IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 11 Ver. IX (Nov. 2017), PP 05-09
www.iosrjournals.org

Prevention, Screening and Diagnosis of Cervical Carcinoma: A Literature Review.

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Abstract: *The human papillomavirus (HPV) is an unenveloped double stranded deoxyribonucleic acid (dsDNA) virus capable of infecting humans and inducing cervical carcinoma in females. HPVs can also be grouped to high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. HPV16 and 18 have been implicated as the commonest aetiologic agent in this disease. Various methods have been used in testing the presence of human papillomavirus including histology, pap smear, polymerase chain reaction and hybridization technique. Pap has been used for cervical carcinoma screening worldwide. Cervarix and Gardasil are effective vaccines against the human papillomavirus type 16 and 18.*

Keywords*: Carcinoma, human papillomavirus, vaccine, hybridization, Pap smear*.

Date of Submission: 04 -11-2017 Date of acceptance: 28-11-2017

I. Background

The human papillomavirus (HPV) is an unenveloped double stranded deoxyribonucleic acid (dsDNA) virus capable of infecting humans and inducing cervical carcinoma in females.[1] HPVs can also be grouped to high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. HPV16 and 18 have been implicated as the commonest aetiologic agent in this disease.[2,3,5] Both of them account for an estimated 70 - 76% of cases of carcinoma of the cervix.[6,7,8,9,10] There are several of Cervical carcinoma prevention and control which programme has several components include - HPV vaccination, cytological screening and management of Pap smear abnormalities, surgical removal of precancerous lesions, cryotherapy for precancerous lesions, laser ablation therapy for precancerous lesions and hysterectomy.

Human Papillomavirus (Hpv) Vaccination

The HPV vaccination programme has been introduced in many countries including the United States of America since the discovery of the vaccine in 2006.[11,12] The HPV vaccine that has been produced following the isolation of the HPV type 16 and 18 by Prof Harald Zur Hausen is the HPV 16 and 18 vaccine.[12,13]
The vaccines are a recombinant vaccine composed of recombinant proteins which are viral like particles.[4,9,14,15] There are two types of vaccine against cervical cancer. They include the bivalent vaccine and quadrivalent vaccine. The bivalent also called ASO4 adjuvant HPV type 16 and 18 vaccine contains growth medium including vitamins, mineral salts, lipids, sodium dihydrogen phosphate dehydrate. The vaccine ingredients include insect cell and viral protein, sodium chloride, water, aluminium hydroxide and bacterial cell protein. It stimulates the production of anti-L1 antibodies against HPV type 16 and 18. The trade name is Cervarix. It is recommended for women between 9 and 12years and given at 0, 1 and 6 months.[7,16, 17,18,19]

The human papillomavirus quadrivalent (type 6, 11, 16 and 18) vaccine protects against types 6, 11, 16 and 18 HPV infections. The trade name is Gardasil. The growth medium is composed of yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminium hydroxyphosphate sulfate and aluminium containing adjuvant. The vaccine ingredient include L- histidine, polysorbate 80, sodium borate, amorphous aluminium hydroxyphosphate sulfate adjuvant, sodium chloride, yeast protein and water. Quadrivalent HPV vaccine approved for use and/or recommended for all females between 9 and 45 years of age, is given at 0, 2 and 6 months.[16,20,21, 22]

Besides HPV 16 and 18, these vaccines do not protect against other oncogenic HPV. Quadrivalent HPV vaccine in addition, protects against HPV 6 and 11 infections which cause genital wart.[3]

Diagnosis Of Cervical Human Papillomavirus Infection

Conventional cytology:

The commonest method of detecting high risk HPV infection in the cervix is with Papanicolaou (Pap) smear. This method of diagnosing HPV infection was introduced in 1949 and named after George Papanicoloau before the cause of cervical carcinoma was discovered in 1976. This has helped reduce the incidence of cervical carcinoma significantly especially in countries with well organised cervical screening programme like the United States of America.[18,19, 22 23,24,25, 26, 27] The cytopathic changes caused by high risk HPV infection in the cervical epithelial cells like those in the transformation zone can be detected using this tool.[2,28,29]

