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Review Article

Chlamydia Infection as a Risk Factor for Cervical Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: We reviewed studies on the prevalence of *Chlamydia* infection as a risk factor for developing cervical cancer in a meta-analysis studies published in that subject area.

Methods: Cochrane Library and PubMed databases were systematically searched for articles (observational and randomized controlled trials) published from 2008-2018. A meta-analysis of studies was performed to analyse the association between chlamydia infection and cervical cancer.

Results: Five articles were included in the final analysis (N=5271). All five articles were case-control studies, of which three studies sampled from population-based registries. All studies involved with sexually active women with minimum 15 years old. Three studies reported the association of *C. trachomatis* infection cervical cancers, two other studies reported *C. trachomatis-HPV* co-infection in association with cervical cancer. Result showed *C. trachomatis* has an overall prevalence of 31.9%, pooled OR 1.96, 95% CI 1.05 to 3.67, OR 2.13, 95% CI 1.78 to 2.54 among cervical cancer. There was a mild publication bias detected at 3.0 effect estimation. Heterogeneity detected from clinical and methodological diversities particularly from *C. trachomatis-HPV* co-infection subgroup analysis, including sampling bias, geographical strain diversity, and different outcome endpoint measured.

Conclusion: *C. trachomatis* infection was significantly associated with the development of cervical cancer. Co-infection of *C. trachomatis-HPV* with cervical cancer is plausibly sound but temporality of *C. trachomatis-HPV* with the development of cervical cancer need to be proven in future prospective cohort studies.

Keywords: *Chlamydia trachomatis*; Human papilloma virus; Sexually transmitted disease; Cervical carcinoma

Background

Cervical cancer is the one of the leading causes of death among women and is the fourth most common cancer among women. In year 2018, the WHO reported 570,000 new cases of cervical cancer worldwide and contribute about 6.6% of all women's cancers. The majority of deaths due to cervical cancer happened in low- and middle-income countries (1). In Malaysia, cervical cancer

(7.7%) is the third most common cancers amongst women after breast cancer (32.1%) and colorectal cancer (10.7%) (2).

Sexual activity is a risk factor for cervical cancer. Human papilloma virus (HPV) types 16 and 18 had been confirmed its oncogenic effect toward cervical cancer (3). However, cancer can be due to multifactorial aetiology (4). Others sexual transmitted infection may contribute in cervical cancer development, including chlamydia trachomatis infection (5, 6).

High mortality rate observed among women diagnosed with cervical cancer. Cervical cancer needs comprehensive approach such as prevention, early diagnosis, effective screening and treatment programmes to reduce its incidence. Prevention strategies in Malaysia focused on HPV vaccines, pap smear screening and health promotion to reduce the risk of cervical cancer. In Malaysia, the surveillance system for all cancer comes under National Cancer Registry accountability (within the jurisdiction of the National Cancer Institute, Putrajaya). The National Cancer Registry will be reporting on Cancer Incidence of Malaysia.

This study was a systematic review of recent papers on *Chlamydia* infection as a risk factor for cervical cancer. If there is convincing evidence of *Chlamydia* infection associated with cervical cancer, then women with history of *Chlamydia* infection may need further screening as they may be at risk for developing cervical cancer.

Methods

A systematic search was related to the relevant articles from two major search engines using Boolean search strategy, search engines including Cochrane Library and PubMed. The articles were filtered to include full articles in English language and only limited to human studies published from the year 2008 until 2018. The 2009 PRISMA checklist was used to illustrate the workflow of articles search for this study. The keywords used to search for the articles were stated as follows:

"Women" OR "Female" OR "MESH term of Women"

AND "chlamydia" OR "Sexually transmitted disease" OR "STD" OR MESH term of "sexually transmitted diseases" AND "Cervical carcinoma" OR "Cervi* cancer" OR MESH term of "Cervi* cancer"

Each keyword was inserted individually, then "OR" was applied to string up the same category of keyword such as in the PICO protocol (population, intervention, comparison and output), and finally all categories were connected using "AND".

