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Review

Utilization of Human papillomavirus (HPV) DNA detection for cervical cancer screening in developing countries: A myth or reality

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Persistent infection by human papillomavirus (HPV) is considered to be the main causative agent of cervical cancer and other anogenital cancers. Of the more than 30 genotypes capable of infecting the anogenital tract, it is estimated that, worldwide, HPV 16 and 18 cause 70% of the cervical cancers. Control through primary prevention has become a distinct reality through a prophylactic vaccine, which may take quite some time for its widespread use. Thus control of cervical cancer through cervical screening strategy is the only viable solution now. Despite the high rates of false negative results associated with cervical cytology, it is still considered as the gold standard for cervical cancer screening in developing countries. The advent of highly sensitive and specific HPV DNA detection techniques has offered a lot of promise for cervical cancer prevention. The severe restriction on the availability of infrastructure, resources and funding in developing countries has made it difficult to adopt HPV DNA detection as a routine cervical cancer prevention strategy. This present discourse is a review of relevant literature using internet search engines such as; PubMed and Google. Due to the limitations of Pap smear, there is need to consider HPV DNA detection as a useful adjunct to Pap smear screening, in order to effectively control cervical cancer in developing countries.

Key words: Human papillomavirus (HPV), DNA detection techniques, cervical cancer.

INTRODUCTION

Cancer of the cervix is the commonest cancer affecting women in developing countries with an estimated lifetime risk of 2 to 4% (Were et al., 2011; Perkins et al., 2010).It is largely preventable and more than 99% have been associated with high-risk human papillomavirus (HPV) as persistent infection of the cervical epithelium which may result in cervical cancer (Meijer et al., 2000). While incidence and mortality rates have fallen significantly in developed countries, 83% of all new cases that occur annually and 85% of all deaths from the disease occur in developing countries (Anorlu, 2008). Cervical cancer screening is considered a highly effective intervention that has led to a 70% reduction in mortality by cervical cancer in developed countries (Chocontá-Piraquive et al., 2010). Previous studies suggest that if a woman was screened for cervical cancer only once in her lifetime, between the ages of 30 and 40 years, her risk of developing cervical cancer would be reduced by 25 to 30% (Goldie et al., 2005). Despite the high morbidity and mortality associated with cervical cancer in developing countries, knowledge, awareness and facilities for the prevention and treatment of cervical cancer are still very

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inadequate in many developing countries, including, Nigeria (Meijer et al., 2000). A study in Kenya revealed that only 12.3% of women had ever had cervical cancer screening and reported barriers to cervical cancer screening such as; fear of abnormal screening results, lack of finance, lack of awareness about the service and the fear of genital examination (Were et al., 2011).

There is currently no consensus regarding medical standards for cervical cancer screening in developing countries. However, Papanicolaou (Pap) smears, followed by colposcopy with biopsy for diagnosis and Loop electrosurgical excision procedure (LEEP) for treatment has become the standard of care for developed countries (Perkins et al., 2010).

Several other methods have been proposed as alternatives to Pap smear screening in developing countries including; Visual Inspection with Acetic Acid (VIA) or with Lugol's Iodine. However, HPV DNA detection remains the most sensitive screening test and studies have shown that it has 65 to 95% sensitivity in identifying women who have precancerous lesions. The cytology-based cervical cancer screening programme requires repeated screening cycles which makes them more expensive (Perkins et al., 2010; Schiffman et al., 2007).

Women who test negative for HPV have been found to have low risk of cervical intraepithelial neoplasia (CIN3) or cancer over 5 years, irrespective of the finding of normal cytology or minor abnormalities (Katki et al., 2011). The interpretation is objective and does not have the inherent subjectivity of visual screening or cervical cytologic methods (Gage et al., 2012). Supported by the aforementioned advantages, cervical screening for carcinogenic HPV infection is now being considered in lieu of cytology for low-income countries (Villa and Denny, 2006).

EPIDEMIOLOGY OF HPV AND CERVICAL CANCER

The epidemiology of both cervical cancer and HPV are closely related because of their causal association. Cervical cancer is the second most common cancer in women worldwide following breast cancer. It remains the commonest however in developing countries where majority of cervical cancer related deaths occur. More than 60% of cases occur in medically-underserved populations as part of a complex of diseases linked to poverty, race/ethnicity, and/or health disparities. According to the WHO, 80% of the 288,000 deaths that occurred among the 471,000 new cases globally were from developing countries in the year 2000 (Urasa and Darj, 2011; Scarinci et al., 2010).

