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Vitamin D Receptor (VDR) Apa1 gene polymorphism increasing the risk of breast cancer women in Bali, Indonesia

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ABSTRACT

Background: Breast cancer is the most common cancer diagnosed in women. It basically caused by a progressive accumulation of genetic disorders. Vitamin D and its receptor (VDR) have been shown to have an effect on the carcinogenesis of breast cancer. Several studies have shown VDR Apa1 polymorphisms became the most prevalent polymorphism of other polymorphism variants of breast cancer. There are still lack of studies that review the relationship of VDR gene polymorphisms, especially Apa1 on breast cancer risk among Balinese woman.
Method: This study was a case-control design- analytic study to see the relationship between Vitamin D receptor Apa1 gene polymorphism and breast cancer risk in Balinese women. There were 42 venous blood samples from breast cancer women and healthy women in Bali. This study was carried out at the Faculty of Medicine Integrated Biomedical Laboratory. DNA isolation was done for sequencing to determine the sequence of gene bases. Then the data were analyzed using SPSS 16.
Results: Univariate analysis showed the characteristics of the subject and research variables. Bivariate analysis showed that the presence of VDR Apa1 polymorphism in Balinese women increased the risk of breast cancer by 5,846-fold higher compared to women without polymorphism (CI95%:1.065- 32.082; P = 0.03). Multivariate analysis confirmed that the VDR Apa1 polymorphism independently influence and increase the risk of breast cancer without being influenced by other variables (95% CI: 1.065-32.082; P = 0.042).
Conclusion: In this study has shown VDR Apa1 polymorphism significantly associated and increased the risk of breast cancer in women in Bali.

Keywords: Breast cancer, Polymorphism, VDR (Vitamin D Receptors) Apa1 gene.
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INTRODUCTION

Breast cancer is the most common cancer diagnosed in women. Based on GLOBOCAN data in 2012, it is estimated there are 1.67 million new cases of breast cancer.[1] Breast cancer is the cause of death by ranks 5 cancer deaths in the world. World Health Organization (WHO) data shows that breast cancer in 2012 has had a death rate of 522,000 people.[2,3] In developing countries, breast cancer has become the leading cause of cancer death in women. In addition, breast cancer is the cause of cancer-related deaths rank second to cervical cancer in developed countries.[3]

Currently researchers have focused on the role of vitamin D and its receptor in breast cancer.[4] Vitamin D in carrying out its role requires a receptor, the Vitamin D receptor (VDR).[5-7] Decreased levels of VDR expression in breast cancer, which is expected to occur as a result of genetic variation in the VDR gene.[8] Several studies have shown that VDR polymorphisms are associated with breast cancer and seven types of polymorphism, those namely, Fok1 polymorphisms on exon II, Bsm1 and Apa1 on intron VIII, Cdx2 on exon I, Taq1 on exon IX, Tru91 on intron VIII, and poly(A) mononucleotides in the 3' untranslated area (3'-UTR).[9-15]

Changes in VDR expression will impact the ability of the active form of Vitamin D to induce transcription of the VDR target gene.[16] A recent study by El-Shorbagy et al and Guo et al, shows that the three variants of the VDR SNP contribute to increased risk of breast cancer that is BsmI, Apa1 and TaqI. Apa1 is the most prevalent polymorphism of the three variants of polymorphism.[17-18] Research by Gou et al., found that SNP in VDR Apa1 were associated with and significantly increased the risk of breast cancer (OR: 2,643; 95% CI: 1,631 ~ 7,012).[18] Another study also showed that the VDR Apa1 polymorphism has a high frequency in women who have an increased risk of breast cancer.[19] VDR Apa1 is also known to be significantly associated with the clinicopathological

Table 1. Baseline characteristics of research subjects (Cases and Controls)

Variable	Group		Nilai P
	Case (N=21)	Control (N=21)	
Age (year)	47.52±10.755	41.95±8.535	0,07
Parity (number of children)	2.33±966	2.24±944	0,748
Menarche (year)	13.71±717	13.57±978	0,592
Status menopause			0,334
Premenopause	12 (28,6%)	15 (35,7%)	
Postmenopause	9 (21,4%)	6 (14,3%)	
History of breast cancer			1,000
Yes	0	0	
No	21	21	
Contraception			0,272
Without contraception	6 (14,3%)	3 (7,1%)	
Hormonal	8 (19,0%)	6 (14,3%)	
Non-hormonal	7 (16,7%)	12 (28,6%)	
VDR Apa1 polymorphism			
Positive	8 (19,0%)	2 (4,8%)	**0,03***
Negative	13 (31,0%)	19 (45,2%)	
Stage			
II	3 (14,3%)		
III	14 (66,7%)		
IV	4 (9,5%)		
Subtype			
Luminal A	7 (33,3%)		
Luminal B	9 (42,8%)		
HER2	1 (2,4%)		
TNBC	4 (9,5%)		
Histology grade			
I	1 (4,8%)		
II	6 (28,6%)		
III	14 (66,7%)		
LVI			
Positive	10 (47,6%)		
Negative	11 (52,4%)		
TIL			
Negative-Low	14 (66,7%)		
Moderate-Severe	7 (33,3%)		

characteristics of breast cancer. This is still a debate because there are several research results that show the opposite.[17]

