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REVIEW ARTICLE

Global Prevalence of Cervical Dysplasia: A Systematic Review and Meta-Analysis

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Abstract

Background Cervical dysplasia is characterized by emerging abnormal cells, including cancerous and precancerous cells in the epithelium of the cervix. Preliminary studies have investigated the prevalence of cervical dysplasia in small sample sizes or in limited geographic areas. Therefore, the present study was conducted with the aim of combining primary studies and estimating the global prevalence of cervical dysplasia using a systematic review and meta-analysis.

Methods The present systematic review and meta-analysis were conducted based on the PRISMA checklist. Articles related to the purpose of the study were obtained from Embase, PubMed, Scopus, WoS and Google Scholar search engine using relevant and validated keywords in MeSH/Emtree. Data analysis was performed using the Random Effects model by Comprehensive Meta-Analysis software (Version 2).

Results In the initial search, 4788 studies were found, of which 11 articles met the inclusion criteria. Global prevalence estimation of high-grade cervical dysplasia was 4.3% (95% confidence interval: 1.8–6.3 percent), and the global prevalence estimate of low-grade cervical dysplasia was 6.2% (95% confidence interval: 3.8–9.8 percent). The highest prevalence of cervical dysplasia was reported in the European continent.

Conclusions The results of the present study indicate a significant global prevalence of high-grade and low-grade cervical dysplasia. Therefore, this issue requires attention to early diagnosis, prevention and treatment of the disease.

Keywords Meta-analysis · Prevalence · Systematic review · Uterine cervicitis

Abbreviations

CI	Confidence interval
HIV	Human immunodeficiency virus
JBI	Joanna Briggs Institute
MeSH	Medical subject headings
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
WoS	Web of Science

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Introduction

Cancer is a genetic disease caused by mutations and changes in the proliferation and death program of cell [1]. The phenomenon of cancer is also a challenge and concern in today's societies [2]. The advances in cytological examination led to the identification of the primary precursor lesion called dysplasia. A name that indicates the malignant potential of these lesions. The concept of dysplasia is equivalent to intraepithelial neoplasia. Cervical dysplasia is a condition characterized by the appearance of abnormal cells, including cancerous and precancerous cells, in the epithelium of the cervix [3]. Cervical dysplasia is often asymptomatic, but it may be detected along with genital warts and abnormal bleeding, spotting after intercourse, vaginal discharge and back pain or during a Pap smear test [4].

Cervical cancer is the third most common neoplasm of the female reproductive system, and the second most common cause of cancer-related death in women [5]. Around the world, about half a million new cases of cervical cancer are detected annually, of which 80% are in developing countries [6]. It is also predicted that the prevalence of this cancer will continue to increase with the increase of high-risk sexual behaviors in recent years [6].

Various studies have reported the association between Human Papillomavirus (HPV), smoking, genital warts, early onset of sexual activity (less than 18 years old), having a sexual partner with a history of intercourse with a person with cervical cancer, and multiple sexual partners with the occurrence of this condition [4, 7, 8]. Also, long-term use of Oral Contraceptive Pill (OCP), birth from a mother with a history of contact with Diethylstilbestrol (DES) during pregnancy, and nutritional deficiency of folate, vitamin A, C and E, beta-carotene, and selenium in the diet are reported as factors associated with cervical dysplasia [9, 10].

There is a proper time interval between the precancerous stages, dysplasia, and cervical carcinoma, so that even in high-grade lesions of dysplasia, the time interval before becoming an invasive cancer takes several years [11]. This period has a special value in screening measures and discovering precancerous lesions.

Various studies have estimated the prevalence of cervical dysplasia in different parts of the world over the past years [3, 12–14]. However, these studies have examined prevalence with small sample sizes and in a limited geographic area. In addition, in none of the studies, the effect of potential factors such as the year of the study, the studied population, continent, and age have not been investigated. There are also contradictions about the prevalence of cervical dysplasia. Therefore, a systematic review and meta-analysis was necessary in order to combine and summarize the results of the studies, investigate the influence of potential factors, end the ambiguity of the results of the studies, and also estimate the global prevalence of cervical dysplasia, while according to our knowledge, such a study has not been done so far. Therefore, the present study was conducted aimed to determine the global prevalence of cervical dysplasia by systematic review and meta-analysis. It is hoped that the results of this study will be noticed by doctors and specialists and they will take control and treatment measures seriously.

