

Oral and Injection Hormonal Contraceptives Uptake and Their Risk to Breast Cancer: A Meta-Analysis

Dian Asih Ning Utami¹⁾, Bhisma Murti¹⁾, Uki Retno Budihastuti²⁾

¹⁾Master's Program in Public Health, Universitas Sebelas Maret

²⁾Department of Obstetrics and Gynecology, Dr. Moewardi Hospital/
Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: Breast cancer cases are the biggest contributor to death in women in the world. One of the risk factors is injectable hormonal contraceptives and pills. Injectable hormonal contraceptives and pills contain synthetic hormones progesterone and estrogen that trigger breast cancer, due to an increase in the content of these hormones in the body, this results in an opportunity to experience uncontrolled cell division resulting in gene mutations in the breast gland. The purpose of this study was to analyze the effect of the use of injectable and pill hormonal contraceptives on the incidence of breast cancer using a meta-analysis study.

Subjects and Method: This research is a systematic review and meta-analysis using PRISMA flowchart diagram guidelines. The article search process was carried out between 2015-2022 using databases including Google Scholar, PubMed, Science Direct and Springerlink. The keywords used in the database search were “contraceptive acceptor women” AND “hormonal contraception” OR “injectable contraceptive” OR “DMPA” OR “oral contraceptive” OR “pills contraceptive” AND “breast cancer” AND “case control”. The inclusion criteria were full text articles with a case control study design, articles in English, multivariate analysis using adjusted odds ratio. Eligible articles were analyzed using the Revman 5.3 application.

Results: A total of 16 case-control articles from Palestine, Saudi Arabia, China, Malaysia, Vietnam, Bangladesh, Finland, Iran, UK, Kenya, Jordan, Algeria, Cameroon and Bangui were carried out in this meta-analysis. Meta-analysis of 7 articles showed that the use of injectable hormonal contraceptives increased the risk of breast cancer 1.52 and was statistically significant (aOR = 1.52; CI 95% = 1.11 to 2.07; p = 0.009). Meanwhile, 9 articles showed that the use of hormonal contraceptive pills increased the risk of breast cancer 1.96 and was statistically significant (aOR= 1.96; CI 95%= 1.19 to 3.23; p= 0.008).

Conclusion: Injectable hormonal contraceptives and pills increase the risk of breast cancer.

Keywords: injectable hormonal contraception, pill hormonal contraception, breast cancer.

Correspondence:

Dian Asih Ning Utami. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: dianasih1998@gmail.com. Mobile: +6281216822211.

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BACKGROUND

Family development is a planned effort that is part of a national development carried out to direct population development and family development to realize a balanced

system and develop quality in all dimensions of the population. The strategy taken by the government in order to regulate population is through the Family Planning (KB) program, namely by reducing the fer-

tivity rate by providing facilities and infrastructure for contraceptives and drugs. Some contraceptives in Indonesia are hormonal contraceptives and non-hormonal contraceptives (BKKBN, 2015).

However, hormonal contraception is one of the risk factors for breast cancer. Breast cancer is influenced by the presence of the hormones estrogen and progesterone in women. Exposure to high levels of estrogen is one of the factors that can increase the incidence of breast cancer risk in women, such as the use of hormonal contraception. Based on the results of previous studies, breast cancer risk factors are multifactorial and interrelated with one another. Several factors are thought to have a major influence on the occurrence of breast cancer according to the Indonesian Ministry of Health (2019) that risk factors for breast cancer in addition to the use of hormonal contraception include family history, age of menarche < 12 years, menopause age > 55 years, physical activity, lifestyle such as alcohol consumption, and smoking, and obesity.

Nationally and globally, cases of breast cancer are the cases that are the biggest contributor to death in women. Data from the Global Burden of Cancer Study from the World Health Organization (WHO) showed that there were 58,256 cases or 16.7% of the total 348,809 cases. Data from the Ministry of Health of the Republic of Indonesia shows that breast cancer ranks first as a type of cancer commonly suffered by Indonesian women (Globocan, 2020). Data on the coverage of active family planning participants by contraceptive method in 2020 shows that the number of family planning users is not much different from the previous year, namely there are more users of hormonal contraceptives than non-hormonal contraceptives. The selection of types of contraceptives in 2020 showed that most of the acceptors chose to use the injection method

of contraception by 72.9%, contraceptive pills by 19.4%, users of implant contraceptives 8.5% and non-hormonal contraception by 12.8% (Ministry of Health RI, 2020).

