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Research Article

VDR and WNT/β-catenin Expression in Invasive Breast Carcinoma of No Special Type: Role and Prognostic Value

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ABSTRACT

Background: Breast cancer prognosis is closely related to tumor size (T stage). The Vitamin D receptor (VDR), found in about 80% of breast cancer cases, inhibits tumor growth, promotes differentiation, and enhances apoptosis. The growth of tumor cells is linked to β-Catenin, an essential element of the Wnt signaling pathway. Both β-catenin and VDR affect breast cancer aggressiveness. This study explored their correlation with the T stage of invasive breast carcinoma of no special type. **Methods:** This research employed a cross-sectional design, applied on paraffin-embedded specimens from patients with invasive breast cancer of no special type (NST) who underwent modified radical mastectomy (MRM) at Dr. Soetomo General Academic Hospital from January 2019 to June 2023. The samples were categorized into four groups based on the T stage. Immunohistochemical staining was performed using VDR and β-catenin antibodies. This study used analytic statistical methods to examine differences and correlations among VDR and β-catenin. **Results:** VDR expression and T stages were significantly different and negatively correlated. Expression of β-Catenin revealed significant differences and had positive correlations with T stages. VDR and β-catenin expressed no significant negative correlation with T stages. **Conclusion:** The study found significant differences and correlations between VDR and β-catenin expression with T stages in invasive breast carcinoma of NST. Both β-catenin and VDR play crucial roles in breast cancer cell proliferation.

Keywords: Breast cancer, Invasive breast carcinoma of no special type, Vitamin D Receptor, β-catenin.

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INTRODUCTION

The most frequent malignancy among women is breast carcinoma. In Indonesia, there were approximately 65,858 (16.6%) new cases in 2020, while the global total was over 2 million (approximately 11.7%).[1] In developed nations such as Indonesia, this particular kind of cancer is the second most prevalent cause of death from cancer, accounting for 22,430 cases (9.6% of the total).[2] From January to December 2022, the Anatomical Pathology Unit of RSUD, Dr. Soetomo Surabaya, recorded a total of 208 invasive breast cancer of NST. Among these cases, 67 were mastectomy cases, and 190 (91.34%) were malignant invasive breast cancer of NST.

Several factors determine the prognosis of breast cancer. Besides to the tumor stage and differentiation degree (grading), the molecular subtype is extremely important.[3,4] Knowledge of the molecular pathways underlying breast cancer pathogenesis has been established and utilized as predictive and prognostic factors for patients over the past decade. Recent studies have investigated various hormonal receptors beyond ER/PR that possess prognostic significance, including the VDR (vitamin D receptor). This receptor is ligand-dependently modulatory of gene expression and belongs to the steroid hormone receptor family.[5] The vitamin D receptor exists in approximately 80% of individual breast tumor samples.[6] Vitamin D can regulate proliferation, differentiation, and apoptosis in various cell types.[7] Prior research indicates that VDR expression correlates with favorable clinical and pathological characteristics across multiple cancer types, including breast cancer.[8,9] According to other research, VDR expression is substantially lower in individuals with bone metastases, suggesting that low VDR expression may increase metastatic potential. VDR expression levels act as a biomarker for predicting the progression of breast cancer.[10]

β-catenin is an essential protein for regulating of Wnt signaling. This protein is crucial for mammary gland development during embryogenesis, pregnancy. One of the most frequently changed pathways in breast cancer is represented by this protein. These alterations include proliferation, metastasis, therapeutic resistance, and phenotype formation in breast cancer.[11-13] Literature indicates that β-catenin expression may serve as a marker for advanced cancer stages and can function as a prognostic indicator in breast cancer.[14-16]

Vitamin D receptors modulate the Wnt/β-catenin signaling pathway by inducing axin gene expression and enhancing GSK3β activity, thereby influencing β-catenin stability. The VDR induces DKK1 gene expression in colorectal carcinoma, preventing the extracellular Wnt/β-catenin pathway and decreasing the proliferation, differentiation, and invasion of cancer cells.[17,18] This study sought to elucidate the relationships and distinctions in VDR and β-catenin expression during breast cancer progression, as measured by tumor size (T stage), and to find the correlation among VDR and β-catenin expression in different T stages.

