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Meta Analysis
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Meta-Analysis: Effects of Hormonal Contraceptive Use and History of Sexually Transmitted Disease on the Risk of Cervical Cancer

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ABSTRACT

Background: Cervical cancer is a sexually transmitted disease (STD) with the fourth largest number of new cases and deaths worldwide. This study aimed to analyze the effects of the use of hormonal contraception and a history of STD on the risk of cervical cancer in women.
Subjects and Method: The meta-analysis was carried out using the PRISMA flowchart and the PICO model. Population: women of reproductive age. Intervention: use of hormonal contraception and history of sexually transmitted infections Comparison: not using hormonal contraception and history of sexually transmitted infections Outcome: Cervical Cancer. The process of searching for articles is by searching through online journal databases which include Google Scholar, Elsevier and PubMed. With keywords "oral pill" OR "1 month injection" OR "3 month injection" OR "implant" OR "hormonal contraception" AND "cervical cancer" OR "syphilis" OR "chlamydia" OR "herpes" OR "gonorrhea" OR "HIV" AND "Sexually transmitted infections" AND "Cross sectional" AND aOR. Articles were selected using the PRISMA flow and data analysis using the Review Manager 5.3 application.
Results: This meta-analysis consisted of 12 articles from Africa and Asia . The total sample was 8,240. The use of hormonal contraception (aOR = 2.34; 95% CI= 1.83 to 4.66; p<0.001) and had history of STD (aOR = 1.97; 95% CI = 1.49 to 2.61; p<0.001) increased the risk of cervical cancer.
Conclusion: The use of hormonal contraception and has history of STD increase the risk of cervical cancer.

Keywords: hormonal contraception, history of sexually transmitted infections, cervical cancer.

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BACKGROUND

Cervical cancer is a sexually transmitted disease with the fourth largest number of new cases and deaths worldwide (Yang et al., 2021). New cases of cervical cancer are detected through the Pap smear test (William et al., 2019). Cervical cancer can be prevented early with screening programs and the human papillomavirus (HPV) vaccine (Shen et al., 2023).

Based on data from the International Agency for Research on Cancer in 2020 it was

stated that the number of new cases of cancer incidence was 9,227,484 women of all ages, with cervical cancer of 604,127 (Sung et al., 2021). Meanwhile, in Indonesia cervical cancer is in second place, the incidence of cancer cases is 213,546 women of all ages, with cervical cancer incidence of 36,633, a percentage of 17.2% (Globocon, 2020).

The use of hormonal contraception has benefits, namely as a delay in pregnancy which is often used by women who work outside (Ningrum et al., 2016), but can have a high risk of cervical cancer if used for a period of more than 5 years (Kusmiyati et al., 2019). In addition, hormonal contraception can increase body mass index (Yosin et al., 2016). There are 2 types of hormones contained in contraception, namely progesterone and estrogen (Alimena et al., 2022). In addition, women who have a history of sexually transmitted infections can be at high risk (Kashyap et al., 2019).

Based on data on the incidence of cervical cancer in women, which are high. Therefore, researchers are interested in conducting a systematic review and meta-analysis on the use of hormonal contraception and a history of sexually transmitted infections on the risk of cervical cancer. This study aims to analyze the effect of the use of hormonal contraception and a history of sexually transmitted infections on the risk of cervical cancer in women.

SUBJECTS AND METHOD

1. Study Design

The study design used was a meta-analytic study. The meta-analytic study design was a systematic study accompanied by calculating research results that met the inclusion criteria. This review will be analyzed systematically using meta guidelines, namely Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA). The time of the study results is in the period 2013-2023. Article searches are carried out for a maximum of 2 months.

The process of searching for articles is by searching through online journal databases which include Google Scholar, Elsevier and PubMed. With keywords “oral pill” OR “1 month injection” OR “3 month injection” OR “implant” OR “hormonal contraception” AND “cervical cancer” OR “syphilis” OR “chlamydia” OR “herpes” OR “gonorrhea” OR ”HIV” AND “Sexually transmitted infections” AND “Cross sectional” AND aOR.

2. Steps of Meta-Analysis

1) Formulate research questions in the PICO format (Population, Intervention, Comparison, Outcome).
2) Search primary study articles from databases such as Google Scholar, Elsevier and PubMed
3) Perform screening by determining inclusion and exclusion criteria and conducting critical assessments.
4) Perform data extraction and analysis using RevMan 5.3 Software
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

The inclusion criteria for this study were full text articles using English and a cross-sectional study design, the relationship size used was the aOR value.

