High parity is associated with increased risk of cervical cancer: Systematic review and meta-analysis of case-control studies

Yohannes Tekalegn (yohannesefa@gmail.com)
Madda Walabu University
Biniyam Sahiledengle
Madda Walabu University
Demelash Woldeyohannes
Wachemo University
Daniel Atlaw
Madda Walabu University
Fikreab Desta
Madda Walabu University
Kebebe Bekele
Madda Walabu University
Tesfaye Assefa
Madda Walabu University
Habtamu Gezahegn
Madda Walabu University
chala kene
Madda Walabu University

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Abstract

Background: Cervical cancer is the fourth most common cancer among women. High parity has long been suspected with an increased risk of cervical cancer. Evidence from the existing epidemiological studies regarding the association between parity and cervical cancer is variable and inconsistent. Therefore, the objective of this systematic review and meta-analysis was to synthesize the best available evidence on the epidemiological association between parity and cervical cancer.

Methods: MEDLINE/PubMed, HINARI, Google scholar, Science direct, and Cochrane Libraries were systematically searched. Cochrane Q statistics and I2 tests were performed to assess heterogeneity among included studies. Begg's test and egger's regression analysis were performed to assess publication bias. A random-effect meta-analysis model was used to compute pooled odds ratio of the association between parity and cervical cancer.

Results: A total of 6975 participants (1998 patients; 4977 controls) were incorporated in the 13 articles included in the final meta-analysis. The meta-analysis revealed that women with parity greater than or equal to three had 2.4 times higher odds of developing cervical cancer compared to women with parity less than three [pooled odds ratio (POR) = 2.4, 95% CI: 1.9-3.2].

Conclusion: High parity is associated with an increased risk of cervical cancer. Strong epidemiological studies are recommended to further explore the mechanisms and role of parity in the causation of cervical cancer.

Background

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells (1). Cervical cancer is considered nearly completely preventable because of the generally slow progression of the disease and the availability of screening and the Human Papilloma Virus (HPV) vaccine (2). Cervical cancer is cancer that forms in tissues of the cervix, the organ connecting the uterus and the vagina. It is usually slow-growing cancer that may not have symptoms at early stages. Every year, about 528,000 new cases of cervical cancer occur among women worldwide (3).

Human Papilloma Virus (HPV) is recognized as a necessary cause of cervical cancer (4–9). However, HPV infection alone is not sufficient to cause cervical cancer and some cofactors modify the progression of the infections to cancer (4,8). Evidence suggests that women's characteristics like age, number of live births or parity, number of pregnancies, age at first sexual intercourse, age at first pregnancy, history of sexually transmitted infections, having multiple sexual partners, and history of long-term oral contraceptives use play role in developing cervical cancer (10–14,14–19).

Previous studies reported a positive association between parity and cervical cancer (10,20–24). Excess risk of cervical cancer among women with high parity is believed to be linked with a high rate of cervical abnormalities during pregnancy (25,26), a high detection rate of HPV among pregnant women (27,28), and some studies also suggest vaginal parity makes local changes to cervical cells due to traumas during birth (11). Though several previous epidemiological studies documented parity as a risk factor for cervical cancer; the reported strength of association is variable and inconsistent. Therefore, this systematic review and meta-analysis aimed to estimate the pooled odds ratios of the association between parity and cervical cancer. This meta-analysis will highlight the strength of association between parity and cervical cancer which will, in turn, helps to ascertain risks of cervical cancer among women with high parity compared to those with low parity.

Methods

Formulation of the questions

The primary aim of this systematic review was: does high parity affect the risk of cervical cancer? If so, to what extent does high parity affect the development of cervical cancer?

Search strategies

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (29) (**additional file 1**). To get potentially relevant articles, a comprehensive search was performed in the following databases: MEDLINE/Pub Med, Hinari, Google Scholar, Science Direct, and Cochrane Library. The following key terms in combination with Boolean operators were used: (*("parities"[All Fields] OR "parity"[MeSH Terms]) OR "parity"[All Fields]) AND (("uterine cervical neoplasms"[MeSH Terms] OR (("uterine"[All Fields] AND "cervical"[All Fields]) AND "neoplasms"[All Fields])) OR "uterine cervical neoplasms"[All Fields])*. To ensure a comprehensive search of the literature, reference lists of included studies were scanned.

