

## Review of Risk Factors in Breast Cancer Incidence: The Main Role of the Age at First Pregnancy

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### ABSTRACT

**Introduction:** According to Indonesia's Global Burden Cancer (GLOBOCAN) in 2020, breast cancer accounted for the highest incidence among cancer cases, contributing to 16.6% of the total cases and causing 9.6% of deaths. In 2021, South Jakarta recorded the highest incidence of breast cancer within DKI Jakarta, with 172 cases out of 299. **Objective:** This study aims to identify the dominant factors influencing the occurrence of breast cancer. **Methods:** Employing explanatory research, the study involved 112 respondents selected through accidental sampling. Logistic regression analysis was employed for multivariate analysis. **Results:** The findings revealed three variables with significance levels (Sig.) less than 0.05: age at first menstruation (Sig.=0.005), age at first pregnancy (Sig.<0.001), and smoking history (Sig.=0.018). Exp (B) results indicated that the age of first pregnancy has the greatest impact, with a likelihood 8.6 times higher. **Conclusion:** Consequently, the study concludes that the age of the woman during the first pregnancy emerges as the most dominant factor influencing breast cancer, pointing to the critical period of estrogen exposure. This study underscores the importance of understanding and addressing these factors in breast cancer prevention and intervention strategies, providing valuable insights for public health initiatives.



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## INTRODUCTION

Breast cancer is the most common cancer in Indonesia, with significant physical, psychological, social, and economic implications. According to the World Health Organization (WHO) Global Burden Cancer (GLOBOCAN) data, breast cancer tops the list of the 10 cancers with the highest global incidence. The other cancers in this list include lung cancer, prostate cancer, colon cancer, stomach cancer, liver cancer, rectal cancer, cervical cancer, esophagus cancer, and thyroid cancer. In 2020, GLOBOCAN reported a total of 2,261,419 new cases of breast cancer worldwide, constituting 11.7% of all cancer cases. Specifically, WHO data indicated that breast cancer is the most prevalent type of cancer, surpassing lung cancer and other forms. The statistics from 2020 further reveal that breast cancer led to 685,000 deaths globally, solidifying its position as the most common cause of death among women and the fifth most frequent cause of cancer-related deaths overall (WHO, 2020a; 2020b).

WHO report in 2020, that the latest cases of breast cancer rank first and the highest incidence is in Africa with 186 thousand cases and 85 thousand causing death. Globally, the highest incidence of breast cancer occurs in Asia as much as 45.4% of all regional regions in the world, followed by Europe with a percentage of 23.5% of all regional regions in the world. Africa is not among the top three highest breast cancer incidence, but Africa is the third regional region that has the highest breast cancer death rate with a percentage of 12.5% of all regional regions in the world after Europe and Asia with percentages of 20.7% and 50.5% of all regional regions in the world respectively (WHO, 2020b).

The *Global Burden Cancer or GLOBOCAN* Indonesia report in 2020 there are 396,914 new cases and 234,511 deaths. The highest incidence occurred in breast cancer with 68,878 (16.6%) cases with 22,430 (9.6%) mortality rates. Followed by cervical cancer with 36,633 (9.2%) cases with death cases reaching 21,003 (9%) (WHO Indonesia, 2020). The Ministry of Health reports cancer cases in Indonesia at 136.2 per 100,000 people. This figure ranks eighth in Southeast Asia, in Asia, Indonesia ranks 23rd. Of these, the highest incidence of cancer in women is breast cancer cases with an incidence rate of 42.1 per 100,000 people and an average death rate of 17 women per 100,000 people (Ministry of Health of the Republic of Indonesia, 2019).

Based on the results of breast cancer screening with Clinical Examination (SADANIS) in DKI Jakarta Province in 2021, 299 cases of breast lumps were found, and the most were found in South Jakarta with 172 cases, while other regions ranged from 23 to 46 findings (Dinkes DKI, 2022). This research is focused on breast cancer patients by not limiting age, with the hope that the results obtained have a wider spectrum, ranging from pubertal age women and adult women of childbearing age to elderly women (menopause). This study aims to identify the most dominant factors affecting the occurrence of breast cancer.