Globally, HPV is regarded as the most common sexually transmitted infection (Scarinci et al., 2010). However, most HPV infections, including carcinogenic HPV genotypes, are typically transient and resolve within 6 to 12 months, sometimes causing mild morphologic changes. In general, carcinogenic HPV is referred to as a necessary but infrequent cause of cervical cancer (Scarinci et al., 2010)

VIROLOGY OF HPV

HPVs are members of the Papillomaviridae family comprising a diverse family of non-enveloped, small circular double-stranded DNA viruses measuring about 55 nm. The DNA of HPV is circular, has a double chain and contains approximately 8000 base pairs. Its genome can be divided into three areas; the long control region (LCR), the early region (E=early), and the late region (L=late) (Alberta et al., 2009).

They have been divided into High-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; Low-risk types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108 and potentially high-risk types: 26, 53 and 66 (Villa and Denny, 2006). Cervical cancer is caused by types of HPV that belong to a few phylogenetically related "high-risk" species (alpha-5, 6, 7, 9, 11) of the mucosotropic alpha genus. The types found most frequently in cervical cancer (HPV-16, 18, 31, 33, 35, 45, 52, 58) and four types less constantly found (HPV-39, 51, 56, 59) were classified in Group 1. The risk of cancer may be an order of magnitude higher for HPV-16 infection than for other high-risk HPV types. HPV-68 was classified as "probably carcinogenic to humans" (Group 2A) with limited evidence in humans and strong mechanistic evidence. The remaining types of HPV in the high-risk alpha species were classified as "possibly carcinogenic" (Group 2B). Finally, HPV-6 and HPV-11, which belong to the alpha-10 species, were "not classifiable as to its carcinogenicity to humans" (Group 3) on the basis of inadequate epidemiological evidence and absence of carcinogenic potential in mechanistic studies (Bouvard et al., 2009).

HPV16 (Figure 1) and HPV18 are the two most carcinogenic HPV types, and are responsible for 70% of cervical cancer and about 50% of CIN3. The HPV genome codes for only eight genes with E6 and E7 being the primary HPV oncoproteins. Each has numerous cellular targets, with p53 and retinoblastoma tumour suppression protein (pRB) being the most important. E6 inhibition of p53 blocks apoptosis, whereas E7 inhibition of pRB abrogates cell-cycle arrest. E7 is the primary transforming protein (Goldie et al., 2005).

Worldwide, HPV16 and 18 are the two most frequently detected types among patients with invasive cervical cancer (ICC). In Nigeria, they account for 78% of HPV positive ICC, which is very similar to the proportion estimated in other world regions (Okolo et al., 2010). HPV 45, 31 and 33 are the next most prevalent types. In Asia, HPV58 and HPV52 are the next most common after HPV16 and 18 (Zandi et al., 2010).

