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RESEARCH ARTICLE

Correlation Between Age at Menarche and Breast Cancer Incidence in Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia (2010-2014)

Endah Zuraidah[1], Nur Fitrianingsih Pujiano Agatha[2], Sarah Qanita Edwar[2], Supri Irianti Handayani[1]

[1]Anatomical Pathology Department, Faculty of Medicine, University of Indonesia – Dr. Cipto Mangunkusumo National General Hospital Jakarta, Indonesia. [2]Medical Education Study Program, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia.

Abstract

Background and objective: Breast cancer is one of the most prevalent malignancies among Indonesian women. Numerous risk factors can increase the likelihood of developing breast cancer, and hormonal factors appear to play a significant role in many cases. This research aimed to determine the relationship between age at menarche and breast cancer incidence in Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia, from 2010 to 2014. **Materials and Methods:** This retrospective cross-sectional study utilized a random sampling technique with a sample size of 98 participants. Data were collected from the Archive Unit of Anatomical Pathology of the Faculty of Medicine, University of Indonesia (FMUI), with further investigation in the Medical Record Unit and Medical Department of Surgery at Dr. Cipto Mangunkusumo National General Hospital, Jakarta. Data analysis was performed using the chi-square test and Fisher's exact test. **Results:** There was no statistically significant association between age at menarche and breast cancer incidence at Dr. Cipto Mangunkusumo National General Hospital, Jakarta, during the study period ($p > 0.05$). The results also indicated that the 40-49 year age group had the highest number of breast cancer cases compared to other age groups. Furthermore, an age at first menstruation of over 12 years was associated with the highest frequency of breast cancer cases in the study population. **Conclusion:** The age at first menstruation did not statistically significantly affect breast cancer incidence at Dr. Cipto Mangunkusumo Hospital, Jakarta, during the period of 2010-2014. However, further research utilizing different study designs and larger sample sizes is recommended.

Keywords: Age at first menache- Breast cancer- Hormonal factor

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Introduction

Cancer is a common non-communicating disease in Indonesia. According to Indonesia Basic Health Research in 2013, this disease was on the third place with the prevalence of 1.4 per 1000 populations or equal to 330 patients [1]. Breast cancer is one of the most frequent type. In 2012, there were 1.7 million females who diagnosed as having breast cancer. Both incidence and mortality are also increasing more than 20% and 14% respectively since 2008. Besides, International Agency for Research on Cancer stated that 1 of 4 women are suffering from this worldwide disease [2]. In Indonesia, breast cancer was considered as a high prevalence disease in 2013, namely 0.5%. As stated in Indonesia Health Profile published by Indonesia Health Department in 2008, the main 10 cancer diseases in hospital were similar since 2004-2008 with the three highest were breast, cervical, and liver cancer. During the time, breast cancer reported cases were increasing each year, starting from 5.297 cases reported in 2004, 7.850 cases in 2005, 8.328 cases in 2006, to 8.277 cases in 2007 [3]. In 2011, Association of Cancer

Corresponding Author:
Dr. Nur Fitrianingsih Pujiano Agatha
Medical Education Study Program, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia.
Email: nurfitrianingsihpagatha@gmail.com

Registries reported breast cancer as the most frequent cancer in Indonesia with 4744 cases [4]. In addition, the data from Dharmais Cancer Hospital that collected during 2010-2013 reported the same finding afterwards. Correspondingly, incidence and mortality rate of breast cancer are increasing [5].

Breast cancer is caused by epithelial cell proliferation towards malignancy that potentially invades surrounding tissues or metastatic to other body parts. This disease usually affects women, but men are also at risk [6]. The cause is still unknown, but multifactorial are thought as the etiology [7]. There are many factors which can emerge breast cancer, such as BRCA1 and BRCA2 genes defect provoking higher proliferation or lower apoptotic in cell. Besides, some risk factors are associated with breast cancer, for example sex, age, family history, breast cancer history, age at menarche, starting menopause elderly, obesity, lack of physical activity, etc [8].

