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ISSN 2249-4863

Journal of Family Medicine and Primary Care

www.jfmpc.com

Official Publication of the Academy of Family Physicians of India

Volume 8 / Issue 5 / May 2019

jfmpc

Original Article

Serum vitamin D level, sun-exposed area, dietary factors, and physical activity as predictors of invasive breast cancer risk among Sudanese women: A case–control study

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Abstract

Background: The role of vitamin D in the development, progression, and prognosis of breast cancer, though widely studied worldwide, has been inconclusive. This study intended to assess the role of some factors (including serum vitamin D level, sun-exposed area, dietary factors, and physical activity) as predictors of the development of invasive breast cancer (IBC) among Sudanese women. **Methods:** A case–control study was conducted on 200 Sudanese women (100 with newly diagnosed IBC and 100 matched healthy females). Serum 25-hydroxyvitamin D was measured through a competitive electrochemiluminescence immunoassay. Matching analysis was adopted by R version 3.4.1 making use of the "MatchIt" package for calculating propensity scores to build a confounder-adjusted, multiple generalized, linear logistic regression model. **Results:** Participants' age ranged from 28 to 85 years with a mean [±standard deviation (SD)] of 48.10 (±12.11) years. The mean (±SD) serum vitamin D level was 12.97 (±8.60) and 13.79 (±6.79) ng/mL in breast cancer and noncancer Sudanese women, respectively [$P = 0.013$; odds ratio (OR) 0.862; 95% confidence interval (CI) 0.766–0.969; $\beta = 0.149$)]. Sun-exposed area ($P = 0.038$; OR 0.013; 95% CI 0.000–0.782; $\beta = 4.339$) is significantly and negatively associated with breast cancer development. While moderate physical activity ($P = 0.0008$; OR 2625.430; 95% CI 26.647–258673.001; $\beta = 7.873$) is significantly and positively associated with IBC risk. Occasional consumption of milk, dairy products, eggs, and fish reduces the risk of developing IBC by 78.1%, 75.0%, 78.4%, and 76.4%, respectively. **Conclusion:** The higher the plasma vitamin D level by one unit, the lower the risk of breast cancer by 13.84%. Sedentary lifestyle, reduced sun-exposed skin area, and low serum vitamin D levels can be considered as predictors of IBC. Encouraging moderate physical activity and consumption of certain foods may, in part, decrease the precipitating risks of breast cancer. More studies and research are needed to confirm these findings.

Keywords: Breast cancer, diet, physical activity, risk factors, Sudan, sun-exposed area, vitamin D

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Access this article online	
Quick Response Code:	Website: www.jfmpc.com
	DOI: 10.4103/jfmpc.jfmpc_197_19

How to cite this article: Husain NE, Suliman AA, Abdelrahman I, Bedri SA, Musa RM, Osman HE, *et al*. Serum vitamin D level, sun-exposed area, dietary factors, and physical activity as predictors of invasive breast cancer risk among Sudanese women: A case–control study. J Family Med Prim Care 2019;8:1706-14.

Background

Breast cancer is a leading cancer worldwide, accounting for 23% of all new cancer cases in women.[1] Its reported incidence rate was 13% in Northern America, 15% in Northern Europe, and 17% in Northern Africa.[1] In Sudan, breast cancer has an incidence rate of 25.1 per 100,000 making it the most prevalent cancer among women.[2] Unfortunately, in Sudan and other African countries, presentation is always late, especially in young women,[2] a matter which necessitates the search for factors other than the known clinical predictors which may guide the clinician for early detection and diagnosis of breast cancer, among which are enviromental and dietary factors.

Vitamin D (representing D2, D3, or both) is a secosterol created endogenously through exposure to ultraviolet light in the sun-unprotected skin or acquired from dietary vitamin D intake. Vitamin D proved to have numerous metabolic and natural capacities.[3] Several studies showed that sufficient 25-hydroxyvitamin D [25(OH)D] levels are essential for protection against several malignancies, including prostate, breast, ovarian, and colon cancer.[4-11] Conversion of 25(OH)D to 1,25 di-hydroxy vitamin D (1,25$(OH)_2$D) in healthy human cells in colon, breast, and prostate has been suggested to play a protective role against carcinogenesis through different mechanisms that include cellular maturation and apoptosis, and inhibiting angiogenesis through enhancing functions of some genes such as *P21* and *P27* to control cellular proliferation.[5-8,12-16] Since vitamin D regulates a range of physiologic procedures comprising modulation of the immune response, opposition to oxidative stress, and modulation of other hormones, it is not unexpected that low serum levels of 25(OH)D have been related to enhanced risks of numerous cancers and cancer mortalities including breast cancer.[12] A reverse correlation between serum 25(OH)D and the chance to develop breast cancer has been suggested by some observational and experimental[12-14] studies, even though the results from some ongoing cohorts of cancer mortality and some case–control studies have been inconsistent.[15-17]

