Vitamin D Levels Among Breast Cancer Patients in a Tertiary Hospital in Lampung, Indonesia

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Abstract: Introduction: Vitamin D levels can vary among populations due to geographical location and sun exposure, dietary habits, lifestyle, and genetic factors. People living in Indonesia may have a higher potential for sun exposure, which can lead to adequate vitamin D synthesis in the skin. Several studies have suggested a potential protective role of vitamin D against breast cancer. Preclinical studies have shown that vitamin D may inhibit the growth and spread of breast cancer cells, induce cell death, and inhibit angiogenesis. Some studies have found an inverse association, suggesting that higher vitamin D levels may be associated with a reduced risk of breast cancer. This study was conducted to obtain the most recent information about the vitamin D levels of breast cancer patients of Indonesian women, especially in Lampung. *Methods*: We performed an observational analysis in an ongoing prospective cohort study of breast cancer patients at Dr. H. Abdul Moeloek Hospital, Bandar Lampung, Indonesia. Sixty-eight subjects were collected from the main study. Information on subjects, sociodemographic characteristics, clinical status, and tumor profile was assessed. Vitamin D level was measured using ELISA methods. The association between sociodemographic and clinical profiles with vitamin D levels was tested using Chi-square. *Results*: Breast cancer patients' mean vitamin D level was low (19.7 ± 6.4 ng/ml). There was no correlation between sun exposure, sociodemographic, and clinical status to Vitamin D levels of breast cancer patients. Patients with comorbidity tend to have a low vitamin D level, primarily type 2 diabetes. *Conclusion:* Low vitamin D levels are frequently found in our population. Further information about vitamin D levels and their association with the survival of breast cancer patients is still challenging to become research questions.

1 INTRODUCTION

Breast cancer continues to evoke fear among the majority of women. It is one of the prevalent malignancies affecting women and the primary contributor to global cancer-related fatalities. Approximately 2.3 million new cases of breast cancer are diagnosed each year (Mattiuzzi & Lippi, 2019; Sung et al., 2021). The current approach to breast cancer treatment involves surgical procedures, chemotherapy, radiotherapy, and hormonal therapy. However, these diverse treatments still have adverse effects on patients. Optimal treatment with minimal side effects has yet to be discovered. Particular natural compounds are purported to enhance treatment efficacy and act as a preventive against breast cancer (Buja et al., 2020; Choudhury et al., 2020; Ren et al., 2020). One such compound is vitamin D (Bernhardt et al., 2021; Grabiec et al., 2013).

Vitamin D, classified as a fat-soluble vitamin, is essential in many biological processes. Operating as a prohormone, it is crucial to managing calcium, phosphorus, and skeletal muscle metabolism. Moreover, vitamin D contributes to cardiovascular and reproductive functions and is involved in various physiological processes, including cell differentiation, apoptosis, inflammation, and insulin sensitivity (Chen & Zhi, 2020; Cosentino et al., 2021; Janoušek et al., 2022). Interestingly, vitamin D is

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recognized in preventing various cancer types, such as colorectal, prostate, ovarian, lung, skin, and breast cancers (Giovannucci, 2009; Kazemi et al., 2022). In preclinical investigations, vitamin D has demonstrated its ability to inhibit the proliferation of cancer cells (Lopes et al., 2012; Zheng et al., 2017), trigger apoptosis (Vanoirbeek et al., 2011), and suppress angiogenesis (Susanti et al., 2018).

While vitamin D can be sourced from dietary consumption, its primary source stems from the synthesis of 7-dehydrocholesterol by epidermal cells upon exposure to UV-B rays from the sun (Chen & Zhi, 2020). Consequently, regions with limited sun exposure necessitate supplementary vitamin D intake to address the body's requirements. As a tropical nation, Indonesia enjoys abundant sunshine throughout the year, theoretically providing ample sun exposure for its population and enabling adequate synthesis of vitamin D in the skin to fulfill bodily needs. However, several studies have revealed a pronounced incidence of vitamin D deficiency, particularly prevalent among the female population in Indonesia (Green et al., 2008; Setiati, 2008). A recent study has revealed a surprising prevalence of 63% in vitamin D deficiency among pregnant women in Indonesia (Octavius et al., 2023).

