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Review

A meta-analysis of human papillomavirus type-distribution in women from South Asia: Implications for vaccination

Neerja Bhatla[a,*], Neena Lal[a], Yan-Ping Bao[b], Timothy Ng[c], You-Lin Qiao[b]

[a] Department of Obstetrics & Gynaecology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
[b] Department of Cancer Epidemiology, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China
[c] GlaxoSmithKline Biologicals, Rixensart, Belgium

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ABSTRACT

Objective: To determine human papillomavirus (HPV) prevalence and type-distribution in women from South Asia, with and without cervical lesions, in order to estimate the impact of an HPV 16/18 prophylactic vaccine in this region and to assess additional types that should be incorporated in new vaccines.
Methods: A meta-analysis was conducted that included studies using polymerase chain reaction to detect HPV-16, -18, -6, -11 and at least one other HPV type, with a minimum of 20 cases in each grade of lesion. Total as well as type-specific prevalence of various HPV types were estimated, stratified by cervical lesion grade, using Stata 9.0 software package.
Results: Nine studies from India fulfilled the inclusion criteria. A total of 558, 52, 52 and 3061 women, respectively with invasive cervical cancer (ICC), high-grade squamous intraepithelial lesions (HSIL), low-grade squamous intraepithelial lesions (LSIL) and normal cytology/histology were included. Overall HPV prevalence was 94.6%, 86.5%, 65.4% and 12.0% in women with ICC, HSIL, LSIL and normal cytology/histology, respectively. In ICC, HPV-16 was the predominant type (64.8%), followed by HPV-18, -45, -33, -35, -58, -59 and -31. The estimated HPV-16/18 positive fraction was 78.9% in women with ICC (87.7% in North and 77.2% in South India), 61.5% with HSIL, 30.8% with LSIL and 3.9% in women with normal cytology/histology. There was no difference in overall HPV prevalence in cervical cancer between North and South India ($P = 0.063$). However, HPV-16 and -45 appeared to be more prevalent in North India ($P = 0.018$ and 0.013, respectively), while HPV-35 appeared to be more prevalent in South India ($P = 0.033$).
Conclusion: It is estimated that HPV-16/18 vaccines will provide over 75% protection against ICC in South Asia. HPV-45, -33, -35 and -58 account for an additional 20% of cervical cancer in this region. The addition of these additional HPV types in a second-generation vaccine could provide optimal cervical cancer prevention in this region.

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* Corresponding author. Tel.: +91 11 26594991; fax: +91 11 26588663.
E-mail addresses: nbhatla@aiims.ac.in, neerja.bhatla07@gmail.com (N. Bhatla).

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1. Introduction

Invasive cervical cancer (ICC) is the second most common cancer among women worldwide, with an estimated incidence of 493,000 new cases and mortality of 274,000 each year [1]. Approximately 85% of the disease burden is seen in women in developing nations. Cervical cancer is the most common cancer among women in South Asia. In India, there are an estimated 132,000 new cases and 74,000 deaths each year. The remarkable difference in the incidence of cervical cancer in developed and developing nations has been attributed to organized, cytology-based screening programs and follow-up of affected women in the former. Such programs have not been feasible in South Asia for logistic reasons. Methods based on visual inspection have been recommended for these countries, but the lower specificity of these methods results in a high referral rate, with its own logistic problems [2].

Persistent infection with carcinogenic human papillomavirus (HPV) types has been recognized as a necessary cause of cervical cancer [3–5]. This led to the evaluation of high risk HPV DNA testing as a primary screening method [6]. At the present time, HPV prophylactic vaccines hold the greatest promise for reduction of the cervical cancer burden in areas with no or limited screening [7,8]. Thus the focus of cervical cancer prevention in developing countries has shifted to the detection and control of carcinogenic HPV types. Since this type-distribution varies in different regions, knowledge of the detailed pattern of HPV type-distribution of each region will be essential for public health policy decisions. This will also form the basis for determining which types should be included in new second-generation HPV vaccines targeted to specific regions.

In previously published meta-analyses of HPV type-distribution, information on South Asia has been limited [9–12]. The aim of the present meta-analysis was to determine HPV type-distribution and prevalence among women of South Asia in order to estimate the potential protection of an HPV-16/18 vaccine and to determine the additional HPV types that should be included in new vaccines for optimal protection against cervical cancer in this region.

