

# Relationship Between Vitamin D Receptor TaqI Polymorphism and the Clinicopathological Features of Breast Cancer Patients at Sanglah Hospital, Denpasar, Bali

Cynthia Lawrence<sup>1</sup>, Agus Eka Darwinata<sup>2\*</sup>, Desak Made Wihandani<sup>3</sup>,  
I Gede Putu Supadmanaba<sup>3</sup>

## ABSTRACT

**Introduction:** Breast cancer is a malignant tumor of the mammary gland. Breast cancer is associated with vitamin D receptor (VDR) TaqI polymorphism. This study aims to prove the relationship between TaqI polymorphism and the clinicopathology of breast cancer in Bali.

**Methods:** This study is an observational analytic study with a cross-sectional design conducted from February to August 2021. A total of 39 sample DNA isolates from breast cancer patients at Sanglah Hospital were enrolled in the study. The independent variable was the VDR TaqI gene polymorphism, while the dependent variable was the clinicopathological breast cancer (clinical stage and histological grading). The examination was carried out by PCR and sequencing. Clinical staging and histological grading of breast cancer were taken from the patient's medical record. The results were analyzed using descriptive and bivariate analysis.

**Results:** TaqI polymorphism of breast cancer at Sanglah Hospital Denpasar was dominated by the wild type TT genotype as much as 59%. This study did not find the CC genotype. The results of the statistical analysis did not find a significant relationship ( $p > 0.05$ ) between TaqI polymorphisms with TT and TC genotypes and clinicopathology of breast cancer but found a significant relationship ( $p = 0.047$ ) with histological grading. The TT and TC genotypes were found to increase the risk of breast cancer severity by 3,810 compared to individuals without the TT and TC genotypes. Analysis of confounding variables with clinicopathological breast cancer found no significant relationship ( $p > 0.05$ ) between the age of diagnosis, menstrual status, and hormonal contraceptive use with the characteristics of the sample.

**Conclusion:** It was concluded that breast cancer patients at Sanglah Hospital Bali had TaqI polymorphisms with TT and TC genotypes. TT and TC genotypes are associated with histological grading and can increase the severity of histological grading in breast cancer patients at Sanglah Hospital Denpasar Bali.

**Keywords:** TaqI Polymorphism, Breast Cancer, Clinicopathological Features.

**Cite this Article:** Lawrence, C., Darwinata, A.E., Wihandani, D.M., Supadmanaba, I.G.P. 2021. Relationship Between Vitamin D Receptor TaqI Polymorphism and the Clinicopathological Features of Breast Cancer Patients at Sanglah Hospital, Denpasar, Bali. *IJBS* 15(2): 223-228. DOI: [10.15562/ijbs.v15i2.349](https://doi.org/10.15562/ijbs.v15i2.349)

<sup>1</sup>Master Program in Anti-Aging Medicine, Faculty of Medicine, Universitas Udayana;

<sup>2</sup>Department of Microbiology, Faculty of Medicine, Universitas Udayana;

<sup>3</sup>Department of Biochemistry, Faculty of Medicine, Universitas Udayana;

\*Corresponding author:

Agus Eka Darwinata;  
Department of Microbiology, Faculty of Medicine,  
Universitas Udayana;  
[darwinfkunud@gmail.com](mailto:darwinfkunud@gmail.com)

Received: 2021-10-11

Accepted: 2021-11-20

Published: 2021-12-30

## INTRODUCTION

Aging is a physiological process that must be experienced by every individual due to increasing age. Aging is identical to a decrease in the physiological function of organs which can be followed by a decrease in a person's quality of life. Along with advances in science and technology, especially in the health sector, it is known that aging is also a major risk factor for cancer. Data from the US National Cancer Institute's Surveillance Epidemiology and

