Conference Paper

Correlation Between Hormonal Contraceptives Use and Age of Menarche with Breast Cancer Among Women in Indonesia: A Systematic Review

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Abstract

Cancer is one of the leading causes of death worldwide. According to GLOBOCAN, International Agency for Research on Cancer 2012, it is known that breast cancer is cancer with the highest percentage of new cases, at 43.3%, and percentage death due to breast cancer by 12.9%. Although the incidence of breast cancer in Asia remains lower than in North America, Western Europe, and Oceania, the rates have been increasing rapidly during the past few decades, and Asian countries now account for 40% of breast cancer cases diagnosed worldwide. Southeast Asian countries have moderate rates for breast cancer, with a higher incidence of one in Indonesia. Breast cancer morbidity and mortality increased among Indonesian women. These increased rateswere associated with higher prevalence of breast cancer risk factors such as hormonal contraceptive use and age of menarche. The purpose of this study was to determine the correlation between hormonal contraceptives use and generation of menarche with breast cancer among women in Indonesia. This study used a systematic review made by PRISMA. Searching for literature sources through online databases such as Science Direct, JSTOR, and Proquest, additional records identified through Google Scholar by using relevant keywords adjusted by inclusion and exclusion criteria. Five studies included in this review. All studies discussed breast cancer among women in several regions in Indonesia. There was a significant correlation between hormonal contraceptives use and age of menarche with breast cancer among women in Indonesia. Women may be more careful in determining the duration of hormonal contraceptive use and avoiding a lifestyle that can accelerate menarche.

Keywords: Hormonal contraception, Age of menarche, Breast cancer, Indonesia

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1. Introduction

Cancer is one of the leading causes of death worldwide. In 2012, about 8.2 million deaths caused by the disease. According to the World Health Organization(WHO),

cancer was one cause of death worldwide and an estimated 84 million people died from cancer in the period 2005 to 2015 [1].

According to GLOBOCAN, International Agency for Research on Cancer (IARC) 2012, it is known that breast cancer is cancer with the highest percentage of new cases, at 43.3%, and percentage death due to breast cancer by 12.9% [2]. Breast cancer is a group of cells abnormally, and multiple growing in breast tissue and is the most common malignant disease found in the female group [3]. Breast cancer is a malignancy in breast tissue that can originate from the ductal epithelium or lobules [4].

In America, there are about 92/100.000 women with breast cancer, with 27/100.000 mortality or 18% of deaths found in women [4]. Although the incidence of breast cancer in Asia remains lower than in North America, Western Europe, and Oceania, rates have been increasing rapidly during the past few decades, and Asian countries now account for 40% of breast cancer cases diagnosed worldwide [5]. The incidence of breast cancer is higher in developed countries, but the mortality is around69% in developing countries [6]. Southeast Asian countries have moderate rates for breast cancer, with a higher incidence of one in Indonesia [5].

Breast cancer is one of the most cancer types in Indonesia. Based on pathological based registration in Indonesia, breast cancer ranks first with a relative frequency of 18.6%. Data of cancer in Indonesia in 2010, according to histopathological data; Cancer Registration Agency Association of Indonesian Pathology Specialists and Cancer Foundation Indonesia estimated the number of incidence in Indonesia is 12 /100.000 women. More than 80% of cases are found to be in an advanced stage [4].

Breast cancer morbidity and mortality increased among Indonesian women. In the Dharmais Cancer Hospital, the number of new cases and death from breast cancer has risen by four years in a row. In 2010, the number of new cases was 711 cases, 93 cases of them caused death. In 2011, the number of new cases was 769 cases, 120 cases of them caused death. In 2012, the number of new cases was 809 cases, 130 cases of them caused death. And by 2013, the number of new cases was 819.217 cases of them caused death. [7]. These increased rates associated with higher prevalence of breast cancer risk factors such as hormonal contraceptive use and age of menarche. This systematic review was conducted to determine the correlation between hormonal contraceptives use and generation of menarche with breast cancer among women in Indonesia.

2. Methods

This study used a systematic review made by prisma 2009. Source literature search began on 10 June 2017 by electronic data based through remote.lib.ui.ac.id/lib.ui.ac.id website. The author conducted searching on Science Direct, JSTOR, and Proquest, additional records identified through Google Scholar. Keywords are Hormonal Contraception AND Age of Menarche AND Breast Cancer AND Indonesia. The criteria inclusion in this study were Indonesian and English language, Indonesia state and the journal year is the last ten years published, starting from 2007 to 2017. The criteria exclusion criteria are apart from the inclusion criteria.

