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Human Papillomavirus Types and Cervical Cancer Vaccine for Sudanese Women: A Review

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Abstract: Cervical cancer is thought to result from different high-risk human papillomavirus (HPV) types. Although many studies have been conducted worldwide regarding HPV infection and its oncogenic properties, limited data are available on the incidence and genotype specific dissemination of HPV in Sudan. The purpose of this review article is to summarize the existing data regarding HPV genotypes in Sudan. To review the distribution of HPV infections, electronic databases (e.g. PubMed, and Google Scholar) were searched for peer reviewed articles in English. The study was performed between January and April of 2019 and comprises a review of six relevant articles that were published prior to 2013. Inclusion criteria included: availability of general population data, cytology and tissue results and the use of polymerase chain reaction (PCR) for HPV detection. The overall infection rate of high-risk HPVs DNA was 173/506 (34%) and within the tissues ranged between 93 and 94% (all the paraffin sections were cancer and precancerous cases). The HPV genotyping in cervical smears were found to range from 2.9% to 50.0%, with the most prevalent types of HPV being 16 (2.9-50.0%), 18 (0-3.4%), 58 (2.9%), and 42 (2.9%). Familiarity of the frequent high risk HPV genotypes found in Sudan, which had a high prevalence of cervical cancer, is essential in order to construct an applicable genotype of the virus in the HPV vaccine. The commercially available vaccines do not prevent infection of the HPV types not contained in the vaccine. Based on this literature, it is clear that the nine-valent HPV vaccine should be considered in Sudan.

Keywords: Human Papilloma Virus Genotypes Vaccine, Cervical Cancer

1. Introduction

Cervical cancer is one of the most common diseases worldwide. The universal prevalence rate of cervical cancer is approximately 11.7%. Among asymptomatic women, the global cervical HPV prevalence rate is estimated to be 10.4% and it differs across geographical sectors, ranging from 6.2% in south-eastern Asia to 31.6% in East Africa, out of which.

Sub-Saharan Africa was found to be the most affected with the highest preponderance rates. In Sudan, cervical cancers are the second most prevalent type of cancer; 90.9% of cancers in Sudan are squamous cell carcinoma, 4.8% are adenocarcinomas, and 4.3% are other epithelial tumors [1]. Viral infections comprise 15-20% of all human cancers and the interaction between a given virus and its correlated cancer ranges from 15-100% [2]. HPV may be co-infected with the human immunodeficiency virus (HIV) and other microorganisms. Co-infections, specifically HIV-HPV infection cause higher HIV reduplication and condition advancement through the activation of cellular mechanisms in the immune system that make cells liable to HIV elevated viral load amount [3]. Most cervical cancers (globally) are due to the human papillomavirus (HPV) infection [4]; HPVs are a large group of viruses, which consist of more than 180 different types, of which, 15 have high oncogenic equity [5]. Infection with HPV can lead to different types of disorders, from benign lesions to cancer. HPV is a DNA virus from the Papillomavirus family. The classification 'high-risk' and 'low-risk' are common and reveal the types that are commonly found in cervical cancers, in contrast to the types that are rarely or never appear in cervical cancers [6]. HPV18 was first described in 1984 by Boshart and his group [7] and is known to be present in a higher proportion of cervical adenocarcinomas than cervical squamous cell carcinomas [8]. HPV is transmitted sexually, and causes a great health

burden in both men and women [9]. Following HPV infection, seropositive men are at an increased risk for developing penile and anal cancer; some studies showed HIV-HPV seropositive individuals are 60% more likely (than healthy individuals) to develop cancer [10]. Additionally, heterosexual HPV-seropositive can transmit HPV into female partners, which increases the risk for cervical cancer [11]. The International Agency for Research on Cancer (IARC) working group classified HPV into 21 types (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73 and 82) that are most prevalent in their association with cervical tumors [12]. However, information regarding HPV infection epidemiology in Sudan is scarce and scattered. Therefore, the purpose of this review article is to summarize the existing data on HPV genotypes in Sudan, provide clarity for future research directions, and to enhance public awareness of HPV infection and HPV-related diseases in Sudan.