The inclusion criteria for the article search for this systematic review were: 1. Full text, primary research articles on cervical cancer (including cervical cancer in-situ and all forms of cervical cancer) and *Chlamydia* infection; 2. Reported outcome in association of *Chlamydia* infection; 3. Reported prevention of *Chlamydia* infection in association with reduced prevalence of cervical cancer. The exclusion criteria for this study were: 1. Reviewed articles - lack of original research work with empirical data 2. The study was conducted in animal / pure genetic studies / pure laboratory experiments 3. Clinical updates or opinion / editorial / perspective articles 4. Clinical tools validation.

A total of 512 articles were retrieved based on keyword search (8 from Cochrane Library, 504 from PubMed). Titles of the articles were screened based on relevance to the objective of this study. From there, 45 articles were subjected to abstract screening (1 from Cochrane Library, 45 articles from PubMed) after removing one duplicated article. Another 40 articles were removed after this process based on the inclusion and exclusion criteria and one more article was removed due to incomplete data for analysis after full text review. The final number of articles for synthesis and analysis is 5 articles (Fig. 1). The quality of these studies was then assessed by using *Newcastle-Ottawa Scale* (7).

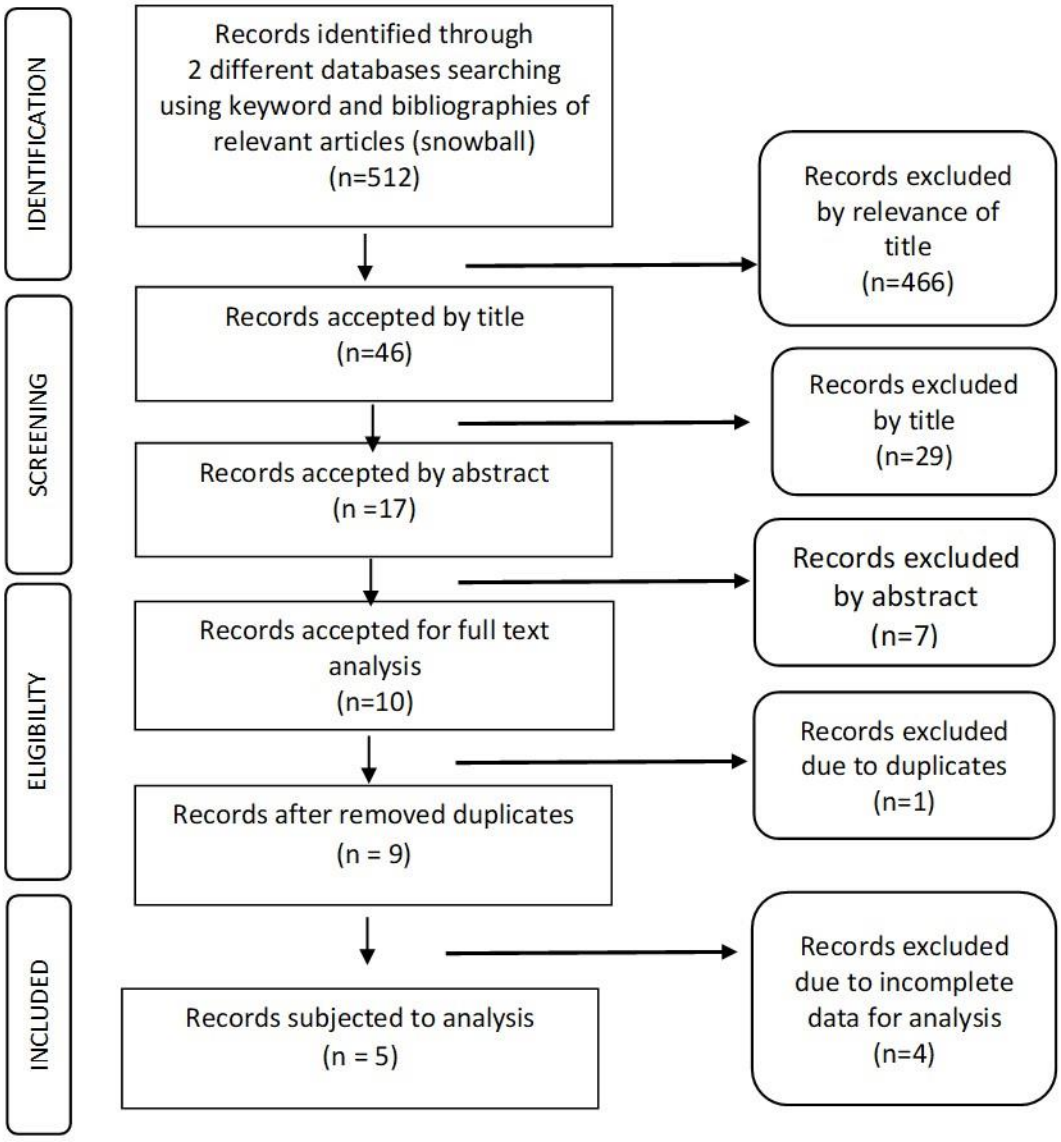

Fig. 1: Process of articles selection

Data Analysis

In the meta-analysis, the data were analysed by using *RevMan* 2011 (8). The strength of association of *C. trachomatis* and cervical cancer was determined by odds ratio (OR) with 95% confidence interval (CI). A random effects model was used in the analysis. The overall effect (pooled OR) was determined by Z test with $P < 0.05$ was considered significant. Level of heterogeneity was estimated using tau^2 DerSimonian-Laird estimator (9), Q test for heterogeneity (10) and I^2 statistic. A Q test with $P < 0.05$ and I^2 statistic > 50% were considered as heterogeneous.

Results

Characteristics of Study

