A review of risk factors in the development of cervical malignancy

Akram Husain RS, Ramakrishnan V*

*Corresponding author: Ramakrishnan V, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Chettinad Health City, Kelambakkam - 603 103, Tamil Nadu, India; E-mail: rkgenes@gmail.com

Abstract

Cancer has become a global threat and public health concern in the member states of World Health Organization's (WHO) Asia, Africa and Western Pacific regions. Cervical cancer is the malignant neoplasm arising from the cells originating in the cervix. The knowledge regarding the risk factors and disease pathogenesis are expanding rapidly. HPV is the prime etiological agent causing cervical neoplasia. They are highly transmissible and now considered the most common sexually transmitted infection in several populations worldwide. A substantial proportion of the cancer burden can be prevented by applying knowledge on cancer control measures and also by implementing large scale screening programs for early detection and treatment. This review mainly focuses on the major risk factors associated with HPV infection and lead to better understanding of cervical malignancy.

Introduction

Cervical malignancy is the second most common gynecologic cancers worldwide and seventh most frequent among overall malignancies. Generally, > 85% of the global cancer burden occurs in developing countries, in which cervical cancer accounts for 15% of all female cancers [1]. The high-risk regions include Middle, West and East Africa, South America, Asia, whereas the incidence rates are low in regions like North America and West Asia. The difference of incidence rates in these areas indicates that environmental, genetic, viral factors play an imperative role in the pathogenesis of Cervical Cancer (CC) [2]. Several epidemiological studies have documented CC risk factors such as early marriage, > 1 sexual partner, low socio-economic status, deficiency of nutrients, poor personal hygiene, long-term use of oral contraceptives, viral infections such as Human Papilloma Virus (HPV), Human Immuno Deficiency Virus (HIV), Herpes Simplex Virus (HSV) type II, history of abnormal Pap smears, genetic risk factors and also exposure to environmental factors [3]. The purpose of this review is to summarize from previously reported studies, the risk factors (Figure-1) that are found to be associated with the pathogenesis and development of cervical cancer.

Human Papilloma Virus

Human Papilloma Virus (HPV) is a non-enveloped with double stranded DNA and about 55 nm in size. HPV genome has three functional coding regions such as E- gene coding for early viral, L - gene coding for late viral function and LCR-Long Control Region. HPV are the most common viruses which are sexually transmitted, found in men and women [4]. Nearly, 100 different HPV subtypes with distinguished variations in genetic and oncogenic potential are documented and they are classified into high and low risk types. The high risk HPV has the ability to infect and develop normal mucosal cells into malignant cells [5]. However, HPV type 16 and 18 genotypes are considered as most prominent strains which are extremely specific and primarily tissue tropic, undergo entire cycle in differentiated squamous epithelial cells. The E6, E7 oncogenes play major role in infection, followed by inhibition of tumor suppressor genes viz. pRb, p53 and suppress the host cell innate immune response to HPV [6]. In addition, the other function of E6 gene is to activate telomerase, where E6 and E7 combine together to immortalize human primary epithelial cells. Even though the expression of E6 and E7 is not sufficient for development of cancer, it can be either directly or indirectly involved in stages of carcinogenesis [7]. HPV infects the basal epithelial cells; the integrin α4β6 HPV receptor mechanism remains unclear. Similarly, HPV E4 protein has been reported to be associated with keratin filaments by affecting the stability of keratin networks and facilitates the release of viral particles in the epithelium. [8]. Confortini et al., reported that nearly 30% of women aged from 18-24 years were infected with some types of human papilloma virus, in which 19.3% of the carriers harbor prominent strains which are extremely specific and primarily tissue tropic, undergo entire cycle in differentiated squamous epithelial cells. [9]. The main source of HPV transmission is sexual behavior, the strongest factor for cervical malignancy. Even though other factors might also be involved in the disease process, still HPV proves to be important in infection. Awareness on preventive, transmission methods and administration of HPV vaccines to prevent from further infection should be emphasized.

Oral Contraceptives (OCs)

OCs are used for birth control measures which include both estrogen and progesterone hormones, they are found to be associated with cervical cancer in most of the Epidemiological Studies [10]. The meta-analysis data from the IARC study among HPV-positive women documented the risk for 5-9 years and > 10
years, revealed that use of OCs for 5 years or above is a cofactor that increase risk to four-fold of CC among HPV-DNA carriers [11]. Further, the steroid hormones play vital role in the initiation and progression of this disease. Women consumed Estradiol have been reported to develop High Grade Squamous Intra Epithelial Lesions (HSIL) that eventually lead to the cervical neoplasia, these hormonal pills indirectly affects the immune response [12]. The hormones present in the OCs may transform the susceptibility of cervical cells to HPV infection causing changes that progress to CC [13]. The hormone-related mechanisms have the ability in influencing the progression of pre-malignant to malignant cervical lesions by promoting integration of viral-DNA into the host genome resulting in the deregulation of E6, E7 expression [14].