Hormonal contraceptives are contraceptives that contain the hormones progesterone and estrogen. This hormone can also affect the uncontrolled growth of breast tissue, leading to breast cancer (Rahma et al., 2019). The use of hormonal contraceptives causes an increase in the hormones estrogen and progesterone in the body of women who use them. An increase in the content of the hormones estrogen and progesterone in the body increases the chance for uncontrolled cell division and DNA mutation or permanent damage to breast tissue. This triggers the presence of cancer cells in the breast tissue both in the ducts and lobules. Three-month injectable contraceptives contain strong progesterone in the form of depots and one-month injections contain progestins and estrogens. While the hormonal contraceptive pill contains ethinylestradiol which is a synthetic estrogen found in the combination pill. Both of these hormonal contraceptives have the same hormonal content, namely estrogen and progesterone, but have different estrogen and progesterone derivatives (Baziad, 2014).

Research that has been carried out to identify and estimate the use of injectable and pill hormonal contraception on the incidence of breast cancer, among others, was carried out by Christopher et al. (2012), women who use injectable contraception have a 2.2 times risk of developing breast cancer. Amadou et al. (2013) said that the use of injectable hormonal contraception has a 1.22 times risk of developing breast cancer compared to those who do not use injectable hormonal contraception. Meanwhile, research by Al-Ajmi et al. (2018) stated that women who have a history of using hormonal contraceptive pills have a

risk of breast cancer by 1.26 times compared to those who do not have a history of using hormonal contraceptives pills. According to Busund et al. (2018) there is a significant relationship between the use of hormonal contraceptive pills, where the risk of experiencing breast cancer is 1.07 times.

Based on the incidence of breast cancer in women, which is still high, this is due to the hormonal content in the body and proper prevention and treatment are needed. In addition, the need for more comprehensive research from the results of previous primary studies on the use of injectable and pill hormonal contraceptives on the incidence of breast cancer, the researchers are interested in conducting a systematic review and meta-analysis of the use of injectable and pill hormonal contraceptives on the incidence of breast cancer.

Systematic review is a method used to synthesize data in primary research by utilizing existing data through a systematic and explicit search process to identify the data listed in the review (Grey et al. 2018), while meta-analysis is an epidemiological study that aims to combine and statistically combine data from primary research results that discuss the same hypothesis so as to obtain quantitative summary results (Mikolajewicz and Komarova, 2019a). This study is expected to prove the effect of using injectable and pill hormonal contraception on the incidence of breast cancer.

SUBJECTS AND METHOD

1. Study Design

This study was conducted using a meta-analysis design. Search articles using databases including Google Scholar, PubMed, Science Direct and Springerlink. The keywords used in the database search were “contraceptive acceptor women” AND “hormonal contraception” OR “injectable contraceptive” OR “DMPA” OR “oral contra-

ceptive” OR “pills contraceptive” AND “breast cancer” AND “case control”.

2. Inclusion Criteria

The inclusion criteria used in this study were full-text articles with a case-control design. The article was published in English from 2015 to 2022. The analysis used was multivariate with adjusted Odds Ratio (aOR).

3. Exclusion Criteria

The exclusion criteria in this study are articles published before 2015 and articles that do not use English.

4. Operational Definition of Variables

The articles included in this study were PICO-adjusted. The article search was carried out by considering the eligibility criteria using the following PICO model: Population= female family planning acceptors. Intervention= 1. Using injectable hormonal contraception; 2. Using hormonal contraceptive pills. Comparison= Not using hormonal contraception. Outcome= Breast Cancer.

Injectable hormonal contraception is contraception that is being used by women who are KB acceptors in the form of injectable contraception.

Hormonal contraceptive pills are contraceptives that are being used by women who are KB acceptors in the form of pill contraceptives.

Breast cancer is the growth of abnormal cells in breast tissue diagnosed by radiological examination.

5. Instrument

This research is guided by the PRISMA flow diagram and the assessment of the quality of research articles using the Critical Appraisal Checklist for Case Control Study. The 12 questions used are as follows:

1. Does this objective clearly address the research focus/problem?
2. Is the case control research method suitable to answer the research question?

