Risk of high-risk human papillomavirus infection and cervical precancerous lesions with past or current trichomonas infection: a pooled analysis of 25,054 women in rural China

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ABSTRACT

Background: Trichomonas vaginitis (TV) infection has obviously been implicated in gynecological morbidity but still unclear in cervical lesions.

Objective: To evaluate the risk of hr-HPV infection and cervical intraepithelial neoplasia grade 2 or worse (CIN2 +) by TV infection.

Study design: The pooled study was conducted among 12 population-based, cervical cancer screening studies throughout China (N = 24,054). HPV was detected by Hybrid Capture®2 (HC2) test. Past TV infection was measured by self-reporting, current TV infection was diagnosed by liquid-based cytology (LBC), cervical lesions was diagnosed by histopathology.

Results: Respective prevalence of hr-HPV and CIN2+ were 17.4% and 3.3%. Out of 24,054 women, 14.6% reported past TV infection, and out of 11,853 women, 9.9% had current TV infection. Current TV-positive women had an increased risk for hr-HPV (OR 1.31, 95%CI: 1.11-1.56). The risk of CIN2+ decreased for hr-HPV positive women with current TV infection (adjusted OR 0.50, 95% CI: 0.30-0.84) and past TV infection (adjusted OR 0.68, 95% CI: 0.54-0.86). Among hr-HPV negative women, no significant associations were observed between past or current TV infection and risk of CIN2+.

Conclusions: Women infected with HPV are more likely to be infected by other types of sexually transmitted diseases. Current TV-positive women had an increased risk for hr-HPV infection compared to currently TV-negative women. Both past and current TV-positive women had a decreased risk for CIN2+, especially among high-risk HPV positive women. More direct investigation into the interaction between TV, HPV, inflammatory signals, and risk of carcinogenesis are further needed.

Abbreviations: hr-HPV, high-risk human papillomavirus; TV, trichomonas vaginalis; CIN, cervical intraepithelial neoplasia; CIN2+(3+), cervical intraepithelial neoplasia 2 or worse (3 or Worse); HC2, hybrid capture®2; LBC, liquid-based cytology; STD, sexually transmitted disease; CICAMS, chinese academy of medical sciences; PATH, program for appropriate technology in health; SPOCCS, Shanxi Province cervical cancer screening study; START, screening technologies to advance rapid testing; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; OR, odds ratios; CI, confidence interval

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1. Background

Human papillomavirus (HPV) is a sexually transmitted disease (STD) and persistent high-risk HPV (hr-HPV) infection is needed for cervical cancer [1]. Most HPV infections resolve within two years [2], but differences in immune systems and exogenic factors affect hr-HPV clearance and progression to invasive cancer. Concurrent STD infection, such as with chlamydia trachomatis, may affect host immunity, incurring a subsequently increased risk of hr-HPV persistence and progression to high-grade cervical intraepithelial neoplasia (CIN +) [7].

Trichomonas vaginalis (TV) has also been hypothesized to accelerate the progression to invasive cervical cancer by causing microtraumas in the cervical epithelium through host inflammatory response, leading to HPV infection of the epithelial basal cells [8,9]. Understanding the association between TV, hr-HPV infection, and progression to CIN+ is important for decreasing CIN+ prevalence. Existing studies that examine the risks of hr-HPV infection and CIN2+ by TV are inconsistent in their conclusions [9–13]. Previous studies were heterogeneous in design, diagnosed HPV with cytology and TV with Pap smear, measured CIN+ with cytology, or did not adjust for CIN+ confounders [3,12–14].

TV is the most prevalent non-viral female STD in the world, with most cases occurring in resource-limited areas [15,16,17].TV infection has been implicated in gynecological morbidity such as pelvic inflammatory disease and pre-term labor [18,19]. Despite these consequences, TV infection remains under-diagnosed, as up to one-third of infected women are asymptomatic [20,21]. Prevalence of TV infection ranges from 3% in developed regions to 10% in low-resource regions [10,22–24].The prevalence of TV across rural China has rarely been estimated. Knowing accurate rates of TV infection would help public-health officials make decisions about health resource allocations.