2. Materials and Methods

2.1. Design

This study was conducted using a computerized systematic search. The Literature search was performed through a detailed survey of the issued peer reviewed articles on HPV infection and cervical cancer in Sudan with publication dates prior to April 20, 2019 using the following databases: PubMed, Scopus, Web of Science and Google Scholar. The search was completed without language limitation between January and April of 2019. The keywords “HPV”, “Sudan”, “genotype”, and “cervical cancer” were used in the search. This resulted in six relevant articles. Abstracts from these six articles were read to determine relevance to this review. Original articles that were included in this review mentioned at least one specific HPV-related test that was being evaluated. Data were included from international journals and local, non-indexed medical journals and the following inclusion criteria were applied: cervical cytology and paraffin wax embedded tissue results available, use of PCR for viral DNA detection and genotyping. Exclusion criteria included articles that were published before 1990 and articles that described the contribution of HPV infection to oral and other types of cancer. Morbidity was not included. The application of these inclusion/exclusion criteria resulted in six relevant articles on the topic of the review. Of the articles reviewed, one was a report from local non-indexed journals that was published in Egypt: Acad. Journal. Biological. Sciences. The link is provided in the list of references. In general, the information available on HPV prevalence in Sudan is very ambiguous and it became obvious that further research studies are necessary in this field.

2.2. Ethical Consideration

This article is based on published data, and hence, ethical approval was not required.

3. Results

HPV Infection in Sudan - Prevalence and Type Distribution

There have been many studies worldwide regarding the epidemiology of HPV infections and oncogenic properties that result from different HPV genotypes. However, limited data are available regarding HPV prevalence, incidence and genotype specific dissemination in Africa, no data regarding the epidemiology of HPV infections are available for the Sudanese population. There are only a few articles in reference to HPV infections in Sudan that have been published in international peer reviewed journals, although there are several articles in local medical journals. The first article in Sudan that investigated HPV genotyping published in an international journal presented the results of 135 patients in the Omdurman Military Hospital [13], and were tested for (beta)-globin using PCR, as described by Jacobs et al. [14], and Human papilloma virus infections were analyzed using a general primer GP5+/6+ mediated PCR enzyme immune-assay (EIA), also described by Jacobs et al. [14]. of these 135 smears, there were 60.7% ß. globin positive samples indicating DNA integrity. HPV DNA was identified in three samples (2.2%) by gel electrophoresis and was positive in four samples (2.9%) as single and multiple infections by PCR-ELISA. The high risk HPV types (16 and 58) were identified in one sample as a mixed infection. The low risk HPV types (40 and 42) were also found as a mixed infection in another patient. HPV types 58 and 42 were identified in the other two patients. They reported that the HPV genotypes identified were not associated with cancer [13]. The search in the international journals for HPV epidemiology has allowed us to identify the largest study of HPV prevalence (400 samples), which was done in the Khartoum state [15]. The study on HPV prevalence and distribution was performed by analyzing prospective cervical smears taken from women attending different hospitals in Khartoum State during the period between July of 2008 and July of 2009. Isolated DNA from cervical scrapes was subjected to PCR of each GP5 (sequence 5" to 3": TTT GTT ACT GTG GTA GAT ACT AC), and GP6 (sequence 5" to 3": GAA AAA TAA ACT GTA AAT CAT ATT C) primers using a PCR processor (PE9600; PerkinElmer) [15]. HPV DNA was found in 144 samples (36.0%) that showed a product that was typical in size (150 bp), as indicated by the standard DNA marker 5. HPV was detected at a high ratio among patients with cervical intraepithelial neoplasia 29/30 (96.7%). Although, that study did not assess the different genotypes of HPV. Another study used cervical smears to investigate 40 cases. HRHPV 16 and 18 were identified in 16/40 (40%) of the cervical tissues and of these, 8/16 (50%) were positive for HPV 16, 6/16 (37.5%) were positive for HR-HPV 18, and 2/16 (12.5%) were positive for both HR-HPV subtypes. PCR was used for these detections [16]. In 2013, Sahar studied human papilloma virus infection among 106 cervical smears. HR-HPV DNA was detected in 29/106 (27.4%) patients using *in situ* hybridization. Using the GenPoint Kit (#K 0620; DAKO) according to the manufacturer's instructions, the risk associated with high risk