3. Are the cases representative of the designated population?
4. Are the selected controls appropriate and acceptable?
5. Are breast cancer research instruments valid and reliable?
6. Have confounding factors been taken into account?
7. Has the researcher controlled for the influence of all confounding factors?
8. Are the results applicable to your research?
9. Was the magnitude of the exposure effect assessed?
10. Was a confidence interval given for the main outcome?
11. Are the results applicable to the designated population?
12. Are the results of this study consistent with other available evidence?

6. Data Analysis

The collected articles are processed using the Review Manager application (RevMan 5.3). Data processing is carried out by calculating the effect size and heterogeneity values to determine the research combination model and form the final

results of the meta-analysis in the form of forest plots and funnel plots..

RESULTS

The article search process was carried out using a database based on PRISMA flow-chart diagrams, which can be seen in Figure 1. The total articles obtained were 16 articles spread across 3 continents, namely Asia, Africa and Europe. 10 articles in Asia, 4 articles in Africa and 2 articles in Europe, can be seen in Figure 2.

The total primary research included in this meta-analysis was 16 articles from Palestine, Saudi Arabia, China, Malaysia, Vietnam, Bangladesh, Finland, Iran, UK, Kenya, Jordan, Algeria, Cameroon, Bangui. The primary research for injectable hormonal contraception on the incidence of breast cancer used 7 case control studies from Palestine, UK, Iran, Finland, Kenya, Bangladesh, Bangui. While the hormonal contraceptive pill on the incidence of breast cancer used 9 case control studies from Vietnam, Algeria, Cameroon, China, Iran, Saudi Arabia, Jordan, Malaysia.



Figure 2. Map of Research Locations for Breastfeeding Relationships with Incidence

