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Research Article

BEWARE OF HUMAN PAPILLOMAVIRUS. A MISCREANT BEHIND MORE THAN JUST BREAST CANCERS (A CAUTION BELL TO YOUNG WOMEN)

Raghavendra Rao M.V[1], Dilip Mathai[1], Kumar Ponnusamy[2], Sateesh Babu.Arja[2], Sireesha Bala[2], Ramanaiah C.J[3], SP Pallavi[1] and MK Sowmya M[4]

[1]Apollo Institute of Medical Sciences & Research, Telangana state, Hyderabad, India
[2]Avalon University School of Medicine, Curacao, Central America
[3]Amina Hospital, UAE,
[4]Emirate group of Hospitals, UAE,

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ABSTRACT

Cervical cancer is the second most common cause of cancer worldwide and the primary cause of cancer in women in developing countries. It is the most frequent cancer among women in India. Cancer often takes years, even decades, to develop after a person gets HPV**.** The Papilloma viridae family is a very large virus family. With the advent of recombinant technology, it was known that there are multiple HPV genotypes. The viruses are classified on the basis of DNA sequence into various genotypes. One group is responsible for causing genital warts and are known as "Low risk" and they do not cause cancer This group is typified by the closely related species HPV 6 and HPV 11. There is another group of 15 oncogenic or high-risk HPV which are responsible for cervical cancer. Of this HPV 16 and HPV 18 accounts for 70% cases and along with HPV 31,33 and 45 more than 80% cases. Cervical cancer is the most frequent cancer in women in India followed by breast cancer. The genital warts are shiny skin colored occasionally enlarges into cauliflower-like lesion isolated or enlarged. These warts are asymmetric present in moist areas (corona or Sulcus), Penile tip, shaft, and scrotum, the inner side of the thigh or lower part of the abdomen.

INTRODUCTION

Persistent infection with human papillomavirus (HPV) specifically high-risk HPV (hr-HPV) types can cause anogenital and head and neck cancers. Both anal cancer incidence and mortality rates have been rising over the past decades. Men who have sex with men (MSM) are at increased risk for and HPV infection and HPV related diseases.(1)

The natural history of cervical HPV infection has been well-characterized. Although there are many similarities between cervical and anal HPV infections. (2). Several studies have reported the incidence and clearance rates of anal hr HPV among human immunodeficiency virus (HIV)-negative MSM, yet these estimates were based on limited time periods(at most 3 years) and might not reflect prolonged persistence in certain individuals(3)

The anal high-risk HPV infection is common among HIV negative MSM. The major risk factor for anal hr- HPV infection among HIV negative MSM was the lifetime number of sex partners.HPV 16 has the highest incidence rate and lowest clearance rate in the group (4)

Corresponding author:* **Raghavendra Rao M.V
Apollo Institute of Medical Sciences & Research, Telangana state, Hyderabad, India

The main high-risk HPV, associated with vaginal intraepithelial neoplasia (VAIN) and vaginal squamous cell carcinoma is HPV-16(5)

The vulvovaginal cancers such as verrucous carcinomas, on-keratinizing squamous cell carcinomas, condylomatous carcinomas, and the vaginal squamous-transitional carcinomas often demonstrate HPV association (6)

Women receiving radiation therapy for cervical cancer, manifest a highest risk for second cancers arising from lower anogenital areas over time which persists to be elevated for more than 40 years(7)

The careful bimanual examination of the entire vaginal mucosa and the vulva is essential as the primary vaginal tumors tend to be multicentre. Vaginal cancer is rare cancer and standardized screening is often not recommended.(8)

Radiotherapy can induce vital changes in cellular morphology which persist for many years and in such circumstances, cytology has a limited role in the follow-up.(9)

Oral cancer is known as the sixth most common cancer in the world so that about 95% of cases are squamous cell carcinoma (SCC), the epidemiological and molecular analysis indicated the HPV is involved,as a factor in oral cancer(10)