2. Materials and methods

2.1. Study selection

Source material was obtained from peer-reviewed published English literature using the following search terms and connectors: bangladesh or bhutan or india or nepal or pakistan or sri lanka AND incidence or prevalence or epidemiology or mortality or morbidity AND hpv or human papillomavirus or cervical cancer or cervix cancer or cervical neoplasms or cervical intraepithelial neoplasia AND polymerase chain reaction. The search was conducted in four databases using either MeSH headings or free-text terms if MeSH headings did not exist from 1992 to end of June 2007: Medline, Current Contents, Embase and Cochrane. References cited in the selected papers were also reviewed and authors contacted.

This analysis was limited to studies fulfilling the following inclusion criteria: (1) the cervical specimens were from Bangladesh, Bhutan, India, Nepal, Pakistan or Sri Lanka; (2) clear description of the pathology or cytology determined classification as follows: ICC, high-grade squamous intraepithelial lesion (HSIL), low-grade squamous intraepithelial lesion (LSIL) and normal cytology/histology; (3) the study included at least one of the four categories (ICC, HSIL, LSIL or normal) and the sample size was greater than 20 for each classification group; (4) clear description of HPV DNA detection methods by PCR; (5) in addition to HPV-16, -18, -6 and -11, the detection of at least one additional HPV type; (6) HPV type-specific prevalence stratified by cervical lesion grade (ICC, HSIL, LSIL or normal). Additional information was requested from the authors where study methods suggested that additional type-specific data were available. Where available, ICC was independently divided into squamous cell carcinoma (SCC) and adenocarcinoma (ADC). If histology-specific HPV type-distribution was not reported or cases included other histology types, they were classified as unspecified ICC. HSIL refers either to lesions cytologically equivalent to HSIL according to the Bethesda system or to lesions histologically confirmed as cervical intraepithelial neoplasia (CIN) 2–3. Cases of carcinoma *in situ* were included as CIN 3. LSIL refers to lesions cytologically equivalent to LSIL according to the Bethesda system, or lesions histologically confirmed as CIN 1. The normal group included women from either population- or hospital-based studies with confirmed absence of disease on cytology or histology diagnosis.

2.2. Data abstraction

For each study, the following key information was obtained: (1) year of publication, (2) country and area of sample, (3) histology/cytology classification [ICC (SCC/ADC/unspecified), HSIL (CIN 2/3), LSIL (CIN 1), normal], (4) diagnosis by histology or cytology, (5) type of cervical specimen (fresh or fixed biopsy tissue, exfoliated cell or combination), (6) PCR primers used for HPV detection, (7) type-specific and overall prevalence of HPV infection, stratified by histological/cytological classification, (8) single or multiple infection.

2.3. Studies included

The literature search included studies published up to June 2007—Medline identified 52 studies; 4 studies were identified by contacting authors and 1 was a conference abstract. Of these, 54 were from India, 2 from Pakistan, 1 from Sri Lanka and none from Bangladesh, Bhutan and Nepal. No additional studies were included from Embase, Current Contents and Cochrane databases.

2.4. Estimation of type-specific prevalence

HPV prevalence data were expressed as a proportion of the number of HPV-positive cases among all cases tested for HPV. Multiple HPV infections were separated into constituent types, thus type-specific prevalence included that in both single and multiple infections. Type-specific HPV prevalence is presented for each histological/cytological classification for the 18 most common HPV types identified in ICC by this review, namely HPV-16, -18, -45, -33, -35, -58, -59, -31, -56, -51, -52, -73, -62, -64, -39, -61, -68 and -82, in descending order. Only studies testing for a particular HPV type contributed to the analysis for that specific type. Consequently, sample size varied among the type-specific analyses.