End Results (SEER) found more than 50% of cancer occurs in individuals over 70 years old.<sup>1</sup> Cancer is one of the highest causes of mortality after cardiovascular disease. The latest data from the Global Burden of Cancer (GLOBOCAN) noted that in 2020 there were 9,958,133 deaths from cancer. Most deaths from cancer each year are caused by lung cancer, liver cancer, stomach cancer, colorectal cancer, and breast cancer.<sup>2</sup> The World Health Organization (WHO) noted that

in 2020 the incidence of new cancer cases worldwide was the most contributed by breast cancer, reaching 2,261,419 out of 19,292,789 total new cancer cases. This figure ranks first in the incidence of new cancer cases among other cancer likes lung cancer, colorectal cancer, prostate cancer, and cervical cancer. While the death rate from breast cancer ranks fourth after lung cancer, liver cancer, and gastric cancer.<sup>2</sup>

Breast cancer is a malignancy that occurs in breast tissue. Based on

epidemiological data, breast cancer owns a mortality rate of 522,000 cases in 2012. In addition, breast cancer cases alone reached 404,000 in Asia with a ratio of 30 cases in 100,000 women. Based on the order of incidence, Indonesia ranks third in Asia with 12% of all diagnosed breast cancer cases.<sup>3</sup> Breast cancer is also known to cause the second-highest mortality after lung cancer with a mortality rate of 22,430 people or around 9.6%.<sup>2</sup> The high mortality rate due to breast cancer is caused by late detection of the disease. In general, patients seek medical help when they are in clinical stages III and IV. The lack of prognostic factors that can predict the behavior of malignant cells in breast cancer results in a poor prognosis. Clinical and pathological findings are considered to be less reliable in prognostic importance because of variations in molecular patterns and signaling pathways within cancer cells.<sup>4</sup>

The incidence of breast cancer is associated with multifactorial, including gender, age, age at menopause, age at menarche, hormone therapy, increased breast density, alcohol consumption, genetic, postmenopausal obesity, first pregnancy after the age of 30, lack of breastfeeding, lifestyle, and environmental factors. Genetic factors that are risk factors for breast cancer include changes in gene expression levels, epigenetic modifications, and polymorphisms. One of the genes that play a role in the pathogenesis and progression of breast cancer is the vitamin D receptor (RVD) gene.<sup>6</sup>

Breast cancer, which occurs due to genetic variations in the RVD gene, there is a decrease in the level of vitamin D receptor expression. RVD polymorphisms there are FokI, BsmI, TaqI, ApaI, and poly(A) have a significant association with breast cancer. The results of research on the relationship of TaqI gene polymorphisms with breast cancer risk are quite varied. TaqI polymorphism allele CC was significantly associated with an increased risk of breast cancer in estrogen receptor-positive patients.<sup>7</sup> A similar study suggests that TaqI polymorphism of TC genotype is significantly associated with the development of breast cancer. In Egyptian women with breast cancer, mortality of patients with CC genotype

(22%) was lower than in patients with TT (41%) and TC (44%) genotypes. Several findings suggest that TaqI SNP is not associated with susceptibility to breast cancer. However, a finding states that TaqI polymorphism of the TT genotype is a protective factor for breast cancer, with a risk reduction rate of 26%.<sup>8</sup>

The degree of differentiation or grade and type of histopathology are two important things to know in determining the diagnosis, prognosis, and therapy of breast cancer. Vitamin D receptor (VDR) is a factor that correlates with prognostication in breast cancer. The expression of the VDR gene was negatively correlated with tumor size and lymph node involvement (LNI) but did not correlate with the grade and status of the estrogen/progesterone receptor.<sup>9</sup> In breast cancer patients, high VDR expression is associated with favorable tumor characteristics such as smaller size, lower grade, estrogen and progesterone receptor positivity, and Ki67 expression.<sup>10</sup> This is different from the results of other studies which state that the TaqI VDR polymorphism is not related to the histopathological grade of breast cancer patients at the Adam Malik Hospital in Medan.<sup>11</sup> Based on the explanation above, the researcher saw that there was a relationship between VDR polymorphism and breast cancer. VDR expression is also associated with clinicopathological features of breast cancer. However, studies linking the relationship between VDR polymorphisms, especially TaqI with clinicopathological features of breast cancer in Indonesia, especially in Bali, are still very rare. The relationship between VDR TaqI polymorphisms and histopathological features of breast cancer patients is an important topic to study as an effort to determine the prognosis method for breast cancer patients.