HPV viruses can enter the body through contacting small wounds of skin and cause hyperproliferation of skin and mucosal epithelial cells. These viruses are one of the etiologic agents in the development of oral cavity cancer by contaminating basal cells of squamous epithelium and oral mucosa and contribute 25.6% to the development of oral pharyngeal carcinoma.(11)

The WHO recommends the use of high-risk HPV(hrHPV) testing for cervical specimens as a screening tool for identifying women at increased risk of cervical pre-cancer and cancer.(12)

Persistent high-risk High-risk human papillomavirus (HR_HPV) infection is a major etiologic factor for cancer of the cervix, vagina, anus, and penis. Studies on women have reported that higher viral load is associated with persistence of the infection and progression to preneoplastic or neoplastic cervical lesions.(13)

Current understanding of HPV load in men is incomplete. It has been suggested that higher versus lower viral load increase the probability of detection of HPV at multiple penile sites, the occurrence of flat penile lesions, and occurrence of type-specific HPV concordance and transmission in couples.(14)

A better understanding of the natural history of HPV infection in male genitalia, including risk factors for higher viral load and impact of DNA levels on viral persistence,is of importance. However, previous studies of male genital HPV load, which have been conducted primarily in western countries have been limited by evaluation of only particular high-risk populations, small sample size, small numbers of follow-up visits, use of semi quantitative measurement of HPV DNA and evaluation of HPV-16/18 alone.(15)

Cervical cancer is the most frequent cancer among women in India, especially in the 15-44 Years of age, Overall, HPV prevalence in India was similar to the high-risk area in Latin America but lower than that observed in some parts of sub-aaasSaharan Africa(16)

The lesions created from infection with HPV are responsible for approximately 5% of all cancers.HPV 16 is most carcinogenic and is frequently the most common HPV found among low-grade lesions and in women without Neoplasia (17)

Currently, there are two vaccines are available. The quadrivalent vaccine has shown 98-100% efficacy in the target population 15-26 years age group with no previous exposure to HPV infection in preventing CIN, and adenocarcinoma related toHPV16/18 over a period of 3 Years.(18)

Short-term risk of progression from incident HPV infection to high-grade neoplasia in young women range from 3-31% (15) Genital HPV is the most common sexually transmitted infection. (The centers for disease control and prevention)(19)

The estimated number of new cases of cervical cancer worldwide was 528,000 in 2012, with an annual global mortality rate of 270,000 deaths. The prevalence of genital warts is approximately 1%, and cytological abnormalities less than 10%. These findings indicate that in apparent infection is far more common than clinically apparent infection(20)

History

In 1972, the association of the human papillomaviruses with skin cancer in epidermodysplasia verruciformis was proposed by Stefania Jabłońska in Poland.

In 1978, Jabłońska and Gerard Orth at the Pasteur Institute discovered HPV-5 in skin cancer (21)

The growth, division, and death of living cells are regulated by their genes. If these functions are out of balance, tumors can form. One reason for this may be the incorporation of virus genes into the genes of host cells. Harald zur Hausen demonstrated in 1983 that cervical cancer in humans is caused by certain types of papilloma viruses (wart viruses), the genes from which are incorporated into the host cells' DNA. This discovery made it possible to develop a vaccine against cervical cancer, which had been the second most common tumor disease in women.

In 1976 Harald zur Hausen published the hypothesis that human papilloma virus plays an important role in the cause of cervical cancer. In 1983 and 1984 zur Hausen and his collaborators identified HPV16 and HPV18 in cervical cancer (22)

The HeLa cell line contains extra DNA in its genome that originated from HPV type 18 (23)

The story of HPV vaccine development can be traced to 1970s-1980s when Harald zur Hausen, linked HPV to cervical cancer. The idea that cancer was caused by a virus was novel and controversial. Ian Trazer demonstrated the potential of synthesizing VLPs from recombinant expressed HPV capsid protein to resemble the actual viral particle.In 1990, Eliav Barr, Kathrin Jansen, and Barry Buckland jointly started their work on the development of a vaccine with such VLPs against cervical cancer. In 1993, the preclinical proof of concept study designed and led by Jansen unambiguously demonstrated the efficacy of a prophylactic HPV vaccine in animals.

