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(RESEARCH ARTICLE)

Analysis of Risk Factors for Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

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Abstract

Breast cancer is a major health problem for women around the world. Based on data from the global observatory center, there were more than 408,661 new cases and nearly 242,099 deaths in Indonesia in 2022. At the Bahteramas Regional General Hospital in Southeast Sulawesi Province, breast cancer as a cause of death continues to increase every year. The purpose of this study was to analyze the risk factors for breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The research design was an observational analytical epidemiology with a case-control study design using a matching procedure. The results of the analysis of the significant effect of age at menarche obtained an OR value of 5.5 (lower limit = 1.200 and upper limit = 51.065). The history of breastfeeding obtained an OR value of 5.0 (lower limit = 1.065 and upper limit = 46.932 OR). The age at first birth obtained an OR value of 1.6 (lower limit = 0.324, upper limit = 10.732). Reproductive history obtained an OR value of 1.0 (lower limit = 0.133 and upper limit = 7.466). The history of hormonal contraceptive use on the incidence of breast cancer after age matching obtained an OR value of 4.5 (lower limit = 1.482 and upper limit = 18.279). Based on multivariate analysis, it was found that breastfeeding history had an OR value of 10.7 (lower limit = 1.837732, upper limit 62.83065) and hormonal contraceptive use history had an OR value (lower limit = 2.077331, upper limit = 27.12047). The conclusion is that age at menarche, breastfeeding history, and history of hormonal contraceptive use are risk factors for breast cancer. Meanwhile, age at first birth and reproductive history are not risk factors for breast cancer. The most influential factor is breastfeeding history.

Keywords: Female; Breast Neoplasms; Breast Feeding; Case-Control Studies

1. Introduction

Cancer is a disease that occurs when cells in the body grow abnormally and uncontrollably [1]. Among the various types of cancer, breast cancer is a major health problem for women around the world. In addition to affecting physical health, this disease also has a significant emotional and social impact on women who experience it [2]. Breast cancer is the most common type of cancer among women, making it one of the most widely recognized health issues globally [3]. In 2022, breast cancer was one of the most common cancers worldwide, with approximately 2.3 million new cases accounting for 11.6% of all cancer cases [4]. In Southeast Asia, breast cancer is a very significant health problem [5]. Every year, breast cancer is diagnosed in approximately 41 out of 100,000 women, with a mortality rate of around 15 women per 100,000. This condition illustrates that even though case detection is increasingly being carried out, efforts to prevent, detect early, and manage breast cancer still face great challenges in this region [4].

Based on data from the global cancer observatory, among the various types of cancer, breast cancer was the highest contributor to mortality [6]. Indonesia is one of the countries with a relatively high burden of breast cancer cases and deaths. In the under-40 age group, Indonesia accounts for about 4% of the total 246,060 cases of early breast cancer

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worldwide. In addition, Indonesia also contributes about 3% of the 666,103 deaths from breast cancer in all age groups, as well as 4% of the approximately 48,700 deaths from early breast cancer (<40 years). This situation underscores the importance of more comprehensive and sustainable efforts in the prevention, early detection, and management of breast cancer in order to reduce the incidence and mortality rates of this disease [7].

The increasing incidence and mortality rates of breast cancer in Indonesia, especially among young women, require integrated and effective health services. In this regard, Bahteramas Regional General Hospital plays an important role as a referral hospital in Southeast Sulawesi Province that is not only focused on treatment, but also on promotional and preventive efforts. Hospital data shows a significant increase in breast cancer cases, from 113 new cases in 2022 to 251 cases in 2024 [8]. Based on the 2024 Bahteramas Regional General Hospital Profile, breast cancer is among the ten most common diseases among inpatients of all age groups at the Bahteramas Regional General Hospital in Southeast Sulawesi Province. In 2020, breast cancer ranked fifth with 251 cases (2.48%), increasing to fourth place in 2021 with 312 cases (2.71%). In 2022, this disease ranked eighth with 267 cases (1.69%), then rose again in 2023 to sixth place with 385 cases (2.10%), and in 2024 remained in sixth place with the number of cases increasing to 424 cases (2.02%). Additionally, breast cancer also showed an increase as a cause of death across all age groups. In 2022, breast cancer ranked ninth as a cause of death with 19 cases (2.0%), increased to eighth in 2023 with 32 cases (3.26%), and in 2024 rose significantly to third with 41 cases (3.87%) [8].

Hormonal balance, especially estrogen, plays a major role in breast cancer risk. Although estrogen is necessary for the development of female reproductive organs, prolonged exposure can make breast cells more susceptible to changes that can trigger cancer [9]. Premenopause usually occurs in women over the age of 40, characterized by the appearance of various changes and early symptoms of menopause that can affect comfort and quality of daily life [10]. According to Anwar, premenopause is a transitional period leading up to menopause, which is generally experienced by women between the ages of 40 and 50 [11]. This study presents new findings by focusing on hormonal risk factors in premenopausal women (aged 40–50), a group that has rarely been studied in relation to breast cancer risk. Based on the above analysis, the high incidence and mortality rates at Bahteramas Regional General Hospital indicate the need for local-based interventions that consider reproductive and hormonal risk factors, especially in the premenopausal age group. Therefore, the purpose of this study is to analyze breast cancer risk factors in premenopausal women at Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

2. Material and methods

This study was conducted in November 2025 at the Oncology Surgery Clinic of Bahteramas Regional General Hospital, Southeast Sulawesi Province. The location was chosen based on the profile of Bahteramas Regional General Hospital, which showed a high incidence of breast cancer, making it representative for the purposes of this study. The study design used comparative analysis with paired samples. To assess the strength of the relationship in the case-control study with age matching procedures, the Odds Ratio (OR) value was used. Bivariate analysis was performed using the McNemar test, while multivariate analysis used conditional logistic regression with the help of the STATA application.

