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The Association Between Number of Parity and Incidence of Woman Breast Cancer at Dr. Cipto Mangunkusumo National General hospital Jakarta A Cross Sectional Study

Endah Zuraidah[1], Primadea Kharismarini[2]*, Sarah Qanita Edwar[2] and Supri Irianti Handayani[1]

[1]Departemen Patologi Anatomik, Fakultas Kedokteran Universitas Indonesia– Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo, Jakarta, Indonesia

[2]Program Studi Pendidikan Dokter, Fakultas Kedokteran Universitas Indonesia

ABSTRACT

Background: Breast cancer remains as one of the many types of cancer that is commonly faced in all countries, including Indonesia. To this day, the leading cause of breast cancer has not yet been found but there are evidences of the probability on risk factors. One of the risk factors that may be related to breast cancer is the number of parity. This study analyzes the association between number of parity and incidence of breast cancer in woman at Dr. Cipto Mangunkusumo National General Hospital Jakarta in 2010 – 2014.

Method: The study design is a cross-sectional study with 123 cases which were obtained using random sampling. The data were acquired from the patient's medical records based on their anatomical pathology examination results and were analyzed using Fisher test.

Results: The number of parity have no significant association against to breast cancer statistically in woman at Dr. Cipto Mangunkusumo National General HospitalJakarta in 2010 – 2014 (p>0,05).

Conclusion: Statistically the number of parity have no significant affect to women breast cancer incidence at Dr. Cipto Mangunkusumo Hospital Jakarta. Further research is needed regarding risk factors that have significant affect for the incidence of breast cancer. This can be realized by using a case-control study design and combining other risk factors, such as age at first delivery. In addition, further research can also consider the type and stage of breast cancer.

***Corresponding author**

Primadea Kharismarini, Program Studi Pendidikan Dokter, Fakultas Kedokteran Universitas Indonesia.

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Introduction

Breast cancer is one of the most common types of cancer faced by the world community, including in Indonesia. All over the world, awareness of the dangers of breast cancer has become a necessity so that October is designated as Breast Cancer Awareness Month. In every year, cases of patients diagnosed with breast cancer increase by 1.38 million cases and causes the death of 458,000 people [1]. In 2010, breast cancer became one of the highest types of cancer in Indonesia, followed by cervical cancer with a total of 12,014 patients (28.7%). This figure differs greatly from the prevalence outside Asia related to race. In 2012, breast cancer was very common in female patients, with 1.7 million new cases occurring worldwide. Breast cancer rank is a second most common in the world [2-4].

Based on the 2011 Cancer Registry Agency (Badan Registrasi Kanker / BRK) report, 4729 cases of breast cancer were found as primary tumors, while male breast cancer patients were found in 47 cases [5,6]. Based on Basic Health Research (RISKESDAS) data (2013), it is estimated that there 347,792 cases of cancer in Indonesia with 61,682 cases of breast cancer in women. These two survey results prove that breast cancer cases are quite high in Indonesia. However, the etiology of breast cancer is uncertain and only various risk factors may play a role. This causes breast cancer is still difficult to prevent.

By tracing data from 20 countries with the highest cases of breast cancer, it is known that breast cancer can be prevented by modifying external risk factors, such as not drinking alcohol, being active in sports and maintaining body weight [2]. Until 2014, risk factors were thought to influence the incidence of breast cancer is age, age at first birth, race, family history, number of parity and hormones of the patient [2]. Number of parity is the number of children born with each birth followed by a gestation period of more than 24 weeks, regardless of whether the baby was born alive or dead [7,8]. It is known that a high parity number can increase the risk of cervical cancer incidence. However, based

on case studies, the patient's risk of suffering from breast cancer actually decreases with an increase in the number of children born [9,10]. Generally, the number of children born with more than 3 children reduces the risk of breast cancer (30%), when compared to women who do not have children (nullipara) [11,12].

In this study, we wanted to know whether the number of children born was related to the incidence of women breast cancer at RSUPN Dr. Cipto Mangunkusumo Jakarta from 2010 to 2014.

Literature Review

Breast cancer is an increase the growth of abnormal breast epithelial cells. The location of breast cancer originate from two types of epithelial cells, namely lobule cells and mammary duct cells. Breast cancer can be caused by internal factors, namely genetic mutations that occur in hereditary (5-10%) or obtained from external factors (85-90%). Examples of inherited gene mutations for breast cancer are the BRCA genes (BRCA1 and BRCA2), p53 and CHEK2 which were found to be genes that suppress the growth of breast epithelial cells so that abnormalities do not occur. The occurrence of acquired gene mutations (acquired gene mutations) may be caused by radiation or chemicals that can induce the formation of cancer cells. Breast cancer can also occur sporadically related to hormonal balance in sex, age at menarche and menopause, reproductive history, lactation and exogenous estrogen. However, the mechanism is still not known with certainty [13,14].

