RESEARCH ARTICLE

Editorial Process: Submission:03/10/2025 Acceptance:09/09/2025 Published:09/13/2025

Osteoprotegerin as a Potential Biomarker for Breast Cancer: A Study of Its Relationship with Bone Health, vitamin D, and Calcium Levels

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Abstract

Background: Breast cancer continues to be a significant global health issue and is associated with various biological indicators, including osteoprotegerin (OPG), a glycoprotein involved in bone metabolism, tumor progression, and immunological modulation. This study examined the potential of OPG as a biomarker for breast cancer and its correlation with bone health, vitamin D levels, and calcium concentrations. **Objectives:** To quantify serum OPG levels in breast cancer patients and assess its viability as a diagnostic biomarker. In addition, to evaluate vitamin D levels due to their established correlation with an increased cancer risk in cases of deficiency. The study also examined parathyroid hormone (PTH) and calcium levels in breast cancer patients. **Methods:** Blood samples were obtained from female volunteers at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq (September 2023 – February 2024). The study comprised three cohorts: healthy controls (G1, n=40), newly diagnosed breast cancer patients (G2, n=45), and patients undergoing chemotherapy (G3, n=45). Serum concentrations of OPG, vitamin D, PTH, and calcium were quantified using ELISA methodologies. **Results:** No statistically significant variations in OPG levels were observed between the control and patient groups, indicating minimal bone resorption during the early stages of breast cancer. Vitamin D levels were markedly reduced in G2 compared with the control group, while G3 showed a modest increase in vitamin D levels attributable to supplementation. Increased PTH levels were observed in breast cancer patients, supporting prior research linking elevated PTH with increased cancer risk. No notable differences were found in serum calcium levels among the groups. **Conclusion:** Vitamin D and PTH levels are crucial in early-stage breast cancer development, underscoring the need for monitoring these factors and questioning the diagnostic efficacy of OPG alone.

Keywords: Breast Cancer- Osteoprotegerin- Parathyroid Hormone- Vitamin D

Asian Pac J Cancer Prev, **26 (9)**, 3399-3404

Introduction

Breast tumors are characterized by abnormal tissue growth and swelling and may be either benign or malignant. Malignant tumors result from the uncontrolled proliferation of abnormal cells, which can form clusters and metastasize to distant organs [1-2]. The incidence of breast cancer significantly increases after the third decade of life [3].

Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor superfamily (TNFRSF11B) and functions as a homodimeric glycoprotein. It is typically produced as a 55–62 kDa glycosylated monomer containing 401 amino acid residues [4]. OPG plays a vital role in various physiological processes, including bone metabolism, inflammation, immune regulation, and tumorigenesis [5]. By binding to TRAIL, OPG inhibits TRAIL-mediated apoptosis, thereby influencing cardiovascular disease, immune system development, mental health, diabetes, tumor progression, metastasis, and pregnancy prevention [6-7].

OPG regulates bone turnover by acting as a decoy receptor for RANKL, inhibiting its binding and preventing the differentiation of osteoclasts responsible for bone resorption [8]. OPG, expressed in various tissues, was initially studied in breast cancer for its role in reducing metastasis-associated bone degradation [9]. Recent findings suggest that breast tumor cells can produce OPG, promoting tumor growth and metastasis by enhancing angiogenesis and inhibiting TRAIL-induced apoptosis [10-11].

About 90% of vitamin D is synthesized in the

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skin through UV exposure, while dietary forms and vitamin D3 are transported to the liver for conversion to 25-hydroxyvitamin D [12]. Vitamin D deficiency in breast cancer patients may hinder chemotherapy and radiation efficacy, potentially inhibit apoptosis through autophagy, and affect gene transcription, hormone production, immune function, and cellular differentiation [13-14]. Multiple studies have reported an inverse relationship between vitamin D levels and various cancers, including breast, colorectal, lung, and renal malignancies [15]. Furthermore, vitamin D status has been correlated with breast cancer prognosis, including tumor stage, size, grade, and lymph node involvement [16].

