Mechanism of Cancer induced by HPV

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Abstract: Human papillomavirus (HPV) is one of the most dangerous and prevailing viruses today and more than half a million people catch cancers induced by HPV every year. However, the mechanism of different cancers induced by HPV is still not clear. Generally, HPV has two major oncogenes E7 and E6 which can be expressed to force the cell to change the cell cycle. Once the normal cell cycle is changed and HPV takes control of it, HPV makes the cell replicate abnormally and finally become cancer cells, including cervical cancer, vaginal and vulvar cancers, and oropharyngeal cancer. The whole process can last for a very long time. This review mainly focuses on how HPV induces different kinds of cancers. Having a better understanding of the mechanism of HPV-inducing cancers would contribute to the research and development of new therapeutic methods.

1. Introduction

Cancer is the biggest and hardest problem in history ever met by humans. With the elongated life expectancy, cancer is a very common disease faced by humans, especially the old ones. In table 1, it shows the statistical cancer cases in 2007 [1]. Oncovirus infection is one of the leading causes of cancer worldwide, making up approximately 12% of the total cancer numbers [2]. Among them, human papillomavirus infection contributes approximately 2% and 7% of the total cancer numbers in more developed and less developed countries, respectively [3]. In the US, every year there are 14 million persons acquiring HPV and 79 million getting infection [4]. From the statistics, it is obvious that HPV has a very high infection rate among humans and there is already a vast amount of infectious people in the world. Therefore, the mechanism of HPV which could cause cancers is one of the biggest problems scientists are working on.

HPV viruses are mostly sexually transmitted. The HPV infection often happens right after the beginning of the sexual activity. In one study, the accumulative occurrence of HPV infection within 1 year among college women after the sexual activity was 28.5% and grew to almost 50% by 3 years [5]. What's more, persons who have a 1-lifetime sex partner are under threat of infection.

For normal people, the name "HPV" is even kind of unfamiliar. Not like other viruses like HIV, HPV is easily neglected by people because the harm of HPV is long-term and not obvious. However, combined with the data above, HPV is a very popular and serious virus that could cause cancer in humans and it is worth our attention to investigate deeply.

In this review, we introduce the background information of HPV, the general mechanism of HPV, and different cancers induced by HPV.

2. Number of Cancer Cases induced by HPV per year

The human papillomavirus (HPV), in addition to cervical cancer, may also cause oropharyngeal, vaginal, penile, vulvar, anal, and rectal cancer. The majority of HPV infections are asymptomatic and clear spontaneously, but continuous infection with oncogenic HPV types may contribute to cancer.

During the years from 2008 to 2012, there were 38,793 HPV-related cancers diagnosed per year. Among them, 59% are females and 41% are males. As a result of multiplying these numbers by the proportions of cancer accounting for HPV, the CDC calculated approximately 30,700 new cases of cancer, including 19,200 in females and 11,600 in males. Detection and treatment of cervical precancers, which can prevent progression to cancer, are possible through screening, and vaccination against HPV types that cause cervical cancer is possible via vaccination. It is possible to receive vaccines against HPV types 16, 18, and 31, which make up 63% and 10% of all cancers induced by HPV in the United States, respectively. HPV 16 is more likely than the other oncogenic HPV types to contribute to cancer [7].

Table.1. Estimated new cancer cases and deaths by sex, US, 2021[1].

