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REVIEW

Association between human papillomavirus and chlamydia trachomatis infection risk in women: a systematic review and meta-analysis

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Abstract

Objectives Human papillomavirus (HPV) and chlamydia trachomatis (Ct) infection lead to severe consequences for women's health. This meta-analysis summarizes the evidence on HPV infection risk in women with chlamydia and chlamydia risk in HPV-positive women.

Methods Medline, Web of Science and Scopus were systematically searched for eligible publications until May 2018. Eligibility criteria included: assessment of HPV/Ct infection; cohort, case–control, cross-sectional study design; and reported risk estimation with its 95% CI for HPV infection in Ct-positive women and/or Ct infection in HPV-positive women. On the PRISMA guidelines, meta-analysis was performed using random effect model.

Results Forty-eight studies met the eligibility criteria. Among women with chlamydia, the odds ratio (OR) of HPV infection is 2.12 (95% CI 1.80, 2.49) and the OR of high-risk HPV infection is 2.32 (95% CI 2.02, 2.65). The OR for chlamydia among HPV-positive women is 2.23 (95% CI 1.70, 2.92).

Conclusions HPV and Ct behave as reciprocal risk factors. In women diagnosed with HPV infection or chlamydia, the screening for the mutual infection could represent a preventive intervention for severe reproductive health outcomes, such as cervical cancer and infertility.

Keywords Meta-analysis · Chlamydia trachomatis · Papillomavirus infections · Sexually transmitted diseases · Systematic review · Women's health

Introduction

Human papillomavirus (HPV) infection and chlamydia are the most common sexually transmitted infections (STI), representing the most common viral and bacterial STI, respectively (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016; Newman et al. 2015). STI prevention and control has widespread public health benefits, as HPV and Chlamydia trachomatis (Ct) untreated infections lead to severe consequences for women's health (WHO 2018). Indeed, HPV is the most important and well-established risk factor for cervical cancer (IARC 1995) and Ct causes serious reproductive tract complications in women, such as pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy (Haggerty et al. 2010; Cates and Wasserheit 1991), and premature pregnancy termination (Rours et al. 2011), and represents the leading cause of tubal factor infertility (WHO 1995; Witkin et al. 2017). Moreover, Ct has been identified as an independent risk

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factor for cervical cancer, both squamous cell carcinoma and adenocarcinoma (Zhu et al. 2016). The prevalence of coinfection by HPV and Ct remains unclearly defined, as HPV infection and Ct infection have commonly an asymptomatic development and may evolve in persistent infection (Witkin et al. 2017; Hoffman et al. 2017). Furthermore, coinfection could relate to worse outcomes, as demonstrated for cervical cancer (Zhu et al. 2016), underlying the relevance of STI prevention and control.

The aim of this systematic review and meta-analysis is to summarize the evidence on the risk of HPV infection in Ct-positive women and the risk of Ct infection in HPV-positive women.

Methods

These systematic review and meta-analysis have been conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al. 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009).

Search strategy and eligibility criteria

We searched the three databases MEDLINE, Web of Science and Scopus, without any restrictions on language, date, or article type, up until May 4, 2018, for studies investigating the risk of Ct infection in HPV-positive women and the risk of HPV infection in women infected with Ct. Articles were identified using the following search terms: ("Chlamydia" OR "Chlamydia trachomatis" OR "Chlamydia infection" OR "Chlamydia trachomatis infection") AND (vaginal OR cervical OR cervix OR vagina) AND ("human papillomavirus" OR "papillomavirus infections" OR "HPV" OR "HPV infection" OR "cervical screening").

Two authors (GN and CG) independently reviewed, assessed the eligibility of titles, abstracts, and studies, and extracted the data. Any disagreements were resolved through discussion with a third author (MC). In addition, we searched the references cited in retrieved articles and recent relevant reviews. The eligibility criteria were defined as follows: (i) assessed the HPV infection or Ct infection in women; (ii) used a cohort, case–control, nested case–control, cross-sectional, or survey study design; and (iii) reported the risk estimation (hazard ratio HR, relative risk RR, or odds ratio OR) as well as its 95% confidence intervals (CI), or sufficient statistics to calculate them, for HPV infection in Ct-positive women and/or Ct infection in HPV-positive women. We excluded studies written in other languages than English, studies providing insufficient or overlapping data and previous reviews and meta-analyses.

Data extraction

Two authors (GN and CG) summarized the following information extracted from the eligible studies: first author, publication year, country, study design, study population characteristics, mean age or age range of patients, Ct/HPV infection assessment method, outcome of interest, and adjustment factors (Electronic Supplementary Material 1—ESM1). Risk estimations and 95% CIs were evaluated.

Outcomes

The outcomes of interest were the detection of Ct in HPV-positive women and the detection of HPV in Ct-positive women. Concerning HPV infection, we grouped HPV genotypes in low-risk HPV (LR-HPV) and high-risk HPV (HR-HPV) according to the literature (IARC 2012; Schiffman et al. 2016). When HPV genotypes were not classifiable in HR- or LR-HPV, or studies reported no detailed HPV genotypes, they have been referred to as "non-classifiable HPV genotypes."

