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# Low vitamin D level increases women's breast cancer risks, Sulaimaniyah, Iraq: A case-control study

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**ABSTRACT**

Vitamin D (Vit D) is essential in maintaining calcium homeostasis and other body processes. It has been widely studied how Vit D affects cell cycle pathways and how it affects the development and prevention of breast cancer (BC). This study aimed to determine Vit D insufficiency linkage to the development of BC. In this case-control study, 130 women (65 BC patients and 65 healthy controls) aged 20–60 years who visited Shar Hospital Breast Center in Sulaimaniyah, Iraq, from December 2021 to May 2022 were included. Patients were selected after their diagnosis had been verified by breast ultrasound, mammography, and core biopsy. The ELISA test was used to measure the concentrations of serum Vit D and expressed in ng/ml. The results showed that the BC patients had considerably lower serum Vit D levels that were <20 ng/L in 66.1% (n=43) and 43.1% (n=28) in healthy controls. Compared to the control group (20.2±8.7), the mean Vit D level in BC patients was lower (17.8±8.6). A logistic regression test revealed a substantial increase in the risk of BC for low-level Vit D concentrations below 20 ng/L (OR 2.59, 95% CI 1.24-5.38; P=0.009). Vit D is still a significant risk factor for boosting the likelihood of developing BC after age and body mass index (BMI) adjustments (AOR 2.30, 95% CI 1.1-4.86; p=0.03 and AOR 3.67, 95% CI 1.55-8.7; p=0.002 for BC patients and controls, respectively). According to the outcomes of our investigations, we concluded that Vit D insufficiency raises the risk of BC among women in Sulaimaniyah, Iraq.

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## Introduction

Fat-soluble Vit D is essential to maintain healthy human physiology, and its insufficiency is prevalent worldwide (1). In addition, it may protect against autoimmune illnesses, cancer, heart disease, fractures, type 2 diabetes, and depression (2). Two modes of Vit D production exist: ergocalciferol (D2) and calciferol (D3). The first is derived from dietary sources, including fatty fish, vegetables, and dairy products. When skin is exposed to UV-B radiation, 7-dihydroxycholesterol (Cholecalciferol), a precursor to Vit D3, is produced. The generation of 90% of Vit D beneath the skin occurs endogenously (3).

The Vit D-binding protein transports the 25(OH)D into the bloodstream, which is further processed in the kidneys to form 1,25(OH)2D. The active form of Vit D, 1,25(OH)2D, has a half-life of 4-6 hours, while the half-life of 25(OH)D is 2-3 weeks. Thus, the latter is used as a biomarker to assess blood Vit D levels (4). Vit D deficiency is a potential risk factor for general mortality in the population; thus, it is a major public health distress (5)

The opinions about the serum levels of Vit D are different according to the recommendations of various medical associations (6). According to the Institute of Medicine's recommendations, Vit D insufficiency is risky if the concentration is <30 nmol/L, inadequate at levels between 30-50 nmol/L, and sufficient at≥50 nmol/L. Contrarily, the Endocrine Society recommendations set a threshold value for Vit D insufficiency of 50 nmol/L and the necessary quantity of >75 nmol/L (7).

Age, family history, breast tissue density, parity, obesity, drinking alcohol, and genetic risk factors, including BRCA mutations, are recognized and established risk factors for BC. Vit D receptor (VDR) polymorphism genes have been linked to an increased risk of BC (2). The regulation of calcium transport during breast-feeding, hormone production, and milk ejection are all critical functions of VDR genes in the mammary gland (8). Numerous initiatives and extensive research have been made to pinpoint Vit D deficiency as a risk factor for BC that should be addressed for cancer prevention. The relation between Vit D deficiency and BC development might be due to that estrogen receptor modulators, tamoxifen, raloxifene, and aromatase inhibitors, which alter the carcinogenesis process, have high toxicity and are ineffective against aggressive estrogen receptor-negative (ER-) BC (9).

According to preclinical research, the cell cycle, inflammatory pathways, and estrogen pathways interact with the Vit D pathway in healthy mammary tissue. As a result, Vit D inhibits cell proliferation while promoting apoptosis

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and cell differentiation in breast tumour tissue (10). Since adequate Vit D levels are linked to a lower risk of BC, this case-control study sought to determine whether low serum Vit D levels are linked to aggressive BC.