2. Objectives

The aims of our pooled analysis of twelve population-based, cross-sectional studies across China are to evaluate the i) prevalence of TV among women in rural China; ii) the association of past TV infection; iii) and current TV infection with the risk of hr-HPV infection and CIN2+.

3. Study design

3.1. Eligible studies and participants included in pooled analyses

3.1.1. Eligible studies

Twelve cross-sectional, population-based studies of cervical cancer screening were conducted in five provinces across China between 1999 and 2008 by the cancer institute of the chinese academy of medical sciences (CICAMS; Beijing, China) and other international research institutes. Women that met inclusion criteria and gave their written, informed consent completed questionnaires and underwent cervical cancer screening; study details were described previously [24–31]. The institutional review boards of CICAMS, Cleveland Clinic, or PATH (program for appropriate technology in health) approved these studies.

3.1.2. Eligible participants

Out of 12 studies (N = 26,088), participants with missing HC2 (Hybrid Capture®2) or pathology test results, key demographic information (listed in Table 2), or past TV infection data, were excluded, leaving 24,054 women with self-reported TV infection data (Fig. 1). Out of these 24,054 women, women from three studies without showing current TV status were excluded, leaving 11,853 women from nine studies with LBC diagnosed TV infection data.

4. Data collection and analyses

4.1. Past and current TV infection and risk factors for TV

Past TV infection was evaluated by questionnaire. Questionnaires were filled out during face-to-face interviews by trained interviewers. Similar questionnaires were provided across all studies in the pooled analysis to include demographic information, sexual behavior, reproductive history, contraceptive practices, and history of sexual transmitted diseases, including TV. To ascertain past TV infection, woman was asked if she was ever diagnosed to be gynecological diseases (including infections of TV, candida, gonorrhea, syphilis and so on) at least by a gynecologist from township health centers. If participants answered 'Yes', they were asked to provide the number of past TV diagnoses in nine studies expect the SPOCCSIII-1, SPOCCSIII-2, SPOCCSIII-3. Current TV infection was diagnosed using cervical cancer screening specimens that had been prepared for LBC slides, according to the Bethesda System.

4.2. HPV detection and pathology diagnosis

hr-HPV was detected by Hybrid Capture®2, which detects the pooled DNA of 13 carcinogenic hr-HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Histological diagnoses were made in each study by expert pathologists, either individually or as a panel. Cases were classified as normal, CIN1, CIN2, CIN3, squamous cell carcinoma (SCC), adenocarcinoma in situ (AIS), or adenocarcinoma. CIN2 or worse (CIN2+) includes CIN2, CIN3, SCC, AIS, or adenocarcinoma for this analysis.

4.3. Statistical analysis

The proportions of past and current TV infection, as well as prevalence of hr-HPV and CIN2+, were calculated per study and in the pooled 24,054 women. The agreement rate between past TV infection and current TV infection was assessed among 11,853 women. Potential risk factors for TV infection were evaluated using odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting for age and study site in logistic regression. The specific categories for risk factors are listed in Table 2.

Associations between TV infection and hr-HPV infection and CIN2+ were assessed using stepwise logistic regression after adjusting for all potential risk factors. In order to avoid the exclusion of participants in regression models, women with missing key demographic information (Table 2), were included by creating a category for "missing" for relevant variables in calculations of summary ORs. The interaction of hr-HPV with TV infection was evaluated using a likelihood ratio test, and further evaluated by hr-HPV stratification. All statistical tests were two-tailed with $p < 0.05$ as statistically significant. Statistical analyses were performed using SAS (9.2).