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METHODS

Study Design and Research Subjects

The cross-sectional design was conducted. The study population consisted of paraffin blocks from modified radical mastectomy (MRM) tissue samples of patients with invasive breast carcinoma of No Special Type (NST) at the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital from January 2019 to June 2023. The research sample comprised paraffin blocks from patients diagnosed with invasive breast carcinoma of NST, adhering to the study's inclusion and exclusion standards.

Variables and Data Collection

The first variable in this study is VDR and β-catenin expression. The expression of VDR occurs in invasive breast carcinoma tumor cells, evaluated using the immunohistochemistry method with monoclonal antibodies against VDR and processed according to the specified protocol. Both the nucleus and the cytoplasm exhibit the positive expression of VDR.[19] Expression of β-catenin in invasive breast carcinoma tumor cells is evaluated using immunohistochemistry with monoclonal antibodies against β-catenin and processed according to the specified protocol. Both the nucleus and the cytoplasm exhibit the positive expression of β-catenin. Two anatomical pathology experts measure VDR and β-catenin expression using an Olympus CX31 binocular light microscope.

The diagnosis and staging of invasive breast carcinoma of NST are established based on the WHO Classification of Tumors, Breast Tumors, 5th Edition, 2019. Invasive breast carcinoma of NST with T staging performed on tumors from MRM specimens that have not received neoadjuvant chemotherapy were divided into 4 groups; T1 (12 cases), T2 (16 cases), T3 (14 cases), and T4 (7 cases).

Staining intensity (I) is classified as: 0 for no staining, 1 for weak, 2 for moderate, and 3 for intense. The proportion of all stained cells (Ptotal) varies from 1% to 100%. The histochemical scoring (H-score), which ranges from 0 to 300, is calculated using the formula: (0xP0) + (1xP1) + (2xP2) + (3xP3). The H-score results are interpreted as follows: 0 for negative (1-49), 1 for weak (50-99), 2 for moderate (100-199), and 3 for strong (200-300).

Statistical Analyses

The data obtained will be statistically tested using the EZR program. Differences in the expression of VDR and β-catenin across several T stages of invasive breast carcinoma of NST will be analyzed using the Kruskal-Wallis test. The differences in VDR and β-catenin expression in each group will be considered significant if a p-value of <0.05 is obtained. Using Spearman's correlation test, this study will analyse the correlation between VDR and β-catenin expression across different T stages of invasive breast carcinoma of NST. Results from the statistical tests will be deemed significant if a p-value of less than 0.05 is achieved.

RESULTS

Sample Characteristics

This study's samples are 49 paraffin blocks that meet the inclusion and exclusion criteria. Statistical calculations were obtained using purposive sampling techniques. Table 1 provides a summary of the distribution of the sample based on age group, tumor grade, and tumor stage. The largest age group is 41-50 years, which accounts for 32.65% of the total. This is followed by the 51-60 years (26.53%), 31-40 years (16.33%), 61-70 years (14.29%), 71-80 years (8.16%), and the smallest group is 20-30 years (2.04%). In terms of tumor grade, Grade III tumors are the most prevalent, occurring in 27 cases (55.10%). The T2 stage is the most frequent tumor stage, with 16 cases (33.00%). The T3 stage follows with 14 cases (29.00%), the T1 stage includes 12 cases (24.00%), and the T4 stage is the least frequent, with 7 cases (14.00%).

Table 1. Sample Characteristics.