3. Results

3.1. Research Risk Factors for Breast Cancer

3.1.1. Risk Factors of Age at Menarche on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Table 1 Risk Factors of Age at Menarche on the Incidence of Breast Cancer in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Control	**Case**			
	Early	Normal	Total	***OR* = 5.5** **95% CI = 1.200 – 51.065** **p-value = 0.022**
Early	1 (2.9%)	2 (5.7%)	3 (8.6%)	
Normal	11 (31.4%)	21 (60.0%)	32 (91.4%)	
Total	12 (34.3)	23 (65.7%)	35 (100.0%)	

Source: Primary Data

Based on Table 1, it is known that of the 35 pairs of premenopausal women in the case and control groups who were matched by age (100%), there were 11 pairs (31.4%) of respondents who experienced early menarche in the case group but normal menarche in the control group, while there were 2 pairs (5.7%) of respondents who experienced normal menarche in the case group but early menarche in the control group.

The results of a large-scale analysis of the effect of age at menarche on the incidence of breast cancer after age matching showed an OR value of 5.5. This means that premenopausal women who experienced early menarche have a 5.5 times greater risk of developing breast cancer compared to premenopausal women who experienced normal menarche. Since the lower limit (lower bound) = 1.200 and the upper limit (upper bound) = 51.065 of the OR at a 95% confidence interval (CI) do not include the value of one, this risk is statistically significant. Thus, after age matching, age at menarche is a risk factor for breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

3.1.2. Risk Factors of Breastfeeding History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Table 2 Risk Factors of Breastfeeding History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Control	**Cases**		**Total**	
	Non-exclusive	Exclusive		
Non-Exclusive	2 (5.7%)	2 (5.7%)	4 (11.4%)	***OR* = 5.0** **95% CI = 1.065 – 46.932** **p-value = 0.038**
Exclusive	10 (28.6%)	21 (60.0%)	31 (88.6%)	
Total	12 (34.3%)	23 (65.7%)	35 (100.0%)	

Source: Primary Data

Based on Table 2 and Table 13, it is known that of the 35 pairs of premenopausal women in the case and control groups who were matched for age (100%), there were 10 pairs (28.6%) of respondents who had a history of non-exclusive breastfeeding in the case group but a history of exclusive breastfeeding in the control group, while there were 2 pairs (5.7%) of respondents who had a history of exclusive breastfeeding in the case group but non-exclusive breastfeeding in the control group.

The results of a large-scale analysis of the effect of breastfeeding history on the incidence of breast cancer after age matching showed an OR value of 5.0. This means that premenopausal women with a history of non-exclusive breastfeeding have a 5.0 times greater risk of developing breast cancer compared to premenopausal women with a history of exclusive breastfeeding. Since the lower limit range = 1.065 and upper limit = 46.932, the OR at a 95% confidence interval (CI) does not include the value of one, indicating that the risk is statistically significant. Therefore, after age matching, breastfeeding history is a risk factor for breast cancer incidence among premenopausal women at Bahteramas General Hospital in Southeast Sulawesi Province in 2025.

3.1.3. Risk Factors of Age at First Birth on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Table 3 Risk Factors of Age at First Birth on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Control	**Cases**		**Total**	
	Childbirth in Old Age	Age at childbirth Young		
Childbirth in Old Age	2 (5.7%)	3 (8.6%)	5 (14.3%)	***OR* = 1.6** **95% CI = 0.324 – 10.732** **ρ-value = 0.726**
Age at childbirth Young	5 (14.3%)	25 (71.4%)	30 (85.7%)	
Total	7 (20.0%)	28 (80.0%)	35 (100%)	

Source: Primary Data

Based on Table 3, it is known that of the 35 pairs of premenopausal women in the case and control groups who were matched by age (100%), there were 5 pairs (14.3%) of respondents who gave birth at an older age in the case group but at a younger age in the control group, while there were 3 pairs (8.6%) of respondents who gave birth at a younger age in the case group but at an older age in the control group.

The results of a large-scale analysis of the effect of age at first birth on the incidence of breast cancer after age matching showed an OR value of 1.6. This means that premenopausal women who give birth at an older age have a 1.6 times greater risk of developing breast cancer compared to premenopausal women who give birth at a younger age. Since the lower limit (lower bound) = 0.324 and upper limit (upper bound) = 10.732 OR at a confidence level (CI) = 95% covers the value of one, the magnitude of the risk is not significant. Therefore, after adjusting for age, the age at first childbirth is not a risk factor for breast cancer incidence in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025.

