Epidemiology of Human Papillomavirus (HPV) Infection among Iranian Women Identified with Cervical Infections: A Systematic Review and Meta-Analysis of National Data

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Abstract

Background: Human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease (STD) in humans. HPV is associated with gynecologic malignancy and cervical cancer among women worldwide. In the current study we sought to determine the prevalence rate of HPV in Iranian women identified with cervical infections.
Materials and Methods: Prevalence rate of HPV in Iran was investigated from 2000-2016 using several databases including Medline, Web of Science, Embase, Google Scholar, Iranmedex, and Scientific Information Database. Statistical analysis was performed by Comprehensive Meta-Analysis (V2.2, Biostat) software. Random effects models were used by taking into account the possibility of the heterogeneity between the studies, which was tested through the Cochran's Q-statistic.
Results: The meta-analyses showed that the prevalence rate of HPV infections was 38.6 % (95% CI, 27.9-50.5) among Iranian women with cervical infections. The further stratified analyses indicated that the prevalence rate of HPV was higher in the studies conducted during the 2000-2008 years.
Conclusion: The results of the present study underscore the need for further enforcement of STD control strategies in Iran. Establishing advanced diagnostic facilities for HPV, vaccination of high risk groups, and continuous monitoring of HPV are recommended for HPV prevention and control.

Key words: Human papillomavirus, HPV, Cervical infection, Iran, Meta-analysis

1. Background

Human Papillomavirus (HPV) was initially recognized in patients with cervical cancer and is one of the most important sexually transmitted viruses in the world (1-3). There are more than 100 known HPV types, of which more than 10 types have been associated with genital cancer (4). Infections caused by carcinogenic HPV types are considered as the major reasons for increase in all cervix infections, invasive cervical region cancer, and neoplasia of intraepithelial cervical carcinoma (5-7). Cervical cancer is one of the usual abnormalities in females' cervix (8), which is the third most common lethal cancer in women with an estimation of 530,000 reports and 275,000 mortality rate in the world per year (9). Investigations conducted in several countries to evaluated the HPV-DNA, indicated that 6.6% of the patients with the age ranges from 15 to74 years were HPV-DNA positive (10). Thus, HPV can be regarded as one of the most important agents causing sexually transmitted diseases (STD) in the world. HPV infections have been indicated to be associated with increased risk of cervix carcinoma (11-12). According to the studies, HPV is responsible for more than 5% of the entire carcinoma worldwide (4, 13-14). In addition, other microorganisms such as *Mycoplasma genitalium*, *Chlamydia trachomatis,* and *Neisseria gonorrhea* are also known as risk factors for the genital area cancers (15-17). Till date, there are limited studies on HPV prevalence in different areas of Iran.

2. Objective

The current study was aimed to investigate the true prevalence rate of HPV among Iranian women identified with cervical infections using a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

3. Materials and Methods
3.1. Literature Search

A database was built for the prevalence rate of HPV in Iran from 2000 to 2016 using several databases including Medline (via PubMed), Web of Science, Embase, Google Scholar, Iran medex, and Scientific Information Database (SID). The research was restricted to the original articles published in English and Persian, presenting the prevalence or incidence of HPV in health-care settings in Iran. The following keywords were used from medical subject headings, titles, or abstracts with the help of Boolean operators (and, or): Human Papilloma Virus, HPV, Prevalence, Cervix, Cervical Cancer, Incidence, and Iran. We also searched bibliographies of retrieved articles for additional references. In addition to articles published in English, we also looked for relevant articles in Persian.

3.2. Inclusion and exclusion criteria

All original articles presenting cross-sectional studies on the prevalence rate of HPV in Iran were reviewed. The selection of the articles to be reviewed was done in three

stages: titles, abstracts, and full texts. Included studies had the following criteria: using standard methods for HPV molecular testing and presenting data on the number of enrolled patients. For safety evaluation, we further included studies conducted on more than 100 subjects. Review articles, studies reported in languages other than English or Persian, meta-analyses or systematic reviews, duplicated publication of the same study, and articles available only in abstract form were excluded from our study. To minimize the potential bias caused by too small sample size, studies with less than 50 subjects were excluded.

