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Serum Vitamin D Deficiency and Risk of Breast Cancer: A Case-Control Study among Multiethnic Women in Malaysia

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Abstract

Objective: Despite emerging studies suggest the beneficial role of vitamin D, evidence on the relationship between vitamin D deficiency and risk of getting breast cancer is till now inconsistent and scarce in Southeast Asia. Therefore, we intended to explore the association between serum 25(OH)D and the risk of breast cancer among the Malaysian woman.

Methods: A case-control study was conducted to examine 231 breast cancer patients and 693 age-matched non-cancer controls. Odds ratios with 95% confidence intervals were measured by multivariate logistic models.

Results: Only11.4% of the participants had a sufficient (≥75 nmol/L) serum 25(OH)D level with no significant difference between cases and controls (p = 0.44). When stratified by <50 and ≥50 years age group, there was no significant association between serum 25(OH)D level (<75 and ≥75 nmol/L) and risk of breast cancer (p = 0.47 and p = 0.36, respectively). Similarly, there was no significant association between vitamin D deficiency and risk of breast cancer, even when different serum 25(OH)D cutoff values(50 and 44 nmol/L) were used.

Conclusion: Malaysian women have significant vitamin D deficiency however there is a no association between vitamin D deficiency and risk of breast cancer. Hence, supplementation with vitamin D may be useful for general health status rather than for the prevention.

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Introduction

Vitamin D3 is the precursor of the steroid hormone calcitriol (1,25(OH)2D3) [1]. Calcitriol regulates the expression of many genes in the human body and regulates various cellular pathways that could be a factor in determining cancer risk and prognosis [1-3]. Vitamin D is produced endogenously in human skin through sun exposure, or exogenously obtained via dietary intake [1]. Moreover, it has been reported that vitamin D independently possesses anti-carcinogenic properties by inhibiting cellular proliferation and inhibiting angiogenesis in both normal and malignant breast cells [3-10].

Both positive and negative inconsistent relation between vitamin D and breast cancer risk have been found among epidemiological [11,12] preclinical, clinical, along with randomized control trial [3]. Due to these contradictory findings, the World Cancer Research Fund and the American Institute for Cancer Research concluded that the association between the intake of vitamin D and decrease in breast cancer risk is still "limited – no conclusion" [12-14]. In the context of Asia specifically, barely a small number of studies have been conducted on the association among vitamin D deficiency and the risk of breast cancer [14,15]. Among Malaysian women, vitamin D levels have consistently been accounted to be very low [16,17]. However, the incidence of breast cancer in Malaysia seems low as compared to other countries where there are optimal vitamin D levels [18].

Overall, the study of vitamin D status and breast cancer risk among women in Southeast Asian countries is still very limited [19]. Therefore, in light of the above, we carried out a case-control study to investigate the association between vitamin D and breast cancer risk among the multiethnic female population in Malaysia by using three different serum vitamin D level cut off points.

Methods

Study Design

This is a case-control study 231 Malaysian Breast Cancer Survivorship Cohort (MyBCC) Study subjects were used as cases [20]. For the hospital controls, 462 female non-cancer patients were randomly selected from the University Malaya Medical Centre Mammogram Cohort Study (UMCS) [21]. As for the population controls, 231 female non-cancer patients were randomly selected from a cohort study on clustering of lifestyle hazard issues and considering its relationship with stress on health and wellbeing among school teachers CLUSTer Study [22]. The cases and controls in the current study were matched by age (±5 years) using a 1:3 (case: control) ratio.

MyBCC is hospital-based an ongoing prospective cohort study recruiting only newly diagnosed breast cancer patients in UMMC. Its main objective is to find out the association between socio-demographic characteristics, lifestyle factors, and the overall survival in addition to the quality of life breast cancer survivors [20]. The UMCS is a cohort study which recruited women aged between 40 and 74 years old with no history of breast cancer who attended opportunistic screening in UMMC from 2014 to 2018 [21]. It was initiated to study the mammographic density, lifestyle and other biological risk factors among non-cancer women and as a control for the MyBCC Study. The prospective cohort CLUSTer study, was conducted in six states in Peninsular Malaysia [22]. Its main objective was to explore the clustering effects of lifestyle risk factors and work-related stress among female school teachers in Malaysia [22]. For the purpose of current study, we are using only secondary data from Kuala Lumpur as our population control as the hospital based cases and controls reside in the same city.

