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Human papillomaviruses-related cancers

Presence and prevention strategies in the Middle East and North African Regions

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Human papillomavirus (HPV) infections are estimated to be the most common sexually transmitted infections worldwide. Meanwhile, it is well established that infection by high-risk HPVs is considered the major cause of cervical cancer since more than 96% of these cancers are positive for high-risk HPVs, especially types 16 and 18. Moreover, during the last 2 decades, numerous studies pointed-out the possible involvement of high-risk HPV in several human carcinomas including head and neck, colorectal and breast cancers. The association between high-risk HPVs and cervical cancer and potentially other human malignancies would necessitate the introduction of vaccines which were generated against the 2 most frequent high-risk HPVs (types 16 and 18) worldwide, including the Middle East (ME) as well as North African countries. The presence of high-risk HPVs in the pathogenesis of human cancers in the ME, which is essential in order to evaluate the importance of vaccination against HPVs, has not been fully investigated yet. In this review, we present an overview of the existing epidemiological evidence regarding the presence of HPV in human cancers in the ME and the potential impact of vaccination against HPV infections and its outcome on human health in this region.

Introduction

An increasing number of malignancies are directly and/or indirectly the result of viral infection. Today, it is estimated that around 20% of human cancer cases worldwide can be linked to virus infections.[1] Progress in this area of cancer research has in large occurred through analysis of cell signaling and growth control pathways that may be altered by viral oncogenes.[2]

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Human papillomaviruses (HPVs) are considered among the major viruses associated with human cancers especially cervical carcinomas.[3] HPVs are currently the most common sexually transmitted infections worldwide, with the majority of individuals who engage in sexual activity becoming infected at some point in their lifetime. HPVs are small, double-stranded DNA viruses that generally infect cutaneous and mucosal epithelial tissues of the anogenital tract.[4,5] To date, over 120 different viral types have been identified, and about one-third of these infect epithelial cells in the genital tract. HPVs are classified as either high risk or low risk, with high-risk types being associated with cancer formation. Infections with low-risk types are generally self-limiting and do not lead to malignancy. For instance, HPV types 6 and 11 are classified as low risk, and infection with these types result in the proliferation of epithelial cells and manifests as warts or papillomas on the skin.[6,7] On the other hand, infections with these viruses (type 16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, and 83) are associated with the development of cervical cancers where more than 96% of these cancers are positive for these viruses.[3,8] Moreover, accumulating evidence suggests that persistent infection with those viruses is necessary for cervical precursors to evolve into invasive carcinomas.[3,9,10] However, it is well known that high-risk HPV infection alone, at least with one type, is not sufficient to induce neoplastic transformation; the high-risk HPV-infected cells must undergo additional genetic changes and/or co-infection with another onco-virus to reach the full cell transformation and consequently tumor formation (refs. 11, 12, and unpublished data).

High-risk HPVs are also important risk factors for other human cancers such as head and neck (HN) and colorectal carcinomas; as roughly 30 and 80% of these cancers are positive for high-risk HPVs, respectively.[13-15] Moreover, it was observed that the presence of high-risk HPVs serve as a prognostic factor in early-stage cervical, HN, and colorectal cancers, and are associated with vascular invasion, lymph node metastases and tumor size.[16-20]

On the other hand, several recent studies, including ours, investigated the presence of HPVs in human breast cancer;[21-26]

these investigations revealed that high-risk HPVs are present in human breast cancers; controversially few studies stated that HPVs could not be detected in breast cancer and normal mammary tissues.[27-29]

In this context, it is important to mention that the prevalence of HPV infections in human-related-cancers is associated with specific geographic locations worldwide, which was confirmed through numerous investigations.[3,5,8] However, there are very limited studies about HPVs and their associated cancers in the majority of developing countries such as the greater Middle East which comprises classical Middle East and North Africa.[30] The greater Middle East area includes Afghanistan, Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates (UAE), and Yemen, as was recently recognized by international politicians.[31] In this paper we will review the presence and distribution of HPVs in human-related cancers in these countries; we will focus on the presence of these viruses in cervical, HN, colorectal, and breast cancers. However, first we will go over the role of high-risk HPVs in carcinogenesis.

