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RESEARCH ARTICLE

Vitamin D Deficiency and Breast Cancer Recurrence in Indonesian Women with Breast Cancer: A Prospective Cohort Study

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Abstract: ***Introduction*****:** Breast cancer remains the most common malignancy and a leading cause of cancer-related mortality among women worldwide, including in Indonesia. Vitamin D deficiency is frequently observed among breast cancer patients. Recent evidence has revealed the potential role of vitamin D in regulating tumor cell proliferation, differentiation, and apoptosis. Moreover, vitamin D deficiency has been associated with increased cancer risk and poorer clinical outcomes in breast cancer. This study aims to determine the frequency and prognostic significance of vitamin D deficiency in Indonesian women with breast cancer.

Methods**:** A prospective study was conducted involving 123 women diagnosed with primary, nonmetastatic invasive breast cancer. Serum 25(OH)D levels were measured at diagnosis, prior to any treatment, using the Chemiluminescent Microparticle Immunoassay (CMIA) method. Vitamin D deficiency was defined as serum levels below 20 ng/mL.

Results**:** The median serum vitamin D level was 19.9 ng/mL (range: 5.7–35.1). Vitamin D deficiency was identified in 65 patients (52.8%). It was significantly associated with higher tumor grade (p = 0.037), lymph node involvement (p = 0.012), larger tumor size (p = 0.041), more advanced clinical stage (p = 0.049), and positive expression of estrogen receptor (ER) (p = 0.034) and HER2 (p = 0.014). Kaplan–Meier analysis demonstrated that patients with vitamin D deficiency had a significantly shorter time to breast cancer recurrence (20.11 ± 0.91 months; p = 0.048). Multivariate Cox regression confirmed vitamin D deficiency as an independent predictor of shorter time to breast cancer recurrence (HR: 3.19; 95% CI: 1.178–8.660; p = 0.023).

Discussion**:** These findings suggest that vitamin D deficiency may serve as a modifiable prognostic biomarker in breast cancer. Its association with aggressive tumor characteristics and shorter time to breast cancer recurrence highlight the potential value of assessing and correcting vitamin D status as part of breast cancer management, especially in Indonesian population.

Conclusion**:** Vitamin D deficiency is common among Indonesian women with breast cancer and independently associated with multiple poor prognostic indicators and shorter time to reccurence.

Keywords: Breast cancer, vitamin D deficiency, prognosis, recurrence, apoptosis, Chemiluminescent Microparticle Immunoassay (CMIA).

1. INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women in Indonesia, accounting for approximately 19.2% of all cancer cases [1]. In 2022, the GLOBOCAN report an estimated 66,271 new breast cancer cases were diagnosed among Indonesian women [2]. The breast cancer incidence has also shown a steady increase over the past two decades, particularly in urban areas [3,4]. In parallel, mortality rates due to breast cancer have also risen, with more than 22,000 deaths reported annually. It is consistent with trends observed in many developing countries, including South East Asian countries [4-6].

Although early detection and treatment have made significant progress in recent years, breast cancer continues to pose a major public health burden in Indonesia. Most of this burden stems from delays in diagnosis and limited access to healthcare services. In addition, cultural norms and physio-

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logical barriers among patients also play a role in late-stage diagnosis, ultimately making treatment more difficult to achieve [7-9].

Prognostic factors play an important role in guiding clinical decisions and improving treatment outcomes in breast cancer patients. Accurate identification of these factors may help clinicians to assess risk and develop individualized treatment plans. The most commonly recognized prognostic indicators include tumor size [10], histological grade [11], and molecular receptor status, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [12,13]. In addition, sociodemographic variables such as age, comorbidities, and family history have also been shown to influence prognosis [14].

Recent studies have increasingly focused on identifying modifiable prognostic biomarkers, especially those related to lifestyle and nutrition. Among these, vitamin D has received growing attention due to its potential role in tumor biology. Vitamin D is a fat-soluble secosteroid hormone, obtained mainly through skin synthesis following ultraviolet B (UVB) exposure. Notably, vitamin D can also be obtained from dietary sources such as fatty fish, fortified dairy products, egg yolks, and supplements [15-17]. In its active form, 1,25-dihydroxyvitamin D (1,25(OH)D), can bind to vitamin D receptors (VDR) in target cells. Through these receptors, vitamin D influences several essential cellular processes, including proliferation, differentiation, apoptosis, angiogenesis, and immune modulation, thereby exerting both anticancer and anti-inflammatory effects [18-20]. Adequate vitamin D status has been associated with lower risk of breast cancer and improved clinical outcomes, highlighting its potential importance as a modifiable biomarker [21-23].

Despite being a tropical country with abundant sunlight, Indonesia has a high prevalence of vitamin D deficiency among women. This paradox is influenced by multiple interacting factors, including dietary patterns and sociocultural practices. Dietary intake of vitamin D is generally low in Indonesia. The Indonesian diet is dominated by rice and plant-based food, with limited consumption of fatty fish, fortified dairy products, and eggs [24-26]. Furthermore, several sociocultural practices contribute to limited sunlight exposure, including clothing style for religious or cultural reasons, the widespread application of skin lightening products that block UVB absorption, and limited outdoor activities [27-29]. These combined factors significantly reduce vitamin D skin synthesis and dietary intake, contributing to low serum 25(OH)D levels among Indonesian women.

Although global evidence has demonstrated a potential link between vitamin D deficiency and poor breast cancer prognosis, this relationship remains understudied in Indonesian populations. Therefore, this study aims to investigate the prognostic significance of vitamin D status in Indonesian women with breast cancer, particularly in relation to time to breast cancer recurrence. The findings may provide valuable insights into the role of vitamin D as a modifiable prognostic factor and inform future clinical strategies to improve outcomes in this population.