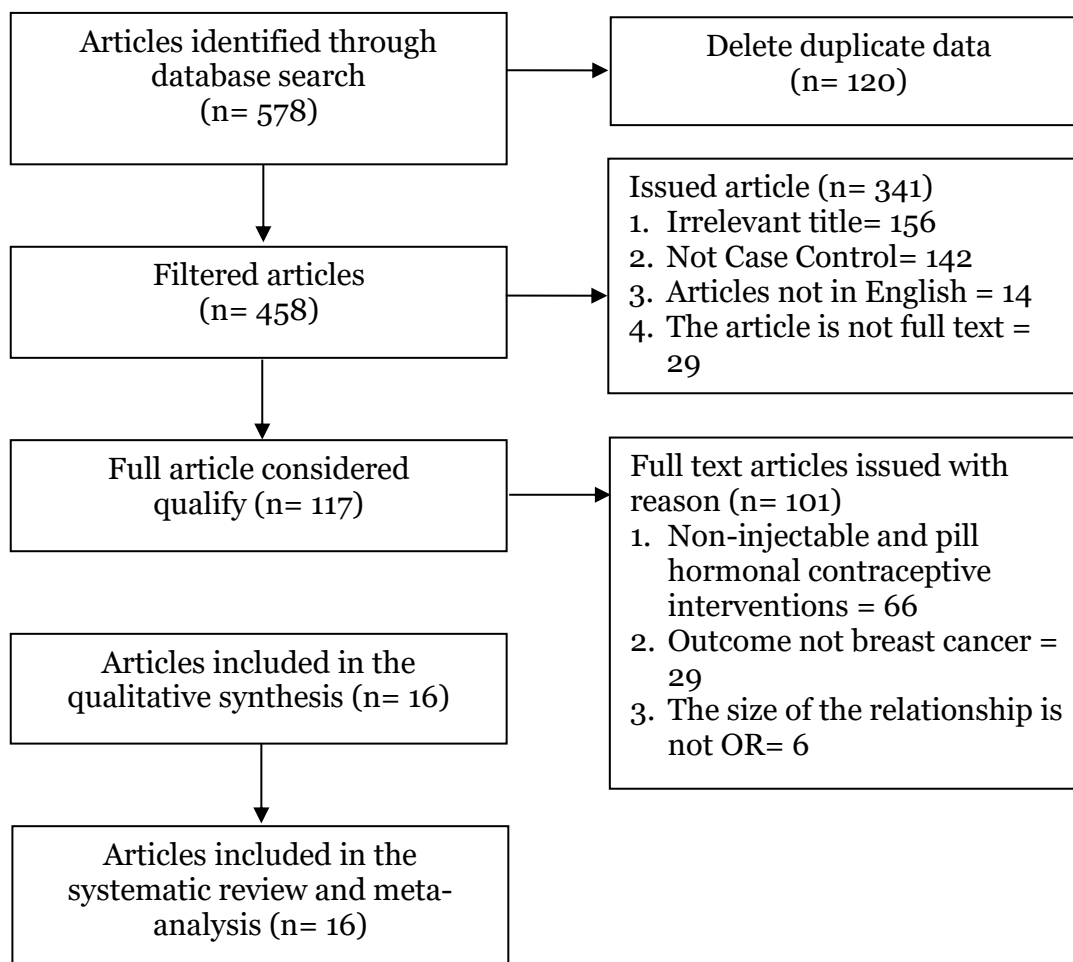


Figure 1. PRISMA Flow Diagram

1. Research Quality Assessment

a. Assessment of the quality of the case control study of the use of injectable hormonal contraception on the incidence of breast cancer

Table 3. Results of the Critical Appraisal Checklist for Case Control Study of the Use of Injectable Hormonal Contraceptives on the Incidence of Breast Cancer

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Sharif dan Khatib (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Vinogradova et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Moradinazar et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Balekouzou et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12
Heikkinen et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Rispah et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Mohite et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Yes= 1; No= 0

b. Assessment of the quality of the case control study of the use of pill hormonal contraception on the incidence of breast cancer

Table 4. Results of the Critical Appraisal Checklist for Case Control Study Use of Hormonal Contraceptive Pills on the Incidence of Breast Cancer

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Cherif et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Paul et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Yuan et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Alipour et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Alsolami et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Andarieh et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Bardaweel et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Tan et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	12
Trieu et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Yes= 1; No= 0

2. Forest Plot

a. Injectable hormonal contraceptives on the incidence of breast cancer

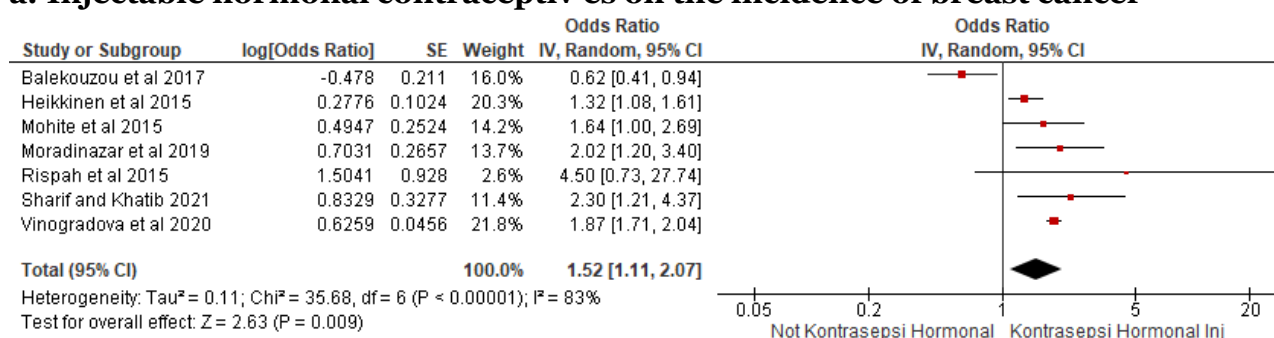


Figure 3. Forest plot of the use of injectable hormonal contraceptives on the incidence of breast cancer

