ORIGINAL RESEARCH ARTICLE

Risk factors for fibroadenoma mammae (FAM) among adult women at the South Tangerang General Hospital in Indonesia

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ABSTRACT

A frequent benign breast tumor, fibroadenoma mammae (FAM), has extra stromal and epithelial components in the breast tissue. Despite not being fatal, FAM increases breast cancer risk, highlighting the necessity to recognize it. Estrogen and progesterone levels during menstruation, pregnancy, and lactation may alter FAM development. Therefore, this study examines FAM risk variables in adult women at South Tangerang Regional General Hospital, Indonesia. Adult women in General Hospital of South Tangerang City, Indonesia were studied using a case-control design with 85 cases and 85 controls. South Tangerang General Hospital recruited volunteers between December 2023 and January 2024 using purposeful sampling. FAM patients with a history of therapy were cases, while Eye Clinic patients without FAM were controls. Viral diseases, major cardiovascular problems in the past three years, and unstable weight were excluded. Multivariate analyses employed multiple logistic regression, while univariate and bivariate analyses used percentages and chi-square test. Fibroadenoma mammae (FAM) prevalence in adult women at South Tangerang General Hospital is highly correlated with age, age of menarche, family history, hormonal contraceptive use, and nutritional status. Abnormal nutrition was the largest risk factor for FAM in hospitalized adult women (aOR = 8.678, $p < 0.000$). The study stresses the link between nutritional state and FAM, with abnormal nutritional status increasing risk. This shows how diet and nutrition affect FAM sensitivity. To reduce FAM prevalence, demographic, genetic, hormonal, and lifestyle factors must be understood and addressed due to their complex interaction. Dietary strategies that promote healthy eating may reduce FAM risk.

Keywords: fibroadenoma mammae (FAM); risk factors; adult women; case-control study

1. Introduction

A fibroadenoma mammae (FAM) is a prevalent benign breast tumor that is encountered frequently in clinical settings[1]. Fibroadenomas, which are distinguished by an overabundance of stromal and epithelial components, frequently manifest as palpable structures in the breast. These lesions are characterized by their clinical variability, which includes a broad spectrum of manifestations from asymptomatic findings to distress and anxiety, and they primarily impact women in their reproductive years[2].

FAM has the character of being painless, movable, well-defined and has a firm, springy consistency. FAM typically manifests at a young age[3]. It is predominantly prevalent among teens and less frequently observed among postmenopausal women[4]. FAM generally does not cause mortality unless there is transformation to

malignancy[5]. Women with FAM have a two to threefold increased risk of developing breast cancer compared to women of comparable age in the general population[6].

Breast cancer, according to a report by the World Health Organization (WHO), is the second most prevalent malignancy affecting Indonesian women, following cervical cancer. In 2018, the incidence of breast cancer and tumor patients in Indonesia increased from 1.4 per 1000 inhabitants in 2013 to 1.79 per 1000 inhabitants. In contrast, basic health research (Riset Kesehatan Dasar) 2018 reports that the prevalence of breast cancer among women in Indonesia is 42.1 per 100,000 individuals, accompanied by an average fatality rate of 17 per 100,000[7].

Based on data obtained from the Indonesian Ministry of Health, the number of cases detected early of breast tumors in women aged 30 to 50 in 2019 amounted to 28,910 cases. Among the 113,838 individuals examined, the province of West Java had the highest incidence, with 6109 cases, detected early. Conversely, the province of Papua reported the fewest cases, comprising a mere four out of a total examination of 1078 individuals. Similarly, a grand total of 91,036 examinations were conducted in the Indonesian capital, DKI Jakarta, which yielded 4610 cases[8].

While the precise etiology of FAM remains uncertain, various factors have been implicated in the development of FAM problems, including familial genetics, age, hormonal imbalances, exposure to radiation, and the use of contraceptives[9,10]. The incidence of familial adenomatous polyposis (FAP) cases is steadily rising each year, giving rise to apprehensions over the presence of breast masses, which are frequently mistaken for malignancies[11].