Vitamin D deficiency is associated with an increased risk of developing several health conditions, including rickets, osteoporosis, type 2 diabetes, cardiovascular disease, and autoimmune disorders (Forouhi et al., 2012; Giovannucci, 2009). It is also linked to an increased risk of developing breast cancer. Women with sufficient vitamin D levels have a lower risk of developing breast cancer than women with deficient vitamin D levels (Atoum & Alzoughool, 2017; Shaukat et al., 2017). This risk applies to pre- and postmenopausal women (Bidgoli & Azarshab, 2014; Kim et al., 2014). Interestingly, in parallel with the prevalence of vitamin D deficiency data, and demonstrating a willingness to partake by signing an informed consent. Conversely, exclusion criteria pertain to breast cancer patients who have undergone chemotherapy or radiotherapy, are currently pregnant, or have declined participation in the study. The final sample size consistent with the inclusion and exclusion criteria comprised 68 breast cancer patients. Ethical clearance for this research has been obtained from the Ethics Committee for Health Research, Faculty of Medicine, University of Lampung, with EC number 2762/UN.26.18/PP.05.02.00/2022.

The data collected in this study included sociodemographic characteristics (age, education, occupation, and duration of sun exposure), clinical information (metastases, types of breast cancer, and

among women in Indonesia, breast cancer has progressively risen, coupled with lower life expectancies relative to other nations in the regions (Susanti et al., 2018). This trend suggests a possible association between vitamin D deficiency and breast cancer in the Indonesian female population.

Vitamin D levels within the body can vary, influenced by various factors, including geographic location, ethnicity, medical conditions, lifestyle, and genetics (Mazahery & Von Hurst, 2015). Despite much evidence establishing a connection between elevated vitamin D levels and a decreased risk of breast cancer, there has been limited study exploring the pattern of vitamin D levels among Indonesian women diagnosed with breast cancer. Therefore, this study was conducted to acquire current insights into the vitamin D levels among breast cancer patients within the female population of Indonesia, with a particular emphasis on Lampung Province, and to explore the association between vitamin D levels and the sociodemographic and clinical characteristics of the affected individuals.

2 METHODS

This study used an observational analytic approach within an ongoing prospective cohort study involving breast cancer patients at RSUD Dr. H. Abdul Moeloek in Bandar Lampung, Indonesia. The study's target population comprises breast cancer patients currently undergoing treatment at Dr. H. Abdul Moeloek Bandar Lampung who met the predetermined inclusion and exclusion criteria. The inclusion criteria encompass patients diagnosed with breast cancer through histopathological and mammographic assessments between 2021 and 2022, possessing comprehensive medical record

comorbidities), and serum vitamin D levels. Sociodemographic data were collected through direct interviews employing a structured questionnaire. Clinical data were collected from medical record data. Serum 25-OH vitamin D levels were measured using the CMIA method by the ARCHITECT i2000SR immunoassay analyzer at the Prodia Clinical Laboratory, Jakarta. Vitamin D levels are expressed in units of ng/mL, where patients are classified as deficient if their levels fall below 20 ng/mL.

The association between sociodemographic and clinical characteristics of patients with serum vitamin D levels was assessed through the Chi-Square test. Differences in mean serum vitamin D levels in various comorbid groups were assessed using the

unpaired t-test and one-way analysis of variance (ANOVA). All statistical tests were conducted at a significance level of 95%.

3 RESULTS

3.1 Sample Characteristics

This study included 68 breast cancer patients as a sample. The average age of the participants was 52.04 years, and 73.5% were over 45 years old. Predominantly, the sample consisted of homemakers (38.2%) with a high school education level (32.4%). Exposure to sunlight was infrequent among most participants (60.3%), and a significant proportion reported having no comorbidities (77.9%). Among the 68 participants, 94.1% were diagnosed with invasive ductal carcinoma (IDC). Lung metastases were the most frequent distant metastases (7.4%). The average vitamin D level among breast cancer patients was notably low, at 19.6 ng/mL, with the majority exhibiting either vitamin D deficiency or insufficiency, as illustrated in Table 1.

