Research article

Patterns of single and multiple HPV infections in female: A systematic review and meta-analysis

Dan Zhou [a,d], Jing Xue [b], Yaqiong Sun [c], Liling Zhu [d], Ming Zhao [a,d], Meimei Cui [a,e], Min Zhang [a,d], Jingjing Jia [a,f], Limei Luo [a,*]

[a] Maternal and Child Health Development Research Center, Shandong Provincial Maternal and Child Health Care Hospital Affiliated to Qingdao University, Jinan, China
[b] Department of Obstetrics and Gynecology, Shandong Provincial Hospital, Jinan, Shandong, China
[c] Key Laboratory of Birth Regulation and Control Technology of National Health Commission of China, Shandong Provincial Maternal and Child Health Care Hospital, Jinan, China
[d] School of Public Health, Jiamusi University, Jiamusi, Heilongjiang, China
[e] School of Basic Medical, Weifang Medical University, Weifang, China
[f] School of Basic Medical, Jiamusi University, Jiamusi, China

ARTICLE INFO

ABSTRACT

Background: Data on the patterns of single and multiple HPV infections are largely limited to small size studies, and the regional difference have not been systematically examined.
Methods: A literature search was conducted using PubMed, Embase, and Web of Science databases up to Sept 22, 2023. The pooled prevalence of HPV infection were calculated using random-effects meta-analysis. Subgroup analysis was used to explore the heterogeneity, and publication bias was evaluated by Egger's test and Begg's test.
Results: There were 121 studies included with 1,682,422 participants. Globally, the most common genotypes of single HPV infection were HPV16 (7.05 %), 18 (1.94 %), 52 (1.93 %), 58 (1.68 %), and 31 (1.53 %), as well as HPV 16 (4.91 %), 31 (2.68 %), 52 (2.20 %), 51 (1.99 %), and 18 (1.96 %) in multiple HPV infections. Apart from HPV16 and 18, HPV52 and 58 were common in Asia, HPV31 and 51 was in Europe, North and South America, and HPV35 and 45 were in Africa. The prevalence of HPV infection among different age groups (<30, 30–50, >50 years age groups) was 20.93 %, 16.27 %, and 18.69 %, respectively. The single HPV infection prevalence in the No-ILs, LSILs, HSILs, and cervical cancer groups were 16.17 %, 51.60 %, 57.12 %, and 62.88 %, respectively, as well as in multiple infections were 5.09 %, 30.93 %, 32.86 %, and 21.26 %
Conclusion: Developing local HPV vaccines is necessary based on the HPV infection pattern. It is essential to educate young women to get vaccinated and encourage elderly women to have regular cervical cancer screenings to reduce the danger of cervical cancer.

1. Introduction

Cervical cancer is a widespread gynecological malignancy [1]. Human papillomavirus (HPV) infection are known to be closely

---

* Corresponding author. Maternal and Child Health Development Research Center, Shandong Provincial Maternal and Child Health Care Hospital Affiliated to Qingdao University, NO. 9-7, Jiangshuiquan Road, Lixia District, Jinan, Shandong, China.
   E-mail address: jmsllm@163.com (L. Luo).

related to cervical cancer [2]. HPV vaccination helps prevent certain HPV-related cancers and diseases caused by HPV genotype [3,4]. Studies have shown that HPV infection is associated with age, smoking, sexual activity, number of sexual partners in a lifetime, and immune deficiency [5]. There are more than 450 HPV genotypes, 54 of which are related to genital tract infection [6,7]. Based on its carcinogenic potential, it can be divided into high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV) [8]. Additionally, it can be divided into single infection and multiple infections based on its infection state [9]. To date on the patterns of single and multiple HPV infections have largely been confined to small-sized studies, a systematic review and meta-analysis are essential to gain a comprehensive understanding of the global pattern of HPV infection.

HPV infection varies significantly between different racial and geographical populations, mainly attributed to the complex interplay between HPV genotypes, immune responses, and genetic factors [10,11]. For example, HPV16 is the most common genotypes globally [12], HPV16, 58, and 52 are the predominant genotypes in Asia [13]. HPV16, 39, 31, 68, 52, and 51 are the most common in Europe [14]. HPV16, 18, and 39 are the primary genotypes in North America [15], and HPV16, 18, 51, and 58 are the most prevalent in South America [16], while in Africa, the five most commonly detected HR-HPV genotypes are HPV16, 52, 35, 18, and 58 [17]. However, due to the regional differences in HPV infection, it is important to tailor the vaccines to the specific patterns of HPV infection in different regions.

The impact of multiple HPV infections on the risk of squamous intraepithelial lesions (SILs) is controversial [18]. Generally, single HPV infection is more common than multiple infections in cases of chronic cervicitis/low-grade squamous intraepithelial lesions (LSILs), while multiple infections are more likely to be found in high-grade squamous intraepithelial lesions (HSILs) [19]. However, some studies have suggested that single HPV infection is more likely to lead to cervical cancer than multiple infections [11,20]. At present, the most effective way to prevent cervical cancer is to take primary and secondary prevention measures.

This study aimed to evaluate the patterns of HPV infection among women globally and regionally, and provide guidance for the development of HPV vaccines, and the regional prevention and treatment of cervical cancer.

2. Methods and methods

2.1. Search strategy and selection criteria

This systematic review and meta-analysis is reported according to PRISMA guidelines [21]. The protocol of this systematic review was published on PROSPERO, number CRD42023472006. Available literature was first searched through the online bibliographic databases PubMed, Embase, and Web of Science databases without language restrictions for studies published from their inception to Sept 22, 2023. The search string used for the research included three main concepts: "human papillomavirus/HPV", "cervical cancer/squamous intraepithelial lesions", "coinfection/multiple infections/single infection". This search strategy, which included all identified keywords and index terms, was customized for each database. The search strategies were detailed in supplementary materials (Table S1).

2.2. Inclusion and exclusion criteria

Inclusion criteria: The study must provide at least one indicator to characterize single and multiple HPV infections in the female genital tract: (1) The number of different infection status of specific genotypes; (2) The number of different infection status of age; (3) The number of different infection status of SILs.