The development of FAM is intricately linked to hormonal fluctuations that transpire in women[12]. The hormones estrogen and progesterone in women that always change during menstruation, pregnancy and breastfeeding are said to be one of the causes of FAM growth[13,14]. Consequently, the objective of this research endeavor was to identify the risk factors associated with FAM in adult women at South Tangerang Regional General Hospital, Indonesia.

2. Methods

2.1. Data source and study design

This study utilized a case-control design and focused on women adults residing in metropolitan areas of South Tangerang City, Indonesia. The sample size comprises 85 cases and 85 control subjects. The sample size was determined using the formula specific to case-control study. The selection of subjects was determined using the purposive sampling technique. Moreover, the participants were enlisted by voluntary involvement at the South Tangerang General Hospital over the period of December 2023 to January 2024. The cases consisted of individuals who had been diagnosed with FAM based on medical record data, as well as a history of therapy for FAM. The controls consisted of patients from the Eye Clinic at South Tangerang City General Hospital, as indicated by the medical record data, and did not include patients with FAM. Participants who had an infectious disease or a serious cardiovascular condition in the past three years, as well as those with an unstable weight (less than a 5% fluctuation in weight in the last three months), were not included in the study.

2.2. Variable of the study

The dependent variable, FAM status, was collected from the hospital medical record as reported by a consultant mammae radiologist. A questionnaire was retrospectively used to collect data on variables like current age, age at menarche, marital status, family history, use hormonal contraception, exclusive breastfeeding, nutritional status, where all variables were categorised dichotomously. The current age variable takes the median age of 45 years as the cut off point with age < 45 years categorised as at-risk, and age ≥ 45 years not at-risk.

The age at which menarche occurred was deemed to be 12 years; therefore, women who commenced menstruation prior to that age had a greater likelihood of developing FAM than those who commenced menstruation at or after the age of 12 years. Unmarried women with a family history of FAM, who have utilized birth planning methods, who have never exclusively breastfed are classified as being at risk.

The nutritional status indicators are determined using body mass index (BMI) calculations, which are obtained by dividing the weight (in kilograms) by the square of the height (in square meters) and categorised into 2 categories, namely normal and abnormal, where respondents were said to have normal nutritional status if they had a BMI of 18.5–22.9 kg/m^2, while respondents were abnormal if they were classified as underweight (underweight (BMI < 18.5 kg/m^2) and (overweight and obese BMI ≥ 23.0 kg/m^2).

2.3. Statistical analysis

This study performed univariate and bivariate analysis using percentages and the chi-square test, then utilized multiple logistic regression to conduct a multivariate test using. The candidate variables with a p-value of less than 0.25 from the bivariate analysis were selected for inclusion in the multivariate analysis. At first, all potential variables were included in the multivariable model for analysis. Subsequently, variables having p values over 0.05 were eliminated from the model in a sequential manner. The final model was generated once all variables with p values > 0.05 or confounding factors were eliminated. The p-values provided were calculated using a two-tailed hypothesis. Statistical Product and Service Solutions (SPSS) for Windows, version 28 (licensed by Faculty of Public Health, Universitas Muhammadiyah Jakarta), was utilized to conduct all statistical analyses.

2.4. Ethics approval

The research was carried out with the necessary ethical approval and permission granted by the Ethical Committee of Health Research, Faculty of Public Health, Universitas Muhammadiyah Jakarta (Komite Etik Penelitian Kesehatan, Fakultas Kesehatan Masyarakat) under the reference number 10.388.C/KEPK-FKMUMJ/XII/2023.

