Background: Injectable hormonal contraception was a major risk factor for breast cancer. The content of the progestin hormone in injection hormonal contraceptives can affect the uncontrolled growth of breast tissue, leading to breast cancer. This study aims to analyze the magnitude of the effect of injection hormonal contraception on the incidence of breast cancer with a meta-analysis study. Method: This research is a systematic review and used a Prisma flow diagram. The process of searching for articles through a database of journals which includes: PubMed, Science Direct, and Google Scholar by selecting articles published in 2010-2020. Keywords used include: “Women Aged 15-80 Years” OR “Women of Menopause” AND “Birth control injections” AND “Breast Cancer”. The inclusion criteria included full-text articles with a case-control study design, articles using English, and multivariate analysis with adjusted odds ratios. Artikel fulfills the requirements for analysis using Revman 5.3 Result: There were 6 articles with the case-control study. A meta-analysis of 6 case-control studies showed that the use of injectable hormonal contraception had a 1.37 times risk of developing breast cancer compared with women using non-hormonal contraception (aOR 1.37; 95% CI 1.09 to 1.71; p = 0.006). Conclusion: Injectable hormonal contraceptives can increase the incidence of breast cancer.

Keywords: Injection Hormonal Contraception, Breast Cancer, Meta-analysis, Reproductive Age

INTRODUCTION

Cancer is a type of non-communicable disease and has an increasing number of cases every year (Ayu et al., 2015). Nationally and globally, cases of breast cancer are cases that are the largest contributor to death in women. Global data shows that there were 58,256 cases or 16.7% of the total 348,809 cases. In addition, Globocan 2018 data reports that there are 2.1 million new cases and it is estimated that this will continue to increase every year. Breast cancer is the
most common cancer suffered by women in the world with a cumulative risk of 4.61, with a mortality rate of 22,692 people (Globocan, 2020).

One of these non-communicable diseases, should not be ignored by individuals, communities, and stakeholders in the health sector. Breast cancer is becoming increasingly difficult and has a long course of treatment. According to the American Cancer Society, breast cancer is influenced by the presence of the female hormones estrogen and progesterone. Exposure to the high estrogen hormone is one of the factors that can increase the incidence of breast cancer risk in women. Based on the results of previous studies, breast cancer risk factors are multifactorial and interrelated with one another. Elsharkawy said that risk factors for breast cancer include family history, use of hormonal contraception, age at menarche, physical activity, age, and obesity (Yulianti, 2016). In another study, it was stated that one of the causes of breast cancer is the use of hormonal contraception in the long term.

Several studies have been conducted to determine and estimate the effect of the use of injectable hormonal contraception on the incidence of breast cancer, one of which was carried out by Morch et al. (2017) which shows that women who use oral hormonal contraceptives are at 1.2 times the risk of developing breast cancer than those who have never used hormonal contraceptives. Busund et al. (2018) also stated that there was a significant relationship between the use of oral hormonal contraceptives and the risk of experiencing breast cancer 1.07 times. According to Alsolami et al. (2019), stated that the use of hormonal contraception has the risk of 6.78 times to experience breast cancer when compared to women who use non-hormonal contraception. According to Li et al. (2012), women who use injectable contraceptives have a 2.2 times the risk of developing breast cancer. Shapiro et al. (2021), women aged 20-54 years who use injectable hormonal contraception have a 0.9 risk of developing breast cancer compared to women who do not use hormonal contraception. Ayu et al. (2015) stated that the use of injectable contraception has a 3.3 times risk of developing breast cancer compared to women who use non-hormonal contraception.

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, more comprehensive research is needed from the results of previous primary studies on the effect of the use of injectable hormonal contraceptives on the incidence of breast cancer. The data obtained by the researchers will be analyzed by using a meta-analysis study design which is an epidemiological study that provides the strongest evidence of causality by combining and statistically combining the results of a number of independent primary studies, if possible, to be combined. In the meta-analysis research, the researcher also tested the same hypothesis, in
the same way, so that a quantitative overview was obtained (Murti, 2018), which would eventually be analyzed with the help of software. RevMan 5.3 has previously synthesized study results to reduce bias.

METHOD

The study design used in this study was a systematic review and meta-analysis, using PRISMA guidelines diagram flow. Article searches were conducted using journal databases including PubMed, Google Scholar, and Science Direct. The keywords used were “women aged 15-80 years” AND “birth control injections” OR “hormonal contraceptive” AND “breast cancer”.

