A Meta-Analysis on Human Papillomavirus Type Distribution among Women with Cervical Neoplasia in the WHO Eastern Mediterranean Region

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Keywords

Human papillomavirus · Cervical cancer · Atypical squamous cells of undetermined significance · Cervical intraepithelial neoplasia · Vaccines · HPV type · Eastern Mediterranean Region (EMRO)

Abstract

Introduction: To date, the human papillomavirus (HPV) vaccine has not been integrated into the national vaccination program of most countries of the WHO Eastern Mediterranean Region (EMRO), except for the United Arab Emirates and Libya. The knowledge of HPV genotype distribution in cervical neoplasia is valuable to predict the impact of current HPV vaccines on cancer prevention and can help the health policymakers to select the most appropriate vaccine types in their countries. **Methods:** Hence, this meta-analysis recapitulates all available data on HPV prevalence and genotypes in women with atypical squamous cells of undetermined significance (ASCUS), cervical intraepithelial neoplasia (CIN) I–III or low- and high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively), and invasive cervical cancer (ICC) in EMRO countries. **Results:** The meta-analysis included 5,990 cases of cervical precancer and cancer. The overall HPV prevalence was 85.4, 71.3, 59.2, and 34.8% in women with ICC, CIN II–III or HSIL, CIN I or LSIL, and ASCUS, respectively. HPV 16 was the most common genotype followed by HPV

18, representing 58 and 16.5% in ICC cases, respectively. **Conclusion:** This meta-analysis showed that the introduction of current HPV vaccines into national vaccination programs and the establishment of comprehensive screening programs in EMRO countries is beneficial by preventing 74.5% of cervical neoplasia.

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Introduction

Global cancer statistics (GLOBOCAN 2018 produced by the International Agency for Research on Cancer [IARC]) reported that cervical cancer is the fourth most frequent cancer in the world, with 569,847 new cases and 311,365 deaths in 2018 [1]. It is estimated that the age-standardized incidence rate and mortality rate of cervical cancer in the WHO Eastern Mediterranean Region (EMRO) are 6.4 and 3.6 per 100,000 females, respectively [2].

Infection with the human papillomavirus (HPV) is common in women, and most of these infections are cleared by the immune system within 6–12 months after infection [3–5]. In a minority of cases, HPV evades the

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immune system and the virus establishes a persistent infection which causes cell abnormalities, eventually progressing to cervical intraepithelial neoplasia (CIN) type III and/or invasive cervical cancer (ICC) [6, 7].

HPVs are classified in four risk categories (1, 2A, 2B, and 3) on the basis of their epidemiological association with cervical cancer: categories 1 and 2A have been defined as carcinogenic and probably carcinogenic and include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73, respectively. Category 2B comprises types that are possibly carcinogenic on account of their close phylogenetic relationship with the well-known carcinogenic types. Category 3 contains noncarcinogenic types such as HPV 6 and 11 [3, 8].

Currently, three prophylactic HPV vaccines (Cervarix[®], Gardasil[®], and Gardasil[®] 9) are available [9]. Globally, it is estimated that HPV 16 and 18 account for almost 70% of ICC [10], thus Cervarix[®] and Gardasil[®] vaccines that include these two HPV types can prevent up to 70% of cervical cancer cases in the world. In addition, the nonavalent HPV vaccine (Gardasil[®] 9), comprising HPV 6, 11, 16, and 18 as well as HPV 31, 33, 45, 52, and 58, elevates the prevention rate of cervical cancer to around 90% [9, 11, 12].

To date, the HPV vaccine has not been integrated into the national vaccination program of most countries of EMRO, except for the United Arab Emirates and Libya [13]. Knowing about the distribution of HPV types is valuable to predict the impact of current HPV vaccines on the prevention of cervical cancer and can help the health policymaker to decide on which vaccine is more beneficial in their countries.

Hence, this meta-analysis recapitulates all available data on HPV prevalence and genotypes in women with atypical squamous cells of undetermined significance (ASCUS), CIN I–III or low- and high-grade squamous intraepithelial lesion (LSIL and HSIL, respectively), and ICC in EMRO countries. As mentioned above, the results of the present study can help the health policymakers to make a decision on the introduction of HPV vaccines in their national vaccination program in this region.