	Estimated New Cases			Estimated Deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
All sites	1,806,590	893,660	912,930	606,520	321,160	285,360
Oral cavity & pharynx	53,260	38,380	14,880	10,750	7,760	2,990
Tongue	17,660	12,960	4,700	2,830	1,980	850
Mouth	14,320	8,430	5,890	2,660	1,690	970
Pharynx	17,950	14,630	3,320	3,640	2,820	820
Other oral cavity	3,330	2,360	970	1,620	1,270	350
Digestive system	333,680	187,620	146,060	167,790	97,560	70,230
Esophagus	18,440	14,350	4,090	16,170	13,100	3,070
Stomach	27,600	16,980	10,620	11,010	6,650	4,360
Small intestine	11,110	6,000	5,110	1,700	940	760
Colon†	104,610	52,340	52,270	53,200	28,630	24,570
Rectum	43,340	25,960	17,380			
Anus, anal canal, & anorectum	8,590	2,690	5,900	1,350	540	810
Liver & intrahepatic bile duct	42,810	30,170	12,640	30,160	20,020	10,140
Gallbladder & other biliary	11,980	5,600	6,380	4,090	1,700	2,390
Pancreas	57,600	30,400	27,200	47,050	24,640	22,410
Other digestive organs	7,600	3,130	4,470	3,060	1,340	1,720
Respiratory system	247,270	130,340	116,930	140,730	76,370	64,360
Larynx	12,370	9,820	2,550	3,750	3,000	750
Lung & bronchus	228,820	116,300	112,520	135,720	72,500	63,220
Other respiratory organs	6,080	4,220	1,860	1,260	870	390
Bones & joints	3,600	2,120	1,480	1,720	1,000	720
Soft tissue (including heart)	13,130	7,470	5,660	5,350	2,870	2,480
Skin (excluding basal & squamous)	108,420	65,350	43,070	11,480	8,030	3,450
Melanoma of the skin	100,350	60,190	40,160	6,850	4,610	2,240
Other nonepithelial skin	8,070	5,160	2,910	4,630	3,420	1,210
Breast	279,100	2,620	276,480	42,690	520	42,170
Genital system	317,260	203,740	113,520	67,830	34,210	33,620
Uterine cervix	13,800		13,800	4,290		4,290
Uterine corpus	65,620		65,620	12,590		12,590
Ovary	21,750		21,750	13,940		13,940
Vulva	6,120		6,120	1,350		1,350
Vagina & other genital, female	6,230		6,230	1,450		1,450
Prostate	191,930	191,930		33,330	33,330	
Testis	9,610	9,610		440	440	
Penis & other genital, male	2,200	2,200		440	440	
Urinary system	159,120	110,230	48,890	33,820	23,540	10,280
Urinary bladder	81,400	62,100	19,300	17,980	13,050	4,930
Kidney & renal pelvis	73,750	45,520	28,230	14,830	9,860	4,970
Ureter & other urinary organs	3,970	2,610	1,360	1,010	630	380
Eye & orbit	3,400	1,890	1,510	390	210	180
Brain & other nervous system	23,890	13,590	10,300	18,020	10,190	7,830
Endocrine system	55,670	14,160	41,510	3,260	1,600	1,660
Thyroid	52,890	12,720	40,170	2,180	1,040	1,140
Other endocrine	2,780	1,440	1,340	1,080	560	520
Lymphoma	85,720	47,070	38,650	20,910	12,030	8,880
Hodgkin lymphoma	8,480	4,690	3,790	970	570	400
Non-Hodgkin lymphoma	77,240	42,380	34,860	19,940	11,460	8,480
Myeloma	32,270	17,530	14,740	12,830	7,190	5,640
Leukemia	60,530	35,470	25,060	23,100	13,420	9,680
Acute lymphocytic leukemia	6,150	3,470	2,680	1,520	860	660
Chronic lymphocytic leukemia	21,040	12,930	8,110	4,060	2,330	1,730
Acute myeloid leukemia	19,940	11,090	8,850	11,180	6,470	4,710
Chronic myeloid leukemia	8,450	4,970	3,480	1,130	670	460
Other leukemia‡	4,950	3,010	1,940	5,210	3,090	2,120
Other & unspecified primary sites‡	30,270	16,080	14,190	45,850	24,660	21,190

*Rounded to the nearest 10, cases exclude basal cell and squamous cell skin cancer and in situ carcinoma except urinary bladder. About 48,530 cases of female breast ductal carcinoma in situ and 95,710 cases of melanoma in situ will be diagnosed in 2020. †Deaths for colon and rectal cancers are combined because a large number of deaths from rectal cancer are misclassified as colon. ‡More deaths than cases may reflect lack of specificity in recording underlying cause of death on death certificates and/or an undercount in the case estimate.

Source: Estimated new cases are based on 2002-2016 incidence data reported by the North American Association of Central Cancer Registries (NAACCR). Estimated deaths are based on 2003-2017 US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention.

According to the WHO [8], the article shows High-income countries offer vaccinations against HPV to girls and routine screenings for women, which could reduce HPV infection. It is possible to identify precancerous lesions at an early stage when they can easily be treated by screening. The prevalence of cervical cancer is often unknown until it has advanced further and symptoms appear in middle and low-income countries due to lack of access to these preventative measures. Additionally, for patients with cervical cancer in late stages, treatment options may be limited (such as chemotherapy, radiotherapy, and surgery), resulting in a higher mortality rate.

