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Vitamin D status and risk for breast cancer in Kenya

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Abstract

Background Vitamin D plays a critical role in bone metabolism, calcium regulation, and various cellular processes, including those linked to cancer. The biologically active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], works through the Vitamin D Receptor (VDR). Polymorphisms in VDR and related genes have been associated with cancer risk, including breast cancer. This case-control study aimed to investigate the relationship between serum vitamin D levels and breast cancer among Kenyan women.

Methods Serum 25-hydroxyvitamin D [25(OH)D] levels were measured in 112 breast cancer patients and 106 controls using electrochemiluminescence.

Results Results indicated that 81.2% of participants had deficient or insufficient vitamin D levels, with controls showing slightly higher sufficient levels compared to cases. Although previous studies suggested an association between higher vitamin D levels and reduced breast cancer risk, our findings revealed no significant link between vitamin D levels and various demographic factors, including BMI.

Conclusion The study underscores the need for public awareness about vitamin D supplementation and further research to clarify the role of vitamin D in breast cancer development, particularly in populations with widespread vitamin D deficiency.

Keywords Vitamin D, Breast cancer

Background

Vitamin D is involved in various physiological processes, including bone metabolism, calcium regulation, phosphorus metabolism in bones and intestines, cell proliferation and differentiation, apoptosis regulation, and modifying cancer risk [1]. Vitamin D from diet or sunshine is biologically inactive. Vitamin D is hydroxylated by the enzyme 25-hydroxylase to form 25-hydroxyvitamin D [25(OH)D] in the liver, also known as calcidiol. The 25-hydroxyvitamin D [25(OH)D] is converted to 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol in Kidney. This is the biologically active form of vitamin D. The 25(OH)D has a longer half-life and therefore it the one measured in serum for vitamin D levels. The 1,25(OH)2D works through Vitamin D Receptor (VDR) that works as a hormonal receptor in some cells by El-Shorbagy [1] linked prostate cancer to low levels to 25(OH)D Shaikh & Jamal [2] demonstrated that there could be a genetic link between polymorphisms in some metabolizing genes, such as adiponectin and VDR is found on chromosome 12 [3]. Low 25(OH)

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D and 1,25(OH)2D levels can be linked to mutations at various loci in VDR and has also been demonstrated in patients with high body mass index (BMI) [4]. A study by El-Shorbagy et al. [1], found the Single nucleotide polymorphisms (SNPs), ApaI and TaqI were linked to breast cancer among Egyptian women. Khan et al. and Voutsadakis [3, 5] had demonstrated similar findings.

Despite this, some studies, such as those by Huss [6] among women in Swedish registry and Vanhevel et al. [7] among several randomization studies, report conflicting results, showing no linear association between higher vitamin D levels and reduced breast cancer risk. Rosso et al. [8] demonstrated significantly low vitamin D levels in younger patients. Excessive weight, including obesity, is a known risk factor for chronic diseases, including malignancies [4, 9]. Obesity can modify the uptake and metabolism of vitamin D and its related components. VDR polymorphisms may affect lipid profiles, waist circumference, and visceral fat. Sufficient vitamin D levels in patients with breast malignancies have been shown to influence VDR gene variations, affecting visceral fat, lipid profiles, and waist circumference in breast cancer survivors. This suggests the potential categorization of patients who might benefit from vitamin D supplementation to improve overall cancer survival [10]. However, Vanlint [11] reported conflicting findings.

Methods

Study design and data collection

This was a case-control study in which blood serum was used to determine the levels of vitamin D in 112 cases and 106 controls. The study participants were recruited from Aga Khan University Hospital, Kijabe Hospital, Kenyatta National Hospital, and Moi Teaching and Referral Hospital. Blood samples were collected from 106 healthy female volunteers without evidence of breast cancer (controls) and 112 newly diagnosed females with breast cancer (cases). The inclusion criteria for the cases were newly diagnosed adult females with breast cancer at any stage, with no prior treatment intervention. Non-breast cancer patients visiting the health facilities for other reasons were recruited as controls. Exclusion criteria included patients on vitamin D and calcium supplements, those who had undergone neoadjuvant therapy, and pregnant or breastfeeding women. Baseline data collected included age, body mass index (BMI), residence, highest level of education, menopause status, parity, and family planning. Serum vitamin D levels (25-(OH) D) were determined in both cases and controls using an electrochemiluminescence method. Vitamin D levels were classified as deficient (< 20 ng/ml), insufficient (21–29 ng/ml), and sufficient (> 30 ng/ml).