Earlier age at menarche is one of the risk factors associated with breast cancer. According to Indonesia Basic Health Research in 2010, first menstruation most happened in 13 years old. In detail, menarche appeared in 9 (0,3%), 10 (1,2%), 11 (3,7%), 12 (17,2%), 13 (20,0%), 14 (17,5%), 15 (15,2%), 16 (4,6%), 17 (3,0%), 18 (1,0%), 19 (0,2%),and 20 years old (0,3%) [9]. In 2013, Priyatin et al [10] conducted a study in Dr. Kariadi General Hospital Medical Center in Semarang found earlier age at menarche significantly increasing the risk of breast cancer. Women in reproductive age with first menstruation happened in less than 12 years old have 2.638-fold higher risk in having breast cancer. In contrary, Das et al [11] reported that 29 of 42 breast cancer patients had their menarche at ≤12 years old, 68 of 144 at 13-15 years old, and 8 of 24 at ≥16 years old. A study in Journal Health Quality found that longer exposure duration to estrogen hormone was associated with higher risk of breast cancer, of which happened in women with earlier menarche age [12]. Therefore, this study is conducted to evaluate the association between age at menarche and breast cancer incident in Dr. Cipto Mangunkusumo Hospital in 2010-2014. The time span chosen (2010 to 2014) associated with patient's survival rate in 5 years with variety of stadium. This study will refer to the result of histopathological examination as the gold standard in diagnosing breast cancer.

Literature Review

Breast Cancer

Breast cancer is an invasive form of tumor characterized by the proliferation of breast epithelial cell [1]. This disease usually develops from ductal and lobular parts of the breast. One of the causes is genetic alteration. Mutation in proto-oncogene and tumor-suppressor-gene is the basic process of oncogenesis. The overexpression of proto-oncogene HER2/NEU gives rise to the 30% amplification in invasive breast cancer and lead to worse prognosis. Besides, mutation in gene encoding estrogen and progesterone receptor (ER/PR) also play the role in the incidence of breast cancer. Based on the gene profile, breast cancer is further divided into 4 subtypes, which are luminal A (ER/PR positive, HER2/neu negative), luminal B (ER/PR positive, overexpression of HER2/NEU), HER2/neu positive (overexpression HER2/neu, ER/PR negative), basal like (ER/PR negative, HER2/neu negative). Each subtype has different clinical manifestations and therapies choice. Besides, 1 of 3 women with breast cancer have mutation in BRCA1 (in chromosome 17q21.3) or BRCA2 (in chromosome 13q12-13). Both genes are tumor-suppressor-gene involved in DNA repairing, transcription process regulation, chromatin remodelling, and protein degradation [13,14].

Additionally, hormonal factor also seems to correlate with breast cancer. Excess of endogenous estrogen or hormonal imbalance are thought to have significant role. Estrogen can stimulate the growth factor production, such as transforming growth factor-α, platelet-derived growth factor, and fibroblast growth factor leading to tumor development by using paracrine and autocrine mechanism. Environmental factors, particularly racial and ethnic,have higher potential to suffer from breast cancer [13,15]. Other correlated risk factors are age, gene mutation, earlier menarche age, advanced maternal age pregnancy, starting menopause elderly, hormonal therapy, higher breast tissue density, oral contraception, cancer or tumor history, family history, smoking, and alcohol consumption [16].

During the physical examination, the presence of mass or nodule in breast is the most common sign indicating breast cancer. A mass is usually painless, hard, and has uneven edges, but sometimes it can be tender, soft, and rounded. Other symptoms that indicating the existence of breast cancer are partial or whole breast swollen, skin irritation, breast or nipple pain, nipple retraction, skin color changing, nipple discharge, and peau d'orange sign which characterized by the appearance and dimpled texture similar to an orange peel [17].

History taking, physical examination, and other medical examinations are needed to confirm a diagnosis. History taking is a communication process using interview to obtain patient's data (identity, symptoms, etc) needed to make a diagnosis and treatment choice. This process can be taken either directly to the patient or indirectly to the guardian [18]. There are some key points to cover in history taking, such as risk factors associated, nipple discharge with its characteristics, breast pain, and malformation changes in the breast [18,19]. Besides, physical examination including inspection and palpation are also crucial. While inspection, attention must be given to inspect for breast skin changes, contours, symmetry, texture, nipple's morphology, and discharge. Any malformations such as mass, nodules, or peau d'orangeneed to be examined [18]. Palpation should be done on sitting and supine position, starting from the normal to pathologic breast using index, middle, and ring fingers. While doing palpation, a careful examination to any nodules, such as the position, size, fixed or mobile, amount, and pain. Besides, the examination also includes areolar to investigate the nipple discharge, axillary and neck to investigate the metastasis [18,19]. Some additional examinations also have the role in confirming