3.2 Association between Sociodemography Characteristics and Vitamin D Levels

This study's sociodemographic characteristics included age, education level, occupation, and sun exposure. Age was categorized into two categories, namely ≤ 45 years and > 45 years. Education level is categorized into education up to senior high school (unschooled, elementary, junior, and senior high school) and higher education (diploma and bachelor). Occupational variables are categorized into not-workers and workers, while sun exposure variables are categorized into high and low exposure. The Chi-Square test results found no significant relationship between these four variables and vitamin D levels (Table 2).

3.3 Association between Clinical Characteristics and Vitamin D Levels

In this study, no significant association was found between the type of breast cancer, the presence of metastases, and comorbidities with vitamin D levels in breast cancer patients ($p > 0.05$) (Table 3). However, the presence of comorbidities appears to affect vitamin D levels. Breast cancer patients with comorbidities tend to have lower vitamin D levels when compared to breast cancer patients without comorbidities (Table 4). When examined further, breast cancer patients with comorbid type 2 DM have significantly lower vitamin D levels when compared to breast cancer patients with comorbid hypertension and no comorbid (Figure 1)

Table 1: Distribution of sociodemographic characteristics, tumor profile, and vitamin D levels.

Variable	N	%
Age, years (Min-Max)	52,04±8,88 (32-73)	
-. ≤ 45 years	18	26,5
-. > 45 years	50	73,5
Education		
-. Unschooled	8	11,8
-. Elementary School	9	13,2
-. Junior High School	9	13,2
-. Senior High School	22	32,4
-. Diploma	7	10,3
-. Bachelor	13	19,1
Occupation		
-. Civil Servant	4	5,9
-. Private employees	4	5,9
-. Farmer	15	22,1
-. Labourer	1	1,5
-. Housewife	26	38,2
-. Others	18	26,5
Sun Exposure		
-. High	27	39,7
-. Low	41	60,3
Comorbid		

-. DM	7	10,3
-. Hypertension	8	11,8
-. No Comorbidities	53	77,9
Type		
-. IDC	64	94,1
-. Clear Cell Carcinoma	1	1,5
-. ILC	2	2,9
-. Mixed	1	1,5
Distant Metastases		
-. Lungs	5	7,4
-. Mammae	1	1,5
-. Subclavicular	1	1,5
-. Brain	1	1,5
-. No Metastases	60	88,2
Vitamin D (ng/mL)	19,7±6,5	
-. Deficiency	35	50,7
-. Insufficiency	29	42
-. Sufficiency	4	5,8

4 DISCUSSION

Vitamin D can be employed as an additional supplement in treating breast cancer. Various studies have proven the ability of this vitamin to induce apoptosis, inhibit proliferation and angiogenesis, and reduce the progression and risk of breast cancer (Lopes et al., 2012; Vanhevel et al., 2022; Vanoirbeek et al., 2011). Additional investigations have also proven that high vitamin D levels can reduce the risk of developing breast cancer (Estébanez et al., 2018; Shamsi et al., 2020).

This study found that most newly diagnosed breast cancer patients had vitamin D deficiency/insufficiency, with an average vitamin D level of 19.7 ng/mL. This value is lower when compared to the established reference value for sufficient vitamin D levels, set at 30 ng/mL (Amrein et al., 2020). This result aligns with several previous studies, which found similar results (Imtiaz & Siddiqui, 2014; Narvaez et al., 2014; Shaukat et al., 2017). Vitamin D deficiency in breast cancer patients is recognized for its involvement in the proliferation of primary tumors and metastases and cancer aggressiveness (Al-Azhri et al., 2017; Williams et al., 2016). This phenomenon can be attributed to the disruption caused by the deficiency in regulating the signaling of the vitamin D receptor and the metabolic enzymes CYP27B1 and CYP24A1. These enzymes facilitate the conversion of serum vitamin D into a form capable of binding to vitamin D receptors. The role of vitamin D receptors in suppressing tumor growth is established; hence, the presence of these imbalances can curtail their effectiveness in restraining tumor progression (Voutsadakis, 2020).