3.3. Data extraction

The following variables were extracted from the included studies: author's name, study time, publication year, settings, the number of investigated patients, and the number of HPV isolates, and the source of isolates. Prevalence of HPV was extracted as well. Two investigator extracted data from all of the included studies independently. Inconsistencies between the reviewers were discussed in order to obtain consensus.

3.4. Quality assessment

Included studies were appraised for quality using a quality assessment checklist, which was designed by Joanna Briggs Institute.

3.5. Meta-Analysis

Analysis was performed using Comprehensive Meta-Analysis (V2.2, Bio stat) software. Generally, we used fixed or random effects models depending on the statistical heterogeneity between the studies to calculate summary estimates. Statistical heterogeneity was quantified by I_2 statistic. In order to assess possible publication bias, Egger weighted regression methods were used. Value of $P < .05$ was considered as an indicative of statistically significant publication bias.

4. Results

4.1. Characteristics of Included Studies

Initially, a total of 55 articles were collected. In secondary screening, 24 cases were excluded based on the title and abstract evaluation (Figure 1). In the next step, 9 out of 31 remaining studies were excluded based on the full text search. At the end, 22 eligible studies were chosen for final analysis. Figure 1 shows why records were excluded based on the assessment of title, abstract, and articles full text.
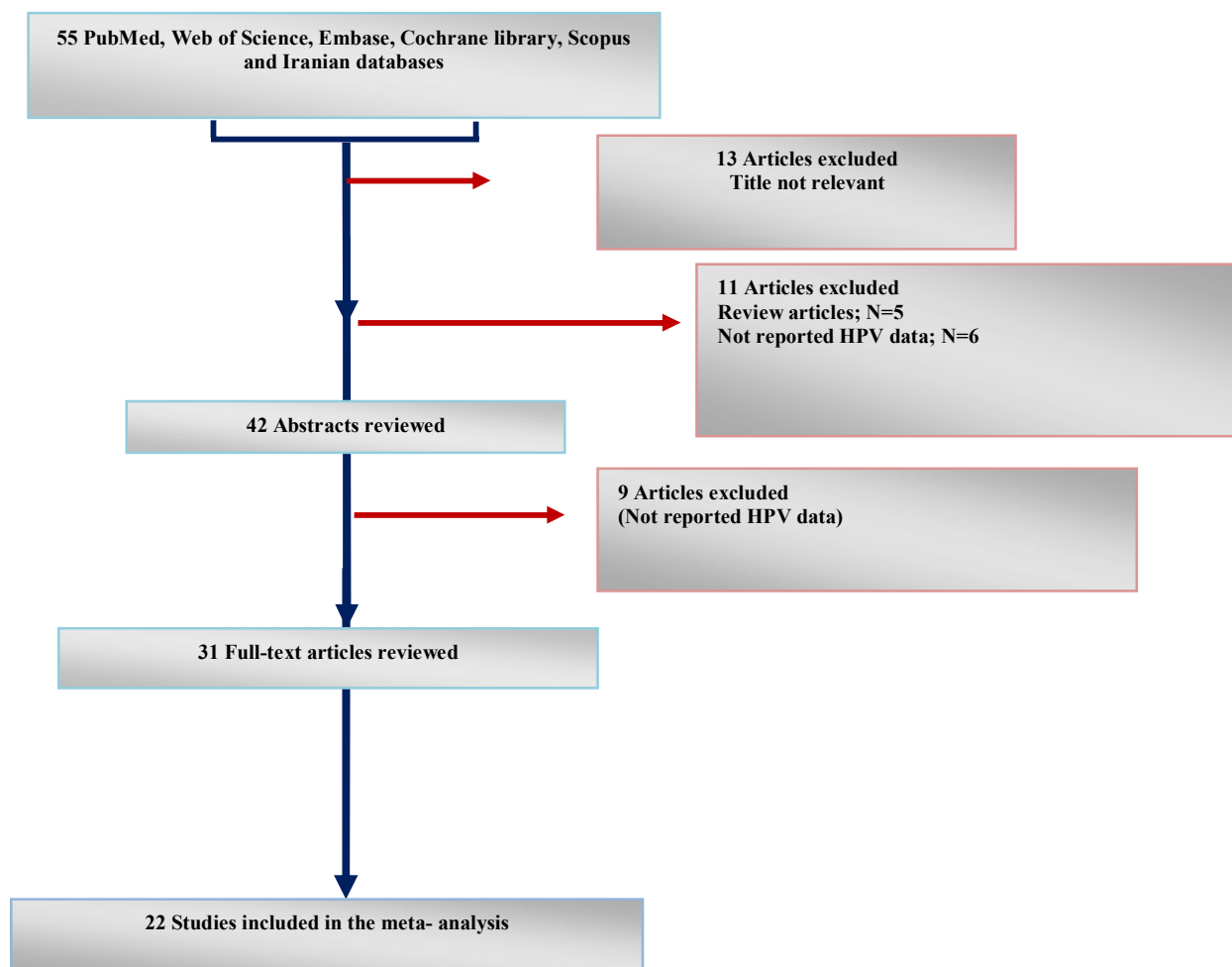