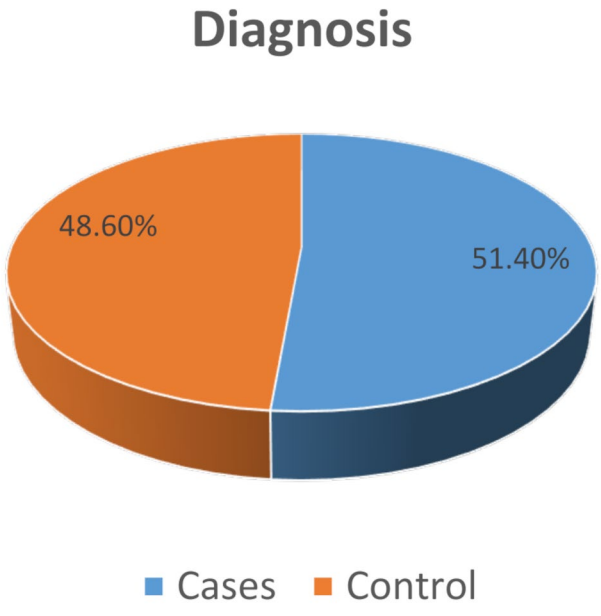

Fig. 1 Study participants' groups

Study setting

The study participants were recruited from Aga Khan University Hospital, Kijabe Hospital, Kenyatta National Hospital, and Moi Teaching and Referral Hospital.

Data management and analysis

All samples were analyzed at the Metropolis International Laboratory, known for its efficiency and standardized automated laboratory methods. Chemiluminescence microparticle immunoassay (CMIA) technology was utilized to determine vitamin D3 levels, with daily internal quality control performed at three levels using third-party Multichem controls (Techno-path Manufacturing Ltd., Ireland). A precision of 5% was maintained during analysis. The required sample size for a 95% two-sided confidence interval for the case-control study with 90% power to detect a risk ratio of 2 for breast cancer was calculated using Epi-info software (reference needed). Descriptive analysis was performed, including proportions and frequencies of demographic characteristics. Measures of dispersion, such as means, medians, and standard deviations for the study participants, were calculated. Finally, a chi-square test was conducted to determine the relationship between vitamin D levels and the risk of breast cancer.

Results

The study involved 218 participants, with 112 breast cancer cases and 106 controls as shown in Fig. 1.

Table 1 outlines the demographic characteristics and vitamin D levels of the 218 study participants, consisting of 112 cases and 106 controls. Notably, the actual participant numbers differed from the originally planned 1:1

Table 1 Demographical features of the study participants

Variable	*n*	%	Variable	*n*	%
Diagnosis			Family Planning Use		
Cases	112	51.4	Yes	156	71.6
Control	106	48.6	No	53	24.3
Total	218	100	Missing	9	4.1
Residence			Total	218	100
Urban	152	69.7	BMI		
Rural	57	26.1	Underweight	1	0.5
Missing	9	4.1	Normal	56	25.7
Total	218	100	Overweight	82	37.6
Highest Education			Obese	65	34.9
Primary	23	10.6	Missing	3	1.4
Secondary	27	12.4	Total	218	100
Tertiary	157	72.0	25(OH)D Levels		
Missing	11	5.0	Deficient	116	53.2
Total	218	100	Insufficient	61	28.0
Menopause			Sufficient	41	18.8
Yes	78	35.8	Total	218	100
No	136	62.4	Age Group		
Missing	4	1.8	< 35	39	17.9
Total	218	100	35–45	73	33.5
Parity			46–54	43	19.7
Null	37	17.0	55 & above	63	28.9
< 3	67	30.7	Total	197	100
≥ 3	105	48.2	Sufficient vitamin D levels		
Missing	9	4.1	Cases	28	68.2
Total	218	100	Controls	13	31.8