2. MATERIAL AND METHODS

2.1. Study Design and Participants

This prospective cohort study was conducted at Dr. H. Abdul Moeloek General Hospital (RSUDAM), Bandar Lampung, Indonesia, between January 2022 and January 2025. A total of 123 eligible participants were included in the study. Participants were aged between 28 and 78 years, with most of them being postmenopausal women. Eligible participants were women diagnosed with primary, nonmetastatic invasive breast cancer who underwent surgical treatment and had histopathological confirmation. Exclusion criteria included patients presenting with recurrence or metastasis at baseline, pregnant or lactating women, and those with incomplete medical records.

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Lampung (Approval number: 2762/UN26.18/PP.05.02.00/2022), and all participants provided written informed consent.

2.2. Outcome Measures

The primary outcome was time to breast cancer recurrence, calculated from the date of surgery to the date of recurrence, death, or the end of the study period, whichever occurred first. Recurrence was confirmed through clinical, imaging, or pathological findings. The secondary outcome was the association of vitamin D status with various clinicopathological prognostic indicators.

2.3. Data Collection

Sociodemographic data, including age and clinical parameters such as histological grade, stage, tumor size, and hormone receptor status (ER, PR, HER2), were collected from medical records. Tumor classification followed the World Health Organization (WHO) criteria [30]. Tumor staging was based on the TNM classification system of the American Joint Committee on Cancer (AJCC), 7th edition [31].

2.4. Vitamin D Measurement

Serum 25-hydroxyvitamin D (25(OH)D) levels were measured directly for this study, prior to surgery or initiation of treatment, using the Chemiluminescent Microparticle Immunoassay (CMIA) method with the ARCHITECT i2000SR analyzer at Prodia Clinical Laboratory, Jakarta. Vitamin D levels were expressed in ng/mL. Deficiency was defined as serum 25(OH)D < 20 ng/mL based on previously established cut-offs [32].

2.5. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with range, depending on data distribution. Categorical variables were presented as frequencies and percentages. The chi-square test was used to evaluate associations between categorical variables. Survival analysis was performed using the Kaplan–Meier method, and

differences between survival curves were assessed using the log-rank test. A multivariate Cox proportional hazards regression model was used to identify independent predictors of tumor recurrence. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Patients Characteristics

A total of 123 patients were enrolled in the study. The mean age of participants was 50.85 ± 9.86 years, ranging from 28 to 78 years. Most patients had no comorbidities (71.5%). Among those with comorbidities (28.5%), the most frequently observed conditions were hypertension and type 2 diabetes mellitus. A majority presented with grade 2 tumors (62.6%), had no lymph node involvement (78.0%), tumor sizes less than 5 cm (66.7%), and clinical stage II disease (65.1%). Regarding hormone receptor status, 62.6% were ER positive, 58.5% were PR positive, and 61.0% were HER2 negative. The median serum 25(OH)D level was 19.9 ng/mL (range: 5.7–35.1 ng/mL), and vitamin D deficiency (<20 ng/mL) was observed in 52.8% of patients. The patient's characteristics are presented in Table **1**.

Table 1. Demographic and clinicalcopathological characteristics of patients (n=123).

Variable	Value
Age (years), mean±SD	50.85±9.86
Comorbidities	-
No	88 (71.5%)
Yes	35 (28.5%)
Histological Grade	-
Grade 1	5 (4.1%)
Grade 2	77 (62.6%)
Grade 3	41 (33.3%)
Lymph Node Status	-
Negative	96 (78.0%)
Positive	27 (22%)
Tumor Size	-
< 5 cm	82 (66.7%)
> 5 cm	41 (33.3%)
Clinical Stage	-
1	5 (4.1%)
2	80 (65.1%)
3	38 (30.8%)
Estrogen Receptor	-
Negative	46 (37.4%)
Positive	77 (62.6%)
Progesterone Receptor	-
Negative	51 (41.5%)
Positive	72 (58.5%)
HER2 Expression	-
Negative	75 (61.0%)
Positive	48 (39.0%)
Vitamin D Level (ng/mL)	19.9 (5.7 – 35.1)
Deficiency	65 (52.8%)
No Deficiency	58 (47.2%)

3.2. Association Between Vitamin D Status and Clinical Characteristics

Vitamin D deficiency was significantly associated with higher tumor grade (p = 0.037), lymph node positivity (p = 0.012), larger tumor size (p = 0.041), and more advanced clinical stage (p = 0.049). Additionally, vitamin D deficiency was significantly associated with positive ER expression (p = 0.034) and HER2 expression (p = 0.014). There was no significant association with PR expression (p = 0.474) (Table **2**).

3.3. Vitamin D Deficiency and Time to Breast Cancer Recurrence

Using a cut-off point of <20 ng/mL to define vitamin D deficiency, Kaplan–Meier survival analysis demonstrated that patients with deficient levels had significantly shorter time to breast cancer recurrence (mean ± SE: 20.11 ± 0.91 months; p = 0.048) compared to those with sufficient vitamin D levels (Fig. **1**).

3.4. Multivariate Cox Regression Analysis

In the multivariate analysis, after adjusting for potential confounders, vitamin D deficiency was found to be an independent predictor of shorter time to breast cancer recurrence, with a hazard ratio (HR) of 3.19 (95% CI: 1.178–8.660; p = 0.023).

4. DISCUSSION

This study found that vitamin D deficiency was highly prevalent among Indonesian women diagnosed with nonmetastatic breast cancer. Vitamin D deficiency was also significantly associated with several adverse clinicopathological features and shorter time to breast cancer recurrence. Notably, vitamin D deficiency remained an independent predictor of recurrence-free survival after adjustment for confounding variables, including age, tumor grade, size, nodal status, clinical stage, and hormone receptor expression.