5. Results

5.1. Baseline characteristics of included studies and participants

Out of 24,054 women, 17.4% (N = 4180) were hr-HPV positive, 3.3% (N = 796) had CIN2+, 14.6% (N = 3518) reported past TV infection, and 9.9% (N = 1170) had current TV infection (Table 1). A high agreement rate of 82.7% was observed between self-reported TV and current TV infection among the 11,853 participants. Median age of cervical cancer screening was 40, with a range of 36–44 in the studies.

The percentage of participants with current TV infection ranged from 0.9% to 22.9%, and with past TV infection ranged from 5.4% to 23.1% between studies. All studies had greater than 8% hr-HPV-positive women, except for SPOCCSIII-3 (6.9%), and START2005 (7.3%). All studies had CIN2+ greater than 2.0%, except for FASTHPV (1.3%),

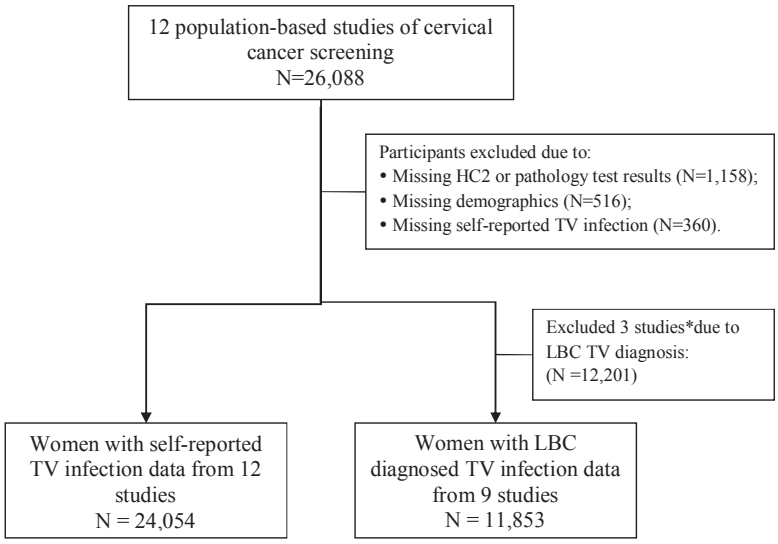

Fig. 1. Study flowchart. TV = trichomonas vaginitis; HC2 = Hybrid Capture® 2; LBC = liquid-based cytology. *Data of LBC-based TV from SPOCCSI, SPOCCSII and START2003 studies had been shown in another paper [38] (SPOCCS = Shanxi Province cervical cancer screening study); START = screening technologies to advance rapid testing).

TV = trichomonas vaginitis; HC2=Hybrid Capture® 2; LBC=liquid-based cytology.
*Data of LBC-based TV from SPOCCSI, SPOCCSII and START2003 studies had been shown in another paper [41] (SPOCCS = Shanxi Province Cervical Cancer Screening Study); START = Screening Technologies to Advance Rapid Testing).

SPOCCSIII-3 (1.2%), START2005 (1.6%), and START2006 (1.6%). Across 12 studies, CIN2+ prevalence ranged from 1.2% in SPOCCSIII-3 to 4.4% in SPOCCSII, with a concomitant increase in hr-HPV prevalence from 6.9% in SPOCCSIII-3 to 23.5% in SPOCCSII.

5.2. Potential risk factors for past TV infection or current TV infection

Women with past TV infection were more likely to be between 30–49 years old, to have middle school or higher educations, early sexual debuts at age ≤16, reported current condom use, had multiple sexual partners, and reported knowing husbands had extramarital affairs (Table 2).

Women with current TV infection were more likely to be 40–49 years old, hr-HPV positive, to have a primary school or lower educations, and had sexual debuts between the ages of 17–20.

