Characteristic of persistent Human Papillomavirus infection in women worldwide: A meta–analysis

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Objectives: We aimed to estimate the genotypes distribution of persistent human papillomavirus (HPV) infection in female worldwide, and provided a scientific basis for the prevention strategies of cervical cancer and the development of HPV vaccines.

Methods: Both English and Chinese databases were researched from the inception to July 2023. The pooled persistent HPV infection prevalence was calculated using a random effects model. The subgroup analysis was performed to explore the heterogeneity. Literature bias was evaluated using funnel plot and Egger's test.

Results: Twenty-eight literatures with 27335 participants were included. The pooled prevalence of persistent HPV infection was 29.37% (95%CI=24.05%~35.31%), and the genotypes with the persistent infection prevalence was HPV16 (35.01%), HPV52 (28.19%), HPV58 (27.06%), HPV18 (25.99%), HPV33 (24.37%), HPV31 (23.35%), HPV59 (21.87%), HPV39 (19.54 %), HPV68 (16.61 %) and HPV45 (15.05%). The prevalence of multiple and single HPV persistent infection were 48.66% and 36.71%, respectively; The prevalence of persistent HPV infection in different age groups(< 30, 30 ~ 39 , 40 ~ 49, > 50) were 29.83%, 28.39%, 22.24% and 30.22%, respectively. The follow-up time was significantly associated with heterogeneity by subgroup analysis (p<0.05), and the prevalence of persistent infections decreased with longer follow-up time.

Conclusions: Multiple infections were more likely to occur persistent HPV infection than single infection. In addition to HPV vaccination, we should emphasize the follow-up management for women under 30 and over 50 years old, women with high-risk HPV infections (HPV59, 39, 68) and multiple infections.

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Abstract

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Keywords: human papillomavirus; HPV; persistent infection; genotype; meta-analysis

Introduction

Cervical cancer (CC) is a common malignant tumor, and ranks the fourth in the incidence of female malignant tumors in the world [1]. It is the only cancer with definite etiology that can be controlled if treated in early stage. Persistent high risk-human papillomavirus (HR-HPV) infection is the main cause of the development of CC [2]. HR-HPV infection is common, especially in sexually active young women, but most infections are transient, spontaneous, and have no clinical symptom. However, 10% of women have persistent HR-HPV infection and are at risk of CC and its precursors [3].

HR-HPV is inclined to bring about persistent infection that has reached an agreement [4-7]. To date, the studies mostly focus on the factors that contribute to persistent HPV infection [8,9]. However, there is no agreement on the specific subtypes of persistent HPV infection was prone to occur. In addition, the relationship between the age and persistent HPV infection is still controversial.

In clinical practice, the study of the specific genotype of HR-HPV persistent infection is of great significance to reduce the incidence of high-grade lesions, which can be a helpful guide for the prevention and treatment of CC. Therefore, we conducted a meta-analysis to obtain the distribution and prevalence of persistent HPV infection in female worldwide, which would further optimize the prevention strategies of CC and provide reference for the development of HPV vaccines.

Materials and Methods

The present meta-analysis was performed following the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [10]. The PRISMA 2009 checklist is attached in Fig 1. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the code of CRD42022339057.

Data Source

Relevant literatures on persistent HPV infection from the inception to July 1, 2023 were collected in Chinese National Knowledge Infrastructure database (CNKI), the Wan Fang database, the Chongqing VIP database, PubMed, Embase and Cochrane library. We used subject words and free words with the following search terms: “Human papillomavirus” and “Persistent infection ”.The complete search strategy is as follows: ("Persistent Infection" [Mesh Terms] OR "infection persistent"[Title/Abstract] OR "persistent infections"[Title/Abstract] OR "long term infection"[Title/Abstract]OR" infection long term"[Title/Abstract]OR "long term infections"[Title/Abstract]OR" chronic infection"[Title/Abstract] OR "chronic infections"[Title/Abstract] OR "infection chronic"[Title/Abstract] OR "persistence" [Title/Abstract]) AND ("Alphapapillomavirus" [Mesh Terms] OR "hpv human papillomavirus"[Title/Abstract] OR "hpv human

papillomaviruses"[Title/Abstract] OR "human papillomavirus hpv" [Title/Abstract] OR "human papillomaviruses hpv "[Title/Abstract] OR "humanpapillomavirus" [Title/Abstract] OR" humanpapillomaviruses" [Title/Abstract] OR "papillomavirus human"[Title/Abstract] OR "papillomaviruses human" [Title/Abstract] OR "HPV"[Title/Abstract]).