Though multiple randomized controlled trials the efficacy of the vaccine was established. Ultimately, the quadrivalent vaccine received food and drug administration (FDA) approval in 2006(24)

In 1993, preclinical proof of concept study designed and led by Dr.Jansen unambiguously demonstrated the efficacy of a prophylactic HPV Vaccine in animals. Through multiple randomized controlled trials, the efficacy of the vaccine was established. Ultimately, Quadrivalent vaccine received Food and Drug Administration (FDA) approved in 2006. In 1998, standardization of cervical cytology reporting took place with the development of the Bethesda system nomenclature

In China ,cervical cancer screening currently covers less than 30% of the population, although the Government has made great efforts to elevate it. China possesses the largest number of cervical cancer patients with 98,900 new cases and 30,500 deaths in 2015.(25)

Interest in human papillomavirus(HPV) infection began in earnest in the 1980s Harold Zur Hausen postulated that infection with these viruses were associated with cervical cancer(26)

It has been reported recently that women prior to coitarche can become infected with high-risk types as well, but this is uncommon (27)

As with cervical cancer, prevention by screening persons at risk may be the best approach to decreasing the incidence of anal cancer. Testing would be followed by treatment of high-grade anal lesions (28)

In 1982, several studies associating HPV type 6 with genital warts, but not cervical cancer, were published. In 1983, HPV type 16 was identified in cervical cancer cells. A year later, HPV type 18 was linked to cervical cancer (29)

Some investigators suggest that annual cervical and anal cytology should be offered to all HIV-positive patients; but only if the infrastructure necessary for the evaluation and management of abnormal cytology results and precancerous lesions is available (30)

Although natural history studies for anal HPV disease are lacking, some suggest that eradication of high-grade anal lesions may decrease the incidence of invasive anal cancer (31)

Where the Research go next?

Women residing in developing countries with a lack of access to cervical screening programs have a higher rate of cervical cancer and poorer cancer-specific survival. Approximately 75% of women living in developed countries have been screened in the past 5 years, as opposed to 5 % of women living in developing countries. Economic and logic obstacles likely impede routine cervical cancer screening for these populations. Many poor countries rely on an alternate method, visual inspection with acetic acid(VIA) for cervical cancer screening. While some studies show a reduction in cervical cancer mortality in communities where VIA are widely used, other studies do not. In addition, the low specificity of VIA is problematic. As newer methods that use detection of oncogenic HPV DNA become available, even resource-limited countries may be able to replace via with these methods and achieve a reduction in cervical cancer result (32).

Major Advances and Discoveries

A recent study in Australia suggests that a rapid and marked reduction in the incidence of genital warts among vaccinated women could be achieved through quadrivalent HPV vaccination.(33)

A study in the united states look at the uptake of HPV vaccine show only 1 out of 3 girls(11-17 Years)have received greater than or equal to one dose of HPV vaccine and much less have completed all the doses they suggested that patient education about the vaccination is necessary to increase vaccine uptake among girls, especially those 11-12 Years olds(34)

Another similar study in Berlin looked at the uptake of the vaccine in 10-Years old since its inception in 2007 and suggests that school programs could be beneficial to increase knowledge regarding HPV vaccination research has shown that HPV is involved in producing gynecological cancer. Papillomaviruses are not cytolytic and do not kill the cells they infect, rather they produce proliferation. Papillomas produce warts, but they also produce premalignant transformations of epithelial surfaces.