Consistent with our findings, several previous studies have demonstrated a significant association between low serum vitamin D levels and unfavorable tumor characteristics, including higher histological grade, lymph node

Table 2. Association between vitamin D status and clinicalcopathological characteristics in breast cancer patients.

Variable	Vitamin D Deficiency		*p* Value
	Yes (n=65)	No (n=58)	
Histological Grade			
Grade 1	4 (80.0%)	1 (20.0%)	0.037*
Grade 2	34 (44.2%)	43 (55.8%)	
Grade 3	27 (65.9%)	14 (34.1%)	
Lymph Node Status			
Negative	45 (46.9%)	51 (53.1%)	0.012*
Positive	20 (74.1%)	7 (25.9%)	
Tumor Size			
< 5 cm	38 (46.3%)	44 (53.7%)	0.041*
> 5 cm	27 (65.9%)	14 (34.1)	
Clinical Stage			
1	4 (80.1%)	1 (20.0%)	0.049*
2	36 (45.0%)	44 (55.0%)	
3	25 (65.8%)	13 (34.2%)	
Estrogen Receptor			
Negative	30 (65.2%)	16 (34.8%)	0.034*
Positive	35 (45.5%)	42 (54.5%)	
Progesterone Receptor			
Negative	25 (49.0%)	26 (51.0%)	0.474
Positive	40 (55.6%)	32 (44.4%)	
HER2 Expression			
Negative	33 (44.0%)	42 (56.0%)	0.014*
Positive	32 (66.7%)	16 (33.3%)	

Note: Exp: * a significant association based on Chi Square test.

involvement, larger tumor size, and advanced tumor stage [33,34]. A recent prospective cohort of 476 women also reported that low serum 25(OH)D was significantly associated with larger tumor size and lymph node positivity [35]. Furthermore, other studies in diference population have shown links between vitamin D deficiency and hormone receptor status, particularly ER and HER2 positivity [36,37].

The association between vitamin D deficiency and tumor aggressiveness can be explained by its biological role in breast tissue. Activation of the VDR modulates the expression of genes governing proliferation, differentiation, and apoptosis. Once the active form of vitamin D binds to its receptor, the receptor makes a heterodimer with retinoid X receptor (RXR) and attaches to vitamin D response elements (VDREs) within target genes. Through this interaction, vitamin D initiates a transcriptional cascade that arrests the cell cycle by up-regulating p21 and p27 and down-regulating cyclin D1/CDK4, thereby preventing the G1/S phase transition [38,39]. Concurrently, vitamin D signaling also triggers apoptosis by increasing pro-apoptotic mediators such as BAX and caspase-3, while simultaneously suppressing the expression of BCL-2, an anti-apoptotic protein [40]. This process thereby ensures the controlled elimination of damaged or transformed cells. In addition, vitamin D inhibits angiogenesis and proliferative signaling by inhibiting VEGF, EGFR, the PI3K/AKT, and Wnt/β-catenin cascade [41,42]. Vitamin D also modulates the tumor microenvironment to favor cytotoxic T-cell activity [43-45].

Conversely, when vitamin D is deficient or VDR expression is diminished, these regulatory mechanisms are weakened. It can lead to uncontrolled proliferation, decreased apoptosis, and enhanced epithelial to mesenchymal transition (EMT) features through up regulation several transcriptional factors. Among them are Snail, Slug, and Twist, which can

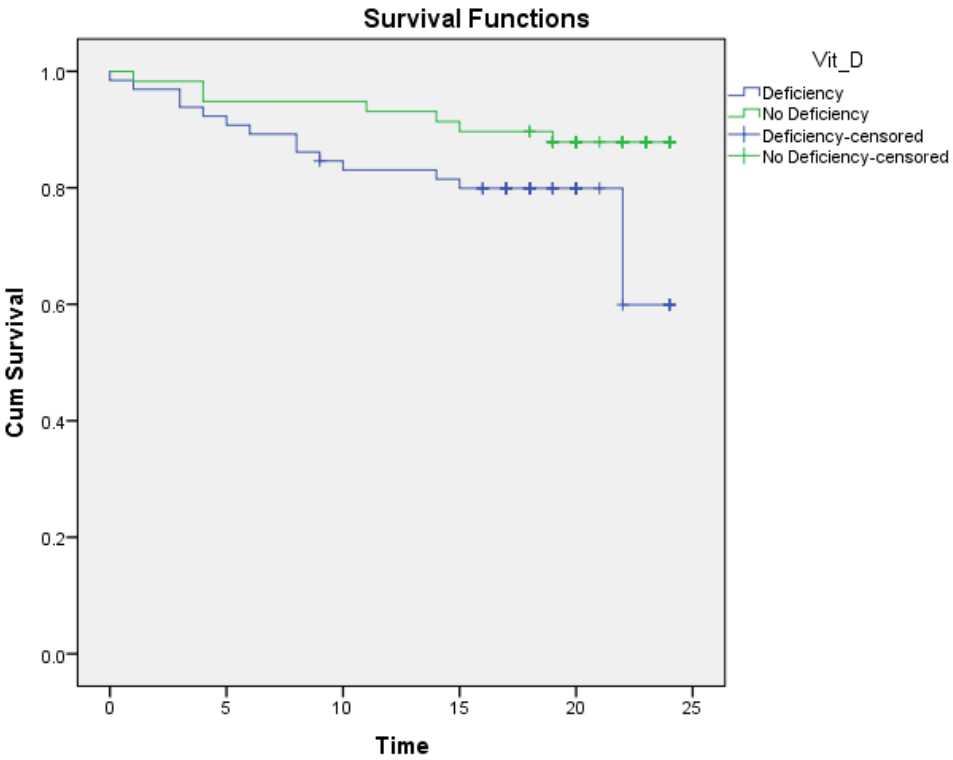

Fig. (1). Kaplan–Meier survival analysis comparing time to breast cancer recurrence between vitamin D deficient and non-deficient patients.

facilitate cellular detachment, invasion, and metastasis [21,34,46]. These molecular disruptions are closely associated with clinical findings, which show higher histological grade, larger tumor size, lymph node positivity, and advanced-stage disease [35,47].