Sexually Transmitted Infections

The HPV infection with other sexually transmitted biological agents such as Human Immuno Deficiency Virus (HIV), Herpes Simplex Virus (HSV), and Chlamydia trachomatis has been inconsistently associated with cervical malignancy [15]. It has been documented that HSV-2 infection may combine with HPV infection in increasing the risk of invasive cancer and they are mediated by the stimulation of inflammatory responses [16]. HIV-positive women have been shown at higher risk of Squamous Intra epithelial lesions when compared with HIV-negative patients. They have low CD4 T-lymphocyte count and the infection can be related to Immuno-compromised state, these findings infer us the importance of host’s immunological factors in carcinogenesis of HPV [17]. A study was performed to support the association of HIV infection with advanced, early-stages cervical malignancy in African population, revealed that strong association for HIV-1, 2 infections in Western Africa [18]. The Chlamydia Trachomatis (CT) is also sexually transmitted playing role in cervical carcinogenesis as co-factor for HPV has been widely investigated with inconclusive results. The CT infection has the ability to increase the risk of squamous cell carcinoma leading to high levels of reactive oxygen species and reduction of host cell-mediated immunity [19].

Genetic Factors

Even though there are various risk factors involved in cervical cancer, genetic factors also play their role in disease pathogenesis. These factors are broadly classified under three genes namely DNA repair genes, Tumor suppressor genes and Oncogenes. A genome wide analysis study in 2013 on cervical cancer have identified two new risk loci which are associated with cervical cancer such as 4q12, 17q12 [20]. The immune response pathway genes TNFA, HLA, IL12A, IL12B, IFNG, IL-10, and CTLA-4 has been found to be associated with CC in Asian and Caucasian ethnic populations [21]. The metabolic genes in cancer such as G6PD, TKTL1, GLUT1 and PG1/AMP in the glycolytic pathway, ACC1, ACLY and FAS in lipogenesis and RRM1, TYMS and RRM2 genes involved in nucleotide synthesis. All these genes play an imperative role in tumor progression and most of these genes are highly expressed in cancer patients [22]. Loss of tumor suppressor genes (p53, pRb) and activation of oncogenes (PIK3CA, Ras and EGFR) play an important role in the development of CC. Several studies have reported somatic mutations in genes like PTEN, STK11, TP53, PIK3CA and KRAS 4–7, copy number variations in cervical carcinoma pathogenesis. Most of the mutations have functional effect on the phenotypes which can be used in earlier diagnosis of this disease [23]. Similarly when concentrating on oncogenes such as PIK3CA, KRAS and EGFR they harbor high rates of potentially targetable pathogenic mutations which are associated with severe forms of the disease. PI3K signaling has been identified as important factor in the HPV transformation models and role in cellular proliferation [24]. With the aid of available high-throughput genotyping methods, Genome-Wide Association (GWA) approaches are being performed in recent years, which provide us the comprehensive knowledge on molecular genetics of these diseases.
Other Co-factors

Smoking

Smoking is also considered as co-factor in cervical cancer. Tobacco smoke contains > 4,000 chemical substances including carcinogens such as polycyclic aromatic hydrocarbons (PAHs), benzo (a) pyrene and volatile N-nitrosamines. Smoking exposure is well documented environmental risk factor leading to many types of cancer such as lung, esophageal, liver and cervical cancers [25]. The carcinogens present in cigarette smoke have been detected in the cervical mucus of smokers, carcinogen-specific DNA adducts (e.g. NNK) have been found in epithelial cells of cervix [26]. Smoking leads to direct exposure of the DNA in cervical epithelial cells to nicotine, cotinine and the exposure of metabolic products resulting in release of aromatic polycyclic hydrocarbons and aromatic amines. The abnormalities related to smoking leads to weak systemic and peripheral immune system, that also include unbalanced systemic production of pro, anti-inflammatory cytokines [27]. These results infer us that tobacco smoking may increase the risk of viral infection and tumor onset in smoking individuals.

Nutrients deficiency

Nutrient deficiency is also considered as a factor involving in HPV carcinogenesis. People from Low socio-economic status are unaware of their diet and face nutrient deficiency which in turn leads to weakened immune system. The dietary intake of anti-oxidants and Vitamin A (carotenoids), Vitamin C (folacin) and Vitamin E (tocopherol) were found to have protective effects against cervical cancer. Low concentrations of serum carotenoids may be associated with the risk of developing cervical intraepithelial neoplasia [28]. The chemo-preventive effect of retinoids was exerted at the tumor promotion phase during carcinogenesis. Theses retinoids block tumor promotion by inhibiting proliferation, inducing apoptosis [29]. Vitamin C acts as antioxidant in hydroxylation reactions, capable of reducing compounds like oxygen and nitrates. They have the ability to inhibit malignant transformation and decrease the chromosomal damage [30].

Conclusion

Increase risk of HPV infection play tremendous role in women causing sexual problems and lead to cervical malignancy which is responsible for high mortality in developing countries. CC is an easily preventable disease, the knowledge and management of risk factors, primary preventive methods must be known beyond their socio-economic status. Additionally, male circumcision has been proved to be associated with low risk of penile HPV infection and thereby risk of cervical cancer in their female partners gets reduced. A well organized cervical cancer screening program can help us to reduce the incidence by 80% as documented from the developed countries. Thus, the implementation of regular cancer screening programs in primary health care and HIV treatment centers may also lead to significant achievement towards cancer prevention. The understanding about disease should lead to improve preventive methods and clinical management strategies, such as tests for identifying abnormal cells and HPV vaccine administration will also help in reducing the mortality, but still awareness of these risk factors should be known to every woman, so that the disease burden gets decreased.

References

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