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Review Article

Cancers Associated with Human Papillomavirus: An Overview of Prevalence in Iran and the Middle East

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Abstract

Human papillomavirus (HPV) has been clearly linked to the occurrence of some cancers such as cervical cancer, anogenital cancer, and head and neck cancer. However, studies suggest that the virus can also be the reason for other forms of malignant diseases. Traditionally, countries in the Middle East, including Iran, were thought to be less exposed to HPV infections due to conservative sexual customs. Moreover, owing to the lack of a proper vaccination program in adolescence, malignancies caused by the HPV virus are increasing and are of concern. Additionally, in the absence of a well-established vaccination schedule, changes in sexual behavior have resulted in an increasing number of young individuals engaging in premarital intercourse. In this article, we provide an overview of the current prevalence of common cancers in Iran closely associated with HPV, the status of vaccination programs aimed at preventing malignancies, and early detection strategies to halt cancer progression.

Introduction

Human papillomavirus (HPV) is linked to the development of several benign and malignant cancers. These nonenveloped particles, are double-stranded circular DNA viruses which impact approximately 50–70% of sexually active people, account for more than 5% of all cancers and approximately 50% of the malignancies worldwide. It has been proven that approximately 225 types of HPV had been identified, which can be divided into five groups, including α, β, γ, μ, and ν, and approximately 15 of the HPV-α viruses are high-risk.[1] Especially high-risk mucosal HPV types, primarily types 16, 18, 31, 33, and 35 are linked to the majority of cervical, penile, vulvar, vaginal, anal, oropharyngeal cancers, and premalignant lesions.[2] It has been shown that the carcinogenicity, of these HPV types results primarily from the activity of the oncoproteins E6 and E7 owing to their impairment of growth regulatory pathways. Cancer is considered one of the most difficult diseases of the 21st century, and a causative relationship exists between HPV and some cancers (Fig. 1).[3–7] HPV remains a taboo topic of discussion in many Middle Eastern countries including Iran.[8] Western countries have taken a hard stance on HPV by introducing preventive vaccines. However, Iran is still grappling with the disease (Table 1),[1] especially since the country is experiencing a shift from conservative sexual customs to more youngsters engaging in premarital relations.[9] This coupled with the fact that HPV vaccination is a preventive measure that is not readily available to all for cultural reasons, might be the cause of a severe increase in cancer cases in Iran in the near future. To curb this trend, it is believed, that sexually transmitted disease control strategies need to be more strongly enforced, and advanced diagnostic facilities for HPV need to be established. At the very least, high-risk groups need to be vaccinated, and constant HPV monitoring as a prevention and control measure must be implemented.[10] In this regard, early detection of HPV infection, followed by injuries because of HPV infection, leads to the prevention of HPV-induced cancers.[1] In this review, we collected information related to the biological mechanisms, prevalence, epidemiology, and the HPV vaccination program in

Keywords: Epidemiology; Human papillomavirus; Prevalence; Vaccination.

Abbreviations: ASR, age-standardized incidence rate; BCa, bladder cancer; CRISPR, clustered regularly interspaced short palindromic repeat; E, early; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR-HPV, high-risk HPV; ICC, invasive cervical cancer; L, late; LMICs, low- and middle-income countries; NACT, neoadjuvant chemotherapy; ORF, open reading frame; PCa, prostate cancer; SCC, squamous cell carcinoma; UC, urothelial carcinoma.

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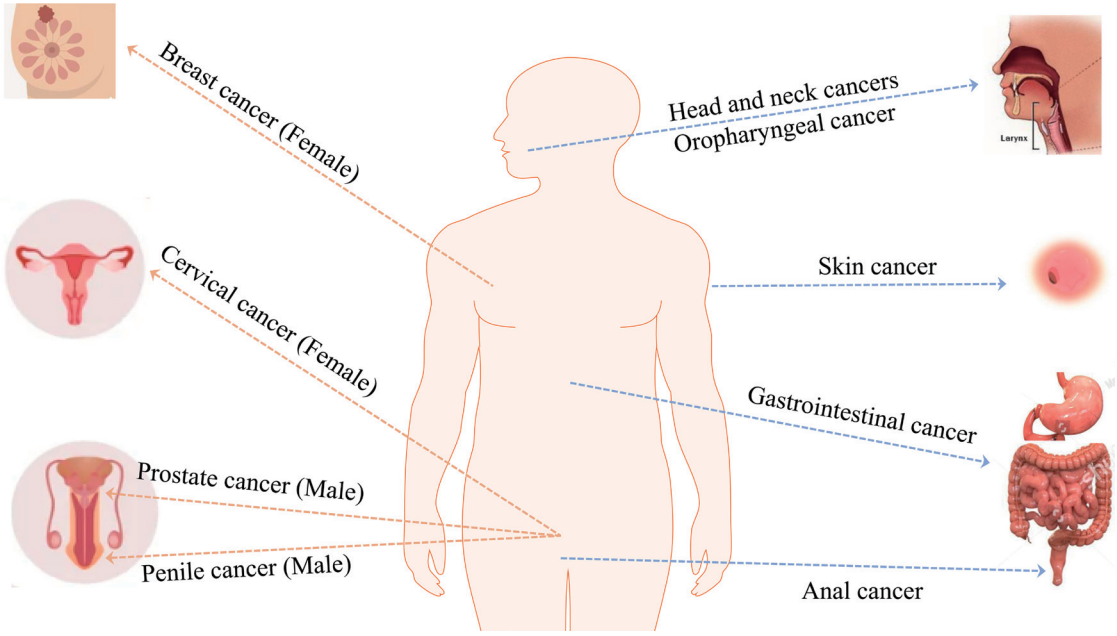

Fig. 1. Association of human papillomavirus with various cancers.

Iran to improve diagnostic methods and also to prevent an increase in the prevalence of HPV-induced cancers.