2.5. Statistical analyses

For each histological/cytological classification of ICC, HSIL, LSIL and normal cytology/histology, sources of variation were introduced into an unconditional multiple logistic regression analysis. These included the following: publication year, population studied, geographical area, histologically determined ICC type (only for ICC), type of specimen for HPV DNA testing and type of PCR primers used. Final logistic models were conducted based on statistically significant variables. Overall adjusted HPV prevalence and 95% confidence intervals (95% CI) for stage of cervical lesion were estimated by adjustment for variables found to be significant in the final model. *P* values comparing type-specific HPV prevalence were calculated using chi-square (χ^2) tests. Type-specific HPV prevalence was compared between HSIL/LSIL/normal with ICC by prevalence ratios (PR) with 95% confidence intervals. All statistical analyses were done using Stata 9.0 statistical package.

3. Results

3.1. Studies included

Of the studies from India, Pakistan and Sri Lanka, nine studies from India fulfilled the inclusion criteria [13–21]. Table 1 shows the details of these with respect to numbers examined, region studied, PCR primers, etc. A total of 3723 women were analyzed, which included 558, 52, 52 and 3061 women with ICC, HSIL, LSIL and normal cytology/histology from 6, 2, 2 and 6 studies, respectively (Table 2). Among 558 ICC cases, the majority had squamous cell carcinoma (SCC, $n = 423$) in comparison to adenocarcinoma (ADC, $n = 29$). Cases where histology was not specified or cases with other histological types (adenosquamous carcinoma-2, neuroendocrine tumour-3) were included in the group unspecified ICC ($n = 106$) (Table 2). Among women with normal cytology/histology, 2204 women were from population-based and 857 women were from hospital-based studies.

3.2. Overall HPV prevalence

The overall crude HPV prevalence was 94.6%, 86.5%, 65.4% and 12.0% in ICC, HSIL, LSIL and normal cytology/histology, respectively (Table 2). Adjusted HPV prevalence was 94.6% (95% CI: 94.0–95.3%) and 11.9% (95% CI: 11.7–12.1%) for ICC and normal cases, respectively. Logistic regression could not be applied to HSIL and LSIL because only two studies were included in these groups. In ICC cases, the difference in HPV prevalence between SCC and ADC was highly significant ($P = 0.000$). HPV prevalence in ICC was higher in North India (98.1%) than in South India (93.4%) but the difference was not statistically significant ($P = 0.063$). HPV DNA was significantly more frequently detected in ICC cases by GP5+/6+ PCR (190/191, 99.5%,) and lowest in specimens using PCR amplification of parts of E6, E7 using primers pU-1M, pU-2R (30/43, 69.8%; $P = 0.000$). With PGMY 09/11 HPV-specific primers and line blot assay HPV detection rate was 95.1% (253/266, $P = 0.008$) and with MY09/MY11 and restriction fragment length polymorphism (RFLP) it was 94.8% (55/58, $P = 0.014$). The difference in detection rates between GP5+/6+ and PGMY 09/11 was also significant ($P = 0.005$).

HPV prevalence increased with dates of study publication, from 93.4% in specimens included in publications before and in the year 2005 to 96.4% after the year 2005, however the difference was not significant ($P = 0.117$).

In women with normal cytology/histology, HPV prevalence was similar in the 857 women included from hospital-based studies (11.6%) and the 2204 women included from population-based studies (12.0%) ($P = 0.717$).

3.3. Summary of type-specific HPV prevalence

The 10 most common HPV types in ICC cases overall, in decreasing order, were HPV-16, -18, -45, -33, -35, -58, -59, -31, -56 and -51 (Table 2). In SCC, the 10 most common types and their percentage prevalence, in decreasing order, were HPV-16 (64.8%), -18 (14.7%), -45 (6.4%), -33 (6.4%), -35 (5%), -58 (3.8%), -59 (2.1%), -56 (1.9%), -31 (1.7%) and -51 (1.4%). Among ADC cases, it was noted to be HPV-16 (51.7%), -18 (34.5%), -31 (6.9%), -62 (5.9%), -33 (3.5%), -42 (3.5%) and -45 (3.5%). Thus, in all histological types HPV-16 and -18 were the most common but subsequently there was a variation most pronounced in the case of ADC. The HPV 16/18-positive fraction was 78.9% overall with some variation between North and South India. After these, HPV-45, -33, -35 and -58 accounted for additional 20% of invasive cervical cancer cases. In the North, HPV 16/18 fraction

Table 1
Details of the nine Indian studies with respect to subjects examined, cervical lesions, area/region studied, population type, HPV DNA source and PCR primers