Characteristics	Frequency	%
Age Group		
20-30 years	1	2.04
31-40 years	8	16.33
41-50 years	16	32.65
51-60 years	13	26.53
61-70 years	7	14.29
71-80 years	4	8.16
Tumor Grade		
Grade I	3	6.12
Grade II	19	38.78
Grade III	27	55.10
T Stadium		
T1	12	24.00
T2	16	33.00
T3	14	29.00
T4	7	14.00

Differences in VDR and β-catenin expression in Various T Stage

The most common level of VDR expression is moderately positive, seen in 21 (42.86%) samples. In the T1 group, strong positive expression is highest, found in 6 (50%) samples, followed by moderate and weak positive in 3 (25%) samples each. In the T2 group, moderate positive expression occurs in 11 (22%) samples, followed by strong positive in 3 (6%) and negative in 2 (4%) samples; no weak positive expression was observed. In the T3 group, weak positive expression is most common, appearing in 8 (57%) samples, moderate positive in 6 (43%) samples, and no strong positive or negative expression. In the T4 group, negative and weak positive expressions are equally common in 3 (43%) samples, with moderate positive in 1 (14%) sample and no strong positive expression (Figure 1A, 1B and 1C).

For β-catenin expression, the most common level is moderately positive, present in 22 (44.9%) samples. In the T1 group, moderate positive expression is highest in 7 (58%) samples, followed by weak positive in 3 (25%) and negative in 2 (17%) samples; no strong positive expression was found. In the T2 group, moderate positive expression is most common in 9 (18%) samples, followed by strong positive in 7 (14%) samples; no weak positive or negative expression was found. In the T3 group, strong positive expression is highest in 10 (71%) samples, with moderate positive in 3 (21%) samples and negative expression in 1 (7%) sample; no weak positive expression was found. In the T4 group, strong positive expression is most common in 4 (57%) samples, followed by moderate positive in 3 (43%) samples, with no weak positive or negative expression observed (Figure 2A, 2B and 2C).

The Kruskal-Wallis test revealed that VDR expression significantly decreases (p=0.00183), while β-catenin expression significantly increases with advancing T stages (p=0.000751) (Figure 1).

Correlation Between VDR and β-catenin Expression Across Various T stages

The relationship between VDR and β-catenin expression across various T stages of invasive breast carcinoma of NST was statistically verified using the Spearman correlation test. The results of the analysis exhibited a significant negative correlation between VDR expression

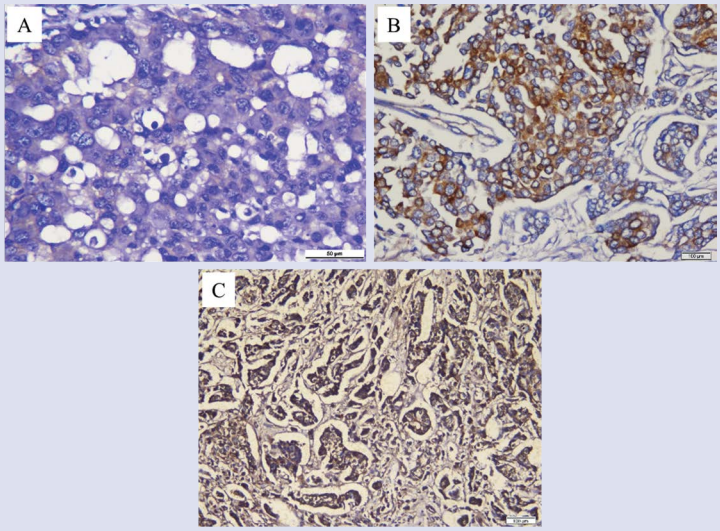

Figure. 1. VDR expression in invasive breast carcinoma of NST tumor cells. (A) Weak positive expression, 400x magnification (B) Moderate positive expression, 200x magnification (C) Strong positive expression, 200x magnification.