the diagnosis, for example mammography, USG, CT scan, MRI, and biopsy. Mammography is an X-ray imaging technique, which consists of screen-film (film based) and full-field (digital based) mammography. USG can be used to differentiate between benign and malignant tumor after mammography identification or patient's mass feeling. This imaging is useful for dense breast patients, especially in younger women due to the limitation of mammography. Besides, MRI can be useful as a screening tool in dense breast women who have high risk developing breast cancer due to their family history. Meanwhile, CT scan are usually used to monitor the metastasis and useful in patients who are contraindicated for MRI. For biopsy technique, there are three available types which are fine-needle aspiration, core needle biopsy, and open biopsy [19].

Age at Menarche

Menarche is the first menstruation cycle in women. Ovulation cycle affected by estrogen hormone is one reproductive factor that potentially increasing the risk of breast cancer. This cycle will increase the breast epithelial cell by inducing its proliferation at the end of luteal phase. If the conception is not happen, the result is apoptotic of the previous cells. Earlier menarche is associated with earlier ovulation cycle onset and increase the exposure with estrogen hormone, thus result in higher risk on developing breast cancer [20].

Estrogen hormone is also essential in sex organ development, secondary sex characteristics, reproduction, and menstruation cycle regulation. The exposure duration of ovarium produced hormone, especially estrogen, has a powerful association with breast cancer risk. Delayed menarche for one year can reduce the risk of future breast cancer by 5% [21]. Both endogenous and exogenous estrogen are capable to cause the proliferation of breast epithelial cells and stimulates its mitotic process. Therefore, the probability of a cell in achieving mutation are increasing. This hormone can get into the target cell, binds with protein receptor, and further binds with hormone response element in nucleus DNA. It results to the activation or suppression of specific gene sequence at the regulation area associated with estrogen that control cell growth and differentiation [22]. The role of estrogen as a mutagen in initiating breast tumorigenesis is still doubtful. Some studies reported that there was not any mutagenic effect in bacterial or mammalia induced by estrogen. In contrary, other studies also reported that weak procarcinogen molecules were found as the materials that contained in estrogen, such as catechol-estrogen intermediate, semiquinone, or reactive quinone. These molecules are capable to induce DNA impairment caused by free radical directly or indirectly. Additionally, they can cause genetic imbalance, and mutation in both cell culture and in vivo. Although estrogen can potentially induce gene impairment, the proliferation effect of it is still considered as the primary mechanism of breast cancer.

Methods

This cross-sectional study was conducted in the Anatomical Pathology department, Medical Records department, and department of Surgery Faculty of Medicine Universitas Indonesia (FMUI) - Dr. Cipto Mangunkusumo National Central Public Hospital from June 2016 to October 2016. The author obtained the secondary data from the department of Anatomical Pathology with further evaluation to the department of Surgery and Medical Records department Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo National Central Public Hospital from 2010 to 2014.

This study included patients that were having pathological anatomy examination in Dr. Cipto Mangunkusumo Hospital, clinically suspected as having breast cancer, and the age of menarche data reported in the patient history. Male patients were further excluded.

The data were then processed using statistical software SPSS version 20.0. The data contains the patient's name, age and age at diagnosis, and age at first menstruation. Hypothesis testing can be done by analyzing the data using the Chi-square test to get the p-value. If the requirements for the chi-square test are not met, the Fisher test is used.

Results

In this study, the data used were patient data with a clinical diagnosis or breast cancer suspicion who underwent an examination at the Department of Anatomical Pathology FMUI, which was then traced to the Medical Records Unit and the Department of Surgery, Dr. Cipto Mangunkusumo Jakarta, in 2010-2014. With the random sampling method, a sample of 98 cases was obtained for data on diagnosed age and age at first menstruation based on inclusion and exclusion criteria. In this study, a demographic analysis was carried out, namely the age at diagnosis and the age at first menstruation. Subjects included in this study were only female.