4. Exclusion Criteria

The exclusion criteria for this study were articles published before 2013 and the measure of the study relationship was incomplete or did not clearly describe the results

5. Operational Definition of Variable

Cervical cancer is the status of women of reproductive age who are diagnosed with cervical cancer, with the category of dead or alive.

The use of hormonal contraception is an action taken to prevent pregnancy**.**

A history of sexually transmitted infections is risky sexual behavior that can be transmitted through sexual intercourse by having multiple partners, either vaginally, orally or anally.

6. Instrument

This review will be analyzed systematically using meta-analysis guidelines, namely Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) and using a critical appraisal checklist Critical Appraisal Checklist for Cross-sectional Study from Master' in Public Health, Graduate School, Universitas Sebelas Maret.

7. Data Analysis

The data in this study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots are used to determine the effect size and heterogeneity of the data. Data processing was carried out based on variations between studies with the fixed effect model.

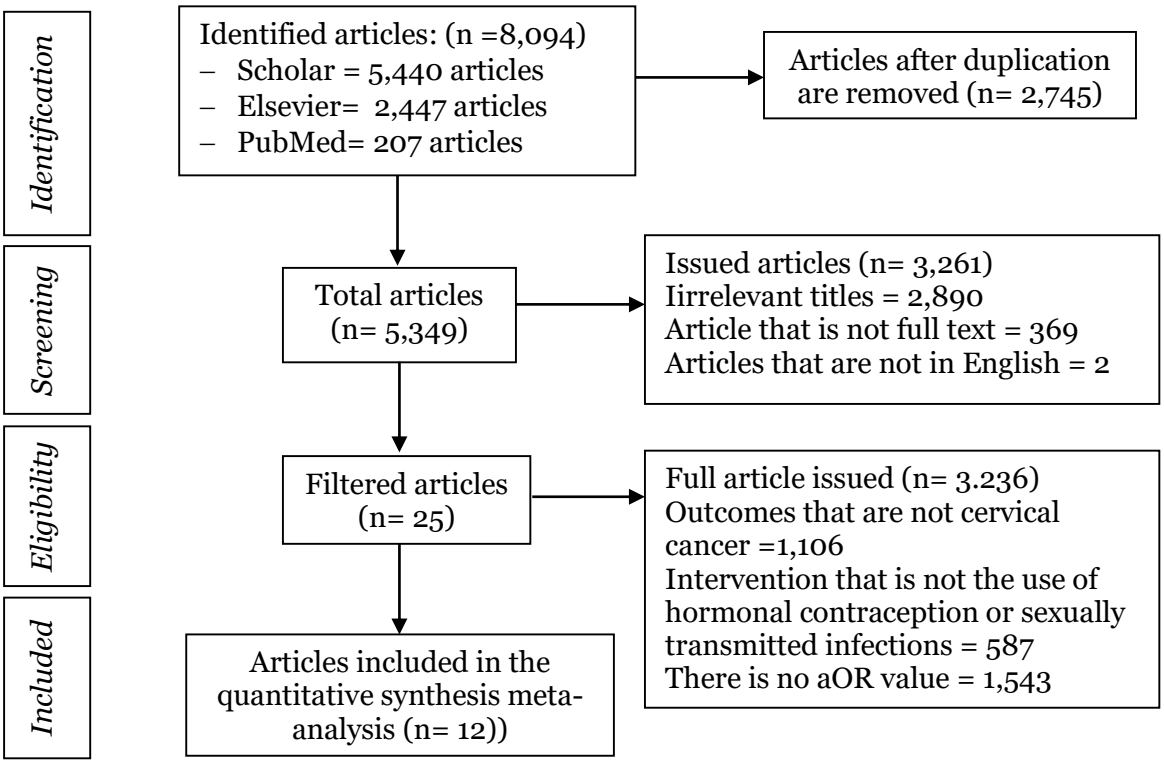

Figure 1. PRISMA flow diagram on the effect of hormonal contraception and a history of sexually transmitted infections on the risk of cervical cancer

RESULTS

The process of searching for articles is by searching through online journal databases which include Google Scholar, Elsevier and PubMed. The process of screening articles according to the study criteria can be seen in the PRISMA flowchart (Figure 1). The initial search process obtained 8,094 then after going through a screening process, 25 articles were obtained which were considered as primary articles of this study, and 12 articles were included in this meta-analysis.