3. Results

3.1. Characteristics of respondents

Table 1 presents a summary of the distribution of respondents, including both FAM cases and controls, along with the characteristics of the respondents. The results of the descriptive analysis of characteristics (**Table 1**) indicated that 51.2% of the respondents were aged younger than 45 years, while 48.8% of the respondents were 45 years and older. 54.7% of the respondents were at risk of experiencing menarche at an age of 12 years or older. 75.3% of the respondents were married at some point. 56.5% of the respondents do not have a family history of familial adenomatous polyposis (FAM). 57.6% of the respondents have used hormonal contraception. 64.7% of the respondents have never breastfed. The majority of the respondents have an abnormal nutritional status, with 85.9% falling into this category.

Table 1. Characteristics of respondents.

Characteristics (n = 170)	Number (n)	Percent (%)
Groups		
Case	85	50.0
Control	85	50.0

Table 1. (*Continued*).

Characteristics (*n* = 170)	Number (*n*)	Percent (%)
Current age		
At risk (<45 years)	87	51.2
Not at risk (≥45 years)	83	48.8
Age at menarche		
At risk (<12 years)	93	54.7
Not at risk (≥12 years)	77	45.3
Marital status		
Never married	42	24.7
Ever married	128	75.3
Family history		
Yes	74	43.5
No	96	56.5
Use hormonal contraception		
Ever	98	57.6
Never	72	42.4
Exclusively breastfed		
Never breastfed	110	64.7
Ever breastfed	60	35.3
Nutritional status		
Abnormal (underweight, overweight, obese)	146	85.9
Normal	24	14.1

3.2. Risk factors of FAM among case and control groups

The bivariate analysis, which utilized a chi-squared test with a significance level below 0.05, provided an initial insight into the characteristics of women afflicted with FAM (**Table 2**). For the multivariate analysis, variables were selected with a significance level of $p < 0.05$ (**Table 3**).

Table 2. Risk factors of FAM among case and control groups.

Variables	Fibroadenoma						*p*-value	OR	95% CI	
	Case		Control		Total					
	n	%	*n*	%	*n*	%			Lower	Upper
Current age										
At risk (<45 years)	26	30.6	61	71.8	87	51.2	<0.0001	0.173	0.090	0.336
Not at risk (≥45 years)	59	69.4	24	28.2	83	48.8				
Age at menarche										
At risk (<12 years)	55	64.7	38	44.7	93	54.7	**0.014**	2.268	1.223	4.203
Not at risk (≥12 years)	30	35.3	47	55.3	77	45.3				
Marital status										
Never married	27	31.8	15	17.6	42	24.7	0.050	2.172	1.057	4.466
Ever married	58	68.2	70	82.4	128	75.3				
Family history										
Yes	44	51.8	30	35.3	74	43.5	0.044	1.967	1.063	3.641
No	41	48.2	55	64.7	96	56.5				

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Table 2. (*Continued*).

Variables	Fibroadenoma						*p*-value	OR	95% CI	
	Case		Control		Total					
	n	%	*n*	%	*n*	%			Lower	Upper
Use hormonal contraception										
Ever	35	41.2	63	74.1	98	57.6	<0.0001	0.244	0.128	0.468
Never	50	58.8	22	25.9	72	42.4				
Breastfed										
Never breastfed	52	61.2	58	68.2	110	64.7	0.422	0.734	0.390	1.379
Ever breastfed	33	38.8	27	31.8	60	35.3				
Nutritional status										
Abnormal (underweight, overweight, obese)	79	92.9	67	78.8	146	85.9	**0.015**	3.537	1.328	9.421
Normal	6	7.1	18	21.2	24	14.1				