Statistical analysis

The statistical software ProMeta version 3.0 (IDo Statistics-Internovi, Cesena, Italy) was used to perform a meta-analysis of the selected studies.

For the overall estimation, the prevalence odds ratios, HR, RR were taken as an approximation to the OR, and the meta-analyses were performed as if all types of ratio were ORs. All results were reported with a 95% CI, and all P values were two tailed.

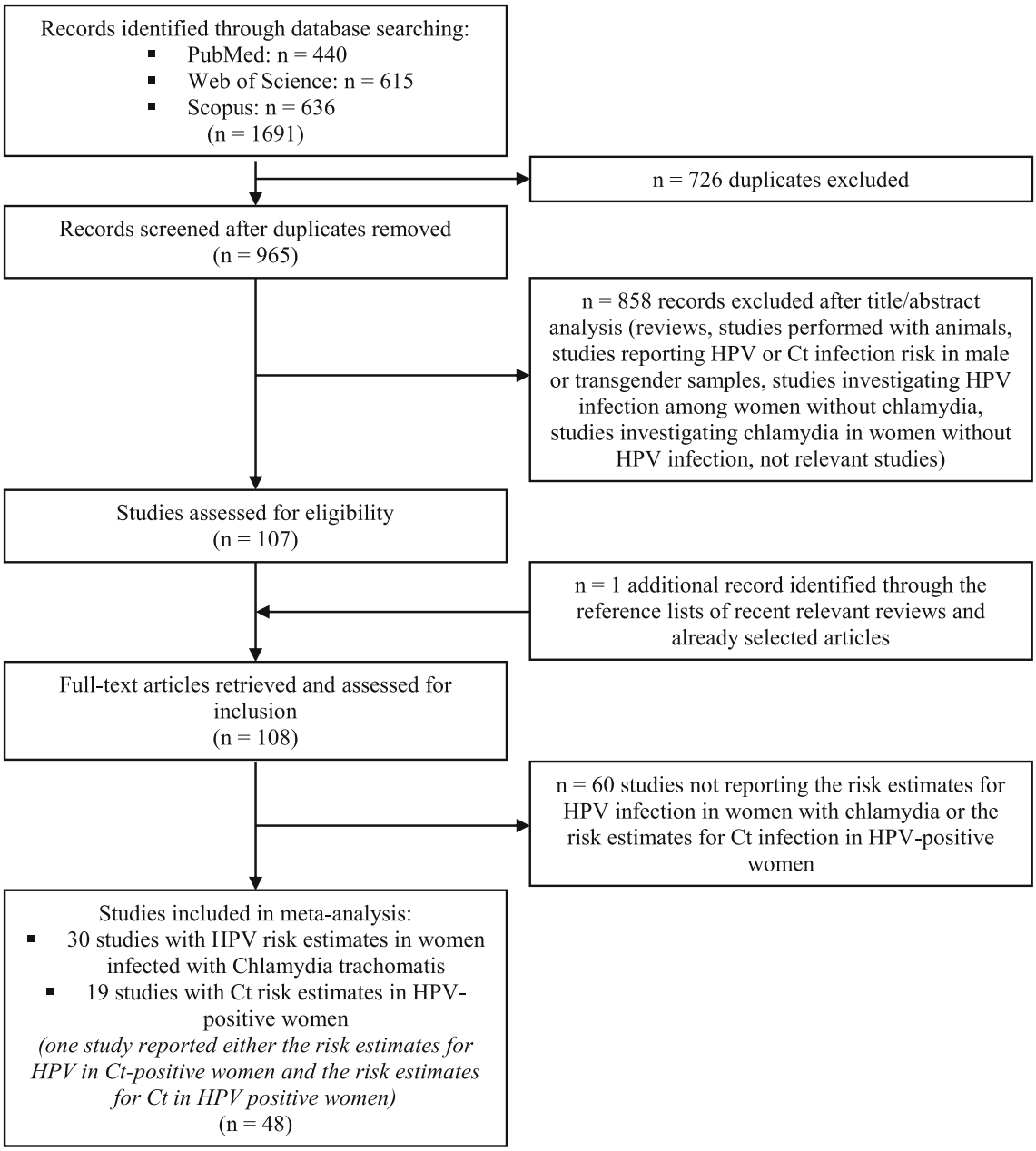
Heterogeneity was assessed by the Cochran's Q statistic (χ^2) and by the I-squared test, deeming $p < 0.05$ as significant. To detect potential publication bias, we performed the Egger's test (Egger et al. 1997) and Begg and Mazumdar's test (Begg and Mazumdar 1994). When a potential publication bias was detected, sensitivity analyses were performed to assess the robustness of our findings. p values reported are from two-sided statistical tests and differences with $p < 0.05$ were considered significant.

We conducted subgroup analyses and several sensitivity analyses to explore the sources of heterogeneity among studies and test the robustness of the associations. Then, we investigated the influence of individual studies on the overall risk estimate, which was estimated by repeating the pooled estimates for the remainder of the studies by omitting a different study at each turn.