Selection Criteria

Inclusion Criteria: (1) Any HPV infection that continued for at least six months with the same genotype was classified persistent HPV infection. (2) The literature must provide the number of persistent infection and the number of positives at least three HR-HPV genotypes. (3) The participants in the study were those who tested positive for HPV. (4) The language was limited to Chinese and English.

Exclusion Criteria: (1) Review, conference reports, etc. (2) Literatures that data were incomplete, or could not be calculated or obtained by contacting the authors. (3) The participants who were pregnant, or those who underwent cervical operation, or those with cervical lesions or other microbial infections. (4) Repeated literatures. (5) Literatures with a quality score <5. (6) In the case of some literatures based on the same population, only the study reporting the most detailed literature was included.

Literature Screening and Data Extraction

Two investigators (MZ and DZ) independently screened the literatures and extracted information. In case of disagreements, they were resolved through discussion or by a third investigator (LML). Risk of bias was assessed separately by two reviewers (MZ and DZ) as recommended by PRISMA. Each literature mainly excerpts the following information: (1) Basic information of included literatures: authors, publication time and the research area. (2) Baseline characteristics of each literature: the number of HPV positive cases, the positive numbers of HPV genotypes, the positive numbers of single / multiple infection and positive number by age group (3) Outcome indicators: persistent HPV infection prevalence, the genotypes of persistent HPV infection prevalence, the persistent HPV infection prevalence in each age group, single/ multiple persistent HPV infection prevalence.

Outcome measurements

The primary outcome of this study was to estimate the prevalence of persistent HPV Infection.

Quality Evaluation of the Literatures

The quality of literatures was assessed by the Agency for Healthcare Research and Quality (AHRQ) checklist. The AHRQ cross-sectional evaluation scale was used to evaluate 11 items with a total score of 11. The higher the total score, the higher the quality of the literature. The

higher the total score, the higher the quality of the literature. The quality of the study was assessed as follows: low quality = 0 ~ 3; moderate quality = 4 ~ 7; and high quality = 8 ~ 11.

Statistical Analysis

We used a systematic analysis approach to calculate the pooled prevalence of HPV persistent infection for all eligible literatures. A random effects model was selected to summarize the effect size. Results of the meta-analysis were reported as pooled prevalence of persistent HPV infection with 95% confidence intervals (CIs). R 4.1.2 (College Station, Texas, USA) was used for the pooled single prevalence of Meta-analysis, Moreover, the heterogeneity between literatures was evaluated with the I^2 index. If $I^2 \geqq$ 50% or $P < 0.05$, the heterogeneity was considered to be significant. Subgroup analysis was performed to investigate the variation between literatures. Finally, we performed subgroup analysis of the study region, year of publication, sample size, quality scores, follow-up time and the source of sample. Finally, literature bias was analyzed by funnel plot and Egger's test. SPSS 26 (Armonk, NY: IBM Corp) was used to perform χ^2 test to find the differences of the persistent HPV infection prevalence in different age groups, and we considered $P < 0.05$ to be significant. To calculate the prevalence of persistent HPV infection, divide the number of persistent HPV infections by the total number of positive cases[11,12].

Results

Characteristic of Included Literatures

Using the search strategies, 10129 literatures were identified, and 2377 duplicates were excluded. After screening the titles and abstracts, 7700 unqualified literatures were eliminated by assessing and reading the full text of each article. Of the remaining 52 literatures, further screening was conducted based on the inclusion and exclusion criteria. Finally, 28 literatures were selected and illustrated in Fig.1. These literatures were from 12 different countries, with the majority of them from China, followed by Denmark, Netherlands, India, Brazil, Italy, Britain, Colombia, Canada, Ghana, United States and South Korea.

The quality of each literature included in the study was evaluated according to the AHRQ. Quality scores of the literatures ranged from 5 to 9, with an average of 7, which can be seen in Table 1. All of the literatures were considered adequate for inclusion in this meta-analysis. 10 literatures had a score of ≥ 8, indicating high-quality studies, and 18 literatures had a score of 4 ~ 7, indicating medium-quality studies. The characterization of the selected literatures was summarized in Table 1.

Overall prevalence of Persistent HPV Infection

The total number of positive results was 26170, and 8706 of them were persistent HPV infection. The overall pooled persistent HPV infection prevalence was 29.37% (95 % CI =24.05% ~ 35.31%), and the forest plot was shown in Fig.2.

The global prevalence of persistent HPV infections by genotypes was HPV16 (35.01%), HPV52 (28.19%), HPV58 (27.06%), HPV18 (25.99%), HPV33 (24.37%), HPV31 (23.35%), HPV59 (21.87%), HPV39 (19.54%), HPV68 (16.61%), and HPV45 (15.05%).