Global epidemiology of HPV infection

HPV is responsible for 4.5% of cancer cases worldwide.[11] There are 80 million HPV-positive individuals in the USA, and HPV oropharyngeal cancer is now more common than HPV cervical cancer.[11] White males in their middle years and who are becoming older tend to have the greatest oropharyngeal cancer incidence rates.[11] Furthermore, between birth and 79 years of age, cervical cancer struck one in 70 women worldwide,[12] and the HPV virus affects one in 10 women globally at some point.[13] Almost 70% of the burden is distributed among less developed regions of the world.[12] With 87,090 fatalities from cervical cancer, India, the second most populous nation in the world, bore a 28% share of the burden.[12] In less developed nations, it is the second most often diagnosed cancer and the third most prevalent cause of cancer mortality among women.[12] Sub-Saharan Africa, Latin America and the Caribbean, and Melanesia have the greatest incidence rates, whereas Western Asia, Australia/New Zealand, and Northern America have the lowest rates.[12]

The prevalence of cervical cancer has fallen by as much as 65% between 1970 to 2011 in various Western nations including Nor-

Table 1. Statistical data of the prevalence and total population of patients with different types of cancer and their HPV positivity status in the Iranian population

Cancer type	Prevalence in the Iranian population (ASR)[1]	Percentage of HPV-positive cases	Prevalence of HPV-positive cancer cases in the Iranian population*	Total population of HPV-positive cancer cases in Iran**
Cervical cancer	2.5	79%	1.975	1,580
Breast cancer	22 (female population)	23.6%	5.192 (female population)	2,077
Head and neck cancer	46.3	44.4%	20.56	16,448
Prostate cancer	9.1 (male population)	30.9%	20.56	16,448
Skin cancer	22.62 (male population); 15.77 (female population)	22.7%	5.13 (male population); 3.58 (female population)	3,484
Colorectal cancer	11.95	22.6%	2.7	2,160
Penile cancer	No data for the Iranian population	55.7%	–	–
Gastro intestinal cancer	19.4 (male population); 17.2 (female population)	16.4	3.18 (male population); 2.82 (female population)	2,400

*Age-standardized ratio per 100,000 persons in the population. **Based on the total population of 85 million in the latest census by the statistical center of Iran. ASR, age-standardized incidence rate; HPV, human papillomavirus.

way.[14] Moreover, rates have fallen in high-risk regions like China as well.[12] Unlike the positive tendencies mentioned above, in various nations, including Finland, the UK, Denmark, and China, the prevalence of cervical cancer has been rising among younger generations.[15] The HPV vaccine holds the potential to alter the epidemiology of the illness, but current HPV vaccination rates are still too low to prevent disease spread.[11]

Molecular biology and pathogenesis

Family *Papillomaviridae* contains small, circular, antidouble-stranded DNA genomes that are arranged in association with cellular nucleosomal histones as minichromosomes.[16] Papillomaviruses are widespread in nature, infecting epithelial cells of the skin and mucous membranes. Viral genome can be found in basal cells, but late gene expression (L1 and L2) is limited to the uppermost layer of differentiated keratinocytes. It has been reported that the HPV genome is functionally divided into three regions, including a noncoding regulatory region referred to as the long control region or upstream regulatory region, that regulates deoxyribonucleic acid replication by dominant the transcription of open reading frames (ORFs); the coding regions of the E1, E2, E4, E5, E6, and E7 genes participate in virus replication, transcription, assembly, and oncogenesis, the encoding region of the L1 and L2 capsid proteins. Most papillomavirus genomes contain eight to ten identifiable ORFs that are classified as either early (E) or late (L) based on their location in the genome. As mentioned, the early and late regions of the ORFs encode viral regulatory and viral capsid proteins, respectively.[17] HPV virus has been reported to enter the basal layer cells through the epithelium or mild abrasion or microtrauma.[18] In this cell layer, the conditions are right for virus replication. Different receptors on the surface of epithelial stem cells participate in virus binding and entry, but the type of receptor varies in high-risk and low-risk types. For example, the α6β1 and α6β4 integrin receptors on the surface of basal cells in low-risk types of HPV-6 and the heparan sulfate receptor participates in the binding of HPV-16 and HPV-33.[19] Moreover, the integration of oncogenic HPV DNA into the host genome is characteristically associated with disruption of the viral E1 and E2 genes, which permit increased transcription of E6 and E7 oncoproteins. These are HPV transforming proteins, which form complexes with retinoblastoma, p53, and other cellular proteins. Several HPV genes play critical roles in cell cycle processes.[20] The E6 and E7 proteins of HPV16 induce abnormal cell proliferation. E6 and E7 oncogenes make these functions available by localizing to the nucleus and binding to cell cycle regulatory proteins. E6 binds to p53, a tumor suppressor protein, inducing its degradation, and E7 binds to protein retinoblastoma–E2F, a tumor suppressor complex, leading to their dissociation. E5 protein is expressed in the α-HPV, and is involved in escaping the host immune response as well as apoptosis. In this regard, it has been shown that, during the differentiation of epithelial cells as well as during the life cycle of the virus, the expression of viral proteins is different.[21] The consensus of these interactions is the transition of the infected cell to the S phase of the cell cycle, which is a crucial point in the cell cycle process.[22] Here, we provide an overview of the current state of common cancers in Iran that are closely linked to HPV.

Immune system and HPV infection

During infection with the HPV virus, following microtrauma to the epithelium, the virus particles reach the target cells (basal cells).[21] According to studies, the HPV virus replication cycle is complete in epithelial cells; nevertheless, infection with the virus does not result in cell lysis, viremia, or inflammation in the target cells.[21] Furthermore, the HPV virus circumvents the immune system response by inhibiting the innate immune activity and delaying the function of the acquired immune response, resulting in persistent HPV infection and cancer development.[21] Primary infections caused by some types of HPV, on the other hand, can be controlled by innate immunity.[23] As previously stated, latent and persistent viral infection develops as a result of the virus escaping the immune system. The HPV virus has been found to affect the immune system, and in the early stages of infection, it reduces oncoprotein expression, resulting in a decrease in viral antigens and, as a result, the inability of local antigen-presenting cells to identify viral antigens, reducing T-cell activity.[19] By altering the transcription of genes encoding Toll-like receptors, adhesion molecules, cytokines, chemokines, and costimulatory molecules participating in the antiviral immune response, HPV causes DNA methylation and histone modification.[19] Moreover, by disrupting antigen processing and T-cell function, the HPV virus, on the other hand, promotes cancer and malignancy. In general, it is worth noting that the function of antigen-presenting cells, such as dendritic cells, Langerhans cells, as well as T cells and natural killer cells, is disrupted during infection with the HPV virus.[19]