## METHOD

### Research Design

This research is a cross-sectional analytical study to see the relationship between the polymorphism of the TaqI vitamin D receptor gene and the incidence of breast cancer at Sanglah Hospital Denpasar Bali. Research variables were analyzed simultaneously at one time without any follow-up procedures. Samples are stored

in biological materials in the form of DNA samples of breast cancer patients as many as 39 samples. This research was conducted at the Integrated Biomedical Laboratory Unit (LBT) of the Faculty of Medicine, Udayana University. Then the sequencing procedure was carried out at PT Genetics Science Indonesia, Tangerang, Banten. The research was carried out from February to August 2021.

### DNA Detection and Sequencing TaqI

To determine the presence of polymorphisms in the RVD TaqI gene, DNA samples from breast cancer patients were amplified using the Polymerase Chain Reaction (PCR) method followed by the sequencing method. The PCR process begins with a pre-denaturation process for 1 minute at 94°C, denaturation at 94°C for 1 minute, annealing process at 60°C for 2 minutes, and extension at 72°C for 2 minutes. To see the results of DNA amplification using the PCR method, electrophoresis was carried out using 1% agarose gel with 1x TAE solvent. Then the gene that is ready to be used is then used for electrophoresis by entering 5 µl of the PCR results and then connected to electric power of 80 mV/200mA for 40 minutes. The results of the electrophoresis were then visualized using a transilluminator system. Furthermore, the PCR results were sent to Genetics Science Jakarta for sequencing. The sequencing results are then read using snap gene software.

### Statistical analysis

Data analysis was divided into descriptive analysis to determine the proportion of each variable tested in this study. Furthermore, bivariate analysis was performed using chi-square to determine the relationship between the results of the TaqI VDR sequencing on clinicopathology and confounding factors such as age at diagnosis, menstrual status, and contraceptive use in breast cancer patients. The results of the analysis are said to be meaningful if  $p < 0.05$ .

## RESULT

### Descriptive Analysis

The study used 39 DNA samples from breast cancer patients treated at the Oncology Polyclinic, Sanglah Hospital,

Denpasar, Bali. The analysis results of the characteristics of the sample data showed that the average of the research subjects diagnosed with breast cancer was  $52.07 \pm 10,719$  years old, with the age of 50 years as many as 22 people (56.4%) and >50 years as many as 17 people (43.6%). Judging from the history of contraceptive use, the majority of the study samples were women with hormonal contraceptive users, as many as 26 people (66.7%). In addition, the research subjects were dominated by post-menopausal women, as many as 25 people (64.1%). Judging from the aspect of tumor pathology, the majority of patients diagnosed at stage III were 16 people (41.1%) with the most common tumor size being T4 as many as 18 people (46.2%), regional lymph node metastases (N1) as many as 18 people (46.2%), grade 3 as many as 17 people (43.6%), and patients with distant metastases as many as 13 people (33.3%) (Table 1).

The 39 isolates of DNA samples were amplified by PCR. Furthermore, sequencing of the PCR product was carried out to determine the presence or absence of the VDR TaqI gene polymorphism. The results of the sequencing found that there were 23 people (59%) with the VDR TaqI gene without polymorphism (non-polymorphism), and 16 people (41%) had polymorphism in the VDR TaqI gene (Table 2). The results of electrophoresis of PCR products and sequencing are shown in Figure 1.

#### Relationship of Stage with RVD TaqI Polymorphism, Age of Diagnosis, Menstrual Status, and Contraceptive Use in Breast Cancer Patients

Bivariate analysis with Chi-Square was conducted to determine the relationship between breast cancer stage and TaqI polymorphism, age at diagnosis, menstrual status, and contraceptive use of patients. Based on the results of bivariate analysis, it is known that there is no significant correlation with the stage of breast cancer patients ( $p > 0.05$ ) (Table 3). Multivariate analysis was not carried out because there was only one variable with  $p < 0.25$ .

