



Evaluation of Serum Markers in Iraqi Patients With Breast Cancer

Yasser Jassim Dawood,¹ Montadher Ali Mahdi,¹ Hameed Muthanna Ahmed,^{2,3} Rusul Saad³

Abstract

Background/Aim: For women, breast cancer is the leading cause of mortality around the world. In addition to genetic subgroups, the treatment of breast cancer depends on biochemical testing to monitor systemic involvement, particularly in the skeletal system. The purpose of the study was to assess the relationship between bone metabolic markers and conventional tumour markers in Iraqi patients to establish a "biochemical signature" of disease progression.

Methods: Sixty participants were split into two groups for a case-control study: 30 Iraqi women (aged 30–45) with stage I–III breast cancer and 30 age-matched healthy controls. In order to minimise menopausal hormonal changes, all participants were in their reproductive years. Advanced immunoassay (CLIA, ELFA, ELISA) and colorimetric methods were used to measure the serum levels of tumour markers carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3), vitamin D3 (25-OH), parathyroid hormone (PTH), alkaline phosphatase (ALP) and calcium (Ca). IBM SPSS v25.0 was used for statistical analysis.

Results: CEA (80.42 ± 24.14) and CA15-3 (90.75 ± 24.78) levels were significantly higher in the patient group than in the control group ($p < 0.001$). Patients had a severe vitamin D3 deficiency (12.18 ± 5.40) as opposed to healthy individuals (45.32 ± 13.31). On the other hand, PTH and ALP levels were significantly higher in the patient group ($p = 0.003$). The serum calcium and phosphorus levels were substantially lower ($p < 0.001$). According to a ROC curve analysis, the AUC for CEA, CA15-3, ALP and PTH was 1,000, indicating full diagnostic accuracy. PTH and ALP were found to have a significant positive relationship ($r = 0.995$).

Conclusions: The information demonstrates a strong correlation between mineral metabolism and oncological markers. The coordinated changes in these markers show that, particularly in women who are not menopausal, breast cancer significantly disrupts bone homeostasis. Concurrent assessment of these traits offers a reliable multifaceted tool to track tumour load and predict skeletal involvement, which may result in more individualised and effective treatment choices.

Key words: Breast neoplasms; Cholecalciferol; Parathyroid hormone; Alkaline phosphatase; Calcium; Phosphorus; Biomarkers, tumour.

1. Iraqi National Cancer Research Centre, University of Baghdad, Baghdad, Iraq.
2. Al-Rusafa First Directorate of Education – Al-Andalus Secondary School for Boys, Baghdad, Iraq.
3. Department of Science, College of Basic Education, Mustansiriyah University, Baghdad, Iraq.

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Corresponding author:

MONTADHER ALI MAHDI
E: montadhermalky@yahoo.com

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Introduction

Worldwide, breast cancer continues to be the most frequent cancer and the leading cause of cancer-related mortality among women. The expression of oestrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) distinguishes its subgroups: luminal A, luminal B, HER2-positive and triple-negative. Beyond these genetic categories, biochemical profiling is becoming increasingly relevant in the treatment of breast cancer to anticipate systemic involvement, particularly in the skeletal system, where distant metastases are most common.¹ Breast cancer and bone metabolism have a mutually beneficial but detrimental interaction. Breast cancer cells have a distinct affinity for the bone microenvironment, frequently resulting in osteolytic lesions. This process is mediated by a “vicious circle” of bone metastasis, in which tumour cells produce chemicals that induce bone resorption, which then releases growth factors stored in the bone matrix, boosting tumour development.²

Vitamin D, particularly 25(OH)D, functions as a steroid hormone, exerting strong anti-proliferative and pro-differentiating actions. According to research, vitamin D deficiency is widespread in breast cancer patients and is correlated with bigger tumour growth and higher histological grade. Breast cancer cells release parathyroid hormone-related protein (PTHrP), which mimics PTH function and promotes hypercalcemia and accelerated bone turnover.^{3,4}

Several studies have shown that breast cancer cells express vitamin D receptors and have established a relationship between vitamin D levels and breast cancer growth.⁵ Furthermore, pre-clinical studies suggest that combining calcitriol with anticancer agents may yield promising results.⁶

Calcium (Ca) and phosphorus (P) minerals serve as the main markers of mineral homeostasis. Hypercalcemia is a prevalent paraneoplastic condition associated with advanced breast cancer. This is attributed to increased osteoclast activity and renal calcium reabsorption, which serves as an essential indicator of the degree of skeletal involvement.^{7,8}