Methods

This was a systematic review and meta-analysis study that estimated the global prevalence of cervical dysplasia. This study was conducted based on the PRISMA 2020 checklist, including the steps: identification, screening, eligibility and inclusion [15]. In order to reduce errors, all steps of searching, identifying, screening, selecting articles, and extracting data were done independently by two researchers (M.K and R.R). In the case of disagreement between the two researchers, a discussion and re-examination was done in pairs and finally a consensus was reached with the opinion of the third researcher (Z.J).

Identification of Articles

In order to find articles related to the research question (what is the global prevalence of cervical dysplasia?), a comprehensive search was done in Embase, PubMed, Scopus and Web of Science (WoS) databases. In order to search, validated keywords in Medical Subject Headings (MeSH) were used for PubMed as well as Elsevier's authoritative life science thesaurus (Emtree) for Embase, and combined using OR and AND operators. We did not apply any time or language restrictions in the search of studies to retrieve all potentially relevant articles until June 2022. Finally, in order to maximize the comprehensiveness of the search, the Google Scholar search engine and the sources of all the articles included in the study were checked manually. As for the search strategy in PubMed, it was determined as follows:

(((((Epidemiology[Title/Abstract]) OR (Prevalen*[Title/Abstract])) OR (Epidemiology[MeSH Terms])) OR (Prevalence[MeSH Terms])) AND ((Cervic*[Title/Abstract]) OR ("Uterine Cervicitis"[MeSH Terms]))) AND (Dysplasia*[Title/Abstract]).

Inclusion Criteria

The inclusion criteria were: original research articles, observational articles (cross-sectional study, cohort study, etc.), Studies conducted in the general population, and studies that reported the percentage or frequency of cervical dysplasia.

Exclusion Criteria

These articles were excluded from the review: studies unrelated to the research question, interventional studies (Clinical trial study, Field trial study and Social trial study), case series, case reports, qualitative studies, articles presented in conferences and proceeding papers, letter to editor, theses and dissertations, secondary studies (review, systematic review, meta-analysis, etc.), animal studies, and articles whose full text was not provided after three emails to the corresponding author.

Selection Process of Studies

All articles received from different databases were entered into EndNote X8 software. Articles that were duplicated in different databases, one of them remained and other duplicates were removed. Then, the names and affiliations of the authors, and the titles of the journals were removed from all the articles. In the next step, the title and abstract of the studies were reviewed and the studies unrelated to the subject were excluded. Then, the full text of the remaining articles were carefully reviewed according to pre-determined inclusion and exclusion criteria, and at this stage, some irrelevant studies were also excluded. Finally, the articles that met all the inclusion criteria entered the qualitative evaluation stage.

Qualitative Evaluation of the Studies

In the present study, the Joanna Briggs Institute (JBI) checklist was used to evaluate the quality of the studies [16]. This checklist includes 9 questions regarding participants, sample frame, sample size, data analysis, study subjects and the setting described in detail, valid methods for identifying conditions, statistical analysis, measure the situation, and adequate response rate. In scoring, if the item is observed, a score of 1, and if it is not mentioned, a score of zero is given. Therefore, the minimum score was zero and the maximum score was 9. Scores of 1–3 were considered as low quality, scores of 4–6 as medium quality, and scores of 7–9 as high quality [17].

Data Extraction

We used a prepared checklist to extract data and summarize the results of primary studies. The items of the checklist included: first author's name, country and continent, year of publication, age of samples, sample size, diagnostic tool, study type, study population, prevalence percentage and JBI score (Table 2).

Statistical Analysis

The index investigated in this study was the global prevalence of cervical dysplasia, and the relative frequency in each study was used to combine the results of the primary studies. Heterogeneity among studies was assessed by I^2 index. The I^2 index less than 50% was considered as "low heterogeneity" and more than 50% was considered as "high heterogeneity". Due to the high heterogeneity between the results of the studies included in the study ($I^2 > 50\%$), the Random Effects Model was used. In this model, the changes of parameter among the studies are also calculated, so the results of this model are more generalizable than the fixed effect model in conditions where heterogeneity is high [18]. To identify the source of heterogeneity, sensitivity analysis was used. Egger's regression intercept was used to check publication bias, because this test detects publication bias more than other tests in meta-analyses with 10–75 articles [19]. Meta-regression was also used to investigate the association between the prevalence of cervical dysplasia with the year of publication and age. Subgroup analysis was conducted by continent, study population and JBI Score. Data were analyzed using Comprehensive Meta-Analysis software (Version 2) and *P*-value less than 0.05 was considered statistically significant.