From Science Direct, it's obtained 12 journals, JSTOR 12 journals, Proquest 91 journals, and google scholar 1640 memoirs. Journals screen by years 2007-2017 was 850. After identification conducted initial screening by reading the titles and abstracts, it's obtained 20 journals, and 838 journals remove because of claim, state, variable and year which were not appropriate with the topic. In the eligibility phase, eight journals were reviewed to decide whether the journals could use and authors got five journals systematically for systematic review.

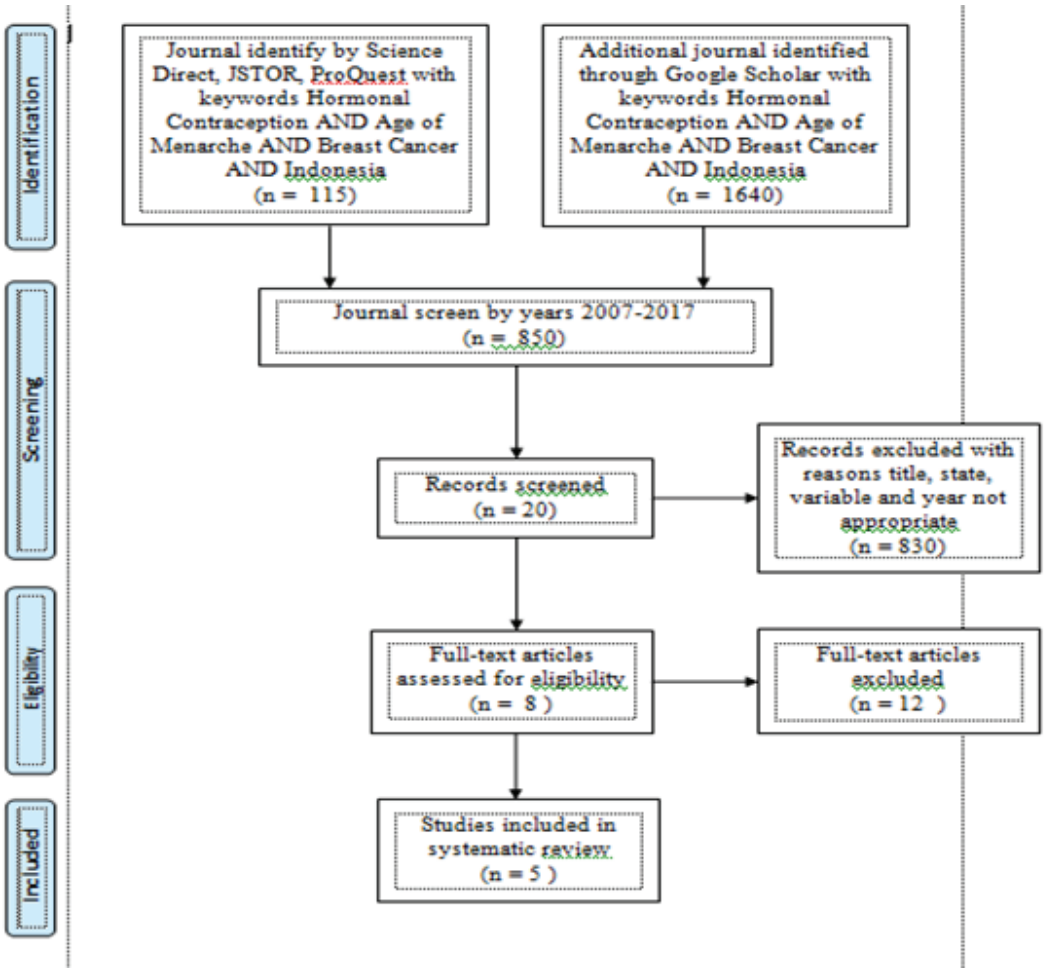

Figure 1: Systematic Review Flowchart.

3. Results

Five studies included in this review. All studies discuss breast cancer among women in several regions in Indonesia.

Based on research conducted by Dwi Kartika Rukmi and Rukmi Handayani (2014), risk factors related to breast cancer according to multivariable analysis were age of menarche <12 (OR: 15.84; CI: 1.27-198.29; p= 0.032) and application of hormonal contraceptive (OR: 3.625; CI: 1.02-12.93; p= 0.040) [8].

The results of the study of Fitria Prabandari and Dyah Fajarsari (2016) found that there is a correlation between breast cancer and age of menarche with p-value 0,013 (OR: 21.242; CI: 1.919-235.181) and there is a correlation between breast cancer and the application of hormonal contraceptive with p-value 0,041 (OR: 12.759; CI: 1,108-146.874) [9].

