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Meta-Analysis

Meta-Analysis: Effect of Oral Contraceptives on Breast Cancer

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ABSTRACT

Background: Breast cancer is a disease characterized by abnormal cell growth in the breast. Until now, breast cancer is a life-threatening disease in women and is the main cause of death among the female population. Oral contraceptives or pills are one of the risk factors for women developing breast cancer. This study aims to determine the effect of oral contraceptives on the incidence of breast cancer.
Subjects and Method: This research is a meta-analytical study and a systematic review. The articles used were obtained from several electronic databases including PubMed, Google Scholar and ScienceDirect. The keywords to search for articles were as follows: Determinant OR risk factor AND breast cancer AND hormonal contraceptive OR oral contraceptive AND case control study. The article under study is a full text article with an observational study design. Articles were collected using the PRISMA diagram, and analyzed using the Review Manager 5.3 application.
Results: A total of 9 case control studies involving 6,811 women with breast cancer from several countries in Asia, Africa, and North America were selected for meta-analysis and systematic review. The data collected showed that women who used oral contraceptives had a risk of developing breast cancer as much as 1.82 times than those who did not use oral contraceptives (aOR= 1.82; 95% CI= 1.43 to 2.33; p<0.001).
Conclusion: Use of oral contraceptives increases the risk of developing breast cancer.

Keywords: oral contraceptives, breast cancer.

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BACKGROUND

Breast cancer is a life-threatening disease in women and is the leading cause of death among the female population (WHO, 2020; Akram et.al, 2017). Globally, there are 2.3 million women diagnosed with breast cancer and 685,000 deaths globally. By the end of 2020, there were 7.8 million living women diagnosed with breast cancer in the last 5 years.

Ferlay et al. (2015) stated that there were 883,000 cases in least developed countries and 794,000 in most developed countries. According to the data, in Iran there are 10 cases out of 100,000 population and 7,000 new cases have been reported every year. While in China, there were 168,013 cases in 2005 and 121,269 cases in 2000 (Akram et al. 2015). In Indonesia alone, breast cancer ranks first in terms of the highest number of cancers and is one of the first contributors to cancer deaths with the number of new cases of breast cancer reaching 68,858 cases

(16.6%) of the total 396,914 new cases of cancer in Indonesia. Meanwhile, the number of deaths reached more than 22 thousand cases (Menkes, 2020).

The most common symptom is the appearance of a painless lump or thickening in the breast. However, a lump in the breast does not mean it is cancer. There are several risk factors that can increase the risk of developing breast cancer such as obesity, harmful alcohol use, family history of breast cancer, history of radiation exposure, reproductive history such as the age at which menstruation begins and age at first pregnancy, and use of hormonal contraceptives (WHO, 2020). can cause an increased risk of breast cancer because the estrogen and progesterone content in oral contraceptives will have an excessive proliferative effect on the breast glands, resulting in normal cell changes to become abnormal (Nasution, et al 2018). This study aims to determine the effect of oral contraceptives on the incidence of breast cancer.

SUBJECTS AND METHOD

1. Study Design

This research is a systematic review and meta-analysis. The articles used in this study were between 1998 and 2020. The articles were obtained from several online databases, namely PubMed, Google Scholar and ScienceDirect. The keywords used in searching the article were determinant OR risk factor AND breast cancer AND hormonal contraceptive OR oral contraceptive AND case control study.

2. Inclusion Criteria

The inclusion criteria in this study were articles with a case control study design. Articles in English. The intervention in this study was the use of oral contraceptives. Research subjects are women with a diagnosis of breast cancer.

3. Exclusion Criteria

The exclusion criteria in this study were duplicated articles and the analysis did not include the aOR value.

4. Operational Definition of Variables

Breast cancer is the most common disease in women worldwide characterized by abnormal cell growth in breast tissue that can be diagnosed by radiological examination and biopsy.

Oral contraceptives are a type of combined oral hormonal contraceptive containing estrogen and progesterone which are consumed for a long time.

5. Study Instruments

Research is guided by PRISMA flow diagrams and assessment of study quality using The Joanna Briggs Institute Critical Appraisal Tools (JBI, 2017).

6. Data Analysis

Data processing was carried out using the Review Manager (Revman 5.3) by calculating the value of effect size and heterogeneity to determine the combined study model and form the final result of the forest plot meta-analysis.

RESULTS

The process of searching for articles using a research journal database is described in Figure 1. The articles in this study came from several countries in the Asian continent, the African continent and the North American continent.