Results

Selection of Studies

Initially, 4777 studies were obtained through searching in various pre-determined databases and 11 articles were added through manual search. The next step included removing 1365 duplicate and overlapping studies in different databases. After examining the title and abstract of the remaining 3423 studies, 3379 studies were excluded due to lack of relevance to the topic and purpose of the study. Then the full text of the remaining 44 studies were reviewed, of which 33 studies were excluded due to not meeting all the inclusion criteria. Finally, 11 articles were included in the study after qualitative evaluation (Fig. 1).

General Characteristics of Studies

The studies were conducted between 1976 and 2021. The largest sample size was in study by Smith et al., with 11,958 people (Smith et al., 2014). All the articles included in the meta-analysis had medium or high quality based on the JBI checklist. Also, all included studies were of cross-sectional type. The characteristics and data of the articles included in the study for high-grade and low-grade are given in Table 1.

Meta-Analysis of the Prevalence of Cervical Dysplasia

Since the I^2 index for the global prevalence of cervical dysplasia showed great heterogeneity between studies (I^2 for high-grade = 97.50% and I^2 for low-grade = 97.54%), the data were analyzed using a random effects model. According to the results of Egger's regression intercept, there was no publication bias in the studies at the 0.05 level (P-value for high-grade = 0.235 and P-value for low-grade = 0.090). After combining the results of the primary studies included in the meta-analysis, the global prevalence of high-grade cervical dysplasia was 4.3 percent (95% confidence interval: 1.8–6.3 percent) and the global prevalence of low-grade cervical dysplasia was 6.2 percent (95% confidence interval: 3.8–9.8 percent). In Figs. 2 and 3, the black square shows the prevalence rate and the length of the line segment on it shows the 95% confidence interval in each study, and the rhombus symbol shows the global prevalence of cervical dysplasia. The results of the sensitivity analysis showed that by removing any of the studies, the final result does not change significantly.

Meta-Regression

Meta-regression was used to investigate the association between publication year, and mean of age with the global prevalence of cervical dysplasia. The results showed that with the increase of the publication year, the prevalence of cervical dysplasia had a downward trend ($P < 0.05$). The association between the mean of age and the prevalence of