Methods

Search Strategy

Four databases including Web of Science, Medline (PubMed), Scopus, and EMBASE were systematically searched to find all studies on HPV prevalence in women with ASCUS, CIN I–III or LSIL and HSIL, and ICC in countries of EMRO up to March 2018. A combination of subsequent MeSH terms, including “Papilloma-

viridae,” “Human,” “Prevalence” OR “Epidemiology,” “Cervix Uteri,” “Female,” “Polymerase Chain Reaction,” and “Name of each Countries in EMRO” were used to search the literature. Figure 1 shows the flowchart of exclusion criteria to select relevant studies for this meta-analysis. As shown in Figure 1, 62 studies were selected. The inclusion criteria were as follows: the possibility of splitting HPV prevalence data for women with different histological/cytological types, use of molecular assays to detect HPV DNA, and performing HPV typing.

Data Extraction

The extraction of data was done by two independent reviewers (M.F. and S.J.). If there was a discrepancy, it was solved by consulting with other members of our team to reach a consensus.

The following information was obtained from each study: first author, name of journal, year of publication, country, study period, sample size, PCR primers, HPV prevalence, prevalence of HPV multiple infection, HPV typing method, and HPV types. Altogether, 946 papers were evaluated, from which 62 articles satisfied the inclusion criteria and were included in this meta-analysis [14–75] (Fig. 1).

Statistical Analysis

The R version 3.5.1 (2018-07-02) package “meta” [76] was used to analyze the data. The inverse variance approach, based on a random effects model (DerSimonian-Laird weights method), was applied to calculate the proportion of pooled HPV [77]. To stabilize the variation of proportions, logit transformation was used. The confidence interval (CI) for individual studies was calculated by the Clopper-Pearson method [78]. Continuity correction of 0.5 was used in studies with zero cell frequencies. Using the I^2 test, statistical heterogeneity was measured and p values less than 0.01 were considered statistically significant.

Results

We conducted this meta-analysis to evaluate HPV prevalence and genotype distribution in women with ASCUS ($n = 831$), CIN I or LSIL ($n = 693$), CIN II–III or HSIL ($n = 547$), and ICC ($n = 3,919$) in 15 countries of EMRO. As indicated in Tables 1 and 2, most samples were from EMRO Asian countries, among which Iran has the largest study samples.

In Table 3, HPV prevalence in women with ICC in EMRO was stratified by country and histological type. The overall HPV prevalence was 85.4% (95% CI: 80.9–88.9%) in this region. Nevertheless, the HPV DNA detection rate was higher in African countries (88.2%) than Asian countries (83.8%) of EMRO.

The HPV prevalence rates among women with CIN I/LSIL and CIN II–III/HSIL were estimated to be 59.2% (48.9–68.9%) and 71.3% (64–77.6%), respectively. In Asian countries, HPV was detected in 62.1 and 70.5% of CIN I/LSIL and CIN II–III/HSIL, respectively. In African

Fig. 1. Flowchart of the systematic literature search on HPV infection among women with cell abnormalities and cancer of the cervix in the Eastern Mediterranean Region (EMRO).

countries, HPV prevalence was 54.4% in women with CIN I/LSIL and 73.4% in those with CIN II–III/. Interestingly, a higher rate of HPV positivity was found in Asian women than in African women (Table 4).

As shown in Table 4, the HPV prevalence was 34.8% (24.1–47.3%) in women with ASCUS lesions. A difference was observed regarding the HPV prevalence in Asian versus African women. Indeed, HPV was detected in 41% of Asian women and 7.4% of African women.

The HPV DNA detection rate was higher in fresh samples compared to formalin-fixed paraffin-embedded samples in ICC and CIN I/LSIL (Fig. 2).

Multiple HPV infections were observed in 12.2% of ICC cases (Fig. 3). As shown in Table 5, the rates of multiple HPV infections were 9.3 and 17% in Asian and African women, respectively. The multiple HPV infection rates were 13.5, 24.8, and 10.5% in women with CIN II–III/HSIL, CIN I/LSIL, and ASCUS, respectively (Table

6). Among all studied groups, the highest rate of multiple infections was found in women with CIN I/LSIL lesions.