Exclusion criteria were as follows: (1) Duplicates, incomplete data and inaccessible full-text publications; (2) Studies subjects were HPV-positive, vaccinated, males/mixed-sex, pregnant women; (3) Studies of comorbidities with other diseases (HIV, oral cancer, esophageal cancer, and trachoma, etc.).

2.3. Data extraction

The citations were retrieved and imported into EndNote X9 (Thomson Reuters, Stamford, CT, USA), and duplicate records were removed. Each study was validated and checked by two reviewers (DZ and JX) and in case of dispute a third reviewer (LML) was assigned. We extracted the following data from included studies: (1) basic information: first author, year of publication, study region, sample size; (2) the number of HPV-positive (include single infection and multiple infections) cases, the number of sample cases in different age groups (<30, 30–50, >50 years age groups) and different levels of SILs, as well as the number of specific HPV genotype, age, region and SILs grade group. (3) outcome: the prevalence of HPV infection (including single infection and multiple infections), genotype specific HPV, and the prevalence of HPV infection, stratified by region, ages, and SILs grade. Of these, 0.01 % (36/354,656) positive samples could not be distinguished between different infection status and were negligible, and the number of different infection status given in the literature was extracted for this study.

The female genital tumors were classified into four grades of SILs diagnosis: No-ILs, LSILs, HSILs and cervical cancer [22]. We included 17 HR-HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68 73, and 82).

2.4. Statistical analysis

Meta-analyses of the pooled prevalence estimates were carried out by R 4.1.2 (R Foundation for Statistical Computing). We applied the Shapiro-Wilk test and Kolmogorov-Smirnov test for normality to select the closest normal distribution for the meta-analysis. The

heterogeneity was examined using the I^2 statistic. If the heterogeneity was high ($I^2 \geq 50$ % or $p \leq 0.1$), it indicated that there was heterogeneity between each study, and a random effect model was used. Conversely, a fixed effect model was selected. SPSS26 (IBM Corp., Armonk, NY, USA) was used to conduct $\chi2$ test to compare the prevalence of HPV infection across different age groups. A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled results. Subgroup analyses were performed to explore the heterogeneity according to the following characteristics: sample source, sample size, study region, year of publication, as well as HPV-positive characteristics. Publication bias was evaluated using Egger's test and Begg's test. Differences were considered as statistically significant when $p < 0.05$.

3. Results

3.1. Characteristics of include literature

This study identified 3741 relevant studies, with 942 duplicates excluded. After reading the titles and abstracts, 2588 studies were excluded, and the remaining 211 studies were read in full-text. According to the inclusion and exclusion criteria, 121 literature were rescreened and ultimately included with 1,682,422 samples (Fig. 1). Most studies involved Asia (51 %), Europe (24 %), Africa (12 %), South America (7 %), and North America (6 %). The publication period extended from 1997 to 2023. The details were in the supplementary materials (Table S2).
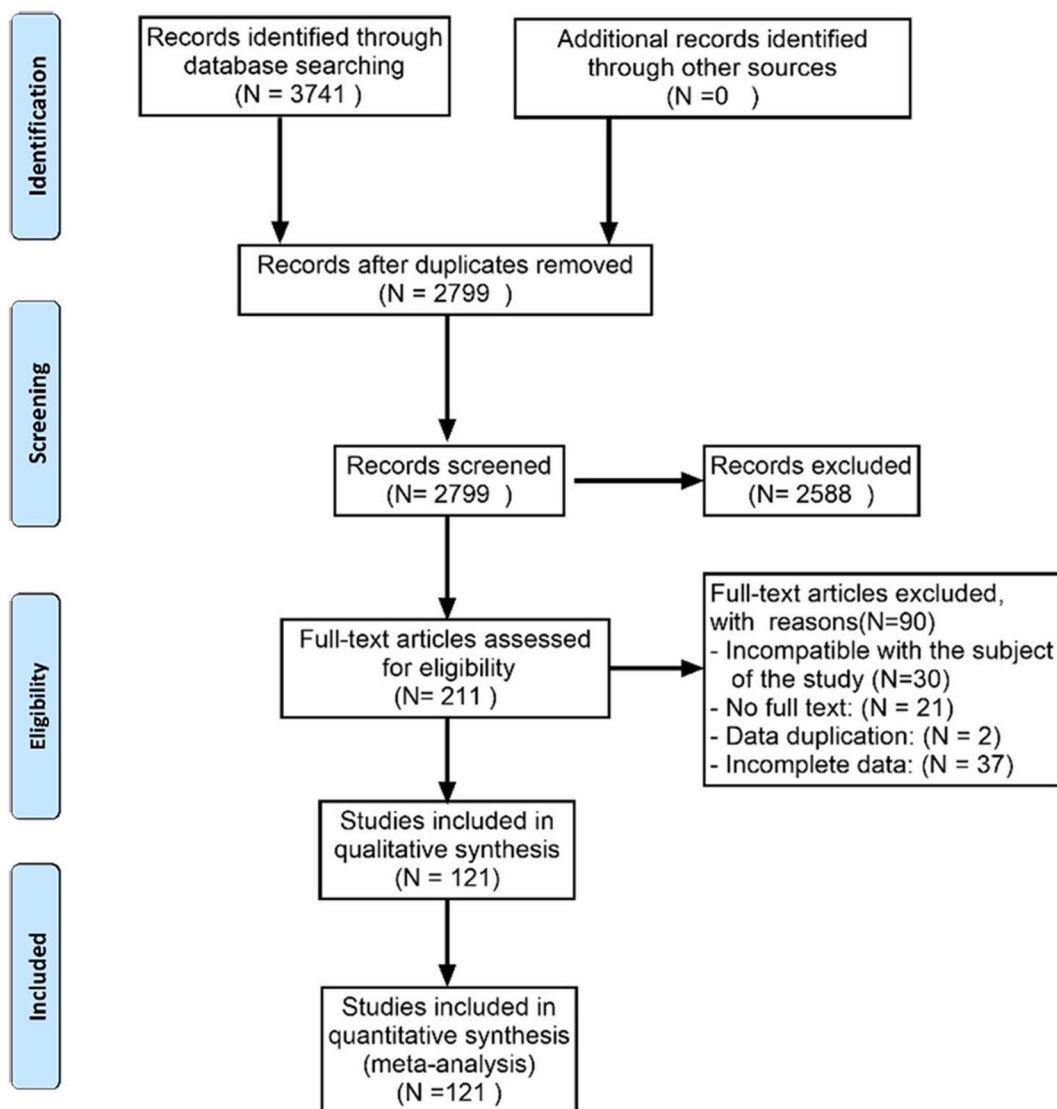

Fig. 1. PRISMA flow diagram of the studies included in meta-analysis.