3.1.4. Risk Factors of Reproductive History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Table 4 Risk Factors of Reproductive History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Control	**Cases**		**Total**	
	Nulliparous	Primipara		
Nulliparous	0 (0%)	3 (8.6%)	3 (8.6%)	***OR* = 1** **95% CI = 0.133 – 7.466** **ρ-value = 1.000**
Primipara	3 (8.6%)	29 (82.8%)	32 (91.4%)	
Total	3 (8.6%)	32 (91.4%)	35 (100%)	

Source: Primary Data

Based on Table 4, it is known that of the 35 pairs of premenopausal women in the case and control groups who were matched by age (100%), there were 3 pairs (8.6%) of respondents who had a nulliparous reproductive history in the case group but a primiparous reproductive history in the control group, while there were 3 pairs (8.6%) of respondents who had a primiparous reproductive history in the case group but a nulliparous reproductive history in the control group.

The results of the analysis of the significant effect of reproductive history on the incidence of breast cancer after age matching showed an OR value of 1.0, meaning that nulliparous reproductive history in premenopausal women is not a risk factor or protective factor for breast cancer compared to premenopausal women with primiparous reproductive history. Since the lower limit range (lower bound) = 0.133 and the upper limit = 7,466 the OR at a 95% confidence interval (CI) covers the value of one, so the risk is not significant. Thus, after age matching, reproductive history is not a risk factor for breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

3.1.5. Risk Factors of Hormonal Contraceptive Use History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Table 5 Risk Factors of Hormonal Contraceptive Use History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025

Control	**Case**		**Total**	
	Long Term	Short Term		
Long Term	8 (22.9%)	4 (11.4%)	12 (34.3%)	***OR* = 4.5** **95% CI = 1.482 – 18.279** **p-value = 0.004**
Short Term	18 (51.4%)	5 (14.3%)	23 (65.7%)	
Total	26 (74.3%)	9 (25.7%)	35 (100.0%)	

Source: Primary Data

Based on Table 5, it is known that of the 35 pairs of premenopausal women in the case and control groups who were matched by age (100%), respondents had a history of long-term hormonal contraception use in the case group, but in the control group, there were 18 pairs (51.4%) who had a history of short-term hormonal contraception use. Conversely, respondents who had a history of short-term hormonal contraception use in the case group, but in the control group had a history of long-term hormonal contraception use, numbered 4 pairs (11.4%).

The results of a large-scale analysis of the effect of hormonal contraceptive use history on the incidence of breast cancer after age matching showed an OR value of 4.5. This means that premenopausal women who have a history of long-term hormonal contraceptive use have a 4.5 times greater risk of developing breast cancer compared to premenopausal women who use short- term hormonal contraceptives. Because the lower limit range = 1.482 and the upper limit range = 18.279 OR at a confidence level (CI) = 95% does not include the value of one, the risk is significant. Thus, after age matching, a history of hormonal contraceptive use is a risk factor for breast cancer incidence among premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025.

3.2. The Most Significant Risk Factor for Breast Cancer Incidence

Based on the results of bivariate analysis using the McNemar test, it was found that the variables of age at menarche, breastfeeding history, and history of hormonal contraceptive use are risk factors for breast cancer, while age at first birth and reproductive history are not risk factors for breast cancer. At this stage, we wanted to determine the factors that have the greatest influence on breast cancer by continuing the analysis at the multivariate level. The variables included based on the previous bivariate analysis are risk factors for breast cancer, namely age at menarche, breastfeeding history, and history of hormonal contraceptive use. Therefore, the researchers conducted a conditional multivariate analysis using multiple logistic regression with the enter method. After the analysis, the following results were obtained:

Table 6 Results of Conditional Multivariate Regression Analysis of Age at Menarche, Breastfeeding History, and History of Hormonal Contraceptive Use on the Incidence of Breast Cancer in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Variable	Coef.	OR	SE	Z	Sig	95% CI	
						Lower	Upper
Age at menarche	1.24185	3.462012	1.016079	1.22	0.222	-0.7496289	3.233329
Breastfeeding History	2.267766	9.657805	0.9090689	2.49	0.013	0.4806241	4.049509
History of Use Hormonal Contraception	1.834254	6.260465	0.6744188	2.71	0.007	0.5084981	3.160011

Source: Primary Data

Based on Table 6, it can be seen that there are still variables with a value of ρ>0.05 and the smallest OR, namely age at menarche, so age at menarche was excluded from the analysis. After that, further analysis was carried out and the following results were obtained:

Table 7 Results of Conditional Multivariate Regression Analysis of Breastfeeding History and Hormonal Contraceptive Use History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Variable	Coef.	OR	SE	Z	Sig	95% CI	
						Lower	Upper
Breastfeeding History	2.374488	10.74551	0.9010143	2.64	0.008	1.837732	62.83065
History of Use Hormonal Contraception	2.015686	7.505878	0.6554214	3.08	0.002	2.077331	27.12047

Source: Primary Data

Based on Table 7 above, it is known that of all variables, only breastfeeding history (ρ value 0.008) and history of hormonal contraceptive use (ρ value 0.002) remained in the multivariate analysis. This is the final model of the conditional multivariate analysis with multiple logistic regression on risk factors for breast cancer in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025. From the results of the conditional multivariate analysis with multiple logistic regression, the final model considered to be the best consists of

breastfeeding history and history of hormonal contraceptive use. The equation is: Breast Cancer = 2.374488*breastfeeding history + 2.015686*history of hormonal contraceptive use.