Results

Selected studies

Overall, the database search yielded 1691 citations. After excluding the duplicates (n = 726), titles and abstracts were screened and 107 potentially eligible articles were retrieved in full text (Fig. 1). We identified one additional record through the reference lists of already selected articles. We excluded further 60 records, which reported no risk estimates for HPV or Ct infection. Therefore, 30 studies met the inclusion criteria for the risk estimation of HPV infection in Ct-positive women and 19 studies were selected for the analysis on the risk estimation of Ct infection in HPV-positive women (Fig. 1).



Ct Chlamydia trachomatis, HPV human papillomavirus, n number

Fig. 1 Flow diagram of the systematic literature search on MEDLINE, Web of Science and Scopus up until May 4, 2018, for studies investigating the risk of Chlamydia trachomatis infection in HPV-positive women and the risk of HPV infection in women infected with Chlamydia trachomatis

Study characteristics

Table S1 (ESM1) shows the detailed characteristics of the selected studies with HPV risk estimates in Ct-positive women. Among the 30 included studies, 22 investigate HPV risk in women with Ct infection (Zhang et al. 2017; Kim et al. 2011, 2016; Liu et al. 2016; Nonato et al. 2016; Imai et al. 2015; Magaña-Contreras et al. 2015; Vriend et al. 2015; Velentzis et al. 2014; Silva et al. 2013; Oakeshott et al. 2012; Conde-Ferráez et al. 2017; Veldhuijzen et al. 2011; Seth et al. 2009; Verteramo et al. 2009; Oh et al. 2009; Denks et al. 2007; Golijow et al. 2005; Giuliano et al. 2001, 2002; Dong et al. 1998; Karlsson et al. 1995), 7 in women with history of Ct infection (Zoa Assoumou et al. 2016; Castellsagué et al. 2014; Roset Bahmanyar et al. 2012; Boardman et al. 2005; Watts et al. 2005; Kjaer et al. 1997; Muñoz et al. 1996), whereas one explores the risk of HPV infection both in women with Ct infection and history of Ct infection (Jamison et al. 1995). The evaluated outcomes are HPV infection and/or subgroup of HPV infection (HR-HPV and LR-HPV). Regarding the outcomes, 15 studies consider non-classifiable HPV genotypes risk (Verteramo et al. 2009; Conde-Ferráez et al. 2017; Zoa Assoumou et al. 2016; Castellsagué et al. 2014; Silva et al. 2013; Oakeshott et al. 2012; Roset Bahmanyar et al. 2012; Nonato et al. 2016; Boardman et al. 2005; Watts et al. 2005; Giuliano et al. 2001; Dong et al. 1998; Muñoz et al. 1996; Jamison et al. 1995; Karlsson et al. 1995), 8 consider HR-HPV risk (Zhang et al. 2017; Kim et al. 2016; Imai et al. 2015; Vriend et al. 2015; Velentzis et al. 2014; Veldhuijzen et al. 2011; Seth et al. 2009; Oh et al. 2009), 4 estimate non-classifiable HPV genotypes and HR-HPV risk (Liu et al. 2016; Magaña-Contreras et al. 2015; Denks et al. 2007; Golijow et al. 2005), 2 report risk estimation for non-classifiable HPV genotypes, HR-HPV and LR-HPV (Kim et al. 2011; Kjaer et al. 1997) and 1 reports the risk estimation for HR-HPV and LR-HPV risk (Giuliano et al. 2002). Twenty-five articles are cross-sectional studies (Conde-Ferráez et al. 2017; Zhang et al. 2017; Kim et al. 2016; Liu et al. 2016; Nonato et al. 2016; Zoa Assoumou et al. 2016; Imai et al. 2015; Magaña-Contreras et al. 2015; Castellsagué et al. 2014; Velentzis et al. 2014; Silva et al. 2013; Oakeshott et al. 2012; Roset Bahmanyar et al. 2012; Veldhuijzen et al. 2011; Seth et al. 2009; Verteramo et al. 2009; Oh et al. 2009; Denks et al. 2007; Golijow et al. 2005; Giuliano et al. 2001, 2002; Dong et al. 1998; Kjaer et al. 1997; Jamison et al. 1995; Karlsson et al. 1995), 4 are cohort studies (Vriend et al. 2015; Kim et al. 2011; Boardman et al. 2005; Watts et al. 2005) and 1 is a case–control study (Muñoz et al. 1996). Six studies were published before 2002 (Karlsson et al. 1995; Jamison et al. 1995; Muñoz et al. 1996; Kjaer et al. 1997; Dong et al. 1998; Giuliano et al. 2001), 8 in the period 2002–2010 (Giuliano et al. 2002; Watts et al. 2005; Golijow et al. 2005; Boardman et al. 2005; Denks et al. 2007; Oh et al. 2009; Verteramo et al. 2009; Seth et al. 2009) and 16 after 2010 (Veldhuijzen et al. 2011; Kim et al. 2011; Roset Bahmanyar et al. 2012; Oakeshott et al. 2012; Silva et al. 2013; Velentzis et al. 2014; Castellsagué et al. 2014; Vriend et al. 2015; Magaña-Contreras et al. 2015; Imai et al. 2015; Zoa Assoumou et al. 2016; Nonato et al. 2016; Liu et al. 2016; Kim et al. 2016; Zhang et al. 2017; Conde-Ferráez et al. 2017). Eleven studies investigated HPV infection risk among women aged less than 36 years with chlamydia (Nonato et al. 2016; Vriend et al. 2015; Castellsagué et al. 2014; Silva et al. 2013; Oakeshott et al. 2012; Kim et al. 2011; Veldhuijzen et al. 2011; Seth et al. 2009; Kjaer et al. 1997; Jamison et al. 1995; Karlsson et al. 1995). One study investigates HPV risk among HIV-positive and HIV-negative women with Ct infection (Watts et al. 2005).