The prevalence of persistent HPV infection in different continents has been established. The top five genotypes in Asia were HPV58 (32.92%), HPV16 (31.65%), HPV52 (29.99%), HPV18 (27.59%), and HPV59 (24.46%). The top five genotypes in Europe were HPV16 (40.21%), HPV31 (38.03%), and HPV33 (33.30%), HPV18 (29.53%, and HPV45 (26.27%), as shown in Table 2.

Prevalence by Multiple/Single infection

The prevalence of multiple persistent HPV infection was 48.66% (95%CI: 9.80% ~ 87.52%), and the single HPV infection prevalence was 36.71% (95%CI=18.54% ~ 57.05%). Compared with single HPV infection, the prevalence of multiple persistent HPV infections was higher ($P < 0.05$), and the prevalence by multiple/single infection was listed in Table 3.

Prevalence by Age

Five studies evaluated the age-specific prevalence, the infection prevalence in these age groups (< 30 years, 30 ~ 39 years, 40 ~ 49 years, > 50 years) were 29.83%, 28.39%, 22.24% and 30.22%, respectively. The results of persistent HPV infection prevalence at different ages were shown in Table 4.

Sources of Heterogeneity, Sensitivity Analysis, and Literature Bias

The heterogeneity test showed that there was significant heterogeneity among the literatures ($I^2 = 98.2\%$, $P < 0.01$), so the random effect model was used in the meta- analysis. Subgroup analysis was conducted according to the area, year of publication, sample size, quality score, follow-up time and the source of sample to explore the heterogeneity. As a rule, at least 3 studies should be available per subgroup. The results showed that the follow-up time might be the sources of heterogeneity ($P < 0.05$). The prevalence of persistent HPV infection decreased gradually with a longer follow-up time. According to the leave-1-out sensitivity analysis, the pooled prevalence of persistent HPV infection was relatively stable. No publication bias was found in the present study according to the results of both funnel plot and Egger's test ($P = 0.085$), as shown in Fig.3-5.

Discussion

This systematic review and meta-analysis presented the most recent information about the distribution and prevalence of persistent HPV infection in women globally. Debate is still ongoing regarding the genotypes of CC resulting from persistent HPV infection [20,21]. A total of 28 studies across 12 countries were identified to evaluate the distribution of persistent HPV infection, providing evidence for the screening, diagnosis, treatment of cervical cancer and the development of HPV vaccines.

Persistent infection with HR-HPV is the primary cause of cervical precancerous lesions or CC [37,38]. More than 200 genotypes of HPV have been recognized, of which more than 40 can infect the genital tract [39]. HPV infection is common, especially in young women, and the majority (~ 90%) of newly acquired HPV infection frequently showed a transient course, a phenomenon routinely described as “viral clearance” [40]. Studies have shown that persistent HPV infection varied significantly across different regions [41,42]. The prevalence of persistent HR-HPV infection was 36.1% in the United States [7] and 26.9% ~ 38.8% in Europe [22,43,44]. The study showed that the persistent HPV infection prevalence was 28.38%, which was linked with 27.86% in Shandong, China [17] and 31.40% in Denmark [24], which was lower than a global meta-analysis in 2013 (43%) [8], and it was higher than Korea (12.40%) [20], the difference may due to the target population's risks of persistent HPV infection, along with the gap between baseline and the intervals of follow-up. At present, the international definition of persistence HPV infection is not unified, and the duration of persistent infection was controversial. Subgroup analysis showed that the follow-up time was the source of heterogeneity. The previous studies have shown that Lower prevalence of persistent HPV infection detected in studies with intervals of 12 months or more compared to studies with intervals of 6 months or less [8].

The distribution of HPV varied greatly in different geographic regions among different ethnic groups [11]. The study revealed that the most common genotype of persistent HPV infection was HPV 16, which was followed by HPV 58, 52, 18, 33, 31, 59, 39, 68, 45,these results were different from the previous studies, which revealed that HPV 16 and 18 were the most prevalent and persistent HPV genotypes [45].Liu found HPV58 and53 were the most persistent genotypes, followed by HPV52, 16 and 39 [21]. However, HPV18, HPV58 and HPV16 were the most common high-risk genotypes of persistent infection in other study [25],and the rank of persistent HPV infection was HPV16, 18, 33, 31, 52, 39, 56, 45, 58, 35, 68, 51, 66 in 2013[8]. In Asian populations, HPV52 and HPV58 were more common, especially in China [46,47]. In North China, HPV52 (21.7%) was the most common HR-HPV, followed by HPV58 (18.2%) [48], while the prevalence of HPV52 and HPV58 was lower in Sweden [49]. The prevalence of HPV45 in European countries was relatively high, especially 7% in Sweden [49]. A global study showed the prevalence of HPV45 was 11.6% [50]. However, the prevalence of HPV45 was low in Asia, only 0.5% in Guangdong, China [51] and 2.2% in India [52]. Most of the study population were from Asia, which might contribute to the lower persistent infection prevalence of HPV45, but higher persistent infection prevalence of HPV52 and 58 in current study. Epidemiological evidence has confirmed that HPV carcinogens are mainly HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. HPV68 is a possible carcinogen because it can transform infected cells into malignant tumor cells [53]. These genotypes are called high-risk [54,55]. Although HPV vaccines have been proved to prevent most genotypes of HPV infection [56], currently available 9-valent HPV vaccine do not fully cover all genotypes of HPV related diseases [54]. Andrea found the prevalence of HPV59 reached 11.5% in cervical cancer patients [57], and it was also found in the top five HPV genotypes detected in different regions of the world, such as Ghana [58], China [59]and Switzerland [60]. 31%

