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Review Article

An Overview of the Genetics of Cervical Cancer

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Abstract
Cervical cancer is the fourth most common cancer in women, and the seventh of all human cancers. It is the most rampant cancer of the female genital tract in the developing world and manifests in two common histological subtypes: squamous cell carcinoma which is derived from squamous cells of the cervix and cervical adenocarcinoma which arose from the glandular cells. Most cases of deaths from cervical cancer occur in the less developed countries of the world where there are ineffective screening systems. Factors that increase the risk for developing cervical cancer include infection by Human Papilloma Virus (HPV) as the main direct factor and other indirect factors such as smoking, dietary habits, age, race, socioeconomic status, sexual history, use of oral contraceptives, high parity and the human immunodeficiency virus infection. Identifying the genetic alterations that predispose to or associate with cervical cancer will help in the screening of patients at risk of the cancer thereby allowing early diagnosis and prompt management with better outcomes. In this review we describe the role of HPV DNA integration into the host cellular genome, the effects of viral E6 and E7 proteins, and the loss of heterozygosity as genetic factors in cervical cancer.

Key Words: *Cervical cancer, genetics, uterus, risk factors, HPV*

INTRODUCTION

This is the cancer of cervix, the lower, narrow end of the uterus. The cervical canal connects the uterus and the vagina (Figure 1). The epithelium of the cervix varies, consisting of two types of cells: squamous cells that form layers in the epithelium and columnar cells that form the glandular epithelium. The junction where these two cell types meet is called the transformation zone (Moscicki, *et al*. 2006). In this zone the columnar epithelium transforms into squamous epithelium and this is the site where dysplasia, the first step in cervical carcinogenesis, develops. Cervical cancer is divided into two types: Cervical squamous cell carcinoma, which is derived from squamous cells, the thin, flat cells that line the cervix and cervical adenocarcinoma, which arise in the glandular cells of cervix, which make mucus and other fluids (Burghardt and Ostor, 1983). Long-lasting infections with certain types of human papillomavirus (HPV) cause almost all cases of cervical cancer. Vaccines that protect against infection with these types of HPV can greatly reduce the risk of cervical cancer. Having a Pap test to check for abnormal cells in the cervix or a test to check for HPV can find cells that may become cervical cancer. These cells can be treated before cancer forms. In other word, cervical cancer can usually be prevented by vaccination or cured if diagnosed, found and treated in the early stages

EPIDEMIOLOGY OF CERVICAL CANCER

Cervical cancer is the fourth most common cancer in women, and the seventh of all human cancer, with an estimated 528,000 new cases in 2012 (IARC, 2012). Cervical cancer has become a global public health problem, with an incidence of over half a million and deaths in excess of a quarter of a million every year (IARC, 2012). Most cases occur in undeveloped and developing countries where there are inadequate or ineffective screening systems (Waggoner, 2003).

RISK FACTORS FOR CERVICAL CANCERS

All women are at risk in developing cervical cancer. The primary factor is infection by HPV. However, other factors that may increase the risk for women developing cervical cancer include smoking, dietary habits, age, race, socioeconomic status, sexual history, use of oral contraceptives, high parity and the human immunodeficiency virus (Figure 2).

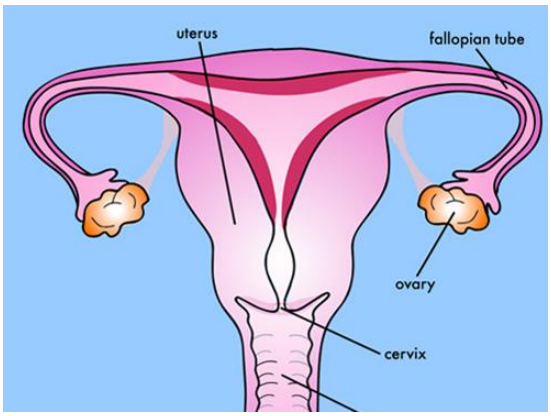

Figure 1
A schematic drawing of the human female reproductive system showing the relative position of the cervix (Kidshealth, 2018)

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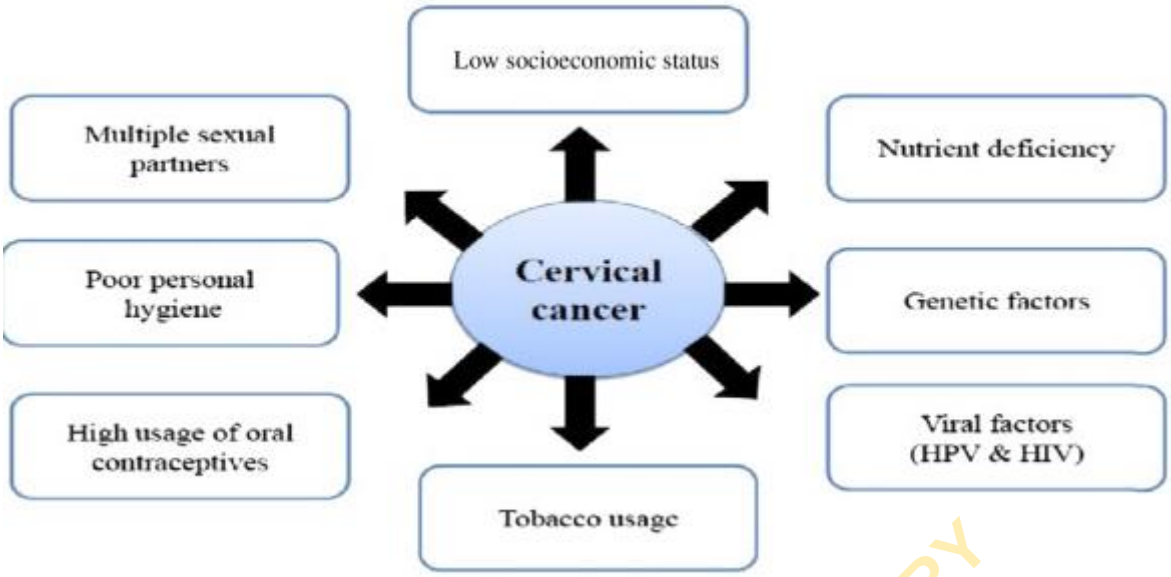

Figure 2.
Development of cervical cancer requires interplay of genetics and environmental risk factors (Husain and Ramakrishna, 2015).

Human Papilloma Virus
The primary risk factor for cervical cancer is the Human Papilloma Virus (HPV). There are several types of HPV, which vary in their ability to transform the cervical epithelium (Cannistra and Niloff, 1996). Genital HPV types are divided into high and low-risk types according to their oncogenic potential (Sigurdsson *et al*., 2007). Infection with high-risk HPV (HR-HPV) is a necessary, but insufficient factor for cervical cancer; additional viral and host genetic events are required to drive cells to the malignant phenotype (Pett and Coleman 2007). HR-HPV is detected in 99.7% of all cases and also in the vast majority of high-grade neoplasia (Lehoux *et al*., 2009).

Smoking
Cigarette smoking is among the most consistently identified cofactors that increase the risk of cervical cancer. Studies have shown that there is a twofold increased risk of development of cervical cancer for smokers compared to non-smoker (Castellsague *et al*., 2002). Although the actual mechanism by which smoking causes an increased risk of cervical cancer is not fully understood, smoking may be associated with the reduction in number of the Langerhans' immune cells in the cervix epithelium (Derchain *et al*., 1996).

Oral contraceptives
Women who are HPV positive and have used oral contraception for five or more years have a threefold increased risk in developing invasive squamous cell carcinoma (Moreno *et al*., 2002). The Upstream Regulatory Region (URR) of HPV 16 contains a glucocorticoid regulatory element that permits E2 independent early gene transcription (Gloss *et al*., 1987). As a result, steroid hormones may enhance viral transcription and stimulate malignant progression.

Sexual history
Women who become sexually active before age of 16 and had multiple sexual partners have a higher risk of developing cervical cancer. This may be because of the higher chance of getting an HPV infection which is a major causative agent of cervical carcinogenesis (Brinton *et al*., 1993).

Low socio-economic status
Low socio-economic status especially in low-resource settings has been recognized as one of the risk factors for many health problems. This is due to the fact that women of low socio-economic ability often have limited income, poor nutrition, less awareness about health issues and preventive behaviour, and less access to health care services such as Pap smear screening. As a result, they are more vulnerable to diseases and illnesses such as cervical cancer (Dos Santos and Beral, 1997).