HPV and cervical cancer

Cervical cancer is the fourth most common cancer in women worldwide.[24] Recent research has proven that the majority of cases develop this type of cancer due to persistent infection with one of the 15 different genotypes of HPVs. Cervical cancer has been found to develop in four major stages, (1) infection of metaplastic epithelium at the cervical transformation zones,[25] (2) viral persistence, (3) advancement of persistent infected epithelium to precancer, and (4) the invasion of basement membrane of the epithelium.[16] In the Middle East, the prevalence of HPV and high-risk HPV (HR-HPV) is 12.3 and 5.2%, respectively. HPV prevalence is greater in Africa than in Eurasia and Asia. In Iran, Turkey, Egypt, and Arab nations, the prevalence of HPV is 14.4, 8.3, 22, and 10.2%, respectively. HR-HPV prevalence is 6.5, 6.2, 6.5, and 3.7% in the listed nations.[26] In general women are most likely to be infected during the first decade of being sexually active, with persistent infections and premalignant lesions being established after 5–10 years. Invasive cancer can take several years to form.[16] However, the main culprit of cervical cancer has been identified as low or high-grade squamous intraepithelial lesions. This is why HPV genotyping is of utmost importance for the effectiveness of HPV screening programs. In this way not only the efficiency would be improved, but also the cost of treatment would be reduced and overtreatment could be avoided.[27] Another important factor for the effectiveness of HPV prevention is the assessment of genotype distribution, which can then help to determine the best vaccines to be used. Meta-analyses suggest that although there are geographical variances of HPV type distribution, HPV 16/18 remains the best preventive vaccine, as it prevents at least two-thirds of cervical cancers and half of all the high-grade squamous intraepithelial lesions in different populations.[28] In Iran, recent studies have shown that the incidence of HPV infections is indeed close to the worldwide statistics and the rate is estimated to increase rapidly over the coming years.[29] City-specific analyses have proven that, genotype 16 is the most common HPV genotype in Iranian women with cervical cancer.[30] The incidence of cervical cancer among Iranian women in general

was reported to be 2.5 per 100 000 ranging from 4.1 to 0.4 on a global scale.[31] The most frequent HPV genotypes among Iranian women were identified as 16 (81.3%), 18 (9.2%), 6 (1.9%), 31 (1.9%), 33 (1.9%), 45 (1.9%) and 58 (1.9%).[32] The expected increase of the HPV incidence rate in Iran can only be curbed by early intervention. This is best accomplished by the combined implementation of HPV vaccination and screening programs. While a combination might seem mutually exclusive, it does indeed act synergistically for prevention.[33] In fact, it was found that there was a high prevalence of HPV infection among Iranian women with normal cytology, which are considered a high risk for transmission in the population. Therefore it is recommended that HPV testing should be carried out in combination with Pap smear tests during screening programs to aid the detection of possible neoplasia and intended infections early on.[34] This is especially important because L1 protein vaccines are very effective in the prevention of HPV 6, 11, 16, and 18, which have been proven to be responsible for cervical intraepithelial neoplasia 1, 2, and 3.[35] While these vaccines are not effective for individuals who have already been infected, these screening programs can be a superb opportunity to offer vaccines to individuals who are most probably already sexually active. Hence, cervical cancer screening programs are of utmost importance and more must be done in Iran, which is a high burden and low resources country and where cultural taboos can make preventive strategies unreachable for many. This is why new and innovative cervical screening strategies are vital. For instance, screening strategies that make use of self-collected vaginal specimens, such as the Xpert HPV assay,[36] in combination with awareness raising strategies could have ground breaking effects on the fight against HPV in countries like Iran. Moreover, the worldwide distribution of cervical cancer fatalities demonstrates significant discrepancies between low and middle-income and high-income nations. Low-income nations accounted for over 90% of the 311,000 fatalities recorded in 2018, continuing a previous trend.[37]

HPV and breast cancer

In the GLOBOCAN 2018 report on cancer incidence and mortality, breast cancer stood out as the second most prevalent cancer among females, representing over 11.6% of all female cancer cases. Additionally, it ranked fifth in global cancer-related fatalities, contributing to 6.6% of overall cancer mortality.[38] Besides, because of early detection in developed countries, the 5-year survival rate for this type of cancer is 83%, vs. 53% in developing countries.[39] Furthermore, it has been reported that the prevalence of breast cancer in Iran is about 8,000 cancers each year, and it is the second and third leading cause of mortality after lung cancer and cardiovascular disease, respectively.[39] Several studies have reported that some viruses such as mouse mammary tumor virus-like sequences and Epstein-Barr virus have important roles in the development of human breast cancer as well.[40] Although HPV is most commonly associated with cervical cancer, the infection has also been strongly linked to the development of breast cancer. The reported prevalence of HPV infection in patients with breast cancer varies widely from 0% to 86.2%.[41] The frequency of HR-HPV is usually six times greater in breast cancer than in normal and benign breast tissue controls. Women who acquire HPV-related cervical cancer have a greater chance of acquiring HPV-related breast cancer than usual. As younger women are more sexually active than older women and hence more vulnerable to HPV infections and HPVs playing a role in breast cancer.[42] Common genotypes associated with breast cancer are HPV 16, 18, 33.[43] Especially among Iranian women with breast cancer, HPV infections have been proven to be highly prevalent. The pooled prevalence of HPV infection among Iranian women (n = 1,539) with breast cancer was reported to be 23.6 (6.7–40.5)%.[43] Furthermore, according to studies, it has been reported that in migrant populations, after one to two generations, the prevalence of cancer is similar to that of the host populations, which indicates the influence of environmental factors on the prevalence of breast cancer.[39] The rate of this cancer has increased from 16% to 28.3% per 100,000 people from 2003 to 2009.[44] Moreover, experiments show that HPV E6 and E7 proteins can convert and immortalize normal human breast epithelial cells and reproductive factors and other factors related to lifestyle are the main variables of breast cancer.[42] Reproductive factors such as noli parietitis, old age at first delivery and lack of breastfeeding increase the risk of breast cancer; The lowest age range (50 years or less) for breast cancer has been reported in Iranian patients.[45] In another investigation, the HPV genome was found in 48.6% of breast cancer samples. Being infected with HPV contributes to the risk of carcinogenesis, either directly or indirectly.[46]