HPV infection was found to be statistically significant [17]. Ebba Abate genotyped the Human Papillomavirus in paraffin embedded cervical tissue samples from women in Ethiopia and Sudan, and included 86 paraffin embedded tissues. PCR was used for DNA detection and 98% (85/86) of the samples were positive for the housekeeping gene, Beta-globin. Probable HR-HPV, the overall HPV DNA was 94% (80/85) Include 17 different HPV genotypes [18]. Huda investigated cervical and oral screening for HR-HPV types 16 and 18 among Sudanese women with cervical lesions. They detected HPV DNA in 93.6% (73/78) of the cancer samples, sixty tumor samples harbored HPV genotype 18. Single infection with this genotype was found in 40 samples (51.3%), while mixed infection was detected in 20 samples (25.6%). The HPV genotype 16 was found in 33 tumor samples. Single infection with this genotype appeared in 13 patients (16.7%), while 20 samples (25.6%) had mixed infections [19].

4. Discussion

The HPV DNA in Sudan was detected in cervical smears and tissue-based HPV genotyping studies of cervical cancer 681 (80.6%) and 164 (19.4%), respectively. Within the cervical smears, the overall infection rate of high-risk HPVs DNA was found to be 173/506 (34%) and within the tissues ranging from 93% to 94% as all the paraffin sections were cancer and precancerous cases. The HPV genotyping in cervical smears were found to range from 2.9% to 50.0%, with the most prevalent types of HPV being 16 (2.9-50.0%), 18 (0-3.4%), 58 (2.9%), and 42 (2.9%). The genotypes within the paraffin section (with the most common HPV genotypes) were 16 (60.4%), and 18 (34.1%). High rates of HPV infection was detected in premalignant conditions. This finding supports the importance of early diagnosis and treatment that can be made on the basis of cytology and confirmed with histopathology. In addition, the results of these studies strengthen the need for the detection of high risk HPV as a screening method for early detection of precancerous stages. Human papillomavirus 16 was the most numerous genotypes identified from all the HPV positive cervical smears and tissue sections. This genotype was also the most persistent in all cancerous and precancerous conditions. The prevalence of HPV 16 over the other genotypes (among these studies) is in agreement with previous reports from different geographical areas [20, 21, 22]. Few studies have been conducted in Africa to assess the distribution of HPV genotypes (HPV 58 was common in the current studies). However, HPV 58 is considered a rare type, and is not commonly reported in most of Europe. However, in Africa, this type has been observed in the east, central, west and in South Africa [23]. This finding could reflect international differences in the distribution of HPV. A high preponderance of high risks for HPV 16, 18 and 58 were determined with the different samples. HPV 16, 18 and 58 were revealed in cervical smear and paraffin blocks 6.8.% (12/175) vs. 42% (99/164), 3.4% (6/175) vs. 34.1% (56/164) and 2.9% (4/135) vs. 15% (12/80) of all HPV positive samples, respectively. Studies have shown that 58 was recorded as the most common HPV genotype in Latin America, East Asia and for Chinese women with cervical pathology [24]. The prevalence of multiple infections reported in two studies that were done on cervical smears and paraffin embedded tissue blocks were found to be due to the high sensitivity of the detection method used. One advantage of the probe based assay is the possibility to easily discriminate heterogeneous PCR groups, which cannot be differentiated by other hybridization methods used for genotyping general PCR products. This may indicate that the incidence of multiple infections may be underestimated in many other studies. However, the scheme with epidemiology of HPV and its relation to cervical cancers in Sudan is not very clear. Recent statistical data regarding cervical cancers epidemiology in Sudan are unsettled. Cervical cancer is appraised to be second, after breast cancer among Sudanese women, and a recent survey from the National Health Laboratory in Sudan illustrate that each year, around 833 Sudanese women are analyzed with cervical cancer (estimated age standardized incidence: 7.9 per 100,000 per year, supplementary, around 534 die from this disease [25]. Studies from Africa, Asia, and South America revealed that the highest reported age standardized incidence rate were found to be 17.9/100,000/year in Zimbabwe and the lowest is 0.11/100,000/year in China. The highest reported age standardized mortality rate was found to be 16/100,000/year in India in 2015, and the lowest: 1.8/100,000/year in Colombia [26]. In comparison to the developed countries of Europe and North America, where the age-standardized incidence of cervical cancer is less than 9% [27], Sudan's statistical data reveals depressing indicators. This imbalance is attributed primarily to the effective and successful implementation of organized cervical cancer screening programs in developed countries, which lead to early detection and appropriate management of precancerous lesions [28].