In this study, the inclusion criteria were full-text articles using an observational study design, namely case-control, articles in English, the analysis used was multivariate with adjusted odds ratio, the research subjects were women aged 15-80 years, the intervention was injection hormonal contraception and the outcome its breast cancer. While the exclusion criteria in this study include articles published before 2010 and languages other than English.

assessment of the quality of research articles was carried out using the Critical Appraisal Skills Program (CASP) for Cohort Study, and the Critical Appraisal Checklist for case-control (CEBMa, 2014). Data analysis using the Review Manager application (RevMen 5.3) was used in analyzing the data in this study. The results of data analysis are in the form of effect size values and study heterogeneity, which will be interpreted in the form of forest plots and funnel plots.

RESULTS

Research from primary studies related to the effect of the use of injectable hormonal contraceptives on the incidence of breast cancer consisted of 6 studies originating from 5 studies from the Asian continent, 1 research from the European continent, 2 studies from the African continent, and 2 studies from the North American continent. Figure 1 shows the region of the retrieved articles that fit the inclusion criteria. Next, we will research the quality assessment of the quality of the article. (Tables 1 and 2). Meanwhile, table 3 shows that there are 5 case-control study articles. The results show that this injection of hormonal contraception affects the incidence of breast cancer.
Assessment of study quality was carried out using the Critical Appraisal Checklist for control assets (CEBMa, 2014). After assessing the quality of the study, 6 articles included in the quantitative synthesis meta-analysis were analyzed using RevMan 5.3. This is a table of results of the assessment of the quality of studies with injection hormonal contraceptive intervention and breast cancer outcomes.

**Figure 1. PRISMA Flowchart**
Table 1. Description of the primary study meta-analysis of the effect of injectable hormonal contraceptives on breast cancer

| Primary Studies | Country                  | Study Design    | Sample | P Population | I intervention       | C Comparison           | O Outcomes                                                                 |
|-----------------|--------------------------|-----------------|--------|--------------|-----------------------|------------------------|---------------------------------------------------------------------------|
| Christoper et al (2012) | United States of America | Control Case    | 1,028  | Women aged 20-44 years | Contraceptive injection | No injectable contraceptives | Breast cancer and medical record data (mammography)                     |
| Urban et al (2012) | South Africa             | Control Case    | 1,644  | Women aged 18-79 years | Injectable contraceptives | Not injectable contraceptives | Breast cancer and medical record data (doctor's diagnosis)              |
| Rispah et al (2015) | West Kenya               | Control Case    | 142    | Women aged 30-60 years | Injectable contraceptives | Not injectable contraceptives | Breast cancer and medical record data (histopathology)                  |
| Mehdi et al (2019) | Iran                     | Control Case    | 620    | 27-49 years old woman | Contraceptive injection | No injectable contraceptives | Breast cancer and medical record data (histological and radiological)    |
| Heikkinen et al (2015) | Finland                  | Control Case    | 52,426 | Female aged 22-60 years | Contraceptive injection | No injectable contraceptives | Breast cancer and medical record data (in situ or invasive)            |
| Amadou et al (2013) | Mexico                   | Control Case    | 2,704  | Women aged 35-69 years | Contraceptive injection | No injectable contraceptives | Breast cancer and medical record data (primary in situ or invasive)      |

*Variables included in the meta-analysis*
Figure 2. *Forest Plot* Effect of Injection Contraceptive Use on Breast Cancer Incidence

The forest plot shows the results of the analysis that Injectable hormonal contraceptives had a weak effect and 1.31 times the risk of developing breast cancer compared to the use or history of non-hormonal contraception and was statistically significant (p = 0.006). The heterogeneity of the research data shows $I^2 = 66\%$. So that the distribution of data is expressed by a heterogeneous (*random effect model*).

![Forest Plot](image)

| Study or Subgroup | log(Odds Ratio) | SE  | Weight | Odds Ratio IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-------------------|-----------------|-----|--------|------------------------------|------------------------------|
| Amadeu, 2013      | 0.077           | 0.0342 | 32.0%  | 1.08 [1.01, 1.15]            |                              |
| Cristofer, 2012   | 0.7088          | 0.0993 | 9.7%   | 2.20 [1.20, 4.00]            |                              |
| Heinöhren, 2015   | 0.1389          | 0.1458 | 21.1%  | 1.22 [0.91, 1.64]            |                              |
| Mehdii, 2016      | 0.7031          | 0.2657 | 11.6%  | 2.02 [1.20, 3.40]            |                              |
| Rispaq, 2015      | 1.5041          | 0.6494 | 1.4%   | 4.60 [0.70, 28.63]           |                              |
| Urban, 2012       | 0.27            | 0.1227 | 23.9%  | 1.31 [1.00, 1.67]            |                              |