Table 2: Association between Sociodemography Characteristics and Vitamin D Levels.

Sociodemography Characteristics	Vitamin D Levels		*p*
	Deficiency	Not deficiency	
Age			
-. > 45 years	19 (38,0%)	31 (62,0%)	0,197
-. ≤ 45 years	10 (55,6%)	8 (44,4%)	
Education			
-. Up to senior high school	19 (39,6%)	29 (60,4%)	0,429
-. Higher education	10 (50%)	10 (50%)	
Occupation			
-. Worker	19 (45,2%)	23 (54,8%)	0,583
-. Not-worker	10 (38,5%)	16 (61,5%)	
Sun Exposure			
-. High	10 (37,0%)	17 (63,0%)	0,448
-. Low	19 (46,3%)	22 (53,7%)	

Table 3: Association between Clinical Characteristics and Vitamin D Levels.

Clinical Characteristic	Kadar Vitamin D		*p*
	Deficiency	Not deficiency	
Metastases			0,715
-. Yes	4 (50%)	4 (50%)	
-. No	25 (41,7%)	35 (58,3%)	
Type			0,305
-. IDC	26 (40,6%)	38 (59,4%)	
-. Non IDC	3 (75,0%	1 (25,0%)	
Comorbid			0,343
-. Yes	8 (53,3%)	7 (46,7%)	
-. No	21 (39,6%)	32 (60,4%)	

Table 4: Difference in Vitamin D Levels between Comorbid and Non-comorbid.

Comorbid	n	Mean±SD (ng/mL)	*p*
-. Yes	15	16,68±6,32	0,041*
-. No	53	20,54±6,31	

Exp: * there is a significant relationship based on the unpaired t-test at α=5%.

This study also revealed that breast cancer patients with comorbidities exhibited notably reduced vitamin D levels compared to those without comorbidities. Moreover, patients with both breast cancer and type 2 diabetes mellitus (DM) displayed particularly deficient vitamin D levels. Vitamin D's interconnection with type 2 DM and hypertension has been long recognized. The deficiency of vitamin D is intricately linked to the onset of type 2 DM (Chagas et al., 2012; Lim et al., 2013) and hypertension (Qi et al., 2017; Zhang et al., 2017). Among patients with type 2 DM, an inadequate supply of vitamin D is responsible for instigating glucose intolerance and interfering with insulin secretion. This disruption is attributed to the activity of the vitamin D receptor, or indirectly, via calcium hormones and inflammatory processes (Chagas et al., 2012).

Vitamin D deficiency stems from several factors: sun exposure duration, lifestyle, genetic predisposition, age, and dietary vitamin D intake. Interestingly, this study found no association between vitamin D levels and duration of sun exposure, lifestyle (education and occupation), and age. This fact leads us to hypothesize that vitamin D deficiency in breast cancer patients is more dominantly caused by a lack of vitamin D intake from food. This hypothesis gains empirical validation from the findings of a pivotal study conducted by Alco et al. (2014). Their investigation reveals that inadequate vitamin D intake corresponds to a remarkable 28.7-fold escalation in the risk of vitamin D deficiency or insufficiency among breast cancer patients (Alco et al., 2014).