3.2. Analysis of HPV infection

The pooled prevalence of HPV infection was 53.72 % (95 % CI: 46.25%–61.02 %), and the prevalence of single infection and multiple HPV infections was 25.60 % (95%CI: 22.59%–29.01 %), 13.43 % (95 % CI: 11.16%–16.08 %), respectively.

Globally, the genotypes of single HPV infection were HPV16 (7.05 %), 18 (1.94 %), 52 (1.93 %), 58 (1.68 %), and 31 (1.53 %), and the genotypes of multiple infections were HPV16 (4.91 %), 31 (2.68 %), 52 (2.20 %), 51 (1.99 %), and 18 (1.96 %). In addition toHPV16 and 18, HPV52 and 58 were prevalent in Asia, HPV31 and 51 were common in Europe, North and South America. Furthermore, HPV35 and 45 appeared to be restricted to Africa. The details of HPV infection in various regions were shown in Table 1.

3.3. Analysis of age and HPV infection

The participants were divided into three groups according to age (<30, 30–50, >50 years age group). The HPV infection prevalence calculated for each age group ranged from 16.27 % to 20.93 %, the prevalence initially decreased from the peak observed among women <30 years age group (20.93 %) until the 30–50 years age group (16.27 %), there is an increasing trend at >50 years age group (18.69 %). After stratification by age, single HPV infection was dominant in all age groups, with the highest prevalence in the <30 years age group (13.70 %). The trend in multiple HPV infections was consistent with the overall trend. The highest prevalence of multiple infections was in the <30 years age group (7.23 %), followed by the >50 years age group (5.74 %) Trends in the proportional distribution of single and multiple HPV infections were roughly the same as for HPV infection prevalence. The difference between age and HPV infection was statistically significant ($p < 0.001$), (Table 2).

3.4. Analysis of single and multiple HPV infections in SILs

There were statistically significant differences in single infection and multiple infections among different SILs ($p < 0.001$). The single HPV infection prevalence in the No-ILs, LSILs, HSILs, and cervical cancer groups were 16.17 %, 51.60 %, 57.12 %, and 62.88 %, respectively, as well as in multiple infections was 5.09 %, 30.93 %, 32.86 %, and 21.26 % (Table 3). Multiple HPV infections are associated with a greater risk of LSILs and HSILs as the duration of the infection was longer, which may speed up the development of cancer.

3.5. Sources of heterogeneity, sensitivity analysis, and publication bias

The heterogeneity between studies was significant, and $I^2 = 99.9$ %. Therefore, the random-effects model was used in the meta-analysis. Subgroup analysis was conducted based on sample source, sample size, study region, publication year, and HPV positive characteristics. The results showed that sample source, sample size, region and year of publication were the main heterogeneity sources of HPV infection (Table 4). With regard to "leave one out" sensitivity analysis, the pooled prevalence of HPV infection remained stable, indicating the reliability of the meta-analysis. According to the Egger's test ($p = 0.059$) and Begg's test ($p = 0.078$), no publication bias was found in this study.

4. Discussion

The study, which summarized 121 studies, aimed to understand the pattern of HPV infection of female genital tract in different regions. This study would provide data support for the development and vaccination of HPV vaccines, as well as personalized and regional prevention and treatment strategies for cervical cancer.

We found that the prevalence of HPV infection in women worldwide was 53.72 %, and the single and multiple HPV infections prevalence were 25.60 % and 13.43 %, respectively. Recent studies reported that HPV infection prevalence was 15.13 %–57.86 % [10, 13], Single and multiple HPV infections were 11.62%–44.35 % [10,13] and 2.78%–14.32 % [23,24], respectively, we performed subgroup analysis and found that the prevalence of HPV infection in patients with abnormal cervix was significantly higher than that in normal cervical populations. In addition to the significant regional differences, the sample size was also a notable source of heterogeneity. The majority of studies with smaller sample sizes (less than 500 participants) were SILs populations which exhibited a relatively higher prevalence. The participants (>3000) were mainly screening populations, and the prevalence was relatively low. Our study found the prevalence of HPV in South America was highest (81.84 %), which was noteworthy.

HPV vaccination helps prevent certain HPV-related cancers and diseases caused by HPV genotypes [3,25]. Regarding the impact of vaccination on HPV prevalence, a large number of studies has confirmed the effectiveness of the vaccine in lowering the incidence of HSIL and cervical cancer among vaccinated women [26–28]. The study found that the risk of genital warts was reduced by nearly 40 % with each dose of HPV vaccines and by 80 % overall after three doses of quadrivalent vaccine, compared with unvaccinated controls [29]. HPV infection is known to be a risk factor for cervical cancer [2]. We found that the most widespread HPV genotypes infection worldwide were HPV16, 18, 52, and 58. Our study has demonstrated that HPV31and 51 were the prevalent genotype in Europe, North America, and South America, which was consistent with previous studies [17,30,31,32]. Additionally, HPV33 was common in Asia, and HPV39 was only common in North America [15,33,34], which was consistent with our findings. HPV35 and 45 were only common in Africa, which was in line with previous study [12,35,36.] A meta-analysis study on the prevalence of vaccine and nonvaccine HPV genotypes in Asia and Africa found that HPV35 appears to be the major correlate of cervical carcinogenesis in Africa, also there was currently no vaccine to prevent HPV35 [17]. HPV35 is the second most common HPV genotype in Africa, closely related to the

Table 1
Results of meta-analysis of genotype distribution in different regions.