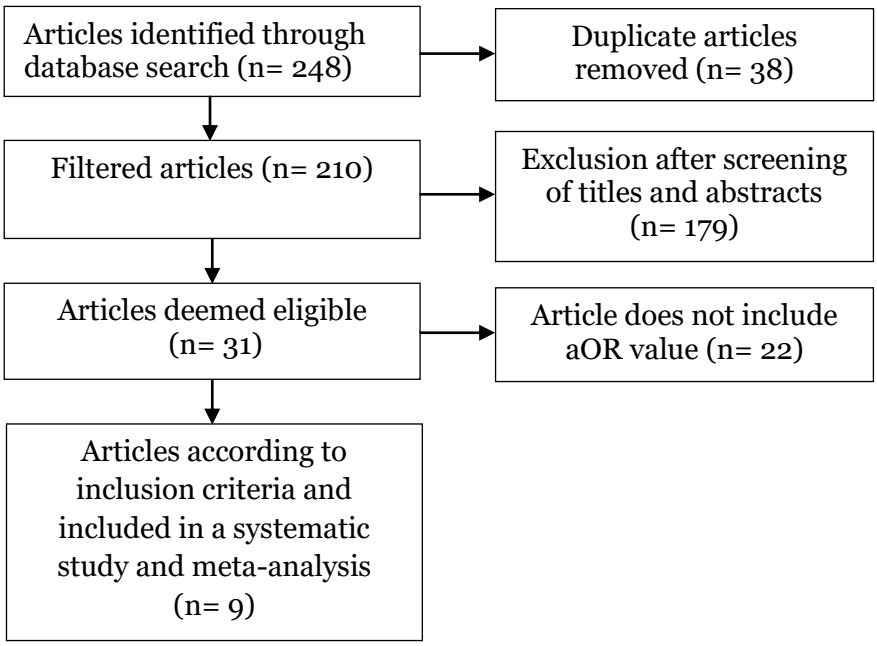

Figure 1. PRISMA Flowchart

Figure 2. Map of study area

Table 1. Assessment of study quality published

No	Indicators	Publication (Author, Year)								
		Bardaweel et al. (2019)	Beaber et al. (2014)	Chie et al. (1998)	Norsa'adah et al. (2005)	Yuan et al. (2019)	Alsolami et al. (2019)	Cherif et al. (2020)	Bethea et al. (2015)	Matalqah et al. (2011)
1	Were the groups comparable apart from the presence of disease in the cases or the absence of disease in the controls?	2	2	2	2	2	2	2	2	2
2	Are the cases and controls appropriate?	2	2	2	2	2	2	2	2	2
3	Were the same criteria used for identification in cases and controls?	2	2	2	2	2	2	2	2	2
4	Is exposure measured in a standard, valid and reliable way?	1	1	2	2	2	2	1	1	2
5	Was exposure measured in the same way for cases and controls?	2	2	2	2	2	2	2	2	2
6	Were confounding factors identified?	2	2	1	2	1	2	2	2	2
7	Are strategies for dealing with confounding stated?	2	2	1	2	1	2	2	2	2
8	Were outcomes assessed in a standardized, valid and reliable manner for cases and controls?	1	2	2	2	2	2	2	2	2
9	Is the exposure period long enough to be meaningful?	2	2	2	2	2	2	2	2	2
10	Is the use of statistical analysis appropriate?	2	2	2	2	2	2	2	2	2
	Total	**19**	**19**	**18**	**20**	**18**	**20**	**19**	**19**	**20**

Note: 1: Yes; 0: No

Tabel 2. Description of the primary studies included in the meta-analysis primary studies

No	Author (year)	Country	Study Design	Sample	Population	Intervention	Comparison	Outcome	aOR (95%CI)
1	Bardaweel et al. (2019)	Yordania	Case Control	450	Women with breast cancer ages 18 to 65	Use of oral contraceptives	No oral contraceptives	Breast cancer	2.25 (1.34 to 3.78)
2	Beaber et al. (2014)	US	Case Control	1,102	Women with invasive breast cancer ages 20 to 49	Use of oral contraceptives	No oral contraceptives	Breast cancer	1.50 (1.30 to 1.73)
3	Chie et al. (1998)	Taiwan	Case Control	174	Women with breast cancer	Use of oral contraceptives	No oral contraceptives	Breast cancer	1.70 (0.90 to 3.21)
4	Norsa'adah et al. (2005)	Malaysia	Case Control	294	Women with breast cancer ages 26 to 70	Use of oral contraceptives	No oral contraceptives	Breast cancer	2.50 (1.30 to 4.81)
5	Yuan et al. (2019)	Cina	Case Control	1,599	Women with breast cancer in the case group	Use of oral contraceptives	No oral contraceptives	Breast cancer	2.06 (1.39 to 3.05)
6	Alsolami et al. (2019)	Saudi Arabia	Case Control	432	Women aged >45 years with breast cancer	Use of oral contraceptives	No oral contraceptives	Breast cancer	6.78 (3.42 to 13.44)
7	Bethea et al. (2015)	Afrika Amerika	–Case Control	1,848	Women with breast cancer	Use of oral contraceptives	No oral contraceptives	Breast cancer	1.15 (1.02 to 1.28)
8	Matalqah et al. (2011)	Malaysia	Case Control	300	Women with breast cancer	Use of oral contraceptives	No oral contraceptives	Breast cancer	2.15 (1.16 to 3.97)
9	Cherif et al. (2020)	Algeria	Case Control	612	Women with breast cancer	Use of oral contraceptives	No oral contraceptives	Breast cancer	1.24 (0.96 to 1.60)