Beyond its associations with tumor biology, vitamin D levels have also been linked to clinical outcomes in breast cancer. Our Kaplan–Meier and Cox regression analyses revealed that patients with vitamin D deficiency experienced significantly shorter time to breast cancer recurrence. These findings align with a previous study indicating that low vitamin D levels predict poorer disease-free survival (DFS) and overall survival (OS) [47-49]. For instance, Mohamed *et al.* found a strong positive correlation between vitamin D levels and both DFS and OS [47]. Almeida-Filho *et al.* also reported a nearly seven-fold higher risk of recurrence in deficient patients (HR: 6.87; 95% CI: 2.35–21.18) [48]. Similarly, in a larger cohort of 1,295 postmenopausal breast cancer patients, Vrieling *et al.* found that low vitamin D levels were significantly associated with poorer survival (HR: 1.6; 95% CI: 1.0–2.4), and a higher risk of distant recurrence (HR: 2.1; 95% CI: 1.3–3.4) [49].

Several biological mechanisms may explain these observations. Vitamin D plays an essential role in inhibiting cancer cell proliferation, enhancing immune surveillance, and maintaining the tumor microenvironment. The active form of vitamin D can directly inhibit tumor cell proliferation by inducing cell-cycle arrest, promoting apoptosis, and inhibiting angiogenesis through downregulating factors like VEGF and TGF-β1 [50,51]. Vitamin D, through VDR activation, enhances the activity of cytotoxic T-cells and natural killer (NK) cell, while reducing the number and suppressive function of Tregs and M2 macrophages, which are essential for eliminating residual or dormant tumor cells after primary therapy [40,43,45,52]. In states of vitamin D deficiency, this immune surveillance is weakened, allowing survival and proliferation of residual tumor cells that can reactivate earlier. This condition results in reduced recurrence-free survival.

Furthermore, vitamin D deficiency promotes the development of a chronic proinflammatory tumor microenvironment. This condition is characterized by elevated levels of proinflammatory cytokines such as IL-6, IL-8, and TNF-α within the tumor microenvironment [51,53]. Such a cytokine-rich milieu provides continuous growth signals that facilitate tumor-cell proliferation and enable them to evade apoptosis [54]. In addition, disturbance in vitamin D metabolism, such as reduced expression of VDR or over-expression of CYP24A1, the enzyme responsible for vitamin D catabolism, can further weaken local anti-tumor activity and enhance oxidative stress. These alterations, thereby create favorable microenvironment conditions for tumor recurrence [46,55-57]. Collectively, immune dysfunction, inflammation, and disrupted vitamin D metabolism may provide a plausible explanation for why patients with low serum vitamin D levels experience earlier recurrence, even after apparently successful initial treatment.

The effect of vitamin D deficiency on prognosis seems especially important among postmenopausal breast cancer patients. In our study, the majority of participants were postmenopausal, which may explain the strong association observed between low vitamin D levels and shorter breast cancer recurrence-free survival. Following menopause, the

decline in estrogen levels reduces the expression and activity of VDR in mammary tissue, thereby amplifying the biological effects of vitamin D deficiency [49,58]. In addition, estrogen deficiency contributes to immune dysregulation and a chronic pro-inflammatory state, both of which can facilitate tumor reactivation in patients with low vitamin D status [38]. These hormonal and metabolic alterations may explain why recurrence occurs earlier in vitamin D deficient postmenopausal women in the present study.

Recent studies have unveiled the role of vitamin D in regulating oxidative stress and cellular signaling in breast cancer. Vitamin D is known to enhance antioxidant enzymes such as SOD, GPx, and catalase, which indirectly limit ROS accumulation and oxidative DNA damage [19,59]. Conversely, deficiency of vitamin D can disrupt redox balance and promote mitochondrial dysfunction, resulting in excessive ROS accumulation that supports tumor growth [60,61]. In addition, vitamin D also modulates iron metabolism by suppressing hepcidin synthesis and regulating ferritin expression [62,63]. These mechanisms has known maintain optimal intracellular iron levels and reduce Fenton reaction–induced oxidative stress. Dysregulation of these pathways in vitamin D deficiency states may contribute to enhanced oxidative injury and facilitate breast cancer progression and recurrence.

In addition to vitamin D deficiency, that influence tumor aggressiveness and recurrence, certain histological variants of breast cancer also display distinct behaviors that merit clinical attention. One example is invasive micropapillary carcinoma (IMPC), a rare subtype accounting for approximately 1-2% of breast carcinomas [64,65]. This subtype is characterized by an "inside-out" cell polarity pattern and a strong lymphotropic tendency, often associated with higher rates of nodal metastasis and poorer prognosis [66]. Advances in surgical oncology have highlighted the emerging role of indocyanine green (ICG) as a fluorescence-guided tracer for sentinel lymph node detection, which provides improved visualization and accuracy in axillary staging, particularly useful in IMPC, where lymphatic spread is common [67]. Furthermore, HER2 overexpression has been observed more frequently in IMPC compared with ductal carcinoma in situ (DCIS), underscoring the aggressive molecular profile of IMPC and its potential responsiveness to anti-HER2-targeted therapies [68]. Recognizing such histological and molecular diversity is important, as it complements the current understanding of how biological and environmental factors, including vitamin D deficiency, contribute to breast-cancer progression and recurrence.

These findings also carry substantial clinical implications. Routine screening of vitamin D levels, particularly those with ER-positive and HER2-positive breast cancer, should be considered by clinicians in Indonesia. Educational initiatives aimed at increasing patient awareness about maintaining adequate vitamin D levels through exposure to sunlight and a balanced diet could be beneficial. Additionally, further randomized clinical trials (RCTs) assessing vitamin D supplementation as adjunctive therapy are essential to confirm potential clinical benefits in improving breast cancer prognosis within the local population.

