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The Effect of Progesterone Levels Changes in the Blood on the Progressivity of Luminal a Breast Cancer

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Abstract: ***Objectives:*** Breast cancer is the most common type of cancer in Indonesia, accounting for 28% of all cancer diseases. This number increases annually (Departemen Kesehatan RI, Statistik morbiditas dan mortalitas di rumah sakit; 2005-2010). Breast cancer in women is associated with progesterone hormone, which is a female reproductive hormone (DeVita, V. T. *et al.*, 2011). Both in-vivo and in-vitro researches on the effect of progesterone on breast cancer progression has been carried out in other studies. However, clinical research on this topic is rarely done. Therefore, the authors were interested in doing this research (Sobri, F. B. *et al.*, 2018). ***Material and Methods:*** This was cross-sectional research. This was a follow-up study from research conducted five years ago in The Department of Surgical Oncology Dr. Moewardi Hospital Surakarta between March to May 2015. Subjects of this study were Luminal A breast cancer patients carried out for progesterone examination in the blood and assessed for TNM stage. Evaluation of progesterone levels in the blood and TNM stage were performed in November to December 2020. ***Statistical analysis:*** In this study data, bivariate and multivariate analyses were carried out. Logistic regression test for ordinal data was used for bivariate analysis, whereas Chi-square/Fisher exact test was performed for data with nominal dichotomy scale. Multivariate analysis was done using logistic regression with a significance p-value <0.05 in the bivariate analysis to determine the odds ratio. Data was significant if p<0.05. ***Results:*** Based on bivariate analysis with logistic regression test and multivariate analysis, progesterone levels in the blood of Luminal A breast cancer patients influence the breast cancer progression, with p-value = 0.037 on bivariate analysis and p-value = 0.031 on multivariate analysis. Increased progesterone levels in the blood of Luminal A breast cancer patients multiplied the risk of breast cancer progression by 12 times. ***Conclusions:*** This study showed that blood progesterone levels had a significant effect on the progression of Luminal A breast cancer patients.

Keywords: progression breast cancer, progesterone, Luminal A.

INTRODUCTION

Breast cancer is one of the main problems of women's health in the world. In Indonesia, breast cancer is the most prevalent cancer discovered, accounting for 28% of cancer patients. The number of breast cancer patients has increased annually. In 2004, there were 5.207 cases, rose to 7.850 cases in 2005, 8.328 cases in 2006, 8.277 cases in 2007, 8.082 cases in 2008 and 12.014 cases in 2009 (Departemen Kesehatan RI, Statistik morbiditas dan mortalitas di rumah sakit; 2005-2010).

Breast cancer in women is associated with progesterone hormone, which is a female reproductive hormone. Menarche at young age, advanced age, nullipara, menopause with obesity, menopause, progestin hormonal contraception, and progestin and estrogen hormonal therapy (HRT) in menopausal patients would increase the development of breast cancer. This strongly showed that higher levels of progesterone hormone increased the risk of developing breast cancer (DeVita, V. T. *et al.*, 2011).

When menstruation, the amount of progesterone hormone in the blood of premenopausal women in the follicular phase was about 1 ng/mL and increased to 10-35 ng/mL after the ovulation phase. In menopausal women, the amount of progesterone hormone was not exceeding 1 ng/mL (Taraborrelli, S. 2015).