Role of High-Risk HPVs Onco-Proteins in Cancer Initiation and Progression

The HPV genome is about 7.9 kb in size and encodes early (E), late (L) proteins and includes a non-coding region (LCR). Early proteins consist of E1, E2, E4, E5, E6, and E7, while L1 and L2 are late proteins. The E1 and E2 genes are expressed first upon viral entry into the host cell, and these encode viral DNA replication proteins.[32] The E5 protein along with E1, E2, and E4 are replication proteins that allow the viral DNA to be replicated as an episome in low copy numbers.[33,34] During the process of differentiation of epithelial cells, the p670 promoter on viral DNA causes increased expression of E1, E2, E4, and E5 proteins, resulting in increased viral DNA amplification. Therefore, E5 is a viral replication protein that helps in replicating the viral episomal DNA.[35]

Presently, it is well-know that high-risk HPV early proteins, including the E5, E6, and E7 onco-proteins, increase cellular alteration and probably lead to HPV induced carcinogenesis.[36,37] For example, recent studies demonstrated that the E5 onco-protein can play an important role in cell transformation and consequently carcinogenesis through its interaction with EGF-R1 signaling pathways (MAP kinas and PI3K-Akt) and pro-apoptotic proteins.[38,39] On the other hand, E6 and E7 are thought to work together in lesions caused by high-risk HPV types such as HPV 16, the 2 proteins are expressed from bicistronic mRNA initiated from the viral early promoter (p97).[40] Both E6 and E7 have functions that stimulate cell cycle progression and both can associate with regulators of the cell cycle.[34,41]

The viral E6 protein complements the role of E7, and is thought to prevent the induction of apoptosis in response to unscheduled S-phase entry mediated by E7.[42] Although the association of E6 with p53, and the inactivation of p53-mediated growth suppression and/or apoptosis has been well documented, E6 can also associate with other pro-apoptotic proteins including Bak and Bax.[43,44] The E6 protein of high-risk HPV types can also stimulate cell proliferation independently of E7 through its C-terminal PDZ-ligand domain.[45,46] E6-PDZ binding is sufficient to mediate suprabasal cell proliferation and may contribute to the development of metastatic tumors by disrupting normal cell adhesion.[46,47] The E7 viral association with members of the pocket protein family such as pRb is well characterized. pRb is a negative regulator of the cell cycle that normally prevents S-phase entry by associating with the E2F family of transcription factors.[41] E7 binding to pRb displaces E2F, irrespective of the presence of external growth factors, and leads to the expression of proteins necessary for DNA replication.[34] Meanwhile it was recently revealed that E5 and E6/E7 can enhance cancer progression through EGF-R1 and Id-1 deregulation.[38,5,48] All of this implicates high-risk HPVs infection in cell transformation and consequently cancer initiation and progression through E5 and E6/E7 onco-proteins of these viruses.