**Table 1. Characteristics of Breast Cancer Patients.**

Parameters	Mean (%)
<b>Diagnosed Age</b>	53.13 $\pm$ 9.28
≤50 years	22 (56.4)
>50 years	17 (43.6)
<b>Stadium</b>	
I	3 (7.7)
II	7 (13.9)
III	16 (41.1)
IV	13 (33.3)
<b>T Tumor</b>	
T1	3 (7.7)
T2	8 (20.5)
T3	10 (25.6)
T4	18 (46.2)
<b>KGB Metastases</b>	
N0	16 (41)
N1	18 (46.2)
N2	3 (7.7)
N3	2 (5.1)
<b>Metastasis</b>	
M0	26 (66.7)
M1	13 (33.3)
<b>Grade</b>	
Grade 1	7 (17.9)
Grade 2	15 (38.5)
Grade 3	17 (43.6)
<b>Contraceptive Use</b>	
Non-Hormonal	13 (33.3)
Hormonal	26 (66.7)
<b>Menstrual Status</b>	
Pre-menopausal	14 (35.9)
Post-menopause	25 (64.1)

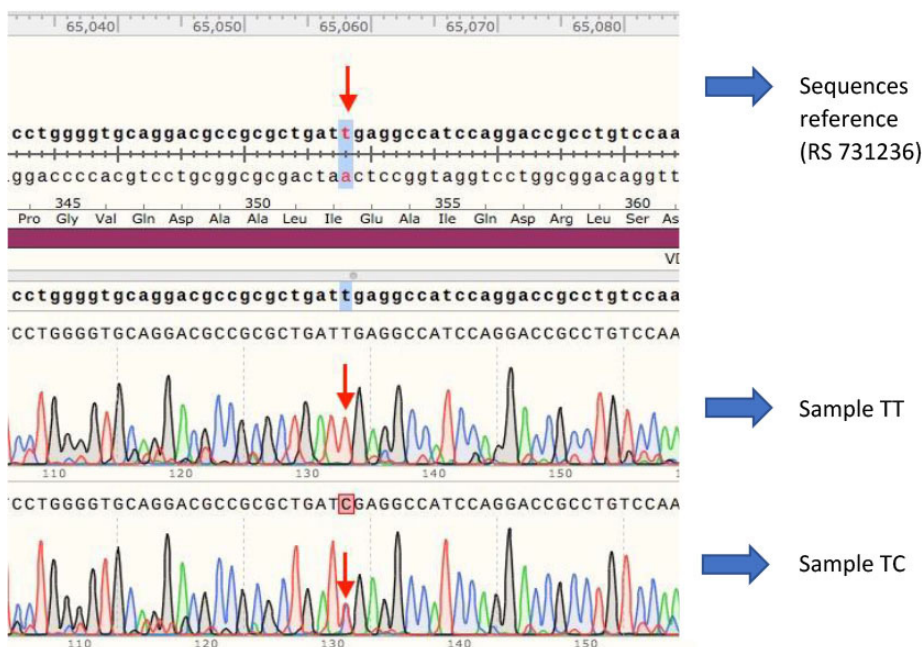
#### Relationship of Histological Grade with RVD TaqI Polymorphism, Age of Diagnosis, Menstrual Status, and Use of Contraceptives in Breast Cancer Patients

The relationship between histological grade and TaqI polymorphism, age at diagnosis, menstrual status, and contraceptive use in breast cancer patients were analyzed using Chi-Square bivariate analysis. Based on the results of the bivariate test, it was found that the TaqI polymorphism was significantly associated with the incidence of high-grade (grade III) breast cancer patients ( $p < 0.05$ ) (Table 4). Meanwhile, age at diagnosis, menstrual status, and contraceptive use did not show a significant relationship with the

histological grade of breast cancer patients ( $p > 0.05$ ) (Table 4). Multivariate analysis was not carried out because there was only one variable with  $p < 0.25$ .

#### DISCUSSION

Based on the findings in this study, the average age of patients diagnosed with breast cancer was 53.13 years, more than half of whom were postmenopausal women (64.1%). The results of other studies showed similar results, where on average, breast cancer patients were diagnosed at the age of 51-53 years with postmenopausal patients as many as 72% of patients.<sup>12</sup> Judging from the history of using hormonal contraception, the results



**Figure 1.** Results of Electrophoresis and Sequencing of PCR Products for the TaqI VDR Gene. (Above) Electrophoresis results of the TaqI VDR Gene PCR product; (Below) Sequencing Results of PCR Products with TT and TC Genotypes. SNP locations are shown in light blue and red arrows.