CIN1 and 26% CIN2 or above were ascribed to HPV51, HPV53, HPV56, HPV68, and among the 14 HPV genotypes did not covered by the 9-valent vaccine, HPV68 had a higher infection prevalence (9.3%) [61]. A higher prevalence of HPV68 was also found in non-vaccine in 2021 [62]. Most women have not received the HPV vaccination and screening for precancerous lesions is generally effective, as long as abnormal results are effectively managed [63]. Due to the high prevalence of persistent infection and carcinogenesis of HPV 59, 39 and 68 in the biological importance of invasive CC, it was recommended to include them in the next generation of preventive HPV vaccines. Also, to prevent cervical cancer, it was necessary to reinforce the follow-up and detect cervical lesions at an early stage, as well as to extend the duration of clinical intervention. This study found that multiple HPV infections were more likely to occur persistent infection than single infection, which was linked with the previous studies [9,64], the reasons were related to the synergistic effects between different genotypes of HPV infections in multiple infections.

To date, the relationship between age and the persistent HPV infection is still controversial. Some studies have reported that lower age was related with increased risk of persistence infection [65,66]. Additionally, other studies found no association between persistent HPV infection and age [67,68], which might be associated with the age and lifestyle of different populations. This study found significant differences between different age groups. The patients under the age of 30 and those over 50 should receive special attention during follow-up since they were more likely to have persistent HPV infection. Given that young women's reproductive systems are still developing and their bodies don't have enough time to fully clear the HPV infection, the high prevalence of persistent infection in these women under 30 may be caused by frequent or inappropriate sexual behavior. One possible explanation for the high persistent infection prevalence in women over 50 years old is that women's immune function gradually weakens with time, which may lead to HPV escape from the host immune system [69]. This was in line with some studies that women over the age of 50 have a high prevalence of persistent infection[18].

There were some limitations in the study. First, there was substantial heterogeneity of the included studies. Despite the fact that heterogeneity is often unavoidable when conducting meta-analyses of observational studies, it does not necessarily mean that the results are invalid[70]. Second, given the limited data of HPV infections in specific age groups, it was difficult to draw clear conclusions about the relationship between age and persistent HPV infection. Third, due to the limited literatures on specific single / multiple persistent infections, the specific genotypes of multiple infections that are prone to occur persistent HPV infections have not been studied yet. Additionally, the relationship between the genotypes of persistent infections and the grade of cervical lesions will be the focus of our next research.

Conclusion

The results will provide a basis for the development of CC screening strategies and HPV vaccines. In addition to HPV vaccination, we should emphasize the follow-up management for

women under 30 and over 50 years old, women with high-risk HPV infections (HPV59, 39, 68) and multiple infections.

Ethics approval and consent to participate

Not applicable.

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Authors' contributions

Ming Zhao, Dan Zhou, Min Zhang, Liling Zhu and Limei Luo contributed to conceive, design the review, Peipei Kang, Meimei Cui, did the data collection analysis for the study. The manuscript was drafted by Ming Zhao and Dan Zhou and Liling Zhu. Ming Zhao, Dan Zhou, Min Zhang, Liling Zhu and Limei Luo reviewed the manuscript originally submitted and revised it following the reviewer’s comments. The authors have read and approved the content of the final manuscript.

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Availability of data and materials

All relevant data is included within the manuscript file.

Ethics approval and consent to participate

Not applicable here, as this is systematic review and meta-analysis.

Consent for publication

All authors agree to publish this paper.

Competing interests

The authors declare that they have no competing interests.

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Table 1(on next page)

Table 1. Basic features of the included literatures.

Table 1. Basic characteristics of the included literatures.