The prevalence of VDR polymorphism variants in Indonesia and Bali is still unknown until now, because there are no studies evaluating the genetic variation patterns of cancer in Indonesia.. Therefore, it is important to conduct a study that evaluates the effect of VDR polymorphisms on the risk of breast cancer, especially in Bali which can be started from one of the polymorphisms with the highest OR, namely Apa1. It is expected that this study will be the beginning of the genomic mapping of breast cancer in Bali and in Indonesia.

METHOD

This research was conducted at Sanglah Hospital in Denpasar, Bali, from May to December 2018 with a total sample of 42 women. This study used a sample of venous blood that has been stored in the Department of Biochemistry, Faculty of Medicine, University of Udayana. Basic data from control subjects were obtained through questionnaires, while other data were recorded on the data collection sheet. The target population in this study were all breast cancer patients in Bali who were treated at Sanglah General Hospital, Denpasar.

This research uses analytical research using a case control study to see the relationship between Vitamin D receptor gene polymorphisms. The dependent variable in the study was breast cancer and the independent variable being the VDR Apa1 gene polymorphism. Confounding variables in this study were breast cancer histology subtypes namely Luminal-A, Luminal-B, HER2 +, and Triple Negative, breast cancer TNM stage and cancer mass size.

The Case inclusion criteria in this study were breast cancer patients in Bali who were treated at Sanglah General Hospital. While the Control inclusion criteria in this study were healthy women in Bali with an age range of 40-65 years.

The exclusion criteria for the case group in this study were elder patients aged <40 years and >65 years outside Bali, breast sarcoma / phillodes tumors, patients who had not completed histopathological examination, a history of immunodeficiency due to disease or treatment and subjects refused to participate in the study. The exclusion criteria for the control group in this study were patients aged <40 years and> 65 years, patients with previous cancer history and patients who refused to be involved in the study.

All data were analyzed using SPSS version 16 software for windows.

RESULT

This study involved 42 subjects consisting of 21 case subjects and 21 control subjects. The mean total age of the research subjects was 44.74±9.99 years. Comparison between control and case groups, the mean age of subjects in elder group and the control group (47.52±10,755 years vs. 41.95±8,535 years), this difference was not statistically significant (P = 0.070). Age also will not affect the polymorphism in each individual, even though the patient checks at different ages repeatedly. This is because polymorphisms occur due to genetic mutations.

In terms of age of menarche, there was no significant difference between the

Table 2. Bivariate analysis between VDaR Apa1 polymorphism and breast cancer risk

Variable	VDR Apa1 polymorphism		P Value	OR	95%CI
	Positive	Negative			
Group			0,03*	5,846	1,065-32,082
Case	8 (19,0%)	13 (31,0%)			
Control	2 (4,8%)	19 (45,2%)			

Table 3. Multivariate analysis of the correlation between VDR Apa1 polymorphism and breast cancer incidence

Dependent Variabe	B	S.E	Wald	OR	95%CI	P
Breast cancer	1,766	0,869	4,132	5.846	1,065-32,082	0.042

case and control groups even though the case group appeared to have a slightly lower mean age of menarche (cases: 13.71±.717 years; controls: 13.57 ± .978 years; P=0.592). The proportion of pre-menopause in the case group was 57.1% (12 subjects) while in the control group, 71.4% (15 subjects) had premenopausal status. However, this difference is not statistically significant (p=0.334). Of all patients, none of the subjects had a family history of breast cancer in either the control or case groups.

In terms of parity, the control and case groups were found to have almost the same mean parity (case: 2.33±.966; control: 2.24±.944; p=0.748). While in terms of contraceptive use, hormonal contraception is a type of contraception most widely used in the case group (8 subjects), but non-hormonal contraception is the most widely used in the control group (12 subjects) . As with other baseline characteristics, there was no significant difference in contraception between cases and controls (p=0.272). Judging from the comparison of the basic characteristics of the variables above, there is no significant difference between the case and control groups. Therefore, both groups can be said to be homogeneous and the effect of confounding variables has been minimized. The basic characteristics of research subjects are described in Table 1.