In ICC cases, the ten most common viral genotypes in descending order were HPV 16, 18, 45, 31, 33, 35, 6/11, 58, 52, and 59, followed by HPV 39, 66, 68, 56, 73, 51, and 53 (Table 5). HPV 16 was the most common type in all countries followed by HPV 18. HPV 16 and 18 accounted for 74.5% of women with cervical cancer. However, HPV 16 and 18 was more frequent in African women with ICC (83.3%) compared to Asian women with ICC (70.8%). According to histological type of ICC, the ten most frequent HPV types in descending order were as follows: HPV 16, 18, 45, 31, 35, 6/11, 58, 33, 59, and 52 in squamous cell carcinoma (SCC) and HPV 16, 18, 45, 35, 58, 31, 6/11, 33, 52, and 53 in adenocarcinoma (ADC). As shown in Figure 4, HPV 18 was more prevalent among women with ADC (33.5%) than SCC cases (18.7%). On

Table 1. Distribution of studies on invasive cervical cancer in the WHO Eastern Mediterranean Region (EMRO), by country

Region	Studies, <i>n</i>	Countries represented	Cases, <i>n</i>	ICC cases by histological type					
				SCC		ADC		unspecified	
				<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
African countries of EMRO (<i>n</i> = 5)	14		1,112	642	57.8	44	3.9	426	38.3
	3	Egypt	100	16	16.0	4	4.0	80	80.0
	1	Libya	67	–	–	–	–	67	100.0
	5	Morocco	563	433	77.0	25	4.4	105	18.6
	1	Sudan	84	78	92.8	6	7.2	–	–
	4	Tunisia	298	115	38.6	9	3.0	174	58.4
Asian countries of EMRO (<i>n</i> = 8)	35		2,807	1,390	49.5	148	5.3	1,269	45.2
	1	Bahrain	50	–	–	–	–	50	100.0
	2	Jordan	119	40	33.6	1	0.8	78	65.6
	17	Iran	1,111	889	80.0	60	5.4	162	14.6
	1	Kuwait	7	–	–	–	–	7	100.0
	6	Pakistan	611	77	12.6	23	3.7	511	83.7
	4	Saudi Arabia	503	83	16.5	7	1.4	413	82.1
	2	Syria	157	97	61.8	16	10.2	44	28.0
	2	Yemen	249	204	81.9	41	16.5	4	1.6
Total (<i>n</i> = 13)	49		3,919	2,032	51.9	192	4.9	1,695	43.2

ICC, invasive cervical cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

Table 2. Distribution of studies on abnormal cervical histology/cytology in the WHO Eastern Mediterranean Region (EMRO), by country

Region	Studies, <i>n</i>	Countries represented	Cases, <i>n</i>	Cases by histological/cytological type, <i>n</i>		
				ASCUS	CIN I (LSIL)	CIN II–III (HSIL)
African countries of EMRO (<i>n</i> = 3)	13		518	61	196	261
	6	Egypt	166	5	19	142
	4	Morocco	162	46	86	30
	3	Tunisia	190	10	91	89
Asian countries of EMRO (<i>n</i> = 8)	21		1,553	770	497	286
	1	Jordan	46	–	18	28
	11	Iran	701	158	360	183
	1	Kuwait	258	175	71	12
	4	Pakistan	57	19	12	26
	1	Saudi Arabia	134	134	–	–
	1	Qatar	62	33	21	8
	1	Yemen	44	–	15	29
	1	UAE	251	251	–	–
Total (<i>n</i> = 11)	34		2,071	831	693	547

ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 3. Meta-analysis of HPV prevalence in women with invasive cervical cancer in the WHO Eastern Mediterranean Region (EMRO), by country and histological type

Region	Countries represented	Cases, <i>n</i>	HPV prevalence, %	95% CI	HPV prevalence by histological type, <i>n</i> (%)		
					SCC	ADC	unspecified
African countries of EMRO (<i>n</i> = 5)		1,112	88.2	82.6–92.2	594 (59.4)	38 (3.8)	357 (36.8)
	Egypt	100	79.3	60.9–90.4	11 (14.1)	4 (5.2)	63 (80.7)
	Libya	67	94.0	85.1–97.7	–	–	63 (100)
	Morocco	563	89.3	79.6–94.7	399 (79.8)	23 (4.6)	78 (15.6)
	Sudan	84	95.2	88.0–98.2	74 (92.5)	6 (7.5)	–
	Tunisia	298	86.9	73.3–94.1	110 (41)	5 (1.9)	153 (57.1)
Asian countries of EMRO (<i>n</i> = 8)		2,807	83.8	78–88.3	983 (44.8)	113 (5.1)	1,098 (50.1)
	Bahrain	50	60.0	46.0–72.5	–	–	30 (100)
	Jordan	119	99.9	94.1–99.9	40 (33.6)	1 (0.9)	78 (65.5)
	Iran	1,111	79.4	70.6–86.1	632 (76.4)	44 (5.3)	151 (18.3)
	Kuwait	7	85.7	41.9–98.0	–	–	6 (100)
	Pakistan	611	91.7	86.7–94.9	75 (13.5)	22 (4.0)	457 (82.5)
	Saudi Arabia	503	86.3	76.7–92.4	80 (19.1)	6 (1.4)	334 (79.5)
	Syria	157	87.4	60.2–97.9	70 (55.6)	14 (11.1)	42 (33.3)
	Yemen	249	49.6	12.2–87.4	86 (76.8)	26 (23.2)	–
Total (<i>n</i> = 13)		3,919	85.4	80.9–88.9	1,576 (49.5)	151 (4.7)	1,455 (45.8)

CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

Table 4. Meta-analysis of HPV prevalence in women with abnormal cervical histology/cytology in the WHO Eastern Mediterranean Region (EMRO), by country

Region	Countries represented	HPV prevalence, %					
		ASCUS	95% CI	CIN I (LSIL)	95% CI	CIN II–III (HSIL)	95% CI
African countries of EMRO (<i>n</i> = 3)		7.4	2.9–17.2	54.4	39.1–68.9	73.4	63.0–81.6
	Egypt	0.0	–	45.3	14.1–80.7	70.8	49.6–85.6
	Morocco	6.5	2.1–18.4	44.3	22.6–68.4	68.7	44–85.9
	Tunisia	10.0	1.4–46.7	69.3	48.0–84.7	79.7	70.1–86.8
Asian countries of EMRO (<i>n</i> = 8)		41	28.9–54.4	62.1	48.4–74.1	70.5	59.9–79.3
	Jordan	–	–	72.2	48.1–87.9	78.6	59.8–90
	Iran	55.2	34.2–74.6	58.5	42.5–72.9	68.8	51.7–82
	Kuwait	34.3	27.6–41.6	88.7	79.1–94.3	66.7	37.6–86.9
	Pakistan	21.0	8.1–44.6	63.0	11.4–95.7	85.7	65.5–94.9
	Saudi Arabia	20.1	14.2–27.8	–	–	–	–
	Qatar	54.5	37.7–70.4	85.7	63.9–95.3	50.0	20.0–80.0
	Yemen	–	–	20.0	6.6–47	69.0	50.3–83
	UAE	17.9	13.7–23.2	–	–	–	–
Total (<i>n</i> = 11)		34.8	24.1–47.3	59.2	48.9–68.9	71.3	64.0–77.6

CI, confidence interval; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Fig. 2. HPV prevalence among women with cell abnormalities and cancer of the cervix in the Eastern Mediterranean Region (EMRO), stratified by type of sample.

Fig. 3. Frequency of multiple HPV infections among women with cell abnormalities and cancer of the cervix in the Eastern Mediterranean Region (EMRO).

Fig. 4. Distribution of HPV types in women with invasive cervical cancer in the Eastern Mediterranean Region (EMRO), stratified by histological type.

the contrary, HPV 16 was more common in women with SCC (56.3%) than ADC cases (47%).

The ten most common HPV types in descending order among women with CIN II-III/HSIL were HPV 16, 18, 31, 6/11, 33, 45, 35, 53, 66, and 56, while in the CIN I/LSIL group the most common types were HPV 16, 6/11, 18, 52, 56, 53, 39, 31, and 40. In women with ASCUS, the ten most frequent HPV types were 16, 6/11, 51, 68, 18, 59, 73, 66, 56, and 53 (Table 6).

Discussion

The pooled data of 60 studies, including 5,990 women with a diagnosis of CIN or ICC in different geographical regions of EMRO, allowed us to estimate systematically the HPV prevalence and genotype distribution in this region.

The overall HPV prevalence was found to be 85.4% (95% CI: 80.9–88.9%) among women with ICC in EMRO. It has been shown that HPV was detected in almost 100%

Table 5. Distribution of HPV types in women with invasive cervical cancer in the WHO Eastern Mediterranean Region (EMRO)