b. Use of Hormonal Contraceptive Pills on the Incidence of Breast Cancer

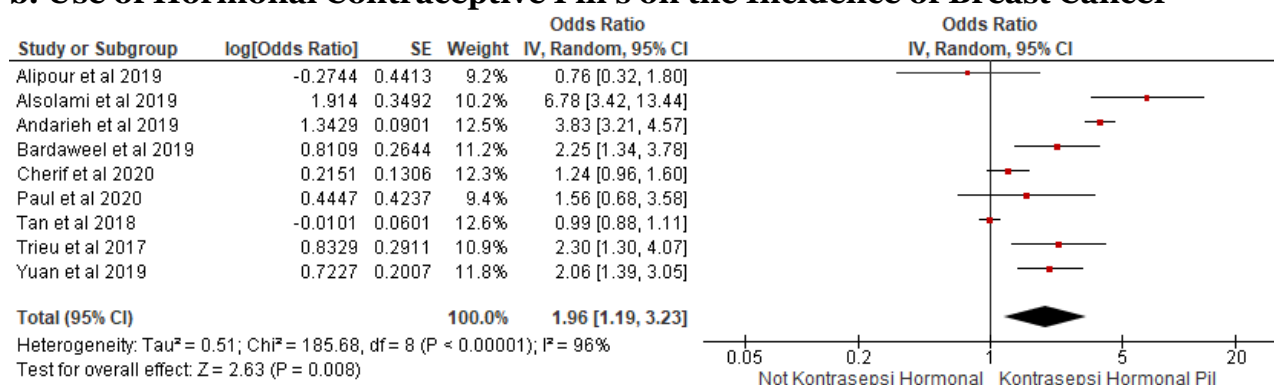


Figure 4. Forest plot of the use of hormonal contraceptive pills on the incidence of breast cancer

Based on the results of the meta-analysis in Figure 3, it shows that there is heterogeneity between studies (I²= 83%; p<0.001) so that the analysis of this study uses the

Random Effect Model (REM). The administration of injectable hormonal contraceptive intervention was able to increase the incidence of breast cancer by 1.52 times

compared to not using hormonal contraception and was statistically significant (aOR= 1.52; 95% CI= 1.11 to 2.07; p= 0.009). While the results of the meta-analysis in Figure 4 show that there is a high heterogeneity between studies ($I^2= 96\%$; $p<0.001$) so the analysis uses the Random

Effect Model (REM). The administration of hormonal contraceptive pill intervention was able to increase the incidence of breast cancer by 1.96 times compared to not using hormonal contraception and was statistically significant (aOR= 1.96; CI 95% = 1.19 to 3.23; p= 0.008).

3. Funnel plot

a. Injectable hormonal contraceptives on the incidence of breast cancer

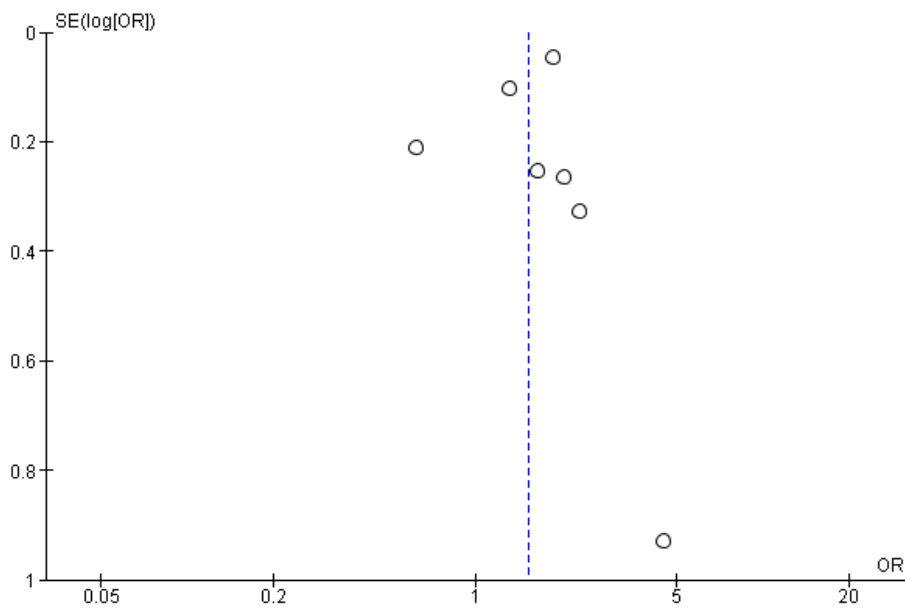


Figure 5. Funnel plot of the use of injectable hormonal contraceptives on the incidence of breast cancer