Approximately 95% of breast cancer is Adenocarcinoma type, which is classified into Carcinoma in situ and Invasive carcinoma. Carcinoma in situ is a proliferation of ductal and lobular neoplasms confined to the basement membrane, whereas invasive carcinoma is a carcinoma that penetrates from the basement membrane into the stroma and generally forms a palpable mass. Histologically, carcinoma in situ is divided into two, namely ductal carcinoma in situ or intraductal carcinoma (DCIS, 80%) and lobular carcinoma in situ (20%), while invasive carcinoma is divided into no-special type (NST, ductal) invasive carcinoma. (79%), invasive lobular carcinoma (10%), invasive tubular carcinoma (6%), invasive mucinous carcinoma (colloid, 2%), medullary carcinoma (2%), papillary carcinoma (1%) and metaplastic carcinoma (<1 %) [14].

The exact cause of breast cancer is still not fully understood, but there are three things that are thought to influence the development of breast cancer, namely genetic changes, hormonal influences and the environment. Approximately 10% of breast cancer occurs due to oncogenes inherited from their parents [14-17].

Like other cancers, mutations in oncogenes and tumor suppressor genes in breast epithelial cells underlie oncogenesis. Several genes Changes in gene expression can divide breast cancer into 4 molecular subtypes, namely luminal A (estrogen receptor positive, HER2/NEU negative), luminal B (estrogen receptor positive, HER2/NEU expression increased), HER2/NEU positive (HER2/NEU overexpression, estrogen receptor negative), and basal-like (estrogen receptor and HER2/NEU negative). These subtypes are associated with different manifestations and different management. In the HER2/NEU gene, there is a change from a normal gene to a proto-oncogene due to increased gene expression. Because these genes aid in the process of epidermal cell growth, the prognosis of patients with these oncogenes is not easy to predict. Amplification of the MYC and RAS genes as well as mutations of the RB and TP53 genes have also been reported in some cases of breast cancer [14-17].

The histological appearance of carcinoma and various precursor lesions is a manifestation of the complex genetic and epigenetic changes that promote carcinogenesis. Cell populations undergoing genetic and epigenetic alterations required for carcinogenesis augment the progression of morphologically visible breast lesions. The initial changes that occur are proliferative changes, which can occur due to reduced growth inhibitory signals, increased pro-growth signals or reduced apoptosis [15,16].

Risk Factors of Breast Cancer

It has been reported that various types of risk factors can influence the incidence of breast cancer, namely age, age at marriage, number of parity, age at menopause, number of abortions, age of first birth over 30 years, duration of breastfeeding, obesity related to body mass index, oral contraceptives, hormonal therapy, consumption of alcohol, cigarettes, education, and family history [9]. All types of risk factors mentioned above are related to the patient's hormonal status and its influence on the estrogen and progesterone hormone receptor genes. This is what causes the incidence of breast cancer to occur more frequently in women, especially during pregnancy. Based on research with case-control studies in Morocco it was reported that there were 252 cases of breast cancer in women who had given birth to > 3 children with a control of 314 patients, while women who had given birth to 1-2 children were found in 46 cases of breast cancer with a control of 33 patients [11]. In this study, we will discuss more about the number of children born and its effect on the incidence of breast cancer. In addition, there is also a cross-sectional study which states that parity is a risk factor for breast cancer (p=0.004) [12].

Number of parity is the number of children born with each birth followed by a gestation period of more than 24 weeks. Based on the definition, the number of parities is divided into four, namely nullipara (not giving birth), primipara (1 child), multipara (> 1 child), and grand multipara (> 5 children) [13-19]. The number of children born is related to the loss of influence Estrogen and progesterone hormones in the female reproductive cycle during pregnancy. This can be regarded as a protective mechanism against genetic mutations that can occur in the breast epithelium [18].

Initially, breast epithelial cells in women who have not given birth have an immature status that facilitates cell proliferation. If the genetic code in the epithelial cells has undergone genetic mutations (ER/PR genes, BRCA1 or BRCA2), these cells will also proliferate so that more and more breast epithelial cells have mutations in these women. However, this possibility can decrease if the woman enters pregnancy. During pregnancy, the reproductive cycle in women will stop temporarily (break). Exposure to these reduced reproductive hormones reduces the risk of breast cancer by 30% in women with multipara status [19]. A study also shows that women who give birth to 5 children experience a 50% reduced risk of breast cancer. The lower the woman's risk of developing breast cancer. Conversely, if a woman decides not to have children (nullipara), the woman's risk of developing breast cancer increases. This increased risk also depends on what other risk factors the woman has.

