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Oral Contraceptive as a Risk Factor of Breast Cancer in Female Patients at Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014

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Abstract

- ***Objective:***

Breast cancer is one of the most prevalent types of cancer among women in Indonesia. Oral contraceptive usage in reproductive age is one of the favorable choices for contraception in Indonesia. Hormonal contraception contains estrogen or progesterone or both to prevent pregnancy Estrogen interacts with mammary epithelial cells via estrogen receptors (ER) which serves as a nuclear transcription factor. Therefore, in this study all the patients are evaluated by the gold standard examination in order to determine the role of oral contraceptive in breast cancer.

- ***Methods:***

This cross-sectional study gained information from the histopathological biopsy collected from the Patients' medical records. Then we analyzed the data using Fisher test in SPSS version 21. This study aims to find the association between oral contraceptive consumption and the occurrence of breast cancer among 114 female Patients in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014.

- ***Result:***

Patients age distribution ranged from 13-83 years old with the largest age group was 41-50 years. Most patients did not choose any contraceptive program as many as 55 people (62.5%). This result showed p values of 0,03 and odds ratio (OR) that is 1,279 (95% CI 1.112 to 1.471) obtained from 114 patients indicates that oral contraceptive consumption had statistically significant result on breast cancer prevalence in Indonesia.

- ***Conclusion:***

Oral contraceptive consumption may have a role as risk factor of breast cancer incidence among female patients in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014

Keywords:- *Breast Cancer; Oral Contraceptive*

I. INTRODUCTION

The prevalence of breast cancer in the world remains high. Breast cancer in Indonesia accounts as the second highest cancer in 2013. In United States of America, quarter million of new breast cancer cases were found in USA in 2017. Breast cancer possess diverse etiologies. It is also accompanied by a variety of risk factors, as well. For instance, several genes may affect the occurrence of carcinomas such as BRCA1 and BRCA2 genes are autosomal dominant. [1] Some habits or lifestyle can also be categorized as a risk factor for breast cancer, such as alcohol consumption and being overweight. Familal history and history of breast disease can also trigger the development of breast carcinoma. [2] Moreover, age and menstrual cycle and reproductive factors may also be risk factors for breast cancer. It can be associated with the use of oral contraceptives may affect the menstrual cycle and reproductive factors in women. [3]

Contraception consists of a variety of hormonal contraception and nonhormonal contraception. Hormonal contraception contains estrogen or progesterone or both to prevent pregnancy. Oral contraceptive can inhibit the formation of follicle-stimulating as a negative feedback mechanism on gonadotropin, thicken the cervical mucus, and inhibit implantation of the fetus. Estrogen inhibits the development of the follicle through a negative feedback mechanism on the axis of FSH, GnRH, and gonads. Moreover, estrogen also prevents bleeding in the middle of the cycle to stabilize the endometrium wall. Estrogen has a wide range of active forms i.e. ethinylestradiol. [3][4]

II. ROLE OF ESTROGEN IN BREAST CANCER

Estrogen possess an essential contribution to the development of breast cancer. Estrogen interacts with mammary epithelial cells via estrogen receptors (ER) which serves as a nuclear transcription factor. Receptors are the most influential in the incidence of breast cancer. ER α expressed on breast, uterus, and ovaries. Often, patients with breast cancer have results with ER +, which is a significant activation of transcription. Also, there is a progesterone receptor or progesterone receptor (PR) genes

that are regulated by estrogen. Receptor isoforms are correlated with breast cancer is more frequently expressed PRB, even though it can also be found in PRA. The emergence of PR is often found in ER + and have a relevant prognosis. Patients who are older than 50 years old often developed an ER+/PR- whereas in ER- / PR+ patients often found nodules development and ER-/PR- may be associated with the response of antiestrogen therapy. [5]

The diagnosis of breast cancer can be confirmed by histopathology procedure collected by Fine Needle Aspiration Biopsy (FNAB), Core Biopsy, and open biopsy. Furthermore, immunohistochemical examination can be conducted to evaluate the estrogen receptor, progesterone receptor, and HER2 to determine treatment and prognosis. Other tests that can be done is mammography, ultrasonography (USG), and Computed Tomography (CT) Scan / Emission Positron Tomography (PET). [1] [6] Therefore, in this study all the patients are evaluated by the gold standard examination in order to determine the role of oral contraceptive in breast cancer.

III. MATERIAL AND METHODS

This study was a retrospective cross-sectional. The minimum data to conduct this study was 88 patients. We collected the 114 data from the result of randomized of pathological biopsy given by Archive Unit of the Department of Anatomical Pathology, Faculty of medicine - Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia. Then, we obtained the information about the contraception history through the Medical Record Unit of Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia.