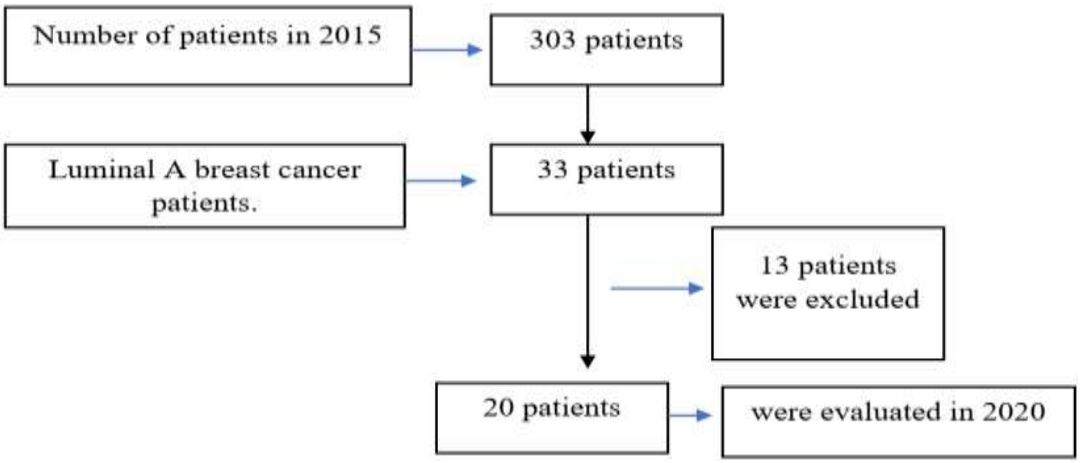
The progression of breast cancer and treatment options are based on the characterization of tumor receptor growth factors, PR-status, ER-status and HER2 (DeVita, V. T. *et al.*, 2011). Luminal A breast cancer subtype are breast cancers with positive receptor hormones. Progesterone works in the breast using progesterone receptor (PR). PR itself is a mediator used to expand into the breast glandular tissue during puberty. Progesterone receptors in breast tissue are PR-B. Progesterone is a hormone that improves breast gland replication. This is the key to the association of progesterone hormone levels in the blood with the progression of Luminal A breast cancer patients.

MATERIAL AND METHODS

This was cross-sectional research. This was a follow-up study from research conducted five years ago in The Department of Surgical Oncology Dr. Moewardi Hospital Surakarta between March to May 2015. Subjects of this study were Luminal A breast cancer patients carried out for progesterone examination in the blood and assessed for TNM stage. Evaluation of progesterone levels in the blood and TNM stage were performed in November to December 2020.

Evaluations were carried out by conducting physical examinations, chest x-ray, breast ultrasonography, abdominal ultrasonography and ELISA test to determine progesterone levels in the blood.

There were 303 patients in the 2015 study. Thirty-three of them were positive for estrogen receptors and progesterone receptors. A total of 20 patients met the inclusion criteria included in this study.



The inclusion criteria were all Luminal A breast cancer patients admitted to previous research conducted by The Department of Surgical Oncology Dr. Moewardi Hospital Surakarta, willing to participate in this research, and signed the informed consent. The exclusion criteria were deceased patients, stopped control, unable to contact, and had an incomplete stage history.

The author aims to conduct this study to determine the effects of blood progesterone levels on the progression of Luminal A breast cancer patients. Therefore, it could be used for further therapy approaches.

RESULTS

The study involved 20 Luminal A breast cancer patients. There were six patients (30%) with stable progesterone levels and 14 patients (70%) with increased progesterone levels. From 6 patients with stable progression, 4 had stable progesterone levels (66.7%), and 2 had increased progesterone levels (33.3%). From 14 patients with increased progression, in the data of patients with increased progression 2 of them had stable progesterone levels (14.3%) and 12 of them had increased progesterone levels (85.7%).

In this study, from subjects' characteristic data, confounding variables were age, menopause, breast cancer grading, breast cancer stage, parity, contraception, and family history of breast cancer. Data were reported in Table 1.

Table 1. Subjects Characteristic.

Variable	Total	Progressivity	
		Stable (n=6)	Increased (n=14)
Age (years)[a]	57.35 +12.48	59.83 +14.88	56.29 +11.77
<40	2 (10.0%)	1 (16.7%)	1 (7.1%)
≥40	18 (90.0%)	5 (83.3%)	13 (92.9%)
Menopause			
No	6 (30.0%)	2 (33.3%)	4 (28.6%)
Yes	14 (70.0%)	4 (66.7%)	10 (71.4%)
Grading			
Grade 1	3 (15.0%)	1 (16.7%)	2 (14.3%)
Grade 2	9 (45.0%)	2 (33.3%)	7 (50.0%)
Grade 3	8 (40.0%)	3 (50.0%)	5 (35.7%)
Stage			
EBC	10 (50.0%)	4 (66.7%)	6 (42.9%)
LABC	9 (45.0%)	2 (33.3%)	7 (50.0%)
ABC	1 (5.0%)	0 (0.0%)	1 (7.1%)
Parity			
Nullipara	1 (5.0%)	0 (0.0%)	1 (7.1%)
1 child/2 children	13 (65.0%)	3 (50.0%)	10 (71.4%)
>3 children	6 (30.0%)	3 (50.0%)	3 (21.4%)
Contraception			
No	12 (60.0%)	2 (33.3%)	10 (71.4%)
Hormonal	8 (40.0%)	4 (66.7%)	4 (28.6%)
Family history			
No	11 (55.0%)	3 (50.0%)	8 (57.1%)
Yes	9 (45.0%)	3 (50.0%)	6 (42.9%)
Progesterone			
Stable	6 (30.0%)	4 (66.7%)	2 (14.3%)
Increased	14 (70.0%)	2 (33.3%)	12 (85.7%)