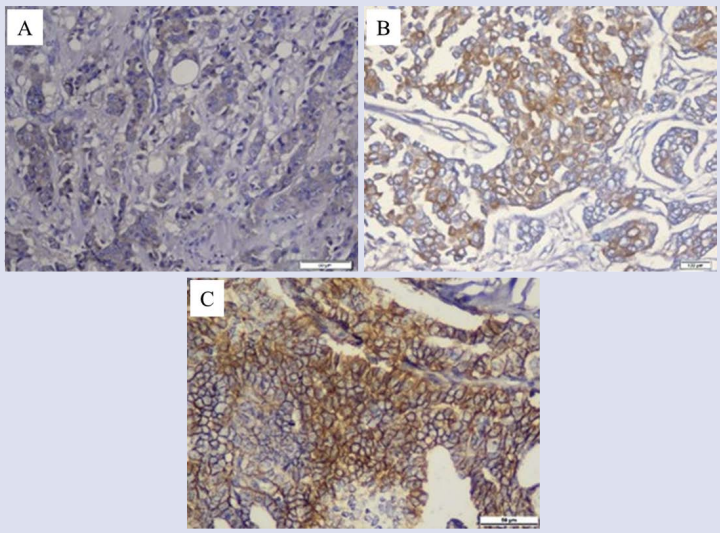

Figure 2. Expression of β-catenin in tumor cells of invasive breast carcinoma of NST. (A) Weak positive expression, magnification 400x (B) Moderate positive expression, magnification 200x (C) Strong positive expression, magnification 200x.

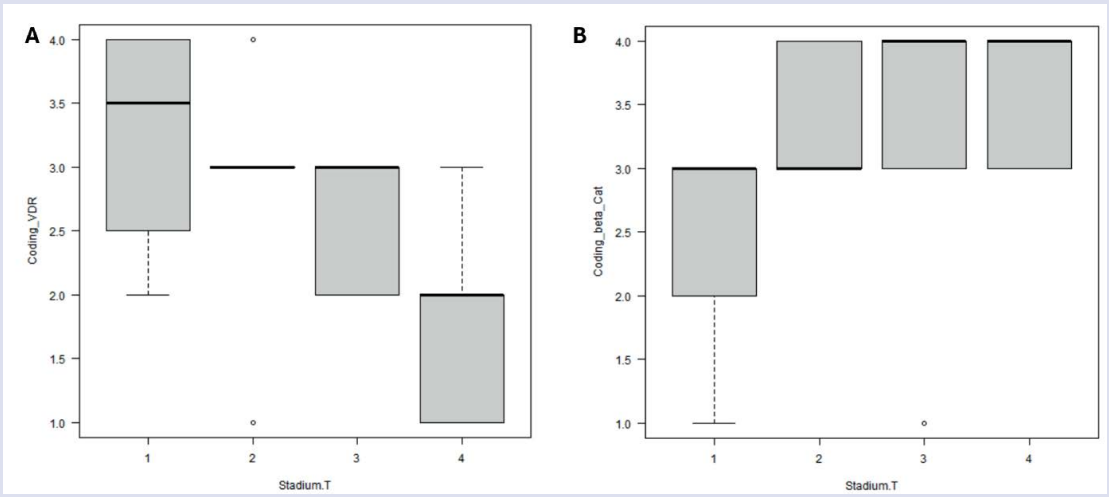

Figure 3. Differences in VDR and β-catenin expression in various T stages. Boxplot diagram showing differences in VDR (A) and β-catenin expression (B) across various T stages (T1, T2, T3, and T4) in invasive breast carcinoma of NST.

Table 2. VDR and β-catenin Expression in Various T Stage

Variable	T Stage				Total	P value
	T1	T2	T3	T4		
	N (%)	N (%)	N (%)	N (%)		
VDR Expression (H-Score)						
Negative (0)	0 (0)	2 (4)	0 (0)	3 (43)	5	
Weak (1)	3 (25)	0 (0)	8 (57)	3 (43)	14	0.00183
Moderate (2)	3 (25)	11 (22)	6 (43)	1 (14)	21	
Strong (3)	6 (50)	3 (6)	0 (0)	0 (0)	9	
Total	12(100)	16(100)	14(100)	7(100)	49	
β-catenin Expression (H-Score)						
Negative (0)	2 (17)	0 (0)	1 (7)	0 (0)	3	
Weak (1)	3 (25)	0 (0)	0 (0)	0 (0)	3	0.000751
Moderate (2)	7 (58)	9 (18)	3 (21)	3 (43)	22	
Strong (3)	0 (0)	7 (14	10 (71)	4 (57)	21	
Total	12(100)	16(100)	14(100)	7(100)	49	

Table 3. Spearman correlation test results between VDR and β-catenin expression.