## METHODS

This study employs a quantitative approach with a cross-sectional design, aiming to investigate the correlation between various risk factors associated with breast cancer. The cross-sectional design allows for the examination of these factors simultaneously at a specific point in time. The research was conducted in South Jakarta during the period from March to August 2023. The study population consisted of inpatients at several cancer treatment facilities in South Jakarta.

Accidental sampling was employed as the sampling technique. This method involved selecting breast cancer patients present or encountered by the researcher during data collection. The inclusion criteria encompassed hospitalized breast cancer patients who were married, cooperative, and willing to participate in the research by providing informed consent. The exclusion criteria included outpatient cases and uncooperative cancer patients, particularly those experiencing stress, seizures, or communication difficulties. The final sample size amounted to 112 individuals.

The independent variables encompassed age (categorized as  $\geq 50$  years and  $< 50$  years), age at first menstruation (categorized as  $\geq 12$  years and  $< 12$  years), age at first pregnancy (categorized as  $\geq 30$  years and  $< 30$  years), family history of cancer, history of breastfeeding (categorized as  $\geq 12$  months and  $< 12$  months), history of hormonal contraceptive use, and smoking history. The dependent variable was the presence or absence of breast cancer. The research instrument employed was a questionnaire, which included inquiries about respondent characteristics and the history of breast cancer.

Bivariate analysis involved the Chi-Square test and Odds Ratio. For multivariate analysis, logistic regression analysis was employed. This study obtained ethical clearance from the Poltekkes Ethics Review Board of the Ministry of Health Tanjung Karang under the reference number 415/KEPK-TJK/VII/2023.

## RESULTS

Univariate analyses to explain each characteristic include: Univariate data consisted of: education, occupation, income, cancer stage, age, age at first menstruation, age of first pregnancy, familial breast cancer, breastfeeding, hormonal contraception, and smoking. Respondents totaled 112 people. After the data is analyzed, the following results are obtained:

**Table 1.** Characteristics of Participants

<b>Variables</b>	<b>Frequency (n=112)</b>	<b>(%)</b>
<b>Education:</b>		
High School	53	47.3
S1 (bachelor's degree)	54	48.2
S2 (master's degree)	5	4.5
<b>Occupation:</b>		
IRT	17	15.2
Merchant	72	64.3
Officer	23	20.5
<b>Income:</b>		
< 5 million	10	8.9
5 - 10 million	24	21.4
> 10 million	78	69.6
<b>Stadium:</b>		
Stadium 2	73	65.2
Stadium 3	39	34.8
<b>Age</b>		
≥ 50 years	73	65.2
< 50 years	39	34.8
<b>First Menstruation</b>		
<12 years	84	75.0
≥12 years	28	25.0
<b>First Pregnancy Age</b>		
≥ 30 years	80	71.4
< 30 years old	32	28.6
<b>Family history of cancer</b>		
None	7	6.3
Exist	105	93.8
<b>History of breastfeeding</b>		
< 12 months	76	67.9
> 12 months	36	32.1
<b>Hormonal Contraceptives</b>		
No	24	21.4
Yes	88	78.6
<b>Smoking/ Passive Smoking</b>		
No	14	12.5
Yes	98	87.5

The distribution of respondents based on their educational background reveals

that 48.2% hold an S1 (bachelor's degree), 47.3% have a high school education, and 4.5% possess an S2 (master's degree). The primary occupation among the respondents is trading, comprising 64.3%, followed by those employed (20.5%) and housewives (15.2%). In terms of income, 69.6% of respondents earn more than 10 million, 20.5% earn between 5-10 million, and 8.9% earn less than 5 million.

Regarding cancer stages, 65.2% of respondents are in stage 2, while 34.8% are in stage 3. The majority of respondents (65.2%) are aged 50 years and above, while 34.8% are below 50 years old. The data on the age at the first menstruation indicates that 75% of respondents had their first menstruation before the age of 12, while 25% experienced it at the age of 12 or older. In terms of the age at the first pregnancy, 71.4% of respondents became pregnant for the first time at the age of 30 or older, with 28.6% having their first pregnancy before the age of 30.