All five studies selected for review were case control studies. The quality of the studies which was assessed using *Newcastle-Ottawa Scale* ranged from 4 to 9 stars. Most of these studies were conducted in a single country except for two studies conducted in multiple countries. Three of the studies

investigated on the risk of *C. trachomatis* in cervical cancer whereas another 2 were on *C. trachomatis* co-infection with HPV (Table 1).

Table 1: Characteristics of selected studies

Reference	***Country***	***Study design***	***Sample population***	***Specimen source***	***Variable used***	***Results***		***Quality***
						Case group	Control group	
(11)	Thailand	Nested case control	Population based registry (age not mentioned)	Serum *C. trachomatis* specific IgG antibodies using microimmunofluorescence Cervical CA – not mentioned	*C. trachomatis*	11/61	36/246	4
(16)	Sweden	Nested case control	Population based registry; women age 15-60 years old	Serum *C. trachomatis* IgG antibodies using ELISA Cervical CA – tissue histology	*C. trachomatis*	17/303	9/297	9
(19)	Finland, Norway, Iceland	Cohort	Population based registry; women age 15-60 years old	Serum *C. trachomatis* IgG antibodies using ELISA Cervical CA – tissue histology	*C. trachomatis*	277/588	818/2846	9
(29)	Brazil	Case control	Women ages 15–83 years	Genotyping of *C. trachomatis* and HPV Cervical CA- cytological cervical smear	*C. trachomatis* with HPV co-infection	111/252	44/370	6
(17)	Costa Rica	Nested case-control	More than 18 years old	Genotyping of *C. trachomatis* and HPV Cervical CA– tissue histology	*C. trachomatis* with HPV co-infection	31/196	22/112	6

Overall Effect Analysis

The overall prevalence of *C. trachomatis* infection among women with cervical cancer was 31.9% whereas the prevalence of *C. trachomatis* in controls was 24.0%. The pooled OR of *C. trachomatis* in cervical cancer was significant, which was 1.96, 95% CI 1.05 to 3.67. In the subgroup analysis, there was also a significant overall effect of *C. trachomatis* alone (without HPV co-infection) risk in cervical cancer with OR 2.13, 95% CI 1.78 to 2.54. However, in the *C. trachomatis* co-infection with *HPV* subgroup analysis, there was no significant association with cervical cancer detected (Fig. 2).