5.3. Risk of hr-HPV infection and CIN2+ by past or current TV infection

5.3.1. Risk of hr-HPV infection and CIN2+ by past TV infection

For women without past TV infection (N = 20,534), 17.1% (N = 3514) were hr-HPV positive. Out of the 3518 women with past TV infection, hr-HPV prevalence increased with the frequency of past TV infection ($P < 0.001$). Past TV infection was not associated with hr-HPV infection (Table 3).

CIN2+ prevalence was 3.4% (N = 695) among women without past TV infection and 2.9% (N = 101) among women with past TV infection, and increased with the frequency of past TV infection ($P < 0.001$). Compared to women without past TV infection, women with one and more then 2 past TV infections had, respectively, a 0.7 (95%CI: 0.52-0.95) and 0.60 (95%CI: 0.42-0.86) decreased risk for CIN2+. Increases in times of past TV infections were significantly associated with a decreasing risk of CIN2+ ($P < 0.001$).

5.3.2. Risk of hr-HPV infection and CIN2+ by current TV infection

CIN2+ prevalence was 2.3% (N = 246) among TV-negative women (N = 10,683) and 1.8% (N = 21) among TV-positive women. Out of TV-negative women, 12.3% (N = 1318) were hr-HPV-positive compared to 15.8% (N = 185) of TV-positive women (Table 3). TV-positive women had an increased risk (OR1.31, 95%CI: 1.11-1.56) for hr-HPV and a decreased risk for CIN2+ (0.57 (95%CI: 0.35-0.92) compared to

Table 1
Distribution of TV infection by laboratory diagnosis and self-reporting across 12 cervical cancer screening studies in China.

Study Name	Year; province of study	N	Median age (year)	LBC-diagnosed current TV N (%) *,†	Self-reported history of TV N (%)‡	hr-HPV prevalence N (%)†	CIN2+ prevalence N (%)†
FASTHPV	2007;Shanxi	774	41.0	9 (1.2)	46 (5.9)	64 (8.3)	10 (1.3)
HC2	2008; Shanxi	507	43.0	36 (7.1)	64 (12.6)	80 (15.8)	11 (2.1)
SPOCCSI	1999; Shanxi	1940	39.0	–	294 (15.2)	364 (18.8)	84 (4.3)
SPOCCSII	2001–2002; Shanxi	8447	40.0	–	1770 (21.0)	1984 (23.5)	375 (4.4)
SPOCCSIII-1	2006; Shanxi	882	36.5	80 (9.1)	103 (11.7)	140 (15.8)	22 (2.5)
SPOCCSIII-2	2006; Xinjiang	864	36.0	8 (0.9)	91 (10.5)	107 (12.4)	17 (2.0)
SPOCCSIII-3	2006; Henan	871	37.0	45 (5.2)	201 (23.1)	60 (6.9)	10 (1.2)
START 2003	2003; Shanxi	1812	37.0	–	388 (21.4)	328 (18.1)	70 (3.9)
START 2004	2004; Jiangxi	1505	39.0	344 (22.9)	81 (5.4)	265 (17.1)	61 (4.1)
START 2005	2005;Gansu	2032	38.0	291 (14.3)	114 (5.6)	148 (7.3)	32 (1.6)
START 2006	2006; Shanxi	2368	42.0	171 (7.2)	129 (5.4)	297 (12.5)	39 (1.6)
START 2007	2007; Shanxi	2052	44.0	186 (9.1)	237 (11.5)	345 (16.8)	65 (3.2)
Total		24,054	40.0	1170 (9.9)	3518 (14.6)	4180 (17.4)	796 (3.3)

LBC = liquid-based cytology; TV = trichomonas vaginitis; hr-HPV = high-risk human papillomavirus; CIN2+ = cervical intraepithelial neoplasia grade 2 or higher. SPOCCS = Shanxi Province cervical cancer screening study; START = screening technologies to advance rapid testing.
*TV infection laboratory diagnosis by liquid-based cytology (LBC). †N = 24,054. ‡N = 11,853.