HPV and head and neck cancer (HNC)

Despite the fact that most cancers of the head and neck are found in the aerodigestive system, including the lips, oral cavity, pharynx, larynx, nose, paranasal sinuses, and nasal cavity; thyroid tumors, salivary gland tumors, lip, and oral cancer have an annual prevalence of about 354,864 cases and 2% of all cancers in 2018, making it the second most common location for HNC.[47] Moreover, the seventh most prevalent kind of malignancy globally is HNC.[48] Owing to differences in biological and clinical indications of HNC-related malignancies, the grade of HNC has been found to differ depending. on the anatomical location of infection.[49] In general, biomarkers for HNC have been found as depth of metastatic cancers of the oral cavity, P16, and HPV positivity; however, they are not regarded for other malignancies associated with HNC.[47] Nevertheless, investigations suggest that drugs like opium, which is the most often used addictive substance in South Asia and Eastern Mediterranean countries, such as Iran, have been associated with various malignancies.[50] Mohebbi *et al.* have demonstrated that opium usage causes a substantial rise in head and neck squamous cell carcinoma (HNSCC) and associated malignancies and that opium use is a risk factor for HNC, according to the Iran Opium and Cancer study.[50] There has been increasing awareness for HNCs or more specifically HNSCC recently, and it seems that HPV-positive HNSCC differs to some extent from HPV-negative HNSCC. It was observed that patients suffering from HPV-positive HNSCC tended to be younger. It has been shown that this population of patients has contracted the disease sexually rather than as a result of prolonged consumption of tobacco and alcohol. A strong correlation between HPV16 and HNCs has been demonstrated in several studies.[51] Moreover, some types of HNC show a correlation with other HPV genotypes such as HPV18, 31, 33, 35.[52] HPV detected in 44.4% of Iranian patients with HNCs.[53] Genotyping in Iranian patients showed that HPV types 16, 18, 2, 27, and 43 were found in HNSCC malignancies.[54] All HNC cases reported in the Middle East and North Africa area had an overall pooled HPV prevalence of 16%. HPV-16 was the genotype most significantly related to HNC in this area, followed by HPV-18. Turkey (48%) and Palestine-Israel (31%), had the highest reported prevalence rates of HPV-associated HNC. HNC-associated HPV prevalence in this area has dropped from 19% in 1998–2010 to 15% in 2011–2014 to 12% in 2015–2019.[55]

HPV and oropharyngeal cancer

HPV is known to cause cutaneous and mucosal infections in adults and children alike. However, research more recently proves that HPV circulates also with newborns.[56] The identification of HR-HPV genotypes in the newborn respiratory tract, which is most frequently found to infect the genital tracts of women of childbearing age, potentially indicates the transmission of HPV infection from mother to child.[56] Study also suggests that there might be a possible link between oral HPV infections and cervical HPV infections and thus oral HPV infections are believed to be among possible covariates of long-term genotype specific persistent cervical HR-HPV infections.[57] Iranian studies prove that both low-risk and high-risk types of HPV are associated with the risk of oral tumors and that type 6 and 18 are the most prevalent types.[58] Also, HPV positivity in Iranian patients with oral lesions and oral mucosa (and saliva) of healthy groups was estimated 17% and 7.2%, respectively.[53] Likewise, a correlation between HPV infections and esophageal squamous cell carcinoma has been reported in Iranian patients (23.6%).[59] Recently, an increase in recurrent respiratory papillomatosis and common laryngeal warts in upper airway systems in both Iranian children and adults has been reported. Research suggests that the major cause of recurrent respiratory papillomatosis is HPV genotypes 6 and 11, which increases the probability of medical intervention.[60] Genotypes HPV 6 and 11 are also proven to be involved in the development of Inverted papilloma, a rare disease which arises in the mucosal membrane of the nasal cavity and paranasal sinus, in Iranian patients. Additionally, it is found that HPV 16 and 18 probably play an important role in the progression from benign to malignant form in Inverted papilloma.[53] HPV also has been reported to be involved in the development of sinosal papilloma, a rare benign lesion characterized by a high recurrence rate and malignant transformation, in Iranian patients. However, HR-HPV has been found to be not important in the transformation to malignancy.[61] The frequency of HPV-positive cases among Middle Eastern oropharyngeal squamous cell carcinoma patients may be much higher than previously considered and HPV-16 was the most prevalent subtype. The population of Middle Eastern nations may demand a more cautious approach to HPV screening and awareness. More study is needed on a global scale to understand nonclassical pathways of HPV exposure better.[62]

HPV and prostate cancer (PCa)