Table S2 (ESM1) shows the detailed characteristics of the selected studies with Ct infection risk estimates in HPV-positive women. Among the 19 selected studies, 9 articles estimate the risk of Ct infection in HPV-positive women without classifiable genotypes (Fogue et al. 2018; Enthumathi et al. 2015; Panatto et al. 2015; Marcone et al. 2012; Finan et al. 2006; Tábora et al. 2005; Baldwin et al. 2004; da Silva et al. 2004; Tamim et al. 2002), 4 consider Ct infection risk in women with HR-HPV infection (Harder et al. 2016; Aghaizu et al. 2014; Yin et al. 2013; Oh et al. 2009), 3 consider Ct infection risk among women with infection by HR-HPV and LR-HPV (Safaeian et al. 2010; Pereira et al. 2010; Franceschi et al. 2007), one evaluates the Ct infection risk among women infected with non-classifiable HPV genotypes, HR-HPV and LR-HPV, single and multiple infection (Molano et al. 2003), one considers the Ct infection risk in women with history of non-classifiable HPV genotypes infection (Hwang et al. 2014) and one estimates Ct infection risk among women with HR-HPV multiple infections (Quinónez-Calvache et al. 2016). We classified the studies considering the HPV prevalence (Bruni et al. 2010) in the study location: 10 studies were categorized as "low prevalence countries" (Harder et al. 2016; Panatto et al. 2015; Aghaizu et al. 2014; Enthumathi et al. 2015; Hwang et al. 2014; Yin et al. 2013; Marcone et al. 2012; Oh et al. 2009; Finan et al. 2006; Tamim et al. 2002) and 7 as "high prevalence countries" (Fogue et al. 2018; Quinónez-Calvache et al. 2016; Safaeian et al. 2010; Pereira et al. 2010; Tábora et al. 2005; Molano et al. 2003; da Silva et al. 2004). Two multisite studies (Franceschi et al. 2007; Baldwin et al. 2004) were not classified as conducted in countries with different HPV prevalence. Thirteen are cross-sectional studies (Fogue et al. 2018; Harder et al. 2016; Enthumathi et al. 2015; Panatto et al.

2015; Aghaizu et al. 2014; Yin et al. 2013; Marcone et al. 2012; Pereira et al. 2010; Oh et al. 2009; Franceschi et al. 2007; Finan et al. 2006; Tábora et al. 2005; Baldwin et al. 2004), 3 are cohort studies (Quinónez-Calvache et al. 2016; Hwang et al. 2014; Molano et al. 2003), 2 are case–control studies (da Silva et al. 2004; Tamim et al. 2002) and 1 is a nested case–control study (Safaeian et al. 2010). Ten studies were published until 2010 (Tamim et al. 2002; Molano et al. 2003; Baldwin et al. 2004; da Silva et al. 2004; Tábora et al. 2005; Finan et al. 2006; Franceschi et al. 2007; Oh et al. 2009; Pereira et al. 2010; Safaeian et al. 2010) and 9 after 2010 (Marcone et al. 2012; Yin et al. 2013; Hwang et al. 2014; Aghaizu et al. 2014; Panatto et al. 2015; Enthumathi et al. 2015; Quinónez-Calvache et al. 2016; Harder et al. 2016; Fogue et al. 2018). Eight studies investigated the risk of chlamydia in HPV-positive women aged less than 36 years (Harder et al. 2016; Panatto et al. 2015; Aghaizu et al. 2014; Hwang et al. 2014; Yin et al. 2013; Pereira et al. 2010; Tábora et al. 2005; da Silva et al. 2004).

Meta-analysis on the risk of HPV infection in Ct-positive women

Twenty-two studies reported the risk estimation as OR, 2 as prevalence odds ratio, 2 as HR and one as RR. The OR estimated in this meta-analysis represents the odds that HPV infection will occur given a diagnosis of Ct infection, compared to the odds of the outcome occurring in the absence of Ct infection. The results are shown in Table 1.