Table 2
Risk factors for past TV infection among 24,054 Chinese women and for current TV infection among 11,853 Chinese women.

	Past TV infection from 12 studies (N = 24,054)			Current TV infection from nine studies (N = 11,853)*		
	N	Yes, N (%)	OR (95%CI)†	N	Yes, N (%)	OR (95%CI)†
Age						
≤29	780	100 (12.8)	1 (ref)	768	11 (1.4)	1 (ref)
30–39	10,527	1505 (14.3)	1.26 (0.98–1.61)	4571	423 (9.3)	5.93 (3.23–10.88)
40–49	11,553	1770 (15.3)	1.35 (1.05–1.73)	5416	662 (12.2)	7.91 (4.32–14.49)
≥50	1194	143 (12.0)	1.21 (0.91–1.61)	1098	74 (6.7)	4.07 (1.05–7.76)
High-risk HPV						
Negative	19,874	2852 (14.4)	1 (ref)	10,350	985 (9.5)	1 (ref)
Positive	4180	666 (15.9)	0.99 (0.91–1.10)	1503	185 (12.3)	1.29 (1.09–1.52)
Highest level of education						
Primary school and below	10,834	1347 (12.4)	1 (ref)	6478	795 (12.3)	1 (ref)
Middle school and above	13,220	2171 (16.4)	1.22 (1.13–2.04)	5375	375 (7.0)	0.55 (0.48–0.62)
Age of sexual debut						
≤16	671	136 (20.3)	1 (ref)	615	47 (7.6)	1 (ref)
17–20	11,042	1574 (14.3)	0.61 (0.50–0.74)	6308	770 (12.2)	3.25 (1.02–10.36)
≥21	12,327	1807 (14.7)	0.58 (0.48–0.71)	4921	353 (7.2)	1.95 (0.61–6.23)
Missing	14		–	9		–
Lifetime number of sexual partners						
0–1	18,608	2384 (12.8)	1 (ref)	10,114	1020 (10.1)	1 (ref)
2	3169	583 (18.4)	1.36 (1.23–1.51)	1147	101 (8.8)	0.90 (0.72–1.12)
≥3	2240	538 (24.0)	1.83 (1.64–2.04)	560	49 (8.8)	0.86 (0.63–1.16)
Missing	37		–	32		–
Parity						
0	281	38 (13.5)	1 (ref)	154	18 (11.7)	1 (ref)
1	2377	366 (15.4)	0.97 (0.68–1.40)	1253	74 (5.9)	0.95 (0.63–1.42)
≥2	21,396	3114 (14.6)	0.96 (0.68–1.36)	10,446	1078 (10.3)	0.91 (0.60–1.37)
Current condom use						
No	23,604	3433 (14.5)	1 (ref)	11,462	1163 (10.1)	1 (ref)
Yes	446	85 (19.1)	1.60 (1.24–2.06)	389	7 (1.8)	0.23 (0.11–0.50)
Missing	4			2		
Known husband extramarital sex						
No	21,103	2805 (13.3)	1 (ref)	10,817	1087 (10.0)	1 (ref)
Yes	2951	713 (24.2)	1.84 (1.67–2.03)	1036	83 (8.0)	0.96 (0.76–1.22)

TV = trichomonas vaginitis; OR = odds ratio; CI = confidence interval; HR-HPV = high risk human papillomavirus.
*TV infection diagnosis by LBC; †Adjusted by age and study site.

Table 3
Risk of hr-HPV infection and CIN2+ by past TV infection among 24,054 Chinese women and by current TV infection among 11,853 Chinese women.