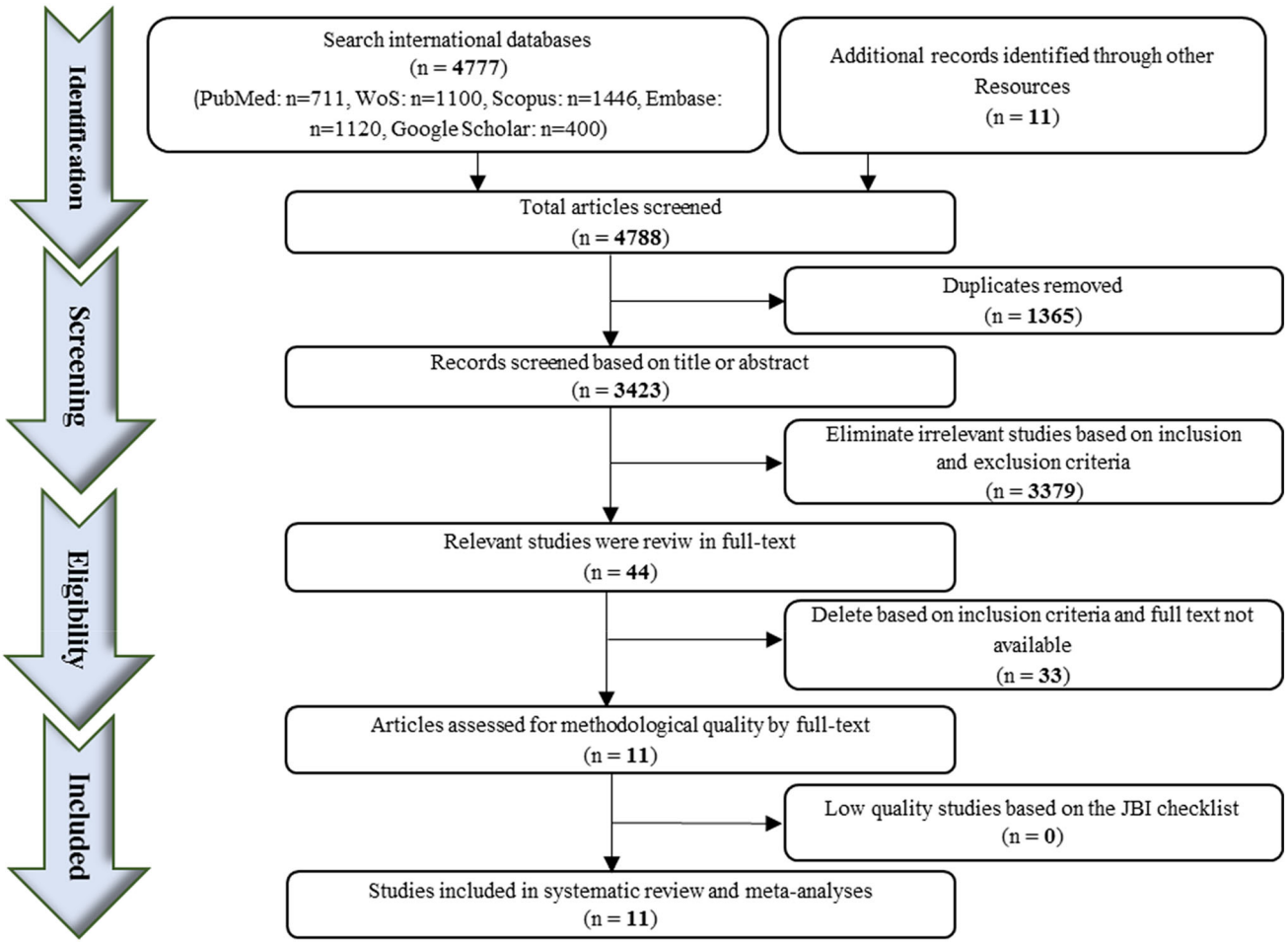

Fig. 1 PRISMA 2020 search flow diagram

Table 1 Characteristics and data of articles entered in systematic review and meta-analysis for high-grade and low-grade cervical dysplasia

First author, year (Reference)	Country (continent)	Sample size (*n*)	Age (year)	Type of study	Diagnostic tool	Prevalence (%)	Population	JBI score
High-grade								
Ory, 1976 [20]	Georgia (Europe)	247	25.23	Cross-sectional study	Biopsy and Pap smear	1.7	General population	6, Medium
Gupta, 2013 [13]	India (Asia)	4703	–	Cross-sectional study	Biopsy and Pap smear	0.91	General population	8, High
Davidson, 1994 [12]	Georgia (Europe)	234	28 (13–45)	Cross-sectional study	Biopsy and Pap smear	19.2	General population	7, High
Azocar, 1990 [21]	France (Europe)	165	27.0	Cross-sectional study	Pap smear	11.0	General population	6, Medium
Briggs, 1980 [22]	USA (America)	48	20.3 ± 15.7	Cross-sectional study	Cytology	8.3	General population	6, Medium
Thay-2, 2019 [11]	Cambodia (Asia)	501	39.23 ± 6.24	Cross-sectional study	Biopsy and Pap smear	8.6	General population	7, High
Yakasai, 2012 [23]	Nigeria (Africa)	740	–	Cross-sectional study	Biopsy and Pap smear	4.86	General population	5, Medium
Smith-1, 2014 [24]	USA (America)	2229	18.5	Cross-sectional study	Biopsy and Pap smear	1.62	General population	7, High
Smith-2, 2014 [24]	USA (America)	5294	25	Cross-sectional study	Biopsy and Pap smear	1.38	General population	7, High
Smith-3, 2014 [24]	USA (America)	11,958	40	Cross-sectional study	Biopsy and Pap smear	1.10	General population	7, High
Mosuro, 2015 [25]	Nigeria (Africa)	280	42.5 ± 11.1	Cross-sectional study	Pap smear	2.1	General population	7, High
Hocke-2, 1998 [26]	France (Europe)	102	30 (17–48)	Cross-sectional study	Colposcopy and Pap smear	2.9	General population	6, Medium
Ogu-2, 2019 [14]	Nigeria (Africa)	104	41.7 ± 5.5	Cross-sectional study	Pap smear	3.81	General population	7, High
Low-grade								
Gupta, 2013 [13]	India (Asia)	4703	–	Cross-sectional study	Biopsy and Pap smear	3.23	General population	8, High
Davidson, 1994 [12]	Georgia (Europe)	234	28 (13–45)	Cross-sectional study	Biopsy and Pap smear	7.2	General population	7, High
Briggs, 1980 [22]	USA (America)	48	20.3 ± 15.7	Cross-sectional study	Cytology	22.9	General population	6, Medium
Yakasai, 2012 [23]	Nigeria (Africa)	740	–	Cross-sectional study	Biopsy and Pap smear	2.83	General population	5, Medium
Smith-1, 2014 [24]	USA (America)	2229	18.5	Cross-sectional study	Biopsy and Pap smear	7.00	General population	7, High