Examining family history, 93.8% of respondents have a family history of breast cancer, while 6.3% do not. Regarding breastfeeding history, 67.9% of respondents breastfed for less than 12 months, and 32.1% breastfed for 12 months or more. In terms of hormonal contraceptive use, 78.6% of respondents have a history of using hormonal contraceptives, while 21.4% do not. Additionally, 87.5% of respondents have a history of smoking, while 15.5% are non-smokers.

**Table 2.** Bivariate analysis (n=112)

Variables	Breast Cancer				n	Total		p-Value
	No n (56)	%	Yes n (56)	%		n	%	
<b>Age</b>								
<50 years	37	33.0	32	28.6	69	61.6	0.437	
≥50 years	19	17.0	24	21.4	43	38.4		
<b>Age at first menstruation</b>								
<12 tahun	49	43.8	35	31.3	84	75	0.005	
≥12 tahun	7	6.3	21	18.8	28	25		
<b>Age at first pregnancy</b>								
<30 years	50	44.6	30	26.8	80	71.4	0.000	
≥30 years	6	5.4	26	32.2	32	28.6		
<b>Family history of cancer</b>								
Ada	52	46.4	53	47.3	105	93.8	1.000	
Tidak Ada	4	3.6	3	2.7	7	6.3		
<b>History of breastfeeding</b>								
<12 months	33	29.3	43	38.4	76	67.9	0.069	
>12 months	23	20.5	13	11.6	36	32.1		
<b>Smoking/ Passive Smoking</b>								
No	54	46.6	42	37.5	92	82.1	0.084	
Yes	6	5.4	14	12.5	20	17.9		
<b>Hormonal Contraceptives</b>								
No	40	35.7	48	42.9	88	78.6	0.107	
Yes	16	14.3	8	7.1	24	21.4		

Based on the data presented in Table 2, it is evident that out of the 112 respondents, 61.6% were aged below 50 years, while 33% of respondents were not afflicted by breast cancer, and 28.6% had been diagnosed with breast cancer. In the age group of 50 years and above, 38.4% of respondents were identified, with 17% not having breast cancer and 21.4% having a history of breast cancer.

Examining the age at which respondents experienced their first menstruation, 75% of them had their first menstruation before the age of 12. Within this group,

43.8% did not have breast cancer, while 31.3% had been diagnosed with breast cancer. On the other hand, among respondents who experienced their first menstruation at the age of 12 years or older, constituting 25% of the total, 6.3% did not have breast cancer, and 18.8% had a history of breast cancer.

Considering the age of respondents at the time of their first pregnancy, 71.4% experienced their first pregnancy before the age of 30. Within this group, 44.6% did not have breast cancer, while 26.8% had breast cancer. Conversely, among respondents with a first pregnancy at age 30 or older (28.6% of the total), 5.4% did not have breast cancer, and 32.2% had breast cancer.

Analyzing family history, it was found that 93.8% of respondents had a family history of cancer. Among these, 46.4% did not have breast cancer, while 47.3% had breast cancer. For the 6.3% of respondents with no family history of cancer, 3.6% did not have breast cancer, and 2.7% had breast cancer.

Exploring the history of breastfeeding duration, 67.9% of respondents had a history of breastfeeding for less than 12 months. Within this group, 29.3% did not have breast cancer, and 38.4% had breast cancer. For respondents with a breastfeeding duration of 12 months or more (32.1% of the total), 20.5% did not have breast cancer, and 11.6% had breast cancer.

Regarding smoking history, 82.1% of respondents reported no history of smoking. Among them, 46.6% did not have breast cancer, and 37.5% had breast cancer. Conversely, among the 17.9% of respondents with a history of smoking, 5.4% did not have breast cancer, and 12.5% had breast cancer.

In terms of hormonal contraceptive use, 78.6% of respondents reported no history of using hormonal contraceptives. Within this group, 35.7% did not have breast cancer, and 42.9% had breast cancer. Meanwhile, among the 21.4% of respondents with a history of using hormonal contraceptives, 14.3% did not have breast cancer, and 7.1% had breast cancer.