Calcium signalling is critical for fundamental cellular processes such as invasion and programmed

cell death and its dysregulation has been linked to cancer progression. Several studies on breast cancer have found that altered expression of calcium channels, pumps and transporters promotes malignant behaviour such as enhanced proliferation, metastasis and resistance to treatment. Increased expression of calcium-permeable channels and aberrant intracellular calcium dynamics have been explicitly associated with aggressive subtypes, indicating that dysregulated calcium signalling is associated with poor prognosis and treatment resistance.⁹ New research has also linked mineral metabolism, namely calcium and phosphate balance, to breast cancer outcomes. Dysregulated phosphate metabolism is linked to aberrant bone mineral density alterations and may impact carcinogenesis and metastatic processes, demonstrating the intricate relationship between mineral homeostasis and cancer biology. These findings promote the exploration of calcium signalling pathways and mineral balance, not only as indicators of disease progression, but also as possible treatment targets in breast cancer.¹⁰

Alkaline phosphatase (ALP) is an enzyme whose blood levels indicate activity in a variety of organs, including bone, liver and kidney. High serum ALP has been linked to the advancement of breast cancer in several clinical studies and may indicate the presence of metastases, especially in the liver and bones. ALP is a valuable biomarker for early prognostic assessment and treatment planning in patients with breast cancer because high levels have also been linked to a poor prognosis.^{11,12}

Increased cancer antigen 15-3 (CA15-3) levels have been linked in several studies to worse patient outcomes and advanced illness, suggesting that they may be useful as a prognostic marker.^{13,14} Its predictive value is questionable, though, as pooled analyses are still limited and some studies found CA15-3 to be significant in univariate analysis but not in multivariate models, notwithstanding these variations.¹⁵

Another serum marker used to detect breast cancer is carcinoembryonic antigen (CEA); however, because of its lower positive rates and greater variability in results, it is not as frequently used as CA15-3. According to certain research, CEA has no predictive value for either primary or metastatic breast cancer.^{16,17} According to other stud-

ies, poor clinical outcomes are associated with elevated CEA levels.^{18,19} These conflicting results highlight the need for more thorough research on CEA as a predictor of breast cancer. A complete picture of the patient's condition can be obtained by concurrently examining tumour markers (CEA, CA15-3) and bone mineral indicators (vitamin D, PTH, ALP, Ca, P). Doctors can differentiate between localised illness and systemic spread thanks to this "biochemical signature." Comprehending these correlations is essential for developing customised treatment plans, reducing the risk of skeletal-related events (SREs) and raising patient survival rates overall.

The purpose of the study was to assess the relationship between bone metabolic markers and conventional tumour markers in Iraqi patients to establish a "biochemical signature" of disease progression.

Methods

Study population

Sixty volunteers made up the research group and they were divided into two groups. The patient group consisted of 30 Iraqi women between the ages of 30 and 45 who had been diagnosed with breast cancer by clinical, radiological and histopathological means. The tumour, node, metastasis (TNM) classification method was used to categorise patients by disease stage, which ranged from stage I to stage III. To ensure that everyone was in their reproductive years and to minimise the biochemical and hormonal changes associated with menopause, this age range was selected. Specialised oncologists treated each patient, who was selected from the Oncology Teaching Hospital in Medical City, Baghdad, Iraq. The research was carried out from 10 February 2026 to 10 March 2026. Thirty age-matched, healthy women without a history of cancer or long-term metabolic issues comprised the control group. Strict inclusion and exclusion criteria were used and no subjects were pregnant, smokers, or alcohol consumers at the time of the study. To ensure the accuracy of the biochemical profile, especially with regard to mineral levels (calcium, phosphorus) and bone metabolism markers (vitamin D3, PTH, ALP), women with systemic conditions such

as diabetes mellitus, hypertension, hyperthyroidism, or psoriasis were strictly excluded. Each participant provided written informed consent before enrolment and completed a structured questionnaire regarding their clinical, medical and personal background.

Specimen collection

Each experiment investigator (individual and control) collected 10 mL of venous blood with plastic disposable 10 mL syringes. The samples were collected in a gel tube. After collection, the gel tubes were centrifuged for 5 min at 3000 rpm. The resulting serum was kept at -20 °C until analysis.