A few studies have been published on 25(OH)D level in blood donors[18] or children,[19] but to the best of our knowledge, there are no published studies regarding 25(OH)D levels and its relation to breast cancer in African countries[18,20] or Sudan. Several cancer prediction models were established worldwide, whereas there was only one in Sudan by Salih *et al.* who developed a simplified tool to predict a woman's lifetime risks of developing breast cancer using a cross-sectional study.[17] They found that age, menarche, family history, and some types of food constituents (vegetables and fruits) act as predictors of breast cancer.[17] However, they did not include vitamin D, sun exposure, or other dietary elements.

This study aimed to address the association between 25(OH)D serum level, sun-exposed area, dietary factors, and physical activity with invasive breast cancer (IBC) risk in Sudanese women.

Methods

The study patients of this observational case–control study included 100 patients who attended the referred clinics at Khartoum Oncology Hospital and confirmed histologically to have IBC within 30 days of the histopathology reporting date. Another 100 cancer-free women were recruited from Family Health Centers (FHCs) in Khartoum State. The state of Khartoum is divided into seven localities with 41 referral FHCs at the time of the study.[19] The population resident in Khartoum state represents all states of Sudan but with variable proportions. Samples were taken in summer and autumn (April to October).

Pregnant and lactating women at the time of enrolment, use of any medication at the time of the study, use of vitamin D supplements, chronic illness or other malignancy, smoking, tobacco, or alcohol consumption, and patients who were diagnosed histopathologically >30 days were excluded. Patients whose blood samples underwent hemolysis were ultimately excluded as well from both cases and controls.

A purposively designed questionnaire was filled by well-trained investigators. Following the signing up of the informed consent, patients were kindly asked to donate 3 mL of venous blood. Red-cap (EDTA) vacutainers were used. Serum was separated immediately using a centrifuge and stored at −80°C till use.

Variables included information about sociodemographic data, known breast cancer risk factors, and vitamin D confounding factors (smoking, alcohol consumption, chronic illness such as renal failure, liver disease, diabetes mellitus, or other endocrine diseases). The use of treatment and having another malignancy were also questioned during the interview. Moreover, the questionnaire involved questions about important food and dietary factors (daily intake of milk, dairy products, fish, egg, and meat). Participants were questioned about their sun exposure hours, body area that is exposed, and use of sun protection (sunscreen) creams. The weight and height of patients were measured at the referred clinic or the Health Center, and the body mass index (BMI) was calculated.

Serum 25(OH)D was measured using the automated analyzer Elecsys 2010 (Roche Diagnostics, Germany) which in principle is a competitive electrochemiluminescence immunoassay (ECLIA). Safety and quality control measures were applied. Vitamin D measurements were categorized according to the Endocrine Society's Clinical Guidelines:[18] deficiency <20 ng/mL, insufficiency 20–29 ng/mL, sufficiency 30–100 ng/Ml, and toxicity >100 ng/mL.

Data were computerized and matched using propensity score matching method to match cases and controls. This is because of the substantial differences that exist in terms of the baseline characteristics between the cases and the control group across the background sociodemographic and clinical variables. We adopted the R version 3.4.1 making use of the "MatchIt" package for calculating propensity scores and performing the matching analysis. The model we built was a multiple generalized linear logistic regression model for the matched data.

Given the outcome variable is categorical, conditional logistic regression was used to calculate the matched odds ratio (OR) and 95% confidence intervals (CIs) for a univariable analysis, and then the independent variables with *P* value <0.05 were chosen for the multiple logistic regression models because using the traditional level (such as 0.05) often fails to identify variables known to be important. Of 130 patients and 251 cancer-free women, logistic regression was done for 200 (100 patients and 100 controls) for all variables under study following matching for the season with further exclusion of all confounding factors. The estimated slope coefficient (β) for univariate logistic regression model containing each variable was calculated. The regression coefficient (β) slope for each model term is the natural logarithm of the OR for that term, hence the estimated OR is the number e raised to the power of regression coefficient. When β >0, the odds and probability increase as the predictor (*x*) increases, and if β <0, the odds and probability decrease as *x* increases. If the entire 95% CI is above 1, this concludes positive association, and if the entire 95% CI is below 1, this concludes negative association. Chi-squared value for the full logistic regression model was 8.548 (*P* = 0.382), indicative of overall good-fit for the model to the data.

Results

In this case–control study, of 381 interviewed women, a total of 100 Sudanese patients with breast cancer and 100 matched apparently healthy Sudanese women from different localities in Khartoum State (1:1) were included.

