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Review Article

Human Papillomaviruses Capable of Causing Cancer in Human

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Abstract

The extremely common worldwide human papillomaviruses have been known to the society since the time of Hippocrates in 300 BC mostly causing genital infections in human. This is observed that human papillomaviruses are extremely contagious viruses affecting only humans. Once infected, a person cannot get rid of them. Most of the individuals are infected even only after the onset of courtship without being engaged in sexual intercourse. These infections are usually asymptomatic resolving spontaneously in due course of time, but if persisted for long, it with pink in colour develops genital warts or precancerous lesions in future. The HPVs developing genital warts are different from that of causing cancers. Only a small number of strains can cause genital warts. The authors opined that the hidden asymptomatic carriers are the most typical risk group of individuals in transmission of these viruses. The aim of this paper is not only to make the people aware of the fact that human papillomaviruses are unknowingly being transmitted in the society via skin to skin contact during oral, genital or anal sex but these viruses if persisted for a longer period of time in the human body may develop cancer in future. The Present paper deals with the study of human papillomaviruses causing cancer in human in the light of recent researches done so far in the field of viral origin of cancer.

Keywords: *Human Papillomaviruses; Genital Warts; Cancer*

Introduction

Viruses are among the few causes of cancer contributing to a variety of malignancies. In 1966, when Peyton Rous was awarded a Nobel prize in physiology and medicine for his discovery of Rous chicken sarcoma virus as a cause of cancer, a renewed interest came in the field of microbial origin of cancer. Viral origin of cancer has been the second most important risk factor for cancer development in human [1]. And, the possible role of viruses in the development of cancer has been the subject of much intensive studies during the past several decades [2].

An HPV is a small, non-enveloped, circular, double stranded D. N. A. virus belonging to the papillomavirus family. This is most common sexually transmitted virus affecting only humans. As HPVs are usually harmless and asymptomatic in most of the individuals, they could be treated as the asymptomatic carriers of low risk HPVs. Similarly, as these low risk HPVs usually do not cause cancer, they produce conta-

gious genital and non-genital skin warts. While most prime locations of these skin warts are arms, chest, hands and feet, the genital warts are located in and around the genitals and/or anal areas. These genital warts are also called as veneral warts or *Condyloma acuminata* [3,4]. These warts can go away on their own in due course of time but if persisted for long can be removed surgically. Though, there is no cure for HPVs, some vaccines can prevent the infections effectively [5-7]. Further, there are some high risk HPVs found in nature which when infected the individuals, who are also immunocompromised may produce precancerous lesions and cancer in future [8-11].

The infections caused by the human papillomaviruses are one of the most common sexually transmitted infections worldwide developing a variety of cancers in human if persisted for a longer period of time [12]. They are the cancers of oral cavity as mouth, tongue, throat, oropharynx and the anogenital cancers like the cancers of vagina, cervix, penis, anus and breasts. The HPVs have been found to cause close to half of all vaginal, penile, anal and oral cancers [13,14]. Similarly, in both developing and non-developing countries breast and cervical cancers caused by the HPVs are the most common cancers found in women globally. Recent studies suggest the HPV connection in its invasiveness of both the cancers [15]. Since, the HPV is a sexually transmitted virus directly to the genital organs or breast through the skin or nipples during sexual contact, this is a generally accepted thought that the HPV which causes cervical cancer has also been found in the breast cancer tissues [12,16]. These viruses have also been found to be involved in prostate cancer [17], lung cancer [18], colorectal cancer [19] and the brain tumor cancer, known as glioblastoma multiforme [20]. The present paper deals with the study of human papillomaviruses, their infection, transmission and the production of cancer in human. This is prepared on the basis of researches done so far in the field of viral origin of cancer. The authors have gone through several original papers in order to explore the facts regarding the human papillomaviruses causing cancer in human.