Serum concentrations of vitamin D3 (25-OH vitamin D) and parathyroid hormone (PTH) were determined using chemiluminescence immunoassay (CLIA) technology with kits supplied by *Abbott Diagnostics* (Lake Forest, Illinois, USA) on the Alinity i system. The tumour marker CA15-3 was evaluated using the VIDAS kit and equipment based on enzyme-linked fluorescence assay (ELFA) technology provided by *bioMérieux* (Marcy-l'Etoile, France). CEA levels were measured using enzyme immunoassay-based ELISA kits and instruments in human serum supplied by *Diagnostic Biochem Canada Inc* (London, Ontario, Canada). Serum ALP activity, along with inorganic phosphorus and total calcium concentrations, was determined using commercially available enzymatic and colorimetric kits provided by *Roche Diagnostics* (Mannheim, Germany) and processed on a Cobas C automated clinical chemistry analyser according to the manufacturer's instructions.

Statistical analysis

The IBM SPSS Statistics application (*IBM Corporation*, New York, United States), version 25.0, was utilised in the analysis. Data were analysed using descriptive statistics and displayed as means $\pm$ standard deviation. The mean values of the sick and control groups were compared with an independent-sample t-test. Statistical significance was determined as $p < 0.05$ with a 95 % confidence interval and high significance as $p \leq 0.01$ with a 99 % confidence range. The correlation coefficient varies from -1 to 1. Positive numbers indicate a positive relationship (when one variable grows, the other increases), whereas negative values indicate a negative link (when one variable increase, the other drops).

Results

There was a very significant increase in the average tumour marker level (CEA and CA15-3) in the patient group compared to the control group. Specifically, CEA concentrations were significantly higher in patients (80.42 ± 24.14) compared with healthy controls (2.23 ± 1.00 ; $p < 0.001$). The average CA15-3 level in patients was 90.75 ± 24.78 , compared to 5.24 ± 2.29 in the healthy population ($p < 0.001$). Significant alterations were seen in measures associated with bone turnover. The sick group had a considerably reduced average vitamin D3 concentration (12.18 ± 5.40) compared to the control group (45.32 ± 13.31 , $p < 0.001$).

In contrast, significant increases were observed in PTH levels (100.75 ± 23.33 vs 31.91 ± 14.68 , $p = 0.003$) and ALP activity (200.08 ± 24.31 vs 87.23 ± 15.56 , $p = 0.003$). The sick group had considerably lower blood calcium levels (6.22 ± 1.00) than the controls (9.69 ± 0.57 , $p < 0.001$). Patients had lower serum phosphorus levels (1.66 ± 0.53) compared to controls (3.64 ± 0.68), although the difference was not statistically significant ($p = 0.051$) (Table 1).

As summarised in Table 2, the results showed exceptional diagnostic accuracy for many markers. CEA, CA15-3, ALP and PTH each achieved an area

Table 1: Comparison of all studied parameters between the groups (breast cancer patients and healthy controls)

Parameters	Group	N	Mean	SD	SE	p-value
CEA (ng/mL)	Control	30	2.23	1.00	0.18	0.001*
	Patient	30	80.42	24.14	4.41	
CA15-3 (U/mL)	Control	30	5.24	2.29	0.42	0.001*
	Patient	30	90.75	24.78	4.52	
D3 (ng/mL)	Control	30	45.32	13.31	2.43	0.001*
	Patient	30	12.18	5.40	0.99	
PTH (pg/mL)	Control	30	31.91	14.68	2.68	0.003*
	Patient	30	100.75	23.33	4.26	
ALP (U/L)	Control	30	87.23	15.56	2.84	0.003*
	Patient	30	200.08	24.31	4.44	
Phosphorus – P (mg/dL)	Control	30	3.64	0.68	0.12	0.051
	Patient	30	1.66	0.53	0.10	
Calcium – Ca (mg/dL)	Control	30	9.69	0.57	0.10	0.001*
	Patient	30	6.22	1.00	0.18	

CEA: carcinoembryonic antigen; CA15-3: cancer antigen 15-3; PTH: parathyroid hormone; ALP: alkaline phosphatase; SD: standard deviation; SE: standard error of mean; D3: cholecalciferol;

Table 2: Diagnostic accuracy of serum markers in breast cancer patients – area under the curve (AUC) analysis