In the overall analysis (*n*.30 studies, *n*.40 effect sizes), we observed a significantly increased risk (OR 2.12; 95% CI 1.80, 2.49) of HPV infection in Ct-positive women (Figure S1a in ESM2), but heterogeneity resulted significantly extreme (I^2 82.70%, $p < 0.0001$). The stratified analyses for HPV genotypes showed a significantly increased risk of infection by non-classifiable HPV genotypes (OR 2.00; 95% CI 1.61, 2.48) with a significantly extreme heterogeneity (I^2 86.97%, $p < 0.0001$) and by HR-HPV (OR 2.32; 95% CI 2.02, 2.65). We observed no statistically significant association with LR-HPV. The HPV infection was associated either to the actual infection with Ct (OR 2.21; 95% CI 2.00, 2.45) and to a positive history of Ct (OR 1.72; 95% CI 1.27, 2.33) with a significantly extreme value of heterogeneity (I^2 92.47%, $p < 0.0001$). Stratifying by study design, we found a significantly increased risk for cross-sectional/case–control studies (OR 2.28; 95% CI 2.07, 2.52), while the analysis on cohort studies showed no significant association and a significantly extreme heterogeneity (I^2 87.57%, $p < 0.0001$). The risk of HPV infection in women with chlamydia resulted significantly increased in every period of publication (Table 1). In the period 2002–2010 we observed an extremely high heterogeneity (I^2 85.55%, $p < 0.0001$). Stratifying by age group, the HPV infection risk resulted significantly increased among women aged less than 36 years (OR 2.04; 95% CI 1.75, 2.38). The forest and funnel plots are shown in ESM2.

Sensitivity analyses

In the sensitivity analyses, no single study substantially modified the overall analysis results, with the exclusion of the study by Watts et al (2005). The analyses performed omitting the study by Watts et al. (2005) showed that Ct-positive women had a higher overall risk of HPV (OR 2.18; 95% CI 1.88, 2.54) and a higher risk of infection with non-classifiable HPV genotypes (OR 2.11; 95% CI 1.71, 2.62). The omission of the study of Watts et al. (2005) reduced the heterogeneity, which remained however extremely high (overall risk of HPV: I^2 72.65%, $p < 0.0001$; risk of infection with non-classifiable HPV genotypes: I^2 80.07%, $p < 0.0001$).

Publication bias

Performing the risk assessment, a significant publication bias was detected by the Egger's test in the overall analysis ($p = 0.0001$) and in the overall analysis performed omitting the study by Watts et al. ($p = 0.0001$). Moreover, the Egger's test detected a significant publication bias in the stratified analysis for non-classifiable HPV genotypes ($p = 0.001$) and in the stratified analysis for non-classifiable HPV genotypes performed omitting the study by Watts et al. ($p = 0.001$). The Egger's test detected a statistically significant publication bias in the period of publication 2002–2010 ($p = 0.015$). The Begg's method detected no significant publication bias in any analyses.

Meta-analysis on the risk of Ct infection in HPV-positive women

Fifteen studies reported the risk estimation as OR, 2 as HR and one study as RR. The OR estimated in this meta-analysis represents the odds that Ct infection will occur given a diagnosis of HPV infection, compared to the odds of the outcome occurring in the absence of HPV infection. The results are shown in Table 2.

The overall analysis (*n*.19 studies, *n*.26 effect sizes) showed a significantly increased risk (2.23; 95% CI 1.70, 2.92) of Ct infection in HPV-positive women (Figure S2a in ESM2), with a significantly extreme value of heterogeneity (I^2 80.86%, $p < 0.0001$). Stratifying the analysis for HPV genotypes exposure, the Ct infection was associated to the infection with non-classifiable HPV genotypes (OR 3.46; 95% CI 2.19, 5.48) with a significant extreme

Table 1 Results of the metanalysis on the risk of HPV infection in Ct-positive women and stratified analyses by exposure (infection or history of Chlamydia trachomatis), study design, year of publication (selected studies were published between 1995 and 2017), and age. (HPV Human Papillomavirus, Ct Chlamydia trachomatis)

Outcome: infection with HPV	Combined risk estimate		Test of heterogeneity			Publication bias	
	Value (95% CI)	*p*	*Q*	I^2 (%)	*p*	*p* (Egger test)	*p* (Begg test)
Overall (*n* = 40)	2.12 (1.80, 2.49)	< 0.0001	225.43	82.70	< 0.0001	0.0001	0.050
Excluding Watts et al. (2005) (*n* = 39)	2.18 (1.88, 2.54)	< 0.0001	138.92	72.65	< 0.0001	0.0001	0.204
Non-classifiable HPV genotypes (*n* = 22)	2.00 (1.61, 2.48)	< 0.0001	161.11	86.97	< 0.0001	0.001	0.225
Excluding Watts et al. (2005) (*n* = 21)	2.11 (1.71, 2.62)	< 0.0001	100.35	80.07	< 0.0001	0.003	0.277
HR-HPV (*n* = 15)	2.32 (2.02, 2.65)	< 0.0001	11.53	0.00	0.644	0.211	0.125
LR-HPV (*n* = 3)	1.59 (0.81, 3.13)	0.180	3.71	46.04	0.157	0.369	0.602
Exposure							
Infection with Chlamydia trachomatis (*n* = 31)	2.21 (2.00, 2.45)	< 0.0001	31.45	4.62	0.393	0.210	0.747
History of Chlamydia trachomatis (*n* = 9)	1.72 (1.27, 2.33)	0.0004	106.28	92.47	< 0.0001	0.093	0.835
Study design							
Cross-sectional/case–control studies (*n* = 36)	2.28 (2.07, 2.52)	< 0.0001	41.55	15.77	0.207	0.803	0.785
Cohort studies (*n* = 4)	1.28 (0.98, 1.66)	0.065	24.14	87.57	< 0.0001	0.424	1.000
Year of publication							
< 2002 (*n* = 9)	1.85 (1.55, 2.22)	< 0.0001	5.16	0.00	0.740	0.888	0.835
2002–2010 (*n* = 11)	1.80 (1.38, 2.34)	< 0.0001	69.21	85.55	< 0.0001	0.015	0.586
Excluding Watts et al. (2005) (*n* = 10)	2.03 (1.45, 2.83)	< 0.0001	41.92	78.53	< 0.0001	0.012	0.421
> 2010 (*n* = 20)	2.43 (2.10, 2.80)	< 0.0001	27.25	30.26	0.099	0.500	0.559
Age group							
Women aged less than 36 years (*n* = 16)	2.04 (1.75, 2.38)	< 0.0001	20.36	26.33	0.159	0.169	0.322