Several studies have shown that vitamin D supplementation to breast cancer patients can increase serum vitamin D levels without inducing toxic manifestations (Alco et al., 2014). While animal-based experimental studies have demonstrated a favorable impact of vitamin D supplementation on breast cancer, clinical investigations have not shown similar results (de La Puente-Yagüe et al., 2018; Linowiecka et al., 2021). Vitamin D supplementation has not shown significant benefits in the effective treatment of breast cancer patients (Zemlin et al., 2023). Nevertheless, the potential benefits of vitamin D supplementation, particularly in individuals with concurrent type 2 diabetes mellitus (DM) conditions, warrant careful consideration, given the diminished vitamin D levels observed in this subgroup. This deliberation is motivated by the intent to avert other ailments linked to vitamin D deficiency, such as rickets and osteoporosis, which can potentially exacerbate the health status of breast cancer patients.

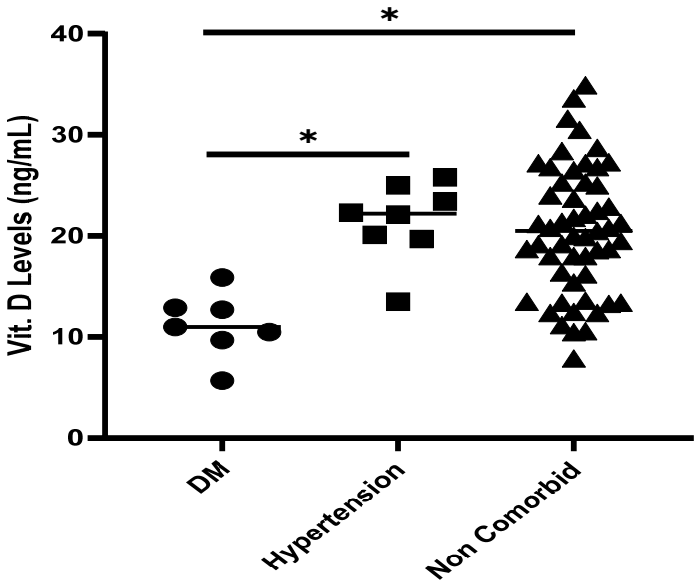

Figure 1: Differences in mean vitamin D levels between comorbid groups.

5 CONCLUSIONS

Vitamin D deficiency is commonly observed among breast cancer patients, especially those with type 2 DM comorbidities. The presence of vitamin D deficiency in breast cancer patients does not exhibit any association with sociodemographic attributes or clinical status. Further information about vitamin D levels and their association with the survival of breast cancer patients is still challenging to become research questions.

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REFERENCES

Al-Azhri, J., Zhang, Y., Bshara, W., Zirpoli, G., McCann, S. E., Khoury, T., Morrison, C. D., Edge, S. B., Ambrosone, C. B., & Yao, S. (2017). Tumor expression of vitamin D receptor and breast cancer histopathological characteristics and prognosis. *Clinical Cancer Research*, *23*(1), 97–103. https://doi.org/10.1158/1078-0432.CCR-16-0075

Alco, G., Igdem, S., Dincer, M., Ozmen, V., Saglam, S., Selamoglu, D., Erdogan, Z., Ordu, C., Pilanci, K. N., Bozdogan, A., Yenice, S., Tecimer, C., Demir, G., Koksal, G., & Okkan, S. (2014). Vitamin D levels in patients with breast cancer: Importance of dressing style. *Asian Pacific Journal of Cancer Prevention*, *15*(3), 1357–1362. https://doi.org/10.7314/APJCP.2014.15.3.1357

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. *European Journal of Clinical Nutrition*, *74*(11), 1498–1513. https://doi.org/10.1038/s41430-020-0558-y

Atoum, M., & Alzoughool, F. (2017). Vitamin D and Breast Cancer: Latest Evidence and Future Steps. *Breast Cancer: Basic and Clinical Research*, *11*, 1–8. https://doi.org/10.1177/1178223417749816

Bernhardt, S. M., Borges, V. F., & Schedin, P. (2021). Vitamin D as a Potential Preventive Agent For Young Women's Breast Cancer. *Cancer Prevention Research (Philadelphia, Pa.)*, *14*(9), 825–838. https://doi.org/10.1158/1940-6207.CAPR-21-0114