Based on the OR value, it is known that breastfeeding history has an OR value of 10.7 with a 95% confidence interval between 1.837732 and 62.83065, meaning that premenopausal women who have a history of non-exclusive breastfeeding have a 10 times higher risk of developing breast cancer compared to premenopausal women who have a history of exclusive breastfeeding 10.7 times higher risk of developing breast cancer compared to premenopausal women who have a history of exclusive breastfeeding. A history of hormonal contraceptive use had an OR value of 7.5 with a 95% confidence interval between 2.077331 and 27.12047, meaning that premenopausal women with a history of long-term hormonal contraceptive use had a 7.5 times higher risk of developing breast cancer compared to premenopausal women who had a history of short-term hormonal contraceptive use. Based on the OR value, it can be concluded that a history of breastfeeding is the most significant risk factor for breast cancer incidence among premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

4. Discussion

4.1. Risk Factors of Age at Menarche on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Menarche is a marker of hormonal maturity in women. An earlier age at menarche (<12 years) is associated with an increased risk of breast cancer [12]. Women who experience menarche at an early age, before 12 years, have a higher risk of developing breast cancer [13].

The results of the analysis of the significant effect of age at menarche on the incidence of breast cancer after age matching showed an OR value of 5.5. This means that premenopausal women who experienced early menarche had a 5.5 times greater risk of developing breast cancer compared to premenopausal women who experienced normal menarche. Thus, after age matching, age at menarche is a risk factor for breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The results of the analysis between age at menarche and breast cancer incidence show that the ρ value is 0.022, so it can be concluded that there is significant relationship between age at menarche and the incidence of breast cancer in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025.

This study found that early menarche is a risk factor for breast cancer. Menarche marks the beginning of puberty in girls and the start of reproductive function. Menstruation occurs as cyclic bleeding from the uterus due to the shedding of the endometrial layer, which is influenced by changes in reproductive hormone levels [14]. Menarche can occur between the ages of 10 and 16, but most girls experience it between the ages of 12 and 14. In Indonesia, this age range is also the most common age for menarche [15]. If menarche occurs before the age of 12, it is categorized as early menarche [16].

Early menarche increases the risk of breast cancer because the body is exposed to estrogen for a longer period of time. This hormonal imbalance can promote abnormal breast cell growth, so women with menarche ≤12 years of age are reported to have up to four times higher risk of breast cancer [17]. In addition to hormonal factors, genetic aspects also influence the risk of breast cancer. Women with a family history of early menarche tend to have a higher risk of breast cancer. Epidemiological studies show that each year of earlier menarche can increase the relative risk of breast cancer by about 5% [18]. The longer the body is exposed to estrogen, the greater the possibility of genetic changes in breast cells. Exposure to estrogen from a young age has a stronger stimulating effect on breast epithelium, thereby increasing the risk of breast cancer, particularly estrogen receptor-positive and lobular types [19].

These findings are in line with research conducted by Hasnita (2019), which showed a significant influence between the risk factor of age at first menstruation and the incidence of breast cancer [9]. The results of Castro's (2024) study reinforce these findings by showing a significant relationship between age at menarche and the incidence of breast cancer, with a p-value of 0.044 [20]. Conversely, the results of this study are not in line with research conducted at Dr. H. Abdul Moeloek Provincial Hospital in Lampung (2017), which stated that there was no relationship between age at menarche and the incidence of breast cancer [21]. Additionally, research conducted at Prof. Dr. W. Z. Johannes Kupang Regional General Hospital also showed that age at menarche was not significantly associated with breast cancer incidence [19]. Previous studies only discussed the risk of early menarche in women in general, while this study specifically discussed the risk of early menarche in premenopausal women (aged 40-50 years) matched by age with the incidence of breast cancer.

4.2. Risk Factors of Breastfeeding History on the Incidence of Breast Cancer in Premenopausal Women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025

During lactation, the body undergoes biological changes that protect the breasts from cancer. This protection occurs through further maturation of breast epithelial cells and delayed ovulation cycles after childbirth [11].

The results of a large-scale analysis of the effect of breastfeeding history on the incidence of breast cancer after age matching showed an OR value of 5.0. This means that premenopausal women who have a history of non-exclusive breastfeeding have a 5.0 times greater risk of developing breast cancer compared to premenopausal women who have a history of exclusive breastfeeding. Thus, after age matching, breastfeeding history is a risk factor for breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The results of the analysis between breastfeeding history and breast cancer incidence show that the value of ρ (0.038), thus concluding that there is a significant relationship between breastfeeding history and breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province.

This study found that a history of non-exclusive breastfeeding is a risk factor for breast cancer. The WHO recommends exclusive breastfeeding for the first six months of life because breast milk is the safest and most optimal source of nutrition for infants [22]. In Indonesia, most mothers have breastfeeding their babies, but only about one in five mothers are able to provide exclusive breastfeeding for six months [23]. The WHO not only recommends exclusive breastfeeding for six months, but also encourages breastfeeding to continue until the age of two years or beyond [24]. A history of non-exclusive breastfeeding is a risk factor for breast cancer. Shorter breastfeeding duration reduces lactational amenorrhea, leading to earlier and more frequent exposure to estrogen, which promotes breast cell proliferation and increases mutation risk. Inadequate breastfeeding duration also limits epithelial cell maturation, making breast tissue more susceptible to DNA damage [25]. Various epidemiological studies report that short breastfeeding duration is associated with an increased risk of breast cancer. Women who breastfeed for less than six months have up to twice the risk, while extending breastfeeding for one year can provide protection by reducing the risk of breast cancer [26].