b. Use of Hormonal Contraceptive Pills on the Incidence of Breast Cancer

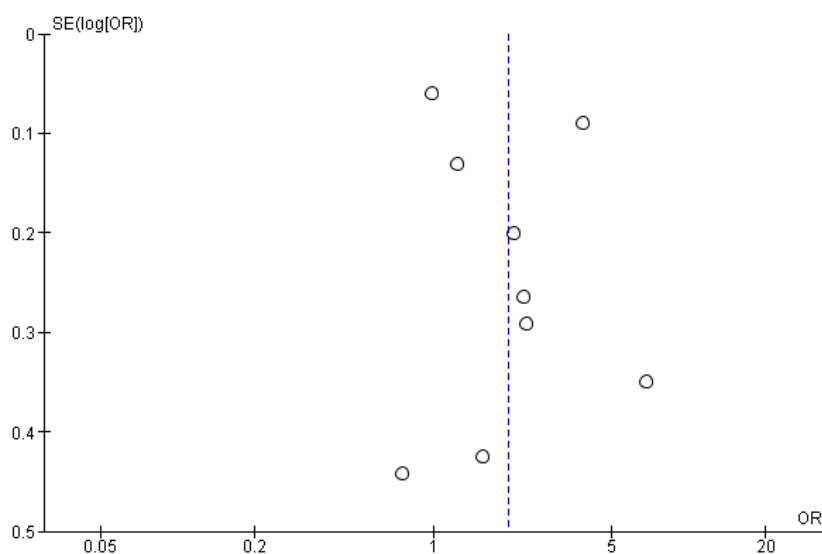


Figure 6. Funnel plot of the use of hormonal contraceptive pills on the incidence of breast cancer

Based on Figure 5, the funnel plot graph looks asymmetrical between the right and left plots, this indicates an overestimated publication bias. The plot on the left is 2 with a standard error between 0 and 0.4, while the plot on the right is 5 with a standard error between 0 and 1 (overestimate). The plot on the left is 4 with a standard error between 0 and 0.5, while the plot on the right is 5 with a standard error between 0 and 0.4.

DISCUSSION

This systematic review and meta-analysis study discusses the use of injectable and pill hormonal contraception on the incidence of breast cancer. The independent variables used in this study were female family planning acceptors who used injectable and pill hormonal contraception. While the dependent variable is breast cancer.

This study uses the results of the aOR statistic from multivariate analysis, which aims to control for confounding factors. Confounding factors can cause research results to be invalid because confounding factors also affect the relationship or affect the population being studied (Anulus et al., 2019).

Use of injectable contraceptives on the incidence of breast cancer

There were 7 primary studies with case control study designs that were carried out by systematic reviews and meta-analyses showed heterogeneity between studies ($I^2=83\%$; $p<0.001$) so the analysis used the Random Effect Model (REM). This heterogeneity is based on the asymmetric distribution between the left and right plots in the funnel plot. Publication bias in case control studies due to variation or diversity between populations as seen from the number of different samples indicated by

primary study articles is caused by the relatively small number of samples ($n = 142$). It also makes the CI range wide. However, the administration of injectable hormonal contraceptive intervention was able to increase the risk of breast cancer by 1.52 times compared to not using hormonal contraception and was statistically significant (aOR= 1.52; CI 95% = 1.11 to 2.07; $p= 0.009$).

The results of this study are supported by research by El Sharif & Khatib (2021) which aims to determine the determinants of breast cancer in women in the West Bank of Palestine which found that there is a relationship between the use of hormones including hormonal contraceptives on the incidence of breast cancer (aOR = 2.30; CI 95%= 1.21-4.37; $p= 0.011$). Other research Moradinazar et al. (2019) which aims to determine the effect of factors related to fertility and hormone use on the risk of breast cancer in women under 50 years of age in Iran. In this study it was found that there was an association between the incidence of breast cancer and the use of hormones including the use of injectable contraceptives and this relationship was stronger in women who used contraception for more than 10 years and was statistically significant (aOR = 2.02; CI 95%= 1.20-3.40; $p= 0.008$). Another study by Vinogradova et al. (2020) stated that women using depot medroxyprogesterone acetate (DMPA) contraception or injections for a period of more than 5 years have a high risk of breast cancer by 1.87 times. High doses of the hormone progesterone are associated with an increased risk of breast cancer, because of this the UK government will endeavor that hormonal contraceptives prescribed to women who use it are at low doses.

