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

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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: Case–control studies reporting the association between parity and cervical cancer were systematically searched in databases like MEDLINE/PubMed, HINARI, Google scholar, Science direct, and Cochrane Libraries. All studies fulfilling the inclusion criteria and published between 2000 and 7 March 2020 were included in this meta-analysis. This study reported according to PRISMA guideline. Cochran's Q-statistics and I^2 tests were performed to assess heterogeneity among included studies. Egger's regression analysis was 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 6685 participants (3227 patients and 3458 controls) were incorporated in the 12 studies included in this meta-analysis. The meta-analysis revealed that women with high parity had 2.65 times higher odds of developing cervical cancer compared to their counterparts (odds ratio = 2.65, 95% confidence interval = 2.08–3.38).

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

Keywords

case–control, cervical cancer, meta-analysis, parity, systematic review

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Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells.[1] Cervical cancer is cancer that forms in tissues of the cervix, the organ connecting the uterus and the vagina. 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.[2,3] In 2018, about 570,000 women developed cervical cancer globally and 311,000 women died from it.[4] HPV is recognized as a necessary cause of cervical cancer.[5–10] However, HPV infection alone is not sufficient to cause cervical cancer and some cofactors modify the progression of the infections to cancer.[5,9] 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.[11–20]

Previous studies reported a positive association between parity and cervical cancer.[11,17,21–24] 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] Although 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 (ORs) of the association between parity and cervical cancer. It will also 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 and meta-analysis is to determine the strength of association between parity and the risk of cervical cancer.

Search strategies

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline[29] (Additional File 1). To get potentially relevant studies, 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.

Inclusion criteria

Population: females of reproductive age and above at risk for cervical cancer.

Exposure of interest: parity.

Outcome of interest: cervical cancer.

Study designs: case–control studies examining the association between parity and cervical cancer were included in this review. Besides, the OR examining the association between parity and cervical cancer shall be given 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.

Time frame: this review included all studies published from January 2000 to March 2020. An electronic database search was conducted from 6 February 2020 to 7 March 2020.

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

Language: only articles reported in English were considered.

Exclusion criteria

Studies with the following characteristics were excluded from this systematic review and meta-analysis:

- Studies whose full text and data were inaccessible.
- Studies which did not report the confounder adjusted OR of the association between parity and cervical cancer.
- Studies conducted on precancerous lesion of cervix.
- Qualitative studies, reviews, commentaries, editorials, letters, interventional studies, and other opinion papers.

Study selection

All identified articles through electronic databases were imported to EndNote X4 software. After removing duplicate articles, two authors (Y.T. and B.S.) 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 Institute's (JBI) Critical appraisal checklist for case–control studies.[30] The tool composed of 10 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 (Y.T. and B.S.) evaluated the risk of bias of the full text considered to be included in the meta-analysis. Any disagreement between two authors was resolved through discussion. The overall risk of bias was then scored according to the number of high risks of bias per study: low ($\leqslant 2$), moderate,[3,4] and high ($\geqslant 5$) (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, OR, and 95% confidence intervals (CIs) for the association between parity and cervical cancer. Two authors (Y.T. and B.S.) 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 analyses. First, ORs were obtained from data reported in the original studies. Then, confounder adjusted ORs were pooled using generic inverse variance method by converting adjusted OR on logarithmic scale and back calculating standard error (SE) based

on the 95% CIs. 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 ORs were pooled using random-effect meta-analysis techniques (DerSimonian and Liard method), which accounts for the variation between studies. The pooled ORs along with their 95% CIs were presented using a forest plot. Subgroup analyses were conducted by countries of original studies, years of publication, confounders adjusted in multivariate analysis, and definitions of high parity on each original study. Univariate meta-regression analyses were also conducted to identify possible sources of heterogeneity. Variables considered in meta-regression were years of publication, study setups (hospital vs cancer registry), age of participants, factors adjusted as confounding variables, and definition of parity used in each original study. We also conducted sensitivity analysis using random-effect model to assess the effect single study on the pooled estimate. Publication bias of the meta-analysis was assessed using Egger's test statistics, and there was no statistically significant publication bias (p-value = 0.2).

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.