**Table 3.** Multivariabel analysis (n=112)

Variables	p-value	Exp(B)	95% C.I. for EXP(B)	
			Lower	Upper
Age	0,241	1,8	0,6	4,8
Age at first menstruation	0,005	4,9	1,6	14,9
Age at first pregnancy	0,000	8,6	2,5	28,8
Family history of cancer	0,699	1,5	0,2	11,3
History of breastfeeding	0,798	0,9	0,3	2,4
Smoking	0,018	0,2	0,1	0,7
Hormonal Contraceptives	0,237	1,9	0,6	6,0

Based on the obtained significance values, it is evident that three variables exhibit statistical significance with a significance level (Sig.) of less than 0.05. Specifically, these variables are the age of the first menstruation (Sig. = 0.005), the age of the first pregnancy (Sig. = 0.000), and family smoking history (Sig. = 0.018).

Upon analysis of the odds ratios or Exp (B), it is noteworthy that the variable with the highest odds ratio is the age of the first pregnancy, with a value of 8.6. This suggests that individuals with a later age at their first pregnancy have an 8.6 times higher likelihood of developing breast cancer compared to those with an earlier age at their first pregnancy

## DISCUSSION

### Association of Age at First pregnancy with Breast Cancer Incidence.

Breast cancer can occur in women whose first pregnancy is after the age of 30 or in women who have never been pregnant. Age at first pregnancy  $\geq 30$  years risk 2.16 times to develop breast cancer compared to first pregnancy at age  $<30$  years. Breast changes during pregnancy have an effect on the occurrence of breast cancer. The risk of breast cancer decreases with each additional birth. This happens because during the first trimester of pregnancy, estrogen will increase very high. If estrogen is high, it will trigger the multiplication process of cells to perform mitosis quickly. This triggers the formation of cancer cells in the breast (Clèries et al., 2018). Other studies say that breast cancer risk factors include hormonal factors such as a woman's age during her first menstruation and a woman's age during her first pregnancy putting women in a condition of prolonged exposure to estrogen (Mørch et al., 2017).

Breast cancer occurs through mechanisms related to steroid hormones in the ovaries. First; Natural estrogens (estrogen and estradiol) that are mutagenic and carcinogenic undergo genotoxic processes in the formation of reproductive estrogens and the reaction of quinone estrogen catechoestrogens with DNA. Second; Such events involve the stimulating effects of estrogen and progesterone on cell proliferation in breast tissue, and potentially increase the risk of breast cancer through tumor stem cells in the breast (DeSantis, Ma, Goding Sauer, Newman, & Jemal, 2017).

Women who give birth to their first child at the age of  $>35$  years will experience breast cancer due to the induction of the hormone estrogen. Pregnancy at a younger age decreases hormone receptor positive cells in gene expression and stem cell proliferation. The decline also includes a decrease in regulation and transformation of growth factors. The older a woman is during her first pregnancy, the less protective effect against pregnancy-induced breast cancer. The first parity that occurs after a woman is  $>35$  years old paradoxically increases the risk of breast cancer compared to nullipara women. Early pregnancy decreases the proportion of positive hormone receptor cells and causes changes in gene expression as well as decreased stem cell/progenitor proliferation. These changes include downregulation and transformation of Transforming Growth  $\beta$ Factor  $\beta$  signals. The action of cells in the epithelium of glands in the breast will modulate the risk of breast cancer (Meier-Abt & Bentires-Alj, 2014).

The results of different studies stated that there was no significant relationship between a woman's age during her first pregnancy and a woman's estradiol levels at childbearing age. The hormone estrogen in breast tissue during pregnancy will have a significant effect on the growth, differentiation and functioning of tissue in the breast (Sari & Pasalina, 2023). High estrogen levels are also a cause of breast cancer in women until menopause (Ahmed et al., 2018).

Women aged 45 who have never given birth or are nullified have a 0.62% chance of being diagnosed with breast cancer. Women aged 45 years who have given birth have a higher chance of 0.66% being diagnosed with breast cancer within 3-7 years (Ministry of Health RI, 2018).