**Table 2. Variations in the VDR TaqI Gene Genotype in Breast Cancer Patients.**

VDR TaqI Gene Polymorphism	Genotypic Variation	Total (%)
Non-polymorphism	TT	23
Polymorphism	TC	16

**Table 3. Results of Bivariate Analysis of the Relationship between Stage and TaqI Polymorphism, Age of Diagnosis, Menstrual Status, and Use of Contraceptives in Breast Cancer Patients.**

Variable	Stadium		P-Value
	Early	Advance	
<b>VDR TaqI Gene</b>			
Non-Polymorphism	7 (70.0%)	16 (55.2%)	0.480
Polymorphism	3 (30.0%)	13 (44.8%)	
<b>Diagnosed Age</b>			
≥50 years	7 (70.0%)	15 (51.7%)	0.464
< 50 years	3 (30.0%)	14 (48.3%)	
<b>Menstrual Status</b>			
Pre-Menopause	1 (10.0%)	13 (44.8%)	0.064
Post-Menopause	9 (90.0%)	16 (55.2%)	
<b>Contraceptive Use</b>			
Non-Hormonal	3 (30.0%)	10 (34.5%)	1.000
Hormonal	7 (70.0%)	19 (70.4%)	

Information: p-value is said to be significant if < 0.05

of this study showed that more than half (62.4%) of the patients were women using hormonal contraception. These results strengthen the statement of Awaliyah et al., which states that women who use

hormonal contraception have a higher risk of developing breast cancer.<sup>13</sup>

Subsequent findings in this study showed that most breast cancer patients at Sanglah Hospital were diagnosed at

stage III (41.1%), with T4 tumor size that had extended to the chest wall directly to the skin (46.2%), lymph node metastases. Ipsilateral axillary region (46.2%) and undiagnosed with distant metastases (66.7%). Judging from the differentiation of cells in tumor tissue, the histological grade was dominated by grade 3 (43.6%). Most of the new research subjects were diagnosed with stage III and grade III breast cancer, which was categorized as high grade. It is due to the ineffectiveness of the early detection system for breast cancer in the community in Indonesia, mainly influenced by the low level of public knowledge.<sup>14</sup> The findings in this study which showed that the majority of patients were diagnosed at grade 3 were also consistent with other studies conducted in Africa and Latin America, namely, the majority of patients were diagnosed at grade 3 (48% for Africa; 47% for Latin America).<sup>15</sup>

The results showed that the TaqI polymorphism was not significantly associated with the breast cancer stage. The results of a similar study did not find a significant relationship between TaqI polymorphisms with every aspect of clinicopathology tested and were not associated with prognosis in breast cancer. Meanwhile, the results of studies in the breast cancer population in Germany showed significant TaqI polymorphisms only in patients with positive estrogen receptors.<sup>6,15</sup>

The insignificant relationship between the TaqI gene polymorphism and the stage of breast cancer in this study was thought to be due to the SNP polymorphism of TaqI so that it did not directly affect tumor size, lymph node status, and breast cancer metastases. TaqI polymorphism has different properties when compared to BsmI and ApaI. This polymorphism is located in the exon region, while the other two types of polymorphism are located in the intron.<sup>16</sup> Specifically, TaqI changed the codon in the exon 9 area of the VDR gene but did not change the type of amino acid it encoded. This change is presumed to affect the post-translational modification process of VDR mRNA, which reduces its stability.<sup>17</sup>

VDR protein expression in peripheral leukocytes of wildtype (TT) individuals

**Table 4. Results of Bivariate Analysis of Histological Grade Relationship with TaqI Polymorphisms, Age of Diagnosis, Menstrual Status, and Contraceptive Use in Breast Cancer Patients.**