3. Cancers Associated with Human Papillomavirus

According to the CDC [9], HPV causes cancers of the vagina, anus, penis, vulva, and oropharynx. HPV causes these types of cancer in a variety of ways and to various extents, which are still under investigation. It has been estimated that more than 90% of cervical and anus cancers, around 70% of vaginal and vulvar cancers, and 60% of penile cancers are induced by HPV. Oropharyngeal cancer (oropharyngeal) has traditionally been caused by tobacco and alcohol, but recent studies suggest that up to 70% of oropharyngeal cancers are induced by HPV. HPV usually disappears on its own after two years, and health problems are not frequently associated with it. Researchers believe that HPV is naturally destroyed by the immune system. For HPV to cause these cancers, it needs to stay in the body for many years. Therefore, repeated HPV infection may be an important cause of cancer.

4. Types of HPV with high and low risks

There are two types of HPV, non-oncogenic (causes warts) and oncogenic (causes cancer), based on whether the virus increases cancer risk. Approximately thirteen HPV types have been found to cause cervical cancer, and most of these types can also cause certain head and neck cancers. Cancer-causing HPV is different from that which causes genital warts. Multiple types of cancer are caused by high-risk HPVs. In addition to HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, there are 14 types which are considered high-risk. The most common HPV-related cancers are HPV16 and HPV182. Four out of five women will have been infected with HPV at some point during their lives by the age of 50. Men are also susceptible to HPV, although the symptoms are usually not as severe as those of women [10].

5. Mechanism of HPV inducing cancer

HPV is a double-stranded DNA virus with a circular genome that encodes early, including E1, E2, E4, E5, E6, and E7 essential for replication, transcription, and transformation, and late genes L1 and L2, encoding for viral capsid proteins [11].

In order to allow for the creation of viral offspring, viral proteins override the normal cell cycle exit that happens in differentiating cells after HPV infection. HPV virions enter cells via a receptor after infecting the epithelia's basal layers, most likely through micro-wounds. Genomes are established as episomes after migrating to the nucleus, and the early HPV promoter is activated. Low levels of viral DNA synthesis resulted in approximately 50-100 genomic copy numbers per cell in these infected cells. After basal cell division, the HPV genome is replicated and amplified and then distributed evenly across the daughter cells. Infected daughter cells that remain active during the cell cycle migrate to the upper layers of the epithelial cells and begin to differentiate. Activation of late promoters with HPV-positive cell differentiation leads to the production of late gene products, which initiates the HPV life cycle leading to high-level amplification of the viral genome. In the upper cortex, the newly formed capsid is coated with viral DNA, which is then released from the cell. Because HPV replication is dependent on host cells, the upper layers of the upper cortex remain intact for DNA synthesis. This process is mainly mediated by E6 and E7 proteins, so HPV infected cells do not exit the cell cycle [12]. In this process, E6 and E7 play a very important role. The cell regulation in normal cells is controlled by two proteins, p53, and pRB. The p53 prevents the genome from initiating cell cycle

checkpoints, RNA repair, and apoptosis. The pRB prevents the replication of damaged DNA in the cell and regulates the cell cycle. When E6 and E7 are expressed, the product proteins interact with p53 and pRB respectively. In the absence of management of p53 and pRB, cells replicate abnormally. As the HPV infected cells replicate without control, HPV is also replicated to produce more viral particles. The repetition continues to become uncontrolled cancer cells.

6. The HPV virus and vaginal and vulvar cancer

By avoiding certain risk factors and having pre-cancerous conditions treated before they progress to invasive cancer, the risk of vulvar cancer can be reduced. A vulvar cancer diagnosis can be influenced by infection with the human papillomavirus (HPV). Women tend to contract HPV when they are younger and are less likely to contract it when they are older. A person contracts HPV by contacting an infected area of their body through skin-to-skin contact. HPV can be transmitted through vaginal, anal, and oral contact, but sexual contact is not required for infection transmission. Skin-to-skin contact with an HPV-infected body part is the only criterion. The virus is spread by direct contact between the genital organs. Even though hand-to-genital contact, a genital infection can spread. Infections caused by HPV have also been shown to spread from one body part to another. To put it another way, an infection in the cervix can spread to the vaginal canal and vulva.