HPV type	Overall		Asian countries of EMRO		African countries of EMRO	
	N ¹	n (%)	N ¹	n (%)	N ¹	n (%)
Any	3,919	3,184 (81.2)	2,807	2,195 (78.2)	1,112	989 (88.9)
Single	2,345	2,059 (87.8)	1,469	1,332 (90.7)	876	727 (83)
Multiple	2,345	286 (12.2)	1,469	137 (9.3)	876	149 (17)
16	3,767	2,185 (58.0)	2,656	1,478 (55.6)	1,112	707 (63.6)
18	3,719	615 (16.5)	2,607	396 (15.2)	1,112	219 (19.7)
31	2,685	106 (3.9)	1,747	81 (4.6)	938	25 (2.7)
33	2,530	79 (3.1)	1,592	48 (3)	938	31 (3.3)
35	2,138	62 (2.9)	1,437	26 (1.8)	701	36 (5.1)
39	2,113	27 (1.3)	1,397	23 (1.6)	716	4 (0.56)
45	2,427	181 (7.4)	1,598	109 (6.8)	829	72 (8.7)
51	1,914	13 (0.67)	1,287	13 (1)	627	0 (0.0)
52	1,914	37 (1.9)	1,287	23 (1.8)	627	14 (2.2)
56	1,914	19 (0.99)	1,243	14 (1.1)	627	5 (0.8)
58	1,914	42 (2.2)	1,287	21 (1.6)	627	21 (3.3)
59	2,072	34 (1.6)	1,243	13 (1)	811	21 (2.8)
68	1,827	17 (0.93)	1,202	3 (0.25)	627	14 (2.2)
73	1,827	15 (0.82)	1,202	7 (0.6)	645	8 (1.2)
6/11	1,997	59 (2.9)	1,365	50 (3.7)	632	9 (1.4)
53	1,701	7 (0.4)	1,124	2 (0.2)	577	5 (8.7)
66	1,741	17 (0.97)	1,164	3 (0.25)	577	14 (2.4)

¹ N, number of cases tested for the given HPV type.

of ICC cases using highly sensitive molecular assays [79]. In this study, the lower detection rate of HPV in ICC cases is probably attributable to certain factors, such as the type of sample (fresh-frozen biopsies or formalin-fixed paraffin-embedded tissues) [80], as HPV was detected at a higher rate in fresh-frozen biopsies (92.6%) than in formalin-fixed paraffin-embedded tissues (79.5%).

The HPV prevalence was estimated to be 71.3% (64–77.6%) and 59.2% (48.9–68.9%) among women with CIN II–III/HSIL and CIN I/LSIL, respectively. Analyzing both groups, the HPV prevalence was found to be different between countries due to the use of less sensitive methods to detect HPV DNA, type of sample, and sample size. The HPV prevalence in women with CIN II–III/HSIL was lower than that in some previous studies that had detected HPV DNA in more than 90% of cases [51, 81].

In women with ASCUS lesions, HPV was detected in 34.8% (24.1–47.3%); however, HPV was detected more commonly in Asian than in African women (41% vs. 7.4%). It has been shown that one of the most important factors affecting the frequency of HPV in this lesion is age [82, 83]. It has been indicated that HPV prevalence was 78% in the 18- to 24-year-old group and 32% in women

over 35 years of age [84]. As a result, it is likely that this discrepancy observed in Asian and African women is due to the age difference of the studied groups. Moreover, it is possible that using less sensitive methods to detect HPV DNA and small sample size are responsible for this inconsistency.

The highest rate of multiple HPV infections was found in women with CIN I/LSIL lesions (24.8%). It has been shown that multiple HPV infections are common, particularly in low-grade lesions [85–88]. While the impact of multiple HPV infections on cancer development is still inconclusive, it is supposed that multiple HPV infections are a significant risk factor for high-risk cervical lesions. Indeed, it has been shown that multiple infections with two or more high-risk HPV infections can increase the risk of moderate/severe dysplasia or cancer development [85].

In this study, HPV 16 and 18 account for 74.5% of women with ICC. This result is in accordance with a previous meta-analysis that reported 72.6% of ICC cases as attributable to HPV 16 and 18 [89]. In the present study, however, the frequency of HPV 16 and 18 was higher in African women with ICC (83.3%) compared to Asian

Table 6. Distribution of HPV types in women with abnormal cervical histology/cytology in the WHO Eastern Mediterranean Region (EMRO)