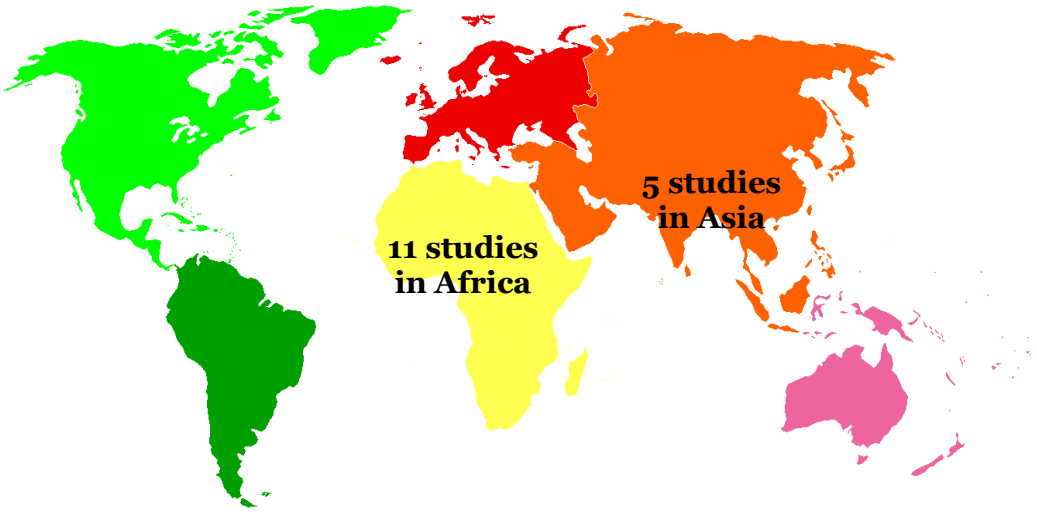

Figure 2. Map of the research area on the effect of hormonal contraception and a history of sexually transmitted infections on the risk of cervical cancer

Figure 2 shows that the primary study in this study contained 12 journals that discussed hormonal contraception and a history of sexually transmitted infections on the risk of cervical cancer, consisting of 11 African continents and 1 Asian continent.

Table 1. Research Quality Assessment (Critical Appraisal)

Author (Year)	Critical Appraisal													
	1a	1b	1c	1d	2a	2b	3a	3b	4	5	6a	6b	7	Total
Abebaw et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Abera et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Amado et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Belayneh et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Berhanu et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Desta et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Fentie et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Geremew et al.(2018)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Kasim et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Mekuria et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

Description of the question criteria:

1. Formulation of research questions in the acronym PICO

a. Was the population in the primary study the same as the population in the PICO meta-analysis?

b. Is the operational definition of exposure/ intervention in the primary study the same as the definition intended in the meta-analysis?

c. Was the comparison used in the primary study the same as that planned for the meta-analysis?

d. Were the outcome variables studied in the primary study the same as those planned in the meta-analysis?

2. Methods for selecting research subjects

a. Descriptive cross-sectional study: Was the sample randomly selected?

b. Analytic cross-sectional study: Was the sample chosen randomly or purposively?

3. Methods for measuring comparisons (intervention) and outcome

a. In analytical cross-sectional studies, do researchers choose samples from the population randomly (random sampling)?

b. As an alternative, if in a cross-sectional analytical study the sample is not selected randomly, does the researcher select the sample based on outcome status or based on intervention status?

4. Design-related bias

If the sample was not selected randomly, has the researcher made efforts to prevent bias in selecting research subjects? For example, selecting subjects based on outcome status is not influenced by exposure status (intervention), or selecting subjects based on exposure status (intervention) is not influenced by outcome status.

5. Methods to control confounding

Whether the primary study investigators have made efforts to control the influence of confounding (for example, conducting a multivariate analysis to control for the influence of a number of confounding factors).

6. Methods of statistical analysis

a. In a cross-sectional study, was multivariate analysis performed? Multivariate analysis included multiple linear regression analysis, multiple logistic regression analysis, and Cox regression analysis.

b. Does the primary study report effect sizes or relationships on multivariate analysis? (eg, aOR, adjusted regression coefficient).

7. Conflict of Interest

Is there a conflict of interest with the research sponsor?