CI confidence interval, *HPV* human papillomavirus, *HR-HPV* high-risk human papillomavirus, I^2 *I*-squared test, *LR-HPV* low-risk human papillomavirus, *n* number, *Q* Cochran's *Q* statistic

heterogeneity (I^2 81.40%, $p < 0.0001$) and to the infection with HR-HPV (OR 1.93; 95% CI 1.51, 2.46). No significant association was observed with LR-HPV or with multiple infections. Ct infection risk resulted significantly increased in high HPV prevalence countries (OR 1.68; 95% CI 1.28, 2.20), while we found the strongest association in low HPV prevalence countries (OR 3.29; 95% CI 2.16, 5.03) but with a significant extreme heterogeneity (I^2 85.37%, $p < 0.0001$). Stratifying by study design, we found a significantly increased risk for cross-sectional/case–control studies (OR 2.57; 95% CI 1.87, 3.54) with a significantly extreme heterogeneity (I^2 82.08%, $p < 0.0001$), for cohort studies (OR 1.50; 95% CI 1.12, 2.01). The risk of chlamydia in HPV-positive women resulted significantly increased in every period of publication (Table 2). We observed a high heterogeneity in the period 2002–2010 (I^2 67.03%, $p < 0.0001$) and an extremely high heterogeneity (I^2 88.75%, $p < 0.0001$). Stratifying by age group, the risk of chlamydia resulted significantly increased among women aged less than 36 years (OR 2.06; 95% CI 1.66, 2.57). The forest and funnel plots are shown in ESM2.

Sensitivity analyses

No single study substantially modified the estimates when the sensitivity analyses investigating the influence of a single study on the Ct infection risk in HPV-positive women was performed.

Publication bias

The risk assessment revealed no significant publication bias in the overall analysis (Egger's test $p = 0.262$ and Begg's test $p = 0.082$). The Egger's detected a significant publication bias in the stratified analysis for the exposure "Multiple infections" ($p = 0.042$). In the stratified analysis for age group, both methods revealed a significant publication bias (Egger's test $p = 0.005$ and Begg's test $p = 0.022$).

Table 2 Results of the metanalysis on the risk of infection with Ct in HPV-positive women and stratified analyses by exposure, HPV prevalence in the study location (defined according to Bruni et al. 2010), study design, year of publication (selected studies were published between 2002 and 2018), and age

Outcome: Infection with Chlamydia trachomatis	Combined risk estimate		Test of heterogeneity			Publication bias	
	Value (95% CI)	*p*	*Q*	I^2 (%)	*p*	*p* (Egger test)	*p* (Begg test)
Overall (*n* = 26)	2.23 (1.70, 2.92)	< 0.0001	130.62	80.86	< 0.0001	0.262	0.082
Exposure							
Non-classifiable HPV genotypes (*n* = 11)	3.46 (2.19, 5.48)	< 0.0001	53.78	8140	< 0.0001	0.714	0.139
HR-HPV (*n* = 7)	1.93 (1.51, 2.46)	< 0.0001	9.80	38.79	0.133	0.532	0.453
LR-HPV (*n* = 4)	1.17 (0.65, 2.11)	0.602	5.75	47.82	0.124	0.808	0.497
Multiple infections (*n* = 3)	1.76 (0.80, 3.88)	0.159	6.70	70.13	0.035	0.042	0.117
HPV prevalence							
High prevalence countries (*n* = 13)	1.68 (1.28, 2.20)	< 0.001	18.47	35.05	0.102	0.067	0.067
Low prevalence countries (*n* = 10)	3.29 (2.16, 5.03)	< 0.0001	61.50	85.37	< 0.0001	0.900	0.060
Study design							
Cross-sectional/case–control studies (*n* = 19)	2.57 (1.87, 3.54)	< 0.0001	100.44	82.08	< 0.0001	0.462	0.115
Cohort studies (*n* = 7)	1.50 (1.12, 2.01)	0.006	8.34	28.05	0.214	0.901	0.652
Year of publication							
2002–2010 (*n* = 16)	2.20 (1.62, 2.99)	< 0.0001	45.50	67.03	< 0.0001	0.703	0.280
> 2010 (*n* = 10)	2.26 (1.39, 3.67)	0.001	79.98	88.75	< 0.0001	0.261	0.325
Age group							
Women aged less than 36 years (*n* = 9)	2.06 (1.66, 2.57)	< 0.0001	9.08	11.90	0.336	0.005	0.022

