcopy and possible biopsy\cite{21,41}. On the other hand, abnormal lesion of any type identified in high-risk women, such as HIV-positive women, calls for colposcopy.\cite{42} Unfortunately, high level of refusal of colposcopy has been reported from Southeastern Nigeria, and the major reasons were the fear of detecting cervical cancer and compromising future fertility.\cite{43} It is likely that the situation for other regions of Nigeria and indeed sub-Saharan Africa, may not be different. This worrisome situation underscores the need for adequate provider initiated counseling on cervical cancer prior to any form of testing.

### Conclusion

Cervical cytology is a key part of the secondary prevention of cervical cancer. In the absence of national guidelines in most developing countries, a provider initiated counseling and testing for cervical cancer is advocated.\cite{13,44} This strategy will ensure that every eligible woman who presents to a healthcare provider for any reason is informed about and possibly screened for cervical cancer. Therefore, basic knowledge of the current etio-pathology of cervical cancer as well as its prevention is very essential for health practitioners in developing countries. It is hoped that their improved knowledge will motivate their involvement in the campaign against this preventable scourge of female reproductive health.

### References

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