The human immunodeficiency virus (HIV)
Studies have shown that women who are infected with HIV are more easily infected with high risk HPV types and are more prone to develop precancerous lesion than HIV-negative women in the same age category (Gaffikin *et al*., 2003). This is most probably because HIV damages the body's immune system and makes it easier for such women to contact HPV.

HISTOLOGICAL SUB-TYPES OF CERVICAL CANCERS
A normal and healthy cervix is pink in colour with the walls consisting of the epithelium and stroma. There are two main types of cervical cancer (1) Squamous cell carcinoma (SCC) and (2) Adenocarcinoma (AC). The SCC arises from the multilayered squamous epithelium of the ectocervix and transformation zone, whereas AC arises from the glandular epithelium of the endocervix (Szalmas and Konya 2009). Squamous cell carcinoma accounts for approximately 90 % and adenocarcinoma for approximately 10 % of cervical cancers (Ndofor *et al*., 2011).

STAGING OF CERVICAL CANCER
International Federation of Gynecology and Obstetrics (FIGO) standard is usually used in the staging of cervical cancer. It has put into consideration clinical parameters like size, depth of penetration into the tissue, and spread within and beyond the cervix (Figure 3).
Stage I: The disease is confined to the cervix (includes sub-stages IA1, IA2, IB1 and IB2 depending on the depth of penetration into the tissue).

Stage II: Cancer has spread outside the cervix into the upper vagina or to the tissue beside the cervix (parametrium), but not to the sidewall(s) of the pelvis (includes sub-stages IIA1, IIA2 and IIB).
Stage III: Cancer has spread to the lower part of the vagina or all the way through the parametrium to the sidewall(s) of the pelvis (includes sub-stages IIIA and IIIB).
Stage IV: Cancer has spread to surrounding organs or distant tissue, such as the lungs and distant lymph nodes (includes sub-stages IVA and IVB). (Koyama *et al*., 2007).

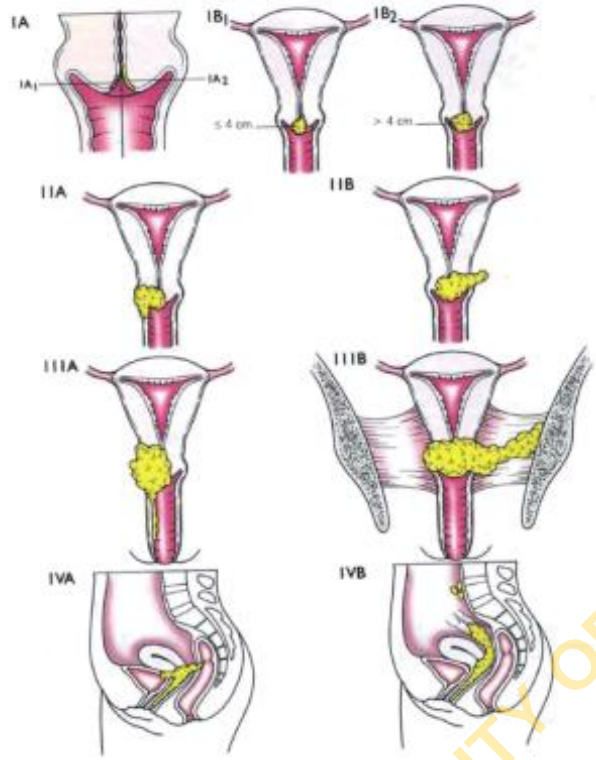

Figure. 3:
Staging of cervical cancer according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) (Koyama *et al.*, 2007).

DIAGNOSIS OF CERVICAL CANCER

Pap test and colposcopy are the major means of diagnosis. These allow the gynaecologist to detect abnormal changes in the cervix. Colposcopy is a widely used method to check the cervix for abnormal epithelia. The gynecologist applies a vinegar-like solution to the cervix and then uses an instrument much like a microscope (called a colposcope) to look closely at the cervix. The doctor may then coat the cervix with an iodine solution (Schiller test) in which healthy cells turn brown and abnormal cells turn white or yellow. The gynaecologist then obtains a biopsy for examination by a pathologist.

CERVICAL CARCINOGENESIS

Cervical cancers progress in a multistep process, from pre-invasive cervical intraepithelial neoplasia (CIN) to invasive stages (Grubisic *et al.* 2009). Most cervical cancers originate from the squamous epithelium near the opening of the cervix (Alberts *et al.* 2002), where the proliferation normally occurs only in the basal layer (Figure 4A). The newly generated cells move towards the surface, differentiate, and form flattened, keratin-rich, non-dividing cells that are sloughed off as they reach the surface (Alberts *et al.*, 2002). It is not unusual to find patches in which this organisation is disturbed in a way that suggests the beginning of a cancerous transformation, called cervical intraepithelial neoplasia (CIN). These changes can be low-grade (CINI), moderate (CINII), or severe (CINIII) (Szalmas and Konya 2009).

In the low-grade lesions, dividing cells are no longer confined to the basal layer, but occupy the lower third of the epithelium (Figure 4B). Most of these lesions will spontaneously regress; however, about 10% might progress to become high-grade lesions. Most of the epithelial layers will then be occupied by undifferentiated dividing cells, which are usually highly variable in cell size and shape (Figure 4C). If untreated, the abnormal tissue may persist and stop progressing or it may regress spontaneously. However, in almost half of the cases with this situation, progression will occur, giving rise to an invasive carcinoma where cells cross or destroy the basal lamina, invade the underlying tissue, and metastasize (Figure 4D).

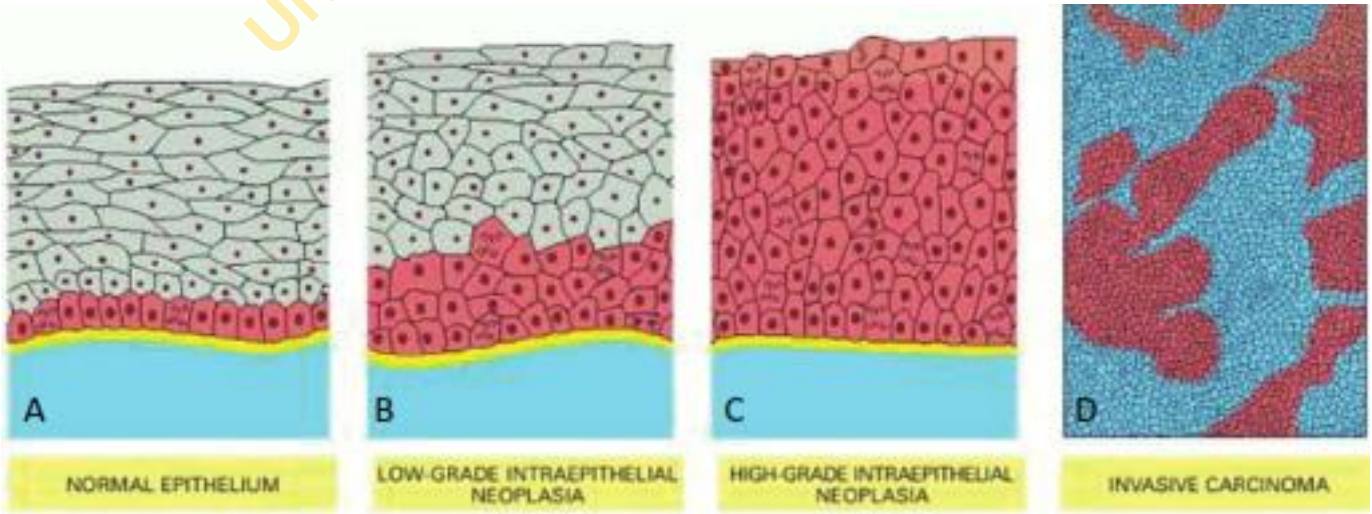

Figure 4:
The stages of progression in the development of squamous cell cervical carcinoma (Alberts *et al*., 2002).