High-Risk HPVs in Cervical Cancer

With a prevalence of 10%, cervical cancer is the second most common cancer (after breast cancer) affecting women around the world.[49] While, it is well established that persistent infections with high-risk HPVs are major risk factors in human cervical cancer. The development of HPV-induced cervical cancer usually requires 15–20 y, providing a window of opportunity for detecting HPVs and/or HPVs-induced cell abnormalities.[50,51] Viral DNA can be detected before cell abnormalities are observed, and Papanicolaou test (Pap test) is used to screen and detect abnormal cells that are possible precursors for malignancies.[52,53] On the other hand, highly safe, immunogenic and effective 2 vaccines have recently been developed that can prevent infection of the 2 most frequent high-risk HPV types (16 and 18).[54,55] These vaccines have now been licensed by National Control authorities in the majority of industrial (developed) countries.[56,57] However, most women from many developing countries including the greater Middle East are not provided with such services;[58,59] in addition, there are no clear evidence about the presence and distribution of high-risk HPVs in human cervical cancers in the majority of these countries,[30,60] which is the first important step to introduce the available HPV vaccines or the next generation of these vaccines. For instance, there are no investigations about the presence of high-risk HPVs in human cervical cancers in Afghanistan, Bahrain, Libya, Mauritania, Oman, Palestine, Qatar, Somalia, and UAE. Meanwhile, recent few studies explored, for the first time, the presence and the distribution of high-risk HPVs in human cervical cancer in Algeria, Egypt, Iran, Israel, Jordan, Kuwait, Lebanon, Morocco, Pakistan, Syria, Tunisia, and Turkey. As shown in **Table 1**, the detected prevalence of high-risk HPVs in women with cervical cancer in these countries varied from ~50% to 98%; and the most frequent HPV types are 16, 18, 31, 33, 45 and 52. Several methodologies and techniques were used in these investigations to categorize the presence of

HPVs, including PCR, ISH, IHC as well as tissue Microarray.[61-97] Finally and based on the limited number of studies in these countries, we believe it is important to re-conduct numerous investigations of large numbers and cases to confirm the incidence of high-risk HPVs in the greater Middle East population.

Table 1. Presence of HPVs in cervical cancers in the greater Middle East countries

Country	HPVs+%	Detected HPV types	Reference
Algeria	97	16 and 18	61,62
Egypt	95	16 and 18	63–65
Iran	64–90	16, 18, 31, 33, and 45	66–72
Israel	95	16, 18, 45, 56, and 68	73–78
Jordan	85	16, 18, 31, 33, 35, 39, 45, 52, and 58	30,79
Kuwait	51	16, 18, 31, 33, 35, 39, 45, 52, and 58	80
Lebanon	43*	16, 18, and 33	30,81
Morocco	88–92	16, 18, 31, 33, and 45	(82,83)**
Pakistan	88–98	16 and 18	84,85
Saudi Arabia	82	16, 18, 31, 33, 45, 52, 56, and 56	86,87
Sudan	82–94	16, 18, 45, 52, and 58	88,89
Syria	95	16, 18, 31, 33, 35, 45, 51, 52, and 58	90
Tunisia	90	16, 18, 31, and 33	91,92
Turkey	77–100	16, 18, 31, 33, and 35	93–97

*Abnormal tissue cases (possibly including some cancer samples). **These studies were performed on cervical cancer biopsies.

High-Risk HPVs in Head and Neck Cancers

Cancers of the HN (upper aerodigestive tract) include neoplasias of the oral cavity, the pharynx (naso-, oro-, and hypopharynx), the larynx and the paranasal sinuses.[98] They encompass a diverse group of cancers that are frequently aggressive in their biological behavior.[99,100] Tumors from each site have a unique anatomy, epidemiology, and therapeutic approach.[101] Head and neck squamous cell carcinomas (HNSCCs) are the predominant tumors of the head and neck comprising more than 95% of all HN cancers.[102,103] The association between HNSCCs and habitual risk factors such as tobacco and alcohol exposure, areca-nut chewing, maté consumption, and thermal injury, has long been recognized.[104,105] In the past decade, appreciation has emerged of a second type of HN cancer that arises from transforming infection with high-risk HPVs.[106,107] Thus, presently it is assumed that high-risk HPVs are important etiological factors in the development of HNSCCs, as roughly 30% of these cancers are positive for high-risk HPVs.[13,14,108] As we mentioned in the introduction section the presence and allocation of these viruses in human-associated-cancers, including HNSCCs, are related to specific geographic locations worldwide.[5,51] Therefore, several investigations explored the presence and distribution of high-risk HPVs in different areas in the world including the greater Middle East which was unfortunately limited to Egypt, Iran, Israel, Pakistan, Sudan, Syria, Turkey, and Yemen (**Table 2**). Data from these countries can be summarized as follows:

In Egypt: Hafed et al.[109] examined the presence of high-risk HPV types 16 and 18 in 34 oral cancer specimens using Digene tissue hybridization kit; they found that 8 cases (23.52%) are positive for these 2 types; from the same country, Mansour et al.[110] investigated the presence of HPV type 16 in 30 HN cancer samples by PCR; their study revealed that 26 (86%) of cases are positive for HPV type 16.