Eligibility criteria

Population: All studies reporting the association between parity and cervical cancer among women.

Exposure of interest: Parity.

Outcome of interest: cervical cancer.

Study designs: Epidemiological studies (Case-control and Cohort studies) examining the association between parity and cervical cancer were included in this review. Besides, the odds ratio (OR) examining the association between parity and cervical cancer shall be given or derived from the original studies to be considered for inclusion into the meta-analysis. Systematic reviews, cross-sectional, case-report, case-series, opinion reports, letters to the editor, short communications, and qualitative studies were excluded.

Setting: This systematic review and meta-analysis included all studies reporting the association between parity and cervical cancer regardless of their study areas.

Timeframe: This review included all studies published after 2000 up to March 7, 2020. An electronic database search was conducted from February 6, 2020, to March 7, 2020.

Publication condition: This review included articles published in peer-reviewed journals.

Language: Only articles reported in English were considered.

Study selection

All identified articles through electronic databases were imported to EndNote X4 software. After removing duplicate articles, two authors (YT and BS) independently screened all articles by their title, abstract and full texts for their eligibility against the predetermined inclusion and exclusion criteria. Subsequently, identified articles were compiled together and discrepancies between the two authors were resolved through discussion to reach a consensus.

Risk of bias

We used Joanna Briggs Institutes' (JBI) Critical appraisal checklist for case-control studies (30). The tool composed of ten parameters: 1) were the groups comparable other than the presence of disease in cases or absence of disease in controls? 2) Were cases and controls matched appropriately? 3) Were the same criteria used for the identification of cases and controls? 4) Was exposure measured in a standard, valid and reliable way? 5) Was exposure measured in the same way for cases and controls? 6) Were confounding factors identified? 7) Were strategies to deal with confounding factors stated? 8) Were outcomes assessed in a standard, valid and reliable way for cases and controls? 9) Was the exposure period of interest long enough to be meaningful? 10) Was appropriate statistical analysis used? Two authors (YT and BS) evaluated the risk of bias of the full text considered to be included in the meta-analysis. The overall risk of bias was then scored according to the number of high risks of bias per study: low (≤2), moderate (3–4), and high (≥5) (**additional file 2)**.

Data extraction

Data were extracted on Microsoft Office Excel spreadsheet. The data extraction format is composed of the primary author's name, year of publication, study period, country, study design, study setup, number of cases, number of controls, odds ratio, and 95% confidence intervals for the association between parity and cervical cancer. Two authors (YT and BS) independently extracted the information. Any discrepancies were resolved through discussion.

Statistical analysis

Extracted data were imported into STATA version 14 software (StataCorp LP.2015, College Station, TX: USA) to perform all statistical analysis. First, odds ratios were either obtained or derived from data reported in the original studies. Then, converted to log odds ratio. Standard error (SE) for the log odds ratios (OR) were computed using SE (log OR) = $\sqrt{}$ (1/a +1/b + 1/c +1/d). Heterogeneity between studies was assessed using Cochran's Q-statistics and I^2 test. In this meta-analysis, the test statistics indicated the presence of significant heterogeneity (I^2 = 78.4%, p<0.001). For this reason, the odds ratios were pooled using random-effect meta-analysis techniques (DerSimonian and Liard method), which accounts for the variation between studies. Natural logarithm (ln) of odds ratios and their respective 95% confidence intervals were used to get pooled odds ratio of the association between parity and cervical cancer. The pooled odds ratios along with their 95% confidence intervals were presented using a forest plot. Subgroup analyses by countries of original studies were conducted. Univariate meta-regression analyses were also conducted to identify possible sources of heterogeneity. Variables considered in meta-regression were years of publication, number of cases, and number of controls. However, none of the variables were found to be a statistically significant source of heterogeneity. Publication bias of the meta-analysis was assessed using egger's test statistics, and there was no statistically significant publication bias (p-value = 0.4).