The first author	Year	Country	Continent	HPV positive number	Case	Follow-up time(months)	Quality score
Xu Y.L.[11]	2021	China	Asia	488	132	24	6
Jin R.[4]	2020	China	Asia	420	-	12	8
Wei D.L.[12]	2019	China	Asia	1586	292	12	6
Zhong X.M.[13]	2018	China	Asia	340	84	12	7
Xu S.S.[14]	2018	China	Asia	1633	347	33	9
Shen L.J.[15]	2018	China	Asia	704	378	12	8
Wang X.Q. [16]	2014	China	Asia	285	74	12	7
Hu M.M.[17]	2021	China	Asia	585	163	12	6
Zhang Q.[18]	2015	China	Asia	760	172	36	6
Long X.[19]	2020	China	Asia	2784	564	24	7
Li M.[6]	2021	China	Asia	10133	4334	24	7
Ingabire C.[20]	2018	South Korea	Asia	105	13	24	8
Liu J.[21]	2020	China	Asia	565	125	12	8
Nielsen A.[22]	2010	Denmark	Europe	1166	314	24	7
Sammarco M. L.[23]	2013	Italy	Europe	55	27	20	6
Stensen S.[24]	2016	Denmark	Europe	2874	901	54	8
Li N.[25]	2017	China	Asia	85	29	12	8
Miranda P. M.[26]	2013	Brazil	South America	89	53	24	6
Cuschieri K. S.[27]	2005	Britain	Europe	126	29	36	5
Sycuro L. K.[28]	2008	America	North America	147	24	36	6
Schmeink C. E.[29]	2011	Netherland	Europe	235	-	25.3	8
Muwonge R.[30]	2020	India	Asia	291	-	10	5
Ye J.[31]	2010	China	Asia	400	218	14	8
Soto-De León S. C.[32]	2014	Colombia	South America	219	-	24	8
Lai C. H.[33]	2008	China	Asia	412	140	23	7
Richardson H.[34]	2003	Canada	North America	124	69	12	7
Bulkmans N. W. J.[35]	2007	Netherland	Europe	620	217	18	7
Krings A.[36]	2019	Ghana	Africa	104	7	48	7

Table 2(on next page)

Table 2. Results of meta-analysis on persistent HPV infection prevalence

1 **Table 2. Results of meta-analysis on persistent HPV infection prevalence.**

HPV subtypes	Persistent infection prevalence % (95%CI)		
	Global	Asia	Europe
HPV16	35.01(29.86~41.06)	31.65(26.36~38.01)	40.21(30.15~50.26)
HPV52	28.19(23.15~34.34)	29.99(23.50~38.28)	24.06(16.55~32.37)
HPV58	27.06(20.31~33.81)	32.92(25.91~39.92)	22.52(18.46~27.46)
HPV18	25.99(19.92~32.50)	27.59(21.22~33.97)	29.53(19.81~41.53)
HPV33	24.37(17.86~31.53)	22.99(17.14~30.10)	33.30(18.87~47.73)
HPV31	23.35(16.58~30.89)	19.28(13.18~26.23)	38.03(24.82~53.29)
HPV59	21.87(13.42~31.71)	24.46(14.00~36.74)	20.25(10.37~39.56)
HPV39	19.54(13.89~25.90)	18.38(12.30~26.55)	22.55(7.70~42.35)
HPV68	16.61(11.52~22.29)	19.21(13.62~25.41)	13.05(5.43~23.33)
HPV45	15.05(9.80~20.93)	14.81(8.57~22.40)	26.27(16.11~42.85)

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Table 3(on next page)

Table 3. Results of single / multiple persistent HPV infection prevalence.

1 **Table 3. Results of single / multiple persistent HPV infection prevalence.**

HPV infection status	Number	Positive number	I^2 (%)	Results of meta-analysis	
				Persistent infection prevalence (%)	95%CI (%)
Multiple infections	3 [18,25,26]	163	92.7	48.66	9.80 ~ 87.52
Single infection	3 [18,25,26]	771	94.0	36.71	18.54 ~ 57.05

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Table 4(on next page)

Table 4. Results of persistent HPV infection prevalence at different ages.

Table 4. Results of persistent HPV infection prevalence at different ages.

Age	The literature number	Positive number	Persistent infection prevalence (%)	χ^2	*p*
< 30	4 [18,22,24,36]	2870	29.83	15.30	0.002
30 ~ 40	4 [18,24,26,36]	1208	28.39		
40 ~ 50	5 [18,20,24,26,36]	643	22.24		
>50	5 [18,20,24,26,36]	321	30.22		

Figure 1

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram to search and identify included studies.