In Iran, several recent studies investigated the incidence of HPVs in human oral and nasopharyngeal carcinomas using PCR and in situ hybridization methodologies; these investigations showed that the presence of these viruses vary from 14.30% to 40.9%; and the most frequent high-risk HPVs are types 16 and 18.[111-114] However one recent study from the same country was unable to detect the presence of HPVs in human oral carcinomas;[115] therefore, the authors of this investigation concluded that HPVs are not etiological factors in Mashhad city area.

In Israel: Niv et al.[116] tested the presence of HPV type 16 in 23 of oral and oroharynx carcinoma cases by PCR; they reported that 4 samples (17.3%) are positive for HPV 16.

In Pakistan: Two studies examined the presence of HPVs especially types 16 and 18 in human oral lesions and carcinomas using PCR and EIA; they revealed that HPV type 16 and 18 are present in 17.9% and 25% of cases, respectively.[117,118]

In Sudan: Three recent investigations examined the presence of HPVs in HN cancers by PCR; these studies revealed that 20 to 65% of cases are positives for high-risk HPVs, and the most frequent HPV types are 16 and 18.[119-121] However, Ibrahim et al.[122] did not detect the presence of HPVs in 14 oral carcinoma samples from the same country.

In Syria: Al Moustafa's group, from McGill University, recently investigated the presence of high-risk HPVs in HN cancer samples from the Syrian population; their data showed that 43% of these cancers are positives for high-risk HPVs. Genotyping of high-risk HPVs is presently under investigation by the same group; however, preliminary data from this study reveal that HPV types 16, 18, 31, 33, and 35 are frequent in HN cancers in Syria (Ghabreau et al., in preparation).

In Turkey: three studies were conducted to explore the presence and distribution of HPVs in HN cancers; these studies showed that the presence of high-risk HPVs vary from 14 to 47.6%, and the most frequent HPVs in the Turkish population are HPV types 16, 18, 31, and 33.[123-125]

Finally, and regarding the presence of HPVs in HN cancer in Yemen, there was only one study comparing the presence of HPVs in developed vs. developing countries by PCR. This study included a small number of human oral carcinomas from Yemen,

Table 2. Presence of HPVs in HN cancers in the greater Middle East countries

Country	HPVs+%	Detected HPV types	Reference
Egypt	23.52–86	16 and 18	109,110
Iran	0–40.9	16 and 18	111–115
Israel	17.3	16	116
Pakistan	17.9–25	16 and 18	117,118
Sudan	0–65	16 and 16	119–122
Syria	43	16, 18, 31, 33, and 35	(Ghabreau et al., in preparation)
Turkey	14–47.6	16, 18, 31, and 33	123–125
Yemen	20	ND	119

ND: not determined.

and it showed that high-risk HPVs are present in approximately 20% of these cancer samples.[119]

In conclusion these studies reveal that the incidence of high-risk HPVs in HN cancer in the Middle East varies from 0% to 65%; and the most frequent HPV types are 16, 18, 31, and 33. However, it is important to highlight that these studies are limited in numbers and cases, and most importantly the majority of them are limited in their scope that included only few types of high-risk of HPVs.