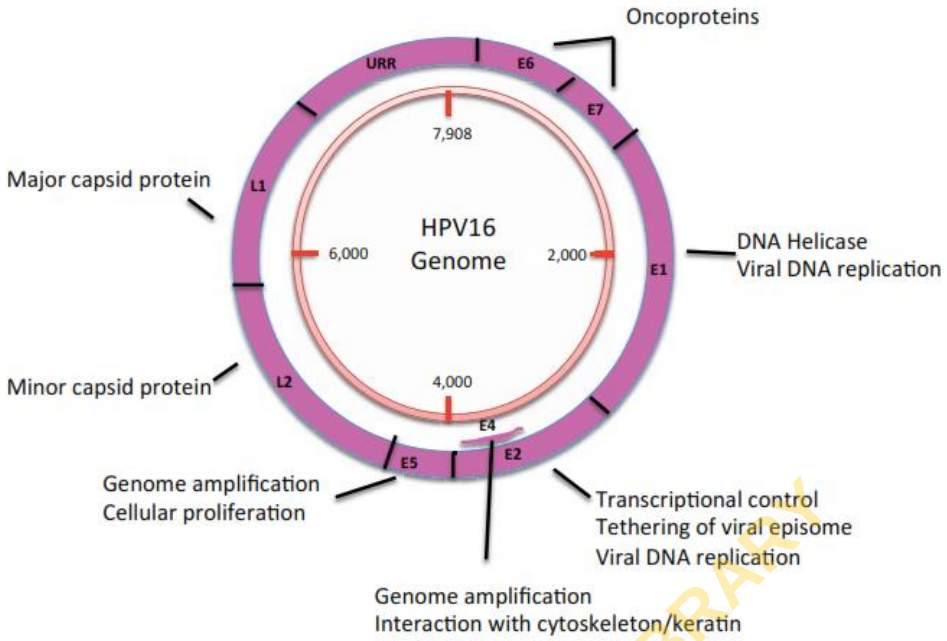

Figure 5: Human Papilloma Virus (HPV) genome map (Burk *et al*., 2009).

PATHOGENESIS OF CERVICAL CANCER

Three major factors have been identified in the pathogenesis of cervical cancer, two of which are related to the presence of HPV. These include the consequences of Human Papilloma Virus (HPV) DNA integration in the cellular genome, the effects of viral E6 and E7 proteins and the accumulation of cellular genetic damage (Wani and Nair, 2003).

Human Papilloma Virus (HPV) infection and cervical cancer: Human papillomavirus is one of the most common causes of sexually transmitted disease in both men and women worldwide. It is associated with a variety of clinical conditions that range from innocuous lesions to cancer (Sigurdsson *et al*., 2007). Human papilloma virus was first suggested to be the causative agent of cervical cancer in 1976 and was identified in the beginning of the 1980s in human genital warts and cervical biopsies (zur Hausen, 2002). It is a circular double-stranded DNA virus with a size of 8 kb (Figure 5). The HPV genome consists of 3 general regions; an upstream regulatory region (URR) containing sequences that control viral transcription and replication. Also is an early region containing open reading frames (ORFs) such as E1, E2, E4, E5, E6 and E7, encoding proteins that are involved in multiple functions like trans–activation of transcription, transformation, replication, and viral adaptation to different cellular environments. There is a third region called late region that is coding for the L1 and L2 capsid proteins that form the structure of the virion and make the viral DNA packaging and maturation possible (Burk *et al*., 2009).

Papilloma viruses belong to the family Papillomaviridae and occur in most mammals and birds. They are highly diverse with over 100 types having been detected in humans and described, based on the DNA sequence (Husain and Ramakrishna, 2015). About 40 HPV types can infect the epithelial and mucosa lining of the anogenital tract and other areas (Steben and Duarte-Franco, 2007). The genital and mucosal types belong to the taxonomy genera alpha-HPV that also contains some cutaneous types, which cause warts (de Villiers, 2004). Molecular epidemiologic studies have shown that some types of HPVs are the principal causative agent of invasive cervical cancer and cervical intraepithelial neoplasia (Walboomers *et al.*, 1999).

The genital HPV types are divided into low risk (LR),which are found mainly in genital warts, and high-risk (HR) types, which are associated with invasive cervical cancer (Munoz *et al.*, 2003). HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 have been enlisted as being carcinogenic in humans (Cogliano *et al*., 2005*)*. Of these, HPV 16 and 18 are responsible for around 90% of all cervical cancer cases (Walboomers *et al.*, 1999). It is also known that infections with more than one HR-HPV type can occur representing a possible reason for development of the cervical cancer (Trottier *et al.*, 2006*)*. Case–control studies, case series, and prevalence surveys have shown that HPV DNA can be detected in 90–100% of all cases.

However, there have been some HPV-negative cervical cancers reported (McGraw and Ferrante, 2014). These findings are believed to be due to artifacts in the current detection methods, or potentially due to loss of HPV DNA during the progression to cervical cancer (McGraw and Ferrante, 2014). In contrast, the prevalence of HPV DNA in women identified as suitable epidemiological controls is between 5–20% in cervical cell samples (Bosch *et al.*, 2002). Based on this, infection with at least one oncogenic high-risk HPV type is suggested as a necessary but insufficient cause of cervical cancer. HPV is a common sexually transmitted infection and every second a woman will get exposed to and be infected with HPV during her lifetime. The prevelence in sexually active young women ranges from 20-46% (Schiffman and Brinton, 1995) and decreases with age. Although, the majority (70-90%) of women infected will clear the HPV within 12 to 30 months (Moscicki *et al.*, 1998), HPV remains the major risk factor for cervical cancer development in older women (Adam, 2000). Figure 6 describes an overview of HPV associated events in the pathogenesis of cervical cancer.

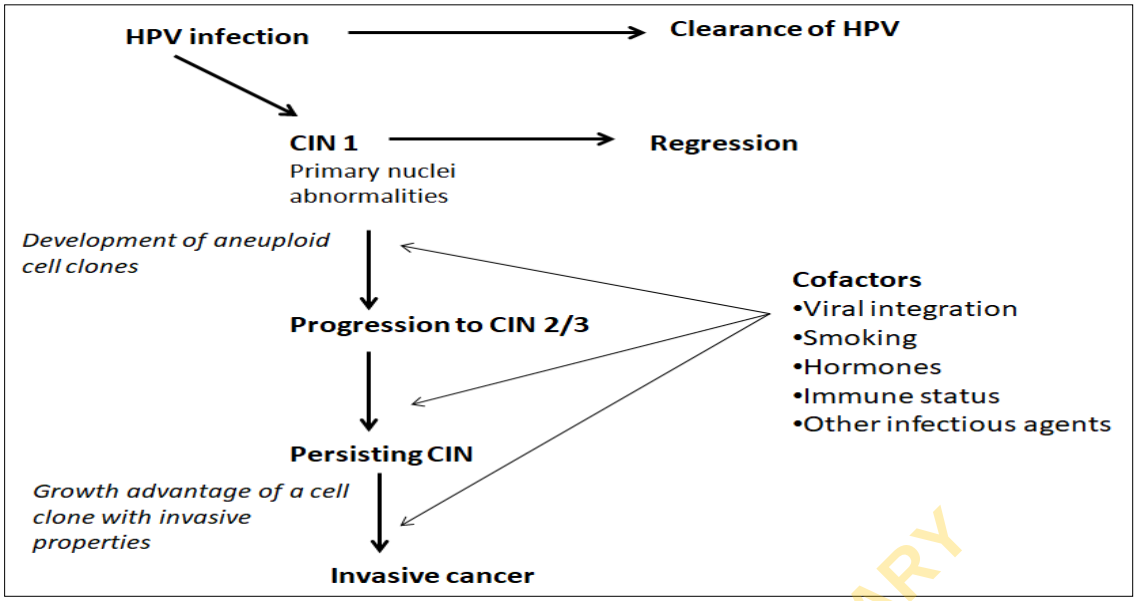

Figure 6:
An overview of HPV associated molecular events in cervical carcinogenesis (Adapted from: Wani and Nair, 2003).