4. Summary of Articles

a. Use of injectable hormonal contraceptives on the incidence of breast cancer

Table 1. Description of the Primary Study of Injectable Hormone Contraceptives Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Populatian	I Intervention	C Comparison	O Outcome	Scale
Sharif and Khatib (2021)	Palestina	Case Control	474	Female contraceptive acceptor	Injectable hormonal contraceptives and pills, social demographics, menarche	Non-hormonal contraceptives	Breast cancer	Medical records (doctor's diagnosis and mammography)
Vinogradova et al. (2020)	UK	Case Control	168,094	Female contraceptive acceptor	Injectable contraceptives/ DMPA, tibolone, levonogestrel	Non-hormonal contraceptives	Breast cancer	Medical record (hispathological examination)
Moradinazar et al. (2019)	Iran	Case Control	620	Female contraceptive acceptor	Injectable contraceptives, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical record (hispatology)
Balekouzou et al. (2017)	Bangui	Case Control	522	Female contraceptive acceptor	Injectable contraception, education, marriage, menarche, menstrual cycle	Non-hormonal contraceptives	Breast cancer	Medical record (in situ or invasive)
Heikkinen et al. (2015)	Firlandia	Case Control	52,426	Female contraceptive acceptor	Injectable hormonal contraceptives, IUD, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical records (mammography)
Rispah et al. (2015)	Kenya	Case Control	142	Female contraceptive acceptor	Injectable contraceptives, smoking, alcohol	Non-hormonal contraceptives	Breast cancer	Medical records (mammography)
Mohite et al. (2015)	Bangladesh	Case Control	434	Female contraceptive acceptor	Injectable contraceptives, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical record (hispathological examination)

b. The Use of Hormonal Contraceptive Pills on the Incidence of Breast Cancer

Table 2. Description of the Primary Study of Hormonal Contraceptive Pills Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Populatian	I Intervention	C Comparison	O Outcome	Scale
Cherif et al. (2020)	Algeria	Case Control	1,227	Female acceptor pill contraceptive	Contraceptive pills, parity, menopause	Non-hormonal contraceptives	Breast cancer	Medical records (mammography)
Paul et al. (2020)	Cameroon	Case Control	1,520	Female acceptor pill contraceptive	Contraceptive pills, age, socio-demography, BMI, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical records (histological and radiological)
Yuan et al. (2019)	China	Case Control	1,599	Female acceptor pill contraceptive	Contraceptive pills, alcohol, smoking, IUD	Non-hormonal contraceptives	Breast cancer	Medical record (in situ or invasive)
Alipour et al. (2019)	Iran	Case Control	499	Female acceptor pill contraceptive	Contraceptive pills, social deography, BMI, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical record (hispatology)
Alsolami et al. (2019)	Saudi Arabia	Case Control	423	Female acceptor pill contraceptive	Contraceptive pills, BMI, menarche, smoking	Non-hormonal contraceptives	Breast cancer	Medical record (in situ or invasive)
Andarieh et al. (2019)	Iran	Case Control	2,381	Female acceptor pill contraceptive	Contraceptive pills, BMI, menarche, parity	Non-hormonal contraceptives	Breast cancer	Medical record (doctor's diagnosis)
Bardaweel et al. (2019)	Yordania	Case Control	450	Female acceptor pill contraceptive	Contraceptive pills	Non-hormonal contraceptives	Breast cancer	Medical records (mammography)
Tan et al (2018)	Malaysia	Case Control	2,080	Female acceptor pill contraceptive	Contraceptive pills, parity, breastfeeding, age	Non-hormonal contraceptives	Breast cancer	Medical record (hispatology)
Trieu et al. (2017)	Vietnam	Case Control	788	Female acceptor pill contraceptive	Hormonal contraceptive pills and injections, social demographics, menarche	Non-hormonal contraceptives	Breast cancer	Medical records (mammography)

DISCUSSION

This systematic review and meta-analysis study discusses the use of injectable and pill hormonal contraception on the incidence of breast cancer. The independent variables used in this study were female family planning acceptors who used injectable and pill hormonal contraception. While the dependent variable is breast cancer.

