

THE USE OF HORMONAL CONTRACEPTION AND BREAST CANCER

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ABSTRACT

The prevalence of breast cancer continues to increase in the world, including in Indonesia. The main factor causing breast cancer is not yet known certainly. The research was conducted to determine the correlation between hormonal contraceptive use and the prevalence of breast cancer. The research design was case control. The sampling technique used purposive sampling. The number of samples was 85 cases and 85 controls. The case group was women with breast cancer at RSUP Dr. Sardjito Yogyakarta in 2017. The control group was a woman who checked herself in Obsgyn RSUP Dr. Sardjito in 2017 who was not breast cancer and other cancers. The data collected through secondary data was taken from medical records. The analysis was done using Chi-square test and logistic regression. There was a significant correlation between hormonal contraceptive use and breast cancer prevalence p-value = 0.004 OR = 2.378 (95% CI 1.2282-4.412). The use of hormonal contraception increased the risk of breast cancer prevalence by 2.378 times. Other risk factors were found at age 40 years old p-value = 0.002 OR = 2.641 (95% CI 1.416-4.925), age of menarche <12 years p-value = 0.004 OR = 2.868 (95% CI 1.366-6.021), obesity p-value = 0.002 OR = 2.875 (95% CI 1.434-5.765), and nullipara p-value = 0.005 OR = 4.000 (95% CI 1.402-11.410). The suggestion was that midwives and prospective acceptors/acceptors of family planning pay attention to the risk factors for hormonal contraceptive use on breast cancer prevalence and other risk factors that affected breast cancer.

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INTRODUCTION

The World Health Organization (WHO) in 2013 explained that the prevalence of cancer increased from 12.7 million cases in 2008 to 14.1 million cases in 2012.¹ According to records from the Center for Data and Information (*Pusdatin*) of the Indonesian Ministry of Health in 2015, the prevalence of breast cancer in Yogyakarta Special Region or *DIY* ranked highest in Indonesia by 2.4%.² Specific causes of breast cancer are still unknown, but according to Moningkey and Kodim there are many risk factors that are considered to have an influence on the occurrence of breast cancer, including reproductive factors, hormonal use, obesity, fat consumption, radiation, family history, and genetic factors.³ Based on the results of the analysis, it is known that age, using contraceptive pills and menopause are risk factors for breast tumors.⁴ The mechanism of breast cancer by estrogen exposure is still controversial because of breast cancer by estrogen exposure is not known with certainty because of estrogen stimulation of epithelial cell division or because it is caused by estrogen and its metabolites which directly act as mutagen.^{5,6}

Coverage of new participants of family planning or *KB* in Indonesia according to the type of contraception in 2016, the use of hormonal contraception was as much as 86.07% and non-hormonal contraception by 13.92%. Then, the coverage of participants was hormonal active as much as 81.97% and non-hormonal as much as 18.02%.⁷ The proportion of active *KB* participants by type of contraception at *DIY* in 2014, users of hormonal contraception were by 27.9% and non-hormonal contraception by 70.4%. In 2015, there was a decrease for hormonal contraceptive users to 24.6% while non-hormonal contraceptive users increased to 74%.⁸ Nationally, the use of hormonal contraception is still high compared to non-hormonal contraception. Whereas in *DIY*, the proportion of users of hormonal contraception decreases, but the prevalence of breast cancer increases. The purpose of this research was to determine the correlation between hormonal contraceptive use and the prevalence of breast cancer. The benefits of this research for midwives were useful to provide information about risk factors for hormonal contraceptive use for breast cancer prevalence so that it could provide a rational choice of contraceptive use.

METHOD

This type of research was observational analytic with a case-control design. The research was conducted at Sardjito Central General Hospital Yogyakarta (*RSUP Dr. Sardjito Yogyakarta*) on July 11th-20th 2018. The population in this research was all women who were treated at *RSUP Dr. Sardjito*. Case samples in this research were all women who were diagnosed with breast cancer in the Ward of *RSUP Dr. Sardjito* in 2017. Control samples were all female patients who were declared never or were not having breast cancer and other cancers, but were using contraception and were undergoing treatment at Obstetrics and Gynecology Polyclinic of *RSUP Dr. Sardjito* in 2017 and not using other exogenous hormonal products such as hormonal replacement therapy. The sample in this research amounted to 85 case samples and 85 control samples selected based on inclusion and exclusion criteria. The sampling technique used purposive sampling. This type of data was secondary data obtained from the patient's medical record.

