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Human Papilloma Virus (HPV) - A Threat to Women Worldwide: Emerging Solutions for Cervical Cancer

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ABSTRACT

Introduction: Human Papilloma Virus (HPV) is a papillomavirus that infects the skin and mucous membranes of humans. It impacts the health of women far more than it impacts men. Approximately 200 HPV types have been identified so far. Some HPV sub-types cause warts (verrucae) and certain others cause cancers including cervical cancer, while others have no symptoms. HPV is the most common sexually transmitted virus infecting human and presents as exophytic verrucous white or pigmented lesions with symptoms of bleeding and pain. The HPV infection and thereby cervical cancer incidence are found to be higher in underdeveloped countries.

Aim and Objective: This review aims at summarising the new advancements in the solutions for cervical cancer especially, the HPV targeted therapeutic vaccine developments and prospects.

Conclusion: The primary reason noted is the lack of access to screening and awareness about risk factors. However, the applicability of these screening in India is questionable. Furthermore, the women (especially Indians) psychologically don't like to have Pap smear when they don't have any abnormal symptoms. Moreover, the Pap smear test is not so efficient to screen before the onset of cervical lesions. More research is needed in screening methods so that best practices for prevention and management can be developed and implemented. Even though there are Food and Drug Administration (FDA) approved HPV vaccines like Gardasil, Gardasil 9, Cervarix, which prevent infection against various high-risk HPV types, HPV associated diseases remain a significant public health problem since the HPV vaccines do not treat the already infected individuals.

Key Words: Cryo microscopy, Prospects, Human papillomavirus, HPV therapeutic, Vaccines, Phytochemicals, Progress in therapy

INTRODUCTION

Human papillomavirus (HPV) infections cause cervical, vulvar, vaginal, penile, anal, and a few head and neck (oropharyngeal) cancers. HPV is considered the major cause of the occurrence of various types of cancer and skin warts.[1] The International Agency for Research on Cancer has found that the cancer sites of the cervix uteri, penis, vulva, vagina, anus and oropharynx, including the base of the tongue and tonsil, have a strong causal relationship with HPV.[2] HPV is transmitted from skin and mucous membrane of an infected individual to a healthy one through direct sexual contact.[3] According to NIH, Human Papilloma Viruses are considered to spread through direct sexual contact. HPV is a non-enveloped, epitheliotropic, double-stranded circular DNA virus, whose gene expression and the life cycle is tightly controlled by epithelial cell differentiation.[4]The sexually transmitted HPV types are categorised into low risk and high-risk HPV's based on their oncogenic potential. The low-risk HPV type causes genital warts and is considered non-cancerous lesions. The high-risk HPV types are potential tumour causing agents. HPV can be classified into two main phylogenetic genera namely α-HPV and β-HPV, which corresponds to the mucosal and cutaneous infection respectively.[5] The CDC statistics revealed the occurrence of about 39,800 HPV-associated cancers in the United States each year from 2009 to 2013.[6] They have highlighted that half of the population is affected by HPV and the recent research has focused on formulating therapeutic drugs, which produce cell-mediated immunity and strong therapeutic effects against established HPV infections and lesions.[7]

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In 2017, the WHO fact sheet revealed that the HPV infection does not show symptoms in most cases, and cervical cancer symptoms tend to appear only at an advanced stage. Hence, regular screening for HPV is important and it highlighted that 90% death by cervical cancer is in middle-income countries.[8] Mortality due to cervical cancer is reduced in women who undergo regular pap screening test followed by diagnostic procedures and treatment. It has also been found that screening with Pap test and HPV DNA for every five years in women 30 years and older, is more sensitive in identifying the cervical abnormalities at an early stage and these two tests reduce the incidence of cervical cancer.[9] The irony is that there is no HPV specific treatment even if it is identified upon screening to prevent the development risk of cervical cancer which is an alarming situation for women worldwide. The existing HPV managements are vaccination for only very few types and non-specific immune-stimulation regimen against HPV infection. Like the HIV, evolution into new sub-types of HPV is the real challenge of HPV vaccination as well as immunotherapy. Hence, understanding the mechanism of action of HPV will help in formulating better antiviral therapeutic agents against HPV. Advancement in 3D microscopic view of HPV using a new imaging technique called cryo-EM or cryo microscopy has helped researchers to get a detailed view of HPV structure, the antigen-antibody binding, the epitope region, and the transformational changes that occur when the HPV virus binds to the cell. It was, therefore, suggested to have improved imaging to better research approaches in future.[10] This review article highlights the HPV infection as a real threat for women and the various advancements in HPV research to solve the present challenges and their impact on cervical cancer management.