Bidgoli, S. A., & Azarshab, H. (2014). Role of vitamin D deficiency and lack of sun exposure in the incidence of premenopausal breast cancer: a case control study in Sabzevar, Iran. *Asian Pacific Journal of Cancer Prevention : APJCP*, *15*(8), 3391–3396. https://doi.org/10.7314/APJCP.2014.15.8.3391

Buja, A., Pierbon, M., Lago, L., Grotto, G., & Baldo, V. (2020). Breast Cancer Primary Prevention and Diet: An Umbrella Review. *International Journal of*

Environmental Research and Public Health, *17*(13), 1–54. https://doi.org/10.3390/IJERPH17134731

Chagas, C. E. A., Borges, M. C., Martini, L. A., & Rogero, M. M. (2012). Focus on Vitamin D, Inflammation and Type 2 Diabetes. *Nutrients*, *4*(1), 52. https://doi.org/10.3390/NU4010052

Chen, Y., & Zhi, X. (2020). Vitamin D Status in Population Functions of Vitamin D in the Reproductive System. *Endocrinology*, *161*(4), 1–12. https://doi.org/10.1210/endocr/bqaa023

Choudhury, H., Pandey, M., Wen, L. P., Cien, L. K., Xin, H., Yee, A. N. J., Lee, N. J., Gorain, B., Amin, M. C. I. M., & Pichika, M. R. (2020). Folic Acid Conjugated Nanocarriers for Efficient Targetability and Promising Anticancer Efficacy for Treatment of Breast Cancer: A Review of Recent Updates. *Current Pharmaceutical Design*, *26*(42), 5365–5379. https://doi.org/10.2174/1381612826666200721000958

Cosentino, N., Campodonico, J., Milazzo, V., De Metrio, M., Brambilla, M., Camera, M., Marenzi, G., Johansson, H., Serrano, D., Raimondi, S., Gnagnarella, P., & Dominguez, L. J. (2021). Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. *Nutrients 2021, Vol. 13, Page 3603*, *13*(10), 3603. https://doi.org/10.3390/NU13103603

de La Puente-Yagüe, M., Cuadrado-Cenzual, M. A., Ciudad-Cabañas, M. J., Hernández-Cabria, M., & Collado-Yurrita, L. (2018). Vitamin D: And its role in breast cancer. *The Kaohsiung Journal of Medical Sciences*, *34*(8), 423–427. https://doi.org/10.1016/J.KJMS.2018.03.004

Estébanez, N., Gómez-Acebo, I., Palazuelos, C., Llorca, J., & Dierssen-Sotos, T. (2018). Vitamin D exposure and Risk of Breast Cancer: a meta-analysis. *Scientific Reports*, *8*(1). https://doi.org/10.1038/S41598-018-27297-1

Forouhi, N. G., Ye, Z., Rickard, A. P., Khaw, K. T., Luben, R., Langenberg, C., & Wareham, N. J. (2012). Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies. *Diabetologia*, *55*(8), 2173–2182. https://doi.org/10.1007/S00125-012-2544-Y

Giovannucci, E. (2009). Vitamin D and cancer incidence in the Harvard cohorts. *Annals of Epidemiology*, *19*(2), 84–88. https://doi.org/10.1016/J.ANNEPIDEM.2007.12.002

Grabiec, M., Walentowicz, P., Sadłecki, P., & Walentowicz-Sadłecka, M. (2013). The role of vitamin D in the carcinogenesis of breast and ovarian cancer. *Polish Gynaecology*, *84*(4). https://doi.org/10.17772/gp/1581

Green, T. J., Skeaff, C. M., Rockell, J. E. P., Venn, B. J., Lambert, A., Todd, J., Khor, G. L., Loh, S. P., Muslimatun, S., Agustina, R., & Whiting, S. J. (2008). Vitamin D status and its association with parathyroid hormone concentrations in women of child-bearing age living in Jakarta and Kuala Lumpur. *European Journal of Clinical Nutrition*, *62*(3), 373–378. https://doi.org/10.1038/SJ.EJCN.1602696

Imtiaz, S., & Siddiqui, N. (2014). Vitamin-D status at breast cancer diagnosis: correlation with social and environmental factors and dietary intake. *Journal of Ayub Medical College, Abbottabad : JAMC*, *26*(2), 186–190.