PCa has been reported to be one of the most common malignancies in humans and the second leading cause of mortality in men. Studies in Iranian patients have shown that the most common genotypes in PCa are HPV-16, 18, 33, and 31. Infection with HR-HPV genotypes, especially HPV16, may play an important role in urinary tract carcinogenesis.[63] The overall HPV prevalence in urinary tract cancers among Iranian patients and control subjects was reported as 30.9% and 5.3%, respectively. Furthermore, a 2013 study by Mokhtari *et al.*,[64] reported that approximately 10% of patients had PCa and 1.1% had benign prostate hyperplasia. Also, in a study, about 20% of the samples were identified as PCa. On this basis, another study conducted by Fatemipour *et al.* in 2020,[65] showed that 36.1% and 15.9% of HPV DNA was found in people with PCa and control individuals, respectively. The most prevalent HPV genotype was HPV18 in urinary tract cancer cases, followed by HPV16 in case groups.[66] Currently the role of HPV in PCa is a matter of great debate. Studies conducted with Iranian patients from Sanandaj city and Tehran city found no significant HPV infection in PCa.[67] However, a study conducted in Kerman, Iran otherwise and finds a link between HPV DNA and prostate carcinomas, especially HR-HPV types 16 and 18.[68] As a result, further studies with larger population samples are needed to clarify the association between PCa and HPV infection.[69] It has also been shown that there are some differences between cervical cancer and PCa due to the lower rate of HPV loading during PCa compared to cervical cancer.[70] For example, in cervical cancer, PCa, squamous epithelial cells, and glandular epithelial cells are more involved, respectively. In addition, because of the association of sexual transmission of the HPV virus with cervical and PCas, there is a direct link between the mortality from these two cancers.[71] Different geographic zones have different HPV-positive rates in PCa. The odds ratios vary greatly across different regions of the world. The Middle East has an odds ratio of around 13.90%. As a result, it is possible to assume that geographical location may also play an important role in the association between infection and cancer.[72]

HPV and skin cancers

Cutaneous squamous cell carcinoma (SCC) is a very common malignant proliferation in the epithelial layer of the skin with aggressive behavior and possible metastasis. Risk factors for SCC include exposure to the sun, a history of sunburn, immunosuppression, and infection with β-HPV, that HPV is a possible risk factor for SCC. Surprisingly, HPV-5 and -8 have been reported to be involved in the formation of SCC associated with β-HPVs.[73] Remarkably, there have been many studies between HPV infections and skin cancer. Mahoudi *et al.* in 2007 found a direct link between nonmelanoma skin cancers and HR-HPV.[74] However, the role of HPV DNA in the pathogenesis of skin cancers in immunocompetent individuals is debatable. According to histological evaluations, HPV was detected in 22.7% of Iranian patients with squamous and basal cell carcinoma. While an association between nonmelanoma skin cancer and HPV infections in immunosuppressed patients exists, a study conducted in Iranian patients found a link between mucosal-type HPV, especially HPV type 18, in immune-competent Iranian squamous cell carcinoma patients.[75] However, further investigation is needed to elucidate the association between skin cancer and HPV infection in Iran, considering other prevalent causes of skin cancer such as sunburn and overexposure to the sun.

HPV and anal cancer

Anal cancer has numerous histological origins. The most prevalent type of anal cancer is anal squamous cell carcinoma, which is associated with anal HPV infection. Specifically, HPV16 and 18 are responsible for around 90% of anal squamous cell carcinomas. In metastatic squamous cell carcinomas of the anal canal, a significant proportion of HPV-positive cases (94%) were also discovered.[76] Additionally, HPV has been proven to be linked to the development of anogenital lesions in men. While receptive anal sex in men has been considered one of the main causes of anal cancer, research reports a high prevalence of β-HPV in the anal canals of heterosexual men who do not report engaging in receptive anal sex. This, therefore, is highly indicative of transmission modes other than penile-anal intercourse.[77] HIV-positive individuals, women with genital tract neoplasia, and solid organ transplant recipients have all been recognized as high-risk categories for anal squamous cell carcinoma and anal HPV infection as well.[76] Because of the high incidence in high-risk populations, screening for anal HPV is not frequently done. In both HIV-negative and HIV-

positive patients, HPV16 is the most prevalent carcinogenic HPV type. The incidence of HPV16 positivity increases with the severity of anal lesions, while the prevalence of other HR-HPV types decreases from anal cancer to high-grade squamous intraepithelial lesions.[76] Iranian studies have shown that the most prevalent genotypes associated with HPV DNA-positive colorectal cancer (22.6%) in Iranian patients are HPV types 51 and 56.[78]

HPV and penile cancer

Penile carcinoma is a rare cancer. According to the International Agency for Research on Cancer, 36,068 new cases were identified worldwide in 2020. Squamous cell carcinoma accounts for the vast majority of penile malignancies (almost 95%). Penile cancer primarily affects men from poor socioeconomic backgrounds.[79] Given differences in the prevalence of penile cancer in different geographical areas, the incidence of this cancer ranges from 0.3–0.6 to 2.8–6.8 per 100,000 people in developed and developing countries, respectively.[80] In addition to geographical location, factors such as phimosis, noncircumcision, genital warts, HPV, precancerous lesions, and other epidemiological factors are involved in the prevalence of this cancer.[81] Based on HPV infection, the precancerous lesions of the penis are divided into two types, including HPV-related lesions and non-HPV-associated lesions.[82] In this regard, it is worth mentioning that Queyrat, Bowen's disease, Bowenoid papulosis, Bushke-Lowenstein tumor, and warty, basaloid, and mixed warty/basaloid are among the lesions associated with HPV infection.[83] Also, it has been shown that, in different histological types of SCC, the high prevalence of HPV infection in basaloid cases is about 76% and 82% in basaloid warts.[84]

As HPV infection is considered the most common viral sexually transmitted infection, the infection is often associated with malignant disorders, especially penile cancer in men. It was reported that a strong relationship between HPV and penile cancer exists among Iranian patients (55.7%), with genotypes HPV6, HPV11, HPV16, HPV18, and HPV52 being the most frequently detected.[85] The most recent report by the International Agency for Research on Cancer indicated that the Asian region has the largest number of penile cancer cases worldwide. In 2020, 20,315 cases were reported in Asia, accounting for 56.3% of all cases. India has the highest incidence rate in Asia, with 1.6 cases per 100,000 people. Regardless of the lack of precise data, the incidence in the area may be decreasing.[79]

HPV and bladder cancer (BCa)

Around 550,000 new instances of BCa are diagnosed each year,[86] and there will likely be 17,980 fatalities from the disease in the USA by the year 2020, making it the tenth most frequent cancer overall.[87] According to several studies, BCa is the most expensive cancer, placing a significant financial burden on both society and the person. It counts as the ninth most prevalent cancer worldwide and the fourth most prevalent malignancy among Iranian men.[88] HPV infection is prevalent in BCa patients, according to recent research, with rates ranging from 2% to 35%.[89] A study from Iran has shown that HPV was present in 35.6% of bladder transitional cell carcinoma tissue specimens using polymerase chain reaction, which was seven times higher than the control group.