Scoring Instructions:

1. Total number of questions = 13 questions. Answer "Yes" to each question gives a score of "2". Answer “Doubtful” give a score of “1”. The answer "No" gives a score of "0".
2. Maximum total score= 13 questions x 2= 26.
3. Minimum total score = 13 questions x 0 = 0. So the total score range for a primary study between 0 and 26.
4. If the total score of a primary study is >= 22, then the study can be included meta-analysis. If the total score of a primary study was <22, then the study was discarded from meta-analysis.

Based on Table 2 on the PICO primary study "the effect of using hormonal contraception on the risk of cervical cancer" a meta-analysis of 7 articles was carried out with the study locations being Ethiopia, Nigeria and Thailand. There are similarities in the primary study, namely the research design using cross-sectional and the size of the AOR (Adjusted Odds Ratio) relationship, the research subjects were women of reproductive age, the intervention was given the use of hormonal contraception with comparison, namely not using hormonal contraception.

Based on Table 3 regarding the PICO summary of primary study sources "the effect of a history of sexually transmitted infections on the risk of cervical cancer," a meta-analysis of 7 articles was carried out with the study location being Ethiopia.

There are similarities in the primary study, namely the study design using cross sectional and the size of the AOR (Adjusted Odds Ratio) relationship, the study subjects were women of reproductive age, the interventions given had a history of sexually transmitted infections with a comparison of no history of sexually transmitted infections. However, there are differences in the number of samples, namely the smallest is 284 and the largest sample is 1.137.

Table 2. PICO summary of primary cross-sectional study articles by sample size (n= 3,557)

Author (Year)	Country	Sample	P	I	C	O
Abebaw et al. (2022)	Ethiopia	404	Women of childbearing age	Installing the latest contraceptive	Not installing the latest contraception	Cervical cancer
Amado et al. (2022)	Ethiopia	460	Reproductive age women 17-40 year	Using contraception and being infected with an infectious disease	Do not use contraception and are infected with sexually transmitted diseases	Cervical cancer
Berhanu et al. (2019)	Ethiopia	301	Women of childbearing age 16-40 year	Use of modern contraceptives	Do not use modern contraceptives	Cervical cancer
Desta et al. (2022)	Ethiopia	855	Women of age19-35 year	Use of modern contraceptives	Do not use modern contraceptives	Cervical cancer
Geremew et al. (2018)	Ethiopia	1,137	Reproductive age women 17-40 year	Using modern contraceptives and sexually transmitted infections	Do not use modern contraceptives and sexually transmitted infections	Cervical cancer
Sekumade et al. (2019)	Nigeria	100	Women of age 15-35 year	Terdapat kontrasepsi hormonal	There are no hormonal contraception	Cervical cancer
Songsiriphan et al. (2020)	Thailand	300	Reproductive age women	contraceptive users	Not using contraceptives	Cervical cancer

Table 3. aOR and 95% CI effect of the use of hormonal contraception on the risk of cervical cancer

Author	aOR	95% CI	
		Lower limit	Upper limit
Abebaw et al. (2022)	2.70	1.56	7.45
Amado et al. (2022)	1.80	0.6	5.3
Berhanu et al. (2019)	1.18	0.44	3.12
Desta et al. (2022)	1.33	0.59	2.99
Geremew et al. (2018)	2.00	0.44	9.07
Sekumade et al. (2019)	5.51	2.85	8.31
Songsiriphan et al. (2020)	2.24	0.82	6.18

Table 4. PICO table summary of cross-sectional articles from primary study sources with sample size (n = 4,683)

Author (Year)	Country	Sample	P	I	C	O
Abera et al. (2020)	Ethiopia	1,000	Women aged 16-40 years old	Having STI	Not infected with STI	Cervical cancer
Amado et al. (2022)	Ethiopia	460	Women aged 19-35 years old	Infected with STI	Not infected with STI	Cervical cancer
Belayneh et al. (2019)	Ethiopia	284	Women aged 17-40 years old	Had history of STI	No history of STI	Cervical cancer
Fentie et al. (2020)	Ethiopia	844	Reproductive age women	Had history of STI	Not infected with STI	Cervical cancer
Geremew et al. (2018)	Ethiopia	1,137	Women of childbearing age	Had history of STI	Not infected with STI	Cervical cancer
Kasim et al. (2020)	Ethiopia	536	Women aged 17-40 years old	Had history of STI	Not infected with STI	Cervical cancer
Mekuria et al. (2021)	Ethiopia	422	Women aged 15-35 year	Had history of STI	Not infected with STI	Cervical cancer