HPV type	Cervical histology/cytology					
	ASCUS		CIN I or LSIL		CIN II–III or HSIL	
	N ¹	n (%)	N ¹	n (%)	N ¹	n (%)
Any	831	243 (29.2)	693	436 (62.9)	547	427 (78.1)
Single	440	394 (89.5)	476	358 (75.2)	245	212 (86.5)
Multiple	440	46 (10.5)	476	118 (24.8)	245	33 (13.5)
16	798	68 (8.5)	693	207 (29.9)	539	232 (43)
18	798	33 (4.1)	682	69 (10.1)	539	73 (13.5)
31	613	11 (1.8)	506	17 (3.3)	428	37 (8.6)
33	613	11 (1.8)	506	10 (1.9)	428	23 (5.4)
35	613	8 (1.3)	435	3 (0.7)	335	9 (2.7)
39	512	4 (0.8)	430	14 (3.2)	294	2 (0.07)
45	613	11 (1.8)	430	7 (1.6)	294	10 (3.4)
51	613	4 (6.5)	411	2 (0.5)	335	2 (0.6)
52	569	9 (1.6)	432	23 (5.3)	290	3 (1.0)
56	569	14 (2.5)	432	22 (5.1)	335	5 (1.5)
58	613	5 (0.8)	411	16 (1.4)	335	4 (1.2)
59	613	2 (3.2)	411	1 (0.2)	219	0 (0.0)
68	613	4 (6.5)	393	9 (2.3)	219	0 (0.0)
73	613	2 (3.2)	393	7 (1.8)	219	0 (0.0)
6/11	317	29 (9.1)	495	97 (19.6)	282	17 (6.0)
40	–	–	65	2 (3.1)	–	–
42	–	–	198	12 (6.1)	–	–
43	292	2 (0.7)	–	–	–	–
44	–	–	198	6 (3.0)	–	–
53	271	7 (2.5)	432	22 (5.1)	169	4 (2.4)
54	271	1 (0.4)	220	4 (1.8)	169	1 (0.6)
61	–	–	170	5 (2.9)	–	–
62	220	3 (1.4)	170	1 (0.6)	–	–
66	271	8 (2.9)	393	16 (1.5)	169	3 (1.8)
67	220	1 (0.4)	170	1 (0.6)	–	–
69	–	–	80	4 (5)	–	–
70	–	–	250	3 (1.2)	–	–
74	–	–	250	2 (0.8)	–	–
81	271	6 (2.2)	220	7 (3.2)	–	–
82	–	–	393	1 (0.25)	–	–
84	292	1 (0.3)	–	–	–	–
87	271	1 (0.4)	–	–	–	–
90	271	3 (1.1)	170	2 (1.2)	–	–
102	–	–	170	1 (0.6)	–	–
106	220	1 (0.4)	170	2 (1.2)	–	–
108	271	1 (0.4)	–	–	–	–

¹ N, number of cases tested for the given HPV type.

women with ICC (70.8%). These data mean that Cervarix[®] can prevent from 70 to 83% of ICC cases in this region. The estimated reduction rate of ICC using the non-valent HPV vaccine (Gardasil[®] 9) is around 94%.

Interestingly, HPV 18 was more prevalent among women with ADC (33.5%) than SCC cases (18.7%). In contrast,

HPV 16 was more common in women with SCC (56.3%) than ADC cases (47%). Many studies throughout the world have shown that HPV 18 is more common in ADC than SCC of the cervix [82, 89–92]. Indeed, the data of one study in Italy have shown that the frequency of HPV 18 is 8.7 and 23.3% in SCC and ADC cases, respectively [91].

In women with CIN II–III/HSIL, HPV 16 was the most frequent type detected in more than half of HPV-positive cases, followed by HPV 18, 31, 6/11, 33, 45, 35, 53, 66, and 56. The observed frequency of HPV 16 and 18 (56.5%) was in line with the study by Hariri et al. [81] that detected these two HPV types in 55.5% of women with HSIL lesions.

In the CIN I/LSIL and ASCUS groups, HPV 16 and 6/11 was dominant, followed by HPV 18, 52, 56, 53, 39, 31, and 40 in CIN I/LSIL cases and HPV 51, 68, 18, 59, 73, 66, 56, and 53 in women with ASCUS.

Remarkably, HPV 6/11 was more prevalent in all studied groups compared to most studies in the world [93]. Therefore, it is tempting to speculate the presence of specific HPV 6/11 variants with higher carcinogenic potential distributed in this region, particularly in Asian countries of EMRO.

In conclusion, HPV 16 was the most common type in all studied groups followed by HPV 18 in ICC and CIN II–III or HSIL patients and HPV 6/11 in CIN I or LSIL and ASCUS cases. This meta-analysis had shown that the

integration of current HPV vaccines into national vaccination programs of EMRO countries is beneficial. Furthermore, it is mandatory to plan for establishing comprehensive screening programs in this region to reduce the burden of cervical cancer.

Statement of Ethics

As this is a meta-analysis there are not ethical conflicts to declare.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

S.J. designed the study. M.F. and N.H. searched and extracted the data. M.F. performed the statistical analysis. S.J. and Z.S. prepared the manuscript.

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