Research by Gusti Ayu Triara Dewi and Lucia Yovita Hendrati (2015), the results of the analysis using binary logistic regression (α= 5%) indicated that the use of hormonal contraceptive (p= 0.028); OR: 3.266) and age of menarche (p= 0.031; OR: 3.492) has a significant correlation with the incidence of breast cancer in women at Dr. Soetomo Hospital [10].

Research by Harianto, Rina Mutiara, and Hery Surachmat (2015) with case-control research designs found that the use of combination contraception pills has the risk to have breast cancer 1,864 times compare with them who don't take that pills [11]. Marice Sihombing and Aprildah Nur Sapardin (2015) on the results of their research found that one of the dominant risk factors of breast tumor among women was the use of contraception with p-value 0.002 (OR: 3.63; CI: 1.63-8.10) [12].

4. Discussion

4.1. Correlation between hormonal contraceptives use and breast cancer

Contraception is one effort that can select to prevent conception and pregnancy. Based on the method, contraception divided into simple contraceptives and modern contraceptives. Modern contraception divided into four processes, namely mechanical, hormonal, chemical, and operative techniques. Hormonal methods of pill, injection, or implant.

Use of hormonal contraceptives can increase the risk of breast cancer. Such hormonal contraceptives can be pills, combination pills, and mini-pills, injections, or implants or plants [13]. The risk of breast cancer incidence associated with long-term use of hormonal contraception.

The use of oral contraceptives over extended periods causes an increased risk of breast cancer. The increased risk of breast cancer also occurs in women who use hormone therapy, such as exogenous hormones. The exogenous hormone can cause an increased risk of breast cancer. The use of hormonal contraceptives can lead to increased exposure of the hormone estrogen in the body. There is an increase in exposure to the hormone estrogen that can trigger abnormal cell growth in certain parts, such as the breast.

4.2. Correlation between age of menarche and breast cancer

Women who have first menstruation at <12 years of age have a slightly higher risk of breast cancer than women who have first menstruation >12 years of age. Increased risk

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TABLE 1: Journal in Review.

Author	Dwi Kartika Rukmi, Dwi Handayani (2014)	Fitria Prabandari, Dyah Fajarsari (2016)	Gusti Ayu Triara Dewi and Lucia Yovita Hendrati (2015)	Harianto, Rina Mutiara, and Hery Surachmat (2015)	Marice Sihombing and Aprildah Nur Sapardin (2015)
Title	Breast Cancer Risk Factors In Women In RSUD Panembahan Senopati Bantul	The Factors That Affect The Incidence Of Breast Cancer In RSU Dadi Keluarga Purwokerto	Breast Cancer Risk Analysis Based On History Of Hormonal Contraception And Age Of Menarche	The Risk Of Using Combined Contraceptive Pills On The Incidence Of Breast Cancer At The Kb Receptor At Perjan RS DR. Cipto Mangunkusumo	Breast Tumor Risk Factors In Women Aged 25-65 Years In Five Sub-Districts Central Bogor
Method	Case-control study method with 33 respondents for either case group or control group involved inclusion criteria. Data surveyed by using a purposeful questionnaire and data of breast cancer cases attained from the patient's medical record.	This study uses a retrospective case-control approach	Type of this study is observational analytic and use case-control design.	The study conducted with survey methods that are observational dimension retrospectiveWith case-control designsHospital-based with election Control group without doing matching	The study design was case-control. Data from baseline data cohort study of risk factors of non-communicable disease in Bogor Tengah district. A cases defined as a positive breast tumor with USG method; a control asdeedt as a respondent with no breast tumor. The ratio between usomef cases and controls was 1:3 without matching. The analysias performed in 61 cases and 183 controls.
Variable	1. Breast cancer 2. Age of first pregnancy 3. Parity history 4. Age of menarche 5. Age of menopause 6. History of benign tumor infection	1. Breast Cancer 2. Age 3. Age of menarche 4. Parity 5. Old nursing 6. History of use hormonal contraception 7. The family history of breast cancer	1. Breast cancer 2. History of hormonal contraception 3. Age of menarche	1. Breast cancer 2. Combination contraception pills	1. Breast Tumor 2. Age 3. Contraceptive pills use 4. Menopause 5. Education 6. Stress 7. High cholesterol 8. Low consumption of vegetables 9. Having a first full-term pregnancy after age 30 years old 10. Ever benign tumor surgery more than once