Discussion

Table 1 describes some of the human papillomaviruses causing warts and cancer in human. The burden of HPV related cancers is much greater. Worldwide, nearly 5% of all cancers are caused by the high risk HPVs with an estimated more than 6 lacs individuals infecting every year. There are at least 200 types of human papillomaviruses have so far been reported to occur in nature. These HPVs are categorized with a specific number given to them as types. HPVs are DNA tumor viruses causing cancer in such a way that they inhibit the function of tumor suppressor protein p53 genes of the host cells [21-24]. They have also reported to alter the glucose metabolism of the host cells [25]. Out of them nearly 40 HPVs are involved in sexually transmitted infections in human. They are grouped either as low or high risk categories of human papillomaviruses. About a dozen strains of HPVs of high risk group have so far been identified. They are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. These are mainly transmitted via vaginal, anal or oral sex [26]. In addition, if these high risk HPVs infections persist for a longer period of time it usually produces cancer. It takes nearly 10 to 30 years after an initial infection until a tumor develops. The high risk group of these viruses develop cervical, anal, penile and oropharyngeal cancers which are caused by HPV types 16 and 18. It causes genital warts on the moist mucous opening surfaces of the body like vagina, anus, mouth and throat. Later on, these warts develop into cancer [27,28].

S. N.	Name of warts and cancer	HPV types	Sources
1.	Common, flat, planter, hand and foot warts	HPV- 1, 2, 3, 4, 5, 7, 10, 22, 28 and 63	Zayko., *et al*. 2018 [3], and Leslie., *et al*. 2019 [4]
2.	Oral and throat cancer	HPV- 6, 7, 11, 13, 16, 32 and 60	Gogilashvili., *et al*. 2012 [29]; Young., *et al*. 2016 [10]; Nowinska., *et al*. 2017 [27]; Syrjanen 2018 [30] and Lisboa., *et al*. 2019 [35]
3.	Anogenital warts	HPV- 6, 11, 42 and 44	Zur Hausen 1991 [1]; Leung., *et al*. 2018 [34]; Leslie., *et al*. 2019 [4] and Lisboa., *et al*. 2019 [35]
4.	Anal dysplasia	HPV- 6, 16, 18, 31, 53 and 58	Zur Hausen 1991 [1]; Palefsky., *et al.* 1998 [8] and Lisboa., *et al*. 2019 [35]
5.	Genital cancer	HPV-16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 66, 68, 73 and 82	Scheffner., *et al*. 1990 [21]; Grulich., *et al*. 2010 [2]; Guan *et. al.,* 2012 [26]; Tolstov., *et al*. 2014 [32]; Stratton and Culkin 2016 [9]; Nowinska., *et al*. 2017 [27]
6.	Cervical cancer	HPV-16, 18, 31, 33, 35, 45, 52 and 58	Zur Hausen 1991 [1] and 2002 [31]; de Sanjose., *et al*. 2010 [38] and Guan., *et al.* 2012 [26]
7.	Breast cancer	HPV-6, 11, 16, 18, 31, 33, 35, 45 and 52	Rosa., *et al*. 2003 [39], Yim and Park 2005 [40], Nadia., *et al*. 2017 [14], Niloofar., *et al*. 2019 [12], Asmita and Rita 2020 [41] and Islam., *et al*. 2020 [16]

Table 1: *Human papillomaviruses causing warts and cancer in human.*

Oral cancers such as the cancer of mouth and tongue are caused by the high risk human papillomaviruses, most specifically a subtype of HPV-16. It also develops the cancer of oropharynx, throat, tonsils and voice box. These cancers are increasing in individuals who have been found to be engaged in changed sexual behaviour of oral sex. In addition, more males than females are developing oropharyngeal cancer. While nearly 90 % of oral and oropharyngeal cancers are squamous cell carcinoma, more than 60% of oropharyngeal cancers have HPV, DNA in them [10,27,29,30]. Similarly, the HPVs have also been found to be associated with less common cancers including anal, vulvar and vaginal cancers in women and penile cancer in men [1,9,11,31-35].