5. Conclusion

Familiarity with the frequent high risk HPV genotypes found in Sudan that have a high prevalence of cervical cancer is essential in order to construct an applicable genotype of the virus in the HPV vaccine. Presently, three prophylactic HPV vaccines are commercially usable. Gardasil and Cervarix, which is a bivalent vaccine accepted for the avoidance of cervical cancer and precancerous lesions caused by HPV 16 and 18 in young females. Gardasil is a quadrivalent vaccine anti-HPV types 6, 11, 16, and 18 [29], and the nine-valent HPV vaccine developed recently to provide protection against HPV types 6, 11, 16, and 18; and is already covered by the Gardasil and the next five most common oncogenic types associated with cervical cancer worldwide (types 31, 33, 45, 52, and 58) [30]. However, the current vaccines do not prevent infection with the HPV types that are not contained in the vaccine. Thus, the data of the present studies are crucial for the confirmation of the most suitable vaccines in an area without much information regarding the HPV disease, like Sudan. From the review given here, it is clear that other HPV

genotypes like HPV 58 should be considered in Sudan. This review provides useful information for future HPV genotyping research and vaccinations for cervical cancer in Sudan. But more importantly, this work reveals the substantial need for further studies on cervical cancer and associated risk factors in Sudan.

6. Limitations

Our study is limited to PubMed, Web of Science and Google Scholar. Thus, it may not cover all the studies conducted in this field; particularly those non-published data or data published in non-indexed local journals, and open access platforms not covered by Google Scholar, PubMed and Scopus. Moreover, we did not assess the publication bias of the articles, as it is not relevant in the context of cervical cancer, HPV DNA or genotypes studies. It is possible that there is considerable under reporting in HPV DNA, genotyping or cervical cancer in our study, particularly since the capacity for cancer diagnoses and data capture is limited in Sudan.

Table 1. *Studies on Cervical Human Papilloma Virus Genotypes Percentage and Detection Methods.*

Study/ year	Sample size	Detection method used	Types N (%)
(Salih et al., 2010)	135 Cervical smear	PCR, There were 60.7% ß. globin positive samples	HRHPV16 4/135 (2.9%) HRHPV58 4/135 (2.9%) LRHPV40 2/135 (1.4%) LRHPV42 4/135 (2.9%)
(Elasbali et al., 2012	40 Cervical smear	PCR	HRHPV 16 8/16 (50%), HRHPV 18 6/16 (37.5%) Mixed 16, 18 2/16 (12.5%)
Mansour et al. 2013	400 Cervical smears	PCR	HR-HPV DNA 144/400 (36.0%)
Gafar et al., 2013	106 Cervical smears	In Situ hybridization (ISH) techniques	HR-HPV DNA 29/106 (27.3%)
Abate et al., 2013	86 paraffin embedded	PCR 98% (85/86) of sample were positive for Housekeeping gene (b-globin) Probable HR-HPV genotype.	HRHPV 16 66/80 (82.5%), HRHPV 18 16/80 (20.0%) HRHPV 31 5/80 (6.2%) HRHPV 33 10/80 (12.5%) HRHPV 35 8/80 (10%) HRHPV 39 3/80 (3.7%) HRHPV 45 14/80 (17.5%) HRHPV 52 2/80 (2.5%) HRHPV 53 5/80 (6.2%) HRHPV 58 12/80 (15%) HRHPV 59 1/80 (1.2%) HRHPV 68 8/80 (10%) HRHPV 39/68 2/80 (2.5%) HRHPV 56/74 2/80 (2.5%) LRHPV 6 8/80 (10%) LRHPV 44 1/80 (1.2%) LRHPV 74 1/80 (1.2%)
(Eltahir, Elhassan and Ibrahim, 2012	78 paraffin section	PCR	HRHPV16 33/78 (42. 3%). HRHPV18 40/78 (51.3%).
Type of specimen Cervical smear Paraffin section Total	 681 (80.6%) 164 (19.4%) 845 (100%)		Cervical smear HPV DNA 173/506 (34%) HRHPV16 69 (8.16%), HRHPV18 86 (10.17%), HRHPV58 4 (0.47%) LRHPV40 2 (0.23%) LRHPV42 4 (0.47%))

Abbreviation

HPV: Human papilloma virus. HR: High risks. LR: Low risk. PCR: polymerase chain reaction. DNA: Deoxyribonucleic acids. N: number.

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