Data in Table 1 showed stable progression and increased progression in the age range of 59.83+14.88 years old and 56.29+11.77 years old, respectively. Most subjects were aged 40 and above.

Four patients (66.7%) with stable progression had menopause, and 10 patients (71.4%) with increased progression had menopause. Based on the grading, three patients (50%) with stable progression had grade 3 breast cancer, and 7 patients (50.0%) with increased progression had grade 2 breast cancer.

Based on the staging, four patients (66.7%) with stable progression had EBC, and 7 patients (50%) with increased progression had LABC.

The number of parity in stable progression patients was one to two child/children in 3 patients (50%) and three children or more in 3 patients (50%), while 10 patients (71.4%) with increased progression had 1 to 2 child/children.

Most patients with stable progression (66.7%) used hormonal contraception, while most patients with increased progression did not use contraception (71.4%), 4 and 10 patients respectively.

There were equally three patients each (50%) with stable progression who had/had no family history of breast cancer. Most patients (57.1%) with increased progression did not have a family history of breast cancer.

Four patients (66.6%) with stable progression had stable progesterone levels, and twelve patients (85.7%) with increased progression had increased progesterone levels.

Bivariate and multivariate analyses of the progesterone effect on the progression of Luminal A breast cancer patients who underwent therapy, with subject characteristics as confounding variables presented in table 2.

Table 2. Bivariate and Multivariate Analysis of Progesterone Effects on Luminal A Breast Cancer Progressivity in Patients Underwent Therapy with Subjects Characteristics as Confounding Variables.

Variable	Bivariate		Multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age (years)[a]				
<40	Ref.	Ref.		
≥40	2.600 (0.135-50.049)	0,521		
Menopause[a]				
No				
Yes	1.250 (0.160-9.765)	1,000		
Grading[b]				
Grade 1	Ref.	Ref.		
Grade 2	1.750 (0.099-30.837)	0,702		
Grade 3	0.833 (0.051-13.633)	0,898		
Stage[b]				
EBC	Ref.	Ref.		
LABC	2.333 (0.310-17.545)	0,410		
ABC	1E+009 (0.000-)	1,000		
Parity[b]				
Nullipara	Ref.	Ref.		
1 child/2 children	0.000 (0.000-ns)	1,000		
>3 children	0.000 (0.000-ns)	1,000		
Contraception[a]				
No	Ref.	Ref.		
Hormonal	0.200 (0.026-1.562)	0,161		
Family history[a]				
No	Ref.	Ref.		
Yes	0.750 (0.110-5.109)	1,000		
Progesterone[ab]				
Stable	Ref.	Ref.	Ref.	Ref.
Increased	12.000 (1.248-115.362)	0,037	12.000 (1.248-115.362)	0,031

Dependent variable= progressivity; ref.= Reference (Comparison); [a]Chi Square test/Fisher exact test; [b] Logistic regression test; * significance at α=5%

Bivariate analysis shown in Table 2 suggested that age (OR=2.600; 95% CI= 0.135-0.049; p=0,521), menopause state (OR=1.250; 95% CI= 0.160-9.765; p=1.000), grade 2 brease cancer grading (OR=1.750; 95% CI =0.099-30.837;p=0.702), grade 3 breast cancer grading (OR=0.833; 95% CI=0.051-13.633; p=0.898), LABC staging (OR= 2.333; 95% CI=0.310-17.545; p=0.410), ABC staging (OR= 1E+009; 95% CI= 0.000-; p=1,000), number of parity one or two (OR=0.000; 95% CI=0.000-; p=1,000), number of parity ≥ 3 (OR= 0.000; 95% CI= 0.000-; p=1,000), use of contraception (OR= 0.200; 95% CI= 0.026-1,562; p=0,161), and family history of breast cancer (OR= 0.750; 95% CI= 0.110-5.109; p= 1,000), had no significant effect on breast cancer progressivity. These variables were not the risk factors of breast cancer progressivity (p>0,05).