High-Risk HPVs in Colorectal Cancer

Colorectal, colon, and rectal, cancer is the third most common malignancy in both men and women worldwide (World Health Organization). Colorectal carcinogenesis is a complex, multistep process involving environmental and lifestyle factors in addition to sequential genetic changes and possibly viral components.[126] On the other hand and as we mentioned above, high-risk HPVs have been established as etiological agents of invasive cervical cancer.[3,17,127] Persistent infection with high-risk HPVs is necessary for the development of premalignant lesions and/or progression of the disease.[3,18] Furthermore, it was pointed-out that high-risk HPVs have carcinogenic effects at several other anatomical sites in women and men such as colorectal.[20,128,129] These studies showed that high-risk HPVs are present in approximately 80% of colorectal cancers, especially in their invasive form worldwide. However, it is important to mention that there are only few studies regarding the presence of HPVs in colorectal cancers in the developing countries including Middle East and North Africa. Unfortunately investigations of HPVs in colorectal cancers in the greater Middle East countries are limited to: Israel, Syria and Turkey (**Table 3**), which can be outlined as follows:

1) A recent study was performed on the presence of HPVs in a cohort of 106 colorectal cancer samples from Israel using PCR and SPF10 INNO-LiPA methodologies; the authors couldn't detect the presence of HPVs in these samples.[130]

2) In Syria: recently Al Moustafa's group investigated the presence of high-risk HPVs and their association with Fascin, Id-1, and P-cadherin genes, which are major regulators of cell invasion and metastasis,[131-133] in human colorectal cancers in the Syrian population. In this study, the authors used PCR and tissue microarray analysis to explore the presence of HPV and E6 expression, respectively, in a cohort of 78 cancer tissues. This study revealed that high-risk HPVs are present in 42 samples (53.84%), which represent the majority of invasive colorectal cases; the most frequent high-risk HPV types in the Syrian population are 16, 33, 18, 35, and 31 respectively. Furthermore, the expression of E6 onco-protein of high-risk HPVs was found to be correlated with Fascin, Id-1 and P-cadherin expression/overexpression in the majority of cancer tissue samples. Data of this investigation showed, for the first time, that high-risk HPVs are present in human colorectal cancers in the Syrian population and their presence is associated with invasive and metastatic phenotype.[134] On the other hand, the same group has been investigating the role of E6/E7 onco-proteins of high-risk HPVs in human normal colorectal cells; data of this study showed that E6/E7 of HPV type 16 are able to induce cellular transformation and migration of human normal colorectal mesenchymal cells but not epithelial ones; this was accompanied by upregulations of D-type cyclins and Cyclin E as well as Id-1 in these cells.[135]

3) Finally: Three studies explored the presence of HPVs in colorectal cancers in Turkey using PCR analysis; the first one found that high-risk HPVs are present in 46 of 56 colorectal cancer tissues which represent 82.14% of the cases.[136] This study revealed that the most frequent HPVs in colorectal cancers in Turkey are HPV types 18 and 33. The second study was conducted on 43 colorectal cancer tissues, and has reported that 55.8% of these cancer cases are positive for high-risk HPVs especially types 18 and 33.[137] However, the third study was unable to detect the presence of HPVs in 106 colorectal cancer samples from the same country.[138] Based on the Syrian and Turkish studies, it is clear that HPV types 18 and 33 are common in colorectal cancers in this area of the Middle East. Thus, we believe that more investigations are necessary to elicit a clear image about the presence and distribution of high-risk HPVs in colorectal cancers in the greater Middle East.

High-Risk HPVs in Breast Cancer

Breast cancer is the most common malignancy in women worldwide; and metastatic breast disease is a major cause of morbidity and mortality in breast cancer patients. Numerous earlier studies reported that high-risk HPVs are present in approximately 50% of human breast cancers worldwide;[21-23,25,26] controversially a few studies revealed that HPVs HPVs were not detected in breast cancer and normal mammary tissues.[27-29] Moreover, studies reporting HPVs-positive breast cancer tissues revealed that certain types of high-risk HPV infections are linked to specific geographic locations.[5,51] Recently, it was pointed out that the presence of high-risk HPVs especially types 16 and 18, in human breast cancer, is correlated with invasive carcinomas.[24,26,139] Meanwhile, it was demonstrated that E6/E7 onco-proteins of HPV type 16 covert non-invasive and non-metastatic breast cancer cells to invasive and metastatic form.[5,48]