When viewed from the clinicopathological characteristics of the case group, it appears that more than half of the samples had stage III (66.7%) with high grade (grade III; 66.7%). Most of the samples had luminal tumors with Luminal B as the dominant subtype (42.9%). Non-luminal breast cancers (HER2 and TNBC) constitute less than a third of the case sample. The proportion of lymphovascular invasion (LVI) in case subjects was almost the same, which is 10 (47.6%) positive subjects and 11 (52.4%) negative subjects.

In terms of tumor infiltrating lymphocyte (TIL) level, 14 subjects (66.7%) had low-negative TIL status and 7 subjects (33.3%) had moderate-severe TIL status. To answer the main objective of this study, bivariate analysis was carried out using the chi-square test because it compared two variable proportions (Polymorphism VDR Apa1 [+/-] and research group [case/control]). Bivariate test results obtained 8 subjects (19%) in the case group had positive polymorphism status in the VDR Apa1 gene while 13 subjects (31.0%) were negative. Only 2 subjects (4.8%) n the control group were polymorphic positive in the VDR Apa1 gene and the rest (19 subjects / 45.2%) were negative.

The results of the chi-square analysis confirmed that this difference was statistically significant and the case group tended to have a higher proportion of positive polymorphisms than the case group (p=0.03). Then, from the results of the risk analysis, an Odds Ratio (OR) of 5,846 was obtained with a confidence interval of 1,065-32,082 (P=0.03) (Table 2**).** This shows that the presence of VDR Apa1 polymorphism in women in Bali increases the risk of breast cancer by 5,846 times higher when compared to women without polymorphism. This difference is significant because the p value is less than 0.05 and the Confidence Interval (CI) does not cross 1, which indicates that the risk value in the case group is higher when compared to the control group.

In order to further evaluate the relationship between VDR Apa1 and the risk and subtype of breast cancer, a multivariate analysis was carried out to see the independent effect of VDR Apa1 on the two variables. Since all tested variables are nominal variables, logistic regression is used in this phase. From the analysis, it was found that the VDR Apa1 polymorphism was significantly associated with breast cancer risk with an OR of 5.846 (95% CI: 1.065-32.082; P = 0.042) (Table 3). It can be seen that the OR obtained from the multivariate analysis is not different from the results of the bivariate analysis even though there is a change in the p value (p=0.042). This shows that the VDR Apa1 polymorphism does indeed independently affect and increase the risk of breast cancer without being influenced by other variables.

DISCUSSION

Breast cancer is one of the most common cancers in women globally with an increasing incidence. Although there have been many developments in breast cancer research in the last decade, the molecular profile of breast cancer which may contribute to the risk of development in women has not been studied extensively, especially in Indonesia. The findings of this study constitute a breakthrough in the field of molecular risk factor profiling in Indonesia because this study is the first study to evaluate VDR polymorphisms in Indonesia. The next section in this chapter will discuss the findings of this research and relate them to findings that have been recorded in the archives of international journal.

In terms of the basic characteristics of the case subject, it can be seen that the dominant subtype in the subject is the luminal subtype where luminal B has a higher prevalence than luminal A. Non-luminal subtypes (HER2 and TNBC) constituted less than a third (28.6%) of the total subjects. In general, the proportion of this subtype still corresponds to the prevalence of global breast cancer, although there is a deviation in the form of luminal B dominance and TNBC in the non-luminal group.[20] The majority of subjects also have stage III and grade III which are classified as high grade which refers to the ineffective early detection system for breast cancer in the

community.[2] In the whole study sample, almost half of the subjects used non-hormonal contraception with 38.1% of the subjects using hormonal contraception.

Polymorphisms in vitamin D are known to play a role in breast cancer carcinogenesis. There are 6 types of polymorphisms in the known VDR gene, namely CDX2, FokI, BsmI, Apa1, TaqI, and PolyA but those that are known to play an important role in cancer carcinogenesis are FokI, Apa1, BsmI, and TaqI.[21,22] The frequency of these four polymorphisms in Asian ethnicities is estimated at 51%, 74%, 7% and 8% for the VDR polymorphisms of the types FokI, Apa1, BsmI, and TaqI.[23] In this study, the frequency of positive VDR Apa1 polmorphisms in breast cancer was 19.0% in the case group and 4.8% in the control group. This frequency is lower than that reported by Uitterlinden et al (2004) which is probably due to genetic variation between races and demographics.[23]

All four VDR polymorphisms have been shown to significantly increase the risk of cancer in general. A meta-analysis by Raimondi et al (2009) showed that FokI and BsmI significantly increased the risk of prostate, breast, skin, ovarian, non-Hodgkin's lymphoma, and colorectal cancer in a Caucasian population. This meta-analysis using 67 independent studies carried out in the continent of Europe and America with the smallest sample number 84 so it can be said that the findings of this meta-analysis are conclusive.[24] Another meta-analysis involving 25 independent studies in Caucasian populations of 24,439 cases and 26,406 controls by Serrano et al. (2016) also reported the same findings. However, this study also found an increased risk of mild all types of cancer by the polymorphism Apa1 (OR: 1.06; 95% CI: 1.01-1.19). The Apa1 polymorphism was also significantly associated with renal cancer (OR = 2.60, 95% CI = 1.39–4.85) and colorectal cancer (OR = 2.32, 95% CI = 1.19-4.54).[25]