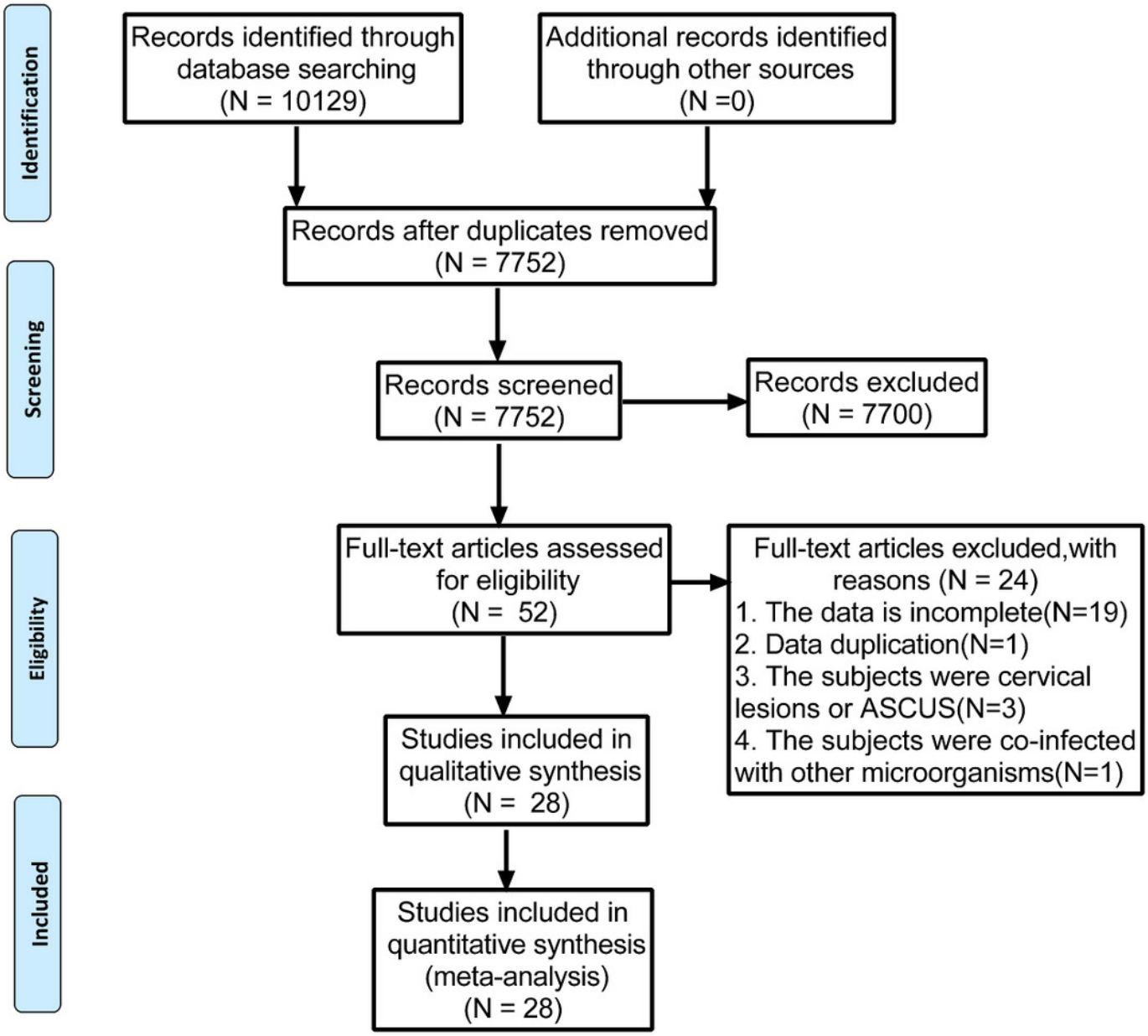

Figure 2

Figure 2. Forest map of persistent HPV infection prevalence

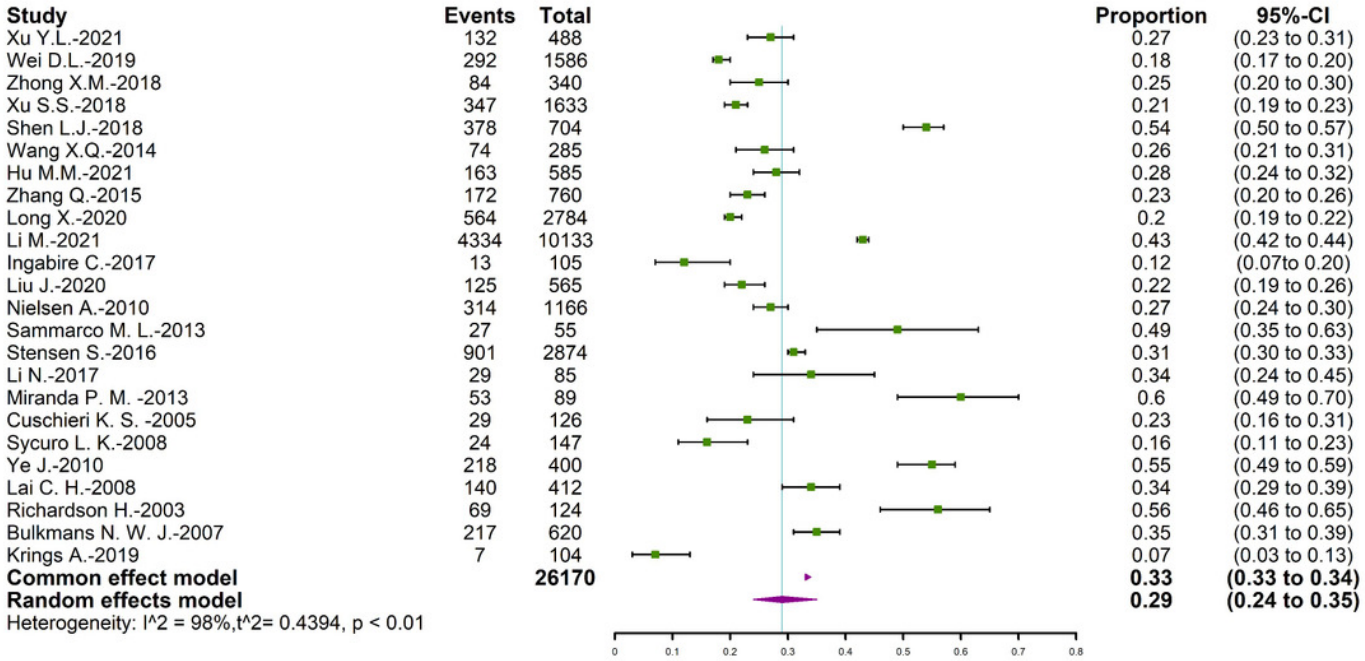

Figure 3

Figure 3. Results of the subgroup analyses to estimation of the prevalence of persistent HPV infection worldwide