Results

Description of study selection

A total of 2392 studies were identified through all databases described above. Of these, 1020 duplicate studies were removed. After screening by their title and abstract, 1345 studies were excluded. Then, 27 studies were assessed for eligibility based on predefined eligibility criteria and risk of bias assessment. Further, 15 studies were excluded[31–45] due to inaccessibility of full text, full articles reported in languages other than English, and the outcome of interest is not reported separately (Additional File 3). Finally, 12 studies were included in this meta-analysis.[13,17,46–55] None of the primary studies included in the current review are type specific for high parity and its relation to cervical cancer (Figure 1).

Characteristics of included studies

As described in Table 1, a total of 12 studies were included in this systematic review and meta-analysis. A total of
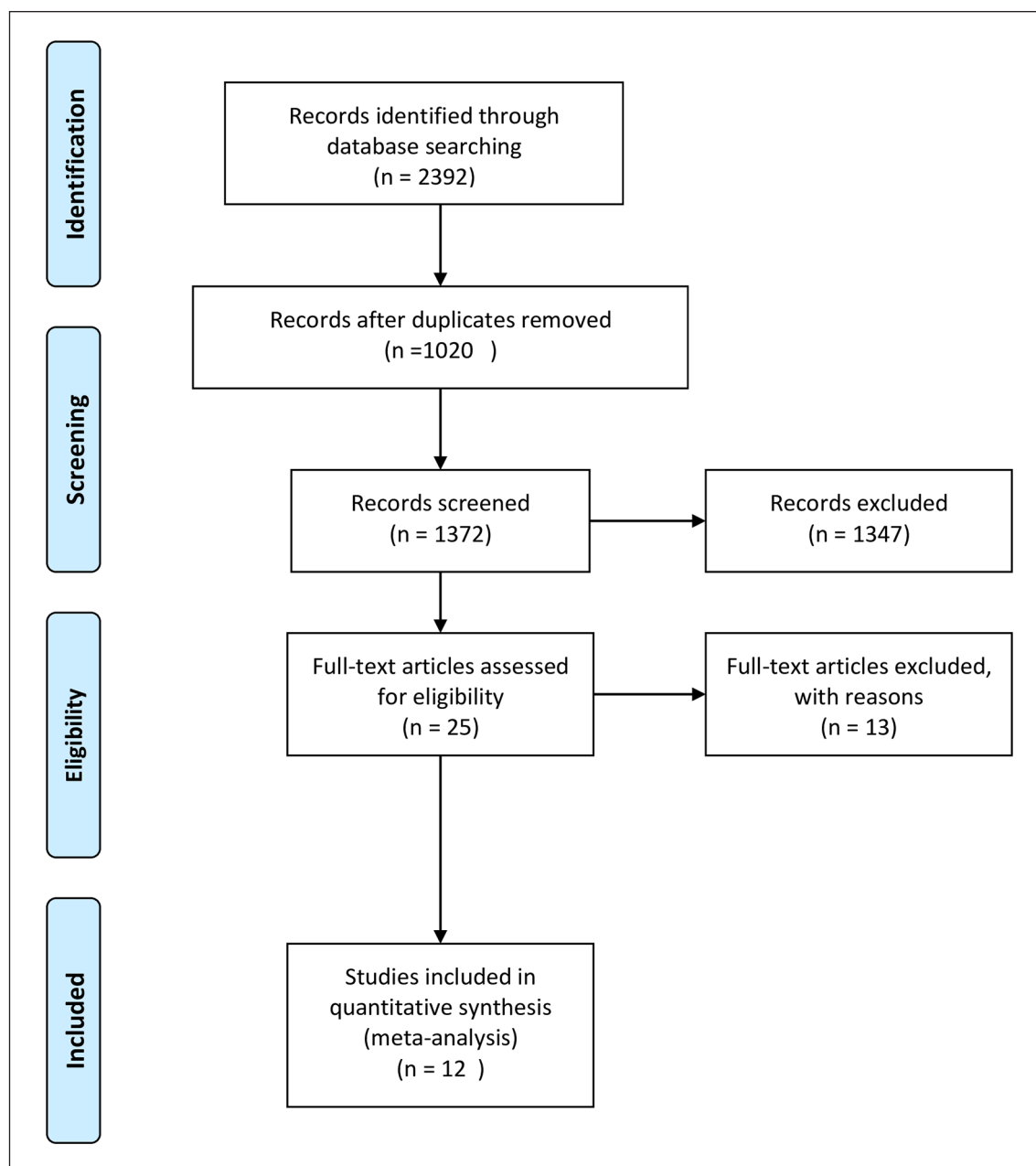
Figure 1. PRISMA flowchart of the article selection process for systematic review and meta-analysis of the association between cervical cancer and parity.