The association of VDR Apa1 polymorphisms with breast cancer has also been extensively evaluated. A case-control study conducted by El-Shorbagy et al. (2017) in a female population in Egypt found a significantly increased risk of breast cancer in women with the VDR Apa1 polymorphism compared to wild-type VDR (OR=3.71, 95% CI: 1.04–13.28).[17] A case-control study in the Chinese population conducted by Guo et al (2015) provides information about the impact of the VDR Apa1 polymorphism on the Mongoloid population. This study, which involved 219 cases and 321 controls, showed that the wild-type VDR type in the Asian female population was protective compared to the VDR Apa1 variant (P=0.004, OR=0.774, 95% CI: 0.212 ~ 0.955).[18] This study also showed that the Apa1, TaqI, and BsmI polymorphisms are genetically linked and have the potential to influence one another as shown that the presence of the three polymorphisms significantly increased the risk of breast cancer with an OR of 2.643 (95% CI: 1.631 ~ 7.012).

However, these studies did not evaluate the polymorphisms of FokI and Cdx2 which have been shown to play a significant role in the increased risk of breast cancer in the caucasian population. Consistent with the above studies, this study also found a significant relationship between VDR Apa1 polymorphism and breast cancer risk similar to the findings in the research of El-Shorbagy et al (2017) and Guo et al (2015).[17,18] Although the number of subjects in this study was relatively small (21 cases and 21 controls), the number of subjects was carefully calculated statistically to maintain the validity of the findings. Based on the results of statistical analysis, this study succeeded in finding an increase in the risk of breast cancer which was classified as large in women in Bali with the VDR Apa1 polymorphism (OR: 5.846; 95% CI: 1.065-32.082). However, this study only evaluates one polymorphism so that it cannot eliminate the possible influence of other polymorphisms that may be associated with VDR Apa1 (FokI, Cdx2, BsmI and TaqI).[18]

Meta-analysis by (Lee and Song, 2014) involving 17,067 case patients and 20,843 control patients also showed an association between VDR gene polymorphisms (FokI, BsmI, Apa1, and TaqI) and the risk of breast cancer in a population of breast cancer patients in Europe (OR = 1.126, 95% CI = 1.026-1.243, p = 0.019).[26] Meta-analysis by (Iqbal and Khan, 2017) involving a larger sample (26,372 case patients and 32,883 control patients) also showed an association between VDR gene polymorphisms (Cdx2, Fok1, Bsm1, Apa1, Bgl1, Taq1, and Poly (A)) against the risk of breast cancer.[27] The results of this study are in line with the findings in this study which indicate a relationship between VDR gene polymorphisms, especially Apa1, and the risk of breast cancer in a sample of women in Bali.

As this study has some shortcomings that should be considered in generalizing the results of this study. Although consistent with the results of previous studies, the sample of this study was collected in one area (Denpasar Municipality) so that there is still a possibility that one particular type of genotype could be concentrated in Balinese women in this location.. Sampling should be carried out in each district so that the female population in Bali from all locations is able to be represented in the sample ideally. Then, as mentioned above, other polymorphisms are not evaluated in this study so as not to eliminate the influence of links from other polymorphisms. The absence of genotypic data for breast cancer in Indonesia also hinders the validation of this finding because comparisons with populations of different races are not always relevant because of the large genetic variation between human populations, especially regarding polymorphisms.

CONCLUSION

The results of this study it can be concluded that the VDR Apa1 polymorphism is significantly associated with and increases the risk of breast cancer in women in Bali.

AUTHOR CONTRIBUTIONS

All literature searches, clinical studies, data acquisitions, data analyses, statistical analyses, and manuscript preparation were conducted by I Putu Gede Fajar Mahayasa. Research concepts, research designs and definition of intellectual content were conducted by I Putu Gede Fajar Mahayasa and I Wayan Sudarsa. Manuscript editing and manuscript review were implemented by I Wayan Sudarsa, I Ketut Widiana, Putu Anda Tusta Adiputra.

CONFLICT OF INTEREST

There is no conflict of interest in writing this research.

RESEARCH ETHICS

Ethics approval was obtained by the ethics commission, Faculty of Medicine, Udayana University, Sanglah Hospital, Bali, Indonesia before this research was carried out with register number 396/UN14.2.2.VII.14/LP/2019.

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