Current Debate

Currently, there is no broad consensus regarding screening for anal cancer and its precursors, including high-grade anal intraepithelial lesions. The reason is a lack of understanding of optimal treatment for low or high-grade anal dysplasia found during cytological screening. Current HIV treatment guidelines suggest that there may be the benefit to screening but an effect on the associated morbidity and mortality of anal squamous cell cancer has not been consistently demonstrated. Virtually all cervical cancers are caused by HPV.(35)

The virus is shed from the epithelial cells of the infected individual, even when the individual is asymptomatic. If an individual is orally infected with one of the high-risk strains (either 16 or 18), the virus will replicate locally in the infected tissue, and as described above, can cause cell transformation, leading to oncogenesis and tumor progression. Because of these risks, the importance of this vaccine for both men and women is becoming blatantly apparent (36)

Head and neck cancer in Australia between 1982 and 2005 show an increasing incidence of potentially HPV-associated oro pharyngeal cancers (37).

Lab diagnosis

The benefit of HPV testing in primary cervical cancer screening has been demonstrated in several randomized controlled trials. (38)

As a result, HPV based screening will replace cytology based screening in a number of countries.HPV assays will also be important for monitoring the effect of HPV vaccination, to determine changes in the epidemiology of viral genotypes.The most thoroughly clinically validated HPV assays are the commercially available Hybrid capture 2 (HC2) and in-house GP5+/6+PCR.These two assays now compete with more than 100 newer commercially available assays.(39)

The overall sensitivity and specificity for high- grade cervical intra epithelial neoplasia (CIN) tend to be similar for the various HPV assays.(40)

In the Danish horizon study,a detailed analysis of positive test results on the same samples demonstrated substantial discordance for four commercially available assays (HC2,Cobas,CLART and APTIMA), particularly for women undergoing primary screening at age 30-65 years. When positive test results any part of the assays were compared, there were many concordant as there were discordant cases.(41)

Hc2 the first HPV DNA test certificated by the food and drug administration (FDA) of the united states for cervical cancer screening in 1999,is a nucleic acid hybrid capture technique that detects pooled high-risk HPV DNA of 13 genotypes. Various clinical trials have verified that the sensitivity and NPV of HC2 in the detection of high grade lesions are higher than those of cytology.(42)

The Europian Research organization on Genital infection and Neoplasia (EUROGIN) in 2008 that HPV DNA testing could be used for primary testing in cervical screening.HC2 has also been regarded as the gold standard for evaluating subsequent HPV detection techniques.(43)

In conclusion,DH3 HPV performs similarly to Cobas HPV as a primary test in screening for women aged 25 years, combined with other advantages of hybrid capture technique, such as reduced laboratory requirements, the DH3 HPV test could be recommended in HPV based cervical cancer screening in developing countries.(44)

Treatment

if a cervical screening test shows abnormal cells on the cervix, it may be necessary to remove them so that they don't develop into cancer. If cervical cancer does develop and is found early, it's usually possible to treat it using surgery. In some cases, it's possible to leave the womb in place, but it may need to be removed. Radiotherapy is another option for some women with early-stage cervical cancer. In some cases, it's used alongside surgery or chemotherapy, or both. There's no cure for genital warts, but it's possible to clear the virus over time. The warts can be removed using creams, freezing or heating.

Vaccination

This is a historical event in Medicine and the prophylactic HPV vaccine have been powerful tools of primary prevention of cervical cancer and other HPV associated diseases. Vaccination has been shown to reduce the subsequent risk of genital warts, precancerous cervical changes and cervical cancer in women. HPV the vaccine prevents infection with HPV virus types that are associated with many cancers, including, Cervical cancer in female, Vaginal and vulvar cancers in females, anal cancer in both male and female Throat cancer in females and males and penile cancer in males. Presently two HPV vaccines are available. A phase 2 trial of an HPV-16 virus-like-particle vaccine carried out by Koutsky et al. seeks to ascertain if a vaccine for the type of papillomavirus most commonly associated with cervical cancer will protect against infection and precancer(45)

Prophylactic vaccines elicit the production of humoral antibodies that neutralize HPV before it can infect host cells(46)

