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Prevalence and Current Scenario of HPV in Pakistan: A Systematic Review and Meta-analysis

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Abstract

AIM: The present study was designed to compile and screen data regarding HPV-related reported diseases to evaluate the status of HPV infection in Pakistan.

METHODS: The literature on the prevalence of HPV in Pakistan was searched in Google Scholar and other search engines using various keywords.

RESULTS: A total of 39 studies published from 2007 to 2018 were reviewed. About 7341 participants have been screened for HPV in Pakistan for the past 11 years, and according to this meta-analysis, the reported HPV prevalence was 23.1%. The highest HPV prevalence rate was observed among cervical cancer cases (80.4%) followed by normal cervical region (61.8%) and oral cancer (40.4%), respectively.

CONCLUSION: The high prevalence of HPV in Pakistan reflects the raised burden of HPV-associated diseases. The health-care system needs to be more organized in terms of awareness and screening programs, diagnosis, and treatment of the disease to reduce the burden of HPV in Pakistan.

Introduction

Human papillomavirus (HPV), approximately 8000 base pairs, double-stranded DNA virus from Papillomaviridae is a sexually transmitted viral infection that affects both genders [1]. HPV infections are mostly asymptomatic and transient but persistent infection could lead to complex conditions like cancers. HPV is an epitheliotropic virus and is a major cause of oral and anogenital cancers all over the world [2], [3]. Based on pathogenicity, it is divided into two subtypes; high risk (HR) and low risk (LR). Low-risk HPV (LR-HPV) infections cause warts or precancerous lesions, whereas high-risk HPV (HR-HPV) infections tend to cause cancers that account for; cervical (100%), anal (88%), vaginal (78%), throat and mouth (30–70%), penile (51%), and vulvar (>25%), with 70% of above-mentioned cancers are due to most common HR-HPV types; HPV 16 and HPV 18 [4], [5].

Approximately 570,000 females and 60,000 males get affected by HPV infection annually. The World Health Organization (WHO) reported that 7.5% of cancer-related female deaths are due to cervical cancer (CC) attributed to HPV infection [6]. The CC is the most common out of all caused by HPV and ranks 3rd in females aged 15 to 44 and it was the 2nd leading cause of death in Asia. Other cancers associated with HPV are less prevalent than CC as compared to vulvar cancer (4%) and vaginal cancer (2%). HPV-related anal and penile cancers are also less incident but all of these are more prevalent in developing countries with more burden in Africa and Asia. Its etiological involvement has been suggested for breast and lung cancer as well. HR-HPV types are related to oropharyngeal cancer with HPV type 16 being the most frequent genotype [7]. Incidence of cervical and other anogenital cancers is more in the developing countries and head-and-neck cancers (HNCs) in high-income countries [8]. HPV prevalence in normal females is also found at 2% worldwide while 10% in Asia [9].

The first study to report HPV prevalence in Pakistan was published in 2007. Since then, only small-scale studies have been carried out that do not evaluate national level estimates of HPV prevalence in the Pakistani population. Hence, the purpose of this systematic review and meta-analysis was to collect, summarize, and review the past data on the prevalence

of HPV in healthy mucosa, as well as its association with various cancers in Pakistan over the span of 13 years. Thus, the present study will not only provide an overview of HPV in Pakistan but also provide support to the Health Ministry of Pakistan to develop health programs and policies. Moreover, the present study data can be used to hold comparisons of HPV prevalence with other parts of the world.

Methodology

Research articles using keywords related to the prevalence of HPV in Pakistan, HPV in the general population, HPV in the normal cervical region, HPV in CC, HPV in normal oral mucosa, HPV in oral addictive habits, HPV in the oral pre-malignant lesion, HPV in oral cancer (OC), HPV in the esophageal region, HPV in breast cancer, and HPV in lung cancer were explored in search engines such as PubMed, Scopus, Web of Science, EMBASE, Google Scholar, and PakMediNet. Following the inclusion criteria, studies were selected after a thorough evaluation which includes: The Pakistani population; comprehensive methodology for the identification of HPV infection, and data regarding the number of participants along with their cities. The systematic review and meta-analysis included 39 studies published from 2007 to 2018. No gender, age, HPV vaccination, and language data were used. The inclusion criteria are shown in Figure 1.