This study uses the results of the aOR statistic from multivariate analysis, which aims to control for confounding factors. Confounding factors can cause research results to be invalid because confounding factors also affect the relationship or affect the population being studied (Anulus et al., 2019).

Use of injectable contraceptives on the incidence of breast cancer

There were 7 primary studies with case control study designs that were carried out by systematic reviews and meta-analyses showed heterogeneity between studies ($I^2=83\%$; $p<0.001$) so the analysis used the Random Effect Model (REM). This heterogeneity is based on the asymmetric distribution between the left and right plots in the funnel plot. Publication bias in case control studies due to variation or diversity between populations as seen from the number of different samples indicated by primary study articles is caused by the relatively small number of samples ($n=142$). It also makes the CI range wide. However, the administration of injectable hormonal contraceptive intervention was able to increase the risk of breast cancer by 1.52 times compared to not using hormonal contraception and was statistically significant (aOR= 1.52; 95% CI= 1.11 to 2.07; $p=0.009$).

The results of this study are supported by El Sharif & Khatib (2021) which aims to determine the determinants of breast cancer in women in the West Bank

of Palestine which found that there is a relationship between the use of hormones including hormonal contraceptives on the incidence of breast cancer (aOR = 2.30; CI 95 % = 1.21-4.37; $p=0.011$). Other research Moradinazar et al. (2019) which aims to determine the effect of factors related to fertility and hormone use on the risk of breast cancer in women under 50 years of age in Iran. In this study it was found that there was an association between the incidence of breast cancer and the use of hormones including the use of injectable contraceptives and this relationship was stronger in women who used contraception for more than 10 years and was statistically significant (aOR = 2.02; 95% CI = 1.20-3.40; $p=0.008$). Another study by Vinogradova et al. (2020) stated that women using depot medroxyprogesterone acetate (DMPA) contraception or injections for a period of more than 5 years have a high risk of breast cancer by 1.87 times. High doses of the hormone progesterone are associated with an increased risk of breast cancer, because of this the UK government will endeavor that hormonal contraceptives prescribed to women who use it are at low doses.

Use of contraceptive pills on the incidence of breast cancer

There are 9 research articles with a case control study design that became the source of a meta-analysis of the use of hormonal contraceptive pills on the incidence of breast cancer. The results of the forest plot showed that there was heterogeneity between studies ($I^2=96\%$; $p<0.001$) so that the analysis of this study used the Random Effect Model (REM). The research article showed that the use of hormonal contraceptive pills had a 1.96 times risk of developing breast cancer compared to non-hormonal contraceptives and the results were statistically significant (aOR = 1.96;

95% CI = 1.19 to 3.23; $p = 0.008$).

The research of Cherif et al. (2020) aims to explore the socioeconomic relationship and risk of breast cancer in Algerian women living in Setif province. So far this is the first epidemiological study of risk factors for breast cancer conducted in Algeria. The result of his research is that the use of hormonal contraceptive pills can increase the risk of breast cancer with a longer duration of use because excessive estrogen is known as an increase in tumor or cancer growth (aOR = 1.24; 95% CI = 0.96-1.60). This study is in line with Alsolami et al. (2019) which states that hormonal contraception is a significant factor for the occurrence of breast cancer (aOR = 6.78; 95% CI = 3.42-13.44; $p = 0.001$).

The primary study of Paul et al. (2020) said that breast cancer risk factors were associated with hormonal contraceptive pills, this was proven significantly ($p > 0.0001$) that it could increase 1.56 the incidence of breast cancer in women in Cameroon. Apart from hormonal contraceptive pills, the most significant risk factors were age, age at first giving birth 30 years, age at first sexual intercourse 18 years, low economic level, smoking, parity. According to research Yuan et al. (2019) the length of use of hormonal contraception also determines the incidence of breast cancer 2.06 is more at risk. After discontinuing the use of hormonal contraception, the risk of breast cancer was still higher in women who had used hormonal contraception for 5 years or more than women who did not use hormonal contraception (aOR = 2.06; 95% CI = 1.39-3.05).

AUTHOR CONTRIBUTION

Dian Asih Ning Utami is the main researcher who selects the topic, searches for and collects study data. Bhisma Murti and Uki Retno Budihastuti played a role in

analyzing the data and reviewing the study documents.

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This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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