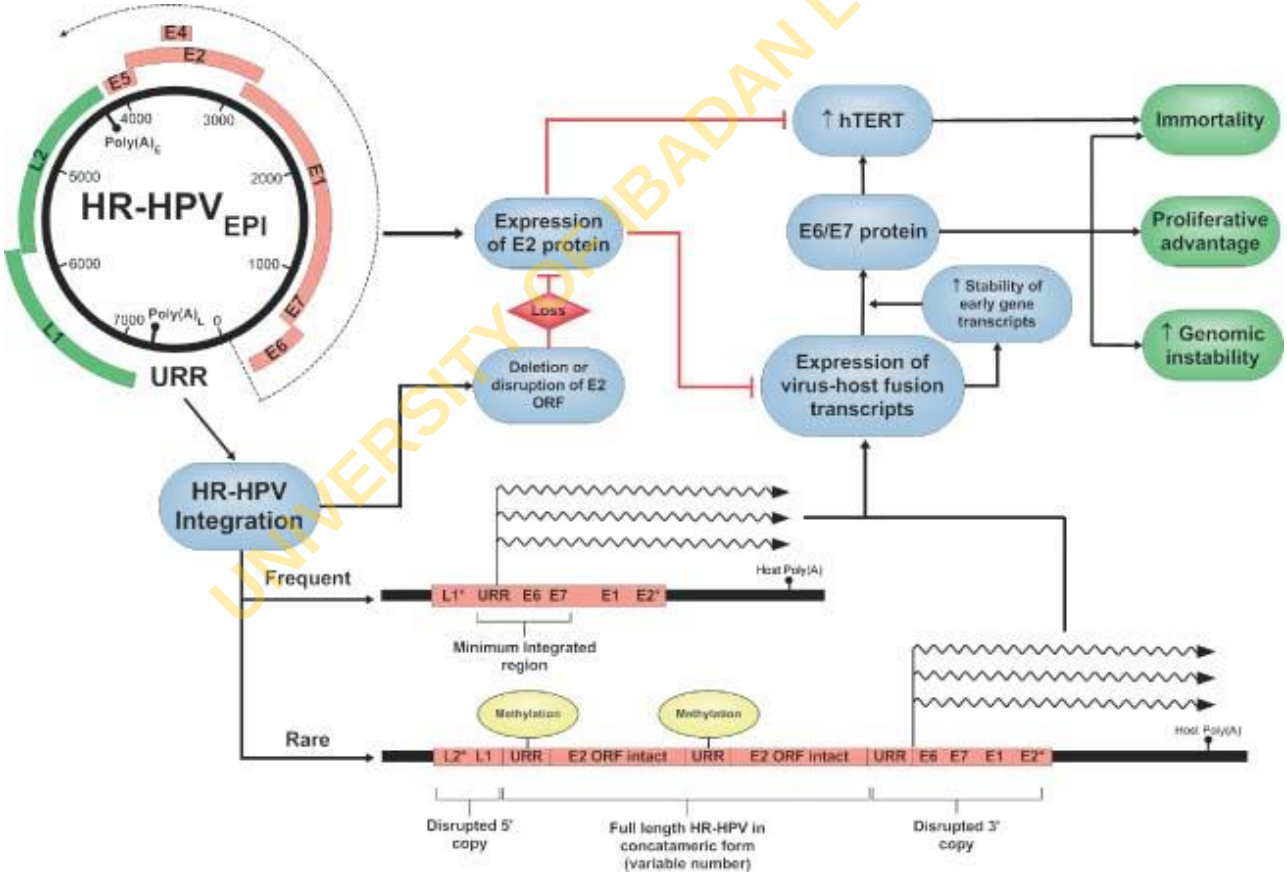

Figure 7:
High Risk HPV (HR-HPV) integration events detected in cervical carcinomas (Pett and Coleman 2007).

For HPV to successfully infect the host, it requires presence of epidermal and mucosal epithelial cells that are still able to proliferate (zur Hausen, 2002). In the basal cell layers the virus only expresses the early genes (E5, E6 and E7), leading to enhanced proliferation of infected cells and their lateral expansion (Figure 7). The next step is to infect the suprabasal layer, where the virus expresses the late genes, initiating replication of the circular viral genome and formation of the structural proteins. When the virus reaches the upper layers of the epidermis, or mucosa, complete viral particles are assembled and released. Munger *et al.*(1989) showed that just the E6 and E7 genes of HR-HPV types were able to immortalize human cells in tissue culture. The E6 and E7 genes are consistently expressed in malignant tissue, and

inhibiting their expression blocks the malignant phenotype of cervical cancer cell (McDougall, 1994). This is partly achieved by the E6 interaction with p53 (Werness *et al*., 1990) and E7 with RB (Dyson *et al*., 1989) leading to inactivation of these tumour suppressor pathways.

The site of integration of the HPV DNA in the host chromosome is between the viral regulatory genes E1 and E2. The E1 and E2 genes activate viral replication through interaction with specific sequences in the HPV genome origin of replication (Hamid *et al*., 2009). Upon integration, the viral regulatory genes and the E6 and E7 genes are expressed from viral promoters, but with a different regulation, in which host factors might play an important role (Gloss *et al*, 1989). From these hybrid viral-cellular aberrant RNA messages, normal E6 and E7 proteins are synthesized. The cellular DNA might undergo complex rearrangements or deletions (Gloss *et al*, 1989). This could therefore be a signature or biomarker for cervical cancer and/or carcinogenesis.

The role of Viral E6 in cervical cancer

The role of E6 in cervical cancer via degradation of p53 protein is summarised in Figure 8. Mucosal high-risk E6 proteins are best known for their ability to associate with the cellular tumour suppressor p53 (Werness *et al.*, 1990). Association of E6 with p53 leads to degradation of p53 via recruitment of an ubiquitin ligase, E6-AP (Scheffner *et al.*, 1993), with subsequent inhibition of the transcriptional regulatory activities of the p53 protein. The E6 proteins from multiple human and animal papilloma viruses bind to cellular proteins other than p53 and E6-AP. These include (*i*) transcription factors such as p300 (Patel *et al.*, 1999), myc (Gross-Mesilaty *et al.*, 1998), interferon regulatory factor 3 (IRF3) (Ronco *et al.*, 1998) and autocrine motility factor 1 (AMF-1/Gps2) (Degenhardt & Silverstein, 2001); (*ii*) factors that determine adhesion, cytoskeleton and polarity, such as paxillin (Vande Pol *et al.*, 1998), the mammalian homologue of *Drosophila* disk–large tumour-suppressor gene product (DLG) (Kiyono *et al.*, 1997), Scribble (Nakagawa & Huibregtse, 2000), membrane-associated guanylate inverted-1 (MAGI-1) (Glaunsinger *et al.*, 2000) and multiple PDZ protein 1 (MUPP1) (Lee *et al.*, 2000); (*iii*) apoptosis factors such as the pro-apoptic Bcl2 protein, Bak (Thomas & Banks, 1998); (*iv*) replication factors and DNA repair factors such as mcm7 (Kukimoto *et al.*, 1998) and XRCC1 (Iftner *et al.*, 2002); and (*v*) other proteins such as E6 target protein 1 (E6TP1) (Gao *et al.*, 1999), E6 binding protein 1 (E6BP1) (Chen *et al.*, 1995) and protein kinase PKN (Gao *et al.*, 2000). In addition, E6 can induce telomerase activity by inducing the expression of human telomerase reverse transcriptase (hTERT) (Veldman *et al.*, 2001).

The role of Viral E7 in cervical cancer

The E7 proteins of High-risk HPV are best known for their ability to associate with the cellular tumour suppressor, pRb (Gage *et al.*, 1990). Association of high-risk E7 with pRb also promotes the degradation of pRb (Jones *et al.*, 1997) through a proteasome-mediated pathway (Gonzalez *et al.*, 2001) and disrupts the capacity of pRb to bind and inactivate functional cellular E2F transcription factors (Chellappan *et al.*, 1992). In addition to binding pRb, high-risk E7 proteins can bind to other pocket proteins (p107 and p130) that are related to pRb (Davies *et al.*, 1993) and also interact with different members of the E2F family of transcription factors (Dyson *et al.*, 1993) associated kinase inhibitors p21 and p27 (Funk *et al.*, 1997).