The participants' age ranged from 28 to 85 years with a mean age [±standard deviation (SD)] of 48.10 (±12.11) years. About 65% of patients with breast cancer were 50 years or younger, and most of them were illiterate or had primary education level. Other sociodemographic characteristics and vitamin D levels of the study participants are shown in Table 1.

The mean vitamin D level in the control group was 13.79 ng/mL (SD = 6.79 ng/mL), which was higher than the mean vitamin D level in the cancer group [12.968 ng/mL, (SD = 8.60 ng/mL)]. The association between vitamin D and the risk of cancer was statistically significant in the logistic regression model [Figure 1], while it was not significant before the propensity score matching. The β estimated slope of coefficient was − 0.148873 [standard error (SE) =0.059923], *P* = 0.0129766. This translates into an adjusted OR of 0.86168 (95% CI = 0.76619–0.96906). That means the higher the vitamin D level by one unit, the lower the risk of breast cancer by 13.84%.

The logistic regression estimates [Table 2] demonstrate that vitamin D level, marital status (single), and sun-exposed area – skin hands and limbs [Figure 2] – are significantly and negatively associated with breast cancer development. While origin, age at menarche, first-degree family history of breast cancer, and moderate physical activity are significantly and positively associated with IBC risk [Figure 3].

The estimate for the effect of being single was −5.248 (SE = 1.788), *P* = 0.003. This translates into an OR of 0.005 (95% CI = 0.000–0.175). That means being single reduces the risk of breast cancer by 99.5%.

The estimate for the effect of age at menarche was 0.517 (SE = 0.216), *P* = 0.017. This translates into an OR of

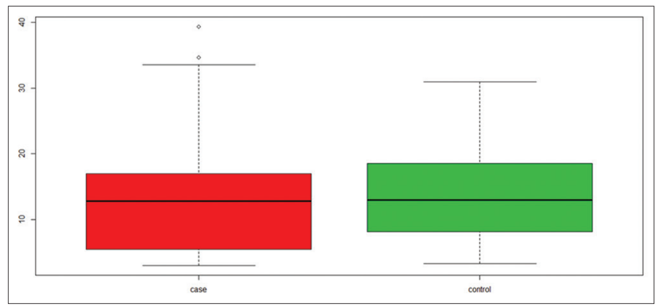

Figure 1: Vitamin D level in the studied Sudanese females with invasive breast cancer (100) and matched healthy women (100); *P* = 0.013

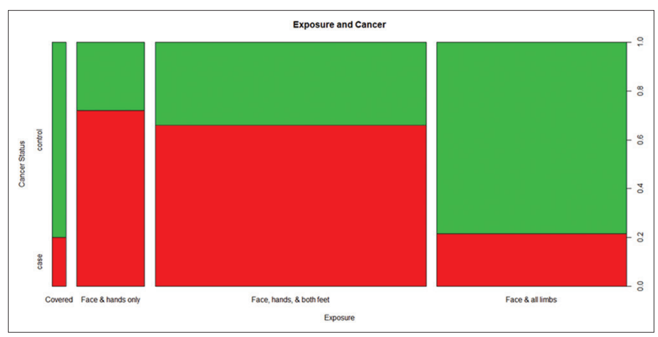

Figure 2: Correlation of sun-exposed area and the risk of developing invasive breast cancer among the studied Sudanese women. *P* value for exposed face and all limbs = 0.038 with an estimated slope coefficient of −4.339

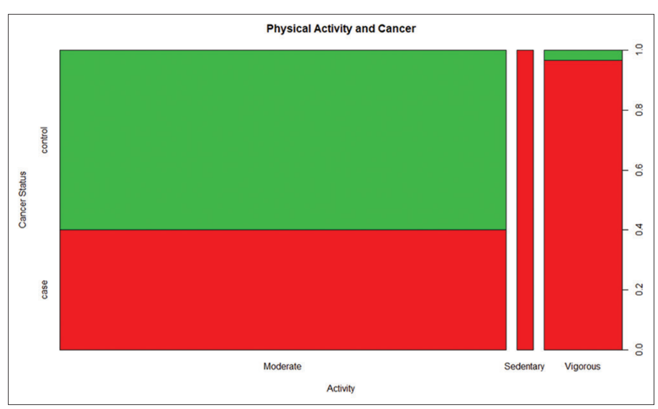

Figure 3: Correlation of physical activity and the risk of developing invasive breast cancer among the studied Sudanese women. *P* value for physical activity = 0.0008 with an estimated slope coefficient of 7.873

Table 1: Sociodemographic characteristics of women included in the study (*n*=200)