Genotype	HPV prevalence (%)											
	Global		Asia		Europe		Africa		North America		South America	
	Single infection	Multiple Infection	Single infection	Multiple infection	Single infection	Multiple infection	Single infection	Multiple infection	Single infection	Multiple infection	Single infection	Multiple infection
HPV16	7.05	4.91	6.49	3.07	8.48	8.71	4.32	5.73	12.07	8.50	18.81	19.22
HPV18	1.94	1.96	1.17	0.89	0.96	3.87	2.1	4.75	2.42	3.22	1.97	6.77
HPV31	1.53	2.68	0.69	0.78	2.84	4.53	0.69	2.47	1.16	4.67	2.23	5.76
HPV33	0.74	1.45	0.87	0.87	0.83	1.88	0.04	0.98	0.6	2.19	0.78	2.87
HPV35	0.40	0.98	0.26	0.37	0.43	1.01	1.04	2.85	0.33	1.48	0.77	3.27
HPV39	0.76	1.13	0.75	0.84	0.69	0.92	0.24	0.49	1.59	2.1	0.57	3.18
HPV45	0.49	1.23	0.29	0.3	0.58	1.34	1.35	3.83	0.54	1.93	0.55	2.00
HPV51	1.02	1.99	0.75	0.8	1.49	3.51	0.35	0.67	1.88	2.59	1.61	6.93
HPV52	1.93	2.20	2.39	1.47	1.56	2.97	0.57	1.21	1.92	2.85	1.75	6.57
HPV53	0.73	1.35	0.47	0.72	1.22	2.28	–	–	0.94	2.72	–	–
HPV56	0.73	1.25	0.57	0.64	0.63	1.44	0.88	1.43	0.79	1.91	0.78	3.65
HPV58	1.68	1.96	1.82	1.21	0.92	2.21	1.61	2.03	0.63	2.3	4.28	10.72
HPV59	0.54	1.03	0.52	0.49	0.38	0.44	0.99	2.17	0.51	2.31	0.59	3.03
HPV66	0.63	1.04	0.46	0.35	0.83	1.58	0.63	1.12	0.81	2.24	–	–
HPV68	0.40	0.76	0.52	0.63	0.27	0.82	0.01	0.73	0.35	0.83	–	–
HPV73	0.13	0.55	0.12	0.24	0.18	0.37	0.27	0.62	0.12	1.32	–	–
HPV82	0.13	0.47	0.11	0.15	0.11	0.63	0.38	0.85	0.14	0.68	–	–

Table 2
Characteristics of HPV infection status in women of different age groups.

HPV infection	<30	30–50	>50	χ [2]	p
		Prevalence			
References (n)	29	26	26		
Sample	135846	440786	116546		
Positive (n/%)	28434 [29.06(22.51–37.51)]	71714 [23.54(17.82–31.11)]	21787 [25.36(18.74–34.33)]	1674.17	<0.001
Single HPV infection(n/%)	18606 [17.54(13.66–22.25)]	57174 [18.26(13.58–24.11)]	15084 [17.48(13.32–22.94)]	51.36	<0.001
Multiple HPV infection(n/%)	9826 [9.62(6.65–13.72)]	14538 [5.54 (3.78–8.13)]	6702 [8.85(5.07–13.56)]	4273.94	<0.001
		Percentage			
References (n)	46	43	41	4088.98	<0.001
Single infection (n/%)	38625 (69.01)	116486 (81.67)	32562 (73.58)		
Multiple infection (n/%)	17344 (30.99)	26146 (18.33)	11692 (26.42)		

Table 3
Analysis of single and multiple HPV infections and SILs.

HPV infection status	Histology				χ [2]	p
	No-ILs	LSILs	HSILs	CC		
			prevalence			
References(n)	16	22	29	26		
Sample	146123	13303	12727	4976		
Single infection (n/%)	23629 (16.17)	6864 (51.60)	7270 (57.12)	3129 (62.88)	22767.40	< 0.001
Multiple infections (n/%)	7433 (5.09)	4114 (30.93)	4182 (32.86)	1058 (21.26)	19332.47	< 0.001
			Percentage			
References(n)	25	31	39	33		
Single infection (n/%)	24986 (55.70)	7991 (17.81)	8498 (18.94)	3383 (7.54)	1131.18	< 0.001
Multiple infections (n/%)	8123 (42.81)	4846 (25.54)	4836 (25.48)	1171 (6.17)		

Table 4
Subgroup analysis results of HPV infection prevalence.

Subgroups	No of studies	HPV prevalence (95%CI)	p
Sample source			<0.001
All No-ILs	28	21.18 (17.24–25.74)	
All SILs	48	82.02 (75.35–87.19)	
Mixed No-ILs and SILs	45	40.28 (31.86–49.30)	
Sample size			<0.001
< 500	36	76.97 (68.21–83.89)	
500–3000	44	60.73 (49.17–71.20)	
> 3000	41	25.26 (19.06–32.65)	
Region			<0.001
Asia	67	39.63 (31.30–48.62)	
Europe	30	69.76 (55.19–81.20)	
Africa	8	62.45 (35.99–83.10)	
South America	9	81.84 (70.85–89.31)	
North America	7	61.19 (40.85–78.26)	
Year of publication			0.002
1997–2011	36	66.11 (52.71–77.34)	
2012–2018	42	58.87 (45.98–70.66)	
2019–2023	43	38.11 (28.81–48.37)	
HPV-positive			0.517
Any HPV	109	54.54 (46.70–62.17)	
HR HPV	12	46.20 (24.72–69.18)	