Table 1 (continued)

First author, year (Reference)	Country (continent)	Sample size (*n*)	Age (year)	Type of study	Diagnostic tool	Prevalence (%)	Population	JBI score
Smith-2, 2014 [24]	USA (America)	5294	25	Cross-sectional study	Biopsy and Pap smear	3.27	General population	7, High
Smith-3, 2014 [24]	USA (America)	11,958	46	Cross-sectional study	Biopsy and Pap smear	1.40	General population	7, High
Mosuro, 2015 [25]	Nigeria (Africa)	280	42.5 ± 11.1	Cross-sectional study	Pap smear	11.8	General population	7, High
Hocke-2, 1998 [26]	France (Europe)	102	30 (17–48)	Cross-sectional study	Colposcopy and Pap smear	10.8	General population	6, Medium
Ogu-2, 2019 [14]	Nigeria (Africa)	104	41.7 ± 5.5	Cross-sectional study	Pap smear	14.29	General population	7, High

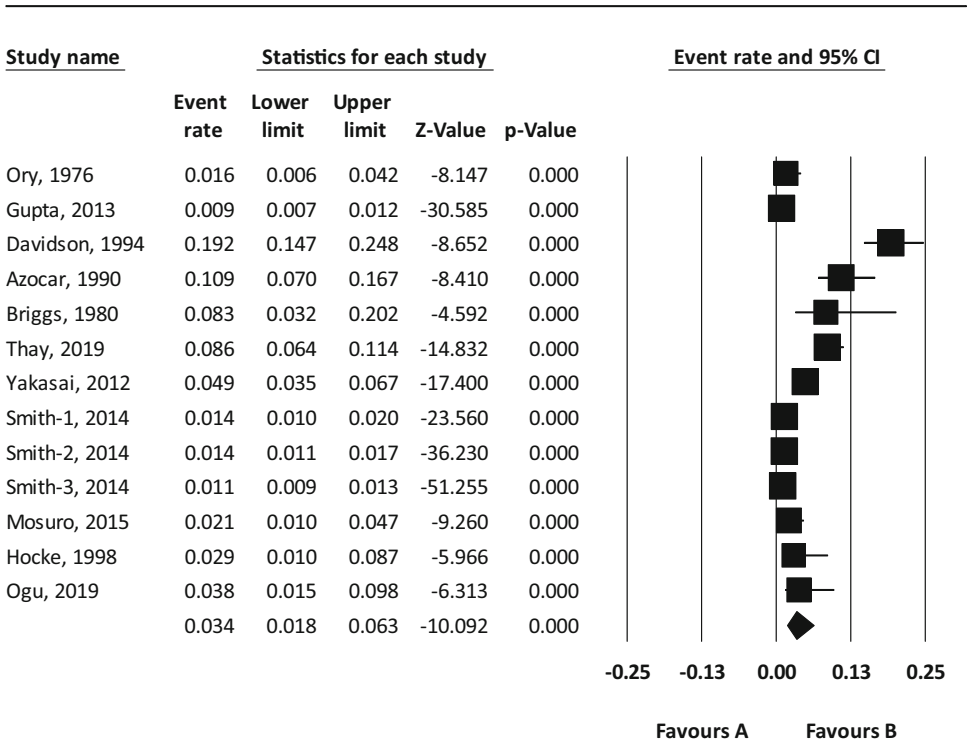

Fig. 2 Forest plot for estimating the global prevalence of high-grade cervical dysplasia based on a random effects model

Meta Analysis

high-grade cervical dysplasia was not significant ($P > 0.05$), but with the increase of mean age, the prevalence of low-grade cervical dysplasia decreased ($P < 0.05$).

