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Risk Factors for Breast Cancer: Hormonal Contraception

Yuniastini^{1*)}, Purwati², Al Murhan³, Mutia Diah Pratiwi⁴

^{1,2,3} Health Polytechnic of Tanjungkarang

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ABSTRACT

By the end of 2020, there were 7.8 million living women, who were diagnosed with breast cancer in the last 5 years, and it makes breast cancer as the most common cancer in women in the world. There are many breast cancer risk factors, and hormonal contraception is one of them. The purpose of this research is to analyze risk factors for breast cancers, which are associated with the duration of contraceptive use. Its benefits are to evaluate the usage of hormonal contraception and to get the data used by the government in order to make health policy in preventing breast cancer. This observational research used case control for its study design. There were 150 women, as samples involved in the research, who were suffering from breast cancers and were registered as patients at Abdul Moeloek General Hospital and Jenderal Ahmad Yani Hospital, and other 150 women who had never been diagnosed with breast cancer. Data were collected by having a direct and telephone interview. The result showed that the number of breast cancer patients who used hormonal contraception was higher than those who use non-hormonal contraception (ratio 55%: 36%). The number of breast cancer patients who used hormonal contraception for 5 years or more was higher than those who used hormonal contraception for less than 5 years (ratio 63%: 29%). Logistic regression analysis showed that there were no associated impacts on the usage of hormonal contraception (p=0,406). There were associated impacts on the duration of hormonal contraception with breast cancers (p=0,00). In conclusion, hormonal contraceptive use increased the risk of breast cancers, and further discussion and individual riskbenefit analysis were needed to be conducted for hormonal contraception users.

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Kata kunci:

Kanker Payudara Kontrasepsi Hormonal

*) corresponding author

Yuniastini Health Polytechnic of Tanjungkarang, University of Lampung.

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ABSTRAK

Hingga akhir tahun 2020, ada 7,8 juta wanita hidup yang didiagnosis kanker payudara dalam 5 tahun terakhir, sehingga menjadikannya sebagai kanker paling umum di dunia. Salah satu faktor resiko kanker payudara adalah kontrasepsi hormonal. Tujuan penelitian ini, menganalisis faktor resiko kanker payudara yang berhubungan dengan penggunaan serta lama penggunaan kontrasepsi hormonal. Manfaat penelitian mengevaluasi penggunaan KB hormonal, serta mendapatkan data yang dapat digunakan pemerintah untuk membuat kebijakan kesehatan dalam pencegahan kanker payudara. Jenis penelitian observasi. Desain case control. Jumlah sampel sebanyak 150 wanita penderita kanker payudara yang terdaftar di RSAM dan RSAY Metro tahun 2019 serta 150 wanita tidak pernah menderita kanker payudara. Teknik pengumpulan data dokumentasi dan wawancara langsung atau pertelepon. Hasil yang didapat, penderita kanker payudara lebih banyak yang menggunakan kontrasepsi hormonal dibandingkan non hormonal (rasio 55%: 36%). Penderita kanker payudara lebih banyak yang menggunakan kontrasepsi hormonal (≥5 tahun) dibandingkan (<5 tahun) (rasio 63%: 29%). Hasil uji

⁴ University of Lampung

regresi logistik, tidak ada pengaruh penggunaan KB hormonal (p=0,406). Ada pengaruh lama pemakaian KB hormonal terhadap kejadian kanker payudara (p=0,00,). Kesimpulan, lama penggunaan kontrasepsi hormonal diindikasikan meningkatkan risiko kanker payudara, sehingga untuk pencegahan kanker payudara, perlu dilakukan diskusi dan analisis risikomanfaat secara individual bagi pengguna kontrasepsi hormonal.

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INTRODUCTION

In 2019, the population of Indonesia was 266,911,905 lives and its population growth rate in between 2015 to 2019 was 1.12. One of the most significant factors affecting population growth rate is the number of fertility, which is measured in Total Fertility Rate (TFR). Indonesia TFR in 2017 was 2.45 per woman (15-49 years old) (BKKBN, 2019). This high number resulted in lots of population issues.

One of the attempts made by the government to deal with the population issue is by family planning movement (UU No.52, 2009). The paradigm in using contraception in family planning so far is still dominated by modern contraception. The modern contraceptive prevalence rate is 83.3%.

Hormonal modern contraception is more desirable than the non-hormonal contraception (Firdy Liwang, et al, 2018). Hormonal contraception user prevalence rate in 2016, 2017, and 2018 was 92.08%, 89.7%, and 76.4% (Dinas Kesehatan Provinsi Lampung, 2020)

Recently, there has been an issue in which hormonal contraceptions increase the risk of breast cancers. The incidence of breast cancer in women in the world in 2020 was 2.3 million, and 685,000 deaths (WHO, 2021). In Indonesia, breast cancer is the most common cancer. The new cases of breast cancer in 2020 was 68,858 cases (16.6%) out of 396,914 new cancer cases, and played a big role as the highest number of cancer-causing deaths, in which there were more than 22,000 cases (Kemenkes, 2022).