Operational definitions

Cervical cancer: In this study, authors included studies that diagnosed cervical cancer through the histological confirmation of cancer.

Parity: Parity is defined as the number of times that a woman has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn.

High parity: In this meta-analysis, we used parity greater than or equal to three as high parity. We made this classification depending on the availability of data among included primary studies.

Results

Description of articles selection

A total of 2392 articles were identified through all databases described above. Of these, 1020 duplicate articles were removed. After screening by their title and abstract, 1340 articles were excluded. Then, 26 articles were assessed for eligibility based on predefined eligibility criteria and risk of bias assessment. Further 13 articles were excluded due to inaccessibility of full text, full articles reported in languages other than English, the outcome of interest is not reported separately, the outcome of interest is not reported, excluded after critical appraisal (**additional file 3**). Finally, 13 articles were included in this meta-analysis (**Fig.1**).

Characteristics of included studies

As described in **Table 1**, a total of 13 articles were included in this systematic review and meta-analysis. A total of 6975 participants (1998 patients; 4977 controls) were incorporated in the 13 articles included in the final meta-analysis. One study reported an association of parity with both Adenocarcinoma and Squamous cell carcinoma of the cervix (31); hence, both results were included in the meta-analysis. All of the included articles were case-control studies. Of all studies included, one study was from China, one from Côte d'Ivoire, one study from

Ethiopia, three studies from India, two studies from Indonesia, one article from Taiwan, one article from Thailand, one article from the UK, and one study from the USA. Regarding the year of publications, the earliest article included in this meta-analysis was published in 2003 (32,33), and the latest was published in 2019 (34,35).

Table 1: List of studies included in the systematic review and meta-analysis of the association between parity and risk of cervical cancer, 2020.

No	Primary author	Year of publication	Study site	Study setups/source	Study design	Number of cases	Number of controls	Age range (years)	COR (95% CI)
1	Cai (36)	2008	China	Hospital	Case-control	110	110	22-72	1.1 (0.6-1.8)
2	Adjorlolo-Johnson (37)	2010	Côte d'Ivoire	Hospital	Case-control	132	120	18-70	4.1 (2.0-8.4)
3	Bezabih (12)	2015	Ethiopia	Hospital	Case-control	60	120	unreported	4.6 (2.8-7.4)
4	Franceschi (32)	2003	India	Hospital	Case-control	193	210	unreported	3.0 (1.8-4.7)
5	Sharma (38)	2018	India	Hospital	Case-control	91	182	20-80	6.48 (2.9-14.2)
6	Thakur (39)	2015	India	Hospital	Case-control	226	226	unreported	2.8 (1.9-4.3)
7	Arfailasufandi (35)	2019	Indonesia	Hospital	Case-control	100	100	unreported	4.1 (2.3-7.6)
8	Putri (34)	2019	Indonesia	Hospital	Case-control	60	60	21-30	3.5 (1.7-7.6)
9	Chen (40)	2005	Taiwan	Hospital	Case-control	45	54	<36	4.9 (2.0-11.8)
10	Natphopsuk (41)	2012	Thailand	Hospital	Case-control	177	177	27-81	1.7 (1.11-2.7)
11	Nesrin (42)	2011	Turkey	Hospital	Case-control	209	1050	unreported	1.6 (1.17-2.14)
12	Green (33)	2003	UK	Cancer registry	Case-control	180	923	20-44	1.4 (1.01-2.04)
13	Green (33)	2003	UK	Cancer registry	Case-control	180	923	20-44	1.5 (1.14-1.92)
14	Shields (43)	2004	USA	Hospital	Case-control	235	722	20-74	1.7 (1.14-2.42)

Association between parity and cervical cancer

As describe in **Fig.2** below, thirteen case-control studies were included in this meta-analysis to determine the association between parity and cervical cancer. The studies exhibited significant heterogeneity (I^2=77.8, p<

0.001), hence, a random effect meta-analysis model was used to estimate the pooled odds ratio. This meta-analysis revealed that parity is significantly associated with cervical cancer. The likelihood of developing cervical cancer was more than two times higher among women with high parity (≥3) compared to their counterparts (<3) (OR= 2.4, 95% CI: 1.9-3.2).