The sample inclusion criteria in this research were having a complete medical record, women diagnosed with breast cancer for the case group, women who were never or were not having breast cancer and other cancers, but using contraception and were undergoing treatment at Obstetrics and Gynecology Polyclinic of *RSUP Dr. Sardjito* Yogyakarta and not using other exogenous hormonal products such as hormonal replacement therapy for the control group. The sample exclusion criteria in this research were women who used hormonal contraception for less than 4 years and women who did not use contraception. The independent variable in this research was the type of contraception. The dependent variable in this research was the prevalence of breast cancer. External variables in this research were age, the age of menarche, obesity status (BMI), and parity. Measuring results were categorized as risky and not risky. After the data was collected, the researcher entered it in the master table then the data was processed using computer software. The analysis used was univariate, bivariate and multivariate analysis. The statistical test was conducted using the Chi-Square test and logistic regression.

RESULTS

Table 1. Correlation of Some Variables with Breast Cancer Prevalence in *RSUP Dr. Sardjito* Yogyakarta in 2017

No.	Characteristic	Cases		Control		Total		p-value	OR	CI (95%)
		n	%	n	%	n	%			
1.	Contraception Type									
	Hormonal	48	56.5	30	35.3	78	45.9	0.004	2.378	1.282-4.412
Non-hormonal	37	43.5	55	64.7	92	54.1				
2.	Age									
	≥ 40 years old	48	56.5	28	32.9	76	44.7	0.002	2.641	1.416-4.925
< 40 years old	37	43.5	57	67.1	94	55.3				
3.	Menarche Age									
	< 12 years old	29	34.1	13	15.3	42	24.7	0.004	2.868	1.366-6.021
≥ 12 years old	56	65.9	72	84.7	128	75.3				
4.	Obesity Status									
	IMT ≥25	34	40	16	18.8	50	29.4	0.002	2.875	1.434-5.765
IMT < 25	51	60	69	81.2	120	70.6				
5.	Parity									
	Nullipara	17	20	5	5.9	22	12.9	0.005	4.000	1.402-11.410
No Nullipara	68	80	80	94.1	148	87.1				
	Total	85	100	85	100	170	100			

Level of Exposure to Hormonal Contraceptive Use with Breast Cancer Prevalence

Table 1 showed that the level of hormonal contraceptive use (risk) in women who had breast cancer (cases) was higher compared to women who did not have breast cancer (56.5% > 35.3%). Based on Table 1 also was known the exposure to external variables that affected the prevalence of breast cancer. The proportion of women aged ≥40 years old (at risk) in breast cancer patients was higher compared to women who did not have breast cancer (controls) (56.5% > 32.9%). The proportion of women who experienced menarche at the age of <12 years old (at risk) in breast cancer patients was higher compared to women who did not have breast cancer (34.1% > 15.3%). The proportion of women who had BMI ≥25 (risk) in breast cancer patients was higher than women without breast cancer (40% > 18.8%). The proportion of nullipara women (at risk) in breast cancer patients is higher compared to women who do not have breast cancer (20% > 5.9%).

Correlation between Hormonal Contraceptive Use and Breast Cancer Prevalence and Correlation between Age, Age of Menarche, Obesity, and Parity with the Prevalence of Breast Cancer

Based on the results of statistical tests, it was found that there was a significant correlation between the use of hormonal contraception and the prevalence of breast cancer in women p-value = 0.004 < 0.05; CI = 95% (1.282-4.412). Women who use hormonal contraception had a 2.37 times chance of developing breast cancer when compared to women who use non-hormonal contraception.

Based on the results of statistical tests, it was found that there was a significant correlation between age ≥40 years old with the prevalence of breast cancer p-value = 0.002 < 0.05; CI = 95% (1.416-4.925). Women aged ≥40 years have 2.641 times the chance of developing breast cancer when compared to

women aged <40 years old. There was a significant correlation between menarche age <12 years old with breast cancer prevalence in women p-value = 0.004 <0.05; CI = 95% (1.366-6.021). Women who experienced menarche at the age of <12 years old have 2.868 times the chance of developing breast cancer than women who were in menarche at age ≥12 years old. There was a significant correlation between obesity (BMI ≥25) with the prevalence of breast cancer in women p-value = 0.002 <0.05; CI = 95% (1.434-5.765). Obese women (BMI ≥25) had a risk of 2.875 times having breast cancer than women who were not obese (BMI <25). There was a significant correlation between nullipara and breast cancer prevalence in women p-value = 0.005 <0.05; CI = 95% (1.402-11.410). Nullipara women had a risk of 4 times breast cancer compared to women who were not nullipara (primipara, multipara).