		β-catenin expression
VDR expression	r_s	-0.188
	p	0.189
	n	49

and the different T stages (r = -0.532, p = 0.0000694), indicating that higher VDR expression is inversely related to the progression of T stages. Furthermore, a significant positive correlation was observed between β-catenin expression and the various T stages (r = 0.506, p = 0.000176), meaning that higher β-catenin expression corresponds with the progression of T stages. Meanwhile, no significant correlation was observed between VDR and β-catenin expression across the different T stages of invasive breast carcinoma of NST (r = -0.188, p = 0.189) (Table 3).

DISCUSSION

This study comprises 49 purposively sampled female participants, aged between 28 and 80, with a mean age of 51.67. Compared to men, women are far more likely to develop breast cancer; women are a hundred times more likely to get breast cancer than men.[4-23] The most common age group is 41-50 (32.65%), followed by 51-60 (28.57%). The 61-70 and 31-40 age groups represent 14.29% of participants, while 71-80 years accounts for 8.16%, and 20-30 years is the least common at 2.04%. It is in line with what Lim et al. found that Asian women are more likely than their Western counterparts to get breast cancer, with peak incidence occurring in Asia between the ages of 40 and 50 and in the West between the ages of 60 and 70. The increasing risk also fluctuates around menopause due to hormonal changes.[24,25,26] Young breast cancer cases often involve BRCA1/BRCA2 mutations and a higher risk of bilateral cancer.[26,27]

This study reports that grade 3 is the most common, accounting for 27 samples (55.10%), followed by grade 2 with 19 samples (38.78%), and grade 1 with 3 samples (6.12%). This result is consistent with research on the clinicopathological features of breast cancer in young women, conducted in Indonesia by Anwar et al. That study found that of the 1259 samples in total, 78.5% were grade 3, with grade 2 accounting for 20.8% of cases.[28] This finding, however, is not consistent with a study carried out in the United States by DeSantis et al., which indicated that the most prevalent type of invasive breast cancer was grade 2..[29] Previous research have reported that tumor grade in breast cancer has prognostic value for outcomes and recurrence rates comparable to lymph node metastasis status. The prognostic value of tumor grade is even greater than tumor size.[4,30]

Immunohistochemical analysis showed significant differences in VDR expression across T stages, with a p-value of 0.001 ($p<0.05$). These findings suggest that higher VDR expression correlates with smaller tumor size (T stage). These results align with previous studies on VDR expression. Based on a study by Voutsadakis et al. on VDR expression and metabolism in invasive breast cancer, tumor characteristics like lower grade, ER positive, PR positive, low Ki67 expression, or molecular subtypes like luminal are associated with positive VDR expression in the nuclei and cytoplasm of breast cancer cells.[31] Similarly, Huss et al. reported that VDR expression correlates with a lower risk of mortality caused by breast cancer. Among other cancer types, VDR malfunction has been linked to an increased risk of breast cancer.[5,7] Activation of the VDR influences tumorigenesis by regulating genes involved in processes like inhibiting cell proliferation, promoting cancer cell differentiation, inducing apoptosis and autophagy, modulating the immune system, and preventing angiogenesis.[32,33]