In our recent study, the prevalence of HPV-16 in men with bladder transitional cell carcinoma was 12.5%, the prevalence of HPV-18 was 37.5%, and the total prevalence was 29.3%.[90] Also, according to Barghi *et al.*,[90] 4.9% of the wives of men with bladder tumors had cervical dysplasia, which was higher than the incidence in Iran. Moreover, according to studies, muscle-invasive bladder cancer accounts for the remaining occurrences of BCa, with roughly 75% being non-muscle-invasive bladder cancer.[90,91] Urothelial carcinoma (UC), SCC, and adenocarcinoma are the three histological subtypes of BCa, with UC accounting for 94% of all cases.[92] However, research has also shown that hereditary factors, occupational exposure to a number of chemical substances, including aromatic amines and arsenic,[93,94] and cigarette use may all be linked to a greater prevalence of BCa.[91] HPV is a DNA virus that belongs to the papillomavirus family, and it attacks cutaneous, or mucosal epithelium. According to studies, HPV is the most prevalent sexually transmitted virus among people.[95]

The genital tract and urine system are anatomically connected. Because of this, HPV has a greater likelihood of infecting the urinary epithelium of the bladder.[96,97] Primary penile cancer was found to be strongly correlated with HR-HPV infection in prior investigations.[98] Numerous studies have shown how HPV infection affects BCa development and prognosis. These investigations determined that one important risk factor for carcinogenesis is the ongoing inflammation brought on by HPV infection. The investigations also revealed that during cell inflammation, reactive oxygen species and reactive nitrogen species produced in epithelial cells cause DNA damage, mutations, and cancer.[99]

On the other hand, it has been suggested that the viral oncoproteins E6 and E7 have significant roles in the development of tumors. The expression of E6 and E7 proteins can be increased by the HPV genome integrating into the host genome.[100] According to Shaker *et al.*,[101] bilharzial BCa had greater rates of HPV 6/11 and 16/18 infection than chronic cystitis. Thus, the authors concluded that HPV 6/11 and 16/18 have a role in the development of bilharzial bladder tumors.[101] According to a study done in a Chinese population, HPV 18, 33, 16, and 39 had roles in the development of BCa in both sexes.[102]

To promote BCa carcinogenesis, HPV-related E6 and E7 proteins inactivate or degrade suppressor-gene associated proteins (p53 and RB1).[103,104] Telomerase reverse transcriptase and telomerase, which are crucial for maintaining telomere lengths and are essential for cell immortality, can be activated by HR-HPV E6 proteins.[105] Additionally, the DNA repair protein (*i.e.*, XRCC1) can be bound and inhibited by the E6 protein of HP16, HPV8, and HPV1 to block DNA repair following breaking and permit the accumulation of mutations in the host genome.[106] To stimulate cell development, E6 can also facilitate the activation of the mitogen-activated protein kinase and epidermal growth factor signaling pathways.[107] By interfering with the functions of cyclin E/cyclin dependent kinase 2 complexes, the E7 protein can cause errors in centrosome duplication and genomic instability.[108]

We determined that HPV infection increased the incidence of BCa by 3.35 times, and that detection techniques and histological subtypes had no impact on this result.[109] To prevent BCa, especially in men, HPV vaccination is essential. Future research should examine the relationship between BCa and HPV infection utilizing extensive population sampling.[109] Additionally, the processes behind these events need to be clarified. In these people, HPV vaccination should be considered. To lower the risk of cancer in both sexes, it is crucial to avoid dangerous sexual behavior and employ barrier techniques.[90]

HPV and gastrointestinal cancer

Gastrointestinal cancer is the fourth most common type of can-

Table 2. Common genotypes causing HPV-associated cancers

Associated diseases	HPV genotype	References
Cervical intraepithelial neoplasia	HPV 6, 11, 16, 18	35
Breast cancer	HPV 16, 18, 33	43
Head and neck cancers	HPV 16, 18, 31, 33, 35,2,27,43	52,54
Oropharyngeal cancer	HPV 6, 18, 11, 16	60,53
Prostate cancer	HPV 16, 18, 33, 31	63
Skin cancers	HPV 5, 8, 18	73,75
Anal cancer	HPV 16, 18, 51, 56	76,78
Penile cancer	HPV 6, 11, 16, 18, 52	85

HPV, human papillomavirus.

cer in the world and is considered the most common cancer in Iran. However, currently, no conclusive data exist to prove a clear causal relationship between HPV infections and gastric and gastrointestinal cancers. Some studies claim to find a strong relationship between HR-HPV type 16 and this form of cancer (16.4%).[110] However, investigations conducted in high-risk regions, such as the northern and northwestern parts of Iran, have yet to provide evidence of an association between gastric cancer and HPV infection.[111] Common genotypes causing cancers are listed in Table 2.[35,43,52-54,60,63,73,75,76,78,85]

HPV vaccination in the Middle East

In high-income nations, Pap smear and HPV testing procedures used in organized cervical screening have prevented Invasive cervical cancer (ICC).[112,113] In order to prevent cervical cancer and HPV oncotype infection, the HPV vaccine was recently effectively launched. But in low- and middle-income countries (LMICs), there are insufficient organized cervical screening programs, which has resulted in inequities and higher mortality to incidence ratios of ICC in these nations.[114] The prevalence of HPV-related cancers in some of the Middle East countries has been summarized in Table 3.[55,115] Muslim women refrain from sexual activity until they are married and their sexual relationships are limited to their single partners for cultural and religious reasons[116,117]; as a result, Iran and numerous other Muslim nations have exceptionally low incidence rates of cervical cancer.