## Materials and Methods

### Patients and study setting

In this case-control-hospital-based study, 130 women (65 BC patients and 65 healthy controls) aged 20–60 who visited Shar Hospital Breast Center, Sulaimaniyah, Iraq, from December 2021 to May 2022 were included. At Shar Hospital Breast Center, BC, patients were chosen after their diagnosis had been verified by breast ultrasound, mammography, and core biopsy. At the same time, healthy control women were selected when they visited for normal check-ups and follow-ups.

### Inclusion criteria

Women aged 20-60 years diagnosed with BC, regardless of their BC grade and stage and those patients without comorbidity were included in this study.

### Exclusion criteria

Women who were pregnant, elderly, nursing mothers, and those who had another type of cancer and those receiving chemotherapeutic drugs were excluded.

### Questionnaire

From the reports of the BC patients, the histopathological diagnosis of BC, grade/stage of the tumor, and hormone receptor type (estrogen receptor-ER/progesterone receptor-PR) were collected using a standard/validated questionnaire. Simultaneously, sociodemographic data of the participants were collected, including age, residency, occupation, education level, marital status, as well as height in meters and weight in kilograms were determined to find body mass index (BMI; $kg/m^2$).

### Study protocol

The serum Vit D level was measured for each BC patient at their first visit. Therefore, we acknowledged a Vit D level inadequacy of 20 ng/L following the National Institutes of Health/Office of Dietary Supplements (ODS) (11).

### Statistical analysis

Epi Data version 4.0 was used to input the data, while Stata version 12 was used to analyze the variables. Descriptive numerical variables were presented as frequencies, percentages, means, and standard deviations. The Chi-square test was used to compare categorical variables, and logistic regressions were calculated to determine potential risk. A P-value of ≤0.05 is deemed to be statistically significant.

## Results

The participant's sociodemographic information and Vit D level about BC incidence are presented in Table 1. When compared to controls, the BC patients had considerably lower serum Vit D levels that were <20 ng/L in 66.1% (n=43) and 43.1% (n=28) in healthy controls.

**Table 1.** The socio-demographics and risk variables for participants.

| Variable | Cases Frequency (%) | Controls Frequency (%) | $\chi 2$ | P-value |
|---|---|---|---|---|
| **Vitamin D level (ng/L)** | | | | |
| Normal (<20) | 22 (33.9) | 37 (56.9) | 6.98 | 0.008* |
| Deficient (>20) | 43 (66.1) | 28 (43.1) | | |
| **Age group (Year)** | | | | |
| <25 | 13 (20.3) | 25 (38.5) | | 0.04* |
| 26-35 | 9.0 (14.1) | 11 (16.9) | 6.4 | |
| ≥35 | 42 (65.6) | 29 (44.6) | | |
| **Residence** | | | | |
| Inside City | 25 (38.5) | 49 (75.4) | | <0.0001* |
| Outside city | 40 (61.5) | 16 (24.6) | 18.1 | |
| **Occupation** | | | | |
| Employed | 11 (16.9) | 14 (21.5) | | 0.5 |
| None employed | 54 (83.1) | 51 (78.5) | 0.45 | |
| **Education level** | | | | |
| Educated | 38 (58.5) | 57 (87.7) | | <0.0001* |
| None educated | 27 (41.5) | 8.0 (12.3) | 14.11 | |
| **Marital status** | | | | |
| Married | 50 (76.9) | 36 (55.4) | | 0.009* |
| Unmarried | 15 (23.1) | 29 (44.6) | 6.7 | |
| **BMI ($Kg/m^2$)** | | | | |
| Normal weight | 12 (23.5) | 11 (22.5) | | |
| Overweight | 31 (60.8) | 22 (44.9) | | 0.1 |
| Obese | 8.0 (15.7) | 16 (32.6) | 4.2 | |

*: Significant difference.

Only 33.9% (n=22) of the BC patients and 56.9% (n=37) of the healthy controls had normal serum Vit D levels (p=0.008) ($\chi2$=6.98). Out of 65 BC patients, 13 (20.3%) were aged <25 years, 9 (14.1%) were 26-35 years, and 42 (65.6%) were >35 years. Regarding the healthy controls, 25 (38.5%) were aged <25 years, 11 (16.9%) were 25-36 years, and 29 (44.6%) were ≥35 years. There was a significant relation ($\chi2$=6.4, p=0.04) between the participant's ages of both groups. Additionally, there was relationship between the two groups in terms of women's residence ($\chi2$=18.1, p≤0.001), education levels ($\chi2$=14.11, P≤0.001), and married status ($\chi2$=6.7, p=0.009). However, there was no significant relation between occupation ($\chi2$=0.45, p=0.5) and BMI ($\chi2$=4, P=0.1) between the two groups (Table 1).