occurrence of cervical cancer in women of African [37]. Therefore, it is essential to screen for HPV35 and treating those infected with HPV45. The HPV genotype in the genitalia belongs to α genus papillomavirus, including α-9 (16, 31, 33, 35, 52, 58), α-7 (18, 39, 45, 59, 68), α-6 (53, 66), α-5 (51) species [38]. A German study reported that nine-valent HPV vaccine reduced anal cancer by 30 % in men and 14 % in women, and that the nine-valent HPV vaccine in boys reduced the incidence of cancer by 24 % [39]. HPV51, a member of tthe α-5 species, is not included in the nine-valent HPV vaccine. HPV51 has shown a higher prevalence, in some cases even surpassing that of HPV16 [32]. A high frequency of multiple infections of HPV 51 with other subtype was found in Italy and Brazil [40,41]. A study in Italy showed that in patients with cervical intraepithelial neoplasia the most common co-infections were HPV 16–18 and 51–52, and also multiple infections of three genotypes, such as HPV 16–51-52 [42]. We recommend the inclusion of HPV51 in HPV vaccines for Europe, North, and South America, as well as HPV35 for Africa. This addition is of great significance for the regional prevention and control of cervical cancer.

It has been speculated that there may be a correlation among different HPV genotypes in multiple infections [43]. There may be antagonistic effects between HPV genotypes in multiple infections [44,45]. Previous studies have shown that multiple infections with α-9 genotype could increase the risk of cervical cancer by 5.3 times, and multiple infections with α-7 genotype could increase the risk of cervical cancer by 2.5 times [46]. Therefore, the same HPV genotype might have a synergistic effect on the induction of cervical cancer by multiple infections. Previous studies have reported that HPV16 existed in most multiple infections and was closely related to cervical cancer [18]. Our study demonstrated that HPV16, when combined with other genotypes (HPV18, 31, 52, 58) constitutes the predominant in patients with multiple infections. Clinical practices should consider these specific genotypes that are more likely to be associated with multiple infections.

We discovered that the prevalence of HPV infection varies among different age groups (<30, 30–50, >50 years age groups), the peak occurred in the <30 years age group, and the second highest rate was observed in the >50 years age group, which was similar to other studies [13,47–50]. Young women were more susceptible to HPV infection, influenced by factors such as sexual activity, hormonal changes, compromised immune systems, and a higher likelihood of acquiring latent viral infections [18]. As women age, the prevalence of HPV infection rises again in >50 years age group, and the effectiveness of their immune system decreases, making them more susceptible to persistent HPV infection or virus activation during the incubation period [51]. Several studies have s reported that the incidence of cervical malignancies exhibits a distinct pattern in all age groups. The occurrence of cervical cancer presents two peak periods: one in women under 30 years old and another in those over 50 years old [12,24,52]. Most sample included in the age groups were from No-ILs population, so the prevalence of HPV infection in all age groups was lower than the pooled prevalence of HPV infection. HPV vaccines demonstrated efficacy in preventing persistent infection and HPV-related precancerous cervical lesions in women within the age range of 27–45 years [53,54]. Additional studies have explored the potential benefits of HPV vaccination in older women, specifically those aged 40–45 years and older. These studies indicate that vaccinating older women can still provide protection against HPV infections and related diseases, such as cervical cancer [55,56,57]. In the UK, the age for discontinuing routine smear tests, known as the 'exit smear' age, is set at 65, meanwhile, in some countries, there are proposals to raise this age limit, enabling women to cease participating in screening programs [58]. Furthermore, the limitations in age stratification within the original study, preclude the possibility of conducting a more nuanced, detailed age-based stratified analysis to reduce HPV infection, it is important for young women (<30 years old) to get vaccinated. Additionally, elderly women (>50 years old) should undergo regular cervical cancer screening.

There was substantial heterogeneity of the included studies. Heterogeneity is often inevitable in meta-analyses of observational studies, and it does not necessarily invalidate the findings [59]. Subgroup analysis found that sample source and sample size are the main sources of heterogeneity of HPV infection. Our study also has certain limitations: (1) Due to limited literature across regions, in the future, we hope to include more data to confirm its reliability. (2) Age stratification is not consistent with the original study, which makes it impossible to make a more detailed stratified analysis of age.

5. Conclusion

Multiple HPV infections aggravate SILs compared with single infection. The development and promotion of HPV vaccines should be carried out based on its regional difference. We advocate for the inclusion of HPV51 in HPV vaccines for Europe, North America, and South America, as well as HPV35 for Africa. It is crucial to raise awareness of the risks associated with HPV infection among young women under 30 years old. Additionally, regular cervical cancer screenings should be made available to women over 50 years old to further reduce the incidence of cervical cancer.

Funding

Ethics approval and consent to participate

No ethical clearance was needed for this publication because all information and data were published previously and were anonymized.