Characteristic	Category	Status		Total (%)	Chi-square (*P*)
		Case	Control		
Age	≤20	0	1	1 (0.5%)	16.404 (0.01174)
	21-30	9	25	34 (17.0%)	
	31-40	22	24	46 (23.0%)	
	41-50	34	29	63 (31.5%)	
	51-60	18	15	33 (16.5%)	
	61-70	14	3	17 (8.5%)	
	≥70	3	3	6 (3%)	
	Total	100	100	200	
Employment	Employed	31	39	70 (35.0%)	1.0769 (0.2994)
	Unemployed	69	61	130 (65.0%)	
	Total	100	100	200	
Education level	Illiterate	35	19	54 (27.0%)	19.87 (0.00018)
	Primary school	35	21	56 (28.0%)	
	Secondary school	20	31	51 (25.5%)	
	University	10	29	39 (19.5%)	
	Total	100	100	200	
	Total	100	233	333	
Origin	States	59	3	62 (31.0%)	70.711 (≤ 0.00001)
	Khartoum	41	97	138 (69.0%)	
	Total	100	100	200	
Socioeconomic status	Low	64	76	140 (70.0%)	3.6 (0.1653)
	Moderate	34	22	56 (28%)	
	High	2	2	4 (2.0%)	
	Total	100	100	200	
Marital status	Single	4	13	17 (8.5%)	5.3846 (0.06773)
	Married	89	82	171 (85.5%)	
	Divorced	0	0	0 (0%)	
	Widow	7	5	12 (6.0%)	
	Total	100	100	200	
Vitamin D status	Deficiency	81	81	162 (81.0%)	1.576 (0.4547)
	Insufficiency	14	17	31 (15.5%)	
	Sufficiency	5	2	7 (3.5%)	
	Total	100	100	200	
	n	**Mean (ng/mL)**	**Std. deviation**	**Median (ng/mL)**	
Vitamin D measurement					
Control	100	12.97	8.60	12.83	
Case	100	13.79	6.79	12.96	
Total	200	13.38	7.74	12.83	

1.677 (95% CI = 1.098–2.561). That means an increase in age at menarche by 1 year increases the risk of breast cancer by 67.7%.

The estimate for the effect of first-degree family history was 3.322 (SE = 0.942), P = 0.0004. This translates into an OR of 27.716 (95% CI = 4.374–175.620). That means that with a first-degree relative with breast cancer, the risk breast cancer increases by 26.72%.

The estimate for the effect of exposing hands and limbs (compared with completely covered women) was −4.339 (SE = 2.088), P = 0.038. This translates into an OR of 0.013 (95% CI = 0.000–0.782). That means that exposing hands and limbs reduces the risk of breast cancer (in comparison to completely covered women) by 98.7%.

In terms of distribution of physical activity among controls and cases, women who reported moderate activities were far more prevalent in the control group (n = 233, 99.6%) than in the cancer group (n = 64, 64%), respectively. Women reporting sedentary and vigorous activities were less in the control group (n = 0, 0% and n = 1, 0.4%)) than in the cancer group (n = 6, 6% and n = 28, 28%). This difference was statistically significant (Chi-squared = 85.682, DF = 2, P-value < 0.001, using Yates correction) as demonstrated in Figure 3.

The estimate for the effect of never drinking milk (compared with drinking 1 L a day) was −1.313 (SE = 0.453), P = 0.004. This translates into an OR of 0.269 (95% CI = 0.111–0.654). That means that never drinking milk decreases the risk of breast cancer (in comparison to drinking 1 L a day) by 73.1%. Also, the estimate for the effect of drinking milk sometimes (compared

Table 2: Multiple binary logistic regression model fitting for the studied Sudanese patients with invasive breast cancer (*n*=100)