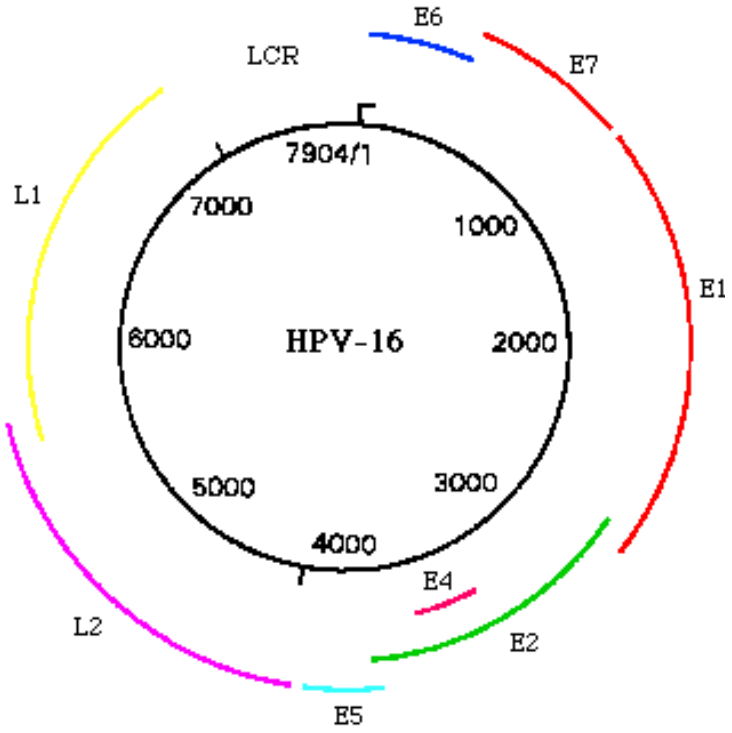

Figure 1. Genetic map of HPV type 16.

AVAILABLE TECHNIQUES FOR CERVICAL CANCER SCREENING

Two new approaches for the cervical cancer prevention have emerged based on the inevitable etiologic link between carcinogenic HPV and cervical cancer. Primary prevention via HPV vaccination to prevent HPV infection; and secondary prevention via carcinogenic HPV detection for identification and early treatment of women with cervical precancerous lesions and early-stage cancers (Scarinci et al., 2010). The latter forms the basis of our review for cervical HPV detection as a means of cervical cancer screening in developing countries.

Other screening techniques for cervical cancer include; conventional exfoliative cervicovaginal cytology; pap smear, fluid sampling techniques with automated thin layer preparation (liquid based cytology), automated cervical screening techniques, neuromedical systems, HPV testing, polar probe, laser induced fluorescence, visual inspection of the cervix, speculoscopy and cervicography.

Papanicolaou cytology

The Papanicolaou ("Pap") cytology is a simple and well-accepted procedure for efficient detection of potentially premalignant HPV-associated cervical lesions through cytological examination of exfoliated cervical cells (Seaman et al., 2010).

Cytological screening programs can be effective for prevention of cervical cancer in the developing world, but rely heavily on effective cytopathology services and call/recall systems to ensure compliance with regular screening assessments among at risk women. Neither of these criteria can currently be met in resource poor settings of most developing countries (Mc Adam et al., 2012). In developing countries, logistic barriers in implementing screening programmes using cytology on Papanicolaou-stained cervical smears to detect precursor cervical lesions have led to failure in reducing cervical cancer incidence and mortality (Quentin et al., 2011). However, a single assessment of cervical cytology has 30 to 50% false negative rate for significant cervical pathology thereby reducing the sensitivity of the test in screening for cervical cancer (Mc Adam et al., 2012).

HPV DNA detection

Carcinogenic HPV DNA testing is more clinically sensitive than cytology for the detection of precancerous lesions and cancer in routine screening. One-time HPV-based screening has also been demonstrated to be superior to Pap smears and visual inspection with acetic acid for reducing cervical cancer mortality. In the United States, carcinogenic HPV testing with cytology has been approved for primary screening of women aged 30 years

and older, who are past the peak of self-limited infections (Quentin et al., 2011). Women aged 30 years and older who test negative for carcinogenic HPV and are cytologically normal are at an extremely low risk for incipient precancer and cancer for the subsequent 10 years or more (Castle et al., 2009).

The maximum benefits of HPV-based screening will be derived more than 10 years after sexual debut when most women will be in their late 20's and early 30's (Scarinci et al., 2010). This forms the basis for the argument that, any positive HR HPV test in women over 30 years is indicative of a chronic HPV infection, which conveys a significant life time risk of development of cervical cancer even in women without currently apparent cytological abnormalities (Mc Adam et al., 2012).

With increased standardization of HPV DNA testing methods in 1990's, reliable data now have emerged from large scale screening programmes. Polymerase chain reaction (PCR) and Hybrid Capture HPV DNA assay (HC II) from Digene diagnostics have become the most frequently used tests for screening purposes. Reliable, sensitive HPV testing methods, such as MY09/MY11 consensus primer PCR and GP5+/GP6+ general primer PCR which type the wide range of genital HPVs have been well standardized (Villa and Denny, 2006; Jiang et al., 1997; De Roda Husman et al., 1995).