	N (%)	Hr-HPV infection			CIN2+		
		Yes, N (%)	Age, study site adjusted OR (95%CI)	Multivariable OR (95%CI)*	Yes, N (%)	Age, study site adjusted OR (95%CI)	Multivariable OR (95%CI)*
Self-reported past TV infection (N = 24,054)							
No	20,536 (85.4)	3514 (17.1)	1 (ref)	1 (ref)	695 (3.4)	1 (ref)	1 (ref)
Yes	3518	666 (18.9)	1.06 (0.97–1.17)	0.99 (0.91–1.09)	101 (2.9)	0.79 (0.64–0.97)	0.70 (0.56–0.88)
1 time	1916 (7.9)	347 (18.1)	1.01 (0.89–1.14)	0.95 (0.84–1.08)	52 (2.7)	0.75 (0.56–0.99)	0.70 (0.52–0.95)
≥2 times	1292 (5.4)	280 (21.7)	1.21 (1.05–1.39)	1.10 (0.95–1.26)	38 (2.9)	0.76 (0.54–2.32)	0.60 (0.42–0.86)
Missing	310 (1.3)	39			11		
P_{-trend}		*< 0.001*			*< 0.001*		
Current TV infection by LBC (N = 11,853)							
No	10,683 (90.1)	1318 (12.3)	1 (ref)	1 (ref)	246 (2.3)	1 (ref)	1 (ref)
Yes	1170 (9.9)	185 (15.8)	1.29 (1.09–1.52)	1.31 (1.11–1.56)	21 (1.8)	0.71 (0.45–1.12)	0.57 (0.35–0.92)

TV = trichomonas vaginitis; LBC = liquid-based cytology; hr-HPV = high risk human papillomavirus; CIN2+ = cervical intraepithelial neoplasia grade 2 or severe; OR = odds ratio; CI = confidence interval.
*Adjusted for age, study site, HPV status, education, age of sex debut, lifetime number of sex partners, parity, current condoms use and known husband's extramarital affair.

TV-negative women.

5.4. Decreased CIN2+ risk among women with past or current TV infection stratified by hr-HPV status

5.4.1. Risk of CIN2+ by past TV infection stratified by hr-HPV status

Among hr-HPV positive women (N = 4180), 15.9% (N = 666) reported past TV infection. CIN2+ prevalence was 19% (N = 669) for women without past TV infection, and 14.4% (N = 96) for those with past TV infection (Table 4).

For hr-HPV-positive women, CIN2+ prevalence increased with the frequency of past TV infections ($P < 0.001$). Compared to women without past TV infection, women with one and ≥2 past TV infections had a decreased risk of CIN2+, respectively, by 0.68% (95% CI: 0.49–0.93) and 0.59% (95% CI: 0.41–0.84).

Among hr-HPV negative women, there was no significant difference between risk of CIN2+ between women with or without past TV infection.

Table 4
Risk of CIN2+ by self-reported past TV infection stratified by hr-HPV infection status among 24,054 Chinese women.

Hr-HPV status	Self-reported past TV infection	N (%)	CIN2+, N (%)	Age, study site adjusted OR (95%CI)	Multivariate OR (95%CI)*
Hr-HPV (−) (N = 19,874)					
	No	17,022 (85.6)	26 (0.2)	1 (ref)	1 (ref)
	Yes	2852[†]	5 (0.2)	1.15 (0.44–3.02)	1.09 (0.41–2.91)
	1 time	1569 (7.9)	3 (0.2)	1.23 (0.37–4.09)	1.23 (0.37–4.12)
	≥2 times	1012 (5.1)	2 (0.2)	1.24 (0.29–5.28)	1.20 (0.29–5.18)
	Missing	271 (1.4)	0		
	$P_{\text{-trend}}$		*0.761*		
Hr-HPV (+) (N = 4180)					
	No	3514 (84.1)	669 (19.0)	1 (ref)	1 (ref)
	Yes	666[†]	96 (14.4)	0.70 (0.55–0.88)	0.68 (0.54–0.86)
	1 time	347 (8.3)	49 (14.1)	0.68 (0.50–0.94)	0.68 (0.49–0.93)
	≥2 times	280 (6.7)	36 (12.9)	0.59 (0.41–0.85)	0.59 (0.41–0.84)
	Missing	39 (0.9)	11		
	$P_{\text{-trend}}$		*< 0.001*		