Currently, two vaccines are FDA approved for prevention of incident HPV infections and cervical neoplasia. The resultant virus-like particles are highly immunogenic, but they are not infectious as they lack viral DNA (47)

Gardasil is a quadrivalent vaccine against HPV types 6,11,16 and 18. Cervarix is a bivalent vaccine against HPV 16 and 18. Each contains a different adjuvant that boosts the immune response of the recipient to the vaccine antigens. Administered in three intramuscular doses during a 6-month period, both vaccines are extremely safe and well tolerated (48)

Both the vaccines have very good efficacy of around 100% against the carcinoma of the cervix caused by the serotype of HPC contained in the vaccines. Bivalent HPV vaccine provides some short-term cross-protection against some of the HPV genetically related to the vaccine types 31/33/45/52/58.

Management

Vaccination against HPV infection has been introduced and is in routine use in many countries. Podophyllotoxin 0.5% cream (contraindicated in pregnancy) applied thrice daily for 3 days, suitable for home treatment for external warts. Cetaphen (Extract Green Tea plant)(Camellia sinensis) is applied by the patient 3 times daily for up to 16 weeks.

Masks should be worn during the procedure and adequate extraction of fumes should be provided. Surgical removal may be used to excise refractory warts, especially pedunculated lesions under local or general anesthesia.(49).

Prevention

Use a new male or female condom or dental dam every time you have vaginal, anal or oral sex. Remember HPV can affect areas not covered by a condom, so this may not offer full protection Use a new dental dam or latex gloves for rimming and fingering (exploring your partner's anus with your fingers, mouth or tongue) or use latex gloves for fisting. Cover sex toys with a new condom for each partner and wash them after use. Remember, the virus is not just passed on through penetrative sex: it can be transmitted through any skin-to-skin contact between genitals. Having multiple partners can increase your risk of getting an HPV infection. If you are having sex with multiple partners, it's even more important to use condoms and have regular STI checks.

Summary

Human papillomavirus (HPV) is a group of viruses that are extremely common worldwide. There are more than 100 types of HPV, of which at least 14 are cancer-causing (also known as high risk type). HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity. Cervical cancer is caused by sexually acquired infection with certain types of HPV.Two HPV types (16 and 18) cause 70% of cervical cancers and pre-cancerous cervical lesions. There is also evidence linking HPV with cancers of the anus, vulva, vagina, penis and oropharynx. Cervical cancer is the second most common cancer in women living in less developed regions with an estimated 570 000 new cases (1) in 2018 (84% of the new cases worldwide).In 2018, approximately 311 000 women died from cervical cancer; more than 85% of these deaths occurring in low- and middle-income countries. Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care. Vaccines that protect against HPV 16 and 18 are recommended by WHO and have been approved for use in many countries. Screening and treatment of pre-cancer lesions in women of 30 years and more is a cost-effective way to prevent cervical cance Clinical trials and post-marketing surveillance have shown that HPV vaccines are very safe and very effective in preventing infections with HPV infections. Cervical cancer can be cured if diagnosed at an early stage.

CONCLUSION

Efforts have been focussed to reduce treatment-related morbidity and prolong survival for improved quality of life. Recent developments in the management of cervical cancer include wider use of Laparoscopic techniques. Use of PET-CT scan for pre-treatment assessment and post-treatment follow up neoadjuvant chemotherapy prior to chemoradiation and radical primary surgery. Chemoradiation offers a small increase in cure rate but the cost of increased immediate toxicity. The presence of genital warts and smoking habits seem to be associated with a higher risk of HR-HPV infection in males. The earlier sexual debut may increase this risk.The characteristics of different HPV types have been studied

extensively and it is now well known that high-risk types, such as HPV16, encode genes that can contribute to cancer progression when aberrantly expressed. During productive infection, however, these genes are carefully regulated and play important roles in virus synthesis and in avoiding detection by the host immune system. It seems that papillomaviruses, like many other DNA tumor viruses, cause cancers when their regulated pattern of gene the expression is disturbed.(50)

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