Test result variables	AUC	SE	p-value	95% CI
CEA	1.000	0.000	< 0.001	1.000-1.000
CA15-3	1.000	0.000	< 0.001	1.000-1.000
ALP	1.000	0.000	< 0.001	1.000-1.000
PTH	1.000	0.000	< 0.001	1.000-1.000
Phosphorus	0.001	0.002	< 0.001	0.000-0.005
Calcium	0.000	0.000	< 0.001	0.000-0.000
Vitamin D3	0.000	0.000	< 0.001	0.000-0.000

CEA: carcinoembryonic antigen; CA15-3: cancer antigen 15-3; PTH: parathyroid hormone; ALP: alkaline phosphatase; CI: confidence interval; SE: standard error of mean;

under the curve (AUC) of 1.000 (95 % CI: 1.000-1.000, $P < 0.001$), indicating an ideal sensitivity and specificity in distinguishing between the two groups. In contrast, markers such as calcium and vitamin D3, which were significantly reduced in patients, achieved an AUC of 0.000. which statistically shows a perfect inverse relationship (ie, lower levels are strictly associated with disease status). Despite the presence of minimal relationships between groups, phosphorus also showed a strong discriminatory power with an AUC of 0.001 (Figure 1). These findings imply that combining these biochemical indicators creates a very accurate diagnostic tool for tracking breast cancer growth and metabolic effect.

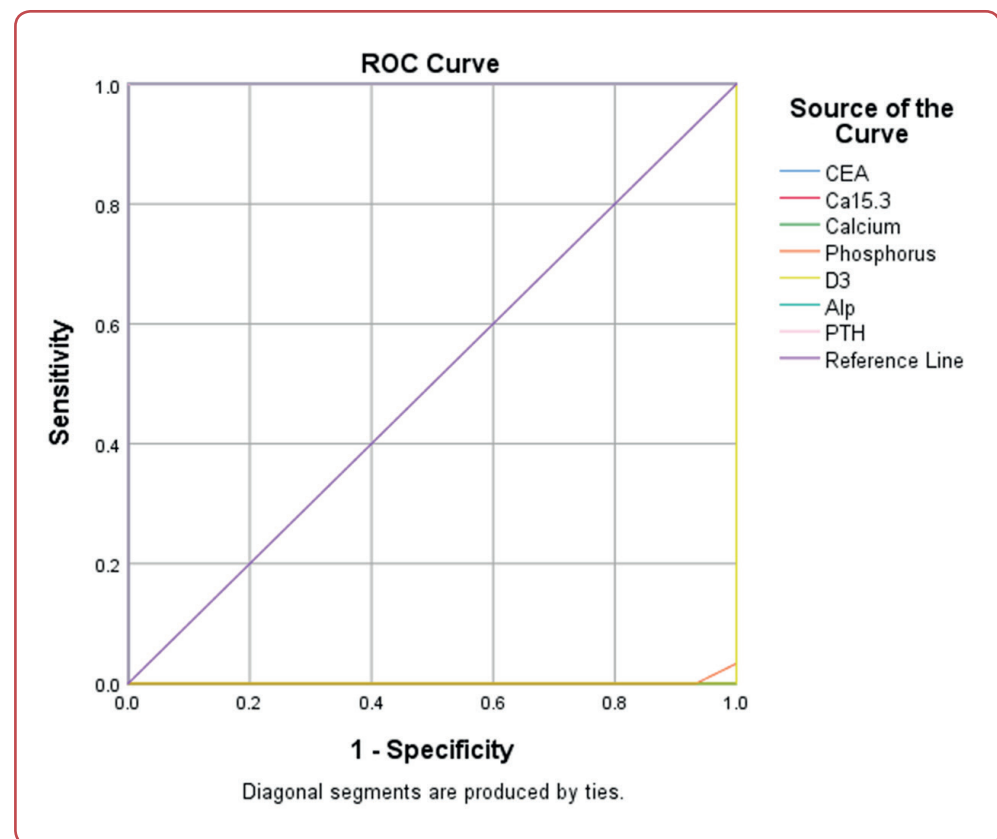


Figure 1: Receiver operating characteristic (ROC) curves demonstrate the excellent sensitivity and specificity of all parameters

CEA: carcinoembryonic antigen; CA15-3: cancer antigen 15-3; PTH: parathyroid hormone; ALP: alkaline phosphatase; D3: cholecalciferol;

Table 3: Pearson correlation matrix for tumour markers and bone metabolism measures in breast cancer patients