	Grade		P-Value
	I-II	III	
<b>VDR TaqI Gene</b>			
Non-Polymorphism	16 (72.7%)	7 (41.2%)	<b>0.047</b>
Polymorphism	6 (27.3%)	10 (58.8%)	
<b>Diagnosed Age</b>			
≥50 years	14 (63.6%)	8 (47.1%)	0.301
< 50 years	8 (36.4%)	9 (52.9%)	
<b>Menstrual Status</b>			
Pre-Menopause	7 (31.8%)	7 (41.2%)	0.546
Post-Menopause	15 (68.2%)	10 (58.8%)	
<b>Contraceptive Use</b>			
Non-Hormonal	7 (31.8%)	6 (35.3%)	0.819
Hormonal	15 (68.2%)	11 (64.7%)	

was on average 78% higher than that of individuals with homozygous polymorphism (CC). Increased VDR expression is associated with decreased breast cancer aggressiveness such as tumor size, ER-negative, triple-negative, and KI-67. Therefore, it allows VDR expression to be a prognostic factor for breast cancer.<sup>18</sup> Research Peng et al. reported that low VDR expression was associated with poor prognostication of esophageal squamous cell carcinoma (ESCC).<sup>19</sup>

Normally, VDR has tumor suppressor properties because VDR activation is known to increase the expression of tumor suppressor genes such as P53 and related proteins such as ATM, p27, and p21. The P53 gene and downstream proteins are very potent tumor suppressor proteins. Activation of these proteins will inhibit the cell cycle and induce a DNA repair response to minimize the occurrence of carcinogenic mutations. In addition, P53 and related proteins also promote cell differentiation. Regarding differentiation, VDR can inhibit proteins involved in cell dedifferentiation such as Wnt-β-catenin signaling and telomeration, but VDR can increase the expression of TGF-β and FOXO3/4 which function in epithelial cell differentiation and direct cell metabolism towards respiration, oxidative (cancer cells metabolize energy mainly through oxidative glycolysis).<sup>20</sup>

Regarding DNA repair, VDR can increase the expression of BRCA1 and Rad50, which play a role in the double-stranded DNA damage repair. Double-

stranded DNA damage is a very harmful mutation because it has the risk of producing chromosomal translocations or fusion of different chromosomes so that it can increase the expression of oncogenic genes many times at sites with active promoters. Regarding DNA damage protection, active VDR restores cellular antioxidant status by increasing the expression of SOD 1 and 2.<sup>20</sup>

TaqI polymorphism, like ApaI and BsmI polymorphism, is a 3' untranslated region (UTR) polymorphism associated with mRNA stability and degradation. The 3' UTR gene is known to be involved in the expression regulation, primarily through regulation of mRNA stability, including for steroid receptors containing extensive 3' UTR, such as alpha glucocorticoid receptors.<sup>21</sup>

Looking at the anti-cancer function of VDR, the presence of TaqI polymorphisms that disrupt the stability of VDR mRNA has the opportunity to reduce the protective effect of VDR. The findings in this study, which showed that the group with the TaqI polymorphism (with the C allele) was significantly associated with higher histologic grades, could also be associated with the decreased normal functioning of the VDR. As previously discussed, TaqI reduces VDR levels by up to 78% when compared to wild-type individuals. Therefore, it can be concluded that the decrease in VDR levels will also decrease its anti-cancer and pro-differentiation effects associated with high histological grades. The histological grade

III here can be defined as cancer tissue with poor differentiation and has a high mitotic rate.<sup>22</sup>

The sampling process which is only carried out at one health center, namely at Sanglah Hospital Denpasar Bali, can lead to the risk of under-representation of genetic variation in different areas and populations. However, this study has provided preliminary data regarding the role of the TaqI VDR polymorphism in breast cancer and the possible high prevalence of the T allele in the Balinese population with a cross-sectional study design. However, this needs to be followed up with studies in a larger population through case-control studies with the number of case samples being patients with advanced-stage or grade III and control samples are patients with early-stage or grade I-II balanced with an in-depth evaluation of clinical effects of this VDR variation. In addition, the anti-aging effect of VDR can be extended to other aging-related diseases such as type 2 diabetes mellitus, Parkinson's, Alzheimer's, and cardiovascular disease which are all related indirectly to chronic inflammatory activation in which vitamin D and its receptors play a significant role.