In General Hospital Dr. H. Abdul Moeloek, the number of breast cancer patients in 2016 was 144 patients, in 2017 was 205 patients, and in 2018 was 206 patients (Yuniastini, Purwati, Rohayati, 2019).

American Cancer Society (2019) stated that one of the risk factors which increased relative risk (RR: 1.1-2) of invasive breast cancer in women was hormonal contraceptive use.

According to Wahidin Mugi, Ratna Djuwita, dan Asri Adisasmita (2018), oral contraceptive use in patients increases the risk of breast cancer. The longer duration of oral contraceptive use tends to have a higher risk of breast cancer. Odds ratio (OR) in patients using oral contraception for <6 years is 1.93 (95% CI 1.23 - 3.03), and OR in patients using oral contraception for 6 years 2.90 (95% CI 1.65-5.09) compared to those not using oral contraception.

The high number of breast cancer incidence, usage of hormonal contraception usage, and the issue of which hormonal contraception usage increases the risk of breast cancers is why the research is conducted.

This writing is originally written by the research team and is a development of the Leading Higher Education Applied Research at the Health Polytechnic of the Ministry of Health of the Republic of Indonesia with the title Risk Factors for Breast Cancer in Lampung.

METHODS

Sample size

Three hundred women living in Lampung, Indonesia, consisting of:

- 1) Case group: 150 women who were recorded and diagnosed with breast cancer in 2016 to July 2019 and who participated in the research
- Control group: 150 women who were not diagnosed with breast cancer and who willingly participated in the research.

Samples were recruited by using nonrandom sampling, which was purposive sampling.

Study design and data collection

This observational research used case control as its study design, and the research was conducted in Dr. H. Abdul Moeloek General Hospital, located in Dr. Rivai street, Bandar Lampung, and Jenderal Ahmad Yani Hospital, located in Jenderal Ahmad Yani street, Metro. Data were collected by data documentation and a direct and telephone interview.

Variable

Dependent variable in this research was breast cancer (0: not diagnosed with breast cancer, 1: diagnosed with breast cancer by the oncology surgeon).

Independent variables in this research were:

- 1) Usage of hormonal contraception (0: not using hormonal contraception, 1: using hormonal contraception)
- 2) Duration of hormonal contraception (0: < 5 years; 1: ≥5 years).

Ethical Clearance

This research was conducted after:

- 1) Ethics compliant number 282/EA/KEPK-TJK/iX/2019 from Ethics Commission from Poltekkes Tanjungkarang had been published.
- 2) Permit letter number 420/59646/6.2/X/2019 from the Director of Dr. H. Abdul Moeloek General Hospital, and permit letter number 890/LL-3/03/2019 from Jend. A. Yani Hospital had been received.

Instrument

The instruments used on the research were medical records and interview guides.

Data analysis

Data were analyzed using chi square and logistic regression, α =0,05.

RESULTS AND DISCUSSION

Breast cancer is the most common cancer in women, which derives from ductal epithelial (15%), and lobules (85%) (Kemenkes, 2018; Suryani Yani, 2020 and WHO, 2021).

Based on table 1, most breast cancer patients were first diagnosed breast cancer before or at the age 50 years old (96 people: 64%), only graduated from elementary school (31%), and had more than two full term pregnancies (54%).

Table 1 Characteristics of Breast Cancer Patients and Non- Breast Cancer Patients In RSUD Dr.H. Abdul Moeloek, And RSUD Jend. Ahmad Yani Metro In 2019

Ch +		Breast Can	cer Patients	Non-Breast Cancer Patients		
Characteristics		N	%	N	%	
Age						
≤ 50 YO		96	64	18	12	
>50 YO		54	36	132	88	
	Total	150	100	150	100	
Education						
Elementary School		46	31	42	28	
Middle High School		39	26	14	9	
Senior High School		44	29	35	24	
Diploma		3	2	17	11	
Undergraduate		14	9	31	21	
Postgraduate		4	3	11	7	
	Total	150	100	150	100	
Full-term pregnancies						
0		5	3	8	5	
1		15	10	12	8	
2		50	33	30	20	
>2		80	54	100	67	
	Total	150	100	150	100	

It was also demonstrated that Javenese ethnic group had the highest number of breast cancer cases (70.7%), while Lampungnese had 20.4%, and other ethnic groups had the rest number of cases.