6685 participants (3227 patients and 3458 controls) were incorporated in the 12 articles included in the final meta-analysis. One study reported an association of parity with both adenocarcinoma and squamous cell carcinoma of the cervix;[56] 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 United Kingdom, and one study from the United States. Regarding the year of publications, the earliest article

included in this meta-analysis was published in 2003,[50,51] and the latest was published in 2019.[47,53] As described in Table 2, among the 12 studies that examined the association between parity and cervical cancer, 10 study reported positive association between high parity and cervical cancer.[13,17,46–48,50,51,53–55]

Association between parity and cervical cancer

As describe in Figure 2, 12 case–control studies were included in this meta-analysis to determine the association between parity and cervical cancer. The studies exhibited

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

Primary author	Year of publication	Study period	Country	Study setups/source	Study design	Number of cases	Number of controls	Age range (years)
Cai et al.[48]	2008	2003–2005	China	Hospital	Case–control	110	110	22–72
Adjorlolo-Johnson et al.[46]	2010	April 1997 to October 1999	Côte d'Ivoire	Hospital	Case–control	132	120	18–70
Bezabih et al.[13]	2015	April 1 to 30 September 2010	Ethiopia	Hospital	Case–control	60	120	Unreported
Franceschi et al.[50]	2003	June 1998 to May 1999	India	Hospital	Case–control	193	210	Unreported
Sharma and Pattanshetty[54]	2018	Unreported	India	Hospital	Case–control	91	182	20–80
Thakur et al.[55]	2015	July 2008 to October 2009	India	Hospital	Case–control	226	226	Unreported
Arfailasufandi et al.[47]	2019	October to December 2018	Indonesia	Hospital	Case–control	100	100	Unreported
Putri et al.[53]	2019	March 2016 to August 2016	Indonesia	Hospital	Case–control	60	60	21–30
Chen et al.[49]	2005	1986–1992	Taiwan	Hospital	Case–control	45	54	<36
Natphopsuk et al.[52]	2012	February 2009 to August 2011	Thailand	Hospital	Case–control	177	177	27–81
Green et al.[51]	2003	1984–1989	The United Kingdom	Cancer registry	Case–control	180	923	20–44
Green et al.[51]	2003	1984–1989	The United Kingdom	Cancer registry	Case–control	180	923	20–44
Muñoz et al.[17]	2002	Unreported	Multicenter	Hospital	Case–control	1673	253	Unreported

significant heterogeneity ($I^2 = 74.6$, $p < 0.001$). Hence, a random-effect meta-analysis model was used to estimate the pooled OR. 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 compared to their counterparts (OR = 2.65, 95% CI = 2.08–3.38).

Sensitivity analysis for the association between parity and cervical cancer

To estimate the effect of individual study on the pooled estimate of the association between parity and cervical cancer, we performed sensitivity analysis using random-effect model. Based on the result, single study has no significant effect on the pooled estimate. The pooled estimated OR ranged between 2.50 (1.97–3.17)[54] and 2.77 (2.19–3.51)[51] after omitting each study (Figure 3).

Exploration of heterogeneity and subgroup analysis

Meta-regression analysis was employed to assess potential sources of heterogeneity using factors like years of publication, study setups (hospital vs registry), age of participants, factors adjusted as confounding variables, and definition of parity used in each original study. Accordingly, study setup and factors adjusted for confounder in multivariate model were found to be significant sources of heterogeneity (Table 3). Furthermore, subgroup analysis was conducted by countries of primary studies, year of publications, study setup, and factors adjusted as confounder in multivariate models of original studies (Table 4).

Publication bias

In this meta-analysis, funnel plot and Egger's test were used to assess presence of publication bias. However, the results show no publication bias at 95% confidence level (*p*-value = 0.1) (Figure 4).

Discussion

Cervical cancer is believed to be cancer emerging from infectious disease origin.[57] The HPV two types specifically, HPVs 16 and 18, explains approximately about 70% of cervical cancer cases.[58] 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.[5] Several epidemiological studies investigated the role of different demographic, sexual, and reproductive factors in the progression of HPV infection into cervical carcinoma.[11,17,39,59–63] This systematic review and meta-analysis investigated the pooled OR of the association between multiple parity and cervical cancer.