Parathyroid hormone (PTH), also known as parathormone, is secreted by the parathyroid glands and regulates serum calcium levels through its actions on bone, kidneys, and intestines [17]. It is essential for bone remodeling and is secreted in response to hypocalcemia, stimulating osteoclastic bone resorption to restore calcium homeostasis [18]. In adults, 99% of total body calcium resides in mineralized tissues such as bones and teeth [19]. The fine-tuned regulation of serum calcium involves PTH, vitamin D (particularly 1,25(OH)2D3), and other factors [20-21]. When plasma calcium levels fall, PTH is secreted, promoting calcium reabsorption in the kidneys and intestines and mobilizing calcium from bones. These effects are counteracted by calcitonin and cortisol when calcium levels rise [22].

Given these physiological interconnections, this study aims to investigate the potential of OPG as a biomarker for early breast cancer detection, assess vitamin D levels in breast cancer patients due to its known association with tumorigenesis, and analyze calcium and PTH levels, given their regulatory relationship with vitamin D, to evaluate their role in cancer risk modulation.

Materials and Methods

This study was conducted at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq, from September 1, 2023, to February 1, 2024. Participants were divided into three groups: Group 1 (Control): 40 healthy women; Group 2 (Newly Diagnosed): 45 women with newly diagnosed breast cancer; and Group 3 (Chemotherapy-treated): 45 women undergoing initial chemotherapy treatment.

All participants were premenopausal women aged between 25 and 45 years. Diagnosis in the patient groups was confirmed through clinical examination and validated by cytological and histopathological analysis (fine-needle aspiration or mammography).

Blood samples were collected, and serum was separated and stored at -20 °C for analysis. The measured parameters included vitamin D, osteoprotegerin (OPG), parathyroid hormone (PTH), and calcium. All parameters were measured using ELISA and standard biochemical techniques.

The OPG kit used Sandwich-ELISA to determine OPG levels in samples. The MicroELISA strip plate was pre-coated with an antibody specific to OPG, and a horseradish peroxidase (HRP)-conjugated antibody was added to each well. The optical density (OD) was measured spectrophotometrically at 450 nm, and the concentration of OPG was calculated by comparing the OD values of the samples to the standard curve.

The kits also employed Microplate Enzyme Immunoassay to determine vitamin D levels, parathyroid hormone concentration, and calcium using the OCPC method. The OD value was proportional to the concentration of OPG in the samples.

Results

Osteoprotegerin (OPG)

In vitro studies on the role of OPG produced by breast tumor cells have demonstrated that OPG can block TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis [23]. Furthermore, in vivo studies have shown that OPG expression by breast tumors can promote tumor growth and metastasis. In addition, it has been shown that OPG stimulates endothelial cell survival and tube formation; thus, it may indirectly promote breast tumor progression through its impact on angiogenesis [24]. As shown in Table 1 and Figure 1, OPG levels did not differ

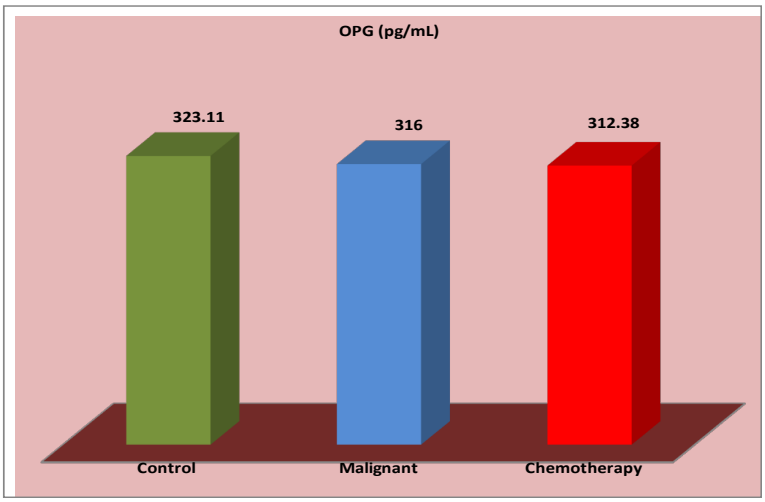

Figure 1. The Levels of Osteoprotegerine (OPG) in All Studied Groups

Table 1. Comparison of Osteoprotegerin (OPG) Levels between Control and Patient Groups