a. Forest plot

The forest plot in Figure 1 shows the effect of the use of combined hormonal oral contraceptives on the risk of breast cancer. Women who use oral contraceptives have a risk of developing breast cancer 1.82 times than those who do not use oral contraceptives, and this effect was statistically significant (aOR= 1.82; 95% CI= 1.43 to 2.33; p<0.001). I^2= 82% means that there is a very heterogeneous variation in the estimation of the effect of oral contraceptives on breast cancer risk between the primary studies in this meta-analysis. Thus, the synthesis of the overall effect estimation of the primary study was carried out using a random effects model approach.

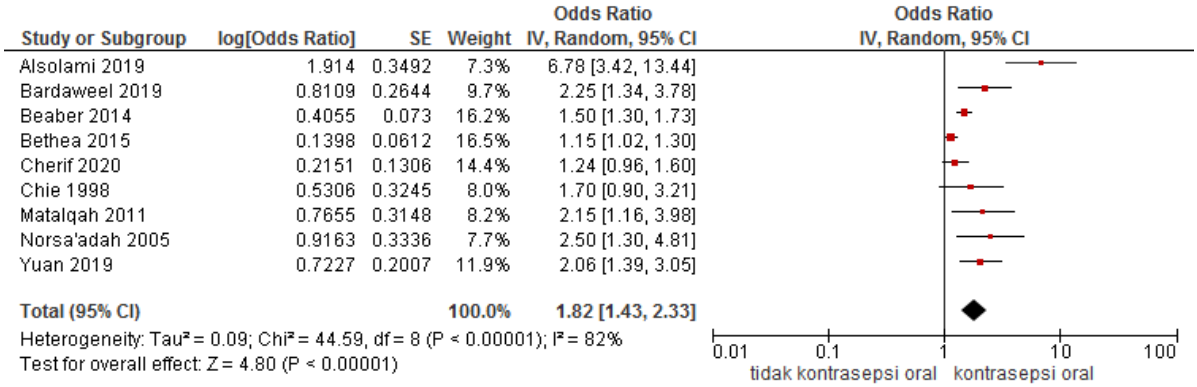

Figure 3. Forest plot of the effect of oral contraceptives on the incidence of breast cancer

b. Funnel plot

The funnel plot of Figure 2 shows that the distribution of the estimated effects is located to the right of the mean vertical line of the estimated effect than to the left. The right side is the same as the location of the estimated diamond shape (mean) which is also to the right of the null hypothesis vertical line in the forest plot (figure 1). Thus, the funnel plot indicates publication bias which tends to overestimate the true effect.

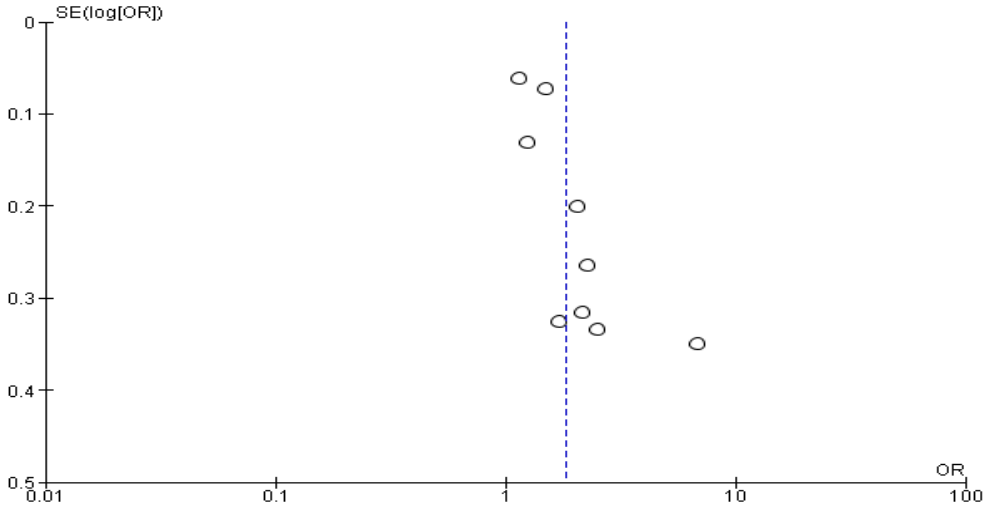

Figure 4. Funnel plot of the effect of oral contraceptives on the incidence of breast cancer

DISCUSSION

Pesticides are an important source of hazards in agriculture that can cause morbidity and mortality worldwide, especially in developing countries. It is estimated that there are 3 million cases of acute pesticide poisoning that occur every year with 250,000 people dying (Gunnel et al, 2007).