Author, year	Cases (*n*)	Cervical lesion	Area/region	Population type	HPV DNA source	PCR primers
Munirajan et al. [13]	43	ICC	Kancheepuram	Hospital	Biopsy/surgical resection	E6, E7, pU-1M, pU-2R
Franceschi et al. [14]	179	SCC	Chennai	Hospital	Cells/biopsy	GP5+/6+
Franceschi et al. [14]	12	ADC	Chennai	Hospital	Cells/biopsy	GP5+/6+
Sathish et al. [15]	58	ICC	Vellore	Hospital	Biopsy	MY09/MY11
Sowjanya et al. [16]	41	SCC	Hyderabad	Hospital	Biopsy	PGMY 09/11
Peedicayil et al. [18]	102	SCC	South and East India	Hospital	Biopsy	PGMY 09/11
Peedicayil et al. [18]	13	ADC	South and East India	Hospital	Biopsy	PGMY 09/11
Peedicayil et al. [18]	4	Others	South and East India	Hospital	Biopsy	PGMY 09/11
Bhatla et al. [19]	101	SCC	Delhi	Hospital	Biopsy	PGMY 09/11
Bhatla et al. [19]	4	ADC	Delhi	Hospital	Biopsy	PGMY 09/11
Bhatla et al. [19]	1	Others	Delhi	Hospital	Biopsy	PGMY 09/11
Franceschi et al. [17]	26	LSIL	Tamil Nadu	Community	Cells	GP5+/6+
Franceschi et al. [17]	20	HSIL	Tamil Nadu	Community	Cells	GP5+/6+
Bhatla et al. [20]	32	HSIL	Delhi	Hospital	Biopsy	PGMY 09/11
Bhatla et al. [20]	26	LSIL	Delhi	Hospital	Biopsy	PGMY 09/11
Franceschi et al. [14]	184	Normal	Chennai	Hospital	Cells	GP5+/6+
Sathish et al. [15]	30	Normal	Vellore	Hospital	Hysterectomy specimen	MY09/MY11
Franceschi et al. [17]	1799	Normal	Tamil Nadu	Community	Cells	GP5+/6+
Bhatla et al. [20]	458	Normal	Delhi	Hospital	Cells/biopsy	PGMY 09/11
Bhatla et al. [21]	405	Normal	Ballabgarh	Community	Cells	PGMY 09/11

ICC = invasive Cervical Cancer; SCC = squamous cell carcinoma; ADC = adenocarcinoma; Others = unspecified ICC includes histology unspecified or other than SCC/ADC; HSIL = high-grade squamous intraepithelial lesions; LSIL = low-grade squamous intraepithelial lesions.

Table 2
HPV type-specific prevalence and prevalence ratios in 3723 women from India, stratified by grade of lesion