EPIDEMIOLOGY OF CERVICAL CANCER

The leading genital cancer among women worldwide is cervical cancer and millions of new cases reported every year. An account of 239,000 deaths has been reported in 2015 and most of them are with squamous cell carcinoma. It differs in the geographic region. Among 100,000 women, 34.8 new cases and 22.5 deaths are reported in sub-Saharan Africa and 4.4 new cases and 1.9 deaths are reported in Western Asia. The cervical cancer rate is very lower in Northern America. The cervical cancer rate is very high in many countries of Central Asia compared to Europe. In Central Asian Countries, 25,700 cervical cancer cases were reported and 12,700 died of it. The mortality rate in Kyrgyzstan is 11.2 per 100,000 and in Tajikistan 4.9 per 100,000. Increasing morbidity, such as pain, bleeding, and kidney failure are the risk factors of cervical cancer and in poor countries; it is difficult to treat cervical cancer.[11]It was reported that 57,000 new cases and 311,000 deaths have occurred in 2018, and the highest cases reported in Eswatini at 6.5%. The global cervical burden can be contributed by India and China, 106,000 cases in China with deaths of 48,000 and 97,000 cases with 60,000 deaths in India.[12] The WHO made a draft global strategy to be achieved within 2030 by focusing on three main factors as; prevention (90% of girls need to be vaccinated for HPV), screening (70% coverage for cancer and 90% coverage for pre-cancerous cervical lesions) and treatment at the early stage of cancer (Managing 90% of invasive cancer).[13]

THERAPY FOR CERVICAL CANCER

The promising results achieved in primary treatments of cervical cancer include surgery or a concurrent chemoradiotherapy regimen consisting of cisplatin-based chemotherapy with external beam radiotherapy and brachytherapy. The cisplatin plus Paclitaxel was found to show less toxicity than cisplatin plus fluorouracil,[14] which implies that the plant-derived drug Paclitaxel is a good option for treating cervical cancer with reduced toxic effects. Intra-cavitary brachytherapy is an integral part of radiotherapy for locally advanced gynecologic malignancies.[15] Treatments other than the primary surgical techniques, which need advanced training and equipment, include carbon dioxide laser ablation, Cavitron Ultrasonic Surgical Aspiration (CUSA), and Mohs surgery.[16] Even though various advancements are found in the treatment process of cervical cancer, the recurrence rate is very high due to a specific set of complications. The present treatment methods are only killing the cancer cells and not eliminating the transforming HPV infection. Hence, future research should aim at finding cost-effective HPV targeted techniques to treat the HPV infection as well as to prevent the recurrence of such infections after treatment.

HPV SCREENING STATUS

Women cervical cancer is the most common and globally positioned the fourth as per the IARC report 2019. To prevent it, the Director-General of WHO made a global call to follow strategies of preventing HPV by improving vaccination, treatment and screening at the early stage. It is predicted that, within the next 65 years, about 35-40 million cancer cases will be reported. Two HPV assays such as; Gene Xpertand care HPV have been prequalified by WHO for the screening of HPV to detect the risk of cervical cancer development at the earliest stage. For LMICs, both assays are used, but their price, management and sensitivity varied. The important tool required for effective screening is traceability, community education, provider training, operational management and quality control. To protect women from developing cervical cancer, it was highlighted that the screening for HPV is very important.[17]They have described the HPV based cervical cancer screening program: main interventions, ideal timelines and main bottlenecks.