Table 2 Measures of dispersions of the study participants

Serum vitamin D (ng/ml	Median (SD)	Minimum	Maximum	Mean	SD
Cases	22.3	6.5	79.09	25.4 (14.4)	14.4
Control	19.1	8.5	72.39	21.8 (11.5)	11.5

ratio (110 cases and 110 controls) due to the loss of some records, particularly from external sources.

The findings reveal that a significant proportion of both cases and controls exhibited low serum 25-hydroxyvitamin D [25(OH)D] levels, with 81.2% of the participants falling into this category. Interestingly, contrary to previous studies, a higher percentage of controls (31%, $n = 33$) had sufficient vitamin D levels compared to cases (13%, $n = 15$). This observation indicates a potential disparity in vitamin D sufficiency between the two groups in our study population.

The majority of women in the study were under 55 years of age (71.1%), resided in urban areas (69.7%), and had attained a tertiary level of education (72%). Additionally, 62.4% were pre-menopausal, and nearly half (48.2%) had given birth to more than three children. Most of the participants were using family planning methods (71.6%), and a substantial proportion (72.5%) were either overweight or obese. The study found a mean of 25.4 (SD: 14.4) in cases and 21.8 (SD: 11.5) in controls according to Table 2.

Table 3 indicates that there were no significant associations between vitamin D levels and various demographic factors, such as body mass index (BMI), residence, educational attainment, menopausal status, parity, and family planning use. However, a statistically significant relationship was found between vitamin D levels and the diagnosis of breast cancer ($p = 0.049$).

Table 4 indicates that there was no statistically significant association between the age of patients and controls and their vitamin D levels.

Although in Table 3, we had stated that BMI had no association with vitamin D levels and the development of breast cancer, Fig. 2 shows that patients who had normal BMI 5 years ago and are now overweight and obese at the point of diagnosis had a higher risk of developing breast cancer compared to those who maintained normal weight ($p = 0.001$). In Fig 3 it is noted that obesity at the time of diagnosis did not impact the development of breast cancer (p=0.141).

Table 3 Comparison of mean 25(OH)D levels among different variables

Variable		*N*	Mean 25(OH)D Levels	Lower Bound	Upper Bound	ρ Value
BMI Level	Underweight	1	31.08			0.906
	Normal	56	23.67	19.8	27.5	
	Overweight	82	23.95	20.9	25.6	
	Obese	76	22.97	20.3	25.6	
Diagnosis	Cases	112	25.38	22.6	28.1	**0.049**
	Control	106	21.88	19.6	24.1	
	Total	218	23.67	21.9	25.4	
Residence	Urban	152	23.47	21.4	25.5	0.980
	Rural	57	23.42	19.7	27.1	
	Total	209	23.46	21.6	25.2	
Highest Education	Primary	23	22.42	17.1	27.7	0.861
	Secondary	27	22.97	18.9	26.9	
	Tertiary	157	23.86	21.7	26.0	
	Total	207	23.58	21.7	25.4	
Menopause	Yes	78	24.4	21.3	27.5	0.430
	No	136	22.9	20.7	25.1	
	Total	214	23.4	21.7	25.2	
Parity	Nil	37	24.0	18.6	29.4	0.838
	≤ 2	67	24.2	20.8	27.6	
	≥ 3	105	23.0	20.8	25.2	
	Total	209	23.6	21.8	25.4	
Family Planning	Yes	156	23.6	21.5	25.7	0.877
	No	53	23.3	19.5	27.1	
	Total	209	23.5	21.7	25.3	

Table 4 Association between vitamin D levels across the age groups

Age Group	Serum 25(OH)D Levels						
	Deficient		Insufficient		Sufficient		ρ Value
	n	%	*n*	%	*n*	%	0.592
< 35	24	20.7	8	13.1	7	17.1	
35–45	40	34.5	23	37.7	10	24.4	
46–54	22	19.3	13	21.3	8	19.5	
55 & above	30	25.9	17	27.9	16	39.0	
Total	116	53.2	61	28.0	41	18.8	