Type	ICC no. (%)	SCC no. (%)	ADC no. (%)	Unspecified ICC[a] no. (%)	HSIL no. (%)	ICC/HSIL PR (95% CI)	LSIL no. (%)	ICC/LSIL PR (95% CI)	Normal no. (%)
Overall	558 (94.6)	423 (97.9)	29 (82.8)	106 (84.9)	52 (86.5)	–	52 (65.4)	–	3061 (12.0)
HPV 16[b]	558 (63.3)	423 (64.8)	29 (51.7)	106 (60.4)	52 (53.9)	1.2 (0.99–1.39)	52 (23.1)	2.7 (2.18–3.44)	3061 (3.2)
HPV 18[c]	558 (15.6)	423 (14.7)	29 (34.5)	106 (14.2)	52 (7.7)	2 (1.16–3.54)	52 (5.8)	2.7 (1.31–5.55)	3061 (0.7)
HPV 45[b]	515 (6)	423 (6.4)	29 (3.5)	63 (4.8)	52 (1.9)	3.1 (0.40–24.70)	52 (0)	–	3061 (0.2)
HPV 33[b]	558 (5.4)	423 (6.4)	29 (3.5)	106 (1.9)	52 (7.7)	0.7 (0.38–1.27)	52 (3.9)	1.4 (0.47–4.15)	3061 (0.6)
HPV 35[b]	558 (5)	423 (5)	29 (0)	106 (6.6)	52 (3.9)	1.3 (0.44–3.89)	52 (3.9)	1.3 (0.44–3.89)	3061 (0.5)
HPV 58	558 (3.6)	423 (3.8)	29 (0)	106 (3.8)	52 (1.9)	1.9 (0.23–15.22)	52 (3.9)	0.9 (0.30–2.86)	3061 (0.3)
HPV 59	457 (2)	423 (2.1)	29 (0)	5 (0)	52 (1.9)	1 (0.11–9.43)	52 (0)	–	3031 (0.5)
HPV 31[c]	515 (1.9)	423 (1.7)	29 (6.9)	63 (1.6)	52 (7.7)	0.3 (0.12–0.52)	52 (7.7)	0.3 (0.12–0.52)	3061 (0.5)
HPV 56	457 (1.8)	423 (1.9)	29 (0)	5 (0)	52 (3.9)	0.5 (0.13–1.62)	52 (7.7)	0.2 (0.10–0.50)	3031 (0.7)
HPV 51	457 (1.3)	423 (1.4)	29 (0)	5 (0)	52 (5.8)	0.2 (0.08–0.63)	52 (3.9)	0.3 (0.09–1.32)	3031 (0.3)
HPV 52	457 (1.3)	423 (1.4)	29 (0)	5 (0)	52 (0)	–	52 (5.8)	0.2 (0.08–0.63)	3031 (0.7)
HPV 73	457 (1.1)	423 (1.2)	29 (0)	5 (0)	52 (1.9)	0.6 (0.05–6.24)	52 (0)	–	3031 (0.2)
HPV 62	266 (0.8)	244 (0.4)	17 5.9)	5 (0)	52 (3.1)	0.2 (0.03–1.45)	26 (3.9)	0.2 (0.01–4.03)	1048 (0.5)
HPV 64	266 (0.8)	244 (0.8)	17 (0)	5 (0)	52 (0)	–	52 (0)	–	2847 (0)
HPV 39	457 (0.7)	423 (0.7)	29 (0)	5 (0)	52 (3.9)	0.2 (0.03–0.91)	52 (0)	–	3031 (0.5)
HPV 61	457 (0.4)	423 (0.5)	29 (0)	5 (0)	52 (0)	–	52 (0)	–	3031 (0)
HPV 68	457 (0.4)	423 (0.5)	29 (0)	5 (0)	52 (1.9)	0.2 (0.01–4.49)	52 (0)	–	3031 (0)
HPV 82	457 (0.4)	423 (0.5)	29 (0)	5 (0)	52 (1.9)	0.2 (0.01–4.49)	52 (1.9)	0.2 (0.01–4.49)	3031 (0.1)

ICC = invasive cervical cancer, SCC = squamous cell carcinoma, ADC = adenocarcinoma, HSIL = high-grade squamous intraepithelial lesions, LSIL = low-grade squamous intraepithelial lesions, PR = prevalence ratio.

[a] Unspecified ICC includes histology unspecified or other than SCC/ADC.

[b] Type-specific prevalence higher in SCC than in ADC.

[c] Type-specific prevalence higher in ADC than in SCC.

accounted for 87.7% which was significantly more than in the South where it accounted for 77.2% ($P = 0.011$).

In ICC, type-specific prevalence of HPV-16 was 64.8% in SCC and 51.7% in ADC but this difference was not statistically significant ($P = 0.157$). The type-specific prevalence of HPV-16, -45, -33 and -35 was higher in SCC than in ADC, whereas the type-specific prevalence of HPV-18 and -31 was higher in ADC than in SCC. HPV-18 was significantly more common in ADC (34.5%) than SCC (14.7%) ($P = 0.005$). In contrast, it was observed that the type-specific prevalence of HPV-45, -33, -35, -58, -59, -31, -56 and -51 was not significantly different in SCC and ADC.