Table 2. Primary studies with available adjusted odds ratios of the association between parity and cervical cancer.

Primary author	Year of publication	Parity	AOR (95% CI)	Adjusted confounders
Adjorlolo-Johnson et al.[46]	2010	>2	5.1 (1.2–21.9)	a
Arfailasufandi et al.[47]	2019	≥3	3.94 (1.47–10.59)	Unreported
Bezabih et al.[13]	2015	3 to 4	4.7 (0.8–27.2)	Unreported
Bezabih et al.[13]	2015	>4	12.4 (2.4–64.2)	
Cai et al.[48]	2008	2	6.05 (0.93–38.59)	Unreported
Cai et al.[48]	2008	3	9.06 (1.32–62.52)	
Cai et al.[48]	2008	>3	16.82 (18.1–150.95)	
Chen et al.[49]	2005	≥3	4.18 (0.71–24.69)	Unreported
Franceschi et al.[50]	2003	0	0.5 (0.1–2.1)	b
Franceschi et al.[50]	2003	3–4	2.6 (1.6–4.3)	
Franceschi et al.[50]	2003	5–6	5.7 (3.0–11.1)	
Franceschi et al.[50]	2003	≥7	5.7 (2.4–13.3)	
Green et al.[51]	2003	1	1.27 (0.69–2.34)	c
Green et al.[51]	2003	2	1.14 (0.63–2.05)	
Green et al.[51]	2003	≥3	1.44 (0.76–2.73)	
Green et al.[51]	2003	1	0.88 (0.55–1.4)	
Green et al.[51]	2003	2	1.41 (0.92–2.17)	
Green et al.[51]	2003	≥3	1.86 (1.16–2.99)	
Natphopsuk et al.[52]	2012	≥3	1.63 (0.62–4.28)	Unreported
Putri et al.[53]	2019	≥3	2.89 (1.18–7.1)	Unreported
Sharma and Pattanshetty[54]	2018	3–5	4.66 (2.04–10.66)	Unreported
Sharma and Pattanshetty[54]	2018	≥6	10.12 (4.33–23.87)	
Thakur et al.[55]	2015	≥3	1.7 (1.25–2.65)	Unreported
Muñoz et al.[17]	2002	1–2	1.81 (1.31–2.52)	d
Muñoz et al.[17]	2002	3–4	2.55 (1.95–3.34)	
Muñoz et al.[17]	2002	5–6	2.83 (2.02–3.96)	
Muñoz et al.[17]	2002	≥7	3.82 (2.66–5.48)	

AOR: adjusted odds ratio; CI: confidence interval.
a indicates age, low socioeconomic status, and lifetime number of sex partners.
b indicates age and area of residence.
c indicates age, recruitment center, age at first intercourse, duration of oral contraceptive use, level of education, number of negative screening results, smoking status and total number of sexual partners.
d indicates study center, age, education, smoking status, age at first intercourse, number of sexual partners, oral contraceptive use, and history of Papanicolaou's smears.

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 the 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.[17] Several epidemiological studies also reported a positive association between parity and cervical cancer.[39–41,64,65]

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.[66]

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.[67] 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.[22,68] 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.[17]