CONCLUSION

Vitamin D deficiency may adversely affect the time to tumor recurrence and is significantly associated with several poor prognostic indicators in breast cancer, including higher tumor grade, lymph node involvement, larger tumor size, advanced clinical stage, and hormone receptor expression. These findings highlight the importance of evaluating vitamin D status as a potentially modifiable prognostic factor in breast cancer management.

STUDY LIMITATIONS

This study has several limitations. This study was conducted at a single center, which may limit generalizability. Vitamin D levels were measured only at baseline, and the study did not assess changes in vitamin D status over time or include supplementation history. Future multicenter studies with longitudinal data collection are warranted to confirm these associations and explore the potential of vitamin D supplementation as an adjuvant strategy in breast cancer care.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: IW: Study concept, study design, and drafting; BAS: Data gathering, data interpretation, and reviewing; AK: Data gathering; S: Study design and drafting; RH: Data gathering and reviewing; BPDJ: Data gathering, formal analysis, and drafting.

LIST OF ABBREVIATIONS

EMT	=	Epithelial to Mesenchymal Transition
ER	=	Estrogen Receptor
HER2	=	Human Epidermal Growth Factor Receptor 2
PR	=	Progesterone Receptor
SOD	=	Superoxide Dismutase
VDR	=	Vitamin D Receptors
VDREs	=	Vitamin D Response Elements

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Lampung (Approval number: 2762/UN26.18/PP.05.02.00/2022).

HUMAN AND ANIMAL RIGHTS

The research protocol complies with established biomedical ethical standards and was conducted in accordance with the principles of the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All participants provided written informed consent prior to enrollment in this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during this study are not publicly available due to privacy and ethical restrictions, but are available from the corresponding author upon reasonable request and approval by the institutional ethics committee.

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CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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AI DISCLOSURE

During the manuscript preparation stage, we used Grammarly (Grammarly Inc., USA) as an artificial intelligence-assisted language editing tool. Grammarly is used to improve grammar, spelling, clarity, and readability of the manuscript. All revisions were reviewed and approved by the authors, who take full responsibility for the originality of the manuscript.

REFERENCES

[1] Gautama W. Breast cancer in Indonesia in 2022: 30 years of marching in place. Indon J Cancer 2022; 16(1): 1-2. http://dx.doi.org/10.33371/ijoc.v16i1.920

[2] Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN sstimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71(3): 209-49. http://dx.doi.org/10.3322/caac.21660 PMID: 33538338

[3] Osborne A, Adnani QES, Ahinkorah BO. Breast cancer incidence in Indonesia: a sex-disaggregated analysis using WHO health equity assessment toolkit data. BMC Cancer 2025; 25(1): 986. http://dx.doi.org/10.1186/s12885-025-14332-4 PMID: 40457229

[4] Ng B, Puspitaningtyas H, Wiranata JA, *et al.* Breast cancer incidence in Yogyakarta, Indonesia from 2008–2019: A cross-sectional study using trend analysis and geographical information system. PLoS One 2023; 18(7): e0288073. http://dx.doi.org/10.1371/journal.pone.0288073 PMID: 37406000

[5] Sedeta ET, Jobre B, Avezbakiyev B. Breast cancer: Global patterns of incidence, mortality, and trends. J Clin Oncol 2023; 41(16_suppl): 10528-8.(Suppl.) http://dx.doi.org/10.1200/JCO.2023.41.16_suppl.10528

[6] Liu H, Shi W, Jin Z, *et al.* Global, regional, and national mortality trends of female breast cancer by risk factor, 1990–2017. BMC Cancer 2021; 21(1): 459. http://dx.doi.org/10.1186/s12885-021-08217-5 PMID: 33894746

[7] Hutajulu SH, Prabandari YS, Bintoro BS, *et al.* Delays in the presentation and diagnosis of women with breast cancer in Yogyakarta, Indonesia: A retrospective observational study. PLoS One 2022; 17(1): e0262468. http://dx.doi.org/10.1371/journal.pone.0262468 PMID: 35025941

[8] Iskandarsyah A, de Klerk C, Suardi DR, Soemitro MP, Sadarjoen SS, Passchier J. Psychosocial and cultural reasons for delay in seeking help and nonadherence to treatment in Indonesian women with breast cancer: A qualitative study. Health Psychol 2014; 33(3): 214-21. http://dx.doi.org/10.1037/a0031060 PMID: 23339645

[9] Kardinah D, Anderson BO, Duggan C, Ali IA, Thomas DB. Short report: Limited effectiveness of screening mammography in addition to clinical breast examination by trained nurse midwives in rural Jakarta, Indonesia. Int J Cancer 2014; 134(5): 1250-5. http://dx.doi.org/10.1002/ijc.28442 PMID: 24037942

[10] Leon-Ferre RA, Dimitroff K, Yau C, *et al.* Impact of extent of disease at presentation on oncologic outcomes according to pathologic response to neoadjuvant systemic therapy among participants of the I-SPY2 clinical trial. J Clin Oncol 2024; 42(16_suppl): 594-4.(Suppl.) http://dx.doi.org/10.1200/JCO.2024.42.16_suppl.594

[11] Grajales R, Gutierrez A, Pichardo C, Gutierrez M, Dip Borunda AK. Survival outcomes and clinicopathological factors analysis of breast cancer patients. A single-institution cohort from 2012 to 2020 in a Mexican population. J Clin Oncol 2023; 41(16_suppl): e13104-4.(Suppl.) http://dx.doi.org/10.1200/JCO.2023.41.16_suppl.e13104