In Iran, for example, it was calculated that the age-standardized incidence rate of ICC was around 5 per 100,000.[31,118] Because of this, ICC is not seen as a significant public health issue, and the majority of these nations lack formal cervical screening programs. Additionally, some Muslim women are apprehensive about getting cervical cancer screening.[119] As a result, despite having a low incidence rate, patients frequently have a bad prognosis and are diagnosed at an advanced stage.[120]

The most significant recommendation in the study by Majidi *et al.* in 2016,[119] was the creation of a national program for ICC prevention. It emphasized that the new approach should take into account the most effective method of screening, the beginning age for screening, and the interval between screenings. Additionally, their study gave priority to developing the national standard for the therapy of precancerous lesions and patient follow-ups. Moreover, they recommended that all Iranian women over 21 years of age who have had sexual activity undergo cervical screening every 3 years, under the country's current screening recommendations.[119]

Furthermore, most of the extended Middle East and North African nations, according to Sancho-Garnier *et al.*,[121] lack governmental guidelines and resources for the care of atypical lesions. They demonstrated that the absence of political awareness and the failure to provide the required funding for cervical screening programs have been the primary barriers to the development of such a nationwide program in these nations.[119] The cervical screening methods used in various nations vary greatly.[122] The three primary variables are screening test type, starting age, and interval between screenings. Three different screening methods (HPV testing, Pap smear tests, and visual inspection with acetic acid) are employed for cervical screening all throughout the world.[114] In the ICC pre-

Table 3. Prevalence of HPV-related cancers in some Middle East countries

Country	Cancers	Ref
Bahrain	Breast cancer, cervical cancer, head and neck cancer, penile cancer, anal cancer, oropharyngeal cancer	55,115
Iran	Breast cancer, cervical cancer, head and neck cancer	55,115
Iraq	Breast cancer, cervical cancer	115
Jordan	Breast cancer, cervical cancer, head and neck cancer	55,115
Kuwait	Breast cancer, cervical cancer, penile cancer, anal cancer, oropharyngeal cancer	115
Lebanon	Breast cancer, cervical cancer, head and neck cancer	55,115
Oman	Breast cancer, cervical cancer, penile cancer, anal cancer, oropharyngeal cancer	115
Turkey	Breast cancer, cervical cancer, head and neck cancer, penile cancer, anal cancer, oropharyngeal cancer	55,115

HPV, human papillomavirus.

ventive programs, sensitivity, specificity, and cost-effectiveness are crucial considerations when choosing the test type, beginning age, and screening intervals. There have been various recommendations to raise the beginning age from 21 to 30 or 35 years and the screening interval from 3 years to 5 years because of the low incidence of cervical cancer in Iran.[31,123] In addition, Majidi *et al.* emphasized that all women should have complete insurance coverage and access to free cervical screening.[119] Otherwise, they reported that the majority of Iranian women would be unable to pay for the follow-up treatments and cervical screening tests.[119] ICC has been successfully prevented by the use of organized cervical screening programs and HPV vaccinations.[119] Iran and many other Muslim nations have low rates of ICC because of cultural and religious factors. In these nations, cervical screening is not routinely conducted. As a result, ICC is typically detected in these nations at an advanced stage with a bad prognosis.[119] Nevertheless, HPV vaccination is not advised in Iran due to the expensive cost of the vaccine and the low prevalence of cervical cancer.

HPV vaccination in Iran

Presently, strong evidence that HPV vaccination protects against cervical precancerous changes in adolescent girls and women who are vaccinated between 15 and 26 years of age.[124] However, long-term follow-up programs are still needed to assess the impact of vaccination on cervical cancer, since only limited data is available from trials in this regard.[124] To date, the most effective vaccine for cancer protection is the nonavalent vaccine (HPV 6/11/16/18/31/33/45/52/58 vaccine).[125] Although HPV vaccination programs for adolescent females are accessible in several places around the world, their effectiveness is strongly linked to population coverage and is enhanced by herd immunity.[126]

Antigen content distinguishes the various subtypes of HPV vaccines.[48] There are now three different vaccine subtypes on the market: HPV2 (bivalent vaccine against HPV types 16 and 18), HPV4 (quadrivalent vaccine against HPV types 6, 11, 16, and 18), and HPV9 (nonavalent vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58).[48] It is believed that nonavalent vaccines may lead to improved immunization and a higher protection rate than other vaccines. Additionally, bivalent vaccines provide important cross protection against HPV types other than 16 and 18 and also give long-term effective protection from HPV 16 and 18. It must be stressed, however, that vaccinations do not as of now replace the need for effective screening and that it is important for both vaccinated and nonvaccinated women to undergo HPV screening.[127] However, strong inequality surrounds HPV vaccine distribution and access, where places with the highest-burden have the least access.[128] Owing to the high cost of the vaccine, this means that there is more delivery to the nontraditional target population because they can afford it.[129]

In 2014, 3.71 million Iranian women were infected with HPV, with the rate rapidly increasing over the years.[119] Currently, 25 to 30 million women over 15 years of age are at risk of cervical cancer in Iran. However, HPV vaccines are currently not included in the national vaccination program in the country, although they are accessible to individuals to buy with their own funds. Nevertheless, research suggests that vaccination can make a great impact on the prevention of cervical cancer particularly in Iran, especially if coupled with the introduction of educational programs in high schools and robust screening programs.[32] It is crucial that national health policymakers and responsible organizations dedicate more attention to HPV vaccinations to prevent cervical cancer from becoming an epidemic in the future.[119]

Strategy and perspective approach for the future

Generally, it is necessary to identify the entire mechanism of HPV pathogenesis as well as the factors that participate in the progression of the disease and its malignancies. As a result, treatment and diagnostic strategies to prevent the over-prevalence of these cancers, as well as mortality and treatment costs, must be developed. On this basis, according to the current evidence and the HPV implications for the immune response, identification of target cells and receptors, viral strategies for evading the immune system, and finally the role of immune cells in suppressing the immune response, can all help researchers develop more effective anti-HPV treatment.[19] As a result, this led to the development of new vaccination techniques and initiatives to prevent illnesses attributed to HPV infection.