HPVs have also been strongly linked to the development of cervical cancer in women. This is most common cancer found in women. This is observed that nearly all cervical cancers are caused by the human papillomaviruses [36]. Zur Hausen discovered HPLV-16 and HPLV-18 strains responsible for 70% cervical cancers in 1986 for which he was awarded Nobel prize for physiology and medicine in 2008 [37]. Further, other HPV types like 31, 33, 35, 45, 52 and 58 have also been found to be responsible for cervical cancer in women [38]. Nearly, all cervical cancers are caused by the human papillomaviruses [26]. There are two main types of cervical cancers caused by the HPVs are squamous cell carcinoma and adenocarcinoma. Both these carcinomas, squamous cell and adeno are found in women in percentages as 80% and 20% respectively [5]. Clinical trials have shown that HPV vaccines are safe and effective [6].

As approximately, 20% of all human cancers are caused by the microbes, numerous studies have shown that high risk HPVs are present in nearly 50% of all human breast cancers worldwide. There are nine HPV types reported to cause breast cancer in women globally. They are HPV6, 11, 16, 18, 31, 33, 35, 45 and 52 [14]. These viruses are transported to the breast either by sexual or non-sexual routes via skin or mucous membrane injuries or abrasions. This is simply done during the course of oral-genital sexual practices carried out with either of the HPV carriers. Human papillomaviruses play an important role in breast cancer development via the formation of E5, E6 and E7 oncoproteins leading to the majority women deaths. These proteins interact with p53 to increase the chromosomal instability and cellular resistance to apoptosis [39-41]. Similarly, other factors like inflammation have also been found to be involved in breast cancer progression. This is mediated by different cytokines and the reactive oxygen nitrogen species (RONS). Different cytokines stimulate the cancer cell proliferations developing tumor in the breast [12]. It appears that the vaccination against HPV is the only way to restrict the disease especially in women [16].

As HPV is a very common virus with there no treatment available so far, we should always remember that having HPV alone does not necessarily mean that one will get cancer. Most of these infections go away by itself over the period of time provided you are not an immunocompromised patient. Similarly, though, there is no way to prevent these infections, one may take some measures to lower the chances of being infected from others. Sometimes, HPV infections do not produce any symptoms and people do not know that they are the carriers of these infections quite unknowingly passing it to others. These infections are generally spread by close contact or by having vaginal, oral or anal sex. The infections may also spread from one to another part of the body. For example, if it is diagnosed as cervical cancer, genital warts may also occur in vagina and vulva. Further, as there is no medical treatment available for persistent HPVs infections running on the border line of producing cancer, if it is treated well within time then it is curable. This is an area of ongoing research [1,31]. Similarly, while there is no specific test for HPV infections in males, it can be detected in females with the help of Pap test. The Pap test is done to detect the cervical cancer. Early diagnosis and timely vaccination for HPVs may save the life. There are three vaccines reported so far as Gardasil®, Gardasil®9 and Cervarix® for the prevention of HPV infections. Receiving an HPV vaccine reduces the risk of infection. But, these preventive vaccines cannot cure an existing HPV infection. Therefore, it is advisable to have these vaccines at or before the age of 12 [6,7].

Conclusion

Human papillomaviruses are the common viruses found in human. More than 200 HPVs are found transmitted via intimate skin to skin contact. Out of these 200, at least 40 are transmitted sexually in which 10 strains have been reported to cause cancer in human. This is usually observed that most of these infections go away on their own without causing any health problems, but in some individuals if

high risk HPVs persisted for long they may develop cancer in future [2,10,26,27]. The authors have opined that we should nothing more to worry about these HPVs causing cancer but to be alert as it usually takes years after being infected for cancer to develop. Similarly, not everyone who suffered from HPV infection will develop the cancer, but unfortunately who develops the cancer, certainly is his bad luck [42,43]. Further, still there is no authentic test so far available to find out a person's current HPV status except the Pap test for cervical cancer screening in women. The precancerous cervical cell changes are being treated with the help of loop electrosurgical excision procedure (LEEP). Here we remove the abnormal tissues from the site. Therefore, cervical cancer might be cured successfully if diagnosed at an early stage. This is good for us. We hope other HPVs cancers will also be successfully diagnosed and treated in future soon.

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Conflicts of Interest

The authors have declared no conflict of interest. They have approved the final version of the manuscript contributing equally.

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