Janoušek, J., Pilařová, V., Macáková, K., Nomura, A., Veiga-Matos, J., Silva, D. D. da, Remião, F., Saso, L., Malá-Ládová, K., Malý, J., Nováková, L., & Mladěnka, P. (2022). Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. *Critical Reviews in Clinical Laboratory Sciences*, *59*(8), 517–554. https://doi.org/10.1080/10408363.2022.2070595

Kazemi, S. M., Esmaieli-bandboni, A., Veisi Malekshahi, Z., Shahbaz Sardood, M., Hashemi, M., Majidzadeh, K., Kadkhodazadeh, M., Esmaili, R., & Negahdari, B. (2022). Vitamin D receptor gene polymorphisms and risk of breast cancer in Iranian women. *Annals of Medicine and Surgery*, *73*(December 2021), 103150. https://doi.org/10.1016/j.amsu.2021.103150

Kim, Y., Franke, A. A., Shvetsov, Y. B., Wilkens, L. R., Cooney, R. V., Lurie, G., Maskarinec, G., Hernandez, B. Y., Le Marchand, L., Henderson, B. E., Kolonel, L. N., & Goodman, M. T. (2014). Plasma 25-hydroxyvitamin D3 is associated with decreased risk of postmenopausal breast cancer in whites: A nested case-control study in the multiethnic cohort study. *BMC Cancer*, *14*(1), 1–7. https://doi.org/10.1186/1471-2407-14-29/COMMENTS

Lim, S., Kim, M. J., Choi, S. H., Shin, C. S., Park, K. S., Jang, H. C., Billings, L. K., & Meigs, J. B. (2013). Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. *The American Journal of Clinical Nutrition*, *97*(3), 524. https://doi.org/10.3945/AJCN.112.048496

Linowiecka, K., Wolnicka-Głubisz, A., & Brożyna, A. A. (2021). Vitamin D endocrine system in breast cancer. *Acta Biochimica Polonica*, *68*(4), 489–497. https://doi.org/10.18388/ABP.2020_5961

Lopes, N., Paredes, J., Costa, J. L., Ylstra, B., & Schmitt, F. (2012). Vitamin D and the mammary gland: a review on its role in normal development and breast cancer. *Breast Cancer Research : BCR*, *14*(3). https://doi.org/10.1186/BCR3178

Mattiuzzi, C., & Lippi, G. (2019). Current Cancer Epidemiology. *Journal of Epidemiology and Global Health*, *9*(4), 217–222. https://doi.org/10.2991/JEGH.K.191008.001

Mazahery, H., & Von Hurst, P. R. (2015). Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. *Nutrients*, *pp. 7*, 5111–5142. https://doi.org/10.3390/nu7075111

Narvaez, C. J., Matthews, D., LaPorta, E., Simmons, K. M., Beaudin, S., & Welsh, J. E. (2014). The impact of vitamin D in breast cancer: genomics, pathways, metabolism. *Frontiers in Physiology*, *p. 5*. https://doi.org/10.3389/FPHYS.2014.00213

Octavius, G. S., Daleni, V. A., Angeline, G., & Virliani, C. (2023). A systematic review and meta-analysis of the prevalence of vitamin D deficiency among Indonesian

pregnant women: a public health emergency. *AJOG Global Reports*, *3*(2), 100189. https://doi.org/10.1016/j.xagr.2023.100189

Qi, D., Nie, X. L., Wu, S., & Cai, J. (2017). Vitamin D and hypertension: Prospective study and meta-analysis. *PloS One*, *12*(3). https://doi.org/10.1371/JOURNAL.PONE.0174298

Ren, X., Xu, P., Zhang, D., Liu, K., Song, D., Zheng, Y., Yang, S., Li, N., Hao, Q., Wu, Y., Zhai, Z., Kang, H., & Dai, Z. (2020). Association of folate intake and plasma folate level with the risk of breast cancer: a dose-response meta-analysis of observational studies. *Aging*, *12*(21), 21355–21375. https://doi.org/10.18632/AGING.103881

Setiati, S. (2008). Vitamin D status among Indonesian elderly women living in institutionalized care units. *Acta Med Indonesia*, *40*(2), 78–83.