There are over 150 serotypes of HPV, out of which only the high-risk serotypes are identified as potential cancer-causing agents.[1] Regular screening of HPV is important for both the vaccinated and the non-vaccinated population because, vaccines will not protect the individuals who are already infected with HPV and also, the vaccine doesn't provide protection against other oncogenic HPV types. Hence, there is a need for screening at regular intervals for both men and women. There are three common types of screening techniques: Pap test, HPV DNA test, and visual inspection with acetic acid.[18]The use of the Pap test is not promoted nowadays because of its complexity and delay in managing the patients. Furthermore, HPV testing is easier to identify the positive cases. It has been found that HPV DNA and HPV RNA test detects precancerous lesions at an early stage. The US FDA has approved the HPV DNA test alone in 2014, as primary screening for cervical cancer in women, aged 25 and older.

HPV screening by Pap test and HPV DNA test (co-testing) are reported to reduce cervical abnormalities.[19] For stratifying CIN-3 risk, Pap cytology and HPV co-testing were considered valuable and the results taken in three-year interval revealed that the risk of CIN 3 was low in the individuals with negative pap test and HPV co-testing.[20] However, it has been found that co-testing is associated with more false positives[9], which may be due to genotypic variations of HPV. Various advanced screening techniques include human papillomavirus [HPV]-based screening with partial genotyping. For women testing positive for HPV16/18, colposcopy is carried out and Liquid-based cytology [LBC] for other oncogenic HPV types. For unscreened and under-screened women, HPV testing on self-collected cervicovaginal samples is done. Self-collection is restricted to the age group of women 30-74, who have never been screened for HPV.[21] Other advanced HPV screening tests approved by FDA for specific HPV types include; i) Cobas HPV Test specific for HPV 18/16 (approved in 2011) [22], ii) Hybrid Capture 2 test which detects 13 types of "high-risk" HPV types (in 2003), iii) Aptima assay test to detect RNA synthesised when the HPV starts creating cervical cancer (in 2011)[23] are highly sensitive and expensive. Hence, there is a need for the development of cost-effective screening techniques for all HPV types with high specificity and sensitivity to prevent false positive detection.

HPV TREATMENTS

There are various types of HPV infection; low-risk HPV infection generally causes warts in various parts of the body including genital region, foot corn, acne and squamous intraepithelial lesions (SIL). Treatment for these kinds of effects by HPV infection includes eliminating the visible lesions and boosting the host immune system to control the viral replication. Treatment of HPV is based on various factors like size, morphology, number and site of lesion, cost of treatment, adverse reaction, and previous treatment. No particular mode of treatment for all the type of HPV infection has been demonstrated.[24] Based on the grade level, various treatment methods like cryotherapy, a loop electrosurgical excision procedure (LEEP) diagnostic excisional procedure (cone biopsy) are given.[25] Pharmacological therapy for the treatment of HPV is classified into two categories namely, immune response modifiers and cytotoxic agents. These drugs are given cutaneously against anogenital warts or condylomata acuminate.[26]The main challenge in HPV treatment is the lack of *in vitro* HPV culture model to study the efficiency of treatments. Hence, no specific drug has been established yet. As a result, cervical cancer causes more than one quarter of a million deaths every year in underdeveloped and developing countries. In SIL patients, if the high-risk type HPV persists, it will be turned into neoplasia and invasive cervical cancer.