The risk of contracting HPV is extremely high. Limiting the number of sexual partners and avoiding having sex with people who have a lot of sexual partners are two ways sexually active people can reduce their risk of contracting HPV. However, there are few timely sexual partners, and there is a risk of infection when having sex. Although HPV infection is common, the body is usually capable of dealing with it on its own. However, in some cases, the infection does not go away and becomes chronic. Chronic infection, particularly for HPV types with a high risk of cancer, can lead to certain cancers, including vulvar cancer. The absence of visible warts does not mean that a person is HPV-infected. HPV infection can go unnoticed for years without causing any symptoms. HPV can infect and spread the virus regardless of whether or not someone has warts (or any other symptom) [13].

HPV infects the undifferentiated proliferative basal cells when epithelial mucosa cells are exposed to tissue trauma. In the stratified epithelial layers, HPV causes infection. The reproduction and differentiation of viruses are closely linked in this way. The ligase chain reaction (LCR), which uses cellular nutrition, ATP, and organelles as feedstock, involves transcription factors that bind to specific elements within the ligase chain reaction (LCR). According to a study by Longworth MS and Laimins LA, E6 and E7 collaborated in the immortalization and inhibition of differentiation of primary human keratinocytes. By combining E7 and the retinoblastoma tumor suppressor protein, protein E6 could be linked to p53 inactivation (pRB). As a result, these proteins bind to host cell proteins with varying affinities, disrupting epithelial differentiation and apoptosis. They aid in the stable maintenance of episomes and stimulate the physiological functions of infected cells during the S phase of the viral life cycle. The E1 and E2 proteins regulate early viral transcription as origin recognition factors. E3-E4 proteins are thought to be involved in modulating late viral functions, though their functions are unknown. E5 is not highly conserved at the nucleotide level. EGF and PDGF, which are linked to late gene viral life-cycle events, influence cellular proliferation. The E5 gene produces a transmembrane protein that regulates cellular protein activity and contributes to cell signaling. The capsid of the virus is made up of the major and minor capsid proteins L1 and L2. Protein L1 can form an icosahedral structure that resembles the structure of viral particles on its own, whereas protein L2 is involved in viral DNA encapsidation and viral DNA entry into host cells. During the self-assembling process as a virus-like particle, the L1 and L2 proteins collaborate to generate progeny virion for increased reproduction (VLP) [14].

7. The HPV virus and oropharyngeal cancer

The most common type of oral cancer is head and neck cancer. Head and neck squamous cell carcinoma (HNSCC) is the sixth to ninth most common cancer worldwide. Oral cancer (OC) and

oropharyngeal cancer (OPC) are frequently confused, and oropharyngeal squamous cell carcinoma (OSCC) is frequently misdiagnosed as oral cancer. According to Soung Min Kim's research, oral and maxillofacial cancer can be classified based on anatomic sites as follows: lip, tongue, mouth, salivary glands, tonsil, oropharynx, nasopharynx, hypopharynx, pharynx unspecified, nose, and sinuses. Oral HPV is transmitted to the mouth through oral sex or possibly other means. People who are infected with oral HPV are very common. Infections of the mouth caused by HPV affect roughly 10% of men and 3.6 percent of women, and they become more common as people get older. Viral genes are expressed sequentially from early to late genes following epithelial squamous differentiation, beginning in basal and para-basal cells, where early portions of the viral genomes are more active, and progressing to higher epithelial layers of both the intermediate and superficial layers, along with virion formation. After desquamation, the virus is expelled from epithelial cells and transmitted via direct or indirect contact, completing productive replication [14].