Risk factors	β slope	SE	*P*	OR	95% CI for OR	
					Lower	Upper
Vitamin D level	−0.149	0.0599	**0.013**	0.862	0.766	0.969
Employment (unemployed)	1.423	1.139	0.211	4.150	0.445	38.685
Origin (states)	6.903	1.679	**<0.0001**	995.256	37.046	26737.972
Marital status (single)	−5.248	1.788	**0.003**	0.005	0.000	0.175
Marital status (Widow)	−2.075	2.779	0.455	0.126	0.001	29.132
Pregnant/lactating	−0.978	1.359	0.472	0.376	0.026	5.396
Age at menarche (years)	0.517	0.216	**0.017**	1.677	1.098	2.561
First pregnancy	0.047	0.084	0.581	1.048	0.889	1.236
Parity	−0.150	0.127	0.240	0.861	0.671	1.104
Pills	1.286	1.259	0.307	3.618	0.307	42.676
First-degree family history of breast cancer?	3.322	0.942	**0.0004**	27.716	4.374	175.620
Menopause	0.888	0.896	0.322	2.430	0.420	14.072
Physical activity (casual)	19.540	1917.925	0.992	3*10^8	0.000	Infinity
Physical activity (brisk)	7.873	2.342	**0.0008**	2625.430	26.647	258673.001
Chronic Illness	0.290	1.571	0.853	1.336	0.061	29.054
Socioeconomic status (low)	−2.969	2.868	0.301	0.051	0.000	14.186
Socioeconomic status (moderate)	−3.494	2.989	0.242	0.030	0.000	10.638
Exposed area (hands)	2.014	1.924	0.295	7.493	0.173	325.395
Exposed area (hands and feet)	0.0146	1.733	0.993	1.015	0.034	30.304
Exposed area (hands and limbs)	−4.339	2.088	**0.038**	0.013	0.000	0.782
BMI	−0.054	0.061	0.382	0.947	0.841	1.068
Dietary factors "milk"						
Never	−1.313	0.453	**0.004**	0.269	0.111	0.654
Rarely	−0.370	0.538	0.492	0.691	0.241	1.983
Sometimes	−1.517	0.381	**<0.001**	0.219	0.104	0.462
1 L a day (reference)						
Dietary factors "dairy"						
Once a day	−0.336	0.714	0.637	0.714	0.176	2.894
Rarely	2.140	0.852	**0.012**	8.500	1.601	45.127
Sometimes	−2.106	0.442	0.633	0.810	0.0001	4644
Never (reference)						
Dietary factors "egg"						
Once a day	−16.564	840.3	0.984	0	0	Infinity
Rarely	0.133	0.572	0.816	1.142	0.372	3.508
Sometimes	−1.530	0.479	**0.001**	0.216	0.085	0.553
Never (reference)						
Dietary factors "fish"						
Once a day	−0.956	1.509	0.527	0.385	0.020	7.404
Rarely	−0.738	0.571	0.196	0.478	0.156	1.469
Sometimes	−1.443	0.568	**0.011**	0.236	0.078	0.719
Never (reference)						
Dietary factors "meat"						
Once a day	0.857	1.294	0.507	2.357	0.187	29.747
Rarely	−1.099	1.528	0.472	0.333	0.017	6.655
Sometimes	−1.156	1.237	0.350	0.315	0.028	3.551
Never (reference)						
Sun protection creams	0.345	0.687	0.616	1.412	0.367	5.428

β: estimated slope coefficient for the univariate logistic regression model containing only this variable; SE: estimated standard error of the estimated slope coefficient; Wald: likelihood ratio test statistic, Wald (G), for the hypothesis that the slope coefficient is 0; df: degree of freedom; OR: estimated odds ratio; CI: 95% confidence interval for the odds ratio. Values in bold show a significant correlation

with drinking 1 L a day) was −1.517 (SE = 0.381), $P < 0.001$. This translates into an OR of 0.219 (95% CI = 0.104–0.462). That means that drinking milk sometimes reduces the risk of breast cancer (in comparison to drinking 1 L a day) by 78.1%.

The estimate for the effect of rarely consuming dairy products (compared with never using) was 2.140 (SE = 0.852), $P = 0.012$. This translates into an OR of 8.500 (95% CI = 1.601–45.127). That means that rarely using dairy products increases the risk of breast cancer (in comparison to never using them) by 75.0%. Therefore, it is possible to suggest that the use of milk and dairy products in reasonable amount may not influence the risk of breast cancer. The estimate for the effect of consuming eggs sometimes (compared with never) was −1.530

(SE = 0.479), $P = 0.001$. This translates into an OR of 0.216 (95% CI = 0.085–0.553). That means that sometimes using eggs reduces the risk of breast cancer (in comparison to never using them) by 78.4%.

The estimate for the effect of consuming fish sometimes (compared with never) was −1.443 (SE = 0.568), $P = 0.011$. This translates into an OR of 0.236 (95% CI = 0.078–0.719). That means that sometimes using eggs reduces the risk of breast cancer (in comparison to never using them) by 76.4%.

All other variables including employment, pregnancy or lactation, age at first pregnancy, parity, use of oral contraceptive pills, age at menopause, chronic illness, socioeconomic status, and BMI were not significantly associated with developing IBC among the studied group.

Discussion

In this case–control study, the serum level of [25(OH)D] was measured for 100 newly diagnosed breast cancer and another 100 noncancer Sudanese females. Following a propensity score matching using a logistic regression model and the control of confounding factors of both vitamin D and breast cancer, the mean level of 25(OH)D shows a statistically significant difference. In other words, the higher the vitamin D level, the less likely would be the risk of having IBC. A similar association between low vitamin D and breast cancer was also observed in case–control studies of Jordanian,[20] Indian,[21] and Pakistani women[22] breast and nonbreast cancer. Interestingly, in Iranian women, low vitamin D was associated with risk of breast cancer only in postmenopausal women.[23] In contrast, in women from Australia, vitamin D was not associated with breast cancer risk.[24] Nevertheless, in their review article by Shekarriz-Foumani and Khodaie published in 2016, they concluded that vitamin D could be associated with breast cancer.[25] The discrepancy in these results can be attributed to the difference in methods of analysis, dietary, ethnic, or other factors that necessitate further studies.