Table 5. aOR and 95% CI data on the effect of a history of sexually transmitted infections on the risk of cervical cancer

Author	aOR	95% CI	
		Upper limit	Lower limit
Abera et al. (2020)	1.71	1.05	2.79
Amado et al. (2022)	4.20	1.40	12.80
Belayneh et al. (2019)	4.51	1.50	13.60
Fentie et al. (2020)	1.46	0.84	2.53
Geremew et al. (2018)	1.27	0.55	2.93
Kasim et al. (2020)	2.57	1.26	5.23
Mekuria et al. (2021)	6.76	1.14	3.90

The forest plot in Figure 3 shows that there is an effect of the use of hormonal contraception on the risk of cervical cancer, and this effect is statistically significant. Women who use hormonal contraception are 2.34 times more at risk of cervical cancer than women who do not use hormonal contraception (aOR = 2.34; 95% CI = 1.83 to 4.66; $p<0.001$). In addition, the forest plot shows heterogeneity of effect estimates between primary studies (I^2= 31%; $p<0.001$). Thus the calculation of effect estimation is carried out using the fixed effect approach.

The funnel plot in Figure 4 shows that the distribution of effect estimates between studies is more to the left than to the right of the average vertical line, especially for primary studies with small samples. Thus these variables show publication bias. Because the distribution of effect estimates is more to the left of the mean vertical line, which is in a different direction from the location of the diamond shape in the forest plot in Figure 3. Therefore, this publication bias tends to underestimate the true effect.

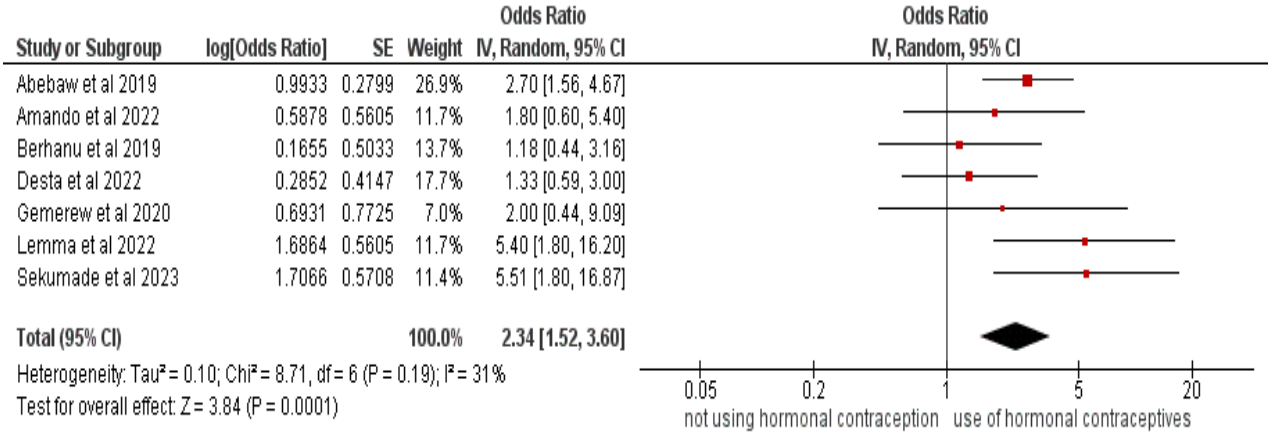

Figure 3. Forest plot of the effect of the use of hormonal contraception on the risk of cervical cancer

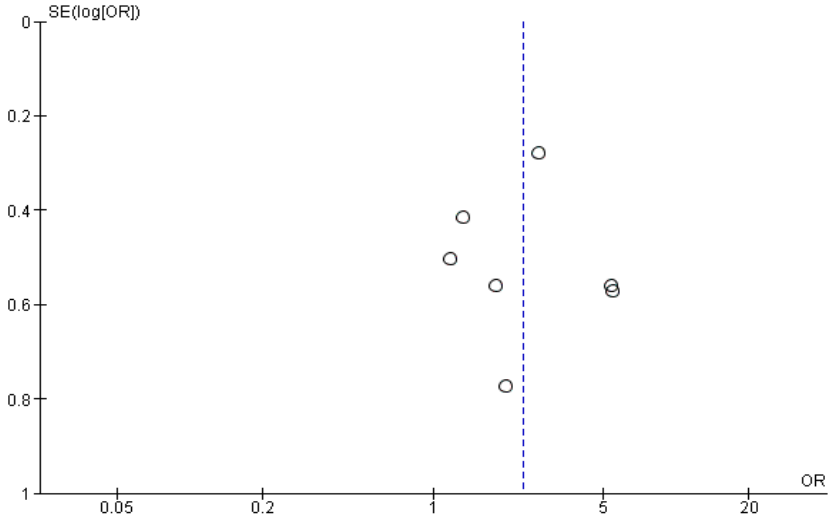

Figure 4. Funnel plot of the effect of the use of hormonal contraception on the risk of cervical cancer