[12] Aristei C, Tomatis M, Antonio Ponti , *et al.* Treatment and outcomes in breast cancer patients: A cross section study from the EUSOMA breast centre network. Eur J Cancer 2024; 196: 113438. http://dx.doi.org/10.1016/j.ejca.2023.113438 PMID: 37995597

[13] Shin DD, Switchenko JM, Marra A, Kalinsky K. Clinical outcomes in patients with early-stage breast cancer in a racially and ethnically diverse patient population. J Clin Oncol 2024; 42(16_suppl): e12532-2.(Suppl.) http://dx.doi.org/10.1200/JCO.2024.42.16_suppl.e12532

[14] Abubakar M, Guo C, Koka H, *et al.* Impact of breast cancer risk factors on clinically relevant prognostic biomarkers for primary breast cancer. Breast Cancer Res Treat 2021; 189(2): 483-95. http://dx.doi.org/10.1007/s10549-021-06294-5 PMID: 34185195

[15] Papadopoulou SNA, Anastasiou EA, Adamantidi T, Ofrydopoulou A, Letsiou S, Tsoupras A. A comprehensive review on the beneficial roles of vitamin D in skin health as a bio-functional ingredient in nutricosmetic, cosmeceutical, and cosmetic applications. Appl Sci 2025; 15(2): 796. http://dx.doi.org/10.3390/app15020796

[16] Gezen-Ak D, Dursun E. Vitamin D, a secosteroid hormone and its multifunctional receptor, vitamin D receptor, in Alzheimer's type neurodegeneration. J Alzheimers Dis 2023; 95(4): 1273-99. http://dx.doi.org/10.3233/JAD-230214 PMID: 37661883

[17] Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D sources, metabolism, and deficiency: Available compounds and guidelines for its treatment. Metabolites 2021; 11(4): 255. http://dx.doi.org/10.3390/metabo11040255 PMID: 33924215

[18] Veeresh PKM, Basavaraju CG, Dallavalasa S, *et al.* Vitamin D3 inhibits the viability of breast cancer cells *in vitro* and Ehrlich ascites carcinomas in mice by promoting apoptosis and cell cycle arrest and by impeding tumor angiogenesis. Cancers 2023; 15(19): 4833. http://dx.doi.org/10.3390/cancers15194833 PMID: 37835527

[19] Vázquez-Lorente H, Herrera-Quintana L, Jiménez-Sánchez L, Fernández-Perea B, Plaza-Diaz J. Antioxidant functions of vitamin D and CYP11A1-derived vitamin D, Tachysterol, and Lumisterol Metabolites: Mechanisms, clinical implications, and future directions. Antioxidants 2024; 13(8): 996. http://dx.doi.org/10.3390/antiox13080996 PMID: 39199241

[20] Dallavalasa S, Tulimilli SV, Bettada VG, *et al.* Vitamin D in cancer prevention and treatment: A review of epidemiological, preclinical, and cellular studies. Cancers 2024; 16(18): 3211. http://dx.doi.org/10.3390/cancers16183211 PMID: 39335182

[21] Torres A, Cameselle C, Otero P, Simal-Gandara J. The impact of vitamin D and its dietary supplementation in breast cancer prevention: An integrative review. Nutrients 2024; 16(5): 573. http://dx.doi.org/10.3390/nu16050573 PMID: 38474702

[22] Nelson OL, Rosales R, Turbov J, *et al.* Vitamin D significantly inhibits carcinogenesis in the Mogp-TAg mouse model of fallopian tube ovarian cancer. Nutrients 2024; 16(19): 3318. http://dx.doi.org/10.3390/nu16193318 PMID: 39408285

[23] Pereira TSS, Marques SSA, Olandoski M, *et al.* Vitamin D and breast cancer risk: Evaluating the association and effective risk reduction. Breast Care 2024; 19(4): 197-206. http://dx.doi.org/10.1159/000539750 PMID: 39185130

[24] Green TJ, Skeaff CM, Rockell JEP, *et al.* Vitamin D status and its association with parathyroid hormone concentrations in women of child-bearing age living in Jakarta and Kuala Lumpur. Eur J Clin Nutr 2008; 62(3): 373-8. http://dx.doi.org/10.1038/sj.ejcn.1602696 PMID: 17342165

[25] Aji AS, Erwinda E, Yusrawati Y, Malik SG, Lipoeto NI. Vitamin D deficiency status and its related risk factors during early pregnancy: a cross-sectional study of pregnant Minangkabau women, Indonesia. BMC Pregnancy Childbirth 2019; 19(1): 183. http://dx.doi.org/10.1186/s12884-019-2341-4 PMID: 31117971

[26] Judistiani RTD, Nirmala SA, Rahmawati M, *et al.* Optimizing ultraviolet B radiation exposure to prevent vitamin D deficiency among pregnant women in the tropical zone: report from cohort study on vitamin D status and its impact during pregnancy in Indonesia. BMC Pregnancy Childbirth 2019; 19(1): 209. http://dx.doi.org/10.1186/s12884-019-2306-7 PMID: 31226954

[27] Chee WF, Aji AS, Lipoeto NI, Siew CY. Maternal vitamin D status and its associated environmental factors: A cross-sectional study. Ethiop J Health Sci 2022; 32(5): 885-94. http://dx.doi.org/10.4314/ejhs.v32i5.3 PMID: 36262702

[28] Jiang Z, Pu R, Li N, *et al.* High prevalence of vitamin D deficiency in Asia: A systematic review and meta-analysis. Crit Rev Food Sci Nutr 2023; 63(19): 3602-11. http://dx.doi.org/10.1080/10408398.2021.1990850 PMID: 34783278

[29] Darling AL. Vitamin D deficiency in western dwelling South Asian populations: an unrecognised epidemic. Proc Nutr Soc 2020; 79(3): 259-71. http://dx.doi.org/10.1017/S0029665120000063 PMID: 32046797

[30] Lakhani S, Ellis I, Schnitt S. Tumors of the breast in world health organization classification of tumors. In: Pathology and genetics of tumors of breast and female genital organs. 4th ed. IARC Press: Lyon; 2012.