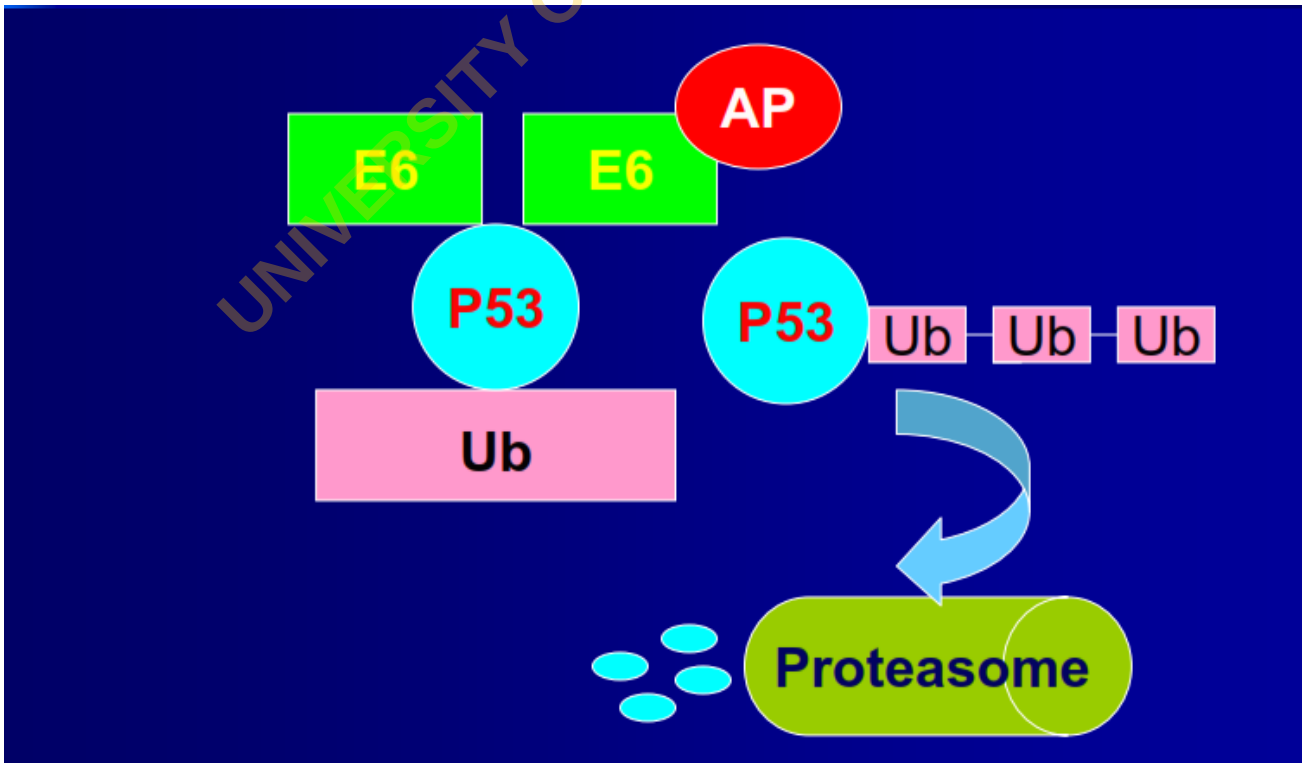

Figure 8:
The E6 protein and cellular ubiquitin-protein ligase E6-AP (E6 associated protein) form a complex which causes the ubiquitination and degradation of p53 resulting in the inhibition of the transcriptional regulatory activities of the p53 protein (Scheffner *et al.*, 1993).

Thus, E7 can associate with and/or alter the activities of multiple cellular factors that normally contribute to the regulation of the cell cycle. Other interactions have been identified between high-risk E7 and cellular factors including the S4 subunit of the 26 S proteasome (Berezutskaya & Bagchi, 1997), Mi2beta, a component of the nuclease remodelling and de-acetylase (NURD) histone complex (Brehm *et al.*,1999), the fork head domain transcription factor MPP2 (Luscher-Firzlaff *et al.*, 1999), the transcription factor activator protein-1 (AP-1) (Antinore *et al.*, 1996) insulin-like growth factor binding protein 3 (Mannhardt *et al.*, 2000), TBP (Phillips and Vousden, 1997), TBP-associated factor110 (Mazzarelli *et al.*, 1995) and a novel human DNAJ protein, hTid-1 (Schilling *et al.*, 1998).

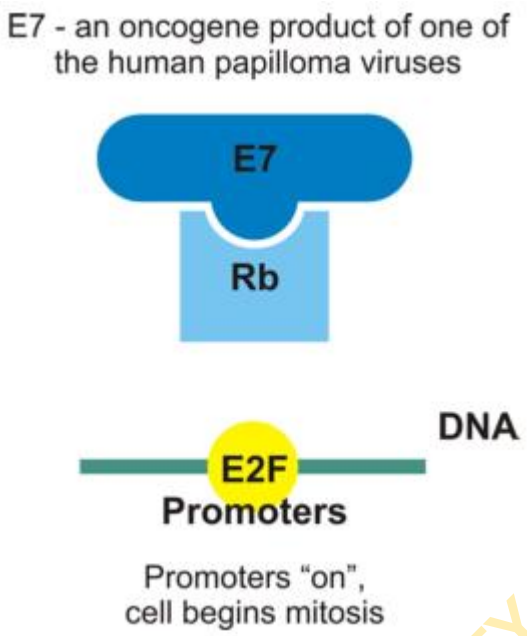

Figure 9:
Interaction between Oncoprotein E7 and Tumour Suppressor Gene Rb disrupts the capacity of pRb to bind and inactivate functional cellular E2F transcription factors (Chellappan *et al.*, 1992).

GENETIC ALTERATION IN CERVICAL CANCER

Several genetic alterations like Loss of Heterozygosity (LOH), point mutations, translocations, and amplification have been identified in cervical cancer cells.

a. Loss of Heterozygosity

Loss of heterozygosity (LOH) is a common molecular genetical change found in different kinds of human cancer. It may result in the loss of a particular DNA region. If the loss is recurrent in a significant number of cases of a particular tumour tissue type, it means that this chromosome region may play a role in tumour carcinogenesis (Tomlinson *et al.*, 1996). The LOH analysis in patients with cervical cancer has been extensively investigated leading to the identification of several chromosomal regions that are recurrently affected. For instance, 3p12-24 has been identified as a target for LOH in both squamous cell carcinomas and adenocarcinomas (Karlsen *et al*., 1994). This LOH in 3p might be an indicator of tumour progression because its frequency increases from 25% in FIGO stage I cases to 100% in stage IV cases (Larson *et al.*, 1997). In addition, 6p21.3 and 6p24 regions have also identified to be associated with LOH. The candidate altered gene on 6p21.3 is TNF-α (Kersemaekers *et al*., 1998). The LOH of TNF-α may make tumour cells less sensitive to the induction of apoptosis. As a result, survival of such a cell is enhanced (Krammer, 1997).

b. Mutation

There have been several studies attempting to detect mutations in genes well know in other tumours. Several cellular genes such as *TP53* (Tornesello *et al*., 2013), *PIK3CA* (Bertelsen *et al*., 2006) c-Myc (Myc) and ErbB2 (Zhang *et al*., 2002), cIAP1 (Imoto *et al*., 2002), Ras (Alonio *et al.*, 2003) PTEN (Cheung *et al*., 2004) and LKB1 (Wingo *et al*., 2009) have been found mutated or functional inactivated in variable proportions of cervical cancers.

(i) p53 Mutation in Cervical Cancer: The p53 gene is located on chromosome 17 p, it has 11 exons, 393 amino acids with a molecular weight of 53kd.The wild type is a tumour suppressor gene and apoptosis inducer, The Mutant type losses its tumour suppressor function by gain of oncogenic function. Functional loss of the tumour suppressor p53 by alterations in its TP53 gene is a frequent event in cancers of different anatomical regions (Petitjean *et al*., 2007; Ojesina *et al* 2014). Mutations in *TP* 53 genes are among the most common genetic alterations in many human malignancies (Vousden, 2002). Up to 90% of *TP* 53 mutations are non-synonymous and determine single amino-acid changes primarily within the DNA binding domain region (exon 5–8) located between codons 125 and 300 (Petitjean *et al*., 2007; Ojesina *et al*., 2014). Mutations in p53 gene are the most frequent genetic events in human cancer estimated to be more than 50% of the human cancers, including cervical cancers.

(ii) Rb Mutation in cancer: The retinoblastoma tumour suppressor gene (rb) encodes a nuclear phosphoprotein, termed p105Rb or pRb, which has been found mutated or deleted in several types of human malignant tumours (Friend *et al*., 1987). Mutations in RB have been found to frequently occur in lung and oesophageal cancers (Fujishita *et al*., 1995; Li *et al*., 1993).