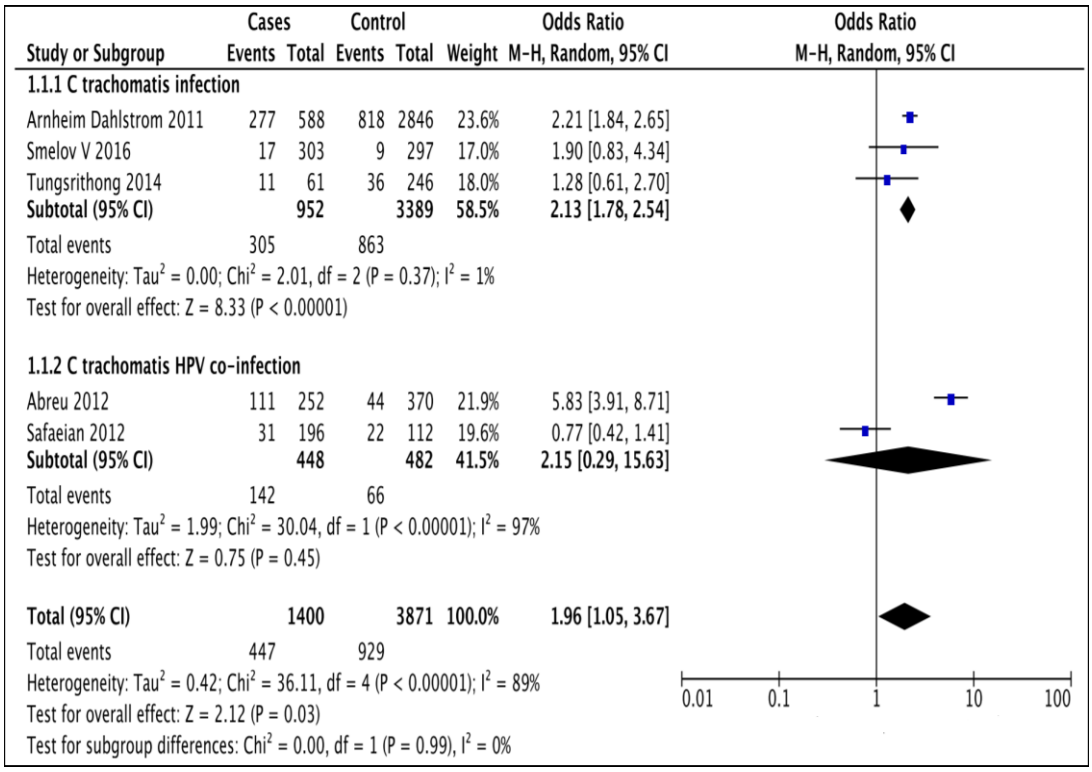

Fig. 2: The association of *C. trachomatis* and cervical cancer sub-grouped by with or without HPV co-infection

Publication Bias Analysis

Funnel plot analysis showed asymmetrical distribution of studies. Two studies were outside of the symmetrical super-imposed lines (Fig. 3). Thus, some publication bias may be present.