HPV VACCINATION AS A MODE OF TREATMENT

The HPV vaccination is given as either a prophylactic vaccine or therapeutic vaccine. The prophylactic HPV vaccination using HPV antigens can reduce the prevalence of HPV infection and thereby, reduce the risk or incidence of cervical cancer development. The existing prophylactic vaccines induce immunity against the L1 protein of HPV particle (Immunization with VLP), but they don't give therapeutic effect on existing infection and established cervical lesions.[27],[28],[29] In contrast, the therapeutic vaccines are targeted at inducing the cytotoxic cells like T-cells to eliminate the HPV infected cells. The present prevalence and persistence of HPV infection globally indicate that most of the underdeveloped areas have less or no exposure to the prophylactic vaccines and these are the places, which are infected epidemically by the HPV. HPV awareness and vaccination do not seem to reduce the HPV infection rate since, half of the population is already infected and may develop cervical cancer if they are not subjected to affordable screening and treatment procedures.[30]Hence, the therapeutic vaccination needs to be strengthened to act on established HPV oncogenic types. In 2016, a survey carried out in 1200 Korean representatives revealed that proper knowledge and awareness of HPV infection and vaccination programmes increase the willingness of the individuals to take up the HPV vaccine.[31] The VLP vaccines do not protect all oncogenic types. Screening of cancer is very important in the reduction of cancer rate and is very less in many countries. The manufacturing cost of the VLP vaccines is very high and not very effective. For improving the HPV vaccination GAVI is an important tool.[32,33]

1. Preventing HPV Infection by Prophylactic Vaccines

To reduce HPV infection, prophylactic vaccines play an important role as it is eliciting a humoral immune response against HPV infection. There are two well established prophylactic HPV vaccines available to act against the L1 capsid proteins. The first developed quadrivalent vaccine was Gardasil®, which has been available since 2006; it provides protection against HPV 6, 11, 16, and 18 for at least 8 years. The second was the Cervarix®, which protects against two serotypes 16 and 18 for more than 9 years.[33] Effectiveness of this HPV vaccine in providing prevention and long-term protection against genital warts was higher in individuals with three doses than one dose since the risk of genital warts rose with age.[34] The effectiveness and immunogenicity study of a new version Gardasil 9® was found to prevent effectively the 9 HPV serotypes such as HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine is cost-effective and approved for clinical use with a promise to prevent for at least 30 years [35], [36],[37]. However, a cross-reactivity challenge exists for all these prophylactic vaccines. The most adverse effect related to the injection site was mild or moderate in intensity due to the high amount of HPV virus particle and AAHS adjuvants. It has been found that the 9vHPV vaccine increased the overall prevention of cervical cancer from 70% to 90% approximately. Regular screening tests should be done to check HPV infection.[38]In over 100 countries prophylactic HPV vaccines that include Cervarix (2vHPV vaccine), Gardasil (4vHPV vaccine) and Gardasil 9 (9vHPV vaccine) are licensed since 2006. WHO confirms the efficacy, safety, and the duration of the prophylactic HPV vaccine. However, the HPV vaccines were terminated by the Japanese government due to the local pain syndrome. So the vaccination rate has decreased to 3.9% in Japan. The recent advancements are the development of neutralizing antibodies along with inactivated pathogens to induce the immunization of HPV vaccine with adjuvants. Immunoglobulin G serum response was promoted by 2vHPV vaccines and required for the production of T helper cell 1 biased cell response. 4vHPV vaccine also was found to produce T helper cell 2 biased cell responses.[29]

In addition to this L1 based vaccine, later the L2 based vaccines using a conserved 11-200 or 20-38 amino acid chain of N-terminal region have been developed.[30] L2 based vaccines provide cross-protection against different types of HPV while the L1 immune response is highly specific. For providing broad cross-neutralization activity, the RG1 epitope within the region is pivotal. Because of the simple format and protection against a wide range of HPVs, the L2s based vaccines are highly acceptable. Many HPV L1 VLP, and HPV L2 based vaccines are produced now using*S. cerevisia, Escherichia coli (E.coli)*, methylotrophic yeast species like *Hansenulapolymorpha (H.polymorpha)* and *Pichiapastpris (P.pastoris) and* undergoing preclinical or clinical studies.[31] However, the immunogenicity is less for L2 based vaccines as a limiting factor for the success. A review article of 1998 has shown the milestone of prophylactic HPV vaccine development starting from the trial of monovalent HPV16 vaccine to the recommendation of an FDA approved vaccine 9vHPV in 2014 with second dosing in 2016 and the recent licencing of a novel E.coli produced bivalent HPV vaccine in China in 2020.[39] However, the prophylactic vaccine coverage of all types of high-risk HPV, phylogenetic evolution, lack of awareness and vaccine cost are the challenges for developing countries.