Discussion

The results highlight a widespread prevalence of low vitamin D levels across both breast cancer cases and controls, with 81.2% of participants exhibiting deficient or insufficient levels. This finding is consistent with some previous studies that have reported low vitamin D levels in similar populations, but it contrasts with others that have found higher vitamin D levels in controls compared to cases [3, 5, 6]. The difference in vitamin D sufficiency between cases and controls in this study may reflect variations in lifestyle, dietary habits, or sun exposure, although these factors were not directly measured. The study reported no statistically significant association between the age of patients and controls and vitamin D levels, although some studies have demonstrated significantly lower levels of vitamin D in younger patients [8]. The lack of significant associations between vitamin D levels and most demographic factors, such as BMI, residence, and education level, suggests that vitamin D deficiency may be a widespread issue across different population subgroups. However, the significant association between vitamin D levels and breast cancer diagnosis supports the hypothesis that vitamin D may play a role in breast cancer development or progression. This is in line with other research that has proposed a link between low vitamin D levels and increased breast cancer risk. While no significant relationship was found between age and vitamin D levels, it is noteworthy that the study did find a relationship between BMI changes and breast cancer risk, where women who were of normal weight five years ago and became overweight or obese had a higher risk of breast cancer. This finding aligns with research suggesting that obesity can influence vitamin D metabolism and contribute to chronic diseases, including cancer [4, 9]. Additionally, studies have shown that vitamin D receptor (VDR) polymorphisms may impact lipid profiles,

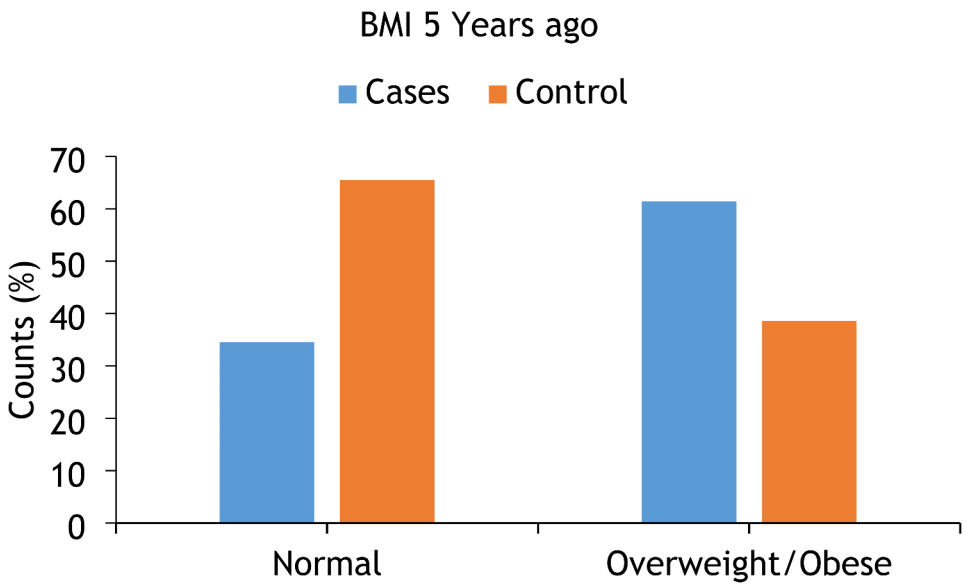

Fig. 2 Comparison of obesity among the participants' groups 5 years ago
ρ value = 0.001