Treatment and outcomes of HPV-related cancer

For a variety of causes, cervical cancer patient outcomes are worse in underdeveloped than in industrialized countries.[130] First, not all treatment units are equally accessible, leaving the majority of the poor without access to care because the majority of facilities are located in metropolitan regions.[131] Because of lengthy treatment and budgetary limitations, completing therapy is also difficult. Last but not least, there is inadequate compliance with national/institutional treatment recommendations.

In the first phases of therapy, surgery is the mainstay. According to a study, perioperative acute complications were similar in LMICs and high-income nations.[132] The availability of adjuvant medicines in high-risk populations, inadequate selection criteria, and the frequent use of neoadjuvant chemotherapy (NACT) before surgery in locally advanced stages all contribute to the unsatisfactory reporting of long-term results.[133] Radiotherapy is still the go-to therapy for locally advanced stages. However, the shortage of radiation resources is startling given the prevalence of cervical cancer. Therefore, NACT usage is more prevalent in low-income countries and LMICs.[133] According to Gupta *et al.*,[134] concomitant chemoradiation in stages IB2eIIB is preferable to NACT followed by surgery. There is a difference in the accessibility of brachytherapy and external beam radiation settings in LMICs like India, with numerous highly populated states having very minimum radiotherapy facilities.[135] Only 22% of Pakistan's population, according to reports, has access to radiation facilities.[136] Furthermore, inconsistent treatment cost caps make it challenging for impoverished women to get timely care. Longer wait periods for patients who need curative radiation are a result of the overuse of the available radiotherapy resources for palliative care. For instance, only 42–54% of countries, including Indonesia, follow worldwide treatment recommendations.[137] Concurrent chemoradiation therapy compliance is a significant issue in locally advanced illnesses. Locally advanced cervical cancer is linked to malnutrition, cancer cachexia, and anemia in LMICs and low-income countries. Cobalt-60 brachytherapy is becoming more popular and might be helpful in treating larger afflicted populations, although its wider application is still unknown. According to a recent study from Zimbabwe, 97% of patients finished their treatments, with the majority doing so in 56 days.[138]

High-grade vulvar intraepithelial neoplasia has been successfully treated with topical agents like imiquimod (immune response modifier), cidofovir (inhibition of viral replication; induction apoptosis), or photodynamic therapy (direct tumor damage and enhancement of antitumor immunity).[139] Cryotherapy, trichloracetic acid, or surgical removal-which has the greatest primary clearance

rate, are therapies for genital warts that healthcare professionals can provide. Therapies used by patients include imiquimod and podophyllotoxin.[139]

Recurrence occurs in 30–40% of patients following successful therapy. A logical combination of existing therapy with fresh medications that target HPV-mediated molecular pathways in cancer might result in even greater gains. Preclinical research is being done on small molecule inhibitors that target the DNA-binding properties of HPV E1/E2 or the anti-apoptotic effects of E6/E7 oncogenes.[100,139] Early clinical trials are evaluating proteasome and histone deacetylase inhibitors, which can improve apoptosis in HPV-positive cancer cells. Immune suppressive regulatory or escape variables that may be systemic or local may be present in chronic HR-HPV infection/neoplasia.[139] Two E6/E7 vaccines have shown modest clinical effectiveness in high-grade vulvar intraepithelial neoplasia patients, which was connected with a robust and widespread systemic T-cell response specific for HPV and the regulation of important local immunological variables.[139] Finally, in addition to vaccination, therapies that can locally alter the balance of immune effectors are being investigated.

Future directions

With the increasing adoption of prophylactic HPV vaccination in the general population, there is a promising trend of declining HPV infection rates. Notably, vaccines such as Cervarix, Gardasil, and Gardasil 9 have demonstrated remarkable immunogenicity, leading to nearly 100% seroconversion rates. However, a persisting gap exists in the field of HPV therapeutic vaccination, as the burden of HPV-related malignancies is expected to remain substantial for years to come. Current treatments for HPV-associated cervical diseases primarily target topical genital warts, lacking a universally recognized gold standard for treatment. Furthermore, the choice of treatment is contingent upon factors including disease severity, HPV infection type, and individual patient preferences.[140] While progress in the development of targeted therapeutic HPV vaccines has had a measured pace, it remains imperative to intensify research efforts aimed at augmenting the immunogenicity of T-cell responses. This necessitates the exploration of diverse delivery systems, vaccine compositions, delivery routes, and the evaluation of various adjuvants. Such methodical endeavors are pivotal for the advancement of HPV treatment strategies within the academic and clinical spheres.[140]

Moreover, the utilization of the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 system to eliminate HPV driver genes or induce loss of function represents a promising avenue for the treatment of HPV-associated cancers.[141] CRISPR/Cas, the recipient of the 2020 Nobel Prize in Chemistry, stands as a rapid, cost-effective, and highly efficient genome-editing technique.[142] Additionally, there are a limited number of advanced techniques, such as CAR-T therapy and radioimmunotherapy, which have exhibited promising outcomes. Nevertheless, it remains imperative to further refine these methods in terms of their efficacy, safety, and specificity before their widespread clinical implementation can be considered.[140]

Conclusions

HPV infections are closely linked to malignant disorders worldwide. While the Western world has taken a serious stance toward fighting the effects of HPV infection through proactive and timely interventions, Developing countries in the Middle East such as Iran need to become more involved in addressing this association within the country. Studies conducted on the Iranian population prove that there indeed is a strong link between some forms of cancer and HPV infection, more large-scale studies are needed to assess the relationship between malignant disorders that have not been linked to HPV clearly. Additionally, vaccination programs must be enforced more seriously and stronger efforts must be made to address the taboo surrounding sexually transmitted diseases such as HPV. This must be done in order to control the effects of HPV and to prevent an epidemic type spread of the disease and subsequent malignant disorders.

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Conflict of interest

The authors declare that they have no conflict of interests.

Author contributions

Conceived the idea for this manuscript and edited subsequent drafts (HBB), literature search, design of the table and manuscript preparation (PSA), literature search, design of the figure and manuscript preparation (RR), and contributed to the drafting of the manuscript (VP, FA). All authors have read and approved the final manuscript.

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