The relationship between breastfeeding and reduced risk of breast cancer can be explained by two main protective theories. First, during pregnancy and breastfeeding, breast cells undergo a more complete maturation process, making them more stable and less likely to undergo malignant transformation. Second, in women who do not breastfeed, changes in milk-producing cells occur more rapidly and can trigger inflammation, which in turn increases the risk of breast cancer, especially the non-hormone-dependent type. Conversely, in women who breastfeed, the process of breast tissue changes occurs more slowly and is not accompanied by excessive inflammation, thus providing a protective effect against the risk of breast cancer [27]. The WHO states that exclusive breastfeeding for six months is beneficial not only for the health of the baby, but also for the mother, one of which is by helping to protect the mother from the risk of breast cancer [28].

The results of this study are in line with research conducted at Dr. Pirngadi General Hospital in Medan, which found that not breastfeeding is significantly associated with breast cancer. These findings confirm the important role of reproductive and hormonal factors in the pathogenesis of breast cancer [29]. In addition, research conducted at Dr. H. Abdul Moeloek Provincial Hospital in Lampung also stated that not breastfeeding was significantly associated with breast cancer [18]. Research conducted at Dr. M. Djamil Padang General Hospital also stated that there was a significant association between breastfeeding history and breast cancer, with a p-value of 0.033 [30]. Research at Dr. Achmad Mochtar Bukittinggi Regional General Hospital showed that women with a history of breastfeeding for less than two years had a higher risk of breast cancer, with statistically significant analysis results (p = 0.005; OR 3.500) [31]. Previous studies only discussed the risk of breastfeeding history in women in general, while this study specifically discussed the risk of non-exclusive breastfeeding history in premenopausal women (aged 40-50 years) matched for age with the incidence of breast cancer.

4.3. Risk Factors of Age at First Birth on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Age at first pregnancy is an important predictor of breast cancer risk. Women who experience their first pregnancy at a younger age tend to have a lower lifetime risk of breast cancer [32]. Conversely, women who experience pregnancy or give birth to their first child after the age of 30 have a higher risk of developing breast cancer [13].

Biologically, first pregnancy triggers permanent changes in the breast gland epithelium, including the differentiation process and changes in the biological properties of breast cells. Breast epithelial cells undergo a longer cell cycle and remain longer in the G1 phase, which is an important phase for DNA repair. The older a woman is when she experiences her first pregnancy, the greater the likelihood of DNA damage that is not fully repaired, accompanied by increased breast

cell proliferation during pregnancy. This condition allows mutated cells to continue to develop, thereby increasing the risk of breast cancer, especially in the first decade after pregnancy [33].

The results of a large-scale analysis of the effect of age at first birth on the incidence of breast cancer after age matching showed an OR value of 1.6. This means that premenopausal women who give birth at an older age have a 1.6 times greater risk of developing breast cancer compared to premenopausal women who give birth at a younger age. Thus, after age matching, age at first birth is not a risk factor for breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The results of the analysis between the age at first birth and the incidence of breast cancer showed a ρ value of 0.726, leading to the conclusion that there is no significant relationship between the age at first birth and the incidence of breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

This study found that advanced maternal age is not a risk factor for breast cancer in premenopausal women. Age at first childbirth may influence breast cancer risk, but its effect is relatively weak and inconsistent. In premenopausal women, first childbirth after age 30 shows no strong association, particularly for ER-negative breast cancer, which is less sensitive to reproductive factors [34]. Conversely, in estrogen and progesterone receptor-positive (ER+ and PR+) breast cancer, giving birth to the first child at the age of over 30 is associated with an increased risk of breast cancer [35]. First full-term pregnancy at a young age provides a strong protective effect against breast cancer. Women who give birth to their first child before the age of 20 are known to have a breast cancer risk that is about half that of women who give birth for the first time after the age of 30 [36]. Older age at first full-term pregnancy is associated with an increased risk of breast cancer. Some studies have even found that women who give birth for the first time after the age of 30 have a higher risk than women who have never given birth [37].

Biologically, giving birth to your first child at an older age can increase the risk of breast cancer because breast epithelial cells remain immature for a longer period of time before undergoing differentiation. The longer these cells remain immature, the greater the chance of mutations and abnormal proliferation that can develop into breast cancer [38]. When pregnancy occurs at an older age, breast cell proliferation increases in preparation for lactation, while the ability of cells to repair DNA damage tends to decrease. As a result, cells with genetic damage are more likely to survive and proliferate, leading to the formation of precancerous lesions and increasing the likelihood of breast cancer. Thus, giving birth to the first child at an age above 30 is one of the reproductive factors that can increase the risk of breast cancer compared to giving birth at a younger age [39].