Additionally, the average age was 32.8±7.7 for BC patients and 32.0±8.4 for healthy controls (p=0.7), while the BMI for BC patients was 27.4±2.9 kg/m$^2$ and for the healthy controls was 28.01±4.9 kg/m$^2$ (p=0.5) (Table 2).

Among the studied women, 45.4% of them had normal Vit D levels, and 54.6% were deficient, with the lowest value of 3.0 ng/ml and a high value of 43 ng/ml, and the mean Vit D value among participants was 18.99±8.8 ng/ml (Table 3). There was a significant relation in Vit D levels between BC patients and healthy controls. BC patients had significantly lower mean Vit D levels (17.8±8.6 ng/ml) than controls (20.2±8.7 ng/ml) (p=0.01) (Table 4).

Table 5 shows Vit D level and other risk factors for BC using logistic regression. The greatest significant risk factor for BC identified was low levels of Vit D (<20 ng/L) (OR 2.59, 95% CI 1.24-5.38; p=0.009). Vit D is still a significant risk factor for boosting the likelihood of developing BC after age and BMI adjustments (AOR 2.30, 95% CI 1.1- 4.86; p=0.03 and 3.67, 95% CI 1.55-8.7; p=0.002, respectively) (Table 6).

## Discussion

In this study, the highest rate of BC was found in patients aged ≥35 years (65.6%) who lived outside of Sulaimaniyah city (61.5%), were not employed (83.1%), had a degree (58.5%), married (76.9%), and over-weighed (60.8%). All these data were significantly associated (p≤0.05) with those found in healthy controls except for BMI and occupation (p≥0.05). These outcomes are controversial to other studies in the same field conducted in various countries (12-14).

**Table 2.** Distribution of participants according to age and body mass index (BMI).

| Variable | Case Mean±SD | Control Mean±SD | P-value |
|---|---|---|---|
| **Age (Year)** | 32.8±7.7 | 32±8.4 | 0.7 |
| **Weight (Kg)** | 74.4±9.1 | 73.2±11.6 | 0.5 |
| **Height (m)** | 1.6±0.06 | 1.6±0.6 | 0.07 |
| **BMI (Kg/m$^2$)** | 27.4±2.9 | 28.01±4.9 | 0.5 |

**Table 3.** Mean distribution of the research population's vitamin D levels.

| Vitamin D amount | Number (%) | Average value Mean±SD | Minimum amount | Maximum amount |
|---|---|---|---|---|
| **Standard value (>20 ng/L)** | 59 (45.4) | 18.99±8.8 | 3.0 | 43 |
| **Deficit (<20 ng/L)** | 71 (54.6) | | | |
| **Total** | **130** | | | |

**Table 4.** Shows the average vitamin D levels for patients and controls.

| Group | No. | Serum Vitamin D Mean±SD | 95% CI | P-value |
|---|---|---|---|---|
| **Case** | 65 | 17.8±8.6 | 15.6 -19.91 | 0.01 |
| **Control** | 65 | 20.2±8.7 | 18.1 - 22.4 | |
| **Total** | **130** | | | |

**Table 5.** Possible risk factors linked to an increase in women's chance of developing breast cancer.

| Factor | OR (95% CI) | Chi-square | P-value |
|---|---|---|---|
| **Vitamin D deficiency** | | | |
| No | 1.0 | 6.9 | |
| Yes | 2.59 (1.24-5.38) | | 0.009* |
| **Age group (Year)** | | | |
| <25 | 1.0 | | |
| 26-35 | 0.63 (0.21-1.95) | 0.4 | 0.04* |
| <35 | 0.35 (0.15-0.84) | 0.01 | 0.01* |
| **BMI (Kg/m$^2$)** | | | |
| Normal weight | 1.0 | | |
| Overweight | 0.77 (0.61-2.08) | 0.6 | 0.1 |
| Obese | 2.19 (0.64-7.34) | 0.2 | 0.2 |

*: Significant difference.

**Table 6.** Adjusted odds ratio and 95% CI for the factors that raise the risks of breast cancer.

| Factor | AOR (95% CI) | Chi-square | P-value |
|---|---|---|---|
| **Vitamin D adjusted for age** | | | |
| Yes | 1.0 | | |
| No | 2.30(1.1-4.9) | 4.9 | 0.03* |
| **Vitamin D adjusted for BMI** | | | |
| Yes | 1.0 | | |
| No | 3.67(1.6-8.7) | 8.3 | 0.002* |

*: Significant difference.