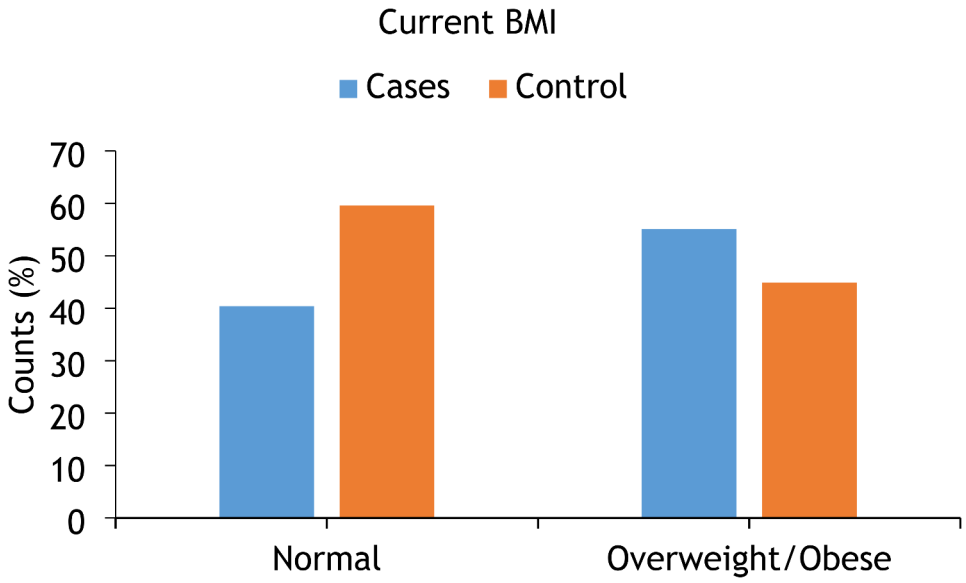

Fig. 3 Comparison of obesity among the participants' groups at recruitment
ρ value = 0.141

waist circumference, and visceral fat, further complicating the relationship between vitamin D and cancer risk [10]. Overall, while this study provides evidence of an association between low vitamin D levels and breast cancer, the widespread deficiency observed in both cases and controls complicates the interpretation of these results. Future research should consider investigating the underlying causes of vitamin D deficiency in this population and exploring the potential benefits of vitamin D supplementation in breast cancer prevention and management.

Recommendations

Future studies will incorporate dietary assessments, sun exposure surveys, and genetic profiling to control for any confounders. The next level of analysis of this work will include multivariable regression models to adjust for these variables.

We aim to include body composition analysis (DEXA scans, waist-to-hip ratios, or visceral fat measurements) to better understand the role of obesity and vitamin D metabolism in future studies.

Our next study will incorporate genetic testing for VDR polymorphisms, SNPs in vitamin D metabolism genes, and potential epigenetic modifications to provide a more comprehensive understanding of vitamin D's role in breast cancer.

Conclusion

Several case-control studies investigating the relationship between vitamin D levels and breast cancer development have reported that normal or elevated levels of vitamin D are associated with a reduced risk of breast cancer. In contrast, our study found that both cases and controls predominantly exhibited deficient or insufficient vitamin D levels. Notably, among the 18.8% of participants with normal or above-normal vitamin D levels, a greater proportion were breast cancer cases. Therefore, based on these findings, it is recommended that efforts be increased to raise public awareness about the importance of vitamin D supplementation for the general population. Additionally, further research is needed, with a larger sample size, to more comprehensively explore the relationship between vitamin D levels and the risk of breast cancer.

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Author contributions

RW, AM, prepared the protocol, supervised data collection and analysis. Also, they wrote the main manuscript, prepared tables and figuresVM, EM, FM, RA, PB supervised the research work and reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by Aga Khan University Ethical Review Committee (ISERC) (Ref No: 2018/Rec-82(v3)) and the KNH-UoN Ethics and Research Committee (Ref No: KNH-ERC/A/378). The study adhered to ethical guidelines throughout its implementation.

The research was conducted in accordance with the Declaration of Helsinki (2013), which outlines ethical principles for medical research involving human participants.

All participants provided written informed consent before inclusion in the study. For participants unable to provide consent, proxy consent was obtained from legal guardians, as approved by the ethics committee.

All data were anonymized to protect participants' confidentiality and privacy. Personal identifiers were stored separately from the research data and accessed only by authorized personnel.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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