Ct Chlamydia trachomatis, *CI* confidence interval, *HPV* human papillomavirus, *HR-HPV* high-risk human papillomavirus, I^2 *I*-squared test, *LR-HPV* low-risk human papillomavirus, *n* number, *Q* Cochran's *Q* statistic

Discussion

STIs are a major public health problem worldwide (WHO 2018), particularly infection with HPV and Ct, as related to invasive cervical cancer and poor reproductive outcomes (Zhu et al. 2016; Cates and Wasserheit 1991; IARC 1995). The high burden of STIs is due not only to individual determinants, such as younger age (Satterwhite et al. 2013), sexual behavior (Aral 2004), and factors associated to sexual risk (Medina-Perucha et al. 2018), but also to structural factors including antimicrobial resistance (Shaskolskiy et al. 2016) and environmental factors (Marshall et al. 2009).

Our meta-analysis suggests that HPV and Ct act as mutual risk factors. Ct infection and history of Ct infection resulted associated positively with the risk of HPV infection; Ct-positive women showed an even higher risk of HR-HPV infection. This association was found to be significant in every period of publication. The risk of HPV infection resulted similarly increased for women aged less than 36 years. In the meta-analysis on HPV infection risk in Ct-positive women, we detected statistically significant high heterogeneity and publication bias. These results were strongly influenced by the study by Watt et al., which investigated the risk of HPV in HIV1-positive and HIV1-negative women. We found that the risk of Ct infection in HPV-positive women remained significantly and similarly increased in every period of publication and among women aged less than 36 years. The risk of infection with Ct was positively associated with HPV infection and HR-HPV infection. Considering HPV prevalence in the countries of study, we found a stronger association in countries with low prevalence of HPV.

Infection with Ct facilitates the entry and persistence of multiple HR-HPV types in cervical epithelium (Paba et al. 2008; Paavonen 2012), as may damage the mucosal barrier (Silva et al. 2014) and plays a role in disturbing and modulating the immune response involved in HPV clearance (Paavonen 2012; Simonetti et al. 2009). Indeed, chronic cervical inflammation related to Ct infection inhibits cell-mediated immunity and its anti-apoptotic effect may influence persistence and progression of infection with HPV (Silva et al. 2014).

Little is known about the possible biological mechanisms which could explain the increased risk of Ct in HPV-positive women observed in our analyses. However, there is evidence that HPV infection modulates the host's immunity (Man and Fiander 2001; Tjiong et al. 2001) and HPV-16 (HR-HPV genotype) has demonstrated to interfere with the first response to infectious agents via Toll-like

receptors and to down-regulate Toll-like receptor 9 (Hasan et al. 2007).

These factors could contribute to increase the risk of Ct infection among HPV-positive women. The World Health Organization (WHO) definition of high-risk carcinogenetic HPV types reflects not only the possible difference in the association with high-grade disease, but also the different risk of HPV persistent infection (Doorbar et al. 2012; Schiffman et al. 2007; Bosch et al. 2008).

The pathogenetic process of HPV is determined by viral proteins function and influenced by the microenvironment at the specific site of infection and the host immunity (Egawa and Doorbar 2017).

The average length of persistence has demonstrated to be different for LR-HPV and HR-HPV genotypes (Bosch et al. 2013). Indeed, the median duration of HR-HPV detection is longer (Rositch et al. 2014). The HR-HPV genotypes are characterized by the ability to persist, even for many years, and, consequently, to drive cell proliferation in the basal and parabasal cell layers at some sites of infection (Barrow-laing et al. 2011; Zhang et al. 2006), whereas LR-HPV share a low-risk HPV lifecycle organization (Middleton et al. 2003). Persistent infection is considered a result of the failure to develop an effective cell-mediated immunity to clear and control the infection (Doorbar et al. 2012).

HPV infection is characterized by an effective evasion of innate immune recognition (Stanley 2012). Indeed, HPV globally down-regulates the innate immune signaling pathways in the infected keratinocyte, leading to an either not present or inadequate recruitment of stromal dendritic cells and macrophages (Kanodia et al. 2007). Moreover, HPV reactivation can occur at site of previous infection (Gravitt 2011).

Considering the high burden of STIs and the complexity and severity of their complications, prevention represents a priority in public health policies. Primary STIs prevention strategies include behavioral intervention and HPV vaccination programs, while secondary prevention includes HPV infection screening program. Primary prevention aims to inform, educate, and communicate the importance of the modification and adoption of safe sexual behavior, and it assumes particular relevance in adolescents, as they present higher rates of STIs and are more likely to change their behavior (Mayaud and Mabey 2004).

HPV vaccination program of preadolescent females is a cost-effective intervention in the context of existing screening programs. The inclusion of preadolescent males has potential direct and indirect benefits, even though in males HPV-related burden of disease is lower and because heterosexual males derive benefits from female-only vaccination via herd immunity, especially when coverage in females is high (Bosch et al. 2013; Canfell et al. 2013).