Our study showed that 81% of both patients with breast cancer and control group have vitamin D deficiency. Importantly, long-standing geographic residency (or origin) in different states of Sudan other than Khartoum was significantly correlated with IBC [$P < 0.0001$, OR 995.256 (95% CI 37.046–26737.972]. However, this is most probably spurious significance since most patients come from the states for the treatment available in Khartoum. Investigations of vitamin D–related genetic variations and breast cancer, though conflicting,[26] might reveal deleterious polymorphisms in a country with such ethnic variation.

Furthermore, vitamin D status has been linked to obesity and metabolic syndrome. Since fat cells express vitamin D receptor (VDR) and obesity is a known risk factor for cancer, vitamin D actions in adipocytes may contribute to its cancer-defensive properties.[27] Matthews *et al.* studied the role of VDR in adipose tissue, chiefly in the setting of the mammary gland on adipose-specific *Vdr* deletion (termed CVF mice). They found that adipose deletion of *Vdr* significantly enhanced density and branching of mammary epithelial cells, thus supporting the assumption that VDR in mature fat cells modifies the metabolic response to high-fat diets and exerts antiproliferative actions on the epithelial cells of the mammary gland.[27] Nevertheless, in this study, the multiple logistic regression models revealed no statistically significant correlation between BMI, IBC, and vitamin D level.

It was theorized that regular sunlight exposure benefits well-being[28] and may reduce the risk of developing breast cancer. Interestingly, in this study, sun exposure hours did not show significant association with breast cancer, but the exposed area did. A woman who does not use whole-body sun protective clothing (Nigab or Hijab) is 0.013 (95% CI 0.000–0.782) less likely to be affected with IBC with estimated slope coefficient (β) of − 4.339 ($P = 0.038$).

The epidemiologic evidence for associations between dietary factors and breast cancer is weak and etiologic mechanisms are often unclear in spite of comprehensive research.[29,30] It has been reported that utilization of meat is associated with heterocyclic amine exposure.[31] In this study, multivariate analysis did not show a significant correlation between dietary meat and IBC. However, milk, dairy products, egg, and fish intake were found to be positively correlated with breast cancer. Similarly, Jamshidinaeini *et al.* stated that dietary but not total intake of vitamin D was connected to the reduced risk of breast cancer.[23] It is noticed that dairy products greatly reduce the risk of developing IBC. Fortunately, in a country like Sudan where most of the people are below the poverty line, the dairy products which can be made at home play a noble alternative for fish and act as an achievable preventive method. Dietary elements that displayed an inverse association with breast cancer involve mushroom and fruits' consumption; however, they were not questioned in this study.[21]

In this study, physical activity was significantly associated with the risk of IBC. Women who practice vigorous physical activity (e.g. brisk daily walking) are 2625.430 (95% CI 26.647–258673.001) less likely to have IBC than those who do not. Similarly, a multivariate analysis (through multivariate logistic regression) of 181 ladies with breast cancer and 197 healthy controls instituted that vitamin D level and the practice of moderate physical activity were considered protective factors for breast cancer.[32] The same study considered menopause and family history of breast cancer as risk factors for breast cancer, agreeing with our findings regarding the positive family history.[32] According to the current study findings, women with a positive first-degree family history of breast cancer have a 27.716 (95% CI 4.374–175.620) higher risk of developing IBC.

The multivariate analysis in this study revealed a statistically significant relationship between age at menarche and IBC. Our result is similar to the studies by Alim and Kiziltan[33] and Salih *et al.*[17] Nevertheless, we do not agree with other studies in the direct correlation of menopausal status and the development of IBC.[32,33] This finding may be attributed to the inherent drawback of the case–control study that some events could not reliably be memorized.

On the other hand, obesity is a recognized risk factor for postmenopausal breast cancer. Calcitriol and dietary vitamin D, acting by numerous interrelated pathways, alleviate obesity-enhanced breast cancer development in a postmenopausal setting.[34] Swami *et al.* exhibited that vitamin D medications diminished insulin resistance, lessened leptin, and expanded adiponectin flagging and furthermore controlled the LKB1/AMPK pathway adding to a general reduction in nearby estrogen production in obese mice.[34] Unlike this study, obesity was recognized to be significantly related to a higher risk of breast cancer in a study done by Deschasaux *et al.* in which BMI and alcohol intake were proposed as being modifiers for the association between vitamin D serum level or its related gene polymorphisms and breast cancer risk.[35]

Limitations of the study

In this study, we adopted the propensity score matching method for matching cases and controls in terms of their demographic background covariates. This method has several advantages.[36] First of all, it relaxes the assumption of a linear relationship between background variables and the probability of breast cancer. Moreover, it excludes controls that have no suitable match in the patient group. However, in the light of time and financial cost, excluding controls or patients from the analysis could be regarded as a substantial drawback of the propensity score matching method. Also, the propensity score matching method has the limitation of assuming minimum unobservable heterogeneity.[37-39]

Also, among the limitations of this study are the small number of breast cancer cases and the lack of concomitant measuring of parathyroid hormone, serum calcium, and phosphate levels. Genetic testing of VDR variants would have empowered the study.