(iii) PTEN mutation in cancer: Phosphatase and tensin homolog (PTEN) is a tumour suppressor gene localized on chromosome 10 (10q23.3) in a region that is often associated with loss of heterozygosity and consequent predisposition to carcinogenesis in a number of malignancies. Genetic, epigenetic and protein expression alterations in PTEN have been described in several types of tumours such as brain, prostate, breast, thyroid and endometrial tumours (Tamguney and Stokoe, 2007). PTEN phosphatase is a negative regulator of the Akt/PKB survival pathway, which is over-expressed in cervical squamous cell carcinoma (CSCC) (Tashiro *et al*., 1997). PTEN protein significantly diminished in CSCC compared to control suggesting that the loss of PTEN expression plays a role in cervical carcinogenesis.

(iv) *PIK3CA* mutation in cancer: Genes involved in the *PI3K* pathway represent potential therapeutic targets for cancers, and *PIK3CA* mutation status may be useful as a biomarker for targeted therapy of cervical cancer. The frequently mutated and constitutively activated PI3K pathway is involved in the pathogenesis of various human cancers including cervical cancers (Xiang *et al*., 2015). The *PIK3CA* is one of the most commonly mutated genes associated with cervical cancers (Ojesina *et al*., 2014). Most *PIK3CA*

mutations found in cervical cancer occur in the helical domain (exon 9), whereas a few *PIK3CA* mutations have been reported to affect the kinase domain (exon 20) (Xiang *et al*., 2015).

(v) LKB1 Mutation

Germline mutations in the *LKB1* tumour suppressor gene (a.k.a. *STK11*) result in Peutz-Jeghers Syndrome (PJS), a hereditary condition characterised by benign gastrointestinal polyps and an elevated risk of malignant epithelial cancers at various anatomic sites (Alessi *et al*., 2006). The *LKB1* gene was shown to undergo somatic mutation in >30% of non-small cell lung cancers (Ji *et al*., 2007) suggesting that *LKB1* may play a broad tumour suppressor role.

Conclusion

Genetic alterations contribute to the pathogenesis of cervical cancer. There have been several studies attempting to detect mutations in genes well known to have point mutations in other tumours (Khalida and Nair, 2003). Several cellular genes such as *TP53* (Tornesello *et al*., 2013), *PIK3CA* (Bertelsen *et al*., 2006) c-Myc (Myc) and ErbB2 (Zhang *et al*., 2002), cIAP1 (Imoto *et al*., 2002), Ras (Alonio *et al.*, 2003) PTEN (Cheung *et al*., 2004) and LKB1 (Wingo *et al*., 2009) have been found mutated or functional inactivated in cervical cancers. A comprehensive knowledge of genetic alterations that predispose one to cervical cancers or are associated with cervical cancers will help in the screening of patients at risk of the cancers thereby allowing early diagnosis. For instance, knowledge of cancer specific mutated genes and aberrant proteins is being developed for an application in the early detection of eight different cancer types using liquid biopsy, a non invasive method (Cohen *et al*., 2018). A multidisciplinary research team at the college of Medicine, University of Ibadan, is presently examining genetic alterations that predispose to or associate with cervical cancers. This will help in screening of patients at risk of the cancer thereby allowing early diagnosis and prompt management with better outcomes.

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REFERENCES

Adam, E., Berkova, Z., Daxnerova, Z., Icenogle, J., Reeves, W. C., & Kaufman, R. H. (2000). Papillomavirus detection: demographic and behavioral characteristics influencing the identification of cervical disease. Am J Obstet Gynecol, 182(2), 257-264.

Alessi, D. R., Sakamoto, K., & Bayascas, J. R. (2006). LKB1-dependent signaling pathways. Annu Rev Biochem, 75, 137-163.

Alonio, L. V., Picconi, M. A., Dalbert, D., Mural, J., Bartt, O., Bazan, G., Dominguez, M., & Teyssie, A. R. (2003). Ha-ras oncogene mutation associated to progression of papillomavirus induced lesions of uterine cervix. J Clin Virol, 27(3), 263-269.

Antinore, M. J., Birrer, M. J., Patel, D., Nader, L., & McCance, D. J. (1996). The human papillomavirus type 16 E7 gene product interacts with and trans-activates the AP1 family of transcription factors. EMBO J, 15(8), 1950-1960.

Berezutskaya, E., & Bagchi, S. (1997). The human papillomavirus E7 oncoprotein functionally interacts with the S4 subunit of the 26 S proteasome. J Biol Chem, 272(48), 30135-30140.

Bertelsen, B. I., Steine, S. J., Sandvei, R., Molven, A., & Laerum, O. D. (2006). Molecular analysis of the PI3K-AKT pathway in uterine cervical neoplasia: frequent PIK3CA amplification and AKT phosphorylation. Int J Cancer, 118(8), 1877-1883.

Bosch, F. X., Lorincz, A., Munoz, N., Meijer, C. J., & Shah, K. V. (2002). The causal relation between human papillomavirus and cervical cancer. J Clin Pathol, 55, 244-265.

Brehm, A., Nielsen, S. J., Miska, E. A., McCance, D. J., Reid, J. L., Bannister, A. J., & Kouzarides, T. (1999). The E7 oncoprotein associates with Mi2 and histone deacetylase activity to promote cell growth. EMBO J, 18(9), 2449-2458.

Brinton, L. A., Herrero, R., Reeves, W. C., de Britton, R. C., Gaitan, E., & Tenorio, F. (1993). Risk factors for cervical cancer by histology. Gynecol Oncol, 51(3), 301-306.

Burghardt, E., & Ostor, A. G. (1983). Site and origin of squamous cervical cancer: a histomorphologic study. Obstet Gynecol, 62(1), 117-127.

Burk, R. D., Chen, Z., & Van Doorslaer, K. (2009). Human papillomaviruses: genetic basis of carcinogenicity. Public Health Genomics, 12(5-6), 281-290.

Cannistra, S. A., & Niloff, J. M. (1996). Cancer of the uterine cervix. N Engl J Med, 334(16), 1030-1038.

Castellsague, X., Bosch, F. X., & Munoz, N. (2002). Environmental co-factors in HPV carcinogenesis. Virus Res, 89(2), 191-199.

Chellappan, S., Kraus, V. B., Kroger, B., Munger, K., Howley, P. M., Phelps, W. C., & Nevins, J. R. (1992). Adenovirus E1A, simian virus 40 tumor antigen, and human papillomavirus E7 protein share the capacity to disrupt the interaction between transcription factor E2F and the retinoblastoma gene product. Proc Natl Acad Sci U S A, 89(10), 4549-4553.

Chen, J. J., Reid, C. E., Band, V., & Androphy, E. J. (1995). Interaction of papillomavirus E6 oncoproteins with a putative calcium-binding protein. Science, 269(5223), 529-531.

Cheung, T. H., Lo, K. W., Yim, S. F., Chan, L. K., Heung, M. S., Chan, C. S., Cheung, A. Y., Chung, T. K., & Wong, Y. F. (2004). Epigenetic and genetic alternation of PTEN in cervical neoplasm. Gynecol Oncol, 93(3), 621-627.

Cogliano, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., & El Ghissassi, F. (2005). Carcinogenicity of human papillomaviruses. Lancet Oncol, 6(4), 204.

Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., Douville, C., Javed, A. A., Wong, F., Mattox, A. *et al*. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science.

Davies, R., Hicks, R., Crook, T., Morris, J., & Vousden, K. (1993). Human papillomavirus type 16 E7 associates with a histone H1 kinase and with p107 through sequences necessary for transformation. J Virol, 67(5), 2521-2528.

de Villiers, E. M., Fauquet, C., Broker, T. R., Bernard, H. U., & zur Hausen, H. (2004). Classification of papillomaviruses. Virology, 324(1), 17-27.

Degenhardt, Y. Y., & Silverstein, S. J. (2001). Gps2, a protein partner for human papillomavirus E6 proteins. J Virol, 75(1), 151-160.

Derchain, S. F., Vassallo, J., Pinto, G. A., Irazusta, S. P., & Andrade, L. A. (1996). Langerhans' cells in cervical condyloma and intraepithelial neoplasia in smoking and non-smoking adolescents. Acta Derm Venereol, 76(6), 493-494.

dos Santos Silva, I., & Beral, V. (1997). Socioeconomic differences in reproductive behaviour. IARC Sci Publ(138), 285-308.

Dyson, N., Dembski, M., Fattaey, A., Ngwu, C., Ewen, M., & Helin, K. (1993). Analysis of p107-associated proteins: p107 associates with a form of E2F that differs from pRB-associated E2F-1. J Virol, 67(12), 7641-7647.