Figure 1. Flow diagram of literature search and study selection.

4.2. The Prevalence of HPV

The pooled prevalence rate of HPV infections among molecular testing-positive cases of HPV was 38.6 (95% CI, 27.9-50.5) (Table 1). The heterogeneity test indicated that there were heterogeneities between the studies (I_2 = 94.786, $P < .001$). The forest plot of HPV prevalence meta-analysis is shown in Figure 2. As shown in Table 1 and Figure 3, no evidence of publication bias was observed ($P > .05$ for Egger weighted regression analysis).
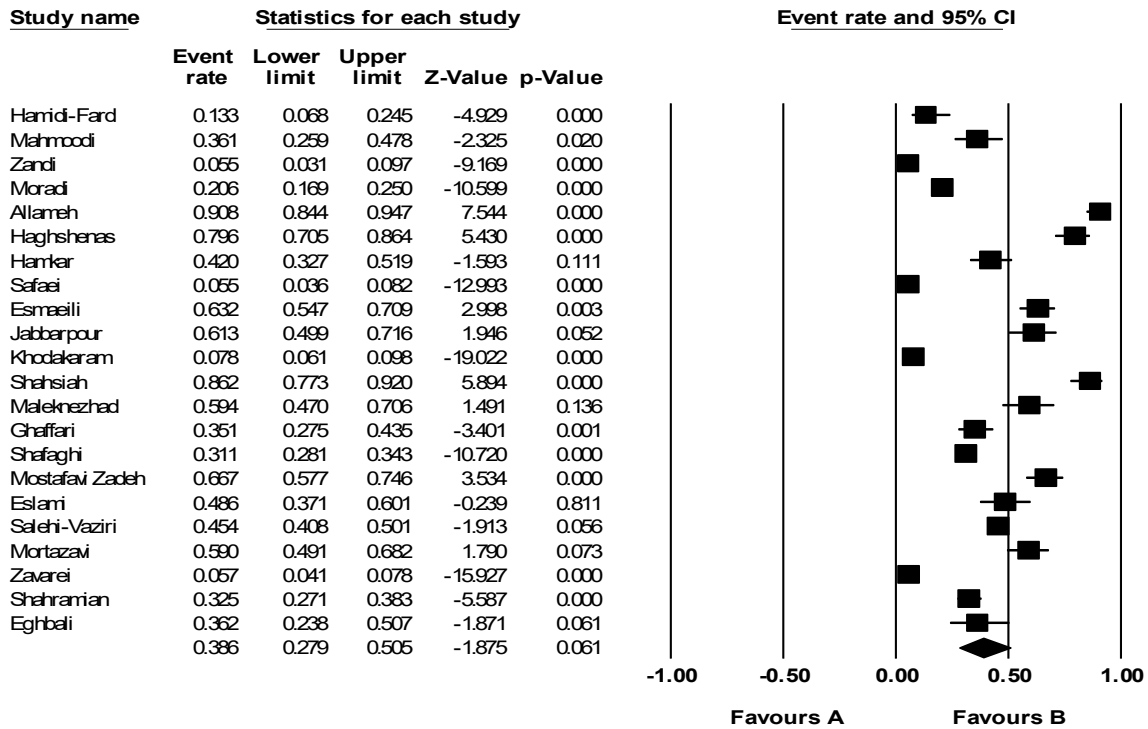
Meta Analysis