Correlations	CEA	CA15-3	D3 vitamin	PTH	ALP	Calcium	Phosphorus
CEA	1	.912**	.968**	.929**	.931**	.913**	.619**
CA15-3	.912**	1	.916**	.938**	.940**	.901**	.651**
D3 vitamin	.968**	.916**	1	.946**	.950**	.949**	.656**
PTH	.929**	.938**	.946**	1	.995**	.932**	.577**
ALP	.931**	.940**	.950**	.995**	1	.943**	.616**
Calcium	.913**	.901**	.949**	.932**	.943**	1	.708**
Phosphorus	.619**	.651**	.656**	.577**	.616**	.708**	1

CEA: carcinoembryonic antigen; CA15-3: cancer antigen 15-3; PTH: parathyroid hormone; ALP: alkaline phosphatase;

The results of the Pearson correlation analysis showed that all of the parameters under study had strong and significant positive relationships ($p < 0.01$, $n = 30$) (Table 3). For instance, a very strong correlation was found between vitamin D3 and CEA ($r = 0.968$) and PTH and ALP ($r = 0.995$), indicating that these biochemical markers are nearly linear. The study group's metabolic rhythm was highly synchronised, as evidenced by the signif-

icant relationships (all $r > 0.90$) that the tumour markers CEA and CA15-3 showed with vitamin D3, PTH, ALP and calcium. The correlations were still statistically significant even though phosphorus had the lowest relative correlation values in the calculations ($r = 0.577$ with PTH and $r = 0.708$ with calcium). The results demonstrate a strong relationship between mineral metabolism and oncological markers, with changes in one indicator corresponding to increases in others.

Discussion

Understanding the course of the disease and identifying potential prognostic indicators depend on the examination of biochemical and tumour markers in patients with breast cancer. Significant variations in tumour markers like CA15-3 and CEA between breast cancer patients and healthy controls were discovered in several studies conducted in Iraqi and regional populations. Higher concentrations of CA15-3 and CEA have been repeatedly linked to advanced stages of the disease and an increased tumour burden in women with breast cancer, demonstrating their value as non-invasive biomarkers in clinical evaluation and disease monitoring.²⁰ For instance, CA15-3 has shown a notable increase in breast cancer patients when compared to control groups, suggesting that it might play a part in early detection and diagnosis. Additionally, correlations between CA15-3 and clinicopathological features suggest that elevated levels of the protein may indicate the severity of the disease and its potential for metastasis.²¹

The outcomes of this investigation are consistent with previous studies that discovered a strong correlation between elevated blood levels of ALP and a poor prognosis for patients with breast cancer. Higher ALP levels have been linked to shorter overall survival (OS) and disease-free or progression-free survival (DFS/PFS), according to several studies, suggesting that ALP may be a significant prognostic biomarker (Ren et al,²² Hao et al²³). Higher ALP correlates with an increasing tumour load and the progression of the disease, especially in advanced stages of breast cancer, which explains this association.

Additionally, presented results demonstrated that elevated ALP levels are significantly associated with a higher risk of metastasis in patients with breast cancer, which is consistent with previous studies. High ALP levels have been linked to both bone and non-bone metastases, especially liver metastases, according to earlier studies (Li et al,²⁴ Mori et al²⁵). These data confirm ALP's involvement as a measure of metastatic activity rather than only a bone-specific indication. As a result, ALP might be regarded as a simple and therapeutically relevant biomarker for early identification of metastatic progression and disease status monitoring in breast cancer patients.

The findings of this study are consistent with earlier experimental, observational and meta-analytic studies demonstrating that vitamin D has a preventive role in breast cancer. Vitamin D, particularly its physiologically active metabolite 1,25-dihydroxyvitamin D (1,25OH₂D), regulates breast cell proliferation, differentiation and death via vitamin D receptors (VDR)-mediated pathways (Deeb et al,²⁶ Feldman et al²⁷). Several studies have shown that normal and malignant mammary epithelial cells express VDR as well as the vitamin D-metabolising enzyme CYP27B1, which enables local conversion of circulating 25-hydroxyvitamin D (25OHD) to its active form (Welsh,²⁸ Lopes et al²⁹). This local autocrine and paracrine activation supports epithelial differentiation and maintenance of growth inhibition. Consistent with these mechanisms, observational studies and a meta-analysis have reported an inverse association between vitamin D levels and breast cancer risk (Chen et al³⁰), supporting presented findings that vitamin D deficiency is associated with adverse disease characteristics.