Table 2 Cross Tabulation Between Hormonal and Nonhormonal **Contraception Usage**

Contracep- tion	Breast Cancer Patients		Non-Breast Cancer Patients		Total	
	f	(%)	f	(%)	f	(%)
Non- Hormonal	26	36	47	64	73	100
Hormonal	124	55	103	45	227	100
p= 0,00 α=0,05						

From table 2, it was known that breast cancer patients used more hormonal contraception compared to nonhormonal contraception (ratio 55%:35%). The chi square analysis shows that there is a difference in the incidence of breast cancer in a group of hormonal and non-hormonal contraceptive users (p=0,00, α =0,05).

Table 3 Cross Tabulation Between the Duration of Hormonal Contraceptive Use and Breast Cancer Incidence

The duration hormonal contracep-tion	Breast Cancer Patients		Non-Breast Cancer Patients		Total	
	f	(%)	f	(%)	f	(%)
<5 YO	33	29	82	71	115	100
≥5 YO	117	63	68	37	185	100

 $p = 0.00 \quad \alpha = 0.05$

The table above demonstrates that most breast cancer patients use hormonal contraception for ≥5 years, compared to those using contraception for <5 years (ratio 63%: 29%). The chi square analysis showed that there were significant differences in the number of breast cancer cases based on the duration of hormonal contraception usage (p=0.000; α =0.05).

Table 4 **Logistic Regression Analysis**

	В	Sig	Exp (B)
Lama KB Hormonal	1.453	0.000	4.275
Constant	910	.000	.402

Logistic regression analysis shows a great significance (p=0.000), in which the duration of contraceptive use significantly affects the incidence of breast cancer.

DISCUSSION

Most breast cancers are invasive (ACS, 2019). The most common subtype (74%) of breast cancer is positive hormonal receptor and negative HER-2 (Noone Anne-Michelle, 2017).

Common early physical sign of breast cancer is a painless lump. Sometimes breast cancer spreads to axillary lymph nodes and causes a lump or swelling, even before the breast, itself, is large enough to be palpated (ACS, 2019).

Other sign and symptoms are breast tenderness, dimple marks, orange peel changes, satellite skin nodule, skin ulceration, inflammatory changes, and mammary papilla changes, such as retraction, papillary secretion (usually sanguine), and eczematous changes (Manuaba Tjakra W:

2010; Paulsen Friedrich & Waschke Jens, 2010; Suyatno & Emir T Pasaribu, 2010; Desen Wan, 2013 dan ACS, 2019).

In this research, the youngest patient diagnosed with breast cancer was 24 years old and the oldest 77 years old. This data was in accordance to ACS (2019) in which breast cancer incidence increases as one gets older until the age at seventh decade.

The average age of breast cancer patients is 47.43 years; median 48 years; mode 42 years. This data is almost in accordance to the research by Sihombing M, Sapardin AN (2014), the majority (68.9%) of breast cancer patients aged 40 years. However, slightly different from the Indonesian Ministry of Health (2018), risk factors that are closely related to the increased incidence of breast cancer include age > 50 years.

Another risk factor for breast cancer is hormonal contraception. In this study, more women had a history of using hormonal family planning (227 people: 75.7%), this is in accordance with the data on the rate of contraceptive use in Lampung, that the number of hormonal family planning users is higher than non-hormonal family planning users (Provincial Health Office, Lampung, 2020).

More people choose hormonal contraception because of its efficiency and effectiveness in using it. Studies have shown that only one in 1,000 women every cycle got pregnant, if they drank the pills, used contraceptive skin patch, or contraceptive vaginal ring correctly (An Official Website of The United States Government,2021).

Hormonal contraceptives are associated with an increased risk of breast cancer in women. In this study, the risk factor for breast cancer is the long use of hormonal contraception.

This result is in accordance with the study by Dewi and Lucia (2013), using multiple logistic regression test (α =5%), which showed that hormonal contraception had a significant relationship with the incidence of breast cancer in Dr. Soetomo General Hospital in 2013 (p=0,028; OR=3,266).

Baeber et al (2014) study with its case-control study design and sample of 1,102 women around 20-49 years old who were diagnosed with invasive breast cancer in between 1990 to 2009, and 21,952 control cases has shown that oral contraceptive use was associated with a higher risk of breast cancer (OR 1.5; 95% CI, 1,3-1,9).

From the results of research by Andini Karisya Tri, Nur Qodir, Mutiara Budi Azhar (2017), with Chi-square test analysis it was found that there was a relationship between breast cancer in women and the use of hormonal contraception for more than five years (p=0.000), oral/pill (p=0.000) = 0.026), injection 3 months (p = 0.035), implant (p = 0.035). However, there was no relationship between the use of injection contraceptives for 1 month more than five years with the incidence of breast cancer (p = 0.465).