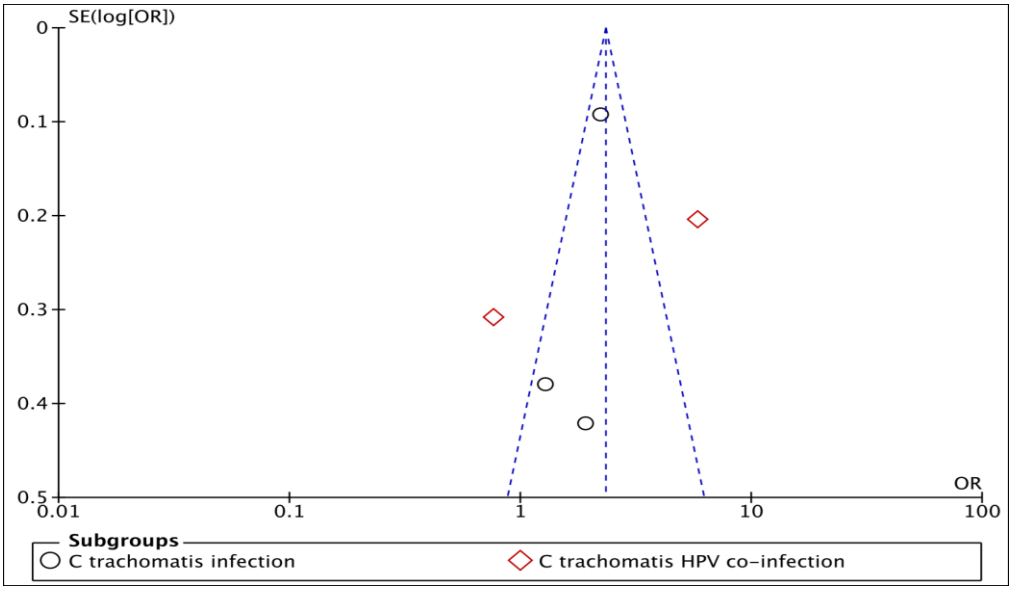

Fig. 3: Funnel plot for the assessment of publication bias

Discussion

Chlamydia trachomatis and Cervical Cancer

This meta-analysis did not find any significant association between *C. trachomatis* infection and development of cervical cancer.

Nested case-control study performed by (11) at Thailand, found that there was no significant association between *C. trachomatis* specific IgG antibodies *Chlamydia* infection and cervical cancer (11). However, we did not include other factors involved to increase the likelihood of malignancy such as p16INK4a and host DNA damage and proliferation as well as DNA damage responses (12, 13).

This result is concurrent with another study, where there was no significant association between *C. trachomatis* IgG, IgA and IgM seropositivity with cervical cancer in 77 samples in Turkey (14). Similarly, in another study, there was no association between the presence of *C. trachomatis* DNA in the cervical specimens and cervical cancer in Iran (15).

A large prospective study via nested case-control with a follow-up period of up to 26 years (16) also did not find any risk for cervical adenocarcinoma conferred by *C. trachomatis* infection. "There was no association between *C. trachomatis* status, as assessed by DNA or IgG, and risk of cervical premalignancy, after controlling for carcinogenic HPV-positive status" (17)."Previous positive associations between *C. trachomatis* and cervical premalignancy could have been caused by confounding by HPV status or by an increased susceptibility to HPV infection among women with a positive *C. trachomatis* status" (17).

Nevertheless, *Chlamydia* Infection has shown to promote host DNA damage and proliferation but impairs the DNA damage response which led to development of cervical cancer (13). *C. trachomatis* induced histone modifications reminiscent of DNA damage and cellular senescence (SAHF) where normal cells cease were divided (13). *C. trachomatis* also activate reactive oxygen species (ROS) and breaking the DNA double-strand, promoting SAHF formation. *C. trachomatis* suppressed the DNA double-strand repair activities as well as facilitate abnormal cell proliferation (13). *Chlamydia* infection also shown to be associated with cervical carcinogenesis (18, 19). However out of three of the studies investigated on the risk of *C. trachomatis* in cervical cancer, only one study showed significant association (19).

In this study, we could not ascertain that *C. trachomatis* infection was significantly associated with increased risk of cervical cancer. Although the pooled OR for the risk of *C. trachomatis* in cervical cancer was 1.42, it was not significant as compared to previous meta-analysis (20) where OR was significant for both prospective study and retrospective study which was 2.21, 95% CI 1.88 to 2.61 and 2.19, 95% CI 1.74 to 2.74 respectively (20). Our findings also contradict another study (19) which indicate of cervical cancer associated with seropositivity *C. trachomatis* with crude OR 2.3, 95% CI 1.9 to 2.7.