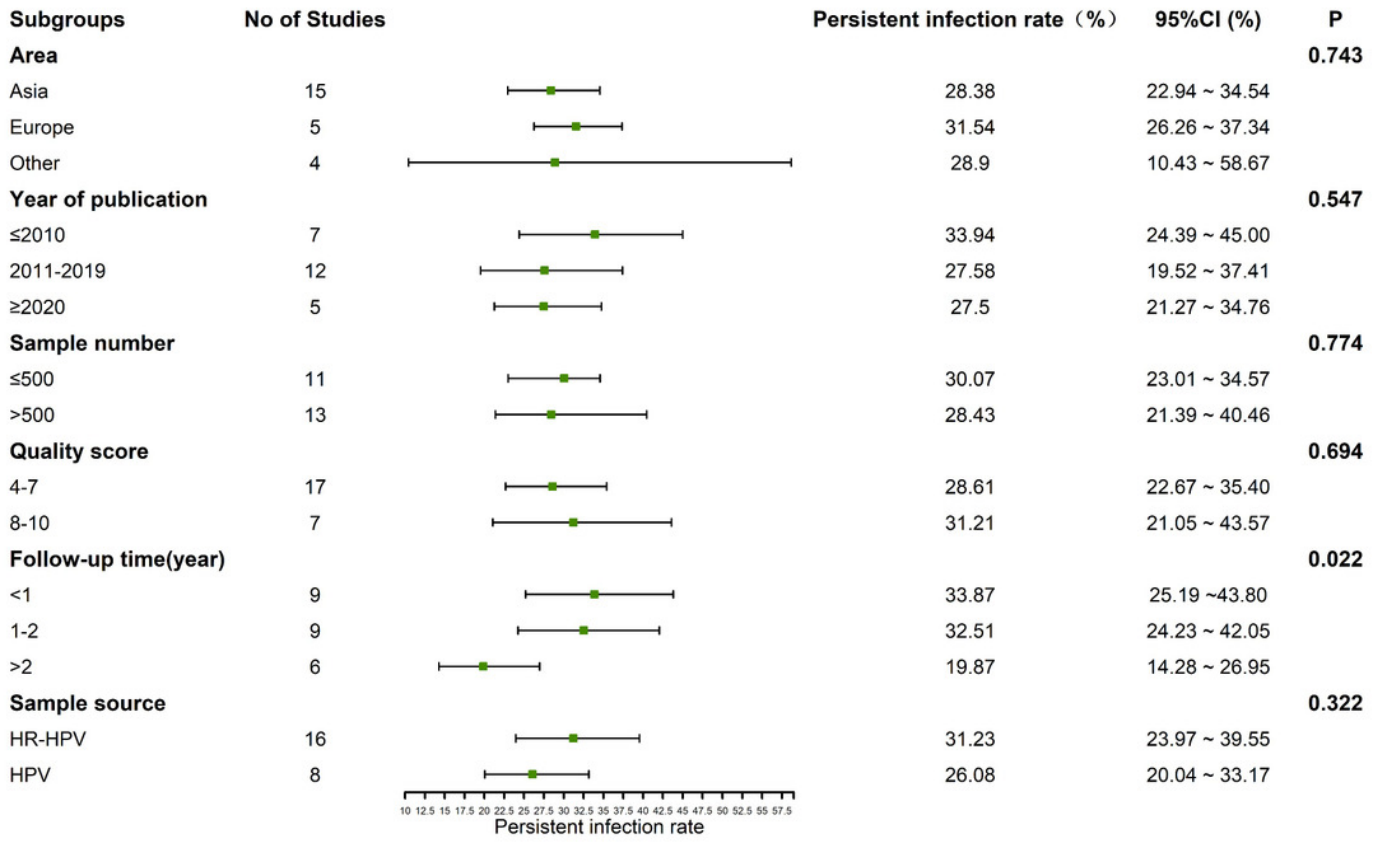

Figure 4

Figure 4. Results of the forest plot to estimation of the prevalence of persistent HPV infection worldwide based on a random-effects model