The histological pattern in ICC in North and South India was not statistically different. The proportion of SCC and ADC in North India was 95.3% and 3.8%, while in South India it was 94.8% and 5.2%, respectively. However, there was variation in the prevalence of the third, fourth and fifth most common HPV types after HPV-16 and -18 in different regions (Table 3). In the North, HPV-16 and -18 were followed by -45, -59 and -33, while in the South it was -33, -35 and -45. In the North, HPV-16 and -45 were significantly more prevalent ($P = 0.018$ and 0.013, respectively); in the South, HPV-35 was more prevalent ($P = 0.033$). Although HPV-33 and -58 were more frequently seen in South India, this difference was not statistically significant ($P = 0.075$ and 0.159, respectively). Similarly, HPV-59 and -31 were more frequently seen in North India but this difference was not statistically significant ($P = 0.575$ and 0.714, respectively).

Table 3
HPV type-distribution in invasive cervical cancer (ICC) in North and South India

North India			South India		
HPV type	No. of cases	(%)	HPV type	No. of cases	(%)
HPV-16	106	73.6	HPV-16	333	61.0
HPV-18	106	14.2	HPV-18	333	16.2
HPV-45	106	11.3	HPV-33	333	6.3
HPV-59	106	2.8	HPV-35	333	6.0
HPV-33	106	1.9	HPV-45	290	4.5
HPV-31	106	1.9	HPV-58	333	3.6
HPV-51	106	1.9	HPV-56	232	2.6
HPV-52	106	1.9	HPV-59	232	2.6
HPV-73	106	1.9	HPV-52	232	1.7
HPV-35	106	0.9	HPV-31	290	1.4
HPV-58	106	0.9	HPV-39	232	1.3
HPV-82	106	0.9	HPV-73	232	1.3
HPV-6	106	0.9	HPV-51	232	0.9
HPV-11	106	0.9	HPV-68	232	0.9
HPV-54	106	0.9	HPV-66	232	0.4
HPV-62	106	0.9	HPV-11	232	0.4
HPV-64	106	0.9	HPV-26	232	0
HPV-84	106	0.9	HPV-42	232	0

A similar sequence pattern of HPV specific type-prevalence was seen in women with HSIL and LSIL. The 10 most common HPV types in HSIL cases were HPV-16, -18, -33, -31, -51, -35, -56, -39, -62 and -45 (HPV-16/-18-positive fraction 61.5%), while in LSIL these were HPV-16, -31, -56, -18, -52, -33, -35, -58, -51 and -62 (HPV-16/-18-positive fraction 30.8%). In the normal group, the 10 most common HPV types were HPV-16, -42, -X, -JC9710, -56, -18, -52, -33, -31 and -35 (HPV-16/-18-positive fraction 4.0%).

The prevalence of single-type HPV infection was 81% in ICC cases, 69.2% in HSIL cases, 51.9% in LSIL cases and 9.7% in normal cases. The prevalence of multiple-type HPV infections was 14% in ICC cases, 23.1% in HSIL cases, 13.5% in LSIL cases and 2.4% in normal cases.

The PR for comparison of ICC to HSIL cases (ICC/HSIL), and ICC to LSIL cases (ICC/LSIL) are presented in Table 2. Prevalence ratios for HPV-16 and -18 were greater than 1, i.e., 1.2 and 2.0 for ICC/HSIL comparison, and 2.7 and 2.7 for ICC/LSIL comparison, respectively.

4. Discussion

This meta-analysis aimed to study the HPV prevalence and type-distribution in South Asia, which is a region composed of countries with overlapping ethnicity and a rich variety of cultural and lifestyle patterns. Eventually, however, the data represents HPV type-distribution among women with and without cervical lesions from India as the studies from Pakistan and Sri Lanka did not meet the inclusion criteria [22–24], while no studies were found from Bangladesh, Bhutan and Nepal. Of the 57 studies found by the literature search, only 9 could be included in the final meta-analysis. Reasons for exclusion of

the other studies were as follows: (1) number of cases in each histological category < 20 [ICC [20,24–26], SIL [15,18,21,26–31] and normal [24,27,32]]; (2) only HPV genotypes 16 and 18 were studied, HPV type was not specified or genotyping was done for <5 types [ICC [22,24–29,33–47], SIL [26–31,34,38,39,44,48,49] and normal [24–29,31,34,37–42,44,48–53]]; (3) a method other than PCR was used to detect HPV types [ICC [23,25,32,33,54–62], SIL [32,55,57,59,60,62–66] and normal [23,25,32,52,55,57,60–62,64–68].