## CONCLUSION

The research results concluded that the RVD TaqI gene polymorphism in breast cancer patients at Sanglah Hospital Denpasar Bali is more dominated by the wild-type TT genotype. Also, there is a relationship between the RVD TaqI gene polymorphism with breast cancer patients' clinicopathological characteristics, especially the risk of increasing histological grade. Further research is needed with a larger sample and regarding the effect of TaqI polymorphisms on clinicopathological conditions, outcomes, and chemotherapy responses of breast cancer patients.

## CONFLICT OF INTEREST

All researchers declare that there is no conflict of interest related to this article.

## ETHICAL APPROVAL

This research has been approved by the ethics committee of Udayana University

with the Ethical Clearance number: 1614/UN14.2.2.VII.14/LT/2021

## FINANCING

This research was conducted using self-financing.

## AUTHOR'S CONTRIBUTION

All authors contributed equally in compiling this research article.

## REFERENCES

- Siegel, R. L., Miller, K. D., & Jemal, A. Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians* 2015, 65(1), 5–29. <https://doi.org/10.3322/caac.21254>
- GLOBOCAN. Summary statistics 2020: World. <https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>
- Bhoo-Pathy, N., Yip, C. H., Hartman, M., Uiterwaal, C. S. P. M., Devi, B. C. R., Peeters, P. H. M., Taib, N. A., Van Gils, C. H., & Verkooijen, H. M. (2013). Breast cancer research in Asia: Adopt or adapt Western knowledge? *European Journal of Cancer*, 49(3), 703–709. <https://doi.org/10.1016/j.ejca.2012.09.014>
- Wihandani D, Adiputra P, & Supadmanaba. Low prevalence of caveolin-1 oncogenic polymorphism G14713A and T29107A among breast cancer patient in Sanglah General Hospital. *Bali Medical Journal* 2017, 6(3), 109-undefined. <https://doi.org/10.15562/bmj.v3i3.743>
- Wacholder, S., Hartge, P., Prentice, R., Garcia-Closas, M., Feigelson, H. S., Diver, W. R., Thun, M. J., Cox, D. G., Hankinson, S. E., Kraft, P., Rosner, B., Berg, C. D., Brinton, L. A., Lissowska, J., Sherman, M. E., Chlebowski, R., Kooperberg, C., Jackson, R. D., Buckman, D. W., ... Hunter, D. J. Performance of Common Genetic Variants in Breast-Cancer Risk Models. *New England Journal of Medicine* 2010, 362(11), 986–993. <https://doi.org/10.1056/nejmoa0907727>
- Abbas, S., Nieters, A., Linseisen, J., Slinger, T., Kropp, S., Mutschelknauss, E. J., Flesch-Janys, D., & Chang-Claude, J. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. *Breast Cancer Research* 2008, 10(2). <https://doi.org/10.1186/bcr1994>
- Atoum, M. F., & Al-Khatib, Y. M. Association between serum 25-hydroxy vitamin D concentration and taqi vitamin D receptor gene polymorphism among Jordanian females with breast cancer. *Chinese Medical Journal* 2017, 130(9), 1074–1078. <https://doi.org/10.4103/0366-6999.204933>
- Reimers, L. L., Crew, K. D., Bradshaw, P. T., Santella, R. M., Steck, S. E., Sirosh, I., Terry, M. B., Hershman, D. L., Shane, E., Cremers, S., Dworakowski, E., Teitelbaum, S. L., Neugut, A. I., & Gammon, M. D. Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk. *Cancer Causes and Control* 2015, 26(2), 187–203. <https://doi.org/10.1007/s10552-014-0497-9>
- Ditsch, N., Toth, B., Mayr, D., Lenhard, M., Gallwas, J., Weissenbacher, T., Dannecker, C., Friese, K., & Jeschke, U. The Association between Vitamin D Receptor Expression and Prolonged Overall Survival in Breast Cancer. *Journal of Histochemistry and Cytochemistry* 2012, 60(2), 121–129. <https://doi.org/10.1369/0022155411429155>