High sulfate content in pesticides can form sulfhemoglobin bonds, which will cause hemoglobin to become abnormal and unable to carry out its function in delivering oxygen. Anemia can occur in patients with organophosphate and carbamate pesticide poisoning because the form of sulfhemoglobin and methemoglobin in red blood cells causes a decrease in hemoglobin levels, resulting in hemolytic anemia. The incidence of hemolytic anemia occurs due to contact with pesticides caused by enzymatic defects in red blood cells and the number of red blood cells and the amount of toxic substances that enter the body.

This meta-analysis investigated pesticide exposure to hemoglobin in pesticide-using farmers with a sample size of 1,714 individuals from 12 cross-sectional studies conducted in America, Africa, Europe, and Asia. The findings of this study explain that exposure to pesticides causes a decrease in hemoglobin. The forest plot results revealed that farmers exposed to pesticides experienced a decrease in hemoglobin compared to farmers who were not exposed to pesticides (SMD= -0.28; 95% CI= -1.10 to 0.54). Consequently, pesticide exposure may be a risk factor for reduced hemoglobin levels in pesticide-using farmers. Confounding factors were found such as length of exposure to pesticides, duration of spraying, age, gender, use of personal protective equipment, and correct hygiene habits.

Pesticide exposure to hemoglobin in farmers who use pesticides is not statistically significant, it can be caused by pesticide exposure which can be influenced by the duration of pesticide use so that it can cause chronic poisoning. Based on the entrance of pesticides into the human body through the skin, mouth (swallowing), and lungs (inhalation). Chronic poisoning can occur due to exposure to toxic substances in low doses over a long period of time. Some of the factors that can influence it include the use of appropriate PPE, the age of farmers who are still productive, proper nutritional status, and proper hygiene habits in pesticide waste management (Mohammed et al., 2013).

A study involving 200 respondents consisting of 100 farmers using pesticides and 100 healthy people as controls in Egypt, revealed that farmers used excessive amounts of pesticides (not as recommended on the packaging) without knowing the toxicological effects. In this study, it was found that pesticide spraying workers who were often exposed to pesticide mixtures showed abnormalities in several hematological parameters and kidney function (Hassanin et al., 2017).

The cholinesterase enzyme is an enzyme found in cellular fluids whose function is to stop the action of acetylcholine by hydrolyzing it into choline and acetic acid. The use of pesticides to control plant pests carries the risk of accidents to

humans in the form of chronic or acute poisoning and death if the poisoning level is severe and is related to the level of cholinesterase inhibition in the blood (Ramsingh, 2010).

This meta-analysis investigated pesticide exposure to hemoglobin in pesticide-using farmers with a sample size of 1,387 individuals from 8 cross-sectional studies conducted in America, Africa, and Asia. The findings of this study explain that exposure to pesticides causes a decrease in cholinesterase levels. The results of the forest plot revealed that farmers exposed to pesticides experienced a decrease in cholinesterase levels compared to farmers who were not exposed to pesticides (SMD= -2.48; 95% CI = -3.68 to -1.27). Consequently, pesticide exposure may be a risk factor for reduced cholinesterase levels in pesticide-using farmers.

If a person is exposed to organophosphate pesticides, cholinesterase will bind to pesticides that are irreversible. Then a reaction will occur with acetylcholine, so that the examination will show a decrease in cholinesterase activity or an increase in acetylcholine levels. The decrease in cholinesterase activity in erythrocytes can last for 1 to 3 weeks, while the decrease in cholinesterase activity in platelets lasts up to 12 weeks or 3 months (Ramsigh, 2010).

Nambunmee et al. (2021) showed that farmers who sprayed pesticides experienced a significant decrease in cholinesterase levels compared to the control group who were not exposed to pesticides. Low AChE indicates excessive pesticide exposure can cause health problems. Another finding from a cross-sectional study in the Northern Thailand region, Thailand which included 97 farmers consisting of 70 conventional farmers using pesticides and 27 as controls who had never been exposed to pesticides and were in good health. This study indicate that conventional farmers who use pesticides have lower cholinesterase levels than modern farmers (Forte et al., 2021).

AUTHORS CONTRIBUTION

Arum Nuryati is the main researcher who selects the topic, searches for and collects research data. Setyo Sri Rahardjo and Bhisma Murti analyzed the data and review research documents.

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CONFLICT OF INTEREST

There is no conflict of interest.

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