Total (95% CI) 100.0% 1.37 [1.09, 1.71]

Heterogeneity: $T^2 = 0.04$, $Q = 14.02$, df = 5 (p = 0.01), $I^2 = 99\%$

Test for overall effect: Z = 2.72 (p = 0.006)

Figure 3. *Funnel Plot* Effect of Injection Contraceptive Use Against Breast Cancer Incidence

The funnel plot is a plot that depicts the estimated effect size of each study on the estimate of its accuracy which is usually the *standard error*. Based on Figure 4.7, the *case-control study* shows a publication bias which is indicated by the asymmetric distribution of right and left plots where 3 plots are on the right and 3 plots are on the left. The plot on the left of the graph appears to have a *standard error* between 0 and 0.2 and the plot on the right has a *standard error* between 0.2 and 1.
DISCUSSION

This systematic study and meta-analysis discuss the effect of injectable hormonal contraceptives on the incidence of breast cancer. The independent variables were analyzed by women aged 15-80 years who used or had a history of using injectable hormonal contraceptives. The dependent variable in this study was breast cancer. The results of the primary study conducted showed that the epidemiological study design with a larger sample size, besides that there were also demographic characteristics that varied in various countries, this will be the basis for giving the conclusion that women who use or have a history of using injection hormonal contraceptives have a significant effect on statistics on breast cancer.

Breast cancer is a disease that is a risk for every woman in the world. One of these non-communicable diseases, should not be ignored by individuals, communities, and stakeholders in the health sector. Breast cancer is becoming increasingly difficult and has a long course of treatment. According to the American Cancer Society, breast cancer is influenced by the presence of the female hormones estrogen and progesterone. Exposure to the high estrogen hormone is one of the factors that can increase the incidence of breast cancer risk in women. 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. Elsharkawy said that risk factors for breast cancer include family history, use of hormonal contraception, age at menarche, physical activity, age, and obesity (Yulianti, 2016).

This study uses previous primary studies that control the confounding factors, this can be seen based on the inclusion requirements of the study using multivariate analysis and the statistical results are adjusted odd ratio (aOR). According to Murti (2018), confounding factors are mixing estimates of the relationship between exposure and disease under study, by other factors that are related, both to disease and exposure. These confounding factors can affect the relationship or effect of exposure on the occurrence of disease that is estimated or estimated by the study is not the same as the relationship or effect that occurs in the target population, or the study results are invalid (incorrect).

The results of this study are supported by the research of 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 hormones for contraception and this relationship was stronger in women who used...
contraception for more than 10 years (aOR = 2.02; 95% CI = 1.2-3.3; p = 0.008 ). Another study by Puri et al (2009) in Patel et al. (2015) also stated that 77.8% of women had used injectable hormonal contraception for more than one year (> 1 year) and as a result had a high risk of developing breast cancer. High doses of estrogen are associated with an increased risk of breast cancer, because of this, the government of Western Kenya ensures that hormonal contraceptives prescribed to women in Kenya are at low doses.

One of the primary studies with a case-control study design, namely by Amadou et al. (2013) said that the use of injectable hormonal contraception has 1.22 times the risk of developing breast cancer compared to those who do not use injectable hormonal contraception. Hormonal contraceptives usually contain the sex hormones estrogen and progesterone. These hormones have been reported to exert different effects on different tissues, but the exact mechanisms associated with breast cancer are not completely clear. The hormone estrogen can increase the rate of cell division in the ductal epithelium of the breast, and increase the likelihood of mutations or promotion of existing mutations. And besides, the progesterone and progestins contained in injectable hormonal contraceptives can enhance this effect.

In line with the research of Urban et al. (2012) said that the risk of breast cancer increased significantly among women who had used injectable contraceptives compared to those who had never used hormonal contraception (aOR = 1.31; 95% CI = 1.03-1.65; p = 0.028). In this study, it was also stated that women who had used both oral and injectable hormonal contraceptives with a long duration of use had an effect on the incidence of breast cancer but were not significantly related (p = 0.4).

Research conducted by Li et al. (2012) showed that injectable contraceptives containing the same progestin as menopausal hormone therapy were found to increase the risk of breast cancer among postmenopausal women by 2.2 times compared with women not using injectable contraceptives (aOR = 2.2; 95% CI = 1.2-4.2; p = 0.010 ). This is in line with research conducted by Heikkinen et al. (2016) that there is a positive relationship between the current use of hormonal contraceptives and the risk of breast cancer, especially in cases diagnosed in recent years.

