

**CERVICAL CANCER AND ITS AETIOLOGY IN SUB-SAHARAN AFRICA: A LITERATURE REVIEW.**

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**Abstract**

Cervical cancer represents a huge burden of non-infectious disease globally. It is the second commonest cancer in the female. There are over half a million deaths recorded every year as result of cervical cancer. The aetiological agent implicated in this disease is the human Papillomavirus. The high-risk human papillomavirus has been mostly implicated. The commonest high-risk human papillomavirus implicated in cervical cancer worldwide is type 16 and 18. The viral infection of the uterine cervical epithelium initially causes the development of precancerous lesions referred to as cervical intraepithelial lesions/squamous intraepithelial lesions which take many years to progress into cancer. The Papanicoulao smear test done for the screening of precancerous cervical lesions has been known to be effective in preventing the disease. The commonest types of cervical cancer are the cervical squamous cell carcinoma and adenocarcinoma.

**Keywords: Human papillomavirus, cancer, cervical, intraepithelial lesion.**

**Background**

Every year there are 530,000 new cases of cervical cancer and an estimated 273,000 deaths from the disease worldwide making it the second most common cause of malignancy in females following breast cancer but the commonest of gynecological malignancy.<sup>1, 2, 3</sup> There are variations in the incidence and mortality of cervical cancer from country to country.<sup>3</sup> Eighty percent (80%) of the burden of this disease is in the developing countries with the women in

developing countries having two to three times a higher incidence of cervical cancer and related mortality compared to those in developed countries.<sup>3, 4, 5</sup> The human papillomavirus (HPV) is an undeveloped double-stranded deoxyribonucleic acid (dsDNA) virus capable of infecting humans and inducing cervical cancer in females.<sup>5</sup>

The Italian physician Rigoni -Stern in 1842 published a paper analyzing the death records in Verona from 1760 to 1839. He found that death from cancer of the uterus

was common in married women and widows but rare in nuns and virgins which are associated with nulliparity and low parity.<sup>6,7,8,9</sup> In 1907, Guiseppe Ciuffo discovered that skin and genital warts were associated with HPV infection.<sup>8,9</sup> In 1934 Peyton Rous and colleague demonstrated that HPV and tar joint action consistently induced squamous cell carcinoma.<sup>10,11,12</sup> The sources of tar according to them is cigarette smoking, smoke from coal or wood burning or even from stoves.<sup>8,13</sup> In 1976, Dr. Harald Zur Hausen a German virologist and Mathias Durst were convinced that HPV was the aetiologic agent in cervical carcinoma and eventually established the pathogenesis. In 1983 and 1984 Dr. Harald Zur Hausen was able to isolate the HPV type 16 and 18 respectively and this led to the development of the vaccine in 2006.<sup>2,14,15, 16, 25,34,35</sup> Since the discovery of HPV 16 and 18, several other high-risk HPV types capable of causing cervical carcinoma have been discovered including types 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70.<sup>2, 14, 15,16</sup>

These viruses are capable of infecting immature squamous epithelium of the stratum germinativum (basal layer) which could be easily found in areas of squamous metaplasia in the squamocolumnar junction or following erosion of the cervix.<sup>2, 10</sup> Ninety percent of those infected are cleared of the infection within two years.<sup>2</sup> When the infection persists it may result in atypical koilocytic changes in the cervical epithelium.<sup>2, 17</sup> At this stage, cervical intraepithelial neoplasia is said to have developed and this could be detected with regular Papanicolaou smear screening. When cervical intraepithelial neoplasia is diagnosed, it could be treated accordingly thus preventing its progression into invasive cervical cancer. This has been largely responsible for the decline in the incidence of cervical carcinoma in developed countries

such as the United States of America.<sup>10,25</sup> Eighty percent of the low-grade squamous intraepithelial lesion (LSIL) and hundred percent of the high-grade squamous intraepithelial lesion (HSIL) are associated with high-risk HPV infections.<sup>2</sup> About forty percent of those with high-risk HPV infection would develop HSIL and of these, ten percent would progress to invasive cervical cancer within a period of ten years.<sup>2, 17</sup>