Statistical analysis

The data obtained from the electronic search engine were reviewed by the two authors individually.

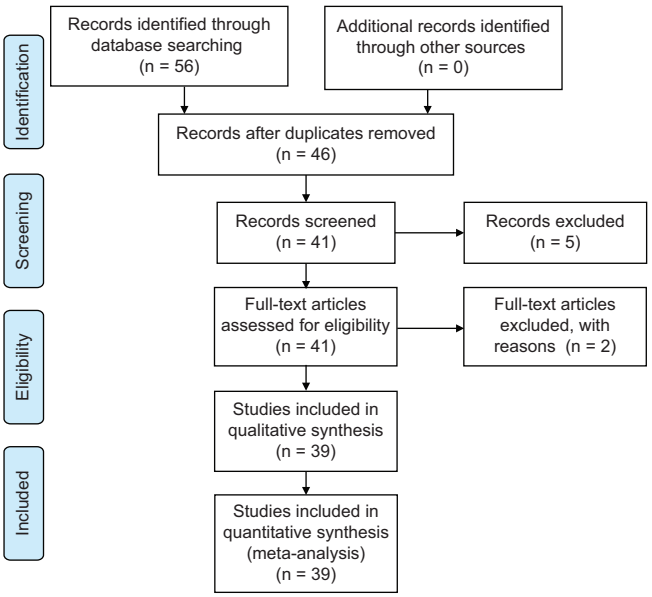

Figure 1: Prisma flow diagram showing the literature search, inclusion and exclusion of the articles for this study

On the SPSS spreadsheet, the record from the eligible articles was retrieved and briefed. After a thorough review by the two authors, any discrepancy was discussed and referred to the third author for the final assessment. The data that were retrieved from the selected articles consisted of a year of study, city of participants, number of participants, a diagnostic technique used, and number of participants positive for HPV infection. The total number of all the screened participants was computed and analyzed. The studies were divided into subgroups based on the prevalence of HPV in the general population, normal cervical region, CC, normal oral mucosa, oral addictive habits, oral pre-malignant lesion, OC, esophageal region, breast cancer, and lung cancer. The prevalence of HPV in these population groups is presented as a mean percentage. The formula of means percentage was calculated by dividing the number of HPV-positive individuals by the total number of participants screened for HPV, along with the standard deviation with a 95% confidence interval for evaluating the uncertainty. The study was carried out using PRISMA as earlier stated by Moher *et al.* [10] (Figure 1).

Most of the articles included in this meta-analysis have a small sample size and were from retrospective assessments of the prevalence of HPV in Pakistan. This limits the characteristic of recorded information for the generalized prevalence of HPV in the Pakistani population. Furthermore, multiple techniques were utilized for the identification of HPV which may result in biasness of the study that is assessed using the following formula:

Margin of error $(ME) \equiv z\sqrt{\left(\frac{p(1-p)}{n}\right)}$

$$ME = 1.96\sqrt{\left(\frac{p(1-p)}{n}\right)}$$

$$n = \frac{p(1-p)z^2}{ME^2}$$

Formula based on t-score

$$ME = t\left(\frac{\sigma}{\sqrt{n}}\right)$$

$$n = \left(\frac{\sigma t}{ME}\right)^2$$

Results

Prevalence of HPV in Pakistan

In the past 11 years, a total of 7341 participants from Pakistan have been screened for HPV infection.