Factors that Most Influence the Prevalence of Breast Cancer

Based on the results of the research obtained the most influential factors with the prevalence of breast cancer in women in *RSUP Dr. Sardjito* Yogyakarta could be seen in table 2.

Table 2. Results of Analysis of the Factors that Most Affect Breast Cancer Prevalence in *RSUP Dr. Sardjito* Yogyakarta

Variable	p-value	Exp (B)	95% CI	
			Lower	Upper
Contraception Type	0,004	2.500	1.244	5.025
Age	0,002	3.448	1.697	7.004
Menarche Age	0.004	3.065	1.313	7.155
Obesity Status (BMI)	0,002	2.650	1.206	5.822
Parity	0,005	4.238	1.322	13.586

Based on Table 2, it was found that parity was the most significantly related factor with the prevalence of breast cancer in women. Nullipara women had a chance of 4,238 times for breast cancer when compared to women who were not nullipara (primipara, multipara).

DISCUSSION

Correlation between Types of Contraception and Breast Cancer Prevalence

Most hormonal contraceptives contained estrogen and synthetic gestagen, but there were also hormonal contraceptives that contained only gestagen.⁹ Estrogen could cause cancer in two ways. The first, acting as "mitogen"; That was, it stimulated breast tissue to increase cell division (mitosis). This sometimes resulted in cancer due to errors in cell division (mutations). Second, certain estrogen metabolism also acted as a carcinogen or genotoxins, by directly damaging DNA, causing cancer cells to form. The effects of estrogen were included in the model. The results showed that the presence of extra estrogen increased the risk of developing breast cancer.^{10,11}

The results of this research showed that the proportion of women using hormonal contraception was 48 women (56.5%) had breast cancer. The results of the chi-square test showed that the p-value = 0.004 with OR 2.378 (95% CI 1.2282-4.412), which meant women who used hormonal contraception had a 2.37 times chance of developing breast cancer compared with women using non-hormonal

contraception. The results of this research were supported by a previous research by Soroush et al (2016) which stated that the length of use of hormonal contraception which could increase 1.52 times the risk of breast cancer prevalence had begun since the use of more than 4 years. This was because after 4 years of use the amount of estrogen would accumulate and multiply.¹² Another research that supported this research was a cohort research conducted by Gabrick, reporting that oral contraceptive use was associated with a significant increase in cancer risk (RR = 3.3).¹³

Changes that occur in the body during hormonal contraceptive use were that all organs of a woman's body that were under the influence of sex hormones would naturally be influenced by hormonal contraception. In these organs certain changes would occur, the occurrence of which depended on the dosage, type of hormone, and duration of use.¹⁴

Correlation of Age with Breast Cancer Prevalence

According to Cancer Research of UK, over time cells in our body could become damaged. As we were aging, this damage accumulated, and could cause cancer. After cells were damaged, they might begin to grow and multiply more than usual, forming a growth called a tumor. This was the beginning of cancer. The more a woman ages, the greater the likelihood of developing breast cancer.

The results of this research indicated that the proportion of women aged ≥ 40 years old was 48 women (56.5%) had breast cancer. The results of the chi-square test showed that the p-value = 0.002 with OR 2.641 (95% CI 1.416 - 4.925), which meant that women aged 40 years old had a chance of 2.641 times for suffering from breast cancer when compared with women aged < 40 years old. The results of this research were supported by a previous research by Sihombing (2014) reporting that the risk of tumor/breast cancer increased with age, the possibility of developing breast cancer at the age of over 40 years old was higher.¹³ Another research that supported the results of this research was Israel A, Rondonuwu, Haroen H, et al (2016) which showed that the distribution of breast cancer patients according to age was obtained data that the highest frequency in the age group 40-49 years was 61 cases (43%).¹⁴

Correlation of Menarche's Age with Breast Cancer Prevalence

The age of menarche that was too early in women, which was less than 12 years caused exposure to the body's estrogen hormone to become faster. Estrogen hormones could trigger abnormal cell growth in certain parts of the body.⁵ When a woman was having early menstruation, the time span between breast development and pregnancy for the first month was usually longer than that of women who were having menstruation later. During this time, breast tissue was immature, more active and susceptible to hormonal influences.¹⁵

The results of this research indicated that the proportion of women who experienced menarche at age < 12 years old as many as 29 (34.1%) had breast cancer. The results of the chi-square test showed that the p-value = 0.004 with OR 2.868 (CI 95% 1.366 - 6.201), which meant that women who experience menarche at the age of < 12 years old have a 2.868 times chance of developing breast cancer when compared to women who menarche at age ≥ 12 years old.