Based on Table 1, the age of the respondents when diagnosed as patients with breast cancer and non-patients were grouped into three groups based on the respondent's age range and ten years of survival rate, namely age <40 years, 40-49 years, 50-59 years, and ≥60 years. In Table 1, the most extensive age distribution is in the age group 40-49 years with the incidence of positive breast cancer as many as 32 people (37.2%) and negative breast cancer as many as two people (16.7%). Followed by the age group 50-59 years with positive breast cancer incidence as many as 23 people (26.7%) and negative breast cancer as many as six people (50%). Then in the age group <40 years, there were 19 positive people diagnosed with breast cancer (22.1%) and one person with negative breast cancer (8.3%). Whereas in the age group ≥60 years, there were 12 people diagnosed with positive breast cancer (14%) and three people with negative breast cancer (25%).

In this study, a statistical test was conducted to see whether the age at first menstruation had an effect on the incidence of breast cancer. The statistical test used in this study was Fisher's test. The test is carried out because

Table 1. Characteristics of the Age Distribution of Breast Cancer Patients and Non-sufferers Based on the Results of the 2010-2014 Anatomicalpathology Examination at RSUPN Dr. Cipto Mangunkusumo Jakarta

Age	Breast Cancer			
	Positive		Negative	
	n	%	n	%
<40 years old	19	22,1	1	8,3
40-49 years old	32	37,2	2	16,7
50-59 years old	23	26,7	6	50
≥60years old	12	14,0	3	25
Total	86	87,8	12	12,2

Table 2. Statistical Test Results of the Effect of Age at First Menstruation on the Incidence of Breast Cancer in 2010-2014 at RSUPN Dr. Cipo Mangunkusumo Jakarta

Age at first menstruation	Breast Cancer				p Value
	Positive		Negative		
	n	%	n	%	
≤12 years old	23	26,7	3	25,0	1,000
>12 years old	63	73,3	9	75,0	
Total	86	87,8	12	12,2	

in the Chi-Square test calculation, 25% of cells have an expected value of less than five.

Table 2 shows the results of the Fisher exact analysis. Data on respondents' age at first menstruation were grouped into ≤12 years and> 12 years. Researchers grouped them based on the average age at first menstruation in Indonesia, namely 12 years (Riskesdas 2010). A total of 23 people with breast cancer experienced their first menstruation at the age of less than or equal to 12 years (26.7%), while three people who were not breast cancer patients also experienced their first menstruation at the age of less than or equal to 12 years (25%). Meanwhile, 63 people with breast cancer at the age at first menstruation were more than 12 years old (73.3%), and nine people without breast cancer (75%).

The chi-square test requirements were not fulfilled in data analysis because 25% of cells had an expected count of less than 5. For 2x2 tables that did not meet the chi-square test requirements, the analysis was performed using Fisher's test. The significant value in Fisher's exact test is 1,000. Because of the p-value is >0.05, statistically age at first menstruation does not affect breast cancer incidence. This study's prevalence ratio was 1.01 with a confidence interval (95%) of 0.997-1.000.

Discussion

Prevalence of breast cancer in Indonesia is still high. This study shows that from 98 samples obtained, 86 people (87.8%) were positive for breast cancer based on the anatomical pathology examination results at RSUPN Dr. Cipto Mangunkusumo Jakarta in 2010-2014.

The results of this study also indicate that the 40-49 year age group is the age group that has the highest number of breast cancer cases (37.2%) compared to other age groups. This is in line with Balasubramaniam et al. in 2013, showing that the 41-50 year age group is the largest age group suffering from breast cancer, namely 54 people (35.5%). A study conducted by Indarti R et al. 24, 2006 explained that the highest number of breast cancer cases was found in the 40-49 year age group (38.5%). Based on the SEER program (Surveillance, epidemiology, and End Results) conducted by the National Cancer Institute (NCI), breast cancer incidence increases with age due to genetic changes or mutations in the body. This makes age a risk factor that affects the incidence of breast cancer. The likelihood of developing breast cancer increases with age, but breast cancer will be more aggressive in patients of reproductive age (15-49 years).