The inclusion criteria include female patients with suspected breast cancer were recorded in the Department of Pathology Faculty of Medicine and/or treatment to the Department of Surgery RSUPNCM and the data recorded in the Medical Record Unit RSUPNCM in 2010 to 2014. The exclusion criteria of this study is men patients with breast cancer. We processed into the software SPSS version 21 with chi-square test, however, one of the cells amount was under 25% of all data so that we analyzed in two-sided 2x2 fischer test. This study obtained a letter ethical assessment from Faculty of Medicine, Universitas Indonesia that is published by Health Research Ethics Commitee - University of Indonesia and Cipto Mangunkusumo Hospital (HREC-FMUI/CMH).

IV. RESULTS

A. Age Distribution

This study divided the age groups based on the classification of the WHO, namely by division by decades. The results of the collected data found that patients in the range of 41-50 years old as many as 29 people (33%). The second-largest age group of patients with an age range of 51-60 years is 28 people (31.8%). Age range 31-40 years group had 14 people (15.9%), the age group over 60 years as many as 13 people (14.8%), 21-30 years age group by 2 people (2.3%) and group under 21 years of age by 2 people (2.3%). (See Table 1.)

Age groups	Frequency	Percentage (%)
<21 Years	2	2.3
21-30 Years	2	2.3
31-40 Years	14	15.9
41-50 Years	29	33.0
51-60 Years	28	31.8
> 60 Years	13	14.8
Total	88	100.0

Table 1:- Age distribution of breast cancer patients in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014.

B. Contraceptive History

In this study, the number of patients who do not follow any contraceptive program as many as 55 people (62.5%). A total of 33 patients (28.9%) used oral contraceptives. (See Table 2.)

Contraception	Frequency	Percentage (%)
Oral Contraception	33	37.5
Injectable Contraception	2	2.3
Intrauterine Device	14	15.9
Implant	29	33.0
No Contraception	55	62.5
Total	88	100.0

Table 2:- Contraception choices distribution of breast cancer patients in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014.

The duration of contraceptive use most, namely 22 patients (25%) use contraception during the following 5 years. Patients who use contraception during 5-10 years as many as 9 patients (10.2%). Patients who use contraceptives for more than 10 years as many as 9 patients (10.2%). However, there were 10 (11.4%) patients whose data regarding the use of contraceptives is unknown or unrecorded. (See Table 3.)

Duration (Years)	Frequency	Percentage (%)
< 5	22	25
5-10	9	10.2
>10	9	10.2
Unknown	29	11.4
No Contraception	38	43.2
Total	88	100

Table 3:- The duration of contraception use of breast cancer patients in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014.

C. Oral Contraceptive as Risk Factor of Breast Cancer

The result of oral contraceptives usage of female patients diagnosed with breast cancer showed 33 (100%) patients with a definite diagnosis and 0 (0%) patients with a negative diagnosis. Whereas patients who did not consume oral contraceptives showed, 78.2% were diagnosed with breast cancer and 21.8%, which is not a breast cancer patient. In data analysis, chi-square test requirements are not fulfilled due to of of the cells (25% of the cells) have expected count value was below 5 patients. So, then the analysis is performed using Fisher's exact test. In this test, the results obtained a significance value with p value = 0.03. Therefore statistically, there is a relationship of oral contraceptive consumption with the incidence of breast cancer in Dr. Cipto Mangunkusumo National Public Hospital, Jakarta, Indonesia in 2010-2014. (see table 4.)

Odds ratio (OR) of this study was 1.279. If the value of OR = 1, the relationship can be declared neutral. If the value of OR <1, then there is a protective relationship, while the value of OR> 1 indicates risk. Therefore, by OR, that is 1.279, then the relationship of oral contraceptive use increases the likelihood of occurrence of breast cancer by 1,226 times than patients who did not use oral contraceptives. (see table 4.)

		Breast Cancer Diagnosis		
	Positive	Percent (%)	Negative	Percent (%)
Oral Contraceptives	33	100	0	0
No Contraception	43	78.2	12	21.8
Total	76	86.4	12	13.6
P.value†	0.03			

† Fischer test, P.value<0.05

Table 4:- Oral Contraceptives as one the risk factors of breast cancer.

V. DISCUSSION

D. Age Distribution

A study by Poosari A et al., (2014) namely the largest age group is the 50-59 age group (39%) followed by the 60-69 age group (31%). Patients were included in the age group with the grouping per decade starting at age 30 to 69 years. The grouping has the same characteristics that use the same age group but also has several different groups but starting at different ages. [7] This is because, in this study, there are no restrictions or criteria regarding age on the subject while the other study, the subject is determined from patients in the age range 30-69 years.