The subgroup *C. trachomatis* infection without HPV infection was significantly associated with cervical cancer which findings similar to another study (20). *C. trachomatis* was identified as an independent predictor of cervical cancer with OR 1.76 (95% CI 1.03-3.01) after adjusted for HPV and age. Castellsagué et al also shown association between *C. trachomatis* sero-positivity and invasive cervical carcinoma with OR 2.3, 95% CI 1.3 to 4.1 after adjusted for HPV infection (18).

Chlamydia and HPV infection are both sexually transmitted diseases; however, the persistent oncogenic type of HPV infection was more likely among women with previous *Chlamydia* infection (21). HPV infection is established as necessary to cause cervical cancer (22, 23), however *C. trachomatis* association with cervical cancer still questionable as many studies varied (11, 17, 24). The result in this study showed no significant association between *C. trachomatis* co-infection with HPV and cervical cancer, which was differ from another study (20, 21, 25).

Association of Chlamydia trachomatis-HPV Co-Infection and Cervical Cancer

Our results suggested the role of *C. trachomatis* in cervical cancer was significant, and the result was

homogenous. The association of *C. trachomatis*-HPV co-infection in causing cervical cancer was shown but there was high heterogeneity in the result. This indicated *C. trachomatis* is found significantly associated with cervical cancer, but when tested for association with HPV, there is discrepancies in various studies. *C. trachomatis* was found more common in HPV-positive cases compared to HPV-negative control, and HPV-*C. trachomatis* co-infections are more frequently observed in cervical cancer compared to healthy control (26). HPV is shown as a risk factor of *C. trachomatis* infection and *C. trachomatis* also was shown as a risk factor for HPV infection (26-28). This is explained by the sexual behaviour inclination on acquiring of both HPV as well as *C. trachomatis*, as both HPV and *C. trachomatis* were sexually transmitted infections. Furthermore *C. trachomatis* infection was significantly associated with HPV persistence (3, 17, 23).

Non-significant prevalence of cervical cancer among *C. trachomatis -HPV* co-infection may occur because both case and control population are selected from a sexually active group with multiple sexual partners (as entry point to capture *C. trachomatis* and *HPV*). As *C. trachomatis* and HPV, both are sexually transmitted disease, the present of either one of the infection will serves as risk factor for cervical cancer (29, 30). Sampling population differences in studies can contribute to the heterogeneity of result.. For example, the number of sexual partners applied in inclusion criteria for (17) is much higher than (29). The age of sampling population in (17), is in broad range from 15-83 years old, which may have higher prevalence of cervical cancer due to the immune system reduction at old age causing failure in apoptosis (17).

Both *HPV* and *C. trachomatis* may have played an independent co-factor role in the development of cervical neoplasia, whereby both are necessary but not sufficient cause of cervical cancer in the absence of other co-factors such as physical elements, other sexually transmitted infections, and immune response (3, 29). There are different *C. trachomatis* strains, where some are found more carcinogenic than another strains (17). This may be a reason that leads to the heterogeneity of result in *C. trachomatis*-HPV co-infection subgroup. Similar observation occurred for HPV which also has several strains. HPV 16, 18 are the high-risk strains and more carcinogenic to other strains, which also leads to different outcome compared to other study (3).

Another reason for heterogeneity is difference endpoint used in the studies, particularly cytological abnormalities. For instance, some papers use cervical cancer as the endpoints while others divided the analysis to CIN 2, CIN 3, LSIL, HSIL, ASCUS, adenocarcinoma, and squamous cell carcinoma (3, 17, 29). The result will vary when tested with different end points that used different cytological stages of cervical carcinogenicity. Other than that, higher number of sexual partners resulted in higher chances of mixed strains for both *C. trachomatis* and HPV, leads to higher rates of carcinogenesis (17, 29).