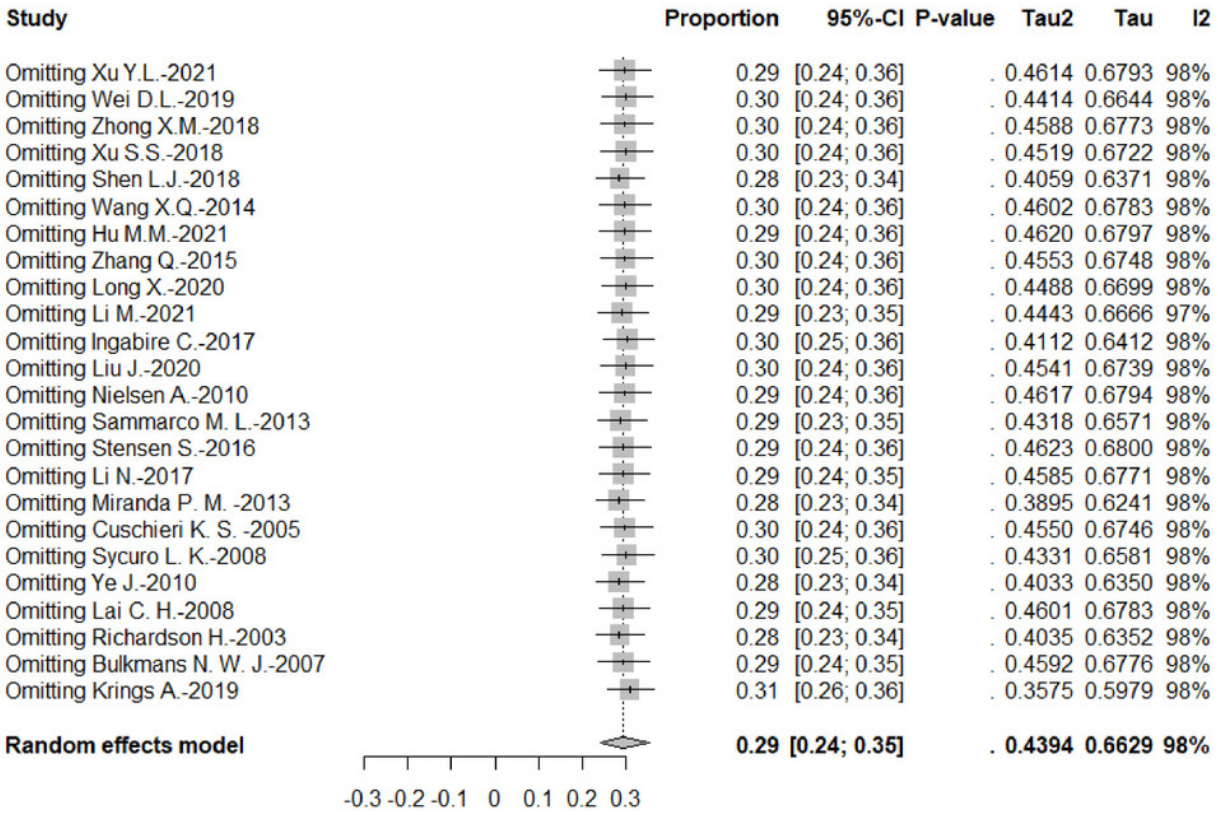

Figure 5

Figure 5. Result of the funnel plot to estimate persistent HPV infection prevalence worldwide