Bivariate and multivariate analysis of progesterone levels, OR= 12.000; 95% CI=1.248-115.362; p=0,037 and OR= 12.000; 95% CI=1.248-115.362; p=0,031, respectively, suggested that progesterone levels had significant effect on breast cancer progressivity. Patients with increased progesterone levels had a twelve-fold risk of increased disease progressivity.

DISCUSSION

Excessive progesterone exposure triggered adaptive hypersensitivity signaling growth factor for ER regulatory pathway. MAPKs that depend on ER activation interacted with Shc and induced phosphorylation that triggered the recruitment of gene-changer adapter molecules. This ER-MAPK activity explained breast cancer's remarkable response to aromatase inhibitors but failed to respond to selective ER modulators designed to inhibit ER transcription activations in the nucleus (Boonyaratanakornkit, V. *et al.*, 2001).

In breast cancer, progesterone act through proto-oncogenes and growth factors to influence breast cell proliferation. In previous in vitro studies (cancer cells that grew in 2-dimensional cultures were added to media that contained progestin), progesterone had a biphasic effect on the proliferation phase, that breast cancer cells experienced an initial proliferation explosion characterized by an increase in S-phase entries, reaching its peak in the first 18 hours of progesterone therapy. The development of the cancer cell cycle was driven by an increase in the G1/S and G2 cycles, p21 and CDK2. This activity regulation ran 24-48 hours (3 cell cycles), then got a period of inhibition of cell growth when p27 was regulated and finally, cell growth stopped at G1/S (Wang, K. *et al.*, 2016). Whereas in vivo (3-dimensional culture), progestin was a mitogenic agent, so PR-B induced an increase of protein cyclin D1 levels which caused an increase of cyclin D1 expression resulting in abundant development of breast cancer cell colonies (Lange, C. A., & Yee, D. 2008). In breast cancer, the active PR activated by

progesterone can occur due to loss of control after examination in the cell proliferation cycle or an increased kinase activity (Diep, C. H. *et al.,* 2016).

In this study, based on the bivariate analysis, age, menopause, breast cancer grading, breast cancer stage, parity, the use of hormonal contraception, and family history of breast cancer did not show a significant effect on the progression of breast cancer patients or not a risk factor for the progression of breast cancer patients because of p-value >0.05.

This study showed that the patient's age had no significant effect on breast cancer progressivity (p=0.521, p>0,05). This was not in accordance with previous studies, which reported that patients younger than 40 years had higher disease progressivity because patients in this age range had more expressive estrogen and progesterone receptors in the breast and were commonly diagnosed with a higher stage of breast cancer (Anders, C. K. *et al.,* 2009; Assi, H. A. *et al.,* 2013; & Wang, K. *et al.,* 2016).

The results of this study also showed that the patient's menopause status had no significant effect on breast cancer progressivity (p=0.100, p>0.05). This result also contradicted the previous study, which stated that the older a woman had menopause, the longer duration of hormone exposure to the body, thus increasing the risk of breast cancer (Barnard, M. E. *et al.,* 2015). Another study reported that the risk of postmenopausal women having breast cancer was lower in the pre-menopausal women of the same age, and the risk increased by 3% each year until the woman had menopause (Cui, Y. *et al.,* 2014).

Our study also showed that grade 2 or grade 3 breast cancer grading (p=0.702 and p=0.898 respectively) did not have a significant effect on breast cancer progressivity (p>0.05). This was not in line with the previous study, which reported that grade 1 breast cancer had lower disease progressivity compared to grade 3 breast cancer (Ehinger, A. *et al.,* 2017). Another study also confirmed that breast cancer progressivity was linearly correlated to the histological grading of breast cancer (Mursyidah, N. I. *et al.,* 2019; Pradhan, A. *et al.,* 2017; & Rakha, E. A. *et al.,* 2010).