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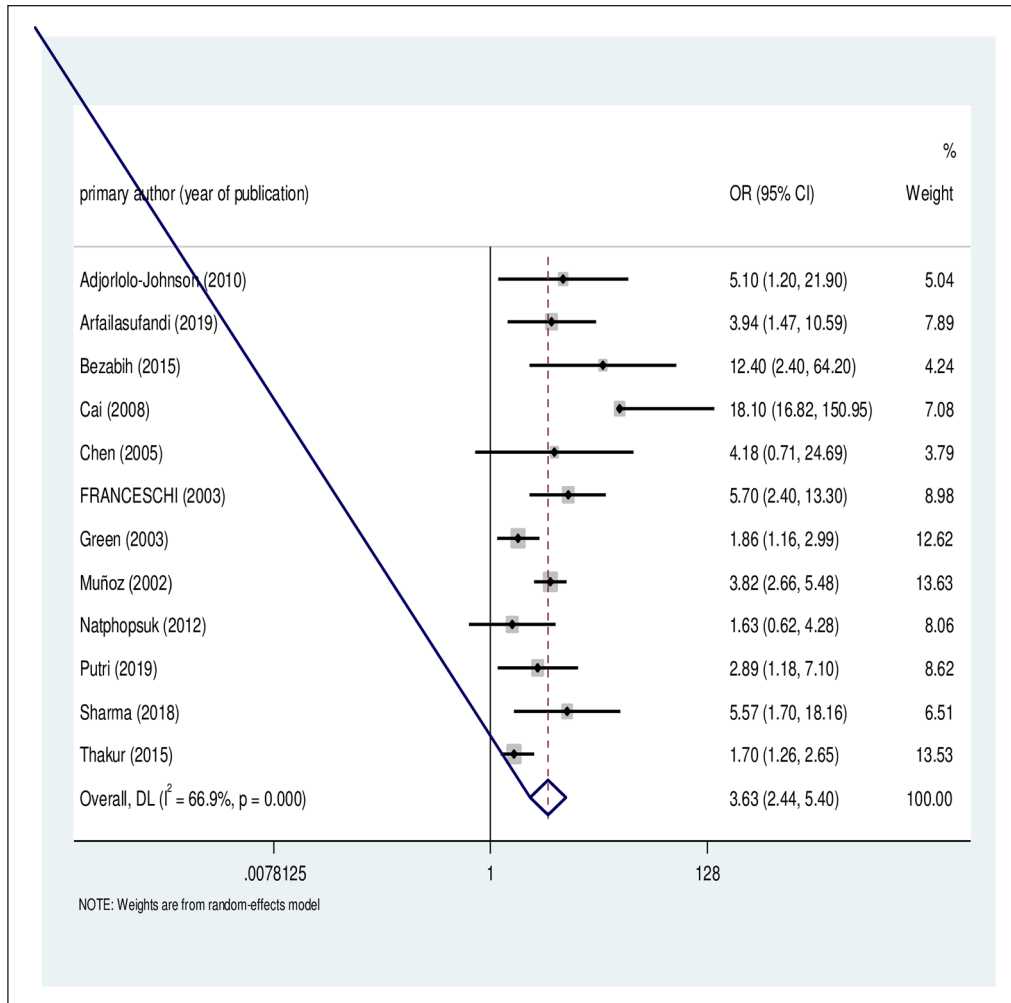
Figure 2. Forest plot of the individual and pooled odds ratios (OR) of association between cervical cancer and parity.
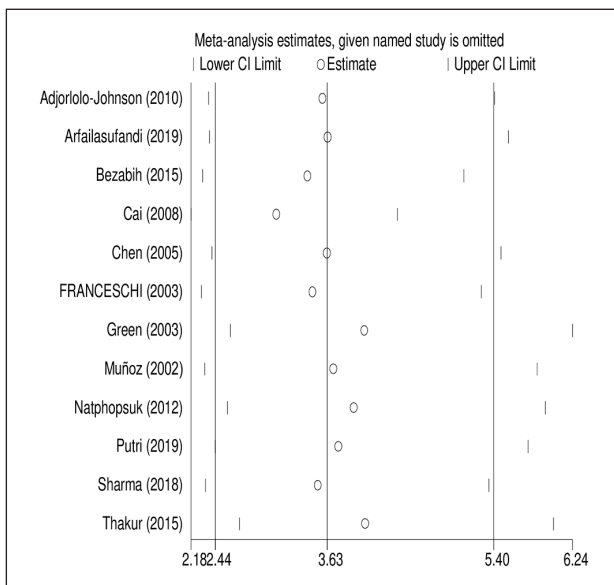

Figure 3. Sensitivity analysis for the pooled estimate of the association between parity and cervical cancer.

Table 3. Meta-regression of factors associated with the heterogeneity of the studies included in estimating the pooled effect of parity on cervical cancer.