Dyson, N., Howley, P. M., Munger, K., & Harlow, E. (1989). The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science, 243(4893), 934-937.

Friend, S. H., Horowitz, J. M., Gerber, M. R., Wang, X. F., Bogenmann, E., Li, F. P., & Weinberg, R. A. (1987). Deletions of a DNA sequence in retinoblastomas and mesenchymal tumors: organization of the sequence and its encoded protein. Proc Natl Acad Sci U S A, 84(24), 9059-9063.

Fujishita, T., Mizushima, Y., Kashii, T., Kawasaki, A., & Kobayashi, M. (1995). No occurrence of DNA-polymerase Beta-gene mutation in human lung-carcinoma cell-lines with k-ras as, p53, or rb gene alterations. Oncol Rep, 2(5), 755-757.

Funk, J. O., Waga, S., Harry, J. B., Espling, E., Stillman, B., & Galloway, D. A. (1997). Inhibition of CDK activity and PCNA-dependent DNA replication by p21 is blocked by interaction with the HPV-16 E7 oncoprotein. Genes Dev, 11(16), 2090-2100.

Gaffikin, L., Ahmed, S., Chen, Y. Q., McGrath, J. M., & Blumenthal, P. D. (2003). Risk factors as the basis for triage in low-resource cervical cancer screening programs. Int J Gynaecol Obstet, 80(1), 41-47.

Gage, J. R., Meyers, C., & Wettstein, F. O. (1990). The E7 proteins of the nononcogenic human papillomavirus type 6b (HPV-6b) and of the oncogenic HPV-16 differ in retinoblastoma protein binding and other properties. J Virol, 64(2), 723-730.

Gao, Q., Kumar, A., Srinivasan, S., Singh, L., Mukai, H., Ono, Y., Wazer, D. E., & Band, V. (2000). PKN binds and phosphorylates human papillomavirus E6 oncoprotein. J Biol Chem, 275(20), 14824-14830.

Gao, Q., Srinivasan, S., Boyer, S. N., Wazer, D. E., & Band, V. (1999). The E6 oncoproteins of high-risk papillomaviruses bind to a novel putative GAP protein, E6TP1, and target it for degradation. Mol Cell Biol, 19(1), 733-744.

Glaunsinger, B. A., Lee, S. S., Thomas, M., Banks, L., & Javier, R. (2000). Interactions of the PDZ-protein MAGI-1 with adenovirus E4-ORF1 and high-risk papillomavirus E6 oncoproteins. Oncogene, 19(46), 5270-5280.

Gloss, B., Chong, T., & Bernard, H. U. (1989). Numerous nuclear proteins bind the long control region of human papillomavirus type 16: a subset of 6 of 23 DNase I-protected segments coincides with the location of the cell-type-specific enhancer. J Virol, 63(3), 1142-1152.

Gonzalez, S. L., Stremlau, M., He, X., Basile, J. R., & Munger, K. (2001). Degradation of the retinoblastoma tumor suppressor by the human papillomavirus type 16 E7 oncoprotein is important for functional inactivation and is separable from proteasomal degradation of E7. J Virol, 75(16), 7583-7591.

Gross-Mesilaty, S., Reinstein, E., Bercovich, B., Tobias, K. E., Schwartz, A. L., Kahana, C., & Ciechanover, A. (1998). Basal and human papillomavirus E6 oncoprotein-induced degradation of Myc proteins by the ubiquitin pathway. Proc Natl Acad Sci U S A, 95(14), 8058-8063.

Grubisic, G., Klaric, P., Jokanovic, L., Soljacic Vranes, H., Grbavac, I., & Bolanca, I. (2009). Diagnostic approach for precancerous and early invasive cancerous lesions of the uterine cervix. Coll Antropol, 33(4), 1431-1436.

Hamid, N. A., Brown, C., & Gaston, K. (2009). The regulation of cell proliferation by the papillomavirus early proteins. Cell Mol Life Sci, 66(10), 1700-1717.

Husain, R. S., & Ramakrishnan, V. (2015). Global Variation of Human Papillomavirus Genotypes and Selected Genes Involved in Cervical Malignancies. Ann Glob Health, 81(5), 675-683.

Iftner, T., Elbel, M., Schopp, B., Hiller, T., Loizou, J. I., Caldecott, K. W., & Stubenrauch, F. (2002). Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1. EMBO J, 21(17), 4741-4748.

Imoto, I., Tsuda, H., Hirasawa, A., Miura, M., Sakamoto, M., Hirohashi, S., & Inazawa, J. (2002). Expression of cIAP1, a target for 11q22 amplification, correlates with resistance of cervical cancers to radiotherapy. Cancer Res, 62(17), 4860-4866.

International Agency for Research on Cancer (IARC). World Health Organization. GLOBOCAN 2012: estimated cancer incidence, and mortality and prevalence worldwide in 2012 Available from: http://globocan.iarc.fr/Default.aspx Accessed October 2017

Ji, H., Ramsey, M. R., Hayes, D. N., Fan, C., McNamara, K., Kozlowski, P., Torrice, C., Wu, M. C., Shimamura, T., Perera, S. A. *et al*. (2007). LKB1 modulates lung cancer differentiation and metastasis. Nature, 448(7155), 807-810.

Jones, D. L., Thompson, D. A., & Munger, K. (1997). Destabilization of the RB tumor suppressor protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis. Virology, 239(1), 97-107.

Karlsen, F., Rabbitts, P. H., Sundresan, V., & Hagmar, B. (1994). PCR-RFLP studies on chromosome 3p in formaldehyde-fixed, paraffin-embedded cervical cancer tissues. Int J Cancer, 58(6), 787-792.

Kersemaekers, A. M., Kenter, G. G., Hermans, J., Fleuren, G. J., & van de Vijver, M. J. (1998). Allelic loss and prognosis in carcinoma of the uterine cervix. Int J Cancer, 79(4), 411-417.

Kidshealth (2018).http://kidshealth.org/en/teens/female-repro.html. Accessed 07 February 2018

Kiyono, T., Hiraiwa, A., Fujita, M., Hayashi, Y., Akiyama, T., & Ishibashi, M. (1997). Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the Drosophila discs large tumor suppressor protein. Proc Natl Acad Sci U S A, 94(21), 11612-11616.

Koyama, T., Tamai, K., & Togashi, K. (2007). Staging of carcinoma of the uterine cervix and endometrium. Eur Radiol, 17(8), 2009-2019.

Krammer, P. H. (1997). The tumor strikes back: new data on expression of the CD95(APO-1/Fas) receptor/ligand system may cause paradigm changes in our view on drug treatment and tumor immunology. Cell Death Differ, 4(5), 362-364.

Kukimoto, I., Aihara, S., Yoshiike, K., & Kanda, T. (1998). Human papillomavirus oncoprotein E6 binds to the C-terminal region of human minichromosome maintenance 7 protein. Biochem Biophys Res Commun, 249(1), 258-262.

Larson, A. A., Kern, S., Curtiss, S., Gordon, R., Cavenee, W. K., & Hampton, G. M. (1997). High resolution analysis of chromosome 3p alterations in cervical carcinoma. Cancer Res, 57(18), 4082-4090

Lee, S. S., Glaunsinger, B., Mantovani, F., Banks, L., & Javier, R. T. (2000). Multi-PDZ domain protein MUPP1 is a cellular target for both adenovirus E4-ORF1 and high-risk papillomavirus type 18 E6 oncoproteins. J Virol, 74(20), 9680-9693.

Lehoux, M., D'Abramo, C. M., & Archambault, J. (2009). Molecular mechanisms of human papillomavirus-induced carcinogenesis. Public Health Genomics, 12(5-6), 268-280.

Li, H. C. (1993). [Mutation and expression of Rb gene in human esophageal cancer]. Zhonghua Zhong Liu Za Zhi, 15(6), 412-414.

Luscher-Firzlaff, J. M., Westendorf, J. M., Zwicker, J., Burkhardt, H., Henriksson, M., Muller, R., Pirollet, F., & Luscher, B. (1999). Interaction of the fork head domain transcription factor MPP2 with the human papilloma virus 16 E7 protein: enhancement of transformation and transactivation. Oncogene, 18(41), 5620-5630.

Mannhardt, B., Weinzimer, S. A., Wagner, M., Fiedler, M., Cohen, P., Jansen-Durr, P., & Zwerschke, W. (2000). Human papillomavirus type 16 E7 oncoprotein binds and inactivates growth-inhibitory insulin-like growth factor binding protein 3. Mol Cell Biol, 20(17), 6483-6495.