Breast cancer staging was proven to have no significant effect on breast cancer progressivity (p=0.410 and p=0.1000 for LABC and ABC staging, respectively, p>0.05). A study by Kasangian reported that luminal A breast cancer with a tumor size of T1 and T2 was classified as EBC and had a better prognosis than breast cancer with a larger tumor size (Kasangian, A. A. *et al.,* 2017). Another research also reported consistent findings. Larger tumor size, lymph node metastasis and distant metastasis increased breast cancer progressivity (Mursyidah, N. I. *et al.,* 2019; Pradhan, A. *et al.,* 2017).

This study showed that the number of parity had no significant effect on breast cancer progressivity (p>0.05). Parity of one or two children and parity of three or more children had an equal p-value of 1.000. This result was not in accordance with the previous study, which suggested that nulliparous women had a higher risk of breast cancer than multiparous women. The breast tissue of nulliparous women never undergo differentiation, so they are more susceptible to neoplastic transformation (Barnard, M. E. *et al.,* 2015; Butt, Z. *et al.,* 2012).

Results in this study showed that the use of contraception had no significant effect on breast cancer progressivity (p=0.161, p>0.05). One study reported that the duration of oral hormonal contraception use could increase the risk of breast cancer by the time when the half-life of the contraceptive pills was up. This hormonal exposure would decrease along with the end of the half-life of contraceptive pills and the duration was individual (Barnard, M. E. *et al.,* 2015). Another study found that the use of combination estrogen and progesterone hormonal contraception increased the incidence of breast cancer (Chlebowski, R. T. *et al.,* 2013).

This study found that the family history of breast cancer did not have a significant effect on breast cancer progressivity (p=1.000, p>0.05). Previous studies suggested that family history of breast cancer increased the risk of breast cancer about 1.5 times up to 2 times from women who did not have any breast cancer types within the family ((Barnard, M. E. *et al.,* 2015).

In this study, the effect of progesterone levels with breast cancer progression had a p-value = 0.037 in the bivariate analysis and p-value = 0.031 in multivariate analysis with an odds ratio value of 12. So that patients' progression significantly affected the breast cancer progressivity, with p-value < 0.05 and increased progesterone levels would increase the risk of breast cancer progressivity 12 times higher.

These results were consistent with previous research that stated that greater progesterone exposure in life would increase the risk of breast cancer (Knutson, T. P., & Lange, C. A. (2014). In another study, authors stated that oral contraceptive administration for more than ten years also increased the risk of all types of breast cancer (Barnard, M. E. *et al.,* 2015). Other studies concluded that the use of *levonorgestrel-releasing contraception intrauterine* for more than ten years increased breast cancer incidence due to its prostagenic and substantial androgenic effects (Lyytinen, H. K. *et al.,* 2010; Soini, T. *et al.,* 2016).

Bivariate analysis in this study showed that age, menopausal state, breast cancer grading, breast cancer staging, number of parity, use of hormonal contraception and family history of breast cancer had no significant effect on breast cancer disease progressivity, i.e., these factors were not the risk factors for breast cancer progressivity ($p>0.05$). In spite of that, progesterone level was proven to have a significant effect on breast cancer progressivity ($p<0.05$). Progesterone level was the only risk factor of breast cancer progressivity found in this study, in which the increased progesterone levels also increased the risk of breast cancer progressivity about 12-fold.

CONCLUSION

In this study, there was a significant effect of progesterone levels on the progression of positive estrogen receptors and positive progesterone receptors breast cancer, with p-values < 0.05 (i.e. bivariate analysis of progesterone levels (p=0,037) and multivariate analysis of progesterone levels (p=0,031). Increased progesterone levels in the blood of breast cancer patients with positive estrogen receptors and positive progesterone receptors multiplied the risk of breast cancer progression by 12 times.

Conflict Of Interest

No potential conflict of interest relevant to this study was reported.

Ethic Approval

This study protocol had been approved by the Head of Surgery Department, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi General Hospital, and the Health Research Ethics Committee of Dr. Moewardi General Hospital (Number 844/VII/HREC/2020).

Author Contribution

All authors contributed equally to the writing process and revising this article.

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