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A review of risk factors in the development of cervical malignancy

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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 oncogenic types [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