Shamsi, U., Khan, S., Azam, I., Khan, A. H., Maqbool, A., Hanif, M., Gill, T., Iqbal, R., & Callen, D. (2020). A multicenter case control study of association of vitamin D with breast cancer among women in Karachi, Pakistan. *PLOS ONE*, *15*(1), e0225402. https://doi.org/10.1371/JOURNAL.PONE.0225402

Shaukat, N., Jaleel, F., Moosa, F. A., & Qureshi, N. A. (2017). Association between Vitamin D deficiency and Breast Cancer. *Pakistan Journal of Medical Sciences*, *33*(3), 645–649. https://doi.org/10.12669/pjms.333.11753

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/CAAC.21660

Susanti, M., Widjaja, S. S., & Siregar, D. R. (2018). Pengaruh Vitamin D terhadap Indeks Apoptosis pada Penderita Kanker Payudara. *Jurnal Kesehatan Andalas*, *7*(2), 182–186. https://doi.org/10.25077/JKA.V7I2.799

Vanhevel, J., Verlinden, L., Doms, S., Wildiers, H., & Verstuyf, A. (2022). The role of vitamin D in breast cancer risk and progression. *Endocrine-Related Cancer*, *29*(2), R33–R55. https://doi.org/10.1530/ERC-21-0182

Vanoirbeek, E., Krishnan, A., Eelen, G., Verlinden, L., Bouillon, R., Feldman, D., & Verstuyf, A. (2011). The Anticancer and Anti-Inflammatory Actions of 1,25(OH)2D3. *Best Practice & Research. Clinical Endocrinology & Metabolism*, *25*(4), 593. https://doi.org/10.1016/J.BEEM.2011.05.001

Voutsadakis, I. A. (2020). Vitamin D receptor (VDR) and metabolizing enzymes CYP27B1 and CYP24A1 in breast cancer. *Molecular Biology Reports*, *47*(12), 9821–9830. https://doi.org/10.1007/S11033-020-05780-1/METRICS

Williams, J. D., Aggarwal, A., Swami, S., Krishnan, A. V., Ji, L., Albertelli, M. A., & Feldman, B. J. (2016). Tumor Autonomous Effects of Vitamin D Deficiency Promote Breast Cancer Metastasis. *Endocrinology*, *157*(4), 1341–1347. https://doi.org/10.1210/EN.2015-2036

Zemlin, C., Altmayer, L., Stuhlert, C., Schleicher, J. T., Wörmann, C., Lang, M., Scherer, L. S., Thul, I. C., Spenner, L. S., Simon, J. A., Wind, A., Kaiser, E., Weber, R., Goedicke-Fritz, S., Wagenpfeil, G., Zemlin, M., Solomayer, E. F., Reichrath, J., & Müller, C. (2023). Prevalence and Relevance of Vitamin D Deficiency in Newly Diagnosed Breast Cancer Patients: A Pilot Study. *Nutrients*, *15*(6), 1–12. https://doi.org/10.3390/nu15061450

Zhang, R., Li, B., Gao, X., Tian, R., Pan, Y., Jiang, Y., Gu, H., Wang, Y., Wang, Y., & Liu, G. (2017). Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. *The American Journal of Clinical Nutrition*, *105*(4), 810–819. https://doi.org/10.3945/AJCN\.116.140392

Zheng, Y., Trivedi, T., Lin, R. C., Fong-Yee, C., Nolte, R., Manibo, J., Chen, Y., Hossain, M., Horas, K., Dunstan, C., Zhou, H., & Seibel, M. J. (2017). 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*, *5*. https://doi.org/10.1038/BONERES.2017.23