According to a prospective cohort study for 10.9 years in Denmark by Morch LS, et al (2017), the risk of breast cancer was higher in women using hormonal contraception than in women not using hormonal contraception, and its risk increased as the duration of contraception usage got longer; however, merely absolute increase in a small risk.

As stated by Wahidin Mugi, Ratna Djuwita, and Asri Adisasmita (2018), oral contraceptive use in patients increased the risk of breast cancer. The longer a woman use oral contraception, the higher risk of breast cancer she will get. OR in patient using oral contraception for less than 6 years was 2.90 (95% CI 1,65–5,09) compared to those not using oral contraception.

Ministry of Health Republic of Indonesia (2018) stated that long-term oral contraceptive use (in the last 10 years) increased relative risk of breast cancer (RR 1.25-1.99).

Based on PERKA BKKBN (2017), there are two types of hormonal contraceptive methods, namely 1) progestin consisting of pills, injections and implants. 2) combined-hormonal contraceptives, consisting of progestin and estrogen, the types are pills and injections.

Hormonal contraceptives are not a definite cause of breast cancer but are a risk factor. This is possible because of the way the contraceptive works, which disrupts the balance of the estrogen and progesterone in the body. Estrogen plays a role in fat deposits, where fat will cause sex hormone binding globulin (SHBG), an estrogen-binding protein to decrease, which causes the amount of estrogen circulating in the blood to increase and enter various cells in the body through its receptors. Estrogen receptors are found in the breast, so the use of hormonal contraceptives will further increase estrogen binding to receptors in the breast gland, which causes the activity of CYP17 (17 α -Hydroxylase/C17,20-lyase) and CYP 19 genes to increase and can cause impaired mRNA splicing.

Progesterone receptors are found in the mammary glands. Progesterone will bind to its receptor to form a complex progesterone receptor element (PRE) or which together with epidermal growth factor (EGF) will induce transcriptional and post-translational activity. When this process continues to occur excessively, there will be an accumulation of genetic errors in the BRCA1, BRCA2, HER2/NEU or p53 genes that cause atypical hyperplasia. With increasing time, atypical hyperplasia can lead to breast cancer.

All those studies above have shown that hormonal contraception increased breast cancer risk. In contrast, WHO (2021) stated that if all risk factors of breast cancer could be modified or controlled, it would have reduced the risk of breast cancer of only 30%. Therefore, risk benefit analysis of hormonal contraceptive use for every single user is needed to be carried out.

Hormonal contraception has several benefits, including controlling the number of pregnancies and interval between pregnancies, and reducing the risk of cancer. A study has shown that oral contraceptive use is associated with several kinds of cancer, including colorectal cancer (incidence rate ratio 0.81; 0.66-0.99), endometrium (incidence rate ratio 0.66; 0.48-0.89), ovary (incidence rate ratio 0.67; 0.50-0.89), lymphatic and hematopoietic cancer (incidence rate ratio 0.74; 0.58-0.94). The increase risk of lung cancer is only seen in women who smoke during recruitment. The increase risk of breast and cervical cancer is seen in oral contraceptive user and disappears within 5 years after stopping oral contraception, without evidence of recurrent cancer in contraceptive users. There is no evidence of a risk of developing new cancers later in life among women who have used oral contraceptives. In short, the statements of all cancer risk in oral contraceptive users are neutral in which there will be benefits of contraceptive use and decreased risks of endometrial, ovary, and colorectal cancers lasting at least thirty years (Iversen Lisa, et al., 2017).

According to Barriga Patricio, Paula Vanhauwaert, and Arnoldo Porcile (2019), hormonal contraception increased a very low risk of breast cancer, and its impact should be evaluated case by case, and it was advisable to take various effects into account. Similarly, BorgesJoão Bosco Ramos, and Renato Zocchio Torresan (2018); Romer Thomas (2019) also stated that risk benefit analysis should be individually carried out to prospective hormonal contraceptive users and final clinical decision making should be discussed based on WHO eligibility criteria.

Careful history taking and physical examination are essential components of contraceptive use counseling. In a case in which the risks increase, decisions must be made on an individual basis. Depending on the nature of the patient's underlying disease, interdisciplinary collaboration may also be necessary.

CONCLUSION AND SUGGESTIONS

The risk factor which is indicated in increasing the breast cancer risk is not simply hormonal contraception usage but the longer duration of hormonal contraception usage.

Knowing the benefits of hormonal contraception, individual risk and benefit analysis and discussion must be conducted for hormonal contraceptive users in order to prevent breast cancer.

This research data can be used for the next researcher and government to make policy and plan to prevent breast cancer.

LIMITATIONS

This study has not included the variables of hormonal contraception type and breast cancer subtype.

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