- Huss, L., Butt, S. T., Borgquist, S., Elebro, K., Sandsveden, M., Rosendahl, A., & Manjer, J. Vitamin D receptor expression in invasive breast tumors and breast cancer survival. *Breast Cancer Research* 2019, 21(1). <https://doi.org/10.1186/s13058-019-1169-1>
- Siregar, K. B. Vitamin D Receptor Gene TAQ 1 (rs 731236) Polymorphism In Breast Cancer Patients ATH Adam Malik Hospital Medan and its Relationship with Histopathology grading. *Biomedical Journal of Scientific & Technical Research* 2018, 6(1). <https://doi.org/10.26717/bjstr.2018.06.001302>
- Kazemian, M.E., A., N., M., S., G., A.M., M., Y., J.-N., M., K., K.R., Z., N., G., A., A., S.H., D., & L.S., R. Vitamin D receptor genetic variation and cancer biomarkers among breast cancer patients supplemented with vitamin D3: A single-arm non-randomized before and after trial. *Nutrients* 2019, 11(6), 1–19.
- Awaliyah, N., Pradjatmo, H., & Kusnanto, H. Penggunaan kontrasepsi hormonal dan kejadian kanker payudara di rumah sakit Dr. Sardjito. *Berita Kedokteran Masyarakat (BKM Journal of Community Medicine and Public Health)* 2017, 33(10), 487–494. <https://jurnal.ugm.ac.id/bkm/article/view/22812>
- Kementerian Kesehatan Republik Indonesia. (2016). *Infodatin Kanker Payudara*. In *InfoDATIN* (pp. 1–3).
- Mishra, D. K., Wu, Y., Sarkissyan, M., Sarkissyan, S., Chen, Z., Shang, X., Ong, M., Heber, D., Koeffler, H. P., & Vadgama, J. V. Vitamin D Receptor Gene Polymorphisms and Prognosis of Breast Cancer among African-American and Hispanic Women. *PLoS ONE* 2013, 8(3). <https://doi.org/10.1371/journal.pone.0057967>
- Ruiz-Ballesteros, A. I., Meza-Meza, M. R., Vizmanos-Lamotte, B., Parra-Rojas, I., & de la Cruz-Mosso, U. Association of vitamin D metabolism gene polymorphisms with autoimmunity: Evidence in population genetic studies. *International Journal of Molecular Sciences* 2020, 21(24), 1–24. <https://doi.org/10.3390/ijms21249626>
- Mahto, H., Tripathy, R., Das, B. K., & Panda, A. K. Association between vitamin D receptor polymorphisms and systemic lupus erythematosus in an Indian cohort. *International Journal of Rheumatic Diseases* 2018, 21(2), 468–476. <https://doi.org/10.1111/1756-185X.13245>
- Al-Azhri, J., Zhang, Y., Bshara, W., Zirpoli, G., E., S., Khoury, T., Morrison, C. D., Edge, S. B., & Christine B. Ambrosone, PhD2, and Song Yao, P. Tumor Expression of Vitamin D Receptor and Breast Cancer Histopathological Characteristics and Prognosis. *Clin Cancer Res*. 2017, 23(1), 97–103. <https://doi.org/10.1158/1078-0432.CCR-16-0075>
- Peng, H., Yu, J., Li, F., Cui, X., & Chen, Y. Decreased vitamin D receptor protein expression is associated with the progression and prognosis of esophageal squamous cell carcinoma: A multi-ethnic cohort study from the Xinjiang, China. *International Journal of Clinical and Experimental Pathology* 2017, 10(2), 2340–2350.
- Jeon, S. M., & Shin, E. A.. Exploring vitamin D metabolism and function in cancer. In *Experimental and Molecular Medicine* (Vol. 50, Issue 4). Nature Publishing Group. 2018. <https://doi.org/10.1038/s12276-018-0038-9>
- Uitterlinden, A. G., Fang, Y., Van Meurs, J. B. J., Pols, H. A. P., & Van Leeuwen, J. P. T. M. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004, 338(2), 143–156. <https://doi.org/10.1016/j.gene.2004.05.014>
- Hopkins, J. *Breast Cancer & Breast Pathology*. 2021. <https://pathology.jhu.edu/breast/staging-grade>



This work is licensed under a Creative Commons Attribution