The results of presented study are consistent with previous research indicating an important role PTH in breast cancer progression. Consistent with previous findings, we observed that elevated circulating PTH levels are associated with an increased risk of metastases and more aggressive disease characteristics.³¹ Previous studies have shown that PTH and its related peptide (PTHrP) stimulate osteoclast activity, promote bone resorption and create a favourable microenvironment for tumour cell colonisation in the skeleton.³² These processes are consistent with presented findings, which indicate that PTH contributes to both skeletal problems and overall tumour growth in breast cancer. Therefore, findings reaffirm the potential predictive utility of PTH as a biomarker of disease severity and metastasis, which is consistent with previous research.

Presented findings are consistent with earlier research suggesting that blood calcium levels play a significant role in breast cancer development. Similar to earlier research, it was discovered that hypercalcemia is linked to advanced illness and the occurrence of metastases, particularly bone metastases (Roodman³³). Elevated calcium levels

can increase tumour development and metastasis by activating calcium-sensing receptors (CaSR), which control the proliferation, migration and survival of breast cancer cells. These processes give biological justification for presented discovery that higher calcium is related with more aggressive disease features, which is consistent with earlier studies.³⁴

In addition, presented findings on serum phosphorus are consistent with earlier research indicating that phosphate metabolism is intimately linked to cancer growth. In breast cancer patients, elevated blood phosphorus levels are linked to increased tumour burden and skeletal involvement.³⁵ Phosphate homeostasis, which is frequently influenced by parathyroid hormone and vitamin D, can affect tumour cell proliferation and osteolytic activity. Our data support the hypothesis that aberrant phosphorus levels might serve as a biomarker of metastatic risk, augmenting the prognostic value of calcium and PTH, as described in the literature.³⁶

Conclusion

This study's findings give compelling evidence that breast cancer in Iraqi women causes major changes in systemic mineral homeostasis and bone metabolism long before clinical symptoms of skeletal failure arise. Data show that individuals have a particular "biochemical signature" that includes a severe deficit in vitamin D3 and calcium, as well as abnormal elevations in PTH and ALP. The nearly flawless diagnostic accuracy of these indicators (AUC = 1.000), together with their significant connection with established tumour markers such as CEA and CA15-3, shows that the "vicious circle" of bone-tumour interaction is active even in young, premenopausal people. This metabolic disruption indicates that breast cancer is a systemic disease that actively enlists the skeletal environment to support its growth. Steps recommended to improve clinical outcomes and survival rates for patients with breast cancer are: during the initial phase, clinical protocols should be updated to include both bone turnover indicators (ALP and PTH) and traditional tumour markers (CA15-3). This facilitates the early detection of metastatic risk and a compre-

hensive evaluation of the patient's condition. In order to stop tumour, spread and support bone health, medical professionals should mandate vitamin D3 screening and aggressive supplementation for all newly diagnosed patients with breast cancer, given the notable deficiency observed.

Future research should focus on longitudinal studies that track these biochemical markers throughout the treatment process (chemotherapy, radiation and surgery) to assess their efficacy in real-time monitoring of treatment response. Investigations into the expression of VDR and calcium-sensing receptors in the Iraqi population are required to determine if genetic variations impact the severity of mineral imbalances found in this study. For patients showing the typical high-PTH/low-calcium profile, early introduction of bone-stabilising agents (such as bisphosphonates or RANKL inhibitors) should be explored to interrupt the "vicious cycle" and prevent skeletal-related events.

Ethics

Study was approved by the Ethics Committee of the Iraqi National Cancer Research Centre, University of Baghdad, Baghdad, Iraq, decision No: 51, dated 8 February 2026.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Yasser Jassim Dawood (YJD):
0009-0003-4019-1841
Montadher Ali Mahdi (MAM):
0000-0002-6896-9278
Hameed Muthanna Ahmed (HMA):
0009-0007-7711-0477
Rusul Saad (RS):
0009-0000-1145-3329

Author contributions

Conceptualisation: YJD
Methodology: YJD, MAM, HMA
Validation: YJD, RS
Formal analysis: MAM, HMA, RS
Investigation: YJD, MAM, HMA
Resources: YJD, RS
Data curation: MAM, HMA
Writing - original draft: YJD, MAM, HMA
Writing - review and editing: YJD, RS
Visualisation: YJD
Project administration: YJD