HPV primary screening is related to a decrease in cervical cancer mortality. The better and earlier detection of precancerous lesions determines reduction in incidence and mortality of cervical cancer. The HPV primary screening showed to be a more effective screening test for both vaccinated and unvaccinated women (WHO 2014; Sharma et al. 2013; Vaccarella et al. 2016).

The combination of primary and secondary prevention strategies could lead to more successful results in cervical cancer prevention, not only in developed but also in low- and middle-income countries (Bosch et al. 2013; Steben et al. 2012).

The implementation of HPV prevention program is challenging worldwide. With appropriate prioritization and resources, the integration of HPV vaccination program in preexisting screening program is feasible, in low- and middle-income and in developed countries (Bosch et al. 2013).

This integration is particularly relevant, considering that less developed regions present a higher prevalence of cervical HPV infection (Bruni et al. 2010).

In more developed regions, with low HPV prevalence (Bruni et al. 2010), the possible future screening options in cohorts of vaccinated women need to be further evaluated to quantify the cost-effectiveness (Bosch et al. 2013; Castanon et al. 2018) and to achieve further improvement in prevention (von Karsa et al. 2015).

Moreover, primary prevention through educating and promoting healthy sexual behavior in the adolescent population remains of critical importance, as cervical cancer and STIs risk perception in HPV vaccinated and unvaccinated girls remains controversial (Hestbech et al. 2016; Grandahl et al. 2017; Jena et al. 2016; Donken et al. 2018; Vázquez-Otero et al. 2016).

Thoroughly understanding the risk factors is a cornerstone for effective prevention and control interventions (Ezzati et al. 2002). In our analysis, HPV-positivity and Ct-positivity influence the risk of reciprocal infection, suggesting that HPV-positive women could benefit from the screening for Ct infection and vice versa. The risk of HPV infection and chlamydia is confirmed among young women, who represent the age group with the highest rates of Ct infection (CDC 2017) and register the highest rates of HPV infection in the prevaccine era (Dunne et al. 2011) and a significantly decreased prevalence after vaccine introduction (CDC 2017).

Considering the high burden of STIs, including chlamydia, worldwide (Unemo et al. 2017; GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016), public health strategies for STIs control are needed.

WHO recommendations suggest the essential components for prevention and care of STIs, which include primary promotion of safer sex behavior, condom promotion

program, promotion of appropriate healthcare-seeking behavior, early detection of symptomatic and asymptomatic infections, comprehensive STI case management, specific services for population at high risk, and integration of STI prevention and care into primary healthcare, reproductive healthcare facilities, private clinics and others (UNAIDS 1998).

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis to summarize the evidence on the risk of HPV infection in Ct-positive women and the risk of Ct infection in HPV-positive women. The present systematic review and meta-analysis have several key strengths. We searched three major databases for eligible studies. The eligibility criteria have been clearly specified, giving rationale. The risk of bias and heterogeneity were assessed for the overall and the stratified analyses.

Our study has several limitations. The main limitation is that HPV infection and Ct infection share the same risk factors, which could represent a possible confounding factor. Moreover, the selected studies investigated the prevalence of different HPV genotypes, which were grouped into three major categories in our analyses (non-classifiable HPV genotypes, LR-HPV and HR-HPV). Several included studies reported risk estimation without adjustment for confounding factors. Another main limitation is the heterogeneity of women in studies. Moreover, the Egger's test detected a significant publication bias in the meta-analysis investigating the risk of HPV infection in Ct-positive women, particularly in the overall analysis, in the stratified analyses estimating the risk of infection with non-classifiable HPV genotypes and in the period of publication 2002–2010, even after the omission of the study by Watts et al. In the meta-analysis on the Ct infection risk in HPV-positive women, a significant publication bias has been detected by Egger's test in the stratified analysis for multiple infections and by both Egger's and Begg's method in the analysis estimating the risk of Ct infection in women aged less than 36 years. As the majority of the selected studies were cross-sectional or prevalence studies, no univocal quality score could be applicable to all included articles. We evaluated and described the heterogeneity with Cochrane's Q and I^2 statistics, being aware that lack of evidence of heterogeneity is not evidence of homogeneity and that both tests are weak and present a variable degree of uncertainty (Ioannidis et al. 2007). Thus, in our meta-analyses, our results and the inferences about heterogeneity should be interpreted with caution.

Further studies are needed to increase the reliability of the results, to evaluate the relationship between HPV infection and Ct infection, and to detect the most effective combination of public health strategies to control the burden of STIs and their complications.

Conclusions

The global burden of STIs represents a major public health issue. Our meta-analysis suggests that HPV infection and Ct infection behave as reciprocal risk factors. When diagnosed with HPV or Ct, the screening for the mutual infection could represent a preventive intervention for severe health problem. The early detection of coinfection could prevent worse reproductive health outcomes related to HPV and Ct, such as cervical cancer and infertility. Public health policies should aim to prevent STIs, offering well-organized and coordinated vaccination and screening programs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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