The results of this study are in line with research conducted at Dr. Ramelan Surabaya Army Hospital (2022), which stated that there was no significant relationship between age at first pregnancy and the incidence of estrogen receptor-positive breast cancer [40]. In addition, research conducted by Hasnita (2019) also showed that the age at first birth had no significant effect on the incidence of breast cancer ($p = 0.821$) [9]. However, these results are not in line with research conducted by Fadhila (2024), which stated that age at first pregnancy was significantly associated with the incidence of breast cancer ($p = 0.021$) [41]. Another study conducted at a Health Care Facility in 2021 stated that the age at first birth above 30 years is associated with the incidence of breast cancer [42].

4.4. Risk Factors of Reproductive History on Breast Cancer Incidence in Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Pregnancy has two different effects on breast cancer risk. In the long term, especially after two decades, the risk of hormone receptor-positive breast cancer decreases by 20–25% in women who have given birth compared to those who have not. This risk tends to be lower if the first pregnancy occurs at a younger age or if a woman has more than one child (multipara) [33]. Conversely, women who have never given birth (nullipara) have a higher risk of breast cancer, reaching about 50% compared to women who have given birth [43]. Pregnancy and lactation promote breast cell differentiation, increasing cellular maturity and resistance to genetic mutations. In contrast, nulliparous women who have never breastfed have a higher risk of breast cancer because their breast cells remain immature and more susceptible to DNA damage [33].

The results of a large-scale analysis of the effect of reproductive history on the incidence of breast cancer after age matching showed an OR value of 1.0. This means that nulliparous reproductive history in premenopausal women is not a risk factor or protective factor for an increased risk of breast cancer compared to premenopausal women who have a primiparous reproductive history. Thus, after age matching, reproductive history is not a risk factor for breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The results of the analysis between reproductive history and breast cancer incidence show that the value of ρ (1.000), thus concluding that there is no significant relationship between reproductive history and breast cancer

incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

This study found that nulliparity was not a risk factor for breast cancer in premenopausal women. Several studies have reported that reproductive history, such as never having given birth (nulliparity), is not always significantly associated with breast cancer. Reproductive factors also appear to have no effect on tumor malignancy, as evidenced by no significant differences between low-grade and high-grade tumors. The study emphasizes that the development of breast cancer is more influenced by other factors, such as genetics, age, race, and physiological factors such as sleep duration, so that the influence of reproductive history is relatively insignificant [44]. Biologically, breast cancer risk is influenced by exposure to ovarian hormones, particularly estrogen and progesterone, which stimulate breast cell growth. Reproductive factors that prolong hormonal exposure, such as late first pregnancy or nulliparity, are associated with an increased risk of breast cancer [37].

This is consistent with the theory of breast cell differentiation. In nulliparous women, breast epithelial tissue never undergoes the permanent differentiation that normally occurs during the first trimester of pregnancy. Without this maturation process, breast epithelial cells remain immature for longer, making them more susceptible to genetic mutations and abnormal proliferation. Epidemiological evidence from the Nurses' Health Studies shows that women who have given birth (parous) have a lower risk of estrogen receptor-positive (ER+) breast cancer than nulliparous women, whereas this difference is not found in ER-negative cancer [45].

In addition, a large aggregate study by Schonfeld et al. (2011) showed that nulliparity can increase the risk of breast cancer not only directly, but also through interaction with other risk factors. Nulliparous women are more susceptible to the effects of postmenopausal hormone therapy, obesity, alcohol consumption, family history, and benign breast disease. The combination of nulliparity and these factors can double the risk of breast cancer. These findings confirm that the absence of full-term pregnancy makes breast tissue more sensitive to hormonal exposure and potentially harmful lifestyles [46]. Women with few births, especially those who have never given birth, tend to face a higher risk of breast cancer than multiparous women. This is due to prolonged exposure to estrogen without the interruption of pregnancy and breastfeeding, which naturally helps lower hormone levels and strengthen breast tissue structure [47].

The results of this study are in line with research conducted by Hasnita (2019), which shows that reproductive history has no significant effect on the incidence of breast cancer ($p = 0.107$) [9]. A study conducted at Dr. M. Djamil General Hospital in Padang stated that there was no significant relationship between parity (nulliparity) and the incidence of breast cancer ($p = 0.476$) [30]. Conversely, the results of this study are not in line with the research conducted by Laamiri (2015), which shows that the parity factor (nulliparity) has a varying relationship with the incidence of breast cancer [48]. Other studies have shown that factors such as number of births (parity), breastfeeding history, and hormonal contraceptive use are significantly associated with breast cancer risk [49].

4.5. Risk Factors of Hormonal Contraceptive Use History on Breast Cancer Incidence Among Premenopausal Women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, 2025

Long-term use of hormonal contraceptives containing estrogen, for more than 10 years, is associated with an increased risk of breast cancer. A study at Prof. Dr. H. Aloei Saboe Gorontalo Regional General Hospital found that patients who used hormonal contraceptives for ≥10 years had twice the chance of developing breast cancer compared to users of short-term contraceptives or those without estrogen [50]. Several types of contraceptives are known to increase the risk of breast cancer [13]. Taking oral contraceptives or undergoing long-term hormone replacement therapy (HRT) is known to increase the risk of breast cancer, although the effect is relatively small [51]. Using hormonal contraceptives, such as birth control pills, for more than 10 years can increase the risk of breast cancer [9].