The study also assessed β-catenin expression, finding that tumor cells most common staining was in the cytoplasm. β-catenin expression at various T stages showed significant differences ($p<0.05$), with higher expression correlating with larger tumor size. The Wnt/β-catenin signaling pathway is activated, leading to the translocation of β-catenin from the membrane to the cytoplasm. This is the basic process behind β-catenin expression in the cytoplasm. The overexpression of β-catenin and its accumulation in the cytoplasm of breast cancer cells is directly linked to low expression of APC, a key finding with significant implications in breast cancer research.[34,35]

Increased β-catenin expression has been linked to tumor progression (T stage) in multiple studies looking at β-catenin expression in invasive malignancies, including breast cancer. Consistent with this study, research by Sefidbakht et al. on β-catenin expression in breast cancer connected to clinicopathological characteristics indicated that β-catenin protein expression is low in stage I tumors and strong in stage III tumors. β-catenin is a multifunctional protein located in the nucleus and cytoplasm of cells and is a key mediator in several signal transduction pathways, including the Wnt pathway[15]. In normal breast tissue, β-catenin is strongly expressed at the luminal epithelial cell membrane but negatively stained in the cytoplasm and nucleus. In contrast, in invasive breast cancer cells, β-catenin is expressed in the nucleus, cytoplasm, and membrane, but the intensity of the staining decreases significantly to negative on the membrane of breast cancer cells.[14,15] The study done by Xu et al. in Hangzhou also revealed that most invasive breast cancer cases of non-specific origin exhibited β-Catenin expression, with 80.6% expressed in the cytoplasm and 12.5% in the nucleus.[13]

The correlation between VDR expression at various T stages showed a negative significant correlation ($p<0.05$), indicating that higher VDR expression is negatively correlated with increasing T stage. Previous research on VDR expression across different cancers, particularly breast cancer, has been extensively documented, with the majority suggesting an inverse relationship between VDR expression and breast cancer aggressiveness. Elevated VDR expression correlates with reduced tumor progression and extended survival rates. Consequently, low VDR expression may serve as a prognostic marker for the progression of various cancers, including breast cancer.[10]

The analysis demonstrated a significant positive correlation between β-catenin expression and the T stages of invasive breast carcinoma of

NST ($p < 0.05$), suggesting that elevated β-catenin expression is linked to higher T stages. Sefidbakht et al. concerning β-catenin expression and localization in breast cancer, indicating that the expression of β-catenin in both the nucleus and cytoplasm is linked to invasion, metastasis, and unfavorable prognosis. The Wnt pathway activation has been rated as a prognostic marker for breast cancer development.[14,36,37]

The correlation between VDR expression and β-catenin was negative. This research reviews how VDR activation can inhibit the Wnt/β-catenin signaling pathway and the results indicate both proteins have opposite expressions at the T stage, but statistically, there was no significant correlation. Breast cancer is a heterogeneous disease that includes genetically and epigenetically distinct groups, each exhibiting diverse clinical presentations. Breast cancer exhibits heterogeneity through varying expressions of ER, PR, and HER2.[3] Several studies showing VDR expression may affect the β-catenin pathway have been proven in colorectal cancer by inducing DKK1 gene expression.[38-40] The role of DKK-1 in breast cancer remains contentious, with direct evidence from studies being notably scarce. Previous studies have indicated that DKK-1 is expressed in hormone-resistant breast cancer, specifically in ER/PR negative cases.[17,18]

This study acknowledges several limitations. Firstly, it did not categorize patients with invasive breast carcinoma of NST by grading, molecular subtype, stage N, or stage M, which may account for the lack of significant correlation between VDR expression and β-catenin. These factors should be considered when interpreting the findings.