Diagnosis

Diagnosis of breast cancer consists of anamnesis, physical examination, and supporting examinations. The anamnesis taken is based on the main complaint and additional complaints. The main complaints are lumps in the breast, speed of breast development accompanied/without pain, nipple discharge, nipple retraction, crusting, peau d'orange, ulceration, venectation, axillary lumps

and arm edema, and additional complaints, namely pain in the vertebrae or femur and tightness in the chest. After anamnesis, then a physical examination is carried out by checking vital signs and examining the breasts [20].

Breast examination can be carried out with three screening measures, namely Breast Self-Examination (BSE), Clinical Breast Examination (SADANIS), and mammography screening. Investigations that can be carried out include routine blood chemistry and blood tests according to stage, tumor markers, radiology such as breast ultrasound and mammography, chest X-ray and abdominal ultrasound, CT scan and PET CT scan, FNAB biopsy, immunohistochemical and histopathological examination as a gold standard [21].

Method

The study design used in this research was a cross-sectional study, to determine whether there was association between the number of parity factor and the incidence of breast cancer in women at RSUPN Dr. Cipto Mangunkusumo in 2010 – 2014.

The inclusion criteria for study subjects were female patients with a clinical diagnosis of suspected breast cancer and had histopathological examination with suspected breast cancer in RSUPN Dr. Cipto Mangunkusumo in 2010 – 2014. Exclusion criteria for study subjects were male sex, did not perform a histopathological examination for suspected breast cancer and data on the number of children born were not recorded on the medical record form of RSUPN Dr. Cipto Mangunkusumo.
The number of parity data will be analyzed using the Chi-Square test with an alternative to the Cell Merger test and Fisher's test to see the p value taking into account the conditions for hypothesis testing. If the p value < 0.05, there is a significant relationship between the number of parities and the incidence of breast cancer, whereas if the p value > 0.05, there is no significant relationship between the number of parities and the incidence of breast cancer.

Result

Research Variable Characteristic

Sample in this study was 123 people obtained from the archives of Anatomical Pathology Department FKUI – RSUPN Dr. Cipto Mangunkusumo with the search continued to the Central Medical Record Unit and the Department of Surgery, Oncology division of the RSCM. The sample of this study met the inclusion criteria and exceeded the minimum sample size of this study, thus obtaining a frequency distribution for age at diagnosis, age at marriage, and age at first delivery in patients who had histopathological examination with suspicion of breast cancer.

The study sample consisted of 105 patients (85.36%) with positive histopathological examination results for breast cancer and 18 patients (14.63%) negative. The characteristics of the study subjects can be seen in table 1. From the sample owned, it was found that in breast cancer patients, the highest frequency of age at diagnosis was in the age group of 41 – 50 years (32.5%). The highest frequency of marriage age in breast cancer patients was found in age < 25 years (52.6%). The highest frequency of age at first delivery was in breast cancer patients with age <25 years (57.4%).

Table 1: Characteristic of Research Subject at Dr. Cipto Mangunkusumo National Hospital in 2010 – 2014

Subject Characteristic	Histopathologic Findings			
	Positive (n=105)		Negative (n=18)	
	N	%	n	%
Diagnosed Aged				
< 21 y.o	1	0,8%	0	0
21 – 30 y.o	7	5,69%	1	0,8%
31 – 40 y.o	25	20,3%	2	1,62%
41 – 50 y.o	40	32,5%	2	1,62%
51 – 60 y.o	35	28,4%	9	7,31%
> 61 y.o	15	12,1%	4	3,25%
Married Age				
< 25 y.o	10	52,6%	3	15,7%
≥ 25 y.o	4	21,1%	2	10,5%
Age of first childbirth				
< 25 y.o	31	57,4%	5	9,3%
≥ 25 y.o	15	27,7%	3	5,5%

Characteristics of Respondents Total Parity

The characteristics of parities number in this study are presented in table 2. It can be seen that categories 1 – 2 children have the highest frequency when compared to other categories with a total of 69 cases (56.1%).