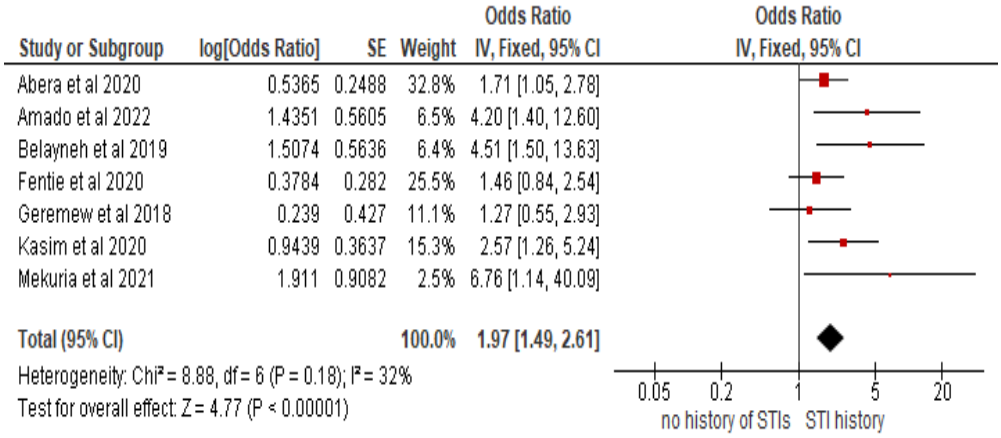

Figure 6. Forest plot of the effect of a history of sexually transmitted infections on the risk of cervical cancer

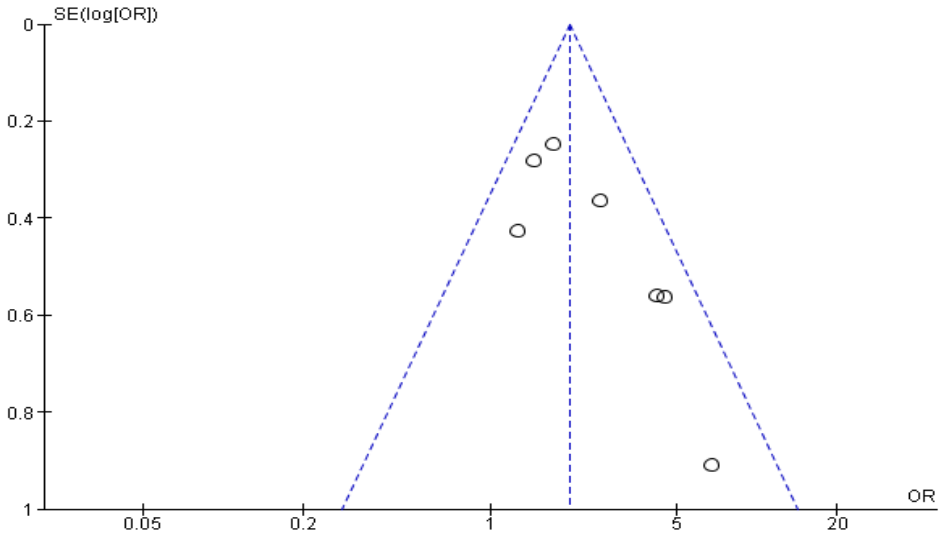

Figure 7. Funnel plot of the effect of a history of sexually transmitted infections on the risk of cervical cancer

The forest plot in Figure 6 shows that there is an effect of a history of sexually transmitted infections on the risk of cervical cancer, and this effect is statistically significant. Women of reproductive age who had a history of sexually transmitted infections were 1.97 times more at risk of cervical cancer than women who did not have a history of sexually transmitted infections (aOR = 1.97; 95% CI = 1.49 to 2.61; p<0.001). In addition, the forest plot shows heterogeneity of effect estimates between primary studies (I^2= 32%; p<0.001). Thus the calculation of effect estimation is carried out using the fixed effect approach.