2. Elimination of HPV by Therapeutic Vaccines

There is a need for the formulation of therapeutic vaccines to treat the already existing HPV infection and the associated diseases. But there is no specific anti-viral drug and the vaccines can induce acquired cellular immune response, which recognizes the infected cells and kills them. Therapeutic vaccines, therefore, aim at inducing a cell-mediated immunity, to kill the target cell. Such vaccines can target all the proteins involved in the entire life cycle of the HPV in the epithelial cells. The L1 and L2 proteins are expressed only in terminal keratinocytes. Hence, the early genes E1, E2, E4, E5, E6, and E7 are ideal targets of therapeutic vaccine development. This can be achieved with HPV peptides, proteins, DNA and also by developing HPV immune-stimulated DC *in vitro*.[22] Most of these vaccines target the oncoproteins E6 and E7, which are responsible for the malignant progression of HPV infection. There are different forms of therapeutic vaccines that are used in the clinical trial phase, and these include bacteria-based vaccines (Lm –LLO-E7),[23] Viral vector-based (TA-HPV),[24] Nucleotide based (pNGVL4a-CRT/E7 –DNA),[25] whole cell-based (1, dendritic cell-based 2, tumour cell-based), peptide-based (HPV 16-SLP),[26] protein(GTL001).[27] The main strategies of HPV therapeutic vaccines are generating specific effectors T- Cell against the expression of oncogene E6 and E7. Recently, many clinical trials for therapeutic vaccines have been conducted with optimization to improve the efficacy. Shortly, the development of these drugs may pave the way for the eradication of HPV infection and associated diseases including deadly cancer.

CHALLENGES IN HPV VACCINATION

The most important issue is the lack of knowledge about HPV and its vaccines, so it should be addressed. Delivery of the vaccines should be affordable, available and acceptable. China approved many HPV vaccines but the availability is very less mainly in lower resources regions. In France, the delivery of HPV vaccines is below 20%. The major issue is that the women or girls are not taking the vaccine even it is given free of cost. HPV based self-sampling kits are avail-

able, which will improve participation as it is acceptable than the clinical sampling.[28]

In Nigeria, the facilities are very less for cervical cancer screening and the awareness is also lower. So 97.9% of women are not screened for cervical cancer. Some of the issues include lack of screening service (44.2%), lack of knowledge (40.7%), reduction in decision-making ability (34.2%), cost of screening (30.1%), and the distance of the centre (23.5%). But the HPV related diseases can be compacted by cytology screening. It provides high sensitivity, high throughput, and negative predictive value. HPV worldwide have licensed two safer quadrivalent and bivalent vaccines. But the use of the vaccines is reduced due to the lack of knowledge and high cost. Cervarix and Gardasil vaccines are donated through GAVI INITIATIVE (Global alliance for vaccine and immunization) at lower price mainly to low-income countries. An issue stated by other countries is that those vaccines contain a high amount of aluminium salt which causes damage to the immune system especially in infants and children which leads to chronic illness.[49]Hence, new safer delivery regimens need to be invented.[27-30]

The exact mechanism behind HPV integration with the host cells is not known yet. Understanding the HPV oncoproteins structure and mechanism of their interactions will help in the formulation of better medicines and effective prophylactic vaccines, which will help in the eradication of HPV shortly. The cryo-electron microscopic examination has given a better understanding of the structure of HPV 16 particle capsids and the structural conformational changes which occur when HPV binds to the cell[10] and the results help in understanding the HPV uptake mechanism during the early stage of virus infection. This imaging technique will help in understanding the antigen-antibody interactions, thus more specific vaccines which prevent and cure HPV infection can be formulated in the future.[31]