[31] Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17(6): 1471-4. http://dx.doi.org/10.1245/s10434-010-0985-4

[32] Malacova E, Cheang PR, Dunlop E, *et al.* Prevalence and predictors of vitamin D deficiency in a nationally representative sample of adults participating in the 2011–2013 Australian Health Survey. Br J Nutr 2019; 121(8): 894-904. http://dx.doi.org/10.1017/S0007114519000151 PMID: 30674358

[33] Hatse S, Lambrechts D, Verstuyf A, *et al.* Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. Carcinogenesis 2012; 33(7): 1319-26. http://dx.doi.org/10.1093/carcin/bgs187 PMID: 22623648

[34] Streb J, Łazarczyk A, Hałubiec P, *et al.* Vitamin D receptor is associated with prognostic characteristics of breast cancer after neoadjuvant chemotherapy—an observational study. Front Oncol 2024; 14: 1458124. http://dx.doi.org/10.3389/fonc.2024.1458124 PMID: 39411136

[35] Manocha A, Brockton NT, Cook L, Kopciuk KA. Low serum vitamin D associated with increased tumor size and higher grade in premenopausal Canadian women with breast cancer. Clin Breast Cancer 2023; 23(6): e368-76. http://dx.doi.org/10.1016/j.clbc.2023.06.003 PMID: 37357130

[36] Swarnkar M, Kumar K, Prasad P, Singhal K. Association between vitamin D deficiency and tumor characteristics in breast cancer patients. Cureus 2024; 16(6): e62296. http://dx.doi.org/10.7759/cureus.62296 PMID: 39006561

[37] Ismail A, El-Awady R, Mohamed G, Hussein M, Ramadan SS. Prognostic significance of serum vitamin D levels in Egyptian females with breast cancer. Asian Pac J Cancer Prev 2018; 19(2): 571-6. http://dx.doi.org/10.22034/APJCP.2018.19.2.571 PMID: 29481024

[38] Seraphin G, Rieger S, Hewison M, Capobianco E, Lisse TS. The impact of vitamin D on cancer: A mini review. J Steroid Biochem Mol Biol 2023; 231: 106308. http://dx.doi.org/10.1016/j.jsbmb.2023.106308 PMID: 37054849

[39] Blasiak J, Chojnacki J, Pawlowska E, Jablkowska A, Chojnacki C. Vitamin D may protect against breast cancer through the regulation of long noncoding RNAs by VDR signaling. Int J Mol Sci 2022; 23(6): 3189. http://dx.doi.org/10.3390/ijms23063189 PMID: 35328609

[40] Welsh J. Vitamin D and breast cancer: Mechanistic update. JBMR Plus 2021; 5(12): e10582. http://dx.doi.org/10.1002/jbm4.10582 PMID: 34950835

[41] Blasiak J, Pawlowska E, Chojnacki J, Szczepanska J, Fila M, Chojnacki C. Vitamin D in triple-negative and BRCA1-deficient breast cancer-implications for pathogenesis and therapy. Int J Mol Sci 2020; 21(10): 3670. http://dx.doi.org/10.3390/ijms21103670 PMID: 32456160

[42] Fleet JC, Desmet M, Johnson R, Li Y. Vitamin D and cancer: a review of molecular mechanisms. Biochem J 2012; 441(1): 61-76. http://dx.doi.org/10.1042/BJ20110744 PMID: 22168439

[43] Karkeni E, Morin SO, Bou Tayeh B, *et al.* Vitamin D controls tumor growth and CD8+ T cell infiltration in breast cancer. Front Immunol 2019; 10(6): 1307. http://dx.doi.org/10.3389/fimmu.2019.01307 PMID: 31244851

[44] Zhang Y, Xu Y, Zhong W, *et al.* Vitamin D and immune checkpoint inhibitors in lung cancer: A synergistic approach to enhancing treatment efficacy. Int J Mol Sci 2025; 26(10): 4511. http://dx.doi.org/10.3390/ijms26104511 PMID: 40429656

[45] Wu X, Hu W, Lu L, *et al.* Repurposing vitamin D for treatment of human malignancies *via* targeting tumor microenvironment. Acta Pharm Sin B 2019; 9(2): 203-19. http://dx.doi.org/10.1016/j.apsb.2018.09.002 PMID: 30972274

[46] Bajbouj K, Sahnoon L, Shafarin J, *et al.* Vitamin D-Mediated anticancer activity involves iron homeostatic balance disruption and oxidative stress induction in breast cancer. Front Cell Dev Biol 2021; 9: 766978. http://dx.doi.org/10.3389/fcell.2021.766978 PMID: 34820382

[47] Mohamed RF, Barakat DBS, Eid S, Kamal DT, Elnaggar MS. Low baseline vitamin D levels increase the risk of bone metastases among females with breast cancer − Hospital based cohort study. Cancer Epidemiol 2023; 85: 102374. http://dx.doi.org/10.1016/j.canep.2023.102374 PMID: 37148827

[48] Almeida-Filho BS, Omodei MS, Buttros DAB, *et al.* Negative impact of vitamin D deficiency at diagnosis on breast cancer survival: A prospective cohort study. Breast J 2022; 2022(1): 1-9. http://dx.doi.org/10.1155/2022/4625233

[49] Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast Cancer Res 2011; 13(4): R74. http://dx.doi.org/10.1186/bcr2920 PMID: 21791049