Conclusion

This study concluded that there is a statistically significant association between serum 25(OH)D level and IBC risk in Sudanese patients ($P = 0.0129766$, adjusted OR of 0.86168, 95% CI = 0.76619–0.96906). The higher the vitamin D level by one unit, the lower the risk of breast cancer by 13.84%.

Logistic regression estimates demonstrate that vitamin D level, marital status, and exposed area are significantly and negatively associated with breast cancer development. While origin, age at menarche, first-degree family history of breast cancer, and physical activity are significantly and positively associated with IBC risk. Moreover, frequent consumption of milk, dairy products, egg, and fish prominently reduces the risk of developing IBC.

Assuming that vitamin D status changes cancer risk, enough vitamin D supply would be an easy, economical, and safe cancer frequency and mortality reduction method. Moreover, anticipating vitamin D insufficiency might be a viable method for decreasing breast cancer occurrence in Sudanese ladies. In addition, since there is a connection between breast malignancy and the way of lifestyle, a reduction in the danger of developing invasive breast disease can be accomplished through changes in lifestyle, encouraging moderate physical activity and consumption of certain food.

Better outlined imminent investigations and clinical trials are expected to additionally affirm the findings of this study and help solve the issue of controversy.

Acknowledgements

The authors would like to thank the Ministry of High Education and Scientific Research, SAMASO, and Total Lab Care for funding this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article. They also thank the study subjects who participated in this study. They forward their greatest gratitude to Khartoum Oncology Hospital and the Family Health Centers who allowed them to conduct the study. Moreover, Hadil Abdelmoniem and Fathi Fargallah who interviewed the participants and collected the blood samples and Omyma Ismaeil who helped in getting permission from the seven localities of Khartoum State also deserve heartfelt thanks.

Availability of data and materials

Data can be obtained from the first author of this article on reasonable request.

Ethics approval and consent to participate

Ethical clearance was obtained from the Ethical Committee of the Ministry of Health –Khartoum State. Permission was taken from Khartoum Oncology Hospital general manager and from the administration of the seven localities of Khartoum State for data and sample collection. Participants were informed about the purpose of the study and the importance of their participation to confirm willingness for participation. Informed written consent was obtained from each patient and control case following their assurance that their information will be kept anonymously.

Consent for publication

Not applicable.

Financial support and sponsorship

This research was partially supported by the Ministry of High Education and Scientific Research, SAMASO, and Total Lab Care, Khartoum, Sudan.