TV = trichomonas vaginitis; LBC = liquid-based cytology; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; hr-HPV = high risk human papillomavirus; hr-HPV (−) = h-HPV negative; hr-HPV (+) = h-HPV positive; OR = odds ratio; CI = confidence interval.
*Adjusted for age, study site, education, age of sex debut, lifetime number of sex partners, parity, current condoms use and known husband's extramarital affair. [†]Percentage is sum of times of past TV infection.

5.4.2. Risk of CIN2+ by current TV infection stratified by hr-HPV status

Among hr-HPV positive women (N = 1503), 12.3% (N = 185) were currently TV-positive. CIN2+ prevalence was 17.8% (N = 235) for women without current TV infection and 9.7% (N = 96) for those with TV infection (Table 5). For hr-HPV-positive women, those with TV had a decreased CIN2+ risk of 0.50-fold (95% CI: 0.30–0.84) compared to those without TV.

Among hr-HPV negative women, there was no significant difference between risk of CIN2+ between women who were currently TV-positive or negative.

6. Discussion

To our knowledge, this is the largest pooled analysis that evaluates hr-HPV infection and CIN2+ risk by TV infection in rural China. Current TV infection prevalence was 9.9%. We found that current TV infection increased risk for hr-HPV infection, and women with either past or current TV infection were less likely to have a concurrent diagnosis of CIN2+, especially among hr-HPV-positive women.

The highest STDs in our pooled studies was the TV infection either by self-reporting or by current LBC diagnosis (other STDs reported low proportion, data now shown). The TV prevalence among our study population, was higher than previous studies conducted in Asia (1% in rural Vietnam; 2.9% in Shandong province, China; 5.7% in WHO Western Pacific region) [15,32,33].

Table 5
Risk of CIN2+ by current TV infection stratified by hr-HPV infection status among 11,853 Chinese women.

Hr-HPV status	Current TV infection by LBC	N (%)	CIN2+ N (%)	Age and site adjusted OR (95%CI)	Multivariate OR (95%CI)*
Hr-HPV (−) (N = 10,350)					
	No	9365 (90.5)	11 (0.1)	1 (ref)	1 (ref)
	Yes	985 (9.5)	3 (0.3)	2.32 (0.64–8.39)	2.12 (0.58–7.76)
Hr-HPV (+) (N = 1503)					
	No	1318 (87.7)	235 (17.8)	1 (ref)	1 (ref)
	Yes	185 (12.3)	18 (9.7)	0.48 (0.29–0.79)	0.50 (0.30–0.84)

TV = trichomonas vaginitis; LBC = liquid-based cytology; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; hr-HPV = high-risk human papillomavirus; hr-HPV (−) = h-HPV negative; hr-HPV (+) = h-HPV positive; OR = odds ratio; CI = confidence interval.
*Adjusted for age, study site, education, age of sex debut, lifetime number of sex partners, parity, current condoms use and husband's extramarital affair.

The significant association observed between current TV and hr-HPV infection are supported by other studies. One study found that TV infection was associated with an increased risk of concurrent hr-HPV [34],and another study reported that low- and high-risk HPV-positive women had greater risk for concurrent TV infection than HPV-negative women [9]. Verteramo et al., however, reported that TV was not significantly associated with HPV infection [10],which could be explained by the small sample of TV-positive women in Verteramo's study, and by the study's assessment of TV association with any HPV infection, not specifically hr-HPV. Another study found TV infection was associated with type-specific and not pooled hr-HPV infection [35],but that study population had high HIV prevalence (> 10%), indicating further investigation is needed between TV, HPV, and concomitant STDs.