Availability of data and materials

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Dan Zhou: Writing – original draft, Conceptualization. **Jing Xue:** Data curation, Conceptualization. **Yaqiong Sun:** Methodology. **Liling Zhu:** Software. **Ming Zhao:** Methodology, Data curation. **Meimei Cui:** Formal analysis. **Min Zhang:** Formal analysis. **Jingjing Jia:** Data curation. **Limei Luo:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Limei Luo reports financial support, article publishing charges, and statistical analysis were provided by Shandong Provincial Maternal and Child Health Care Hospital Affliated to Qingdao University. Limei Luo reports a relationship with Shandong Provincial Maternal and Child Health Care Hospital Affliated to Qingdao University that includes: employment. Limei Luo has patent pending to Approved. The authors declare no conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35736.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA: a cancer journal for clinicians 66 (2016) 7–30, https://doi.org/10.3322/caac.21332.
[2] F.X. Bosch, A. Lorincz, N. Muñoz, C.J. Meijer, K.V. Shah, The causal relation between human papillomavirus and cervical cancer, Journal of clinical pathology 55 (2002) 244–265, https://doi.org/10.1136/jcp.55.4.244.
[3] M. Falcaro, K. Soldan, B. Ndlela, P. Sasieni, Effect of the HPV vaccination programme on incidence of cervical cancer and grade 3 cervical intraepithelial neoplasia by socioeconomic deprivation in England: population based observational study, Bmj 385 (2024) e077341, https://doi.org/10.1136/bmj-2023-077341.
[4] H.C. Johnson, E.I. Lafferty, R.M. Eggo, K. Louie, K. Soldan, J. Waller, et al., Effect of HPV vaccination and cervical cancer screening in England by ethnicity: a modelling study, Lancet Public Health 3 (2018) e44–e51, https://doi.org/10.1016/s2468-2667(17)30238-4.
[5] K.A. So, I.H. Lee, K.H. Lee, S.R. Hong, Y.J. Kim, H.H. Seo, et al., Human papillomavirus genotype-specific risk in cervical carcinogenesis, Journal of gynecologic oncology 30 (2019) e52, https://doi.org/10.3802/jgo.2019.30.e52.
[6] A.A. McBride, Human papillomaviruses: diversity, infection and host interactions, Nat. Rev. Microbiol. 20 (2022) 95–108, https://doi.org/10.1038/s41579-021-00617-5.
[7] Guidelines for the diagnosis and treatment of cervical cancer (2022 update). http://www.nhc.gov.cn/yzygj/s2911/202204/a0e67177df1f439898683e1333957c74/files/361f086b71214c4e8336fa7d251dc020.pdf.
[8] N. Muñoz, F.X. Bosch, S. de Sanjosé, R. Herrero, X. Castellsagué, K.V. Shah, et al., Epidemiologic classification of human papillomavirus types associated with cervical cancer, N. Engl. J. Med. 348 (2003) 518–527, https://doi.org/10.1056/NEJMoa021641.
[9] M. Arbyn, S. de Sanjosé, M. Saraiya, M. Sideri, J. Palefsky, C. Lacey, et al., EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease, Int. J. Cancer 131 (2012) 1969–1982, https://doi.org/10.1002/ijc.27650.
[10] J. Kim, M. Kim, J.Y. Park, Evaluation of the characteristics of multiple human papillomavirus (HPV) infections identified using the BD Onclarity HPV assay and comparison with those of single HPV infection, J Pathol Transl Med 56 (2022) 289–293, https://doi.org/10.4132/JPTM.2022.08.02.
[11] E.L. Dickson, R.I. Vogel, M.A. Geller, L.S. Downs Jr., Cervical cytology and multiple type HPV infection: a study of 8182 women ages 31-65, Gynecol. Oncol. 133 (2014) 405–408, https://doi.org/10.1016/j.ygyno.2014.03.552.
[12] S. de Sanjosé, M. Diaz, X. Castellsagué, G. Clifford, L. Bruni, N. Muñoz, et al., Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis, Lancet Infect. Dis. 7 (2007) 453–459, https://doi.org/10.1016/s1473-3099(07)70158-5.
[13] Y. Shen, Y. Huang, W. Wang, J. Zhang, X. Chen, L. Zhang, et al., Prevalence and genotype distribution of HPV infection among women in Xiamen, China, Front. Microbiol. 14 (2023), https://doi.org/10.3389/fmicb.2023.1130226.
[14] H. Sousa, A. Tavares, C. Campos, J. Marinho-Dias, M. Brito, R. Medeiros, et al., High-Risk human papillomavirus genotype distribution in the Northern region of Portugal: data from regional cervical cancer screening program, Papillomavirus Res 8 (2019), https://doi.org/10.1016/j.pvr.2019.100179.
[15] M.A. Oyervides-Muñoz, A.A. Pérez-Maya, C.N. Sánchez-Domínguez, A. Berlanga-Garza, M. Antonio-Macedo, L.D. Valdéz-Chapa, et al., Multiple HPV infections and viral load association in persistent cervical lesions in Mexican women, Viruses 12 (2020), https://doi.org/10.3390/v12040380.
[16] P. Dalgo Aguilar, C. Loján González, A. Córdova Rodríguez, K. Acurio Páez, A.P. Arévalo, J. Bobokova, Prevalence of high-risk genotypes of human papillomavirus: women diagnosed with premalignant and malignant pap smear tests in Southern Ecuador, Infect. Dis. Obstet. Gynecol. 2017 (2017), https://doi.org/10.1155/2017/8572065.
[17] J.O. Okoye, C.F. Chukwukelu, S.I. Okekpa, S.I. Ogenyi, I.N. Onyekachi-Umah, A.A. Ngokere, Racial disparities associated with the prevalence of vaccine and non-vaccine HPV types and multiple HPV infections between Asia and Africa: a Systematic Review and Meta-Analysis, Asian Pac. J. Cancer Prev. APJCP 22 (2021) 2729–2741, https://doi.org/10.31557/APJCP.2021.22.9.2729.
[18] J. Na, Y. Li, J. Wang, X. Wang, J. Lu, S. Han, The correlation between multiple HPV infections and the occurrence, development, and prognosis of cervical cancer, Front. Microbiol. 14 (2023) 1220522, https://doi.org/10.3389/fmicb.2023.1220522.
[19] Y. Li, H. Wang, Y. Zhang, X. Jing, N. Wu, Y. Hou, et al., Correlation between multi-type human papillomavirus infections and viral loads and the cervical pathological grade, Int. J. Gynaecol. Obstet. 152 (2021) 96–102, https://doi.org/10.1002/ijgo.13406.
[20] K.L. Salazar, H.S. Zhou, J. Xu, L.E. Peterson, M.R. Schwartz, D.R. Mody, et al., Multiple human papilloma virus infections and their impact on the development of high-risk cervical lesions, Acta Cytol. 59 (2015) 391–398, https://doi.org/10.1159/000442512.
[21] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ 339 (2009) b2700, https://doi.org/10.1136/bmj.b2700.
[22] L.D.C. Alarcón-Romero, J. Organista-Nava, Y. Gómez-Gómez, J. Ortiz-Ortiz, D. Hernández-Sotelo, O. del Moral-Hernández, et al., Prevalence and distribution of human papillomavirus genotypes (1997–2019) and their association with cervical cancer and precursor lesions in women from Southern Mexico, Cancer Control 29 (2022), https://doi.org/10.1177/10732748221103331.
[23] A. Tabibzadeh, M. Panahi, B. Bouzari, M.T. Haghi Ashtiani, F. Zamani, Arzati H. Teimoori, et al., Distribution of human papillomavirus genotypes in suspected women cytological specimens from Tehran, Iran, Iran. J. Microbiol. 14 (2022) 112–118, https://doi.org/10.18502/ijm.v14i1.8812.
[24] H. Zhang, S. Zhang, Prevalence and genotype distribution of human papillomavirus infection among female outpatients in Northeast China: a population-based survey of 110,927 women, Arch. Gynecol. Obstet. 308 (2023) 35–41, https://doi.org/10.1007/s00404-022-06653-7.
[25] T. Malagón, E.L. Franco, R. Tejada, S. Vaccarella, Epidemiology of HPV-associated cancers past, present and future: towards prevention and elimination, Nat. Rev. Clin. Oncol. 21 (2024) 522–538, https://doi.org/10.1038/s41571-024-00904-z.
[26] M. Drolet, É. Bénard, N. Pérez, M. Brisson, Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis, Lancet 394 (2019) 497–509, https://doi.org/10.1016/s0140-6736(19)30298-3.
[27] J.J. Hernandez-Aguado, D. Sánchez Torres, E. Martínez Lamela, G. Aguión Gálvez, E. Sanz Espinosa, A. Pérez Quintanilla, et al., Quadrivalent human papillomavirus vaccine effectiveness after 12 years in Madrid (Spain), Vaccines 10 (2022), https://doi.org/10.3390/vaccines10030387.