Also, the relatively early age at first menstruation can be a risk factor for breast cancer. The first menstruation (menarche) is characterized by monthly fluctuations in hormonal levels, ovulation, and cell proliferation in the breasts. Breasts begin to develop 1 or 2 years before the end of menarche, and during puberty, the breast tissue will develop rapidly. The results of epidemiological studies show that women with the age of first menstruation <12 years have a 10-25% greater risk of developing breast cancer. However, the age at first menstruation is sometimes difficult to determine due to incorrect recall in patients. The relatively early age of the first menstruation will prolong exposure to the hormone estrogen. Studies have also shown that these women have higher estrogen levels in the years after their first menstruation during their reproductive years. The first menstruation at an early age is also associated with more regular ovulation cycles with shorter cycle lengths. The age at first menstruation that is delayed by one year can reduce breast cancer risk by 5% in later life. This is because both endogenous and exogenous estrogen triggers the proliferation of the breast epithelium, which stimulates the mitosis of breast epithelial cells, thereby increasing the number of cell divisions that have the chance to become a genetic mutation. The mechanism of estrogen to induce breast

cancer, namely estrogen can cause de novo breast cancer through a receptor-dependent or receptor-independent mechanism. Through its receptor-mediated action, E2 induces cell proliferation, a factor associated with breast cancer development. Chances are, there will be errors in DNA replication and cause mutations that increase cell division. The occurrence of cell proliferation will be extreme in adult breasts when the levels of E2 and progesterone are very high. In addition, the carcinogenic effects of estrogen can also occur through the action of estrogen metabolites. E2 induces DNA damage through 4-OHE2, 2-OHE2, O2, and 16-OHE2 causing breast cancer.

Based on data from the Basic Health Research (Riskesdas) in 2010, women in Indonesia generally experience their first menstruation at 13. Women who are at risk of developing breast cancer are women with the first age of early menstruation, namely 12 years or less than 12 years. In this study, 26 women (26.5%) had their first menstruation at the age of 12 years or less than 12 years and 23 of them had breast cancer.

In this study, there was no significant effect between age at first menstruation on breast cancer incidence in Dr. Cipto Mangunkusumo Jakarta, but this is only statistical. Based on the study, women who experience their first menstruation at an early age are more at risk of developing breast cancer based on the mechanism that has been described. This is also supported by previous studies showing that age at first menstruation <12 years was significantly associated with breast cancer incidence. One possibility that occurs is due to differences in research methods compared to previous studies. Research conducted by Anggorowati L with a case-control study design using measuring instruments in questionnaires and medical records showed a significant relationship between the age of first menstruation and breast cancer. The sample used was 118. Likewise, the research conducted by Rianti E in 2012 with a sample of 126. This study also used a case-control study design. In comparison, the research measuring instrument used the results of the photo rontgents and questionnaires. However, some studies show no relationship between breast cancer incidence and the age at first menstruation. The research was conducted by Das S et al. in India with a case-control study design. The measuring instruments used were questionnaires and histopathological examination. The sample used is 210. Another study that uses histopathological examination as a measuring tool is research by Laamiri FZ with a case-control study design. The measuring instruments used were histopathologic and mammography examination. The sample used was 800. This study shows that there was a significant relationship between the age of the first menstruation and the incidence of breast cancer.

In this study, there are several limitations. At the time of data collection, there was a limit to the number of sample takers in the Medical Record Unit Dr. Cipto Mangunkusumo Jakarta. Besides, there were obstacles such as the unavailability of some data carried out by random sampling so that the sample used was negligible. However, in this study, the data used were data from histopathological examination, which is the gold standard examination for breast cancer clinical diagnosis.

In conclusion, based on the results of this study, namely the age group 40-49 years is the age group with the highest frequency of breast cancer incidence based on the results of anatomic pathology examinations 2010-2014 at Dr. Cipto Mangunkusumo Jakarta. Age at first menstruation> 12 years is the age with the highest frequency of breast cancer based on the results of anatomic pathology examinations in 2010-2014 at RSUPN Dr. Cipto Mangunkusumo Jakarta. Also, statistically, this study's results indicate that the age at first menstruation did not significantly affect breast cancer incidence in Dr. Cipto Mangunkusumo Hospital Jakarta in 2010-2014.

Suggestion

The researcher's suggestion regarding further research is research on the effect of late menopause on breast cancer incidence. This is because the late menopausal age factor is also suspected to be a risk factor for mutations due to the exact mechanism, namely increased exposure to the hormone estrogen. In addition, research that uses a case-control or cohort study design is also recommended for further research. This is because cross-sectional studies such as those conducted in this study have weaknesses, such as the weakest correlation between risk factors and their impact compared to other analytic studies.

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