Variables	OR (95% CI)	*p*-value
Year of publication	1.0 (1.001–1.1)	0.04*
Age of participants	0.84 (0.68–1.02)	0.08
Study setup	0.39 (0.22–0.66)	0.001*
Definition of parity	1.02 (0.94–1.10)	0.5
Factors adjusted for confounder	0.77 (0.60–0.98)	0.03*

OR: odds ratio; CI: confidence interval.
*Significant at $p < 0.05$.

risk of cervical cancer increases. However, if the woman is not HPV infected, vaginal parity does not make difference whether it is high or low because birth trauma can heal by itself.[69] 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.[17]

Table 4. Subgroup analysis of the association between parity and cervical cancer.

| Variables	Subgroup	Number of studies	AOR (95% CI)	Heterogeneity across the studies		Heterogeneity between groups (p-value)
				I^2 (%)	p-value	
Country	China	1	12.6 (5.39–29.46)	0	<0.001	<0.001
	Côte d'Ivoire	1	5.1 (1.2–21.9)	0	<0.001	
	Ethiopia	1	7.9 (2.37–26.28)	0	0.43	
	India	3	3.45 (1.95–6.12)	79.4	<0.001	
	Indonesia	2	3.32 (1.71–6.46)	0	0.64	
	Multicenter	1	2.64 (1.99–3.5)	67.8	0.025	
	Taiwan	1	4.18 (0.71–24.65)	0	–	
	Thailand	1	1.63 (0.62–4.28)	0	–	
	The United Kingdom	1	1.30 (1.05–1.62)	5.8	0.37	
Year of publication	2000–2010	6	2.39 (1.80–3.16)	77.1	<0.001	0.16
	2011–2020	6	3.71 (2.12–6.51)	68.4	0.002	
Study setups	Hospital	11	3.45 (2.66–5.48)	65.8	74.6	<0.001
	Registry	1	1.30 (1.04–1.62)	5.8	–	
Factors adjusted in multivariate model	a	1	5.1 (1.19–21.79)	0	–	<0.001
	b	1	3.11 (1.47–6.58)	72.8	0.012	
	c	1	1.3 (1.05–1.62)	5.8	0.37	
	d	1	2.64 (1.99–3.5)	67.8	0.025	
	e	8	4.67 (2.74–7.96)	68.5	<0.001	

AOR: adjusted odds ratio; CI: confidence interval.
a indicates age, low socioeconomic status, and lifetime number of sex partners.
b indicates age and area of residence.
c indicates age, recruitment center, age at first intercourse, duration of oral contraceptive use, level of education, number of negative screening results, smoking status, and total number of sexual partners.
d indicates study center, age, education, smoking status, age at first intercourse, number of sexual partners, oral contraceptive use, and history of Papanicolaou's smears.
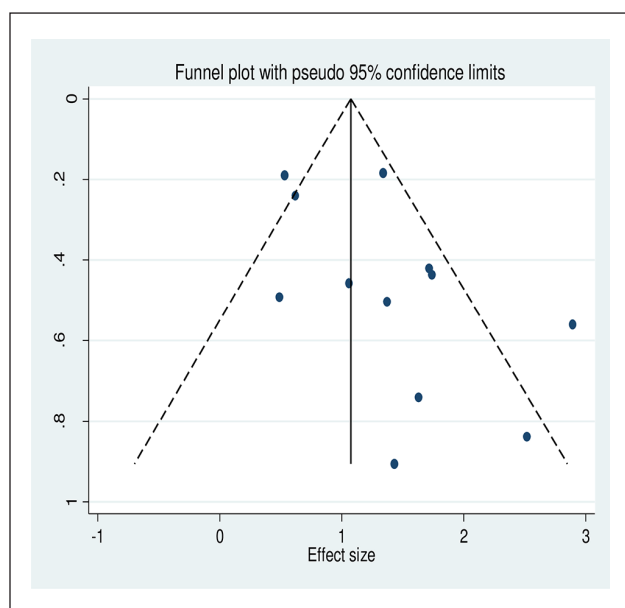
Figure 4. Funnel plot for the meta-analysis of the association between parity and cervical cancer.

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. A 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[68] 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 systematic review and meta-analysis has several limitations and results should be interpreted considering the following points. First, this meta-analysis did not examine the effect of vaginal or cesarean parity separately. Also, this study did not 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 and none of the included studies are cohort and exposure-specific primary studies. Finally, due to differences in definitions of high parity across studies, the pooled OR is not directly interpretable as a relative risk associated with a given number of births, but rather an indicator of the mean trend across studies which have examined high parity as a risk factor for cervical using different definitions.

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.

Author contribution(s)

Yohannes Tekalegn: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.
Biniyam Sahiledengle: Conceptualization; Formal analysis; Methodology; Validation; Visualization; Writing—review & editing.
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Availability of data and materials

All relevant data are within the manuscript and its supporting information files.

Supplemental material

Supplemental material for this article is available online.

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