Author	Dwi Kartika Rukmi, Dwi Handayani (2014)	Fitria Prabandari, Dyah Fajarsari (2016)	Gusti Ayu Triara Dewi and Lucia Yovita Hendrati (2015)	Harianto, Rina Mutiara, and Hery Surachmat (2015)	Marice Sihombing and Aprildah Nur Sapardin (2015)
Analysis	Data analysis applied chi-Square (α=0.05) and double logistic regression	Data analysis using non-statistical analysis or referred to as a simple statistical analysis. To test the hypothesis about the relationship between two variables used Chi-Square. The result of the bivariate analysis will be analyzed using logistic regression on each variable with p-value <0.25	Analysis of the effect of the history of hormonal contraception and menarche age on breast cancer incidence done by using multiple logistic regression test. Influence and risk are known by comparing with p-value and calculating odds ratio with CI:95%.	To see the highest risk of contraceptive pill use with the risk of breast cancer is used Odds Ratio calculation then tested Cochran's & Mantel-Haenszel Statistics.	Data were analyzed using a computer program. Univariate analysis to know the distribution of frequency and amount of proportion of each variable. Bivariate analysis was conducted to determine the relation of the dependent variable with the independent variable. If the result of bivariate analysis yields p <0.25, then the variable goes into multivariate analysis stage. Multivariate analysis by using logistic regression to know the relation of the dependent variable with an independent variable by controlling variable confounding or intruder.
Result	Risk factors related to breast cancer cases according to multivariable analysis were; age of first pregnancy ≥30 years old (OR: 44.67;CI: 3.25–614.11; p=0.004), Parity History >2 children (OR: 10.07;CI:1.59–63.91; p=0.014), age of menarche <12 (OR: 15.84; CI: 1,27–198.29;p=0.032), age of menopause ≥55 years old (OR: 0.007;CI: 0.00–0.18; p=0.003), and history of benign tumor infection (OR:62.15;CI: 3.33–1158.97; p=0.006).	There is no correlation between age and the incidence of breast cancer in RSU Dadi Family Purwokerto. There is a correlation between the age of menarche with the crate of breast cancer in RSU Dadi Family Purwokerto. There is a parity relationship with the incidence of breast cancer in RSU Dadi Family Purwokerto. There is a correlation between the duration of breastfeeding with breast cancer occurrence in RSU Dadi Family Purwokerto. There is a history of the relationship between hormonal contraceptive use with the incidence of breast cancer in RSU Dadi Family Purwokerto. There is a correlation between a family history of breast cancer with the idenmpact of breast cancer in RSU Dadi Family Purwokerto.	The results of the analysis used binary logistic regression (α = 5%) indicated that the use of hormonal contraceptives (p = 0.028; OR = 3.266) and age of menarche (p = 0.031; OR = 3.492) has an significant correlation with incidence of breast cancer in women	The research results show that the use of combination contraception pills has the risk to have breast cancer 1.864 times bigger compare with them who don't take that pills.	The results showed that the proportion of breast tumor in five villages of Bogor Tengah district was 3.4%. There were only 3 variables statistically significant associated with breast tumor, namely aged ≥ 40 years old (ORadj 8.82; 95%CI 2.73-25.51), the used contraceptive pills (ORadj 3.63; 95%CI 1.63-8.10), and menopause (ORadj 3.58; 95%CI 1.38-9.28). There is no significant relationship between education, stress, high cholesterol, low consumption of vegetables, having a first full-term pregnancy after age 30 years old, and ever benign tumor surgery more than once with the incidence of breast tumor/ cancers.