3.3. Multivariate logistic regression results

In South Tangerang General Hospital, the prevalence of fibroadenoma mammae (FAM) among adult women is strongly connected with factors such as current age, age of menarche, family history of FAM, use hormonal contraception, and nutritional status, as shown in **Table 3**. This table provides a summary of the factors that are linked with FAM using Model III. Respondents who are currently 45 years old or younger were found to be protective factors of FAM [aOR = 0.211 (0.095–0.467); *p* < 0.000] as compared to responding individuals who were older than 45 years old. A higher risk of FAM was seen among respondents with a family history of FAM [aOR = 2.310 (1.097–4.866); *p* < 0.000]. Additionally, respondents with a family history of FAM had a higher risk of FAM [aOR = 2.151 (1.021–4.531); *p* < 0.044] in comparison to respondents who did not have a family history of FAM. There was a substantial protective factor in the incidence of FAM among respondents who had used hormonal contraception [aOR = 0.260 (0.113–0.596); *p* < 0.001]. Lastly, the nutritional status of adult women at South Tangerang General Hospital in Indonesia is the factor that determines the highest risk of FAM [aOR = 8.678 (2.613–28.820); *p* < 0.000].

Table 3. Estimated of FAM incidence (multiple logistic regression analysis), *n* = 170.

Variables	Model I				Model II				Model III			
	p-value	aOR	CI 95%		*p*-value	aOR	CI 95%		*p*-value	aOR	CI 95%	
			Lower	Upper			Lower	Upper			Lower	Upper
Current age	0.000	0.210	0.092	0.478	0.000	0.215	0.097	0.479	0.000	0.211	0.095	0.467
Age at menarche	0.026	2.340	1.106	4.951	0.027	2.315	1.098	4.881	0.028	2.310	1.097	4.866
Marital status	0.554	1.408	0.454	4.370	0.521	1.442	0.472	4.405	-	-	-	-
Family history	0.055	2.104	0.986	4.492	0.045	2.146	1.018	4.523	0.044	2.151	1.021	4.531
Use hormonal contraception	0.010	0.297	0.119	0.746	0.010	0.297	0.119	0.745	0.001	0.260	0.113	0.596
nd	0.787	1.119	0.494	2.533	-	-	-	-	-	-	-	-
Nutritional status	0.001	10.171	2.748	37.649	0.001	9.983	2.727	36.547	0.000	8.678	2.613	28.820

4. Discussions

The analysis findings indicate that individuals under the age of 45 exhibit a reduced risk of developing mammary fibroadenoma in comparison to those aged 45 years and above. Several prior studies have established that age below 45 years is, in fact, a greater risk factor for the development of FAM[13,15,16]; this finds oppositional to the inverse relationship. The control group in this study consisted mostly of responders

who were at a FAM risk age, which is defined as being younger than 45 years old.

This hypothesis offers a plausible account for the disparity in findings when compared to prior research. If the control group in the current study predominantly comprised persons below the age of 45, it implies that the comparison group used to evaluate the risk of developing breast fibroadenoma may not effectively represent the wider community. Previous researchers have found that those below the age of 45 are more likely to acquire fibroadenoma. However, it is possible that the control group in these studies comprised individuals from a wider age range or explicitly focused on older age groups. The current study may unintentionally bias the comparison and yield conflicting outcomes by mostly including younger participants in the control group[17–19].

Additionally, an earlier study found that a later age at menarche is typically correlated with a reduced likelihood of developing FAM[17]. This is in line with the findings of the study which states that respondents with menarche age < 12 years are at higher risk of having FAM (aOR = 2.310). The onset of menstruation in females, known as menarche, is influenced by the length of time that the body is exposed to the hormones estrogen and progesterone[20].

Menarche, the initial phase of menstruation, is distinguished by monthly variations in hormonal concentrations, ovulation, and cellular proliferation within the breasts. Breast development begins one to two years prior to the occurrence of menarche, and it accelerates significantly during puberty[21], factors that contribute to the breasts' size and shape. Hormones, including estrogen, are of paramount importance in these processes as they regulate the development of breast tissue and its capacity to operate in anticipation of future lactation[22].