Figure 2: Forest plot of the individual and pooled odds ratios (OR) of association between cervical cancer and parity

Subgroup analysis and exploration of heterogeneity

As described in **Fig.3**, Subgroup analysis was conducted by countries where the studies were carried out. Accordingly, positive associations were observed between parity and cervical cancer in studies conducted in Côte d'Ivoire, Ethiopia, India, Taiwan, Thailand, Turkey, the UK, and the USA except the study reported from China.

Fig 3: Subgroup analysis of the association between cervical cancer and parity by countries

Test of heterogeneity

Meta-regression analysis was employed to assess potential sources of heterogeneity. Accordingly, years of publication, the number of cases and controls were not significant sources of heterogeneity (**Table 2**).

Table 2: Meta-regression of factors associated with the heterogeneity of the studies included in estimating the pooled effect of parity on cervical cancer

Variables	Coefficient	P-value
Year of publication	0.09	0.413
Number of cases	0.004	0.563
Number of controls	0.0001	0.883

Discussion

Cervical cancer is believed to be cancer emerging from infectious disease origin (44). The human papillomavirus (HPV) two types specifically, HPVs 16 and 18 explains approximately about 70% of cervical cancer cases (45). Despite the fact HPV infection is the necessary cause in the etiology of cervical cancer, HPV infection alone is not a sufficient cause for the occurrence of the cases (4). Several epidemiological studies investigated the role of different demographic, sexual, and reproductive factors in the progression of HPV infection into cervical carcinoma (10,23,46–51). This systematic review and meta-analysis investigated the pooled odds ratio of the association between multiple parity and cervical cancer.

In this meta-analysis high parity is associated with a higher risk of cervical cancer. This finding is supported by the multicenter case-control study conducted by International Agency for Research on Cancer (IARC). This multicenter study reported that nulliparous women were at lower risk of cervical cancer whereas there were clear trends of increased risk of cervical cancer as the number of full-term pregnancies increased among parous women (16). Several epidemiological studies also reported a positive association between parity and cervical cancer (46,52–55).

The previous studies reported an association between full-term pregnancy and cervical cancer. The possible explanations were concentrations of estrogen and progesterone level in blood are known to increase during pregnancy and reach the highest levels in the last weeks of gestation. These hormonal changes are perhaps responsible for the alterations in the junction between the squamous and columnar epithelium (transformation zone) occurring during pregnancy. Squamous metaplasia of the transformation zone also increases during pregnancy to reach a maximum during the third trimester (56).

Some other studies have also explained the association between multiple pregnancies and cervical cancer could be due to high detection of cervical abnormalities among pregnant women (25,26), probably due to migration of endocervix during pregnancy (57). There are also assumptions that traumas to the uterine cervix during vaginal delivery might be a possible explanation for the positive association between cervical cancer and parity (21,58). Cesarean delivery was not associated with cervical cancer as vaginal delivery does, which might strengthen the speculation that traumas during the vaginal delivery might increase the risks (16).

A large cohort study conducted in Taiwan reported that high vaginal parity is not a sufficient cause by itself unless that women also HPV infected. They explained that if the woman is HPV infected and had high vaginal parity, the virus can easily integrate due to the birth traumas, and the risk of cervical cancer increases. However, if the woman is not HPV infected, vaginal parity doesn't make difference whether it is high or low because birth trauma can heal by itself (59). Similarly, a multicenter case-control study by IARC reported that women with baseline HPV infection and multiple pregnancies had a higher risk of developing cervical cancer compared to women with a low number of pregnancies (16).