OPG	Group			P-value		
(pg/mL)	Con. (G1) N=40	Mal. (G2) N=45	Chem. (G3) N=45	G1 & G2	G1 & G3	G2 & G3
Mean ± SD	323.11 ± 104.73	316.0 ± 123.98	312.38 ± 109.02	0.941	0.919	0.998

Significant at P≤0.05 - Highly significant at P<0.001 - Non-significant at P>0.05

Table 2. Comparison of Vitamin D Levels between Control and Patient Group

Vitamin D (ng/mL)	Group			P-value		
	Con. (G1) N=40	Mal. (G2) N=45	Chem. (G3) N=45	G1 & G2	G1 & G3	G2 & G3
Mean ± SD	21.04±2.80	4.88 ± 1.67	8.98 ±1.43	0.001	0.001	0.001

Significant at P≤0.05 - Highly significant at P<0.001 - Non-significant at P>0.05

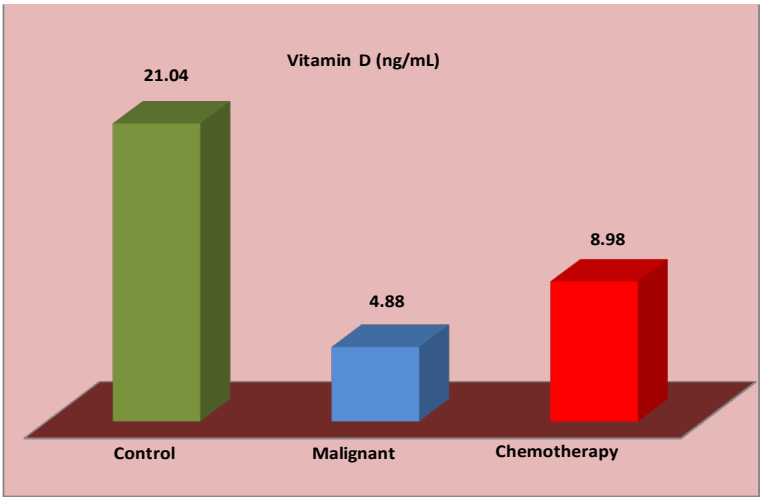

Figure 2. The Levels of Vitamin D in All Studied Groups

significantly among the three groups. This suggests that OPG may not serve as a reliable biomarker for early-stage breast cancer. The absence of significant elevation implies that bone resorption had not yet commenced in the early stages of the disease. While elevated PTH is often linked to bone metabolism, its increase in this context did not appear to influence OPG levels. Estrogen levels in premenopausal women may play a regulatory role in maintaining bone turnover within normal limits.

Vitamin D

Vitamin D enhances cancer cell death, while calcitriol stimulates apoptosis, generates reactive oxygen species, disrupts mitochondria, and promotes cytochrome C release in cancer patients [25]. Calcitriol's suppressive effects on invasion and metastasis may be due to its potent antiangiogenic activity, which could contribute to its role in inhibiting these processes [26]. Vitamin D's anti-inflammatory mechanism involves mediators such as cytokines, chemokines, prostaglandins, and reactive oxygen and nitrogen species in tumor tissue [27]. Severe vitamin D reduction in patients predicts increased estrogen receptor and aromatase expression, leading to greater disease incidence, consistent with the current study.

Research suggests that angiogenesis, the process of generating new blood vessels from existing vasculature, is a crucial step in tumor progression and metastasis [28]. The Vitamin D Receptor (VDR) affects cell cycling, proliferation, differentiation, and apoptosis through 1,25(OH)2D directly or indirectly in various cells and tissues [29]. Table 2 and Figure 2 demonstrate a highly significant reduction in 25-hydroxyvitamin D levels in breast cancer patients, particularly in the newly diagnosed group (G2), compared with the control group (G1). The chemotherapy group (G3) showed slightly higher levels due to early-stage vitamin D supplementation as part of their treatment protocol. Vitamin D deficiency is known to contribute to carcinogenesis by impairing apoptosis, promoting angiogenesis, and inducing immune dysregulation.