References

- Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, et al. Breast cancer: pathogenesis and treatments. *Signal Transduct Target Ther*. 2025 Feb 19;10(1):49. doi: 10.1038/s41392-024-02108-4.
- Lemma S, Di Pompo G, Porporato PE, Sboarina M, Russell S, Gillies RJ, et al. MDA-MB-231 breast cancer cells fuel osteoclast metabolism and activity: A new rationale for the pathogenesis of osteolytic bone metastases. *Biochim Biophys Acta Mol Basis Dis*. 2017 Dec;1863(12):3254-64. doi: 10.1016/j.bbadis.2017.08.030.
- Kane JF, Johnson RW. Re evaluating the role of PTHrP in breast cancer. *Cancers (Basel)*. 2023 May 9;15(10):2670. doi: 10.3390/cancers15102670.
- Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: global perspective. *Ann Epidemiol*. 2009 Jul;19(7):468-83. doi: 10.1016/j.annepidem.2009.03.021.
- de La Puente-Yagüe M, Cuadrado-Cenzual MA, Ciudad-Cabañas MJ, Hernández-Cabria M, Collado-Yurrita L. Vitamin D: And its role in breast cancer. *Kaohsiung J Med Sci*. 2018 Aug;34(8):423-427. doi: 10.1016/j.kjms.2018.03.004.
- Abdulrazaq ZA, Al-Ouqaili MTS, Talib NM. The impact of circulating 25-hydroxyvitamin D and vitamin D receptor variation on leukemia-lymphoma outcome: Molecular and cytogenetic study. *Saudi J Biol Sci*. 2024 Jan;31(1):103882. doi: 10.1016/j.sjbs.2023.103882.
- Millen AE, Wactawski-Wende J, Pettinger M, Melamed ML, Tyllavsky FA, Liu S, et al. Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D clinical trial. *Am J Clin Nutr*. 2010 May;91(5):1324-35. doi: 10.3945/ajcn.2009.28908.
- Anastasopoulou C, Mewawalla P. Malignancy-Related Hypercalcemia. [Updated 4 Mar 2025]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482423/>.
- Bantsimba-Malanda C, Ahidouch A, Rodat-Despoix L, Ouadid-Ahidouch H. Calcium signal modulation in breast cancer aggressiveness. *Cell Calcium*. 2023 Jul;113:102760. doi: 10.1016/j.ceca.2023.102760.
- Brown RB, Bigelow P, Dubin JA. Breast cancer and bone mineral density in a U.S. cohort of middle aged women: associations with phosphate toxicity. *Cancers (Basel)*. 2023 Oct 21;15(20):5093. doi: 10.3390/cancers15205093.
- Chen B, Dai D, Tang H, Chen X, Ai X, Huang X, et al. Pre treatment serum alkaline phosphatase and lactate dehydrogenase as prognostic factors in triple negative breast cancer. *J Cancer*. 2016 Nov 25;7(15):2309-16. doi: 10.7150/jca.16622.
- Sobecki JN, Rice LW, Hartenbach EM. Bone health and osteoporosis screening in gynecologic cancer survivors. *Gynecol Oncol*. 2021 Feb;160(2):619-24. doi: 10.1016/j.ygyno.2020.11.028.
- Kacan T. The prognostic value of high pretreatment plasma D dimer levels in non metastatic breast cancer patients with absence of venous thromboembolism. *Int J Hematol Oncol*. 2016;26:136-44. doi: 10.4999/uhod.161266.
- Zheng Y, Shao X, Wang X, Shi L, Huang Y. Prognostic impact of circulating HER2 extracellular domain (ECD) in women with metastatic breast cancer. *J Clin Oncol*. 2015;33(15_suppl):e22038. doi: 10.1200/jco.2015.33.15_suppl.e22038.
- Ebeling FG, Stieber P, Untch M, Nagel D, Konecny GE, Schmitt UM, et al. Serum CEA and CA15-3 as prognostic factors in primary breast cancer. *Br J Cancer*. 2002 Apr 22;86(8):1217-22. doi: 10.1038/sj.bjc.6600248.