Subgroup Analysis

Due to the high heterogeneity between studies, subgroup analysis was performed according to different continents, and quality. The highest prevalence of high grade and low

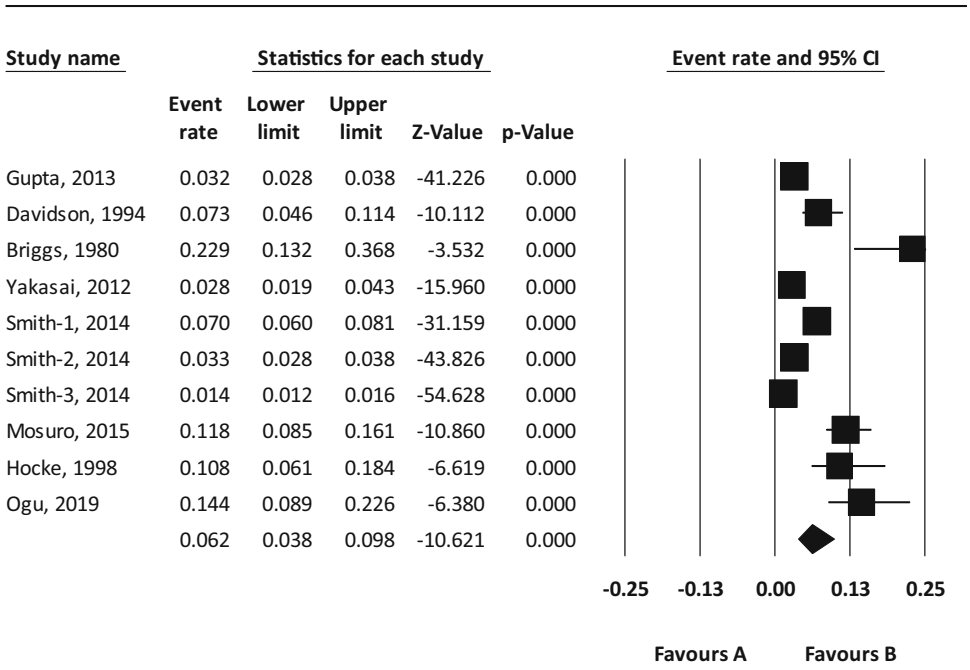

Fig. 3 Forest plot for estimating the global prevalence of low-grade cervical dysplasia based on a random

Meta Analysis

grade cervical dysplasia belonged to the European continent with 6.4% (95% confidence interval: 2.3–16.5%), and 8.5% (95% confidence interval: 5.8–12.4), respectively. There was no significant difference in the prevalence of cervical dysplasia between studies with high and medium quality (Table 2).

Discussion

The present systematic review and meta-analysis were conducted with the aim of determining the global prevalence of cervical dysplasia. The prevalence of high-grade cervical dysplasia was 4.3% after combining the results of 13 primary studies included in the study with a sample size of 26,605 people, and the prevalence of low-grade cervical dysplasia was 6.2% after combining the results of 10 studies included in the study with a sample size of 25,692 people. The highest quality score based on the JBI checklist was belonged to the study by Gupta et al., with a score of 8, in which the prevalence of high-grade cervical dysplasia was reported at 0.9% and the prevalence of low-grade cervical dysplasia at 3.2% [3], which was lower than the overall estimate.

Cervical dysplasia is strongly associated with human papillomavirus (HPV). HPV type 16 is involved in 90% of cervical cancers and 50–70% in cervical dysplasia. Also, herpes simplex virus (HSV) type 2 is another cause of cervical dysplasia and cancer that is transmitted through sexual intercourse [27]. HPV is transmitted through sexual intercourse (vaginal, anal and oral). This virus can also enter the body through skin contact with the skin of the genital area of an infected person and be transmitted to the other parts of the body such as the cervix [28]. There are various factors that increase the risk of developing cervical dysplasia such as immunodeficiency disorders, immunosuppressive drugs such as those used in organ transplants, childbirth before the age of 16 years, having sex before age of 18 years, having different sexual partners, smoking, being overweight, long-term use of OCP or long-term use of a hormonal IUD, family history, having more than 3 pregnancies, and a diet with insufficient amounts of fruits and vegetables [13]. In general, it takes 5–10 years for a dysplasia to turn into cervical cancer, although this time may be shorter in some cases [29].