4.1. Overall HPV prevalence

This meta-analysis presents data on HPV type-specific prevalence in 3723 women, thereby increasing notably the number of cases included from the Indian subcontinent in previous reviews. Overall HPV prevalence in 558 ICC cases (94.6%) though lower than the almost 100% prevalence detected using the most sensitive PCR HPV detection methods [4], was nevertheless similar to the worldwide HPV prevalence of 83–89% in ICC cases reported by Clifford et al. [9]. A previous meta-analysis from Asia reported an overall prevalence rate of 85.9%, while the prevalence in South Central Asia, including India and Iran, in that meta-analysis was found to be 90.5% [12]. The higher prevalence in the present meta-analysis may be due to the higher sensitivity of the newer PCR primers such as MY09/MY11, PGMY 09/11 (line blot assay) and GP5+/6+ PCR primers used in recent studies. We did not compare the type of tissue specimen, i.e., biopsy vs. exfoliated cells as out of the six studies included in the ICC meta-analysis, five used histology and only one used cytology in addition to histology [14].

Previous studies reported that HPV prevalence is the same in SCC and ADC cases and concluded thereby that HPV infection is the primary causal agent for both SCC and ADC consistently worldwide [9,12,69,70]. In the present meta-analysis, the difference in HPV prevalence in ADC was significantly lower than in SCC. In part, this may be due to the smaller number of cases of adenocarcinoma.

The overall crude HPV prevalence in HSIL and LSIL from India was found to be 86.5% and 65.4%, respectively. These values are similar to those reported previously for Asian population (80.8% and 72.8%, respectively) [12]. However, no cases were included for HSIL and LSIL analysis from South Central Asia. In the present review also, only crude rates could be obtained and adjusted prevalence could not be calculated as only two studies from India fulfilled the inclusion criteria. Clifford et al. found the overall HPV prevalence as 84.2% in HSIL and 67.1% in LSIL [10,71].

4.2. HPV type-specific prevalence

HPV-16 was the predominant type found in Indian women, with and without cervical neoplasia. In ICC, the attributable fraction of HPV-16 was 63.3%, which is higher than the figure of 45.9% in 3091 women with ICC from Asia in Clifford's previous systematic review and 52.4% in 5954 cases of ICC from a meta-analysis from Asia by Bao et al. [9,12]. HPV-16 was more common than HPV-18 in all histological categories. This is in consonance with other analyses from Asia with respect to SCC [9,72]. However, Bao et al. found HPV-18 to be the more common type in ADC in Asia rather than HPV-16 (34.4% vs. 32.3%) [12]. In contrast we found the proportion of HPV-18 to HPV-16 to be 34.5% vs. 51.7% in ADC.

The HPV 16/18-positive fraction in women with cervical cancer is used to estimate the prospective benefit of an HPV 16/18 prophylactic vaccine for the primary prevention of cervical neoplasia. Under the supposition that a vaccine with 100% efficacy in prevention of HPV-16 and -18 infections (assuming 100% coverage) it can be expected to reduce the total cancer burden in India by more than 78.9%. This is greater than other studies done from Asia which reported 67% HPV 16/18-positive fraction [12]. In fact, in North India, HPV-16/18 will provide 84% protection but in South India, HPV-16/18 will provide only 74.5% protection ($P = 0.0678$). Data for ICC from North India came from a single study, while there were five studies from the South. However, while the histological types and HPV prevalence rate were the same in the two regions, yet the HPV types differed.

After HPV-16 and -18, the six most common HPV types in ICC were HPV-45, -33, -35, -58, -59 and -31. HPV-45, -33, -35 and -58 account for an additional 20% of cervical cancer in this region. A tailored HPV vaccine according to regional prevalence would best serve the population in primary prevention for ICC. Our analysis indicated that the prevention of HPV-16, -18, -45 and -33 could likely provide ~90% protection against ICC. Four of the first five HPV types found in India are similar to the global scenario (India—HPV-16, -18, -45, -33 and -35; Africa—HPV-16, -18, -45, -33 and -31; Europe—HPV-16, -18, -33, -31 and -45; North America/Australia—HPV-16, -18, -31, -33 and -45; and South/Central America—HPV-16, -18, -31, -45 and -33) but unlike the rest of Asia where HPV-58 and -52 as the next common HPV types in Asia after HPV-16 and -18 [9,12,73].