Childbirth affects breast cancer, especially age, genetic mutations, and family history. But the risk of breast cancer after childbirth does not occur instantly. The period of the beginning of the first menstruation and the age of the first pregnancy in women takes a long time. This period of time is thought to be a risk factor for breast cancer because at that time women experience more and longer exposure to estrogen. The hormone estrogen that is long exposed to women can cause the risk of cancer. This is

because the increase in mitosis due to the hormone estrogen triggers tissue proliferation and inhibits *apoptosis*. *Apoptosis* is the process of tissue death, occurring normally during the process of tissue development and aging in all tissues of the body in this case breast tissue. Mitosis increases gene mutations when DNA replication (*Deoxyribo Nucleid Acid*). Adipose gathering formed from the hormone estrogen will excrete *aromatase* (Fard, Rouhollah, & and Nahid Nafisi, 2018).

Older age in women during the first pregnancy is a risk factor for breast cancer. This is thought to be due to longer exposure to estrogen. So the older a woman is in her first pregnancy, the higher her risk of developing breast cancer. Risk factors for breast cancer due to age during the first pregnancy are factors that can be changed, because it is important for women to get pregnant and give birth at childbearing age or 20-30 years.

### **The relationship of the age at the first menstruation with breast cancer.**

As it is known that women who are exposed to estrogen for a long time are at risk of breast cancer. The menstrual process, the hormone estrogene will increase in the follicular phase and decrease in the luteal phase. This estrogen hormone acts as a carcinogen in the process of increasing the risk of breast cancer. Early menstruation causes the risk of breast cancer. This is because young age causes women to get exposure too quickly to estrogen. Menstruation is a cycle that occurs for 28-35 days. If the menstrual period before the age of 12 years and menopause occurs after the age of 55 years is at risk of exposing women to hormones longer, and at risk of breast cancer (CDC, 2023).

Inline with the results of this study states that there is no association between the age of early menarche and breast cancer. Younger usia during menarche increases the risk of breast cancer twofold (OR, 2.83; 95% CI, 1.02-7.86) (Dati, Sasputra, Rante, & Artawan, 2021). Similar opinions say that breast cancer is associated with the first menstruation at the age of <12 years, menopausal age >55 years, history of multigravida and history of breastfeeding less than 12 months (Herawati et al., 2022).

Interviews conducted with 90 women showed that the first menstruation of <12 years was associated with breast cancer risk. The incidence of the first menstrual age of <12 years in the case group was 48.9% higher than in the control group of 20.0% (Dewi & Hendrati, 2016).

The age of women during the first menstruation is earlier related to the length of exposure to the hormone estrogen which will affect the process of tissue proliferation including breast tissue. This can eventually lead to breast cancer. So the younger the age a woman has her first period, the higher her risk of developing breast cancer. However, this can be anticipated by improving lifestyle and early detection.

### **Association of Smoking History with Breast Cancer Incidence.**

Smoking behavior in respondents or in their families can have an effect on increasing the risk of breast cancer. Active smoking is associated with an increased risk of breast cancer (Maria, Sainal, & Nyorong, 2017). Nicotine in tobacco can cause angiogenesis in breast tissue with a mechanism resembling endogenous angiogenesis factor (Agustina, 2022). Other supporting studies state that women who smoke play a role in the incidence of breast cancer (Gaudet et al., 2013). Cigarette smoke contains 20 chemical compounds that induce breast cancer. Some of these compounds are lipophilic, deposited in the adipose tissue of the breast. By epithelial cells milk is metabolized and activated. Women who smoke have detectable metabolites in breast fluid and a higher prevalence of cigarette-specific DNA supplemental products and p53 mutations in breast tissue than nonsmokers. Active

smokers are at risk of lower postmenopausal mammography density and breast cancer effects (Gaudet et al., 2013). Smoking is a factor that can be changed. Smoking is associated with breast cancer. Nicotine triggers angiogenesis in breast tissue.

## CONCLUSION AND RECOMMENDATIONS

The most influential factor contributing to breast cancer is identified as the age at first pregnancy. Recommendations for breast cancer prevention efforts include educating women of reproductive age from adolescence onward. Moreover, it is advised to closely monitor factors known to trigger breast cancer, such as the age of the patient, age at first pregnancy, family history of breast cancer, breastfeeding practices, smoking history, and the history of hormonal contraceptive use. Additionally, promoting routine reproductive health check-ups is essential for women at various life stages, including during pregnancy, childbirth, postpartum, and as they age. These comprehensive measures aim to enhance awareness, early detection, and proactive management of risk factors associated with breast cancer among women.

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