Even though several epidemiological studies examined the association between cervical cancer and different reproductive characteristics of women; the role of high parity and mechanisms in the causation of cervical cancer is unclear. There are several hypotheses regarding the effect of parity in the development of cervical cancer. Few studies suggest that vaginal parity could cause trauma to the cervix which could be responsible for cervical cancer developments and some other studies justified the role of parity by explaining hormonal changes during pregnancy might be responsible for the changes in cervical cells. There are also studies speculating high parity might be associated with a longer duration of oral contraceptive use which might, in turn, leads to cervical cancer development. Despite there are debates regarding the mechanism and role of parity in the development of cervical cancer, there is plenty of strong evidence which supports the positive association between parity and cervical cancer.

Limitations

This meta-analysis didn’t examine the effect of vaginal or cesarean parity separately. Also, this study didn't explore separately the interaction between HPV infection and high parity on cervical cancer development. This meta-analysis included case-control studies which were published in the English language only.

Conclusion

This meta-analysis revealed that parity is positively associated with cervical cancer risks. Women with high parity had higher odds of developing cervical cancer compared to those with relatively low parity. Epidemiological studies with strong designs are recommended to examine the mechanisms and role of parity in the causation of cervical cancers.

Abbreviations

CI: Confidence interval; HPV: Human Papilloma Virus; OR: Odds ratio

Declarations

Authors’ contributions

YT: Conceptualized, designed the study and data curation, performed the analysis, wrote, and approved the final manuscript. BS &DW: Data curation and performed the analysis, and approved the final manuscript DA, FD, KB, TA, HG & CK: Contribute to the analysis, critically reviewed the manuscript, and approved the final manuscript. All authors read and approved the final manuscript before submission.