Research conducted by Al-Amri, et al., (2015) stated that the average age of breast cancer incidence there is 48 years, so these results support this research. This could be due in patients with breast cancer who take oral contraceptives, hormone exposure contained in the body does not directly affect the proliferation of breast epithelial cells but requires a process and other factors such as gene mutations and lifestyle. [8]

E. Contraceptive History

In this study, the selection was based on the effects produced by the use of oral contraceptives. Besides being more convenient to use, the chances of return of fertility in patients using oral contraceptives are higher than other contraceptives. In a study by the Urban M et al., (2012), there are 57% of black women patients who did not use any contraception in South Africa. While there are 13% of patients taking oral contraceptives alone, and there are 18% of patients who only use the contraceptive injection. As for the remaining 12% of patients use both. The different types of contraception use with characteristics in this study because there are differences in the population and the type of study conducted on two other studies and research so that the demographic data of the different type of contraception. [9]

In another study by Anggorowati (2013), distribution of the duration of contraceptives use was divided within 5 years. There are 51% of patients who use contraception, and there are 49% of patients who use contraception for more than 5 years. The duration tends to differ with the characteristics of both duration on the other. This could be due to differences in population, the number of research samples were fewer in other studies, and different kind of studies are case-control studies. [10]

F. Oral Contraceptive as Risk Factor of Breast Cancer

A systematical review conducted by Gierisch et al. (2013) noted that the use of oral contraceptives might increase the likelihood of breast cancer that were statistically significant. In this study were also presented in the absence of a meaningful relationship with the duration of use of oral contraceptives but there is a relationship between the last user distance closer (current use) with the emergence of a significant incidence of breast cancer. [11] A meta-analysis study by Park et al. (2016) in South Korea, found that oral contraceptives influenced the incidence of breast cancer. In this study, explained that the value of the Relative Risk (RR) at 1:31 with the results for the use of oral contraceptives. In addition, the analysis is performed on patients over the age of 20 years in 2010, showed figures obtained increased RR for the use of oral contraceptives. Thus, in this study, it was stated that the use of oral contraceptives as a risk factor for breast cancer incidence. [2]

In a meta-analysis study conducted Beral et al. (2012) The use of oral contraceptives is good with a duration under five (5) years and above five (5) years have relationships with the increase in the incidence of breast cancer. A case-control study carried out by the Work et al. (2014) in the United States, Canada, and Australia in 2014 showed that oral contraceptive use has the effect varied according to the type of breast cancer with Estrogen Receptor (ER) and Progesterone Receptor (PR). [5]

In general, use of oral contraceptives have a protective effect in patients with this type of breast cancer with a duration of fewer than 5 years and the use of more than 5 years showed an increased risk of breast cancer. However, found the numbers RR> 1 in patients with contraceptive use before 1975. This could be due before 1975, the formula contained in oral contraceptives containing estrogen and progestin more to improve the interaction of estrogen and progestin with estrogen receptor (ER) and progesterone receptor (PR) in the breast. [4]

However, a cohort study conducted by Ritte et al. (2013) in Europe states that oral contraceptives do not have a significant relationship with the type of breast cancer hormone receptor (HR) positive and negative. [6] Phipps et al. (2011) conducted a case-control study in breast cancer patients with this type of triple-negative (ER-, PR-, HER2) states that there is no significant relationship to the use of oral contraceptives with the incidence of triple-negative breast cancer types. In a case-control study by Bethea et al. (2014), the use of oral contraceptives, especially with a long duration increases the risk of breast cancer types ER- and ER + triple-negative of the female population of African descent (African American). [12][13]

In general, there is a trend of rising significantly to the incidence of breast cancer with the consumption of oral contraceptives, especially in a study conducted at current present. Although these types of studies carried out is generally a case-control or cohort studies, the results gathered have significant results with RR which tend to be higher than the OR found in this study. The incidence of breast cancer can be caused by an exogenous synthetic hormone imbalance of oral contraceptives caused by the stimulation of estrogen receptors or estrogen receptor (ER) and progesterone receptor or progesterone receptor (PR), which stimulates proliferation of epithelial cells in breast cancer. Other than that, BRCA1 and BRCA2 gene mutations may increase the incidence of breast cancer when traced to genetic testing or family history search was a similar type of cancer. As for the difference in results in some studies can be caused by different types of studies, different research time, different types of populations, sample age restrictions, usage duration and final classification of contraception, and the distribution of types of breast cancer.

In this study, the data collected by the data through medical records so that details regarding oral contraceptives such as the duration, type, age of first use, and final consumption may not be completed. This study also using cross-sectional method (cross-sectional) so it can be researched with other types of studies with more extensive observational studies and a more significant number of samples. Besides, this study did not restrict the age of the subject and the type of breast cancer.

VI. CONCLUSION

Oral contraceptives showed a significant association with the incidence of breast cancer in female patients. Therefore, women who consumed oral contraceptives should conduct periodic checks for the prevention and early detection of breast cancer incidence in the future.

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