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Event rate and 95% CI
Hamidi-Fard	0.133	0.068	0.245	-4.929	0.000	
Mahmoodi	0.361	0.259	0.478	-2.325	0.020	
Zandi	0.055	0.031	0.097	-9.169	0.000	
Moradi	0.206	0.169	0.250	-10.599	0.000	
Allameh	0.908	0.844	0.947	7.544	0.000	
Haghshenas	0.796	0.705	0.864	5.430	0.000	
Hamkar	0.420	0.327	0.519	-1.593	0.111	
Safaei	0.055	0.036	0.082	-12.993	0.000	
Esmaeili	0.632	0.547	0.709	2.998	0.003	
Jabbarpour	0.613	0.499	0.716	1.946	0.052	
Khodakaram	0.078	0.061	0.098	-19.022	0.000	
Shahsiah	0.862	0.773	0.920	5.894	0.000	
Maleknezhad	0.594	0.470	0.706	1.491	0.136	
Ghaffari	0.351	0.275	0.435	-3.401	0.001	
Shafaghi	0.311	0.281	0.343	-10.720	0.000	
Mostafavi Zadeh	0.667	0.577	0.746	3.534	0.000	
Eslami	0.486	0.371	0.601	-0.239	0.811	
Salehi-Vaziri	0.454	0.408	0.501	-1.913	0.056	
Mortazavi	0.590	0.491	0.682	1.790	0.073	
Zavarei	0.057	0.041	0.078	-15.927	0.000	
Shahramian	0.325	0.271	0.383	-5.587	0.000	
Eghbali	0.362	0.238	0.507	-1.871	0.061	
	0.386	0.279	0.505	-1.875	0.061	

Favours A   Favours B

Figure 2. Forest plot of the meta-analysis on prevalence of HPV in cervical samples of Iranian patients.

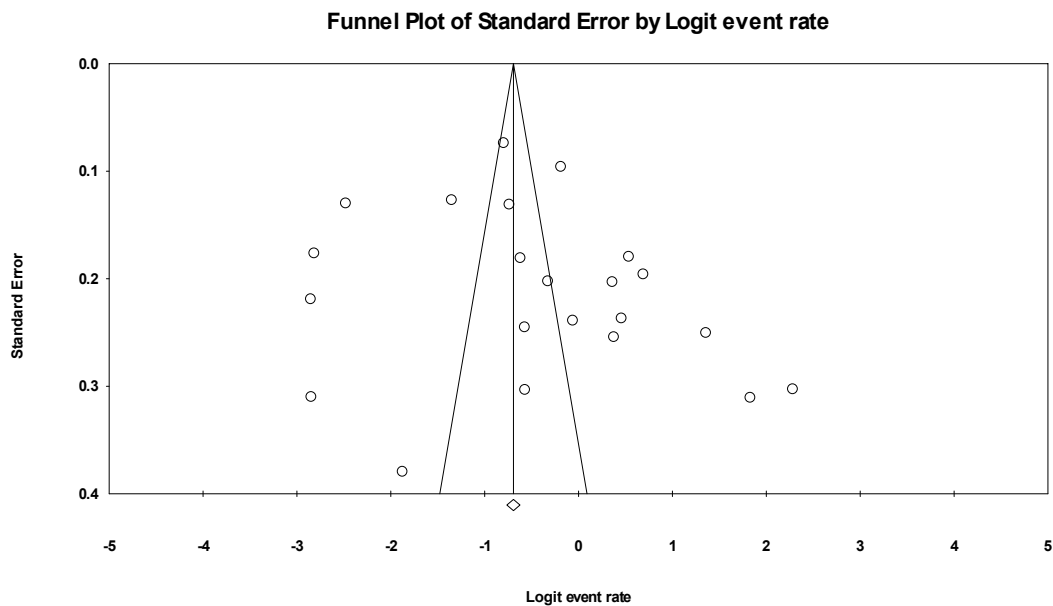### Funnel Plot of Standard Error by Logit event rate