Table 3. The presence of HPVs in colorectal cancers in the greater Middle East

Country	Sample	Cases	HPVs+%	Reference
Israel	Paraffin	106	0.00	Gornick et al.[130]
Syria	Paraffin	78	53.84%	Ghabreau et al.[134]
Turkey	Frozen	56	82.14%	Salepci et al.[136]
	Frozen	43	55.8%	Buyru et al.[137]
	Paraffin	106	0.00	Yavuzer et al.[138]

Therefore and based on these studies, we believe that high-risk HPVs are present and play important roles in human breast carcinogenesis and metastasis; however, the present of these viruses in the populations of the Middle East is limited to few studies from Syria, Turkey, and Tunisia (**Table 4**) which are matched with other investigations worldwide about the presence and absence of these viruses in human breast cancers. Herein, we review these few studies. In order to identify the presence of high-risk HPV in human breast cancer in Syria, Al Moustafa's group investigated the incidence of high-risk HPV types 16, 18, 31, 33, and 35 in a cohort of 113 breast cancer samples from Syrian women by PCR analysis using specific primers for their E6 and/or E7 genes and tissue microarray analysis. This study revealed that 69 (61.06%) of the 113 samples are HPV positive and 24 (34.78%) are co-infected with more than one HPV type; in addition, HPV types 16, 18, and 31 are present in 10, 11, and 8 cancer tissues, respectively. In contrast, 63 and 42 cancer tissues were positive for HPV types 33 and 35, respectively.[24] Therefore, the authors concluded that the most frequent high-risk HPVs in breast cancer in Syrian women are HPV types 33 and 35.

Gumus et al.[140] analyzed 50 breast cancer and normal tissue samples, by PCR, from Turkey for the presence of low-risk HPV type 11 and high-risk HPV types 16, 18, and 33. Thirty-seven malignant breast tissues (74%) were reported positive for HPVs. In addition, 16 normal breast tissue samples (32%) were also shown to be positive. HPV type 18 was detected in 20 of the HPVs–positive malignant tissue samples (54.4%) and in 9 of the HPVs–positive normal tissue samples (56.3%). HPV type 33 was found in 35 (94.6%) of the HPVs–positive cancer tissue samples and in 14 (87.5%) of the HPVs–positive normal tissues.

Finally, Hachana et al.[29] examined the presence of HPVs in a cohort of 123 breast cancer tissues in Tunisian women by PCR analysis. The authors of this investigation failed to detect HPVs in breast cancer in Tunisia.

In conclusion, we believe that HPVs are present in human breast cancer since the majority of the investigations, including 2 from the Middle East, confirmed this fact.[5] On the other hand, 2 recent meta-analysis studies confirmed this conclusion.[141,142] Therefore, we assume that high-risk HPVs are present and could play important roles in the initiation and progression of human breast cancers through E5, E6, and E7 onco-proteins of these viruses,[5,24,48] as it was established in human cervical and HN cancers. Thus, we encourage other colleagues in the Middle East to investigate the presence and distribution of HPVs in breast cancer in their respective countries, which can help in future prevention and treatment of these cancers especially their invasive forms, by HPV vaccines and blocking the expression of HPV-onco-proteins, respectively.