[28] C.S. Racey, A. Albert, R. Donken, L. Smith, J.J. Spinelli, H. Pedersen, et al., Cervical intraepithelial neoplasia rates in British Columbia women: a population-level data linkage evaluation of the school-based HPV immunization program, J. Infect. Dis. 221 (2020) 81–90, https://doi.org/10.1093/infdis/jiz422.

[29] E. Herweijer, K. Sundström, A. Ploner, I. Uhnoo, P. Sparén, L. Arnheim-Dahlström, Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study, Int. J. Cancer 138 (2016) 2867–2874, https://doi.org/10.1002/ijc.30035.

[30] P.J.C. Miranda, B.S. Chagas, J.D.C. Silva Neto, Correlation between human papillomavirus infection and histopathological diagnosis of women in Northeast Brazil, J. Med. Virol. 92 (2020) 3799–3806, https://doi.org/10.1002/jmv.26101.

[31] A. Piana, G. Sotgiu, C. Cocuzza, R. Musumeci, V. Marras, S. Pischedda, et al., High HPV-51 prevalence in invasive cervical cancers: results of a pre-immunization survey in North Sardinia, Italy, PLoS One 8 (2013) e63395, https://doi.org/10.1371/journal.pone.0063395.

[32] J. Gallegos-Bolanos, J. Alejandra Rivera-Dominguez, J. Miguel Presno-Bernal, R. Daniel Cervantes-Villagrana, High prevalence of co-infection between human papillomavirus (HPV) 51 and 52 in Mexican population, BMC Cancer 17 (2017), https://doi.org/10.1186/s12885-017-3519-7.

[33] H. Wang, X. Cheng, J. Ye, X. Xu, Y. Hong, L. Sui, et al., Distribution of human papilloma virus genotype prevalence in invasive cervical carcinomas and precancerous lesions in the Yangtze River Delta area, China, BMC Cancer 18 (2018), https://doi.org/10.1186/s12885-018-4330-9.

[34] S. Kumari, V.M. Bhor, Association of cervicovaginal dysbiosis mediated HPV infection with cervical intraepithelial neoplasia, Microb. Pathog. 152 (2021), https://doi.org/10.1016/j.micpath.2021.104780.

[35] L. Bruni, M. Diaz, X. Castellsagué, E. Ferrer, F.X. Bosch, S. de Sanjosé, Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings, J. Infect. Dis. 202 (2010) 1789–1799, https://doi.org/10.1086/657321.

[36] B. Serrano, S. De Sanjosé, S. Tous, B. Quiros, N. Muñoz, X. Bosch, et al., Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions, Eur. J. Cancer 51 (2015) 1732–1741, https://doi.org/10.1016/j.ejca.2015.06.001.

[37] M. Pinheiro, J.C. Gage, G.M. Clifford, M. Demarco, L.C. Cheung, Z. Chen, et al., Association of HPV35 with cervical carcinogenesis among women of African ancestry: Evidence of viral-host interaction with implications for disease intervention, Int. J. Cancer 147 (2020) 2677–2686, https://doi.org/10.1002/ijc.33033.

[38] J. Zhao, Q. Zhan, J. Guo, M. Liu, Y. Ruan, T. Zhu, et al., Phylogeny and polymorphism in the E6 and E7 of human papillomavirus: alpha-9 (HPV16, 31, 33, 52, 58), alpha-5 (HPV51), alpha-6 (HPV53, 66), alpha-7 (HPV18, 39, 59, 68) and alpha-10 (HPV6, 44) in women from Shanghai, Infect. Agents Cancer 14 (2019) 38, https://doi.org/10.1186/s13027-019-0250-9.

[39] M. Dadar, S. Chakraborty, K. Dhama, M. Prasad, R. Khandia, S. Hassan, et al., Advances in designing and developing vaccines, drugs and therapeutic approaches to counter human papilloma virus, Front. Immunol. 9 (2018) 2478, https://doi.org/10.3389/fimmu.2018.02478.

[40] R.R. Figueiredo Alves, M.D. Turchi, L.E. Santos, E.M. Guimarães, M.M. Garcia, M.S. Seixas, et al., Prevalence, genotype profile and risk factors for multiple human papillomavirus cervical infection in unimmunized female adolescents in Goiânia, Brazil: a community-based study, BMC Publ. Health 13 (2013) 1041, https://doi.org/10.1186/1471-2458-13-1041.

[41] A. Piana, G. Sotgiu, P. Castiglia, S. Pischedda, C. Cocuzza, G. Capobianco, et al., Prevalence and type distribution of human papillomavirus infection in women from North Sardinia, BMC Publ. Health 11 (2011) 785, https://doi.org/10.1186/1471-2458-11-785.