In sub-Saharan Africa, the cervical cancer screening programme has a poor coverage.<sup>18</sup> A study done by Parkin et al in 2002 comparing the coverage of cervical cancer screening programmes in 57 countries showed an effective coverage of the cervical screening to be 40% on the average and in the 30 developing countries that were surveyed it was 19% on the average.<sup>18</sup> Similarly, a study by Louie et.al in 2009 stated the cervical cancer screening coverage in sub-Saharan Africa to be 2 to 20% in the urban areas and 0.4 to 14% in the rural areas.<sup>19</sup> Sixty to eighty percent (60 - 80%) of the women who develop cervical cancer in sub-Saharan Africa live in the rural areas with no opportunity of taking part in a cervical screening programme.<sup>20,21,22</sup> Also, the cervical cancer screening programme has been found to have a better coverage among those of higher socio-economic class which still put the people of sub-Saharan Africa among those that would have poor coverage of the screening programme.<sup>19</sup> Similarly, a publication in the WHO bulletin from a study by Sankaranarayanan et al in 2001, showed that there are generally no organized cervical cancer screening programmes in sub-Saharan Africa.<sup>25</sup> With the foregoing, there is little wonder 80% of the burden of death from cervical cancer is in the developing countries.<sup>10</sup> On the other hand, studies have shown an increase in the proportion of adenocarcinoma of the cervix

in many developed countries with organized cervical screening programme.<sup>23,24</sup>

With the introduction of the vaccination against HPV 16 and 18 vaccine, there is hope of achieving a significant reduction in the burden of cervical carcinoma. Globally, about 70% of cervical cancers are preventable by this vaccine. There are two available vaccines against HPV 16 and 18 which include the bivalent vaccine Cervarix (HPV 16 and 18 vaccines) and the quadrivalent vaccine Gardasil (vaccinated against HPV 6, 11, 16 and 18). These vaccines are composed of viral-like proteins produced from recombinant technology and are capable of stimulating an immunologic response. If this vaccine could be introduced into the national immunization programme, the ability to achieve a successful coverage like other vaccines in the programme is feasible.

The human papillomaviruses (HPV) which cause cervical cancer are non-enveloped viruses which possess icosahedral symmetry, 72 capsomers and double-stranded circular DNA genome with the nucleus as its site of replication. The viral genome is divided into an early region, which is necessary for neoplastic/malignant transformation; a late region, which codes for the capsid proteins; and a regulatory region which contains the origin of replication and control elements for transformation and replication.<sup>22</sup> There are eight open reading frames (E1 to E8) in the early region and two in the late region (L1 and L2), all of which are located on the same strand of DNA.<sup>22</sup>

#### **Aetiopathogenesis of Cervical Carcinoma**

The aetiologic agent responsible for causing cervical carcinoma is HPV. The high-risk oncogenic HPV is responsible for this malignant transformation in cervical epithelium. The virus infects immature squamous epithelium. This immature squamous epithelium can be found

following erosion of the cervical epithelium exposing the immature cells or it may be from squamous metaplasia at the squamocolumnar junction of the cervix. When it infects the cell, the virus integrates its DNA into that of the cell and begins to produce oncoproteins E5, E6, E7 but E6 and E7 are usually responsible for the malignant transformation.<sup>2, 10, 25</sup>

E6 Oncoprotein binds to p53 and stimulates ubiquitin-dependent proteolytic degradation of p53, thus interrupting the death pathway. E6 also up-regulates telomerase, preventing replicative senescence. Also, E7 binds to hypophosphorylated Rb protein, promoting its proteolytic degradation thus allowing E2F to freely stimulate transcription. E6 and E7 induce centromere duplication and genomic instability.<sup>2, 17</sup> These two Oncoproteins promote deoxyribonucleic acid (DNA) synthesis and interrupt p53 mediated apoptosis or cell growth arrest in mutant cells. These effects of these Oncoproteins result in malignant transformation of the cells. The integration of HPV virus into host DNA may be associated with chromosomal abnormalities.<sup>10,17</sup>

These HPV infections are sexually transmitted infections and the prevalence is higher in women who recently commenced sexual activity. It is commonly seen in women between the ages of 15 and 25years.<sup>2</sup> Within 2years of acquiring the infection it is usually cleared in most persons. It is persistent infection by these oncogenic viruses that result in malignant transformation of the infected cells.<sup>17</sup> Several factors have been associated with persistent infection. These include: Multiple sexual partners, high parity, cigarette smoking, low socioeconomic status, immunosuppression, use of oral contraceptives and young age at first sexual intercourse.<sup>2</sup>

### **Cervical Lesions/ Neoplasia (CIN)**

The HPV infect the immature squamous epithelium and cause cytopathic effects such as koilocytic atypia with nuclear atypia and perinuclear halo in the cytoplasm. Initially, these cytopathic changes are found in the premalignant lesions of the cervical epithelium referred to as squamous intraepithelial neoplasia or cervical intraepithelial neoplasia.<sup>10</sup> In cervical intraepithelial neoplasia, there are obvious atypic changes in the epithelium but with no evidence of a breach of the basement membrane. They are graded into three Cervical Intraepithelial Neoplasia (CIN) I, Cervical Intraepithelial Neoplasia II, and Cervical Intraepithelial Neoplasia III.