Early diagnosis of this disease is the most important step in its treatment. Patients with dysplasia usually require long-term follow-up to prevent recurrence or relapse, persistence, or progression to cancer [30]. Physical examinations can be done at intervals of 3–6 months. This approach allows the treatment of recurrent or persistent dysplasia or the diagnosis of cancer [31]. Screening methods available to diagnose cervical dysplasia include cervical cytology and high resolution anoscopy (HRA) [32]. However, these

Table 2 Subgroup analysis of cervical dysplasia prevalence

Grade	Subgroups		Number studies	Point estimate	Lower limit	Upper limit	*P*-value	*P*-value between	I^2 (%)	Tau
High-grade cervical dysplasia	Continent	Africa	3	0.038	0.023	0.062	0.000	0.007	45.31	0.320
		America	4	0.015	0.022	0.022	0.000		82.98	0.325
		Asia	2	0.029	0.003	0.222	0.002		99.09	1.633
		Europe	4	0.064	0.023	0.165	0.000		91.45	0.998
	JBI Score	High	8	0.027	0.012	0.061	0.000	0.233	98.26	1.181
		Medium	5	0.050	0.027	0.092	0.000		77.28	0.609
Low-grade cervical dysplasia	Continent	Africa	3	0.080	0.029	0.202	0.000	0.000	94.33	0.918
		America	4	0.051	0.022	0.116	0.000		98.83	0.880
		Asia	1	0.032	0.028	0.038	0.000		0.000	0.000
		Europe	2	0.085	0.058	0.124	0.000		12.11	0.107
	JBI Score	High	7	0.053	0.031	0.091	0.000	0.457	98.08	0.757
		Medium	3	0.091	0.024	0.289	0.001		94.48	1.205

methods are not universally performed, and their role in the management of patients with cervical dysplasia is unknown [32].

Considering the change in population structure, culture, diet, genetics, number of births, age of marriage and childbirth, contraceptive methods, sexual relations, etc. in different countries and geographical regions, we decided to do a subgroup analysis according to different continents. The highest prevalence of cervical dysplasia was reported in the European continent. One of the reasons for this is screening and better diagnosis methods. Of course, the number of articles reported on some continents, including Asia and Africa, is limited, and it is necessary to conduct more primary studies with larger sample sizes in these continents to estimate the prevalence more accurately.

The results of meta-regression showed that the prevalence of cervical dysplasia has decreased in recent years. Among the reasons, we can mention the increase in people's awareness, early screenings and diagnoses, increase in the quality of health services, promotion of health education, creation of pro-health policies, HPV vaccination in women and men, and media support in providing health messages. Therefore, it seems necessary to increase these preventive measures to reduce the amount and complications of cervical dysplasia.

The high prevalence of cervical dysplasia shows the necessity of investigation and follow-up for this disease. Considering the complications and problems caused by cervical dysplasia and its great impact on different aspects of life, it requires special attention from officials and experts. In order to reduce the spread of this disease, one should be familiar with it, find the right solution, implement these solutions and follow up the results of the actions; this policy is effective when it is implemented at the individual, group and organizational level.

Some of the limitations of this research were the possibility of not obtaining all the unpublished articles and reports and the non-uniformity of the method of implementing the articles. In addition, due to high heterogeneity in studies (more than 95%), we had to perform subgroup analysis, which reduced a small amount of heterogeneity. However, there is still high heterogeneity in most subgroups, which may be caused by the sample size, demographic characteristics, and study methodology. The current study included only articles conducted in the general population, so it is necessary to estimate the prevalence of cervical dysplasia in other populations such as patients with polycystic ovaries, infertile women, people with HIV, organ transplants, etc.

Conclusions

The results of the present systematic review and meta-analysis showed that the prevalence of high-grade and low-grade cervical dysplasia is high, especially in the European continent. Therefore, this issue calls attention to early diagnosis, necessary measures for prevention and timely treatment of this disease.

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Author's contributions MKn and ZJ contributed to the design, MKn, ZJ and RR participated in most of the study steps. ZJ and MKn

prepared the manuscript. MKn, ZJ and MKm assisted in designing the study, and helped in the, interpretation of the study. All authors have read and approved the content of the manuscript.

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Availability of data and materials Datasets are available through the corresponding author upon reasonable request.

Declarations

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

Ethics approval and consent to participate Ethics approval was received from the ethics committee of deputy of research and technology, Kermanshah University of Medical Sciences (IR.KUMS.REC.1401.219).

Consent for publication Not applicable.

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