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Competing interests

The author declares that they have no competing interests

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Figures

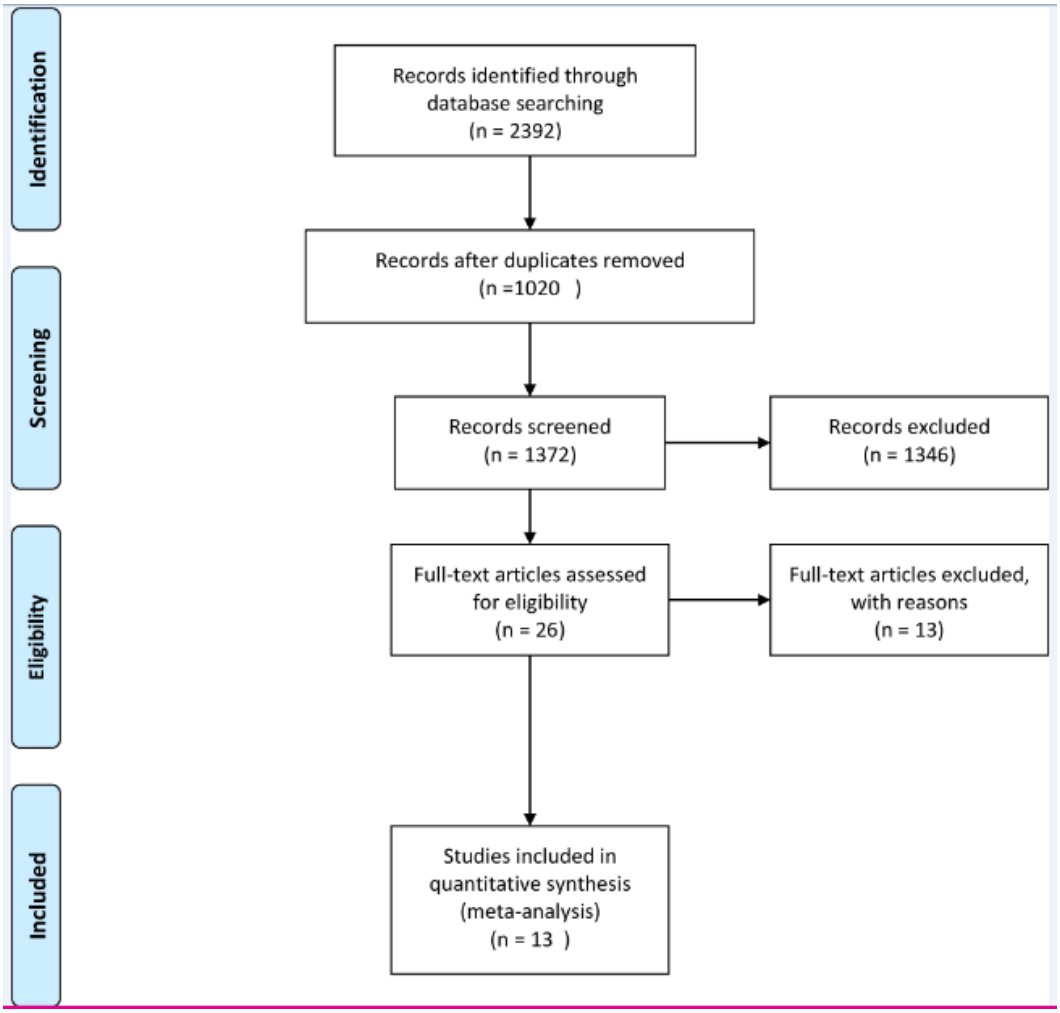

Figure 1

Study flowchart.