According to our findings, Vit D insufficiency was found in 66.1% of BC survivors and 43.1% of healthy women, with significant differences between them. These results agreed with that of Shaukat et al. 2017 in Pakistan, who detected that 88.7% of BC patients and 55.8% of controls had Vit D insufficiency (12). Also, a study by Imtiaz and Siddiqui, 2014 found that Vit D deficiency in 99% of BC victims and 90% of healthy females (15). These deficiencies in women might be due to insufficient diets rich with Vit D, not exposing sufficiently to the sun, and screening regularly for Vit D levels.

Moreover, in this research, BC patients had considerably lower mean serum Vit D levels (17.8±8.6) than healthy controls (20.2±8.7). Our results are consistent with those conducted by Karthikeyan et al. 2018 in India (22.33±8.19 ng/mL for BC patients vs. 37.41±12.9 ng/mL for healthy controls; p=0.0001) (16), as well as research from Pakistan by who found the mean serum Vit D of 9.6±5.0 ng/mL and 15.2±10.0 ng/mL for BC patients and healthy controls, respectively (15). Furthermore, another systematic review at Tehran Medical University, Iran, concluded that Vit D deficiency has been more prevalent in BC patients than in comparable matched control populations, and the risk of BC has increased with low Vit D levels (17).

Furthermore, according to our logistic regression analysis, Vit D insufficiency was a more significant risk factor for developing BC (2.59 95% CI 1.24-5.38; p=0.009). Our research's findings concur with those of a case-control study conducted on China's population, which indicated women with the highest quartile Vit D level showed a significantly decreased BC risk (Q4 vs Q1: OR=0.10, 95% CI=0.06–0.15) and every 1.0 ng/mL increment of plasma Vit D level led to a 16% lower odds of BC (OR=0.84, 95% CI=0.81–0.87; P<0.001) (18). Also, another study conducted by Shamsi et al. 2020 in Pakistan indicated that women with low serum Vit D (<20 ng/mL) had a higher risk of BC (OR = 1.65, 95%CI: 1.10, 2.50), while those with a history of Vit D supplementation one year before enrollment, had a significant protective effect against BC (OR = 0.32, 95% CI: 0.24, 0.43) (14). Hence, Vit D remained the higher risk factor for raising the likelihood of BC even after we adjusted it for the women's age and BMI (AOR 2.3, 1.1-4.68; p=0.03 vs 3.67, 1.55-8.7; p=0.002, respectively).

Even though increased weight significantly did not affect the likelihood of developing BC, 60.8% of BC patients and 44.9% of healthy controls were overweight. These findings are similar to those of Yerushalmi et al. 2017 in Israel, who found that BMI negatively impacted the likelihood of developing BC (19). Similarly, research conducted in Canada by Quail and Dannenberg in 2019 found that weight gain affects the possibility of BC development and progression (20) and another study in the USA by Bernard and Wellberg in 2021 (21). Finally, our research showed that being older does raise the chance of developing BC, which is at odds with other studies (22, 23).

Thus, the research on the environmental elements that raise the chance of developing BC should be done with different methods for measuring Vit D levels.

## Conclusions

In conclusion, patients with BC had much greater rates of Vit D insufficiency than healthy controls. There are direct relations between Vit D deficiency and age groups, while no relation was found with BMI. There are limitations to this study, including a small sample size, short duration of study, and not enough laboratory tests; therefore, more research is needed to back up our findings.

## Declarations

### Ethical approval and consent to participate

The Technical College of Health's scientific and ethical committees revised and approved the research protocol (No. 22/10/02/2020-CoH), while the Breast Center at Shar Hospital confirmed IBR. On the other hand, written informed consent to participate in this study was obtained from participants and they were left free to quit the study at any time without giving a declaration. All works in this study were complied with the guidelines for human studies and conducted ethically by the World Medical Association Declaration of Helsinki.

### Consent for publication

Not applicable.

### Availability of data and materials

Data are available with the corresponding author and can be provided upon request.

### Competing interests

The authors declared that there is no conflict of interest in this manuscript.

### Funding

No fund was obtained to conduct this study from any agency or organization.

### Authors' contributions

Mardin Othman Abdulqadir: Conceptualization and data collection with writing the original manuscript. Niaz Mus-

tafa Kamal: Data analysis, validation, resources and writing the original manuscript. Heshu Sulaiman Rahman: Figuring out and creating tables, manuscript correction, revision, edition, and submission.

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