One of the primary studies with a case-control study design, namely by Rispah et al (2015), showed that the CI range was very wide (0.7 to 28.9). This can be caused by missing data during the follow-up process. This missing or missing data is probably data in the group exposed to positive risk factors, so this can lead to a weak relationship measure, namely an aOR of 0.11 and a wide CI range. While other causes may be due to the number of samples that are too small.
CONCLUSION

The use of injectable contraceptives has a risk of breast cancer although it has a small effect. The content of the hormones estrogen and progesterone that is too many causes abnormal cell growth and division.

ABBREVIATIONS

CI: confident interval; aOR: adjusted odds ratio.

COMPETING INTEREST

No conflict of interest

AUTHORS' CONTRIBUTION

Dilma as the main author plays a role in providing research concepts, analyzing data, and interpreting the results of the analysis. Eti Poncorini plays a role in the grammar of the article and conducts critical appraisal. Setyo Rahardjo determined the appropriate research method and extracted the articles.

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REFERENCES

Ortega-Overa, C., Angeles-Llerenas, A., McKenzie, F., Biessy, C., Hainaut, P., & Romieu, I. (2013). Hormonal therapy and risk of breast cancer in Mexican women. *PLoS ONE, 8*(11). https://doi.org/10.1371/journal.pone.0079695

Ayu, G., Dewi, T., Hendrati, LY, Ua, FKM, Epidemiology, D., & Ua, FKM (2015). Analysis of breast cancer risk based on the history of hormonal contraceptive use and age. *JBE, Vol. 3, No. January 1, 2015* : 12–23, 3, 12–23.

CEBMa (2014). *Critical Appraisal for a cross-sectional study*. Amsterdam.

Globocan (2020). Indonesia - Global Cancer Observatory. WHO; International Agency for Research on Cancer, 2018', *Https://Gco.Iarc.Fr/Today/Data/Factsheets/Populations/360-Indonesia-Fact-Sheets.Pdf*, 256, pp. 1–2. Available at: *https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf*.

Heikkinen, S., Koskenvuo, M., Malila, N., Sarkeala, T., Pukkala, E., & Pitkäniemi, J. (2016).
Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment. Cancer Causes and Control, 27 (2), 249–258. https://doi.org/10.1007/s10552-015-0702-5

Heikkinen, S., Koskenvuo, M., Malila, N., Sarkeala, T., Pukkala, E., & Pitkäniemi, J. (2016). Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment. Cancer Causes and Control, 27 (2), 249–258. https://doi.org/10.1007/s10552-015-0702-5

Ministry of Health (2015). Breast Cancer Management Guide. Ministry of Health of the Republic of Indonesia, pp. 1–50. Available at: http://kanker.kemkes.go.id/guidelines/PPKPayudara.pdf.

Ministry of Health (2019). Indonesia Health Profile 2019, Ministry of Health of the Republic of Indonesia.

Ministry of Health Republic of Indonesia Research and Development Agency (2018) 'Main Results of Basic Health Research, Ministry of Health of the Republic of Indonesia, pp. 1–100. Available at: http://www.depkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf.

Ministry of Health Republic of Indonesia Research and Development Agency (2018) 'Main Results of Basic Health Research, Ministry of Health of the Republic of Indonesia, pp. 1–100. Available at: http://www.depkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf.

Li, CI et al. (2012). Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age. 72(June 2010), pp. 2028–2036. DOI: 10.1158/0008-5472.CAN-11-4064.

Moradinazar, M. et al. (2019). Hormone therapy and factors affecting fertility of women under 50-year-old with breast cancer. Breast Cancer: Targets and Therapy, 11, pp. 309–319. DOI: 10.2147/BCTT.S218394.

Murti, B. (2018). Principles and Methods of Epidemiology Research. V. Karanganyar: Public Health Study Program.

Patel, K., Moi, U., Torrorey, R., Moi, U., Rono, S., & Eldoret, U. (2015). Risk Factors Associated with Aggressive Forms of Breast Cancer Seen in Young Women of Western
Urban, M., Banks, E., Egger, S., Canfell, K., O'Connell, D., Beral, V., & Sitas, F. (2012). Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black South African women: Case-control study. *PLoS Medicine, 9* (3), 1–12. https://doi.org/10.1371/journal.pmed.1001182

Yulianti, I. (2016). Breast Cancer Risk Factors. *Journal of Public Health, 4*. Available at: https://ejournal3.undip.ac.id/index.php/jkm/article/view/14162.