Conflicts of interest

There are no conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int JCancer 2015;136:E359-86.
2. Saeed IE, Weng HY, Mohamed KH, Mohammed SI. Cancer incidence in Khartoum, Sudan: First results from the Cancer Registry, 2009-2010. Cancer Med 2014;3:1075-84.
3. Hossein-nezhad A, Holick MF. Vitamin D for health: Aglobal perspective. Mayo ClinProc2013;88:720-55.
4. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: An updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med2011;155:827-38.
5. Harris DM, Go VL. Vitamin D and colon carcinogenesis. JNutr 2004;134 (12 Suppl):3463S-71S.
6. Shui IM, Mucci LA, Kraft P, Tamimi RM, Lindstrom S, Penney KL, *et al.* Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: Aprospective nested case-control study. J Natl Cancer Inst 2012;104:690-9.
7. Holick MF. Vitamin D and sunlight: Strategies for cancer prevention and other health benefits. ClinJ Am Soc Nephrol2008;3:1548-54.
8. Freedman DM, Looker AC, Abnet CC, Linet MS, Graubard BI. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988-2006). Cancer Res 2010;70:8587-97.
9. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, *et al.* Vitamin D and prevention of breast cancer: Pooled analysis. JSteroid BiochemMol Biol 2007;103:708-11.
10. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002;94:1867-75.
11. Atoum M, Alzoughool F. Vitamin D and breast cancer: Latest evidence and future steps. Breast Cancer (Auckl) 2017;11:1178223417749816.
12. Holick MF. Vitamin D deficiency. N EnglJMed 2007;357:266-81.
13. Holick MF. Vitamin D: Extraskeletal health. RheumDis Clin North Am 2012;38:141-60.
14. Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: An epigenetic perspective. CurrOpinClin NutrMetab Care 2012;15:567-79.
15. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. EndocrRev 2005;26:662-87.
16. Adams JS, Hewison M. Update in vitamin D. JClin EndocrinolMetab 2010;95:471-8.
17. Salih AM, Alam-Elhuda DM, Alfaki MM, Yousif AE, Nouradyem MM. Developing a risk prediction model for breast cancer: Astatistical utility to determine affinity of neoplasm (SUDAN-CA Breast). EurJMed Res 2017;22:35.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. JClin EndocrinolMetab 2011;96:1911-30.
19. State MoHoK. Ministry of Health of Khartoum State. Available from: http://www.ksmoh.org.sd.
20. Atoum MF, Al-Khatib YM. Association between Serum 25-hydroxy Vitamin D Concentration and TaqI Vitamin D Receptor Gene Polymorphism among Jordanian Females with Breast Cancer. ChinMed J 2017;130:1074-8.
21. Sofi NY, Jain M, Kapil U, Seenu V, Kamal VK, Pandey RM. Nutritional risk factors and status of serum 25(OH)D levels in patients with breast cancer: A case control study in India. JSteroid BiochemMol Biol2018;175:55-9.
22. Shaukat N, Jaleel F, Moosa FA, Qureshi NA. Associationbetween Vitamin D deficiency and breast cancer. PakJ Med Sci 2017;33:645-9.
23. Jamshidinaeini Y, Akbari ME, Abdollahi M, Ajami M, Davoodi SH. Vitamin D status and risk of breast cancer in Iranian women: A case-control study.J Am Coll Nutr 2016;35:639-46.
24. Bilinski K, Boyages J. Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: An observational case-control study. Breast Cancer Res Treat 2013;137:599-607.
25. Shekarriz-Foumani R, Khodaie F. The correlation of plasma 25-hydroxyvitamin D deficiency with risk of breast neoplasms: A systematic review. IranJCancer Prev 2016;9:e4469.
26. Shi J, Grundy A, Richardson H, Burstyn I, Schuetz JM, Lohrisch CA, *et al.* Genetic variation in vitamin D-related genes and risk of breast cancer among women of European and East Asian descent. Tumour Biol 2016;37:6379-87.
27. Matthews DG, D'Angelo J, Drelich J, Welsh J. Adipose-specific Vdr deletion alters body fat and enhances mammary epithelial density. JSteroid BiochemMol Biol 2016;164:299-308.
28. van der Rhee HJ, de Vries E, Coebergh JW. Regular sun exposure benefits health. MedHypotheses 2016;97:34-7.
29. Playdon MC, Ziegler RG, Sampson JN, Stolzenberg-Solomon R, Thompson HJ, Irwin ML, *et al.* Nutritional metabolomics and breast cancer risk in a prospective study. AmJClin Nutr 2017;106:637-49.
30. Van Ryswyk K, Villeneuve PJ, Johnson KC, Epidemiology Research Group TC. Dietary patterns and the risk of female breast cancer among participants of the Canadian National Enhanced Cancer Surveillance System. CanJ Public Health 2016;107:e49-55.
31. Kotepui M. Diet and risk of breast cancer. Contemp Oncol 2016;20:13-9.
32. Oliveira Sediyama CM, DiasMM, Pessoa MC, Queiroz AR, Suhett LG, Freitas RN, *et al.* Lifestyle and vitamin D dosage in women with breast cancer. Nutr Hosp 2016;33:584.
33. Alim NE, Kiziltan G. Assessment of risk factors of obesity and diet on breast cancer in Ankara, Turkey. PakJMed Sci 2016;32:1537-42.
34. Swami S, Krishnan AV, Williams J, Aggarwal A, Albertelli MA, Horst RL, *et al.* Vitamin D mitigates the adverse effects of obesity on breast cancer in mice. Endocr Relat Cancer 2016;23:251-64.
35. Deschasaux M, Souberbielle JC, Latino-Martel P, Sutton A, Charnaux N, Druesne-Pecollo N, *et al.* Weight status and alcohol intake modify the association between vitamin D and breast cancer risk. J Nutr 2016;146:576-85.
36. Ravallion M. Evaluating anti-poverty programs. In: Chenery H, Srinivasan TN, editors. Handbook of Development

Economics. Vol. 4. Ch. 59. Amsterdam: Elsevier B.V.; 2008. p. 3788-840.

37. Essama-Nssah B. Propensity Score Matching and Policy Impact Analysis-A Demonstration in EViews: The World Bank: Washington D.C.; 2006.

38. Haukoos JS, Lewis RJ. The propensity score. JAMA 2015;314:1637-8.

39. King G, Nielsen R. Why propensity scores should not be used for matching. Copy at http://j mp/1sexgVw Download Citation BibTex Tagged XML Download Paper. 2016;378.