#### **Cervical Intraepithelial Neoplasia 1 (CIN-1)**

In this lesion, the superficial cells of the cervical epithelium display variable but mild atypia, which may include viral cytopathic effect (koilocytosis). Slight nuclear abnormalities are present throughout. Maturation is present in the upper two-thirds of the epithelium.<sup>2, 10, 17</sup>

#### **Cervical Intraepithelial Neoplasia II (CIN II)**

There are neoplastic basaloid epithelial cells in lower half to two-thirds of the cervical epithelium. Maturation is in the upper half of the epithelium with mitotic figures confined to the lower two-thirds of the epithelium. Nuclear atypia may be present throughout.<sup>17</sup>

**Cervical Intraepithelial Neoplasia III (CIN III):** Here maturation is absent or may be present in the upper third of the epithelium. Mitotic figures are present throughout. There is usually full thickness epithelial dysplasia.<sup>17</sup>

CIN1 is also referred to as low-grade squamous intraepithelial lesion (LSIL) while

CIN2 and CIN3 are referred to as high-grade squamous intraepithelial lesion (HSIL).<sup>2</sup>

#### **Squamous Cell Carcinoma**

Approximately 80% of cases of cervical carcinoma worldwide are squamous cell carcinoma. Ten percent (10%) of the low-grade squamous intra epithelial lesion (SIL) progress to high-grade SIL. Ten percent (10%) of the high-grade SIL progress to become invasive squamous cell carcinoma.<sup>2, 14</sup>

HPV16 and 18 have been implicated as the commonest aetiological agent in this disease.<sup>2, 17, 37</sup>

Both of them account for an estimated 77% of cases of invasive squamous cell carcinoma of the cervix.<sup>21, 26-30, 31</sup> A worldwide study done by Clifford et al in 2003 showed that 46-63% of invasive squamous cell carcinoma was caused by HPV 16 while 10-14% was caused by HPV 18 with overall HPV prevalence of 84.3% in invasive squamous carcinoma.<sup>31</sup> Also, a study done in Uruguay by Boris N et al in 2013 showed the prevalence of HPV 16 infection to be 67.6% in invasive cervical carcinoma and that of HPV 18 to be 8.5%.<sup>23</sup> Similarly, a study done by Denny et al in 2010 using specimens from patients in Nigeria, Ghana, and South Africa show that 83.5% of invasive cervical cancers were squamous cell carcinoma and 90.4% of invasive cervical cancer were HPV positive. Fifty-one percent (51%) were HPV 16 positive and 17.2% were HPV 18 positive.<sup>50</sup> Also a study was done in Ibadan, Nigeria by Okolo C et.al in 2000, showed prevalence of HPV 16 in invasive cervical cancer to be 67.6% and that of HPV 18 to be 10.3% both of which accounted for 77.9% of cases.<sup>6</sup> A study done in Ile Ife, Nigeria by Fadahunsi et al in 2013 showed that the commonest high-risk HPV type infection in women are 16, 53, 18 and 52.<sup>33</sup> Macroscopically, the tumour can be exophytic or endophytic invading surrounding structures.<sup>10, 14</sup>

The keratinizing type is composed of whorls of malignant squamous epithelial cells with individual keratinization that may be surrounding pearls of keratin.<sup>10</sup> The nonkeratinizing type is composed of sheets and nests of malignant squamous epithelial cells which may possess individual keratinization in some areas and pearls of keratin are absent.<sup>2, 10</sup> Warty type is composed of malignant squamous epithelial cells with a warty appearance.<sup>10</sup> Verrucous type is composed of malignant squamous cells with hyperkeratotic undulating, warty surface invading surrounding structures. It does not metastasize but has the tendency to recur after excision. Papillary type is positive for HPV 16, they are composed of thin or broad papillae lined by epithelium showing features of CIN and the underlying tumor is composed of typical squamous cell carcinoma.<sup>10</sup> Basaloid type is composed of nests of immature squamous cells with some individual keratinization in the center of the nest. keratin pearls are rare. It is predominantly caused by HPV 16. Lymphoepithelioma-like type is composed of islands of poorly differentiated cells in a background of intensely infiltrated lymphocytes. The cells are uniform, possessing vesicular nuclei with prominent nucleoli. The cells have a syncytial appearance.