[50] Bajbouj K, Shafarin J, Sawan A, Shehada A, Elkhalifa WE. Abstract 5030: Vitamin D exhibits therapeutic anti-tumor and anti-angiogenic potential by reducing VEGF levels and altering TIMP/MMP system in breast cancer. Cancer Res 2020; 80(16_Supplement): 5030-0.(Suppl.) http://dx.doi.org/10.1158/1538-7445.AM2020-5030

[51] Henn M, Martin-Gorgojo V, Martin-Moreno JM. Vitamin D in cancer prevention: Gaps in current knowledge and room for hope. Nutrients 2022; 14(21): 4512. http://dx.doi.org/10.3390/nu14214512 PMID: 36364774

[52] Prasanth D, Khan PA, Jamal-E-Fatima , *et al.* Vitamin D-induced mechanisms in cancer prevention and therapy: Recent advances and future opportunities. Animal Model Exp Med 2025; 2025(00): ame2.70087. http://dx.doi.org/10.1002/ame2.70087 PMID: 40985271

[53] Li J, Luco AL, Camirand A, St-Arnaud R, Kremer R. Vitamin D regulates CXCL12/CXCR4 and epithelial-to-mesenchymal transi-

tion in a model of breast cancer metastasis to lung. Endocrinology 2021; 162(7): bqab049.
http://dx.doi.org/10.1210/endocr/bqab049 PMID: 33693593

[54] Liu W, Zhang L, Xu HJ, *et al.* The anti-inflammatory effects of vitamin D in tumorigenesis. Int J Mol Sci 2018; 19(9): 2736.
http://dx.doi.org/10.3390/ijms19092736 PMID: 30216977

[55] Zeng R, Li H, Jia L, *et al.* Association of CYP24A1 with survival and drug resistance in clinical cancer patients: a meta-analysis. BMC Cancer 2022; 22(1): 1317.
http://dx.doi.org/10.1186/s12885-022-10369-x PMID: 36527000

[56] Shang QX, Yang YS, Zhang HL, *et al.* Vitamin D receptor induces oxidative stress to promote esophageal squamous cell carcinoma proliferation *via* the p53 signaling pathway. Heliyon 2024; 10(1): e23832.
http://dx.doi.org/10.1016/j.heliyon.2023.e23832 PMID: 38234882

[57] Na SY, Kim KB, Lim YJ, Song HJ. Vitamin D and colorectal cancer: Current perspectives and future directions. J Cancer Prev 2022; 27(3): 147-56.
http://dx.doi.org/10.15430/JCP.2022.27.3.147 PMID: 36258716

[58] Mei Z, Hu H, Zou Y, Li D. The role of vitamin D in menopausal women's health. Front Physiol 2023; 14: 1211896.
http://dx.doi.org/10.3389/fphys.2023.1211896 PMID: 37378077

[59] Mastali PV, Hoseini R, Azizi M. The effect of short-term vitamin D on the antioxidant capacity following exhaustive aerobic exercise. Afr Health Sci 2023; 23(1): 584-91.
http://dx.doi.org/10.4314/ahs.v23i1.61 PMID: 37545926

[60] Berridge MJ. Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. Philos Trans R Soc Lond B Biol Sci 2016; 371(1700): 20150434.
http://dx.doi.org/10.1098/rstb.2015.0434

[61] Dentino P, Mora J, Zuo L. Vitamin D deficiency and its role in pathologies of oxidative stress: A literature review. Cureus 2025; 17(8): e90042.
http://dx.doi.org/10.7759/cureus.90042 PMID: 40951130

[62] Mohamed AA, Abd Almonaem ER, Mansour AI, Algebaly HF, Khattab RA, El Abd YS. Importance of studying the levels of hepcidin and vitamin D in Egyptian children with chronic hepatitis C. J Transl Int Med 2019; 7(1): 15-21.
http://dx.doi.org/10.2478/jtim-2019-0004 PMID: 30997352

[63] Zouine N, Lhilali I, Godderis L, El Midaoui A, El Jaafari S, Filali-Zegzouti Y. The interplay between vitamin D deficiency, iron status, and anemia risk in Moroccan women of reproductive age: A cross-sectional analysis. Epidemiologia 2024; 5(4): 805-27.
http://dx.doi.org/10.3390/epidemiologia5040055 PMID: 39727427

[64] Verras GI, Mulita F, Tchabashvili L, Grypari IM, Sourouni S, Panagodimou E. A rare case of invasive micropapillary carcinoma of the breast. Prz Menopauzalny 2022; 21(1): 73-80.
http://dx.doi.org/10.5114/pm.2022.113834

[65] Cheng L, Yu X, Zhang H, Zhang HJ, Jia Z, Wang X. Advances in invasive micropapillary carcinoma of the breast research: A review. Medicine 2024; 103(1): e36631.
http://dx.doi.org/10.1097/MD.0000000000036631 PMID: 38181281

[66] YHAM E, Radwan AH, Gareer SWY, *et al.* Micropapillary breast carcinoma in comparison with invasive duct carcinoma. Does it have an aggressive clinical presentation and an unfavorable prognosis? BMC Cancer 2024; 24(1): 992.
http://dx.doi.org/10.1186/s12885-024-12673-0 PMID: 39129012

[67] Pinelli M, Gerardi C, Lettieri E, *et al.* Comparison of Indocyanine Green with conventional tracers for sentinel lymph node biopsy in breast cancer: A multidisciplinary evaluation of clinical effectiveness, safety, organizational and economic impact. PLoS One 2024; 19(8): e0309336.
http://dx.doi.org/10.1371/journal.pone.0309336 PMID: 39208241

[68] Perron M, Wen HY, Hanna MG, Brogi E, Ross DS. HER2 immunohistochemistry in invasive micropapillary breast carcinoma: Complete assessment of an incomplete pattern. Arch Pathol Lab Med 2021; 145(8): 979-87.
http://dx.doi.org/10.5858/arpa.2020-0288-OA PMID: 33212478