Table 1: Brief evaluation of HPV infection in different Pakistani population groups

Study population	Number of studies (n)	Total no. of population (n)	Negative for HPV (n)	Positive for HPV (n)	Percentage (%)	CI (p = 0.05)	
						Lower (95%)	Upper (95%)
Normal cervical region	6	2690	2546	145	5.4	1.69796	10.6720
Cervical cancer	8	810	129	681	84	62.3900	98.4374
Normal oral mucosa	5	1177	1062	115	9.7	4.3467	18.7732
Oral addictive habits	2	1262	1011	251	19.8	16.840	21.5590
Oral premalignant lesions	2	85	79	6	7.1	4.7443	9.8556
Oral cancer	10	828	498	330	40	23.3859	57.4540
Esophageal cancer	2	163	148	15	9.2	−8.10735	37.1073
Lung cancer	2	30	22	8	26.6	0.52386	43.5761
Breast cancer	2	296	243	53	17.9	16.9136	18.4863
Total	39	7341	5738	1604	21.8	9.109	39.608

The review of entire 39 articles published so far from 2007 to 2018 reports a cumulative HPV prevalence of 21.8% (1604 out of 7341) in Pakistan (Table 1). The overall number of participants positive for HPV in various population groups from Pakistan is shown in Table 1.

HPV in normal cervical mucosa and cervical cancer

In six multiple studies on normal cervix, 2690 participants were tested for HPV infection, among them (145/2690), 5.4% were positive for cervical HPV infection (Table 2) [11], [12], [13], [14], [15], [16]. A variation in percentages from all of the selected studies shows 95% CI: 1.69–10.6 (Table 1) which represents biasness of samples among the studies (SD = 5.58; SE = 2.28). Whereas, eight different studies from all the major cities of Pakistan [14], [17], [18], [19], [20], [21], [22], [23] investigated HPV prevalence in CC cases in the Pakistani population. These studies together screened 810 cases and reveal that 84% were positive for HPV (Table 2). Most commonly investigated HR-HPV genotypes in CC were HPV-16 and HPV-18 mostly conducted on relatively smaller sample sizes, the largest sample being 280 females, and the smallest 50. Three studies screened 201 participants from Karachi, observed that 151 (75.1%) [14], [19], [22] whereas the studies conducted in Lahore on 465 CC cases noticed that 398 (85.5%) [17], [18], [23] were found positive for cervical HPV infection (Table 2). The present study reported an increased SD (25.93) and SE (9.195) from the data collected by all published studies, which proposed an increased bias between the gathered data.

HPV in normal oral mucosa and oral cancers

Five multiple studies, mostly from Karachi, Pakistan [24], [25], [26], [27] [28], evaluated the prevalence of HPV infection in normal oral mucosa and stated a 9.7% prevalence of HPV (SD = 8.20; SE = 3.68) (Table 3) whereas a total of 10 studies [26], [28], [29], [30], [31], [32], [33], [34], [35], [36] from all over Pakistan were carried out on 828 OC cases reporting that 330 (40%) were positive for HPV (SD = 27.4; SE = 8.69). The mainstream of OC studies (n = 7) was from Karachi which screened n = 613 participants and revealed that n = 224 (36.5%) of OC cases were positive for HPV infection. However, only two studies were