The funnel plot in Figure 7 shows that the distribution of effect estimates between studies is more to the right than to the left of the mean vertical line, especially for primary studies with small samples.

Thus the funnel plot shows publication bias. Because the distribution of effect estimates is more to the right of the mean vertical line, which is in the same direction as the location of the diamond shape in the forest plot. Therefore, this publication bias tends to overestimate the true effect (overestimate).

DISCUSSION

1. The effect of the use of hormonal contraception on the risk of cervical cancer.

There were 7 primary research articles included in this meta-analysis, 5 articles coming from Ethiopia, 1 article coming from Nigeria and 1 article coming from Thailand. The sample size is 3.557. This meta-analysis concluded that there was an effect of the use of hormonal contraception on the risk of cervical cancer (aOR = 2.34; 95% CI = 1.83 to 4.66; p<0.001). This meta-analysis demonstrated heterogeneity in effect estimates between primary studies (I^2= 48%; p<0.001). Thus the calculation of effect estimation is carried out using the fixed effect approach.

The funnel plot shows that the distribution of effect estimates between studies is more to the left than to the right of the vertical mean line, especially in primary studies with small samples. Thus these variables show publication bias. Because the distribution of effect estimates is more to the left of the mean vertical line, the direction is different from the location of the diamond shape in the forest plot. Therefore, such publication bias tends to undermine the true

effect (underestimate).

This meta-analysis uses studies that have controlled for confounding factors because it uses an Adjusted Odds Ratio (aOR) effect size in selected primary studies. This is in line with the results of a study by Abebaw et al., (2022) which showed that women who used the latest contraception were 2.7 times more at risk of developing cervical cancer compared to women who did not use the latest contraception (aOR= 2.7; 95% CI= 1.56 to 7.45). Study by Sekumade et al (2019) which shows that women who use hormonal contraception are 5.51 times more at risk of developing cervical cancer compared to women who do not use hormonal contraception (aOR=5.51; 95% CI=2.85 to 8.31).

2. Effect of sexually transmitted infections on the risk of cervical cancer.

The primary studies included in this meta-analysis totaling 7 articles originating from Ethiopia. The sample size is 4,683. This meta-analysis concluded that there was an effect of sexually transmitted infections on the risk of cervical cancer and this effect was statistically significant. Women of reproductive age who have a history of sexually transmitted infections are 1.97 times more at risk of cervical cancer than women who do not have a history of sexually transmitted infections (aOR=1.97; 95% CI= 1.49 to 2.61; p<0.001). This meta-analysis demonstrated heterogeneity in effect estimates between primary studies (I^2= 32%; p<0.001). Thus the calculation of the estimated effect is carried out using the fixed effect approach.

The funnel plot shows that the distrbution of effect estimates between studies is more to the right than to the left of the mean vertical line, especially in primary studies with small samples. Thus these variables show publication bias. The distribution of effect estimates is more to the right of the mean vertical line, which is in the same direction as the location of the diamond shape in the forest plot. Therefore, this publication bias tends to overestimate the true effect (overestimate).

This meta-analysis uses studies that have controlled for confounding factors because they use the Adjusted Odds Ratio (aOR) effect size in selected primary studies. This is in line with the results of a study by Amado et al., (2022) which showed that women infected with sexually transmitted diseases were 4.2 times more at risk of developing cervical cancer compared to women who were not infected with sexually transmitted diseases (aOR= 4.2; CI 95%= 1.4 to 12.8). A study by Belayneh et al., (2019) showed that women with a history of sexually transmitted infections were 4,515 times more at risk of cervical cancer than those without a history of sexually transmitted infections (aOR= 4.515; 95% CI 1.496 to 13.602). Study by Kasim et al., (2020) showed that women who had a history of sexually transmitted infections were 2.57 times more at risk of cervical cancer than women who did not have a history of sexually transmitted infections (aOR=2.57; 95% CI= 1.26 to 5.23). Study by Safitri et al., (2020) which shows that the behavior of preventing sexually transmitted infections can be carried out with peer-based interventions.

AUTHORS CONTRIBUTION

Siti Damayanti is the main researcher who selects topics, searches for and collects study data. Uki Retno Budihastuti and Bhisma Murti analyzed the data and reviewed atudy documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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