Figure 3. Funnel plot of the meta-analysis on prevalence of HPV in cervical samples of Iranian patients.

Table 1. Meta-analysis of prevalence of HPV infections in cervical samples of Iranian patients.

Subgroups	No. of study	Prevalence of HPV (95% CI)	n/N	Heterogeneity test, I2 (%)	Heterogeneity test, *P* value	Egger's test, t	Egger's test, *P* value
Overall effects	22	38.6(27.9-50.5)	1508/5244	94.786	<.001	0.983	.336
Research period 2000-2008 (30-41)	12	46.5(28.2-65.8)	685/2160	94.861	<.001	1.700	.119
Research period 2009-2016 (42-51)	10	29.9(18.3-44.9)	823/3084	94.805	<.001	0.037	.971

n = Number of HPV / N = Number of cervical samples

5. Discussion

The present systematic review and meta-analysis indicated the prevalence rate of HPV infections in Iranian patients identified with cervical infections. Our analyses showed that the prevalence rate of HPV infections was 38.6% (95% CI, 27.9-50.5) among Iranian women with cervical infections (Table 1). Such a high prevalence rate of HPV (38.6%) among women with cervical infections may be due to several factors (18-19). First, lack of hygiene and organized screening programs for prevention and control of STD. The second factor which can be accounted for the high prevalence rate of HPV is the insufficient information available about some types of HPV responsible for infections (20). It seems that the determination of HPV types is very important for designing programs suitable for infection control and treatment (21-23).

Our results also showed an increase in HPV prevalence rate (46.5%) during the 2000-2008 years (95% CI, 28.2-65.8) in comparison with the studies conducted during the 2009-2016 years (Table 1). Observed decrease in HPV prevalence rate in recent years could be due to such reasons as: the use of HPV vaccine and the increased hygiene level in different Iranian populations (24-25). Previous studies reported different HPV prevalence ranges in cervical infections, even some studies were unable to report HPV in cervical infections (26-29). The different results in the studies conducted in Iran could be attributed to such factors as the studies condition; the type of histopathological sampling; sample transferring and storage condition; the type of method used for HPV detection; molecular technique; time of study; and patient's age, racial and ethnicity.

There are some limitations for this study that should be discussed. First of all, only published studies were accepted to be included in the present meta-analysis. Thus, as with any systematic review, the existence of the potential publication bias should be accounted for. Second, heterogeneity was detected among the included studies. Third, it wasn't able to fully represent the prevalence rate of HPV in Iran because the extent of HPV has not yet been examined in some regions of Iran.

6. Conclusions

The results of the present study underscore the need for further enforcement of STD control strategies in Iran. Establishing advanced diagnostic facilities for HPV, vaccination of high risk groups, and continuous monitoring of HPV are recommended for HPV prevention and control.

Conflict of interest

We declare that we have no conflict of interest.

Authors' Contribution

All of authors contribute to this study.

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