16. Nan J, Li J, Li X, Guo G, Wen X, Tian Y. Preoperative serum carcinoembryonic antigen as a marker for predicting the outcome of three cancers. *Biomark Cancer.* 2017 Feb 16;9:1-7. doi: 10.1177/1179299X17690142.
17. Elfagieh M, Abdalla F, Gliwan A, Boder J, Nichols W, Buhmeida A. Serum tumour markers as a diagnostic and prognostic tool in Libyan breast cancer. *Tumour Biol.* 2012 Dec;33(6):2371-7. doi: 10.1007/s13277-012-0500-6.
18. Dai D, Chen B, Tang H, Wang B, Zhao Z, Xie X, et al. Nomograms for predicting the prognostic value of pre therapeutic CA15 3 and CEA serum levels in TNBC patients. *PLoS One.* 2016 Aug 25;11(8):e0161902. doi: 10.1371/journal.pone.0161902.
19. Lee JS, Park S, Park JM, Cho JH, Kim SI, Park BW. Elevated levels of preoperative CA15-3 and CEA serum levels have independently poor prognostic significance in breast cancer. *Ann Oncol.* 2013 May;24(5):1225-31. doi: 10.1093/annonc/mds604.
20. Mahmood ES, Majeed MI, Taha IG. Estimation of serum tumor markers and some biochemical parameters of breast cancer patients. *Chemist.* 2023;94.
21. Shao Y, Sun X, He Y, Liu C, Liu H. Elevated levels of serum tumor markers CEA and CA15 3 are prognostic parameters for different molecular subtypes of breast cancer. *PLoS One.* 2015 Jul 24;10(7):e0133830. doi: 10.1371/journal.pone.0133830.
22. Ren HY, Sun LL, Li HY, Ye ZM. Prognostic significance of serum alkaline phosphatase level in osteosarcoma: a meta analysis of published data. *Biomed Res Int.* 2015;2015:160835. doi: 10.1155/2015/160835.
23. Hao H, Chen L, Huang D, Ge J, Qiu Y, Hao L. Meta-analysis of alkaline phosphatase and prognosis for osteosarcoma. *Eur J Cancer Care (Engl).* 2017 Sep;26(5). doi: 10.1111/ecc.12536.
24. Li D, Lv H, Hao X, Hu B, Song Y. Prognostic value of serum alkaline phosphatase in the survival of prostate cancer: evidence from a meta-analysis. *Cancer Manag Res.* 2018 Aug 30;10:3125-3139. doi: 10.2147/CMAR.S174237.
25. Mori K, Janisch F, Parizi MK, Mostafaei H, Lysenko I, Enikeev DV, et al. Prognostic value of alkaline phosphatase in hormone sensitive prostate cancer: a systematic review and meta analysis. *Int J Clin Oncol.* 2020 Feb;25(2):247-57. doi: 10.1007/s10147-019-01578-9.
26. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer.* 2007 Sep;7(9):684-700. doi: 10.1038/nrc2196.
27. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* 2014 May;14(5):342-57. doi: 10.1038/nrc3691.
28. Welsh J. Vitamin D and breast cancer: insights from animal models. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1721S-4S. doi: 10.1093/ajcn/80.6.1721S.
29. Lopes N, Sousa B, Martins D, Gomes M, Vieira D, Veronese LA, et al. Alterations in vitamin D signalling and metabolic pathways in breast cancer progression: a study of VDR, CYP27B1 and CYP24A1 expression in benign and malignant breast lesions. *BMC Cancer.* 2010 Sep 11;10:483. doi: 10.1186/1471-2407-10-483.
30. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. *Breast Cancer Res Treat.* 2010 Jun;121(2):469-77. doi: 10.1007/s10549-009-0593-9.
31. Edwards CM, Johnson RW. From good to bad: the opposing effects of PTHrP on tumor growth, dormancy, and metastasis throughout cancer progression. *Front Oncol.* 2021 Mar 22;11:644303. doi: 10.3389/fonc.2021.644303.
32. Yin JJ, Selander K, Chirgwin JM, Dallas M, Grubbs BG, Wieser R, et al. TGF β signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development. *J Clin Invest.* 1999 Jan;103(2):197-206. doi: 10.1172/JCI3523.
33. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;350:1655-64. doi: 10.1056/NEJMra030831.
34. Ban J, Fock V, Aryee DNT, Kovar H. Mechanisms, diagnosis and treatment of bone metastases. *Cells.* 2021 Oct 29;10(11):2944. doi: 10.3390/cells10112944.
35. Brown RB, Bigelow P, Dubin JA, Mielke JG. High dietary phosphorus is associated with increased breast cancer risk in a U.S. cohort of middle aged women. *Nutrients.* 2023 Aug 25;15(17):3735. doi: 10.3390/nu15173735.
36. Alobaidy NA, Ali HH, Mohammad AT. Associations of vitamin D, calcium, magnesium and phosphorus with pre and postmenopausal breast cancer patients in Iraqi women. *Onkol i Radioter.* 2023;17(11):1-5.