Parathyroid Hormone (PTH)

This study indicates that the carcinogenic effect of PTH increases the risk of breast cancer. Previous cohort studies support these results, showing an association between higher levels of PTH and breast cancer risk [30]. The current study also found an increased risk of breast cancer in women with hyperparathyroidism, contradicting a meta-analysis that found no significant association between hypoparathyroidism and breast cancer risk [31]. The parathyroid glands regulate calcium and phosphorus levels by secreting PTH, which stimulates the conversion of 25-hydroxy vitamin D into 1,25-dihydroxy vitamin D (calcitriol). PTH indirectly increases 1α-hydroxylase

Table 3. Comparison of Parathyroid Hormone PTH Levels between Control and Patient Groups

Parameters PTH	Group			P-value		
(pg/mL)	Con. (G1) N=40	Mal. (G2) N=45	Chem. (G3) N=45	G1 & G2	G1 & G3	G2 & G3
Mean ± SD	68.52 ± 20.44	167.79 ± 35.21	136.52 ± 58.56	0.001	0.001	0.779

Significant at P≤0.05 - Highly significant at P<0.001 - Non-significant at P>0.05

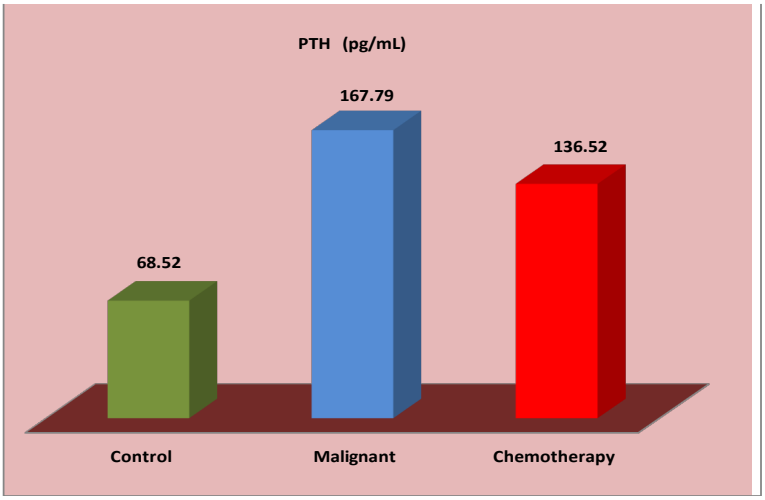

Figure 3. The Levels of PTH in All Studied Groups

activity, releasing vitamin D into the circulation and stimulating calcium uptake from the intestine [32].

According to Table 3 and Figure 3, PTH levels were significantly higher in both patient groups (G2 and G3) compared with the control group (G1), with no significant difference observed between the patient groups themselves. The increase in PTH appears to be a physiological response to decreased vitamin D and calcium levels. However, elevated PTH has also been implicated in promoting tumor growth and cancer progression. This finding is consistent with previous cohort studies linking hyperparathyroidism with increased breast cancer risk, although some meta-analyses report conflicting results.

Discussion

Calcium

Evidence suggests that calcium exerts at least part of its anticarcinogenic effects through vitamin D. For example, calcium is one of the key mediators of apoptosis

Table 4. Comparison of Calcium Levels between Control and Patient Groups

Calcium (mg/dL)	Group			P-value		
	Con. (G1) N=40	Mal. (G2) N=45	Chem. (G3) N=45	G1 & G2	G1 & G3	G2 & G3
Mean ± SD	9.28 ± 0.43	9.23 ± 0.38	9.21 ± 0.45	0.866	0.78	0.986

Significant at P≤0.05 - Highly significant at P<0.001 - Non-significant at P>0.05