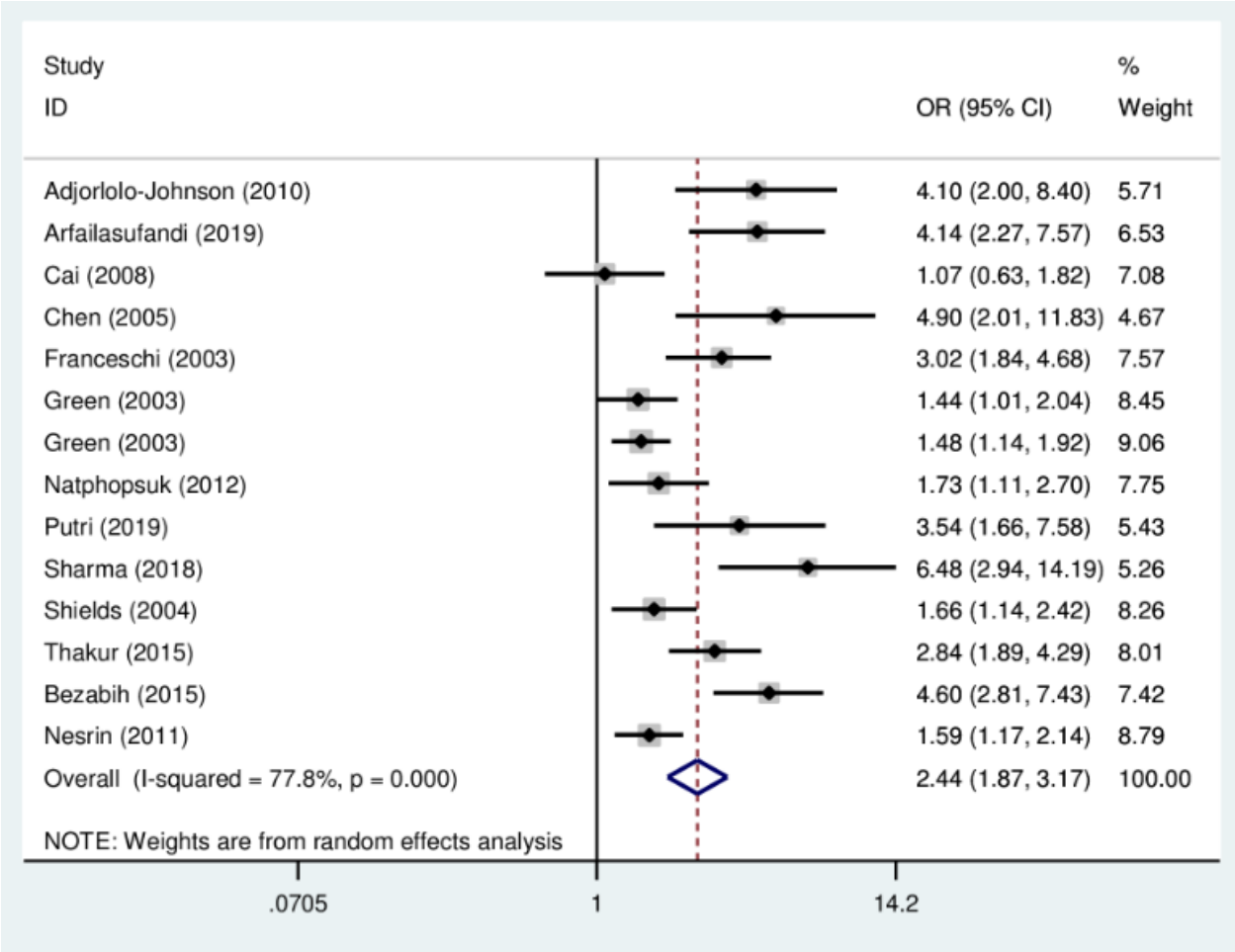

Figure 2

Forest plot of the individual and pooled odds ratios (OR) of association between cervical cancer and parity

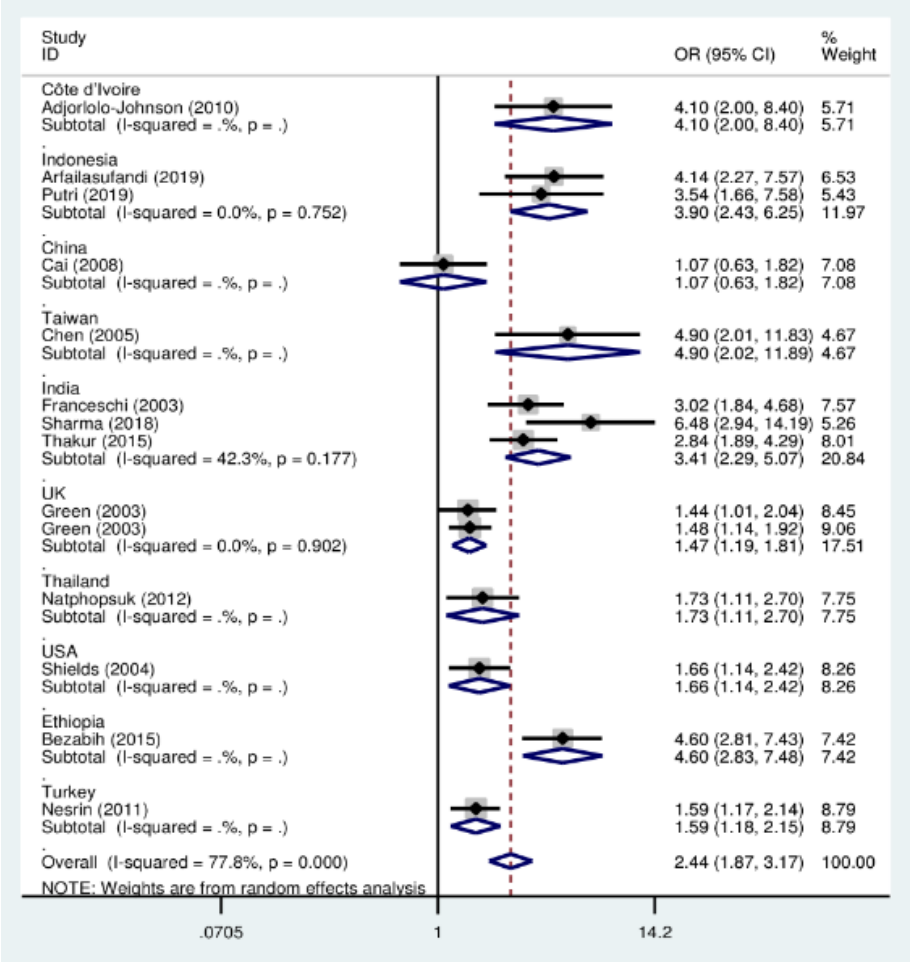

Figure 3

Subgroup analysis of the association between cervical cancer and parity by countries

Supplementary Files

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- additionalfile1.docx
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