Table 2: Prevalence of HPV in normal cervix and cervical cancer

Region	Sample size	HPV positive cases	HPV %	Sample types	Technique use	Year duration	Reference
Prevalence of HPV in normal cervix							
Islamabad, Rawalpindi, Gujarat	92	3	3.26	Cervical secretions	PCR	2015	Abdullah *et al.*, 2016 [11]
Islamabad, Rawalpindi and Rahim Yar Khan	1011	48	4.74	Cervical scrape	PCR RT-HR HPV typing	2014–2016	Aziz *et al.*, 2018 [12]
Karachi	350	54	15.4	Cervical scrapes	PCR Pap test	------	Khan *et al.*, 2016 [13]
Karachi	877	19	2.2	Exfoliated cervical cells	PCR and LBC	2004–2008	Raza *et al.*, 2010 [14]
Karachi	160	17	10.6	Cervical scraping	PCR with GP5/GP6, TS16-A/ TS16-B and TS18-A/TS18-B, Pap smear	2012	Shahid *et al.*, 2015 [15]
Peshawar	200	4	2	Cervical scraping	PCR with GP5+/6+; type specific primers for HPV 16 and 18; beta-globin. Pap smear	2012–2013	Akbar *et al.*, 2015 [16]
Prevalence of HPV in cervical cancer cases							
Lahore	280	245	87.5	FFPE	SPF 10 broad-spectrum PCR DNA enzyme immunoassay genotyping by LiPA25.	2005–2010.	Loya *et al.*, 2016 [17]
Karachi	91	83	92.2	FFPE	PCR GP5+/6+; beta-globin; LBC	2004–2008	Raza *et al.*, 2010 [14]
Lahore	102	88	86.2	Smears	PCR	2008–2009	Saba *et al.*, 2015 [18]
Karachi	60	59	98.3	FFPE	PCR with GP5/GP6; TS 16; TS 18; beta-globin	1991–2005	Khan *et al.*, 2007 [19]
Islamabad, Rawalpindi	67	59	88	FFPE	GP5/GP6; TS 16; TS 18; beta-globin	2010–2013	Gul *et al.*, 2015 [20]
Punjab	77	73	94.81	FFPE Fresh samples	GP5+/GP6+; TS 16; TS 18; C16E7; C18E7, beta-globin	2007–2010	Siddiqa *et al.*, 2014 [21]
Karachi	50	9	18	FFPE	PCR My 09/My 11; GP5+/6+	2003–2008	Yousuf *et al.*, 2010 [22]
Lahore	83	65	78.3	FFPE	PCR for E6 & E7 region; type specific primer for HPV 16 & 18	------	Zahid and Shakoori, 2016 [23]

*PCR: Polymerase chain reaction, RT-HR-HPV: Real-time high-risk human papillomavirus, LBC: Liquid-based cytology, Pap: Papanicolaou, FFPE: Formalin-fixed paraffin-embedded.

Table 3: Prevalence of HPV in normal oral mucosa and oral pharyngeal cancer

Region	Sample size	HPV positive cases	HPV %	Sample types	Technique use	Year duration	Reference
Prevalence of HPV in normal oral mucosa							
Quetta	192	47	24.5	Scraping of oral epithelial cells	RT-PCR with HPV 16 & HPV 18 primers Nested PCR	2011	Gichki *et al.*, 2012 [24]
Karachi	450	14	3.1	Oral rinse	PCR with Gp5+/Gp6+, HPV 16 and HPV 18	2012–2013	Baig *et al.*, 2015 [25]
Karachi	35	3	8.6	Saliva by drooling method	HPV-16 & 18 by real-time PCR method	2011–2012	Khyani *et al.*, 2015 [26]
Karachi	300	23	7.6	Oral rinse	PCR with GP/5+GP/6+and HPV genotype kit	2014	Irshad *et al.*, 2015 [27]
Karachi	200	28	14	Oral rinses	PCR using Gp5+/Gp6+and RT-PCR for HPV 16, 18 specific primers	2015–2016	Zil-e-Rubab *et al.*, 2018 [28]
Prevalence of HPV in oral cancer cases							
Lahore	48	27	56.2	FFPE	PCR, RT-PCR	1996–2002	Castillo *et al.*, 2011 [29]
Karachi	133	21	15.7	Oral rinse with slight use of brushing	PCR Gp5+/Gp6+. Type specific primers for 6 & 11, real-time PCR for 6 & 11	2014–2015	Perveen *et al.*, 2016 [30]
Karachi	140	95	67.9	-	PCR	1991–2004	Ali *et al.*, 2018 [31]
Karachi	100	15	15	FFPE	PCR and IHC	----	Akram *et al.*, 2019 [32]
Islamabad	95	74	78	FFPE	PCR with GP5/GP6; TS16; TS18; beta-globin histopathological examination	2005–2010	Azhar *et al.*, 2018 [33]
Karachi	35	15	42.9	Saliva by drooling method	RT-PCR with HPV-16 & 18	2011–2012	Khyani *et al.*, 2015 [26]
Lahore	72	5	14.4	FFPE	PCR with GP5/GP6 and MY9/MY11	2015–2017	Kashif *et al.*, 2018 [34]
Karachi	47	32	68.1	FFPE	PCR and IHC	2010–2013	Awan *et al.*, 2017 [35]
Karachi	58	0	0	FFPE	PCR	2015–2017	Naqvi *et al.*, 2020 [36]
Karachi	100	46	46	Oral rinses	PCR using Gp5+/Gp6+and RT-PCR for HPV 16, 18 specific primers	2015–2016	Zil-e-Rubab *et al.*, 2018 [28]