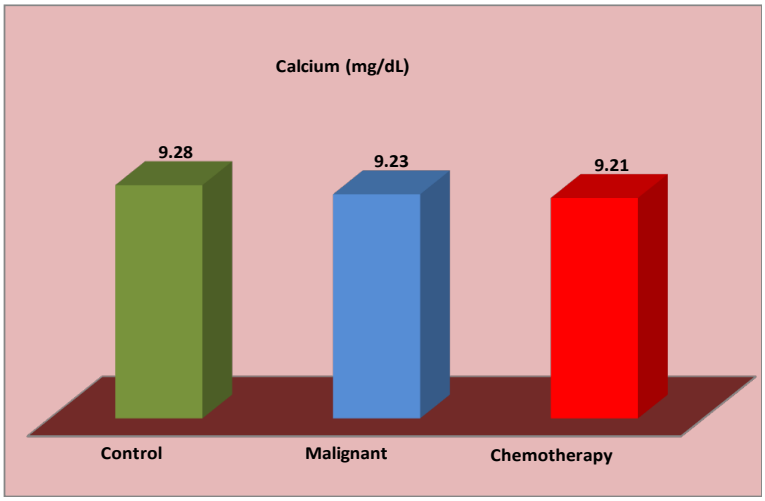

Figure 4. The Levels of Calcium in All Studied Groups

induced by vitamin D compounds in breast cancer cells [33]. Calcium has also been shown to reduce fat-induced mammary cell proliferation by maintaining intracellular calcium concentration [34]. Moreover, vitamin D and calcium are metabolically interrelated and highly correlated dietary factors that may influence breast cancer risk through a variety of shared or independent mechanisms [32]. A case-control study found a positive association between calcium concentrations in benign breast tissue and subsequent breast cancer risk, while another study reported that increasing extracellular calcium concentrations released the growth inhibition of 1,25(OH)D on breast cancer cells [33].

When blood calcium levels fall, the parathyroid glands respond by releasing additional PTH to restore calcium levels to normal [35]. High parathyroid hormone levels cause calcium release from bone into the bloodstream, leading to hypercalcemia and osteoporosis [36]. Low vitamin D levels lead to high PTH levels, increasing calcium concentrations, which have been linked to benign tumors and elevated breast cancer risk [37]. As shown in Table 4 and Figure 4, serum calcium levels did not differ significantly among the study groups and remained within normal physiological ranges. This suggests that calcium homeostasis was maintained despite the observed vitamin D deficiency and elevated PTH. In early-stage breast cancer, compensatory mechanisms such as enhanced calcium absorption in the gut and reabsorption in the kidneys mediated by PTH may prevent bone resorption. Moreover, calcium plays a key role in vitamin D-induced apoptosis and regulation of cellular proliferation, which may be relevant to breast cancer pathophysiology.

In conclusion, this study assessed the use of OPG, vitamin D, calcium, and PTH as biomarkers in breast cancer. Vitamin D deficiency was strongly associated with breast cancer, while PTH was significantly elevated, potentially contributing to tumor development. These findings emphasize the importance of vitamin D and PTH in breast cancer risk and progression. Although OPG may not serve as a useful standalone biomarker for early detection, its potential role in advanced disease stages warrants further investigation. Additional research is also required to clarify the long-term implications of vitamin D deficiency and elevated PTH on breast cancer prognosis and therapeutic response.

Author Contribution Statement

Shahad A. Jarallah conceived the study; Ali Abdul Rasool Hussein and Ola H Fadhil collected and analyzed data; Nuha Majeed Farhan contributed to the statistical analysis and manuscript writing. All authors reviewed and approved the final version.

Acknowledgements

The authors would like to thank the Oncology Teaching Hospital in Medical City, Baghdad, for its valuable contribution to sample collection, and Al-Mustansiriyah University for its support in the analysis of the results.

Ethical approval

Ethical approval was obtained from the Scientific Committee of the College of Medicine, Al-Mustansiriya University.

Conflict of interest

The authors declare no conflict of interest

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