Table 2: The Frequency of Parity Number Based on Histopathological Examination

Parity of Number	Histopathologic Findings			
	Positive		Negative	
	N	%	n	%
Nullipara (No Child)	12	9,8%	3	2,4%
1 – 2 of child	57	46,3%	12	9,7%
≥ 3 of child	36	29,3%	3	2,4%

The Association between Number of Parity and the Incidence of Breast Cancer

In table 3, the results of the hypothesis test for the number of parity on the incidence of breast cancer at RSUPN Dr. Cipto Mangunkusumo in 2010 - 2014. In Fisher's test, the p value obtained was 0.703. The value of p> 0.05 means that statistically there is no significant relationship between the number of parities and the incidence of breast cancer. The prevalence ratio of this study was 0.0041 with a Confidence Interval value of 0.907 – 1.14.

Table 3: Hypothesis Testing of Association Between Number of Parity and the Incidence of Breast Cancer

Number of Parity	Diagnosis				
	Breast Cancer (+)		Breast Cancer (-)		P value
	N	%	N	%	
Nullipara (No Child)	12	81,2%	3	18,8%	
Multipara (≥1 Child)	93	86,0%	15	14,0%	
Total	105	85,4%	18	14,6%	

Discussion

This research was conducted to all suspected breast cancer patients at RSUPN Dr. Cipto Mangunkusumo, who has histopathological examinations in 2010 – 2014. From 2293 data used as the study population, 123 samples were obtained by random sampling. The first data obtained from this study sample is the age at diagnosis which is grouped based on the average distribution of the age at patients diagnosis. Based on the results, it was found that the greatest frequency for the age category in breast cancer patients was the age group of 41-50 years (32.5%). This age group is still included in the reproductive age, both in terms of active reproduction and work.

According to Hall et al's study conducted in Carolina regarding African-Americans and Caucasians, it was stated that African-Americans had the highest average age <45 years and decreased incidence after age 50 when compared to Caucasian women. 10 Both studies This shows that although age is a risk factor for the incidence of breast cancer, race also affects the amount of risk that patients have, so further consideration is needed if they pay attention to the age factor alone because it is not necessarily applicable in Indonesia. The number of confounding factors caused the age factor not to be analyzed in this study but age data was used as the basic data to see the distribution of the samples obtained based on the results of histopathological examination. Further investigation was carried out on samples related to reproductive factors, namely age at marriage, age at first birth and number of parities [22].

In this study, only 19 data the age of marriage were included in the medical records owned by the sample of this study. In breast cancer patients, the greatest frequency in the marriage age category was in the age group <25 years (52.6%). In patients with negative histopathological examination results, the greatest frequency in the category of married age was also in the age group <25 years (15.7%). Marriage age is a risk factor for breast cancer which is included as a reproductive factor. Although, the factor of marriage age is not a major factor in increasing the risk of breast cancer because there are many confounding factors that can play a role and have a higher significance than the factor of marriage age. In a study by Balasubramaniam et al., it was concluded that women who married after the age of 21 had a 2.5 times greater risk of developing breast cancer. This data on the age of marriage is one of the factors related to the characteristics of the second sample, namely the age at first childbirth.

Based on the results, there were only 54 data on the age of first childbirth in the medical record data for this study sample (n = 123). In breast cancer patients, the highest age at first birth was in the <25 years age group, namely 31 people (57.4%). In patients with negative histopathological examination results, the highest frequency was in the group of patients with birth age <25 years, namely 3 people (9.3%). Data on age at first birth were not analyzed in this study because the data obtained did not meet the minimum sample size for that category. Although not all patient data includes data on the age of first delivery, this data is one of the factors related to the risk factors discussed in this study, namely the number of parity factors. This is related to the similarities that underlie the emergence of the protective effects of these two factors, namely the existence of a resting period during pregnancy which causes a decrease in exposure time to the hormone estrogen.

The number of parity is the number of children a woman has. The number of children one has means the number of births experienced after passing through the pregnancy. In nulliparous women, the risk increases significantly (30%). 13 This happens because patients who have no history of childbirth are considered to have never experienced a pregnancy ≥ 36 weeks. The period of pregnancy is key in increasing the risk of breast cancer because when conception occurs, the menstrual cycle in these women will stop temporarily. This rest period will decrease the woman's estrogen exposure so that the woman's risk of developing breast cancer will decrease [11-26].

Stopped menstrual cycles provide less exposure time to the hormone estrogen than women who do not have children. This happens because estrogen is a hormone that can trigger the formation of cancer cells by using estrogen receptors or

during estrogen metabolism. Both of these ways will induce the proliferation of breast epithelial cells. Proliferating cells have the opportunity to experience genetic mutations when replicating DNA so that when cells mutate, these cells can multiply with the help of induction from the hormone estrogen. However, it is said that the gestation period has a double effect. The double effect in question is that when a child is born, the risk will increase drastically within 5 years, but will also decrease slowly in the long term [25,26]. This drastic increase is again caused by an increase in estrogen levels after birth.