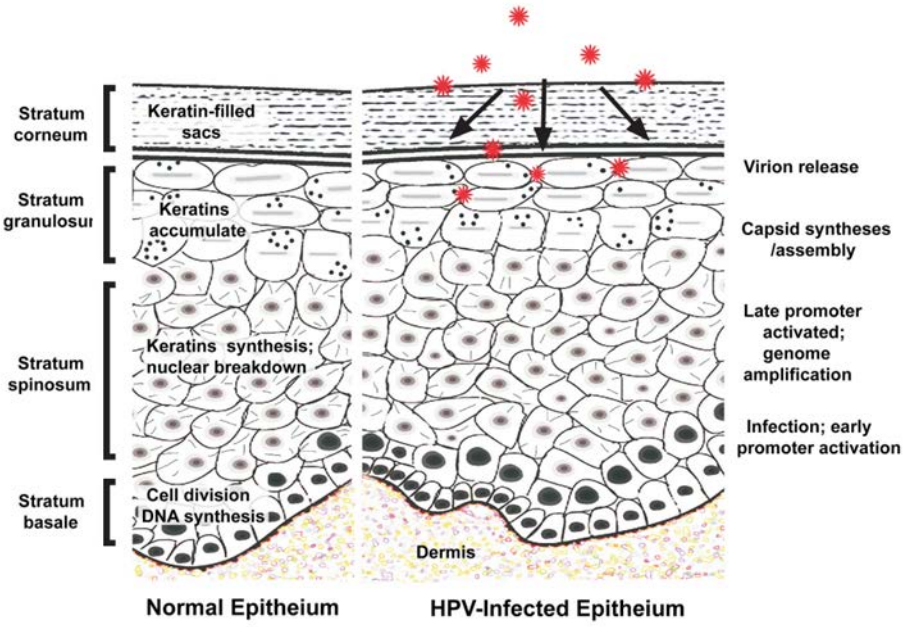

Figure 1. The difference between normal and HPV-infected epithelial cells is depicted in this diagram. The granular and stratum corneum layers release viral virions, which infect the basal layer directly. In the late and early stages, this involves the synthesis of capsids and the activation of promoters. Human papillomavirus in oral cancer, Soung Min Kim. 2016 Journal of the Korean Association of Oral and Maxillofacial Surgery [14]

The HPV integration process involves the disruption of viral episomal DNA, the publication of E1 and E2 ORFs, as well as the retention of E6 and E7 segments. This leads to a disruption of cell control mechanisms as well as increased proliferation of infected cells (Fig. 1). Consequently, chromosomal aberrations are more likely to occur and excessive viral proteins are produced, interfering with cellular replication [15].

8. The hrHPV vaccine for prevention of cancer

Because there is no treatment for people who have been infected with HPV, vaccine prevention is one of the HPV treatments. Three vaccines have been prequalified so far: There is a 9-valent HPV vaccine (Gardasil 9, 9vHPV), a quadrivalent HPV vaccine (Gardasil, 4vHPV), and a bivalent HPV vaccine (Cervarix, 2vHPV) that all protect against HPV 16 and 18, which cause more than 70% of cervical cancers. Vaccines, on the other hand, cannot treat HPV infection or HPV-related diseases like cancer [8]. The third vaccine is the 9-valent HPV vaccine, which protects against five more oncogenic HPV strains that cause 20% of cervical malignancies. These vaccines not only protect against HPV

type 6 but also against HPV type 11, which is responsible for anogenital warts. HPV vaccinations are exceedingly safe and effective at preventing HPV infections, high-grade precancerous lesions, and invasive malignancy, according to clinical trials and post-market surveillance. Vaccines have a better effect if they are administered at a younger age. As a result, the WHO recommends that girls receive vaccines between the ages of 9 and 14 before beginning sexual activity. Between the ages of 11 and 12, the CDC recommends that boys get vaccines.

9. Conclusion

The present review examined the relationship between HPV and cervical cancer, vaginal and vulvar cancers, and oropharyngeal cancer. HPV has a different mechanism to infect each cancer. The immune system can also destroy HPV naturally. From HPV infection to CIN and from CIN to cervical cancer, the immune system plays an important role. It is essential for disease progression for the immune system to become compromised. Once HPV infection has progressed to cervical cancer, it affects the immune system to become more tolerant, resulting in persisting hrHPV infection and progression of cervical lesions. Infections caused by the human rhinovirus (hrHPV) can be prevented with the hrHPV vaccine. As HPV integrates with vulvar and vaginal cancer, it creates productive infections throughout the stratified epithelia. Ligase chain reactions determine HPV expression by binding to specific elements and playing a role in cellular and viral transcription factors. As part of the HPV integration process with Oropharyngeal cancer, viral episomal DNA is disrupted, as is the publication of the E1 and E2 ORFs, as well as the replication of the entire viral genome retention of E6 and E7 segments. Although HPV is now incurable, various forms of preventive vaccinations have been created with the goal of increasing the virus's and tumor cells' immune responses.

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