DISCUSSION

Based on the reviews summarized and presented at Asia-Oceanic Research Organization in Genital Infection and Neoplasia (AOGIN) 2018, and the 32nd International Papillomavirus Conference (IPVC), the Director-General of the World Health Organization (WHO) announced that cervical cancer can be cured affordably by implementing the draft static plans. Their main goal is to prevent cervical cancer by improving the vaccination among 90% of females globally. The prophylactic vaccination is implemented in high-income countries on large scale, however, the supply of HPV vaccines and the acceptance of the need for vaccination among young adolescent girls is the current challenge in these countries. It was highlighted that clinical validation such as dose efficacy, bridging, safety studies are required for the infant immunization against HPV. For LMIC, vaccinating the young girls at a large coverage (80-100% coverage and 70% screening twice per lifetime) should be prioritized, which can reduce cervical cancer from 16 per 100 000 to less than 4 per 100 000 in between 2020 and 2080.[32]

For treating HPV induced lesions, a therapeutic regimen plays a major role. It is possible to eradicate HPV-transformed cells through immune response produced by HPV genes that carry the recombinant vaccinia virus. The E2 of HPV is getting much attention as an effective target for developing therapeutic vaccines as it plays a major role in transmitting the HPV into the new cells in the cervix epithelium. Tumour can be eliminated through MVA E2 vaccines that stimulate the production of antibodies and cytotoxic cells that act directly on the transformed cells. MVA E2 vaccines are promising agents for preventing as well as treating cervical cancer and did not show any side effects when tested in the patient.[21]

Current Status and Future Prospects of Cervical Cancer Therapy

In Germany, the cervical cancer prevention analysis was attempted by Wolfsburg Pilot Project for non-hysterectomies women (30-70 years old), where cervical cancer diagnosed in the first screening compared with subsequent round was the primary focus. The women can freely choose HPV test or Pap smear under health insurance companies within a five years gap. The positive women are referred to colposcopy and the next screening should be after five years for negative women.[12]

The current therapies for cervical cancer are only cytotoxic which causes injuries to normal cells. Furthermore, since the high-risk type HPV is the inducer of cervical cancer, the recurrence rate is also very high in cervical cancer treatment. Cisplatin, the key drug used for cervical cancer, gives rise to adverse side effects such as nephrotoxicity and neurotoxicity[33],[34]. For pursuing better health, medicinal plants are nature's gift. Several studies have proven that plants contain bioactive compounds that can act against particular cancer. *Allium Wallichil* contains phytochemicals like cateroids, flavonoids, terpenoids, *Paeoniasuffruticosa* has phytochemicals such as polysaccharides (HSS, DASS, HBSS, CASC) and all these can suppress cervical cancer. Phytochemicals identified in *Medicagoscutellata* are trypsin inhibitor, which can decrease cervical cancer as well as other types of cancers. The bioassay-guided fractionation of these phytochemicals may achieve a better anti-cancer therapy.[35] Black raspberries and their compounds are the promising ones for cervical cancer in chemoprevention. *Boswellia Srerata* can induce apoptosis and kill cancer cells by the hydro alcoholic compound.[56] Furthermore cervical cancer treatment will be effective only when the causative HPV is targeted. But so far no drug formulation with anti-viral property is available for

cervical cancer therapy. The efficient anti-viral potential of garlic extract containing allicin was shown by Weber and his research group *in vitro* on HeLa cell line.[27]

The vaccines and screening programs have been developed in the area of HPV over the last 36 years. But the investigation is still going on for HPV related cancer and HPV infection. The most promising area of research worldwide is immunotherapy, but it has not been approved by FDA. Risk factor screening programs and global implementation of vaccines programs should be followed for the reduction of HPV associated cancer. Screening by HPV-FASTER and vaccination should be compelled to youngsters.[28]

CONCLUSION

In future, if research is focused on understanding the mechanism of action of HPV in the host, it might pave way for formulating better therapeutics. More awareness should be given on the importance of vaccination at an early stage itself. There is a need to work towards formulating a single vaccine with high immunogenicity, specificity, safety and patient acceptance, which can act against all types of HPV. Continuous screening for HPV at regular intervals followed by HPV targeted treatment can reduce the deaths caused due to cervical cancer. Researchers are focussing on natural extracts for the treatment of cancer. Phyto-molecules have high biocompatibility and biodegradability that can increase efficacy in cervical cancer therapy. Research works are currently undergoing for the evaluation of phytochemicals that act against HPV in cervical cancer cells.

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