The reporting system for Pap smear is the Bethesda system first introduced in 1988, amended in 1991, updated in 1999 and modified in 2001

Bethesda system 2001 classifies squamous cell abnormalities into four categories:

- ASC(Atypical squamous cells)
- ASC-US(atypical squamous cell of undetermined significance): here the lesion has cellular abnormalities suggestive of SIL.
- ASC-H(atypical squamous cells cannot exclude high SIL).
- LSIL(low grade squamous intraepithelial lesions).
- HSIL(high-grade squamous intraepithelial lesion).
- Squamous cell carcinoma.[22,30,31,32]

II. Monolayer cytology

This is a new method of processing specimen for Papanicoloau smear. Studies have shown that it has a higher sensitivity when compared to the conventional method. It reduces the number of false-negative results. The specimen is usually collected with a cervical brush which provides more adequate epithelial cells almost twice that of other collection device. The specimen collected are preserved immediately. The methods that create this uniform monolayer prevents drying artefacts, removes contaminating mucus, bacteria, yeast, proteins and red blood cells.[23, 34,35] The two methods of liquid based cytology include:

- Thinprep system-The samples are collected in buffered alcohol preservative. The sample is then mixed. To achieve uniform sampling, it is dispersed by high-speed rotation. To draw the suspension through the polycarbonate paper a vacuum is applied. The cells are filtered and the number of cells that is deposited in the filter paper is controlled by the microprocessor.[45] The filtered cells are transferred in a 20mm monolayer by touching the microscope slide with the filter paper. The slide is then stained manually using Papanicolaou stain.[23]
- Surepath system: This has a unique easy to use collection process that standardizes the collection process and ensures 100% of the collection sample is sent to the laboratory for processing. The cells are collected with a brush/spatula and the cells dropped into a surepath vial, capped and sent to the laboratory immediately for processing. In this system, the specimen is collected in ethanol-based preservative. Density gradient centrifuge is used to remove inflammatory cells and non-diagnostic debris. Gravity dispersion is used to sediment the enriched cellular sample onto an adhesive-coated microscope slide within a 13mm diameter circle. The slide is then stained automatically using modified Pap stain and a separate stain is used for each slide.[33]

  Two computerised systems have been recently introduced. They are-
- AutoPap which have been approved for primary screening and rescreening
- PapNet which have been approved for rescreening

  These systems are designed to ensure an objective evaluation of Pap smear. Abnormal cells are displayed on the screen for review and analysis.[33,35]

Visual inspection with acetic acd/ lugol's iodine (via/vili) and colposcopic biopsy

Following an abnormal Pap smear, 3% acetic acid is applied to the cervix and it is examined using a bright filtered light with the aid of a colposcope following which a colposcopy-directed biopsy could be done. Areas of dysplasia or carcinoma can be visualised as areas of acetowhitening and abnormal vascular patterns. Similarly, Lugol's iodine could be applied to the cervix. This can be visualised as mahogany brown or black appearance in normal areas of the cervical epithelium with intracellular glycogen and yellow in areas of dysplasia or carcinoma composed of cells lacking intracellular glycogen. A biopsy is taken from these areas.

Histology

Histologically, viral cytopathic changes in the cervical epithelium could be seen when histological sections from the uterine cervix are examined under the microscope.[2, 33]

Molecular biomarkers

Various antigens have been used as immunohistochemistry markers for the detection of HPV infection. Some of these markers are specific for a particular HPV type but others are not. The antibodies that are used could be monoclonal or polyclonal. The antigens include :

p16: This one marker, p16INK4A has been well studied. p16 is a cyclin dependent kinase inhibitor. It is involved in cellular senescence. It inhibits the cell cycle. The expression of p16 has been altered in various malignancies. Its expression is increased in high risk HPV infection associated with squamous intraepithelial lesions.[22]

Cyclin B1: The expression of this cell cycle regulatory protein is known to increase in cervical carcinoma due to an increase in expression of E6/E7 proteins by HPV 16 and 18. Cyclin B1 is expressed early in the disease. It is a marker used for detecting high-risk HPV infection of the cervical epithelium early.[33]

Cyclin E: The expression of this regulatory protein increases in cervical squamous intraepithelial lesions and invasive squamous cell carcinoma of the cervix.