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Discussion	History of benign tumor infection was the risk factor with the most significant influence. The result of the dual variable test with chi-square described a relation between age $\geq$30 years old, history of exclusive breastfeeding, radiation exposure, family history, and application of hormonal contraceptive.	The risk of developing breast cancer increases with age. About 1 in 8 invasive breast cancers are found in women younger than 45, while about 2 of 3 invasive breast cancers found in women age 55 or older. Studies have found that women who use oral contraceptives (birth control pills) have a slightly higher risk of developing breast cancer than women who have never used it.	Modern contraception divided into four methods, namely mechanical, hormonal, chemical, and operative techniques. The use of hormonal contraceptives can increase the risk of breast cancer. Such hormonal contraceptives may be pills, birth control pills, and mini-pill pills, injections, or implants. Combined birth control pills contain estrogen and progesterone hormones to prevent ovulation. The hormone progesterone inhibits the FSH (stimulating follicle hormone) Secretions that inhibits egg cell maturation. The hormone estrogen helps the formation of the endometrium or mucous membranes that line the uterine wall. The endometrium still forms, but no eggs are ripe so that pregnancy can not occur. Side effects that may arise as a result of the use of this contraceptive pill are a headache, heart palpitations, weight gain, increased blood pressure, nausea, irregular menstrual bleeding, decreased milk production, and so on. Women who previously had a heart attack, cerebral hemorrhage, chest pain, blockage of blood vessels, breast cancer, and liver dysfunction. The use of oral contraceptives for long periods causes the risk of breast cancer to increase. The increased risk of breast cancer also occurs in women who use hormone therapy, such as exogenous hormones. The exogenous hormone can cause an increased risk of breast cancer. Menarche age is too early in women, i.e., less than 12 years causing exposure to the hormone estrogen in the body to be faster. The hormone estrogen can trigger the growth of cells in certain body parts abnormally. The mechanism of the occurrence of breast cancer by exposure to estrogen is still not known for sure due to estrogen stimulation of epithelial cell division or because caused by estrogen and its metabolites that directly act as mutagen so that it can create cancer cells in the breast	Cochran's & Mantel-Haenszel Statistics test results obtained an odds ratio of 1.864. Thus the use of a contraceptive pill has a risk of 1.864 timesmore likely to develop breast cancer than no contraceptive pill users. The result of a significance test of odds ratio value equal to 1.864 (95% Confidence Interval) obtained a p-value of 0.118 for 2-sided (two tail).p> α= 0.05 (not significant). Because the value of p = 0.118> 0.05, the hypothesis is rejected, meaning that although the contraceptive pill users have a risk of 1.864 times greater than non-users of combined contraceptive pills against breast cancer incidence the risk is not significant as a risk factor for cancer incidence breast. So the combined contraceptive pill is only a mild risk factor for the impact of breast cancer	Commonly used oral contraceptives are a combination of estrogen and progestin and are thought to be risk factors for increased incidence of tumors/breast cancer worldwide, including in Indonesia.The growth of breast tissue is susceptible to estrogen. Therefore women exposed to this hormone in a long time will be a significant risk to breast cancer.

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Conclusion and suggestion	Risk factors that had relations to breast cancer cases were the age of first pregnancy ≥30 years old, parity history >2 children, the age of menarche <12 years old, the age of menopause ≥55 years old, and history of benign tumor infection.	Variables that influence breast cancer incidence are the age of menarche, duration of breastfeeding, history of hormonal contraceptive use and family history of breast cancer.	The use of hormonal contraceptives and age of menarche has a significant correlation with the incidence of breast cancer. Expected that the community can be more accurate in determining the duration of hormonal contraception usage and avoid lifestyle can accelerate the occurrence of menarche.	Users of combined contraceptive pills have a risk of 1.864 times higher for breast cancer than non-users of combined contraceptive pills. However, the risk is not as significant as a significant risk factor for breast cancer. Combined contraceptive pills only as a mild risk enhancer against the incidence of breast cancer in Perjan RS. Cipto Mangunkusumo	The dominant risk factors of breast tumor among women were aged 40 years old and over, the used contraceptive pills and menopause.

of breast cancer is due to the duration of estrogen exposure that is longer and slightly higher.

When a woman experiences her first period, the function of ovarian cycles that production of estrogen begins. The longer a woman is exposed, the higher the risk for breast cancer she gets. In addition to being presented, the regularity of the menstrual cycle also plays a role. The balance of the period describes the frequency of exposure, so the faster a woman gets a higher exposure compared to women whose regular menstruation is slower or has a long menstrual cycle [14].

Menarche age is too early in women, less than 12 years causing exposure to the hormone estrogen in the body to be faster. Estrogen hormone can trigger the growth of cells in certain parts of the body is not normal. The mechanism of the occurrence of breast cancer by estrogen exposure is still not known for sure due to estrogen stimulation of epithelial cell division or because of a cause by estrogen and its metabolites that directly act as mutagens that can cause cancer cells in the breast [15].

5. Conclusion

There is a significant correlation between hormonal contraceptives use and age of menarche with breast cancer among women in Indonesia. The longer the duration of hormonal contraceptive use, the higher the risk of breast cancer. Women who are more at risk of breast cancer are women with a first menstrual period of fewer than 12 years. Based on the systematic review, authors have a few suggestions: women may be more careful in determining the duration of hormonal contraceptive use, avoiding a lifestyle that can accelerate menarche, need to do early detection regularly with breast self-examination and then followed by examination mammography every year, and need understanding of prevention efforts, early diagnosis, curative or palliative treatment and good rehabilitation efforts.

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The online library University of Indonesia that has given access to the world's colossal database look for a systematic review

Ethical approval

No ethical approval

Competing Interest

No competing interest

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