Although the factors that influence the risk of breast cancer vary widely and are not limited to reproductive factors, the aging population and low fertility rates suggest that women have an important role in the incidence of breast cancer [26,27]. This supports the theory of related reproductive factors. with breast cancer, especially on the number of children they have. However, parity does not always have the desired effect [28]. The protective effect that patients have ≥ 5 children will be related to the effect caused by the increase in the number of births itself, namely the increased risk of cardiovascular disease and ischemic disease to increased mortality [29,30].

However, the results of hypothesis testing from this study stated that there was no significant relationship between the number of parities and the incidence of breast cancer in the study population. This can be seen from the Fisher test results which produce a p value of 0.703 which exceeds the p value limit of 0.05. The interpretation of the results of this statistical test is that parity does not affect the incidence of breast cancer and is not a risk factor in this population. However, these results are only statistical results. There are many publications that support the theory that the factor number of parity is significantly associated with the incidence of breast cancer. In addition to linking it to hormonal factors, parity numbers are also associated with age and breast cancer subtypes [31].

An article review also introduces the term Parity Associated Breast Cancer (PABC) which can be interpreted as breast cancer associated with parity [32]. Breast cancer is breast cancer that is diagnosed within 2 – 5 years after normal birth [33,34]. PABC is generally shows worse symptoms, is not well differentiated and is at a high stage with less time to progress [35]. From this article it was concluded that PABC is more often associated with triple negative breast cancer (TNBC) [32-36]. Another study conducted by Shinde et al also stated the same thing, namely an increase in the number of parities associated with TNBC [37]. In Indonesia, to be precise at H. Adam Malik General Hospital, Medan, a study was conducted of 82 people to determine risk factors for breast cancer [12]. In this study it was said that there was a strong relationship significant relationship between parity and the incidence of breast cancer (p=0.004). Research conducted by Ardiana et al also stated that the number of parity affects the incidence of breast cancer [38].

However, various other studies have provided inconsistent results because there is no specific breast cancer risk assessment method that can be used by the general public [39,40]. In 2016, a study in Hong Kong released an assessment model for breast cancer risk in women in Hong Kong. This is realized by adding modifiable factors, such as sleep quality. With that, the research becomes more accurate. The results of this study also show that the risk of breast cancer in women in Hong Kong is not related to the number of children they have (p=0.137) [41].

In addition, a study conducted in Singapore stated that the risk factors possessed by women with suspected breast cancer had different levels for each race. This study compared the reproductive risk factors of Chinese, Malay and Indian patients [39]. Based on this study, it was found that the effect of multiparous breast cancer that occurs during the premenopausal period differs in each ethnic group. An increase in the number of parities reduces the risk of breast cancer in the Malay race, but not in the Chinese and Indian races [39]. Malay race women who have one child have twice the risk of breast cancer than Chinese women who have one child. This risk then disappears after giving birth to ≥ 3 children [40]. This study proves that the number of parity factors is not necessarily a risk factor that significantly influences the incidence of breast cancer in certain populations with different races.

Based on the discussion above, it was concluded that in this study population, the number of parity did not have a significant relationship with the incidence of breast cancer (p=0.703). Although less significant when compared with other risk factors, parity remains a risk factor for breast cancer. This is supported by several journals that have been mentioned previously.

In collecting medical record data, it is difficult to find data on suspected breast cancer patients with negative histopathological examination results because the data has been lost or there is no clear information. This causes the number of patients who become cases is quite high when compared to controls. This study uses a cross-sectional study that is used to determine the relationship of a variable.

This research is expected to be the basic data for further research to examine the same risk, namely the number of parity. However, this research can also be an opening in examining other risk factors such as lifestyle, stress, and obesity for breast cancer in Indonesia. This study is also based on the results of histopathological examination in patients with suspected breast cancer. Histopathological examination is a standard breast cancer examination so that it becomes an advantage of this study.

Conclusion

In breast cancer patients at RSUPN Dr. Cipto Mangunkusumo 2010 – 2014, the age range diagnosed with the highest frequency was in the age range 41 – 50 years (32.5%), the highest frequency of first marriage was in the age group <25 years (52.6%) and the frequency of first age the highest birth rate was in the age group <25 years (57.4%). Statistically, the number of parity did not have a significant association with the incidence of breast cancer in women at RSUPN Dr. Cipto Mangunkusumo Jakarta in 2010 – 2014 (p>0.05).

Suggestion

Further research is needed regarding risk factors that have significant for the incidence of breast cancer. This can be realized by using a case-control study design and combining other risk factors, such as age at first delivery. In addition, further research can also consider the type and stage of breast cancer.

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