The hormonal fluctuations that occur during puberty have implications for breast health in addition to physical development. Individuals may experience significant variation in the duration and rate of these developments, which may be impacted by environmental, nutritional, and genetic factors[23]. For example, an earlier initiation of menarche has been linked to heightened susceptibility to specific breast ailments and diseases in old age, including fibroadenomas and potentially breast cancer, as a result of extended estrogen exposure throughout one's lifespan[24,25].

Individuals who reported a familial predisposition to FAM were found to have a twofold increased risk of developing the condition in comparison to those who did not have such a family history (aOR = 2.151). Those who have a familial predisposition to FAM have an exceptionally heightened likelihood of developing the condition. This observation highlights the possibility that hereditary or genetic elements play a role in the formation of fibroadenomas[26]. The observed twofold rise in risk indicates that familial genetic composition may have an impact on the properties of breast tissue, predisposing individuals to this benign condition[27].

Some researchers have shown a connection between a family history of breast cancer in close relatives and a higher likelihood of developing benign tumors[28,29]. Existing research suggests that the manner in which familial history influences the risk of fibroadenoma may be mediated by genetic variants, shared environmental factors, or a combination of the two. The hormonal regulation and response of breast tissue to hormonal changes during puberty, pregnancy, and other periods of hormonal fluctuation may be influenced by these genetic factors[30].

In addition, by comprehending this genetic correlation, potential avenues for earlier surveillance and management strategies for individuals with a family history of increased risk can be identified. As an illustration, individuals with a documented familial predisposition to fibroadenomas might be advised to undergo more frequent clinical examinations or adhere to personalized screening protocols. This would enable for more efficient management and monitoring of breast tissue changes[26,31,32].

There was a substantial protective factor in the incidence of FAM among respondents who had used

hormonal contraception [aOR = 0.260 (0.113–0.596); $p < 0.001$]. Hormonal contraceptives typically function by modulating the levels of estrogen and progesterone[33], the pivotal hormones implicated in the menstrual cycle and the growth of breast tissue. These contraceptives frequently regulate hormone levels to a consistent condition, minimizing the fluctuations that are characteristic of a normal menstrual cycle. Stabilization can reduce the probability of hyperplastic alterations in breast tissue that occur before disorders such as fibroadenomas[34].

A multitude of hormonal contraceptives operate by inhibiting the process of ovulation. Every ovulatory cycle usually results in variations in hormone levels, especially estrogen, which might promote the growth of breast tissue. Hormonal contraceptives can decrease the frequency of ovulatory cycles in women, which can reduce the stimulation that may lead to the development of fibroadenomas[35].

Certain contraceptives contain progestin, which has the ability to inhibit the effects of estrogen on breast tissue[33]. This indicates that they have the ability to neutralize the growth-promoting impact of estrogen on the cells and tissues of the breast, specifically the epithelium and stroma, which are the sites where fibroadenomas form. Progestin's presence maintains breast tissue in a less active and more inactive condition, hence lowering the likelihood of developing benign tumors[4].

Prolonged usage of hormonal contraceptives has been linked to alterations in breast density. Reduced breast density has been associated with decreased breast tissue growth, potentially leading to a decreased likelihood of developing fibroadenomas[36]. The length of time that contraceptives are used also has a notable impact. Extended utilization of hormonal contraceptives has been linked to a stronger safeguarding impact against benign breast conditions, such as fibroadenomas. Extended exposure to regulated hormone levels contributes to the long-term stability of breast tissue[37].

The nutritional status of adult women at South Tangerang General Hospital in Indonesia is the determinant of the greatest risk of FAM, according to a multivariate analysis employing multiple logistic regression (aOR = 8.678). Recent studies have investigated possible correlations between obesity or body weight and the likelihood of developing fibroadenoma. There is some evidence to suggest that a higher body mass index is associated with a greater risk of developing fibroadenomas. The correlation in question might be ascribed to hormonal fluctuations that are linked to adiposity[38].