Different methodologies and study designs used in testing for HPV, *C. trachomatis* and cervical cancer status may yield a different result due to differences in sensitivity and specificity, such as those using serological methods compared to various molecular methods (29). This could be further confirmed in the different methods (17)for the detection of *C. trachomatis,* where kappa for IgG and DNA, did not achieve good agreement (17). This may indicate that *C. trachomatis* and HPV infection are more likely to prevail in the patient's immune system, although it has not shown many changes in the cells. *C. trachomatis* related cell injury (chronic inflammation) has greatly reduced cell-mediated immunity as described by (29). Other than that, differences in serotype of *C. trachomatis* such as serotypes B, D, E, G, and J, were reported more likely associated with cervical cancer compared to serotypes C, F, H, and K. The association with different serotypes of HPV such as HPV 16 and 18 with other serotypes in relation to different outcomes of cervical cancer, including CIN2, CIN3, ASGUS, ACUS, HSIL, LSIL may produce different significant factors (26, 31). This may explain the different outcome of HPV-*C. trachomatis* co-infection studies result at different geographical region that

have different pre-dominant HPV and *C. trachomatis* genotypes (29).

C. trachomatis by itself is the most common aetiology of sexually transmitted disease. It often causes chronic inflammation at various sites of the reproductive organ by decreasing the number of antigens presenting cells and reducing cell-mediated immunity leading to cell transformation (29). At a cellular level, *C. trachomatis* could activate the MEK-ERK pathways and causes accelerated cell proliferation, inhibiting infected cell apoptosis, promotes host DNA damages and alters DNA damage response (13, 26, 32-34). *C. trachomatis* could help HPV to escape cell mediated immune response by decreasing the number of antigens presenting cells, thus reducing the ability of cell-mediated immunity. This explained the relation of *C. trachomatis* to HPV persistence; and the access of HPV to its host cells in the basal layer of the cervical epithelium (26, 34, 35). Therefore, *C. trachomatis* may play a role in the early stage of cervical cancer based on the cervical cancer-risk associated genotypes (3, 31). When detected during late stage, *C. trachomatis* infection may have been resolved, resulting in a low association of *C. trachomatis* and cervical cancer. However, the chronic inflammation in reproductive system that have occurred, can continue to progress towards malignant changes. This may be the reason of false negative association between *C. trachomatis*-HPV in the development of cervical cancer.

Limitations

Most of our quantitative assessment studies were based on observational studies of the association between HPV co-infection and *C. trachomatis*. Due to this characteristic, data on prevalence of *C. trachomatis* and cervical cancer was acquired simultaneously from the analysis, rather than from longitudinally measured data. In view of difficulty on tackling the problems of confounding factors that could be intrinsically existed in the included studies, inadequate control of confounders in included studies may bias the results in overestimation or underestimation of risk estimates. There was a possibility of bias on visualization of funnel plots in this meta-analysis. Although the search strategy was using well-known databases, the retrieved literature might potentially not be comprehensive enough. Some completed studies with non-significant statistical association between *C. trachomatis* and cervical cancer has never been published due to the likelihood to be accepted by journal was lower. The underlying interaction between *C. trachomatis* and cervical cancer risk needs to be confirmed in longitudinal or prospective cohort studies to provide more definitive evidence concerning the role of this pathogen in promoting cervical carcinogenesis with or without HPV-mediated. Thus, such study design mentioned warrant future prospective research.

Conclusion

C. trachomatis infection was significantly associated with the development of cervical cancer. This study supports the evidence that *C. trachomatis* infection is one of the risk factors of cervical cancer. Women infected with *C. trachomatis* have a higher risk of developing cervical cancer. HPV infection may become the necessary but insufficient factor for cervical cancer. The co-infection of *C. trachomatis*-HPV with cervical cancer is most likely true, with plausibility, biological gradient, coherence, and experimental evidence of the Bradford Hill's criteria being fulfilled. Temporality of the co-infection of *C. trachomatis*-HPV may be proven in other studies. Therefore, treatment of *C. trachomatis* to protect against pelvic inflammatory disease and infertility among women would potentially prevent cervical cancer. *C. trachomatis* screening should be expanded among high-risk women, especially when they are also presented with HPV infection.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or fal-

sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

Non-declared.

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