Previous studies that evaluated the association between TV infection on HPV persistence and CIN+ had inconsistent results. Several studies reported no causal role for TV on cervical cancer [36,37]. A frequently cited *meta*-analysis of 24 studies showed an increased relative risk for cervical cancer with TV infection; [13] however, this analysis was powered by only two cohort studies (Gram 1992; Zhang 1991). Gram's 1992, Zhang's 1991 and Vikki's 2000 cohort studies diagnosed HPV infection using cytology [12].Another cohort study reporting increased risk of CIN+ by TV did not adjust for HPV infection for cervical cancer [14].

Decreased CIN2+ risk by past and current TV infection in our study is supported by results in other studies. In Vikki's 2000 cohort study, TV-positive women had a decreased incident rate for invasive cervical cancer compared to precancerous lesions [3]. In Zhang's 1995 cohort study, the risk of TV infection increased with increasing numbers of negative Pap smears ($P_{trend} = 0.0001$) [14].Watts et al. reported decreased HPV persistence with TV infection [11]. In addition, the pooled cross-sectional cervical-cancer screening study of 13,024 women from the START2003, SPOCCSI and SPOCCS II studies (not shown in our pooled analysis), also found that current TV prevalence was negatively correlated with cervical histology and cytological severity [38]. This decreased risk of CIN2+ among HPV positive women is most likely due to the fact that women infected with HPV are more likely to have other STD infections, but women co-infected with HPV and other STDs may give priority to treatment for pre-cancer lesions than for STDs. Given the complex influences of concomitant gynecological infections such as TV on cervical cancer progression among hr-HPV-positive women, regular screening and treatment for STDs as well as gynecological cancers should be a priority for women and public health officials.

Our pooled analysis has several strengths. All studies in the analyses

were conducted by CICAMS staff using similar protocols, making results comparable. Senior CICAMS or international pathologists and cyto-pathologists reviewed all cytology and histology results. Past studies used cytology to diagnose cervical cancer, which leads to mis-classification bias, as TV infection can falsely be diagnosed as ASCUS [39]. We were able to reliably evaluate potential risk factors for past and present TV infection because the participants answered similar intake questions. Another strength is that we measured TV infection with LBC and self-reporting, high agreement rate for two measures was reported in our study. The accuracy of LBC for TV diagnosis is comparable to DNA detection, with respective sensitivities of 99.5% and 95%, and specificities of 96.2% and 98% [40]. LBC and DNA detection for TV diagnosis are more accurate with less false-positives than Pap smears (sensitivity of 61.4% and specificity of 99.4%) [37,41].

Our study did have some limitations. We can't distinguish symptomatic infections or asymptomatic infections for self-reported TV. Most of "past TV" may be symptomatic, because of intolerable discomfort enforcing women forward to the gynecologic examination. However, there were a large portion of women passively examined for TV infection when they were participating in the annually national cervical cancer program in rural China. Eight out of the 12 studies were based in Shanxi, China, a high HPV-prevalent province, which results in a selection bias of women and partners with more risky sexual behaviors. We did, however, adjust for sexual risk factors in our analyses of CIN2+ risk by past or current TV infection. For women with past TV infection, the TV detection methods and their accuracies, treatment, and age of infection are unknown. To compensate, we evaluated past TV infection using a large sample size. Cervical cancer screening history was not recorded so we could not evaluate the potential effect of screening on TV and CIN+ association.

Future cohort studies should investigate CIN+ risk by TV infection as a primary aim. Chronic cervical microbial infection has been hypothesized to induce inflammation, leading to carcinogenesis [7], but certain inflammatory molecules have also been reported to be protective against cellular damage [42]. More direct investigation into the interaction between TV, HPV, inflammatory signals, and risk of carcinogenesis are needed.

In conclusion, we show a decreased risk of CIN2+ with past or current TV infection among hr-HPV positive women in this large-scale, pooled analysis that warrants further investigation.

Conflict of interest

No author has conflicts of interest to declare.

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