[42] A. Spinillo, B. Dal Bello, P. Alberizzi, S. Cesari, B. Gardella, M. Roccio, et al., Clustering patterns of human papillomavirus genotypes in multiple infections, Virus Res. 142 (2009) 154–159, https://doi.org/10.1016/j.virusres.2009.02.004.

[43] M. Plummer, S. Vaccarella, S. Franceschi, Multiple human papillomavirus infections: the exception or the rule? J. Infect. Dis. 203 (2011) 891–893, https://doi.org/10.1093/infdis/jiq146.

[44] K. Sundström, A. Ploner, L. Arnheim-Dahlström, S. Eloranta, J. Palmgren, H.O. Adami, et al., Interactions between high- and low-risk HPV types reduce the risk of squamous cervical cancer, J. Natl. Cancer Inst. 107 (2015), https://doi.org/10.1093/jnci/djv185.

[45] Z. Wu, T.-Y. Li, M. Jiang, L. Yu, J. Zhao, H. Wang, et al., Human papillomavirus (HPV) 16/18 E6 oncoprotein expression in infections with single and multiple genotypes, Cancer Prev. Res. 12 (2019) 95–101, https://doi.org/10.1158/1940-6207.CAPR-18-0343.

[46] D. Saslow, D. Solomon, H.W. Lawson, M. Killackey, S.L. Kulasingam, J. Cain, et al., American cancer society, American society for colposcopy and cervical pathology, and American society for clinical pathology screening guidelines for the prevention and early detection of cervical cancer, Am. J. Clin. Pathol. 137 (2012) 516–542, https://doi.org/10.1309/ajcptgd94evrsjcg.

[47] Z. Lan, J. Zhang, H. Li, R. He, Q. Zhao, F. Yang, Prevalence of human papillomavirus genotypes and related cervical morphological results in southern Hunan Province of China, 2018-2020: baseline measures at a tertiary institution prior to mass human papillomavirus vaccination, Front. Microbiol. 13 (2022) 1094560, https://doi.org/10.3389/fmicb.2022.1094560.

[48] H. Li, P. Li, L. Huang, L. Sun, H. Ren, P. Li, Prevalence characteristics of cervical human papillomavirus (HPV) infection in the Zhoupu District, Shanghai City, China, Virol. J. 17 (2020) 84, https://doi.org/10.1186/s12985-020-01352-8.

[49] X. Wang, Y. Song, X. Wei, G. Wang, R. Sun, M. Wang, et al., Prevalence and distribution of human papillomavirus genotypes among women attending gynecology clinics in northern Henan Province of China, Virol. J. 19 (2022) 6, https://doi.org/10.1186/s12985-021-01732-8.

[50] H. Yu, J. Yi, Y.L. Dou, Y. Chen, L.J. Kong, J. Wu, Prevalence and genotype distribution of human papillomavirus among healthy females in beijing, China, 2016–2019, Infect. Drug Resist. 14 (2021) 4173–4182, https://doi.org/10.2147/IDR.S332668.

[51] J. Wang, D. Tang, J. Wang, Z. Zhang, Y. Chen, K. Wang, et al., Genotype distribution and prevalence of human papillomavirus among women with cervical cytological abnormalities in Xinjiang, China, Hum. Vaccines Immunother. 15 (2019) 1889–1896, https://doi.org/10.1080/21645515.2019.1578598.

[52] S. Brismar-Wendel, M. Froberg, A. Hjerpe, S. Andersson, B. Johansson, Age-specific prevalence of HPV genotypes in cervical cytology samples with equivocal or low-grade lesions, Br. J. Cancer 101 (2009) 511–517, https://doi.org/10.1038/sj.bjc.6605165.

[53] L. Wei, X. Xie, J. Liu, Y. Zhao, W. Chen, C. Zhao, et al., Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: a randomized, placebo-controlled trial with 78-month follow-up, Vaccine 37 (2019) 3617–3624, https://doi.org/10.1016/j.vaccine.2018.08.009.

[54] C.M. Wheeler, S.R. Skinner, M.R. Del Rosario-Raymundo, S.M. Garland, A. Chatterjee, E. Lazcano-Ponce, et al., Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study, Lancet Infect. Dis. 16 (2016) 1154–1168, https://doi.org/10.1016/s1473-3099(16)30120-7.

[55] R. Suk, K. Liao, C.X. Bauer, C. Basil, M. Li, Human papillomavirus vaccine administration trends among commercially insured US adults aged 27-45 years before and after advisory committee on immunization practices recommendation change, 2007-2020, JAMA Health Forum 3 (2022) e224716, https://doi.org/10.1001/jamahealthforum.2022.4716.

[56] E.L. Thompson, A. Garg, A.M. Galvin, J.D. Moore, M.L. Kasting, C.W. Wheldon, Correlates of HPV vaccination intentions among adults ages 27-45 years old in the U.S, J. Community Health 46 (2021) 893–902, https://doi.org/10.1007/s10900-021-00968-3.

[57] L.P. Hurley, S.T. O'Leary, L.E. Markowitz, L.A. Crane, J.R. Cataldi, M. Brtnikova, et al., US Primary care physicians' viewpoints on HPV vaccination for adults 27 to 45 Years, J. Am. Board Fam. Med. 34 (2021) 162–170, https://doi.org/10.3122/jabfm.2021.01.200408.

[58] R. Landy, P. Windridge, M.S. Gillman, P.D. Sasieni, What cervical screening is appropriate for women who have been vaccinated against high risk HPV? A simulation study, Int. J. Cancer 142 (2017) 709–718, https://doi.org/10.1002/ijc.31094.

[59] J.J. Noubiap, E.V. Balti, J.J. Bigna, et al., Dyslipidaemia in Africa-comment on a recent systematic review - authors' reply, Lancet Glob Health 7 (2019) e308–e309, https://doi.org/10.1016/s2214-109x(18)30517-5.