#### **Adenocarcinoma**

This type of cervical carcinoma makes up to 15% of all cervical carcinomas.<sup>2, 26</sup> It is the second commonest type of cervical carcinoma following squamous cell carcinoma. HPV infection has been found in 76% of cases.<sup>24</sup> HPV 18 is the commonest cause followed by HPV 16.<sup>2, 17, 26-30</sup> A worldwide study done by Bosch et al in 1995 shows that HPV was the cause of 56% of adenocarcinomas.<sup>27, 32</sup> Also another worldwide study by Clifford et al in 2003 found that 37% to 41% of cervical adenocarcinomas were caused by HPV 18

while 26% to 36% were caused by HPV 16.<sup>26</sup>

The mucinous endocervical variant account for 70% of cervical adenocarcinoma of the cervix and the tumor is composed of proliferating glandular epithelium. The cells are mainly endocervical cells with large hyperchromatic nuclei and scanty cytoplasm.<sup>2, 10, 14</sup> The mucinous intestinal variant resemble adenocarcinoma of the colon and may contain goblet cells, paneth cells, and endocrine cells.<sup>10</sup> Mucinous signet-ring cell variant is rare and usually is a focal finding in mucinous adenocarcinoma. The mucinous minimal deviation variants are rare but highly differentiated mucinous adenocarcinoma that is difficult to differentiate from normal glands. Mucinous villoglandular variant possesses a frond-like pattern and is composed of moderately to well-differentiated epithelial cells with one or several layers of columnar cells. Some of these cells contain mucin.<sup>10</sup> Endometrioid adenocarcinoma form 30% of all adenocarcinoma of the cervix. Histologically, they possess features of endometrioid adenocarcinoma. Serous adenocarcinoma has a complex papillary pattern with frequent psammoma bodies. Mesonephric adenocarcinoma is usually from remnants of mesonephric duct characterized by tubular glands lined by cuboidal epithelial cells with eosinophilic secretion within the lumen of the glands. Early invasive adenocarcinoma displays minimal stromal invasion.

#### **Adenosquamous Carcinoma:**

This type of cervical carcinoma constitutes about 1 – 2% of all cervical carcinomas.<sup>10</sup> HPV 18 is the commonest cause of adenosquamous carcinoma of the cervix.<sup>28, 22, 37</sup> This tumor commonly occurs in young women.<sup>37</sup> Histologically, it is composed of a mixture of malignant squamous cells and glandular elements. The glandular elements

contain many mucin-producing cells and the tumor may be poorly differentiated.<sup>9</sup>

The glassy cell variant accounts for 1-2% of cervical carcinoma. This tumor which is frequently and rapidly metastatic is composed of large cells with distinct borders and ground glass appearance.

#### **Adenoid Cystic Carcinoma**

This is a rare tumor of the cervix. Most of the patients are over 60 years. This tumor is characterized by cystic spaces containing hyaline materials surrounded by palisades of epithelial cells. There is marked nuclear pleomorphism with the high mitotic rate. Necrosis is common.<sup>17</sup>

#### **Adenoid Basal Carcinoma**

They are rare cervical tumors. A tumor is composed of well-differentiated small nests of basaloid cells with areas of focal gland formation or central squamous differentiation.<sup>10</sup>

#### **Neuroendocrine Tumours**

This group of tumors is composed of malignant neuroendocrine cells, which are positive for synaptophysin, neuron-specific enolase, and chromogranin A.

Small cell carcinoma type accounts for 1-6% of cervical carcinomas. Squamous or glandular differentiation may be present. HPV type 18 has been associated with this cancer. Large cell carcinoma is composed of large cells with abundant cytoplasm, large nuclei with prominent nucleoli. A carcinoid tumor has an organoid appearance with uniform cells possessing abundant eosinophilic cytoplasm. Atypical carcinoid tumor has features of cytologic atypia with increased mitotic activity and foci of necrosis.<sup>10</sup>

#### **Undifferentiated Carcinoma**

This type of cervical carcinoma lacks specific differentiation.

#### **Screening and Prevention of Cervical Carcinoma**

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.

#### **Conclusion**

Cervical cancer is common cancer in females especially in sub-Saharan Africa, making it a big public health challenge. The recent developments in molecular pathology have been of great help in the prevention, diagnosis, and management of cervical cancer. As medical science continues to advance with new research findings, we hope that the problem of this disease would soon be a thing of the past.

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