PCR system had an analytical sensitivity of 10-100 copies of HPV-DNA per sample. The modified hybrid capture system (HC II) uses 13 probes for high risk HPV types (16,18,31,33,35,39,45,51,52,56,58,59 and 68). The chosen analytic sensitivity limit of the HCII assay for high risk HPV types was 1 pg/ml (corresponding to 5000 or more HPV DNA copies).

HPV tests may better forecast which women will develop CIN3+ over the next 5 to 15 years than cytology. Incorporation of HPV testing into cervical cancer screening strategies has the potential to allow both increased disease detection (improving benefits) and increased length of screening intervals (decreasing harms such as the psychosocial impact of screening positive, additional clinical visits and procedures, and treatment of lesions destined to resolve) (Saslow et al., 2012).

A study has suggested that HPV testing with separate HPV16 and HPV18 detection could provide an alternative, more sensitive, and efficient strategy for cervical cancer screening than do methods based solely on cytology (Castle et al., 2011). Women aged 35-65 years who are cytology negative but HPV positive (in co-testing) are recommended to have HPV 16/18 genotyping at a 5 year screening interval in lieu of a more frequent 3 year interval with cytology alone (Saslow et al., 2012). Further evidence was highlighted in a study which suggested that for women over 30 years in a low resource setting without access to cytology, a single locally conducted test for high risk HPV with effective intervention could reduce cervical cancer risk as effectively as intervention based on cytology conducted in an accredited laboratory (Mc Adam et al., 2012).

Visual inspection with acetic acid (via) or lugol's iodine

VIA involves washing the cervix with 3 to 5% acetic acid and then looking for changes indicative of precancerous lesions. It has been proposed as an alternative to Pap smear screening in developing countries due to its attractive features which include low cost, simple administration and immediate availability of results. Typically recommended as part of a "see-and-treat" algorithm which involves screening women with VIA and treating those with abnormal exams using cryotherapy ablation in the same visit. The VIA is not only cheap, it maximizes adherence to follow-up therapy, and has been shown to be more cost effective than screening with Pap smears in low resource settings. The "See-and-treat" option falls below the current standard of care in developed countries, however, because no pathologic diagnosis is obtained to ensure the adequacy of treatment and its false positive rate is higher, resulting in more colposcopy referrals (Were et al., 2011).

Optical imaging and spectroscopy

Optical imaging and spectroscopy are non-invasive means of assessing the morphologic and biochemical changes associated with the development of precancer at the point-of-care. Optical technologies can improve the accuracy and availability of cervical cancer screening. Battery powered digital cameras can obtain multi-spectral images of the entire cervix highlighting suspicious areas and high-resolution optical technologies can further interrogates suspicious areas. Targeted contrast agents have also proven to be useful for highlighting changes in biomarkers of cervical neoplasia. This approach has high sensitivity, but lower specificity. However, currently available imaging instrumentation is expensive and bulky, making it difficult for use in low-resource settings of most developing countries (Thekkek and Richards-Kortum, 2008).

CONCLUSION

Cervical cancer is largely a preventable disease, curable also, if detected early. During the last decades, cervical cancer screening was based on cytological abnormality detection. Since the HPV has been identified to be the main risk factor for cervical cancer, the detection of HPV DNA in cells of the cervix has been investigated as a surrogate marker for high cancer risk. In comparison to Pap smear tests, HPV DNA based screening reaches a higher sensitivity to detect pre cancerous lesions. A major

limitation of the HPV DNA detection, however lies in the fact that HPV tests have a lower specificity because transient HPV infection, are relatively frequent in younger women, and because both HPV infection and cytological abnormalities regress in most cases without progressing to cancer.

Finally, in view of the high rate of false negative results, more frequent screening intervals and a relative need for a higher level of expertise, cytology based screening method is cumulatively more expensive. But with a more objective interpretation, higher sensitivity and increased length of screening intervals, HPV (especially 16 and 18) detection combined with cytology (co-testing) appears more promising in women more than 30 years of age.

RECOMMENDATION

Co-testing using HPV (especially 16 and 18) detection among women more than 30 years as an adjunct to cytology should be considered even in low resource settings. However, a simple, accurate, affordable, rapid and acceptable HPV detection test need to be developed as it would have even greater potential in reducing the burden of cervical cancer in the developing world.

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