*RT-PCR: Real-time polymerase chain reaction, LBC: Liquid-based cytology, Pap: Papanicolaou, PCR: Polymerase chain reaction, IHC: Immunohistochemistry, FFPE: Formalin-fixed paraffin-embedded.

conducted in Lahore regarding the HPV prevalence in OC and screened 120 OC cases out of which n = 32 (26.6%) were positive for HPV infection (Table 3).

HPV in oral addictive habits and oral premalignant lesions

Two comprehensive studies on oral addictive habits carried out in Karachi [25], [37], revealed that 251/1262 (19.8%) individuals were positive for HPV infection with SD = 1.69 and SE = 1.20, respectively (Table 4). Whereas, two studies on the prevalence of HPV in oral premalignant lesions from Karachi [26], [32] screened 85 individuals and reported that n = 6 (7.1%) were positive for HPV infection (Table 4). The SD (1.83) and SE (1.30) of these studies show less biasness among the studies population.

HPV in esophageal cancer

Based on the current meta-analysis, there were only two studies conducted in Pakistan on the association of HPV with esophageal cancer, reporting overall 9.2% of samples were positive for HPV infection in esophageal cancers with 3% and 26% in the two studies, respectively [29], [38] (Table 4).

HPV in lung cancer and breast cancer

There are only two studies conducted in Pakistan on the association of HPV with lung cancer (LC). In both studies, HPV16 was the only type identified. In the first study, out of nine formalin-fixed paraffin-embedded (FFPE) samples from lung cancer patients, 1 (11.1%) was found to be positive for HPV16. While in the second study, 7 (33%) out of 21 squamous cell carcinomas showed the presence of HPV in lung cancer.

The prevalence of HPV in breast cancer is 17.7 % (53/296) with SD = 0.565 and SE = 0.401 (Table 5) [39], [40].

Discussion

This is the first nationwide meta-analysis on the prevalence of HPV infection among the Pakistani

Table 4: Prevalence of HPV in individuals with oral addictive habits, oral premalignant lesions, and esophageal cancer cases

Region	sample size	HPV positive cases	HPV %	sample types	Technique use	Year duration	Reference
Prevalence of HPV in individuals with oral addictive habits							
Karachi	262	47	18	Oral rinse with gentle brushing	PCR with Gp5+/Gp6+.	2010	Baig *et al.*, 2012 [37]
Karachi	1000	204	20.4	oral Rinse	PCR with Gp5+/Gp6+, HPV 16 and HPV 18	2012–2013	Baig *et al.*, 2015 [25]
Prevalence of HPV in patients with oral premalignant lesions							
Karachi	35	3	8.6	Saliva by drooling method	HPV-16 & 18 by RT-PCR method	2011–2012	Khyani *et al.*, 2015 [26]
Karachi	50	3	6	FFPE	RT-PCR of HPV 16 and HPV 18 and IHC	----	Akram *et al.*, 2019 [32]
Prevalence of HPV in esophageal cancer cases							
Peshawar	121	4	3	FFPE	ELISA	January–June 2017	Tasneem *et al.*, 2019 [38]
Lahore	42	11	26	FFPE	PCR, RT-PCR	1996–2002	Castillo *et al.*, 2011 [29]

*RT-PCR: Real-time polymerase chain reactions, IHC: Immunohistochemistry, FFPE: Formalin-fixed paraffin-embedded, PCR: Polymerase chain reaction, ELISA: Enzyme-linked immunoassay.