The PR of HPV-16, -18 and -35 in ICC/HSIL and ICC/LSIL were greater than 1, indicating that HPV-16, -18 and -35 are more likely to progress to cervical cancer from HSIL and LSIL than are other HPV types, supporting the results of previous studies [10,12]. HPV-45 and -58 have a higher progression potential from HSIL to ICC and HPV-33 appeared to have a higher progression potential from LSIL to ICC. This was similar to the meta-analysis from Asia in which HPV-16, -18 and -45 had the highest risk of progression [12].

The HPV 16/18-positive fractions were 61.5% in HSIL and 30.8% in LSIL, and ranged 56.8–66.2% and 26.1–31.6%, respectively. Our findings show higher prevalence than those from a previous review from Asia which showed that the HPV 16/18-positive fractions were 41.3% in HSIL and 26.8% in LSIL and ranging from 36–50%, and 11–33%, respectively [12]. This is in keeping with the higher HPV 16/18 fraction seen in ICC cases also.

The overall adjusted HPV prevalence in normal cases was 11.9%, which was similar to other geographical regions of the world (range 7.7–13.9%) but somewhat lower than other pooled analyses from this region (14.2–14.4%) [11,12]. However, the HPV prevalence in Nigeria in normal cases was reported to be high (25.6%) whereas, a low prevalence of HPV in normal women was found in Spain and Vietnam (1.4% and 1.7%, respectively) [11]. The estimated percentage of adults (15–49 years) living with HIV/AIDS by the end of 2005 as reported by WHO was 3.9% in Nigeria, 0.6% in Spain and 0.5% in Vietnam. It is possible that impairment of cellular immunity by HIV could contribute to a higher prevalence of HPV infection in Nigeria [74].

Bao et al. found significantly higher HPV infection in women from hospital-based studies (25%) than from population-based studies (10.9%) but we did not observe this difference [12].

This study provides a detailed description of overall and type-specific HPV prevalence in India, stratified by region. With a larger sample size than previously reported and a systematic review of literature, these findings notably improve our understanding of HPV prevalence in women with and without cervical neoplasia in South Asia. A study from Sri Lanka reported HPV-16 and -18 infection in 11/15 and 3/15 cases, respectively in SCC cases and 3/15 and 0/15 cases, respectively in normal cases [24]. A study from Pakistan determined that overall HPV infection was present in 59 cases, HPV-16 was found in 56 cases and HPV-18 was found in a single case out of total 60 cases of ICC [22]. Though these studies did not qualify for this meta-analysis, there appears to be a high prevalence of HPV-16 and -18 in these countries as well. More studies with a larger number of cases using sensitive tech-

niques are required to have adequate data from all countries in the region.

This meta-analysis had certain limitations. Although a large number of studies from South Asia were identified, only nine fulfilled the inclusion criteria and all of these were from India. Even these are not representative of each region of this vast country. Large areas like western and central India are not well represented. Most studies have focused on invasive cancer so the total number of cases of HSIL and LSIL were small. In fact since only two studies qualified, logistic regression could not be applied. Nevertheless this is the first report on this category from this region.

HPV testing was done by varying PCR primers which amplify a broad but different range of HPV DNA type (Table 1). Since these PCR primers amplify individual genotypes with varying sensitivities, this is a potential source of bias [75]. However, this fact was taken into account while estimating the results. Also the rate of multiple infections might in fact be an underestimation as some studies tested for only a subset of HPV genotypes.

In conclusion, HPV-16 and -18 have a higher prevalence in squamous intraepithelial lesions and cervical cancer patients in India and neighboring countries of South Asia. First generation HPV 16/18 vaccines have the potential to provide 75–80% protection against ICC in India. The HPV type-distribution is more like that seen in Europe, Africa, etc., than like other parts of Asia. HPV-45, -33, -35 and -58 accounted for additional 20% cases of cervical cancer and should be considered for inclusion in second-generation HPV vaccines. More studies are needed from other parts of the region. For the present, this data confers a strong basis for incorporation of HPV 16/18 vaccination as a primary prevention program in South Asia.

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