The results of a large-scale analysis of the effect of hormonal contraceptive use history on breast cancer incidence after age matching showed an OR value of 4.5. This means that premenopausal women who have a history of long-term hormonal contraceptive use have a 4.5 times greater risk of developing breast cancer compared to premenopausal women who use hormonal contraceptives for a short period of time. Thus, after age matching, a history of hormonal contraceptive use is a risk factor for breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025. The results of the analysis between the history of hormonal contraceptive use and the incidence of breast cancer showed that the value of ρ (0.004), so it can be concluded that there is a significant relationship between the history of hormonal contraceptive use and the incidence of breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

This study shows that a history of long-term hormonal contraceptive use is a risk factor for breast cancer. Contraception is a method of preventing pregnancy, either through the use of devices or medications that aim to regulate or delay the reproductive process [26]. The WHO classifies contraceptive methods into two main categories, namely hormonal and non- hormonal. Hormonal methods work by preventing ovulation, thickening cervical mucus, and thinning the endometrium, and are available in various forms, such as pills, hormonal IUDs, vaginal rings, implants, and injections. Meanwhile, non- hormonal methods include copper IUDs, male and female condoms, and permanent procedures such as vasectomy and female sterilization. The WHO emphasizes that this diversity of choices allows each individual to choose the method that best suits their health conditions, reproductive needs, and personal preferences [52].

Contraceptive use aims to prevent unintended pregnancies, reduce maternal and infant morbidity and mortality, and support healthy family planning [53]. According to the WHO, contraception also helps delay adolescent and high-risk pregnancies, reduce unsafe abortions and mother-to-child HIV transmission, and provide social benefits such as improved education and increased women's participation in society [52]. In Indonesia, the use of traditional contraception is slightly higher than modern methods. However, among couples of childbearing age (PUS), hormonal methods are the primary choice, with injections reaching 53%, pills 18%, and implants 11.7% [24]. A history of long-term hormonal contraceptive use (more than 5 years) has been shown to be a risk factor for breast cancer [31]. Synthetic estrogen and progesterone in hormonal contraceptives stimulate breast cell proliferation, increasing mutation risk and cancer development. Hormonal contraceptive use has been reported to raise breast cancer risk up to threefold, partly by promoting the growth of breast cancer stem cells [54]. Long-term use of hormonal contraception, particularly oral contraceptives, is associated with an increased risk of breast cancer due to hormonal imbalance, stimulation of breast cell proliferation, and genetic mutations. Studies by Bardaweel et al. (2019) and Motie et al. (2021) report a strong association, with age and duration of use being important risk factors; therefore, individual risk assessment and regular monitoring are recommended [55].

The results of this study are in line with research by Hasnita (2019), which shows that the duration of contraceptive pill use has a significant effect on the incidence of breast cancer (p = 0.05; OR = 3.16) [9]. In this study, the duration of contraceptive pill use was proven to be the most dominant risk factor (p = 0.035). A study at Dr. Pirngadi General Hospital in Medan also showed that in young women aged 16–40 years, hormonal contraceptive use was significantly correlated with the incidence of breast cancer. This emphasizes the important role of reproductive and hormonal factors in the development of breast cancer [29]. Research at Dr. H. Abdul Moeloek Provincial Hospital in Lampung (2017) stated that hormonal contraceptive use was associated with breast cancer incidence [18]. Several studies have reported that the relationship between hormonal contraceptive use and breast cancer risk is not always consistent, so the effects may vary depending on individual factors and duration of use [48].

Conversely, research at Dr. Soegiri Lamongan Regional General Hospital found that there was no significant association between the duration of hormonal contraceptive use and the incidence of breast cancer (p = 0.775) [56]. Another study conducted at a health care facility in 2021 also stated that contraceptive use for more than 4 years was not associated with the incidence of breast cancer [42]. Previous studies only discussed the risk of hormonal contraceptive use in women in general, while this study specifically discussed the risk of long-term hormonal contraceptive use in premenopausal women (aged 40- 50 years) matched for age with the incidence of breast cancer.

4.6. The Most Significant Risk Factors for Breast Cancer Incidence in Premenopausal Women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025

Based on bivariate analysis, it was found that the variables of age at menarche, breastfeeding history, and history of hormonal contraceptive use were risk factors for breast cancer, while age at first birth and reproductive history were not risk factors for breast cancer. This was followed by multivariate analysis, which found that the factors with the greatest influence on breast cancer incidence were modifiable factors, namely non-exclusive breastfeeding history with an OR value of 10.7 and long-term hormonal contraceptive use history with an OR value of 7.5 (see Table 7). Thus, it can be concluded that breastfeeding history is the factor with the greatest influence on breast cancer incidence in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.

Statistically, the effect of age at menarche has a sufficiently high significance value that it must be excluded from the model. Thus, the model obtained explains the effect of breastfeeding history and hormonal contraceptive use history on the incidence of breast cancer in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025. From the results of conditional multivariate analysis with multiple logistic regression, the final model considered to be the best was obtained, consisting of breastfeeding history and hormonal contraceptive use history. The equation is: Breast Cancer= 2.374488*breastfeeding history + 2.015686*hormonal contraceptive use history.