Table 5: Prevalence of HPV in lung cancer and breast cancer cases

Region	Sample size (n)	HPV positive cases (n)	HPV %	Sample types	Technique use	Year duration	Reference
Prevalence of HPV in lung cancer							
Islamabad	9	1	11.1%	FFPE	Conventional PCR with GP5+/GP6+, type specific with HPV 16 and HPV 18	2012–2014	Ilahi *et al.*, 2016 [39]
Lahore	21	07	33%	FFPE	PCR southern blotting RT-PCR	1996–2002	Aguayo *et al.*, 2010 [58]
Prevalence of HPV in breast cancer cases							
Rawalpindi	46	8	17.3%	Formalin-fixed paraffin embedded (FFPE)	Polymerase chain reaction (PCR_ with GP5+/GP6+, type Specific with HPV 16 and HPV 18	2012–2014	Ilahi *et al.*, 2016 [39]
Islamabad	250	45	18.1%	FFPE	PCR	2012–2014	Naushad *et al.*, 2017 [40]

*RT-PCR: Real-time polymerase chain reaction, PCR: Polymerase chain reaction, FFPE: Formalin-fixed paraffin-embedded.

population. This meta-analysis and systematic review evaluated 39 published articles from Pakistan to assess broadly the prevalence of oral, genital, lung, and breast HPV infection. To date, there has been no nationwide screening of HPV in Pakistan to report the national prevalence of HPV infection. The overall prevalence of HPV infection in Pakistan varies slightly among its different cities. The distribution of HPV prevalence throughout the world also varies significantly, permitting worldwide regional division. According to this meta-analysis, an HPV prevalence of 23.1% was observed in the Pakistani population (Table 1). Multiple international studies reported the prevalence of HPV infection among healthy women which was 21.8% in Oceania and assessed to be 30.9% in 2019, 21.1.% in Africa, Europe (14.2%), America (11.5%), and Asia (9.4%) respectively [41], [42], [43].

The worldwide prevalence of genital HPV infection in males is somewhat similar to that of females (3.5–45% vs. 2–44%) [44], [45].

The global prevalence of HPV infection among males was higher in South African men (17.2%), whereas lowest in Asia (3.2%) [46]. Ishibashi *et al.* stated that the raised prevalence of all HPV genotypes was observed in developing countries in contrast to developed countries [47]. These previous data collectively guide us to the conclusion that the most obvious HPV infection prevalence and incidence were observed in both healthy, unhealthy, and genders of the low- and middle-income countries [41].

Infection with HPV is frequent in females. This study reports HPV prevalence of 5.4% in the normal cervix which is higher than the findings of the Human Papillomavirus and Related Diseases Report by ICO/IARC HPV Information Centre (0.5%), and is lower than the worldwide meta-analysis carried out by De Sanjosé *et al.* from 1995 to 2005 reporting overall HPV prevalence of 10.4%. Moreover, they also reported region-wise prevalence of HPV in Africa (22.1%), Central America and Mexico (20.4%), North America (11.3%), Europe (8.1%), and Asia (8%) in normal cervical cytology [43]. Likewise, Bruni *et al.* also reported an 11.7% prevalence of HPV infection in their meta-analysis of 1 million females with normal cytology [41]. However, country-specific adjusted HPV prevalence varies from 1.6% to 41.9% [43]. Likewise, another meta-analysis from Brazil reported that overall HPV prevalence among females was 25.41% [48].