The results of this research were supported by a previous research by Butler et al (2002) in Rasjidi (2010) that in younger (< 12 years old) in menarche

there was an increased risk of breast cancer (OR = 1.5).¹³ Other studies that supported the results of this research were research by Setiowati DAI, Eddy HT, and Roostantia IS (2016) which showed that the age of early menarche in the case group was more than the control group. Out of the 70 women who had early menarche, 39 people (56%) had breast cancer and 31 (44%) people did not have breast cancer.¹⁶

Correlation of Obesity (BMI) with Breast Cancer Prevalence

Fat tissue was a major place in estrogen production. Estrogen was stored in adipose tissue (fat tissue). Women with excess body weight and a high BMI had high estrogen levels. Obesity was also related to the low number of SHBG which played a role in increasing the amount of estradiol.¹³ Storage of excess fat would cause estrogen synthesis to increase so that exposure to estrogen was more and increased breast cell proliferation.^{12,17}

The results of this research indicated that the proportion of obese women (BMI ≥ 25) as many as 34 (40%) had breast cancer. The chi-square test results showed that p-value = 0.002 with OR 2.875 (CI 95% 1.434 - 5.765), which meant that obese women (BMI ≥ 25) had a 2.875 times chance of developing breast cancer when compared to women who were not obese (BMI < 25). The results of this research were supported by previous studies by Pamela J and Goodwin (2016) which say that obesity had been associated with an increased risk of most cancers and poor breast cancer outcomes.¹⁸

Correlation between Parity with Breast Cancer Prevalence

Nullipara could increase the risk of developing breast cancer because it was longer exposed to estrogen than women who had children. There was a higher level of estrogen in women developing breast cancer risk than women who did not have breast cancer. High estrogen hormone levels during a woman's reproductive period, especially if not interspersed with hormonal changes in pregnancy, seem to increase the chances of growth of cells that had been genetically damaged and caused cancer.^{13,19}

The results of this research indicated that the proportion of women with nullipara as many as 17 (20%) had breast cancer. The results of the chi-square test showed that the p-value = 0.005 with OR 4,000 (CI 95% 1.402 - 11.410), which meant that women who were nullipara have four times the chance of developing breast cancer when compared to women who were not nullipara. The results of this research were in line with the research by Cici Priyatin, Elisa Ulfiana, and Sri Sumarni (2013) which showed that OR > 1 = 4.353 which could increase risk, this meant that parity risks increasing the prevalence of breast cancer.²⁰ Other studies that were in line with the results of the research was a research by Desiyani Nani (2009) who said that based on the Chi-square test p = 0.010 (p \leq 0.05) was obtained, it showed that the number of children was related to the prevalence of breast cancer in menopausal female respondents.²¹

Most Influential Factor of Breast Cancer Prevalence

The most influential risk factor for breast cancer was parity, namely nullipara. The results of this research were supported by Desiyani Nani's research

which stated that the factors most at risk for the prevalence of breast cancer in women were the number of children and family history of cancer.²¹ Nullipara could increase the risk of developing breast cancer because it was longer exposed to estrogen than women who have child. High estrogen hormone levels during a woman's reproductive period, if not punctuated by hormonal changes in pregnancy, increased the chances of growth of cells that had been genetically damaged and cause cancer.^{13,19}

CONCLUSION

Based on the results of research that had been done, the researchers conclude, the level of exposure to hormonal contraceptive use in women who had breast cancer was higher than women who did not have breast cancer, which was 56.5%. The use of hormonal contraception was significantly correlated with the prevalence of breast cancer with OR 2.3378 95% CI (1.282-4.412). Other factors that were significantly correlated with the prevalence of breast cancer were age ≥ 40 years OR 2.641 95% CI (1.416-4.925), age < 12 years menarche OR 2.868 95% CI (1.366-6.021), obesity (BMI ≥ 25) OR 2.875 CI 95% (1.434-5.765), and nullipara OR 4 95% CI (1.402-11.410). The factors that most influenced the prevalence of breast cancer in women in *RSUP Dr. Sardjito* Yogyakarta was parity namely nullipara.

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