Exclusive breastfeeding is the feeding of breast milk alone, without any other food or drink, to infants from birth to 6 months of age [57]. The purpose of exclusive breastfeeding is to guarantee the baby's right to receive breast milk, protect mothers in providing exclusive breastfeeding, and strengthen the role and support of families, communities, and local and central governments in supporting the continuation of exclusive breastfeeding [58]. A history of non-exclusive breastfeeding has been statistically proven to be the most dominant risk factor for breast cancer in premenopausal women compared to those with a history of exclusive breastfeeding.

Breastfeeding plays an important role in reducing the risk of breast cancer through several biological mechanisms. First, breastfeeding suppresses ovulation, causing mothers to experience a period of postpartum amenorrhea. This condition reduces exposure to estrogen, which is known to play a role in the development of breast cancer [24]. Second, breastfeeding promotes the differentiation and maturation of breast epithelial cells, while helping to eliminate cells with DNA damage through the process of exfoliation. This mechanism makes breast tissue more resistant to mutations and reduces the likelihood of carcinogenic transformation [59].

The duration of breastfeeding affects the level of protection against breast cancer. Meta-analysis studies show that breastfeeding for more than 12 months can reduce the risk by almost half compared to women who do not breastfeed or only breastfeed for a short period of time. Conversely, breastfeeding for less than 6 months actually increases the risk significantly [60]. The protective effect of breastfeeding against breast cancer also applies to more aggressive types of cancer, such as triple-negative, as well as to women who are carriers of the BRCA1 mutation [59].

In addition to direct hormonal effects, breastfeeding triggers the hypothalamus to decrease estrogen and progesterone secretion and increase prolactin production to support lactation. With the reduction of these reproductive hormones, breast cell growth stimulation also decreases, thereby reducing the risk of cancer [60]. The benefits of breastfeeding are not only felt by the mother, but also by the baby. Breast milk provides complete nutrition, antibodies, and immune factors that support the baby's growth, immunity, and cognitive development. In fact, children who have been breastfed have a lower risk of developing breast cancer in adulthood [61].

At the molecular level, breast milk also exhibits protective effects. The α-lactalbumin and oleic acid complex forms a HAMLET/liprotide structure that can destroy breast cancer cells by damaging the plasma membrane, while normal adult cells remain safe from this effect [62]. In addition, enzymes such as lysozyme and lactoferrin also play a role in protection. Lysozyme helps inhibit bacterial proliferation, while lactoferrin binds iron, which is essential for microbial growth, thereby supporting the overall health of the infant [63].

This study found that a history of non-exclusive breastfeeding was the most dominant factor influencing the incidence of breast cancer. These findings were reinforced by previous research by Giudici (2017), which showed that after multivariate analysis, breastfeeding history had the greatest influence on breast cancer risk in premenopausal women, with an OR of 2.15 [64]. Conversely, other studies show that a history of hormonal contraceptive use has the greatest influence on the incidence of breast cancer. For example, Fadhila (2024) reported that the dominant factor related to breast cancer risk is hormonal contraceptive use, with an OR value of 4.872 [65]. Additionally, Hasnita (2019) stated that after multivariate analysis, the duration of contraceptive pill use was the most dominant variable affecting breast cancer risk, with a p-value of 0.03 [9]. Research by Maysarah (2018), using multivariate analysis with conditional logistic regression, shows that the variables that most influence the incidence of breast cancer at H. Adam Malik General Hospital are a family history of breast cancer, obesity, and duration of hormonal contraceptive use [66].

5. Conclusion

- Early menarche increases the risk of breast cancer by 5.5 times in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025.
- A history of non-exclusive breastfeeding carries a 5.0 times higher risk of breast cancer in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025.
- Age at first childbirth is not a risk factor for breast cancer incidence in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025, with an OR of 1.6 and ρ (0.726) > α (0.05).
- Reproductive history is not a risk factor for breast cancer incidence in premenopausal women at Bahteramas Regional General Hospital, Southeast Sulawesi Province, in 2025, with an OR of 1.0 and ρ (1.000) > α (0.05).
- A history of long-term hormonal contraceptive use carries a 4.5 times higher risk of breast cancer in premenopausal women at the Bahteramas Regional General Hospital in Southeast Sulawesi Province in 2025.
- The factor that has the greatest influence on the incidence of breast cancer in premenopausal women at Bahteramas Regional General Hospital is a history of breastfeeding, with an OR of 10.7 and ρ (0.008) < α (0.05).

Compliance with ethical standards

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Disclosure of Conflict of interest

There is no conflict of interest in this study.

Statement of ethical approval

This study has received ethical approval from the Ethics Committee of Bahteramas Regional General Hospital, Southeast Sulawesi Province, as well as from IAKMI (Indonesian Public Health Experts Association). The approval was granted after a thorough review of the research protocol, including the study objectives, methodology, potential risks and benefits, participant protection measures, and data confidentiality procedures. All research activities were conducted in full compliance with applicable ethical standards and guidelines for research involving human subjects.

Statement of informed consent

As a researcher, I affirm that I have provided complete, clear, and comprehensible information to the prospective participant regarding the objectives of the study, the procedures to be undertaken, the potential benefits and risks, the principles of data confidentiality, as well as the participant's right to refuse or withdraw from the study at any time without any consequences. I ensure that the entire process of obtaining informed consent is conducted ethically, voluntarily, without coercion, and in accordance with established research ethics standards. Accordingly, I guarantee that the participant has received sufficient information to make an informed and responsible decision regarding their participation in this study.

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