However, the reported prevalence of CC HPV (84%) in this meta-analysis is similar to the Report by ICO/IARC HPV Information Centre (88.1%) and also to the worldwide meta-analysis on HPV virus in invasive CC conducted by Clifford *et al.* in 2003 on 10,058 cases (83–89%) [49]. This rise in CC with a low prevalence of cervical HPV is a striking finding in this analysis. This contrast in disease etiology and outcome may suggest a huge gap in the current data on cervical HPV in healthy individuals of Pakistan. In a country where CC is the third most common cancer, there is a great need for studies with a bigger sample size to address the discrepancies in the existing data on HPV, its prevalence, its most common genotypes, and their role in CC in Pakistan [49].

As for Pakistan, very few studies were conducted on oral HPV and were mainly from one major city of the country, that is, Karachi. In addition, these studies despite being from the same city, reported greatly variated data on oral HPV (OHPV) prevalence. The prevalence of OHPV in normal oral mucosa ranges from 3.1% to 14%. Similar is the situation for the prevalence of HPV in OC which ranges from 15% to 68.1% in overall data (Table 3).

The present study estimate reveals a higher OHPV prevalence in Pakistan (11.5%) than the systematic review on the epidemiology of HPV (7.7%) from 1995 to 2017 in healthy oral mucosa [50]. However, the result of this study is in line with the meta-analysis conducted by Colpani *et al.* in Brazil which stated that in the oral region, HPV overall prevalence was 11.89% [48]. As for the prevalence of OHPV (40.8%) in OC, it is similar to the meta-analysis conducted on OC in 2015 covering the region of South, East, and Southeast Asia revealing an approximate HPV prevalence of 36% and also with the study carried out in India (39.2%) [51], [52]. Thus, this study arises the need of furthers research in this area to explore the updated OHPV prevalence and its associated risk factors such as sexual attitude and addictive habits.

The reported prevalence of HPV in the pre-malignant lesion (7.1%) is lower in contrast to the worldwide meta-analysis by Jayaprakash *et al.* (2011) and de la Cour *et al.* (2020) reporting 24.5% and 27.2%, respectively [53], [54]. Both the studies reported HPV16 as the predominant genotype in oral premalignant lesions.

Esophageal cancer is the eighth most common cancer globally, with an estimated 455,784

new cases in 2012, and the sixth most common cause of death, with an estimated 400,156 deaths. Furthermore, the number of esophageal cancer deaths may be increased to 728,945 by the year 2035 [55]. The present meta-analysis reported 9.2% of HPV relevance in esophageal cancer. However, the study carried out by Castillo *et al.* (26%) in Lahore is in contrast with existing study data whereas similar to the global prevalence of HR-HPV infection in esophageal cancers (22.2%) [29]. Similarly, a meta-analysis by Li *et al.* stated that HPV prevalence in esophageal squamous cell carcinoma is 22.2% (95% confidence interval [CI], 18.3-26.7%) and 35.0% (95% CI, 13.2-65.7%) among esophageal adenocarcinoma, respectively [56]. The etiology of esophageal cancer remains unclear. Infectious agents have also been suggested as direct carcinogens or promoters in esophageal carcinogenesis. However, a meta-analysis conducted in 2016, indicated that HPV infection may not be of prognostic utility in the evaluation of factors contributing to esophageal cancer [55]. Thus, the etiological role of HPV in esophageal cancer remains questionable. On the contrary, another meta-analysis conducted on HPV16 and HPV18 association with esophageal cancers, reported that HPV infection rate in the esophageal cancer group was 46.5%, suggesting that HPV infection and the incidence of esophageal cancer are closely associated. Hence, it is difficult to draw any conclusion with such variated data and further large-scale studies need to be conducted.