Mazzarelli, J. M., Atkins, G. B., Geisberg, J. V., & Ricciardi, R. P. (1995). The viral oncoproteins Ad5 E1A, HPV16 E7 and SV40 TAg bind a common region of the TBP-associated factor-110. Oncogene, 11(9), 1859-1864.

McDougall, J. K. (1994). Immortalization and transformation of human cells by human papillomavirus. Curr Top Microbiol Immunol, 186, 101-119.

McGraw, S. L., & Ferrante, J. M. (2014). Update on prevention and screening of cervical cancer. World J Clin Oncol, 5(4), 744-752.

Moreno, V., Bosch, F. X., Munoz, N., Meijer, C. J., Shah, K. V., Walboomers, J. M., Herrero, R., & Franceschi, S. (2002). Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet, 359(9312), 1085-1092.

Moscicki, A. B., Schiffman, M., Kjaer, S., & Villa, L. L. (2006). Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine, 24 Suppl 3, S3/42-51.

Moscicki, A. B., Shiboski, S., Broering, J., Powell, K., Clayton, L., Jay, N., Darragh, T. M., Brescia, R., Kanowitz, S., Miller, S. B., Stone, J., Hanson, E., & Palefsky, J. (1998). The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr, 132(2), 277-284.

Munger, K., Phelps, W. C., Bubb, V., Howley, P. M., & Schlegel, R. (1989). The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol, 63(10), 4417-4421.

Munoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J., & Meijer, C. J. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med, 348(6), 518-527.

Nakagawa, S., & Huibregtse, J. M. (2000). Human scribble (Vartul) is targeted for ubiquitin-mediated degradation by the high-risk papillomavirus E6 proteins and the E6AP ubiquitin-protein ligase. Mol Cell Biol, 20(21), 8244-8253.

Ndofor, B. T., Soliman, P. T., Schmeler, K. M., Nick, A. M., Frumovitz, M., & Ramirez, P. T. (2011). Rate of port-site metastasis is uncommon in patients undergoing robotic surgery for gynecological malignancies. Int J Gynecol Cancer, 21(5), 936-940.

Ojesina, A. I., Lichtenstein, L., Freeman, S. S., Pedamallu, C. S., Imaz-Rosshandler, I., Pugh, T. J., Cherniack, A. D., Ambrogio, L., Cibulskis, K., Bertelsen, B., *et al*. (2014). Landscape of genomic alterations in cervical carcinomas. Nature, 506(7488), 371-375.

Patel, D., Huang, S. M., Baglia, L. A., & McCance, D. J. (1999). The E6 protein of human papillomavirus type 16 binds to and inhibits co-activation by CBP and p300. EMBO J, 18(18), 5061-5072.

Petitjean, A., Mathe, E., Kato, S., Ishioka, C., Tavtigian, S. V., Hainaut, P., & Olivier, M. (2007). Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat, 28(6), 622-629.

Pett, M., & Coleman, N. (2007). Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? J Pathol, 212(4), 356-367.

Phillips, A. C., & Vousden, K. H. (1997). Analysis of the interaction between human papillomavirus type 16 E7 and the TATA-binding protein, TBP. J Gen Virol, 78 (Pt 4), 905-909.

Ronco, L. V., Karpova, A. Y., Vidal, M., & Howley, P. M. (1998). Human papillomavirus 16 E6 oncoprotein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. Genes Dev, 12(13), 2061-2072.

Scheffner, M., Huibregtse, J. M., Vierstra, R. D., & Howley, P. M. (1993). The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell, 75(3), 495-505.

Schiffman, M. H., & Brinton, L. A. (1995). The epidemiology of cervical carcinogenesis. Cancer, 76(10 Suppl), 1888-1901.

Schilling, B., De-Medina, T., Syken, J., Vidal, M., & Munger, K. (1998). A novel human DnaJ protein, hTid-1, a homolog of the Drosophila tumor suppressor protein Tid56, can interact with the human papillomavirus type 16 E7 oncoprotein. Virology, 247(1), 74-85.

Sigurdsson, K., Taddeo, F. J., Benediktsdottir, K. R., Olafsdottir, K., Sigvaldason, H., Oddsson, K., & Rafnar, T. (2007). HPV genotypes in CIN 2-3 lesions and cervical cancer: a population-based study. Int J Cancer, 121(12), 2682-2687.

Steben, M., & Duarte-Franco, E. (2007). Human papillomavirus infection: epidemiology and pathophysiology. Gynecol Oncol, 107(2 Suppl 1), S2-5.

Szalmas, A., & Konya, J. (2009). Epigenetic alterations in cervical carcinogenesis. Semin Cancer Biol, 19(3), 144-152.

Tamguney, T., & Stokoe, D. (2007). New insights into PTEN. J Cell Sci, 120(Pt 23), 4071-4079.

Tashiro, H., Blazes, M. S., Wu, R., Cho, K. R., Bose, S., Wang, S. I., Li, J., Parsons, R., & Ellenson, L. H. (1997). Mutations in PTEN are frequent in endometrial carcinoma

but rare in other common gynecological malignancies. Cancer Res, 57(18), 3935-3940.

Thomas, M., & Banks, L. (1998). Inhibition of Bak-induced apoptosis by HPV-18 E6. Oncogene, 17(23), 2943-2954.

Tomlinson, I. P., Novelli, M. R., & Bodmer, W. F. (1996). The mutation rate and cancer. Proc Natl Acad Sci U S A, 93(25), 14800-14803.

Tornesello, M. L., Buonaguro, L., & Buonaguro, F. M. (2013). Mutations of the TP53 gene in adenocarcinoma and squamous cell carcinoma of the cervix: a systematic review. Gynecol Oncol, 128(3), 442-448.

Trottier, H., Mahmud, S., Costa, M. C., Sobrinho, J. P., Duarte-Franco, E., Rohan, T. E., Ferenczy, A., Villa, L. L., & Franco, E. L. (2006). Human papillomavirus infections with multiple types and risk of cervical neoplasia. Cancer Epidemiol Biomarkers Prev, 15(7), 1274-1280.

Vande Pol, S. B., Brown, M. C., & Turner, C. E. (1998). Association of Bovine Papillomavirus Type 1 E6 oncoprotein with the focal adhesion protein paxillin through a conserved protein interaction motif. Oncogene, 16(1), 43-52.

Veldman, T., Horikawa, I., Barrett, J. C., & Schlegel, R. (2001). Transcriptional activation of the telomerase hTERT gene by human papillomavirus type 16 E6 oncoprotein. J Virol, 75(9), 4467-4472.

Vousden, K. H. (2002). Switching from life to death: the Mizing link between Myc and p53. Cancer Cell, 2(5), 351-352.

Waggoner, S. E. (2003). Cervical cancer. Lancet, 361(9376), 2217-2225.

Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J., Peto, J., Meijer, C. J., & Munoz, N. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol, 189(1), 12-19.

Wani, K., & Nair, C. K. (2003). Genetic alterations in cervical cancer. Indian J Exp Biol, 41(8), 789-796.

Werness, B. A., Levine, A. J., & Howley, P. M. (1990). Association of human papillomavirus types 16 and 18 E6 proteins with p53. Science, 248(4951), 76-79.

Wingo, S. N., Gallardo, T. D., Akbay, E. A., Liang, M. C., Contreras, C. M., Boren, T., Shimamura, T., Miller, D. S., Sharpless, N. E., Bardeesy, N., Kwiatkowski, D. J., Schorge, J. O., Wong, K. K., & Castrillon, D. H. (2009). Somatic LKB1 mutations promote cervical cancer progression. PLoS One, 4(4), e5137.

Xiang, L., Li, J., Jiang, W., Shen, X., Yang, W., Wu, X., & Yang, H. (2015). Comprehensive analysis of targetable oncogenic mutations in chinese cervical cancers. Oncotarget, 6(7), 4968-4975.

Zhang, A., Maner, S., Betz, R., Angstrom, T., Stendahl, U., Bergman, F., Zetterberg, A., & Wallin, K. L. (2002). Genetic alterations in cervical carcinomas: frequent low-level amplifications of oncogenes are associated with human papillomavirus infection. Int J Cancer, 101(5), 427-433.

zur Hausen, H. (2002). Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer, 2(5), 342-350