Disturbances in dietary status, such as being overweight or obese, can result in hormonal abnormalities, specifically affecting estrogen levels. Adipose tissue, often known as fat tissue, has the ability to synthesize estrogen using an enzyme called aromatase. This enzyme transforms androgens into estrogens. Increased levels of estrogen are associated with several non-cancerous breast disorders, such as fibroadenomatosis (FAM), due to the important function that estrogen plays in the growth and development of breast tissue[39].

Obesity frequently correlates with insulin resistance, a state in which the body's cells exhibit reduced responsiveness to insulin. This can result in elevated levels of insulin and insulin-like growth factors (IGF) in the bloodstream. These variables are recognized to stimulate cell proliferation, particularly in breast tissues, which may result in the development of fibroadenomas[40].

Chronic inflammation is caused by an excess of body fat. Cytokines, produced by adipocytes, are inflammatory mediators that can impact cellular processes in different tissues, including the mammary gland. The presence of inflammation in the body can facilitate the development of non-cancerous tumors like fibroadenomas[40,41].

Obesity causes a greater accumulation of fat in the breast, which might potentially affect the surrounding environment of breast tissue. This modified environment has the potential to facilitate the development and expansion of fibroadenomas. Adipokines are endocrine hormones released by adipose tissue, and their concentrations are frequently modified in cases of obesity. These modifications can influence diverse

biological pathways, including those implicated in the proliferation and specialization of cells in breast tissues. Obesity is linked to a greater occurrence of various diseases, and the specific ways in which it impacts the likelihood of certain ailments such as FAM can differ. However, it is generally advised to maintain a healthy weight through food and exercise as part of overall health initiatives in order to limit the risk of numerous diseases, including breast problems such as fibroadenoma[42].

5. Limitation

One of the constraints of this research is that data collection on specific variables was conducted autonomously by participants, thereby precluding the ability of the researchers to oversee and ensure the accuracy of the completed questionnaire. Recall bias may potentially arise in this study due to the limitations of the respondents in recollecting specific events, including the age of menarche, the duration of birth control use, and the duration of lactation. In this case, the age of first menstruation may correspond to the age of menarche. The scarcity of FAM references in the study's background and discussion hindered researchers' ability to establish comparisons between the data and the findings of prior investigations. Furthermore, this investigation is constrained to establishing the presence or absence of a correlation; it does not delve into the investigation of cause and effect between variables; and it is not capable of computing the prevalence of a disease, which is an inherent limitation of the case-control study design.

6. Conclusion and suggestions

The study highlights the considerable influence of nutritional status on the prevalence of FAM; those classified as having an aberrant nutritional status demonstrate a considerably elevated risk of developing FAM. This highlights the significance of dietary patterns and general nutritional status in regulating the vulnerability to FAM. The study also underscores the complex interplay of demographic, genetic, hormonal, and lifestyle factors influencing the prevalence of fibroadenoma mammae (FAM) in adult women. To effectively reduce and prevent FAM, it is crucial for managers and planners to implement targeted interventions. Firstly, promoting nutritional education and regular physical activity can help mitigate the risk associated with abnormal nutritional status, identified as the most significant risk factor for FAM. Secondly, healthcare providers should be encouraged to discuss the benefits of hormonal contraceptives, which have been shown to provide a protective effect against FAM. Thirdly, early screening and genetic counseling for women with a family history of FAM can lead to timely interventions. Lastly, public awareness campaigns should be launched to educate women about the risk factors and encourage early medical consultation. By adopting these evidence-based strategies, we can enhance breast health and reduce the incidence of FAM among women.

Author contributions

Conceptualization, SJ and NL; methodology, NL; software, SJ and NL; validation, SJ, MF and NL; formal analysis, MF and NL; investigation, MF and AA; resources, AA; data curation, NL; writing—original draft preparation, SJ, MF, NL, AA, GA and ML; writing—review and editing, SJ, MF and GA; visualization, AA and GA; supervision, SJ, MF and GA; project administration, ML; funding acquisition, SJ and MF. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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