The LC in Pakistan is the third most common cancer in Pakistan. It accounts for 5.6% of all cancers and 7.8% of deaths caused by all cancer in 2018 [57]. The role of HPV in LC is yet another debatable topic due to contradicting reports. In both the studies, HPV16 was the only type identified. In the first study, out of nine FFPE samples from LC patients, 1 (11.1 %) was found to be positive for HPV16. No significant correlation was found between HPV prevalence and the clinicopathological features of large-cell lung carcinoma. While in the second study, 7 (33%) out of 21 squamous cell carcinoma (SCC) showed the presence of HPV in LC, concluding a frequent HPV16 integration in SCC, although the low viral load casts doubt respects a direct etiological role of HPV in lung carcinomas [39], [58] (Table 5). However, a meta-analysis conducted in China (2015) on the presence of HPV in LC reported that HPV (including low- and high-risk HPV) prevalence was higher among LC patients than among non-cancer controls (37.57% vs. 10.54%) [59]. A statistically significant association was observed between HPV and LC patients (95% CI: 3.09–10.40, $p < 0.001$) with HPV18 and HPV16 being the most common genotypes with a mean of 35.47% in LCs [59]. Hence, due to contradicting results, further studies need to be conducted on the etiological association of HPV with LC, as well as its prevalence in Pakistan.

Breast cancer is the most common cancer in women in Pakistan, with the highest incidence in Asia. In 2020, 25928 new cases and 13,725 deaths were reported [57]. Very limited data is available from Pakistan regarding role of HPV in causation of breast cancer. The present study reported a 17.7% (53/296) prevalence of HPV in breast cancers which is a matter of serious concern [39], [40] (Table 5). The role of HPV in the pathogenesis of breast cancer is an active debate fuelled by contradicting reports. However, a meta-analysis conducted in 2010 revealed that 24.49% of breast carcinoma cases were associated with HPV, 32.42% occurred in Asia, and 12.91% in Europe [60]. The four most commonly identified HPV genotypes, in the order of decreased prevalence, were HPV33, 18, 16, and 35 [60]. Another meta-analysis conducted in 2016 on case-control studies reported that with an increase in HPV infection, risk of breast cancer increases (SOR = 4.02, 95% CI: 2.42-6.68; I2 = 44.7%) [61]. Both the studies suggested that it is difficult to rule out the possibility of the association between HPV and breast carcinoma at present according to available publication proofs. Hence, further research must be conducted on the prevalence of HPV in breast cancer to develop a proper strategy for an easily prevented disease and a reduced breast cancer burden nationwide.

Limitations

There are some limitations of the present study. The study period is limited from 2007 to 2018 as the data on HPV prevalence were available during this time period only. Pakistan is a vast country consisting of four provinces, and the HPV prevalence in a few cities was stated in a limited number of studies or not assessed at all. Therefore, the population in our study might not be the representation of the entire general population of Pakistan. The raised discrepancy between studies might influence the exact prevalence of HPV infection, which may be due to different geographical areas, sample types, HPV identification methods, and patients characteristics such as age and gender. Therefore, large population-based sample size is required for the improved evaluation of HPV prevalence in Pakistan. Moreover, as this review only assesses the prevalence of HPV infection in Pakistan, hence, it is recommended to carry out a worldwide systematic review on HPV prevalence.

Conclusion

The prevalence of HPV has been increased in Pakistan in recent years confirming the high prevalence of HPV. However, very few studies mostly targeting

small population groups with varied data have been conducted on HPV prevalence and its association with the general population, normal cervical region, CC, normal oral mucosa, oral addictive habits, oral pre-malignant lesion, OC, esophageal region, LC, and breast cancer. The largest association of HPV has been observed in OC followed by CC and then breast cancer whereas a debatable association was observed with esophageal and LC. Diseases associated with HPV are preventable; therefore, it is essential and beneficial to plan for starting comprehensive awareness, screening, and vaccination programs in this region to decrease the burden of HPV infection and its associated diseases.

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