CONCLUSIONS

This study reveals several key findings regarding the expressions of VDR and β-catenin at various T stages. It was observed that higher T stages, indicating larger tumor sizes, are associated with lower VDR expression and higher β-catenin expression. VDR expression decreases significantly as the tumor size increases, showing a strong negative correlation. Conversely, β-catenin expression increases with larger tumor sizes, reflecting a moderate positive correlation. However, no significant negative correlation was observed between VDR and β-catenin expressions, suggesting that their effects on tumor growth are independent.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A. Cancer statistics for the year 2020: An overview. Intl Journal of Cancer. 2021;149(4):778–89.
3. Turner KM, Yeo SK, Holm TM, Shaughnessy E, Guan JL. Heterogeneity within molecular subtypes of breast cancer. American Journal of Physiology-Cell Physiology. 2021;321(2):C343–54.
4. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer—epidemiology, classification, pathogenesis and treatment (review of literature). Cancers. 2022;14(10):2569.
5. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Experimental & molecular medicine. 2018;50(4):1–14.
6. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S. The 2019 WHO classification of tumors of the breast. Histopathology. 2020 [cited 2024 Jul 20];77(2). Available from: https://nottingham-repository.worktribe.com/output/4758580
7. Welsh J. Vitamin D and breast cancer: Mechanistic update. Journal of Bone and Mineral Research Plus. 2021;5(12):e10582.
8. Huss L, Butt ST, Borgquist S, Elebro K, Sandsveden M, Rosendahl A. Vitamin D receptor expression in invasive breast tumors and breast cancer survival. Breast Cancer Res. 2019;21(1):84.
9. Shi Q, Han XP, Yu J, Peng H, Chen YZ, Li F. Decreased vitamin D receptor protein expression is associated with progression and poor prognosis of colorectal cancer patients. International journal of clinical and experimental pathology. 2020;13(4):746.
10. Seiler J, Ebert R, Rudert M, Herrmann M, Leich E, Weißenberger M. Bone metastases of diverse primary origin frequently express the VDR (vitamin D receptor) and CYP24A1. Journal of Clinical Medicine. 2022;11(21):6537.
11. Sheikh A, Niazi AK, Ahmed MZ, Iqbal B, Anwer SMS, Khan HH. The role of Wnt signaling pathway in carcinogenesis and implications for anticancer therapeutics. Hered Cancer Clin Pract. 2014;12(1):13.
12. Wang Z, Zhang H, Hou J, Niu J, Ma Z, Zhao H. Clinical implications of β-catenin protein expression in breast cancer. International journal of clinical and experimental pathology. 2015;8(11):14989.
13. Xu X, Zhang M, Xu F, Jiang S. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities. Mol Cancer. 2020;19(1):165.
14. Sefidbakht S, Saeedipour H, Saffar H, Mirzaian E. Determination of β-catenin expression in breast cancer and its relationship with clinicopathologic parameters. Asian Pacific Journal of Cancer Prevention: APJCP. 2021;22(11):3493.
15. Ali Salman R, Abdullatef AlBairuty GA, Abdul-Rasheed OF. Study of β-Catenin as Immunohistochemistry Marker in Women with Breast Cancer. Iraqi Journal of Science. 2021;62(2). Available from: https://search.ebscohost.com/loginaspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=00672904&AN=149098132&h=bhbjfwf5eGQ2k1eevDZ1AjyQu%2FWOPMqcXqaX5wNnJI%2B38U5iph%2Bj6OIWc%2Bc9jeP%2BX86qSphWDiU%2BzXAO6oOcYQ%3D%3D&crl=c
16. Mukherjee N, Panda CK. Wnt/β-catenin signaling pathway as chemotherapeutic target in breast cancer: an update on pros and cons. Clinical breast cancer. 2020;20(5):361–70.
17. Johnson AL, Zinser GM, Waltz SE. Vitamin D3-dependent VDR signaling delays ron-mediated breast tumorigenesis through suppression of β-catenin activity. Oncotarget. 2015;6(18):16304.
18. González-Sancho JM, Larriba MJ, Muñoz A. Wnt and vitamin D at the crossroads in solid cancer. Cancers. 2020;12(11):3434.
19. Welsh J. Vitamin D and breast cancer: Past and present. The Journal of steroid biochemistry and molecular biology. 2018;177:15–20.
20. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. Cancers. 2021;13(17):4287.
21. Muhammad T, Susilaningrum D, Tanggo VVC. Study of Ordinal Regression Method for Supporting Factors Investigation in Stages Condition of Breast Cancer Patients in Dr. Soetomo Surabaya Hospital, Indonesia. EKSAKTA: Berkala Ilmiah Bidang MIPA. 2021;22(3):220–9.

22. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes & diseases. 2018;5(2):77–106.
23. Zheng Y, Trivedi T, Lin RC, Fong-Yee C, Nolte R, Manibo J. Loss of the vitamin D receptor in human breast and prostate cancers strongly induces cell apoptosis through downregulation of Wnt/β-catenin signaling. Bone research. 2017;5(1):1–12.
24. Huang J, Ngai CH, Deng Y, Tin MS, Lok V, Zhang L. Cancer Incidence and Mortality in Asian Countries: A Trend Analysis. Cancer Control. 2022 Nov;29:107327482210959.
25. Rakha EA, Chmielik E, Schmitt FC, Tan PH, Quinn CM, Gallagy G. Assessment of predictive biomarkers in breast cancer: challenges and updates. Pathobiology. 2022;89(5):263–77.
26. Lim YX, Lim ZL, Ho PJ, Li J. Breast cancer in Asia: incidence, mortality, early detection, mammography programs, and risk-based screening initiatives. Cancers. 2022;14(17):4218.
27. da Silva JL, Nunes NCC, Izetti P, de Mesquita GG, de Melo AC. Triple negative breast cancer: A thorough review of biomarkers. Critical reviews in oncology/hematology. 2020;145:102855.
28. Anwar SL, Raharjo CA, Herviastuti R, Dwianingsih EK, Setyoheriyanto D, Avanti WS, et al. Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study. BMC Women's Health. 2019 Dec;19(1):28.
29. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019;69(6):438–51.
30. Tsang JY, Gary MT. Molecular classification of breast cancer. Advances in anatomic pathology. 2020;27(1):27–35.
31. Voutsadakis IA. Vitamin D receptor (VDR) and metabolizing enzymes CYP27B1 and CYP24A1 in breast cancer. Mol Biol Rep. 2020;47(12):9821–30.
32. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nature reviews cancer. 2014;14(5):342–57.
33. Vanhevel J, Verlinden L, Doms S, Wildiers H, Verstuyf A. The role of vitamin D in breast cancer risk and progression. Endocrine-related cancer. 2022;29(2):R33–55.
34. MacDonald BT, He X. Frizzled and LRP5/6 receptors for Wnt/β-catenin signaling. Cold Spring Harbor perspectives in biology. 2012;4(12):a007880.
35. Hashemi M, Hasani S, Hajimazdarany S, Ghadyani F, Olyaee Y, Khodadadi M. Biological functions and molecular interactions of Wnt/β-catenin in breast cancer: Revisiting signaling networks. International Journal of Biological Macromolecules. 2023;232:123377.
36. Shen T, Zhang K, Siegal GP, Wei S. Prognostic value of E-cadherin and β-catenin in triple-negative breast cancer. American journal of clinical pathology. 2016;146(5):603–10.
37. Dev A, Vachher M, Prasad CP. β-catenin inhibitors in cancer therapeutics: intricacies and way forward. Bioengineered. 2023;14(1):2251696.
38. Larriba MJ, González-Sancho JM, Barbáchano A, Niell N, Ferrer-Mayorga G, Muñoz A. Vitamin D is a multilevel repressor of Wnt/β-catenin signaling in cancer cells. Cancers. 2013;5(4):1242–60.
39. Pendas-Franco N, Aguilera O, Pereira F, González-Sancho JM, Munoz A. Vitamin D and Wnt/β-catenin pathway in colon cancer: role and regulation of DICKKOPF genes. Anticancer Research. 2008;28(5A):2613–23.
40. Zhang Y, Wang X. Targeting the Wnt/β-catenin signaling pathway in cancer. J Hematol Oncol. 2020;13(1):165.

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