E7 Oncoprotein for HPV 16 or 18: E7 oncoprotein expression increases following high risk-HPV infection associated with cervical squamous intraepithelial lesions and invasive cervical carcinomas. This E7 protein could be specific for each type of high risk -HPV including types 16, 18 and 45. Immunohistochemical methods involving the use of polyclonal or monoclonal antibodies against these protein has been shown by Ehehalt et al in 2007 to be highly specific when compared to other methods of HPV diagnosis.[18] Immunohistochemistry could be used to detect HPV type16 E7 oncoprotein or HPV type18 E7 oncoproteins.

Polymerase chain reaction (PCR) for HPV DNA detection

Type specific PCR: This type of PCR is done based on the presence of sequence of variation in the E6 and E7 genes of HPV types. Type-specific PCR for fourteen high-risk HPV have been developed. This PCR target 100bp in the E7 open reading frame (ORF). The analytical sensitivity of the assays is between 10 and 200 HPV copies per sample. It is used mainly for research purpose because of the need to use multiple PCR amplifications.[22,33]

General primer PCR: In this type of PCR the primer is able to amplify a broad spectrum of HPV subtypes in just one PCR amplification. MY09 and MY11 target a 450bp in the L1 ORF. GP5+/GP6+ primer target a region within that of the MY09 target.[22,33]

Liquid hybridization:

Hybrid capture assay have been widely studied but the Hybrid Capture II is now widely used. This method uses chemilumnescence detection to qualitatively detect the presence of HPV. In this method the DNA in the sample of the patient is first denatured and mixed with RNA probe pool in buffer solution in a tube. Two pools of RNA probes are used. Probe A pool detects low risk HPV while probe B detects high risk HPV.[24,33]

Line probe reverse hybridization assay

First deoxyribonucleic acid (DNA) is extracted from the tissue or cells. Ethanol precipitation of the DNA is done. The supernatant is aspirated and the DNA pellets is dissolved in distilled water.

SPF-10 PCR is performed using 10µl of the DNA extract in a final reaction volume of 50µl. All samples are run with a 1:10 dilution. The amplified PCR products are tested using a probe hybridization with a cocktail of conservative probes recognizing, at least, 54 mucosal HPV genotypes in a microtiter plate format for the detection of HPV/DNA. Optical densities (OD450) are read on a microtiter plate reader. HPV/DNA positive samples are subsequently analysed by HPV SPF-10 $LIPA_{25}$ (version 1: Labo Biomedical Products, The Netherlands), a reverse hybridization technique that detects 25 high-risk and low-risk HPV types (6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 74). The sequence variation within the SPF-10 primers allows the recognition of these different HPV genotypes, except for types 68 and 73, as their interprimer regions are identical and cannot be distinguished by this test. After PCR, 10µl of the amplimers are used to perform reverse hybridization for HPV genotype identification. Positive hybridization on the strips is visualized as a purple band by means of a precipitating colour substrate on the probe site. Specimens that were HPV/DNA positive but did not hybridize with any of the 25 probes are coded as HPV type X (uncharacterized type). SPF-10 $LIPA_{25}$ PCR detection and typing analysis are performed.

HPV mRNA detection:

This test detects the mRNA for E6 and E7 oncogenes. The assay can be automated using any instrument capable of detecting fluorescence. This assay could be done on a Pap smear slide and visualized using a fluorescence microscope. The sensitivity of this method is up to 100% while the specificity is about 70%.[33]

III. Conclusion

Cervical carcinoma is the commonest gynaecological malignancy worldwide. The recent developments in molecular pathology have been of great help in the prevention, diagnosis and management of cervical cancer. With the development of molecular diagnostic technique and as medical science continues to advance we hope that soon this disease would be eradicated.

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*Godstime I. Irabor. "Prevention, Screening and Diagnosis of Cervical Carcinoma: A Literature Review." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.11 (2017): 05-09