Prevention Strategies of HPVs Infection

It is well know that more than 80% of human adults are liable to HPVs infection during sexual intercourse; and the vast majority (90%) of HPVs-infected people will eliminate these viruses from their bodies within 3 y after the infection.[143] However, persistent infections with high-risk HPVs could initiate cancers such cervical, HN, colorectal, and breast, as mentioned above. More importantly, several recent studies revealed that E5 and E6/E7 onco-proteins of high-risk HPVs could enhance cancer progression to its metastatic form, which is responsible for the majority of cancer related deaths.[3,5,38,48] Therefore, HPVs vaccination is an important step to prevent the initiation of HPV-associated cancers and their metastasis. Accordingly, virus-like particle (VLP)-based vaccines opened a prospective path for the prevention of benign and malignant HPV-related diseases caused by more prevalent HPV types.[145,146] Two prophylactic vaccines against HPVs have been developed. Gardasil® is a quadrivalent vaccine consisting L1 proteins of HPV types 6, 11, 16, and 18. The second one is Cervarix™ which is a bivalent vaccine containing L1 proteins of HPV types 16 and 18. Both preventive vaccines Gardasil® and Cervarix™ are well tolerated and able to generate high titers of neutralizing antibodies against HPV types; however, these vaccines do not cover all high-risk HPVs that cause human cancers.[54,55] They can protect humans against around 70% of the HPV associated cervical cancers. Thus, generating new HPV VLP-based vaccines will be required for protection against a broader range of high-risk HPVs that cause human cancer.[147,148] It is evident that the distribution and presence of high-risk HPVs in human-associated-cancers are related to specific geographic locations worldwide.[5,51] Therefore, it is essential to conduct numerous studies about the presence of high-risk HPVs in their associated cancers to select the best vaccine to prevent HPV infections. In addition, HPV vaccinations are expensive and vaccination programs have not yet been made affordable in low and middle-income countries, which include the majority of the Middle East with some exceptions.[149] For instance, recently the Health Authority of the United Arab Emirates introduced HPV vaccine free of charge for high school girls entering grade 11,[150,151] becoming the first state in the Middle East to do so; however, this decision was not based on any evident studies about the presence and distribution of high-risk HPVs in cervical cancer or any high-risk HPV-related cancers in the UAE population.

Table 4. List of studies regarding the presence of HPVs in human breast cancer in the Middle East and North African countries

Country	Sample	Cases	%HPVs+	Reference
Syria	Paraffin	113	61.06	Akil et al.[24]
Turkey	Frozen	50	74.00	Gumus et al.[140]
Tunisia	Paraffin	123	0.00	Hachana et al.[29]

Although, based on the Syrian and Turkish studies of cervical and breast cancers and the cost of actual HPVs vaccines, we believe that it is necessary for the Middle East population to wait for the new generation of HPVs vaccine. The new generation vaccine is a nonavalent (nine-valent) which is expected to include HPV types 16, 18, 31, 33, 45, 52, and 58 altogether which are implicated in more than 90% of HPV-related cancers, in addition to types 6 and 11.[148,152] This will considerably simplify the calculation of the comparative cost-effectiveness of new generation vaccines, since, to a first approximation, incremental effectiveness will be driven by further reductions in the majority of HPV-related cancers and their progression. However, more extensive studies about the presence of HPVs in human cancers in the Middle East are necessary to prevent HPV-infections through the selection of the right vaccination for the population of this area.

Conclusions and Recommendations for Future Research and HPV Vaccination

In this paper, we have discussed the interrelationship between high-risk HPV infections and their associated cancers including cervical, HN, colorectal, and breast in the Middle East and North Africa. While data of HPVs and their related cancers worldwide are evident, however understanding this topic in the Middle East is still unclear. Thus, it is crucial to incite decision-makers in the Middle East to support cancer research including identification of specific types of onco-viruses related to this region in order to make an informed decision regarding vaccination possibilities for their population. There are many factors that should be considered before the introduction of the existing HPV vaccines in this region, including the incomplete data about the presence and distribution of HPVs in human cancers in the Middle East and cost-effectiveness of the available vaccines as well as the availability of the second generation of HPV vaccine which will be against the 9 most frequent HPV types worldwide.

Options for the prevention of HPV-associated cancers include HPV vaccination and sexual health education, which could also protect people from other sexually transmitted diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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