Assessment of vitamin D level and other variables

Blood samples were collected during the recruitment period: MyBCC Study (2012–2015), UMCS Study (2014–2015) and CLUSTer Study (2012-2013). For all three studies, 3 mL of non-fasting venous blood was obtained from all the participants. The serum 25(OH)D concentration of each sample was measured in order to evaluate the vitamin D status of the participants because this is the primary circulating vitamin D form. Furthermore, it has been shown that serum 25(OH)D concentration is a good indicator of cumulative exposure to sunlight and vitamin D dietary intake and can thus be used to represent vitamin D status [16,23]. Electrochemiluminescence Immunoassay (ECLIA) method using the Cobas E411 Immunoassay Analyzer, serum 25(OH)D levels were measured. All the biochemical analyses were performed in the Clinical Diagnostic Laboratory at UMMC, which maintain international standard (MS ISO 15189). The inter assay coefficient of variation was 8.5% at 27.48 nmol/L and 3.6% at 65.59 nmol/L. Many agencies and scientific associations have developed recommendations for regulation on most favourable serum 25(OH)D concentrations and vitamin D supplementation. For instance, the Institute of Medicine's bone-centric guidelines recommend a target 25(OH)D concentration of 50 nmol/L [9]. However, more recent vitamin D supplementation guidelines which focus on the pleiotropic effects of vitamin D, recommend a goal 25(OH)D concentration of 75 nmol/L, plus age, body weight, disease condition, and race-dependent doses ranging between 400 and 2000 IU/day (10). Three different cut off values (75, 50 and 44 nmol/L) were used as reference. Vitamin D was classified as sufficient if the serum 25(OH)D level was ≥75 nmol/L and nonsufficient if <75 nmol/L [10]. In the current study, serum 25(OH)D was used as dichotomous variable because there were very few samples that had a serum 25(OH)D ≥75 nmol/L (cases: 10.0% and controls: 11.8%). In addition, the level of vitamin D was defined as sufficient if the serum 25(OH) D level was >50 nmol/L and nonsufficient if <50 nmol/L [24]. In the current study, vitamin D also was defined as sufficient if the mean serum 25(OH)D level was >44 nmol/L and nonsufficient if the mean serum 25(OH)D level was <44 nmol/L.

Socio-demographic information were collected from a self-administered questionnaire. However, there was no data available on OCP and HRT usage among the population control group. The body mass index (BMI) of the participants was calculated in kg/m^2. The BMI cut-off was defined by using the Asian BMI standard range[25] in which normal is defined as 18.5–22.9 kg/m^2, overweight as 23.0–27.4 kg/m^2 and obese as >27.5 kg/m^2.

The study received prior ethical approval from the Medical Ethics Committee at UMMC (MEC Ref. No: 2018725-6526). Written informed consent was acquired from the participants. All testing was done in agreement with the approved guidelines.

Statistical analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS version 20). The p value <0.05 was used for statistical significance. Descriptive data were used to explain the socio-demographic and anthropometric measurements, clinical features, and serum vitamin D level. Frequency and percentage were demonstrate for categorical

variables. The continuous variables were described as mean ± standard deviation for normally distributed data otherwise as median (interquartile range) for non-normally distributed data. The cases and control's characteristics and the different levels of serum 25(OH)D were calculated with the chi-square test to compare the significant variables. A logistic regression analysis stratified by age (<50 and >50 years) was performed to explore the association between the different levels of serum 25(OH)D and the risk of breast cancer. In addition, to assess the association adjusting for important confounders multivariate logistic regression was performed, i.e., age and ethnicity.

Results

The background characteristics of all the participants are shown in **Table 1**. Cases and controls were appropriately matched for age. Only 11.4% of the women had a sufficient level (≥75 nmol/L) of serum 25(OH)D. In comparison to the hospital controls (54.25 ± 6.70) and cases (54.00 ± 6.89), the population controls (50.07 ± 5.31) were significantly younger (p < 0.001). Population controls were more likely to be of Malay ethnicity. Compared to cases, controls were more likely to be educated, postmenopausal, and HRT users, but less likely to be OCP users (for HRT and OCP data we used hospital controls only). The mean (SD) serum 25(OH)D of cases, overall controls and total population was 42.43 (±22.53), 44.30 (±21.88) and 44.14 (±22.05) nmol/L, respectively. There was no significant difference in the serum 25(OH)D level of the cases and the controls (p =0.44).

The serum 25(OH)D level was available for all 924 women. The differences in characteristics between serum 25(OH)D levels (sufficient = ≥75 nmol/L and insufficient = <75 nmol/L) are presented in **Table 2.** Among those with a sufficient serum 25(OH)D level, a greater proportion were aged 50 years or above (85.7%) compared to those aged <50 years (14.3%) (p < 0.001). There was a significant difference in serum 25(OH)D level among the different ethnic groups (p = 0.001). Out of those with a sufficient level of serum 25(OH)D, the majority were Chinese (55.2%), followed by Malay (28.6%) and Indian (16.2%). After eliminating the population controls, the data on 693 participants was used in the chi-square test in order to determine whether there were any differences in the serum 25(OH)D level according to menopausal status, OCP used, and HRT used. From **Table 2**, postmenopausal women (94.1%) were more likely to have a sufficient serum 25(OH)D level as compared to premenopausal women (5.9%) (p < 0.001). Also, those who had not used HRT (68.2%) were more likely to have a sufficient serum 25(OH) D level as compared to those who used HRT (27.1%) (p = 0.001).

Table 3, shows the difference in serum 25(OH)D level between cases and controls using the three different cut off values of 75, 50 and 44 nmol/L. These different cut off values were used in the chi-square test to find out whether there were any significant differences by cut off serum 25(OH)D level between cases and controls when stratified by age. The results in the table show that there was no significant difference in the serum 25(OH)D levels between cases and controls according to age group.

The association between the different serum 25(OH)D levels and breast cancer risk as stratified by age is presented in **Table 4**. It can be seen that there was no significant association between serum 25(OH)D level (<75 and ≥75 nmol/L) and risk of breast cancer when stratified by the two different age groups (<50 and ≥50 years) (p = 0.466 and p = 0.363, respectively). Similarly, there was no significant association between the different age groups and the risk of breast cancer when using the two other serum 25(OH)D cut off values of 50 and 44 nmol/L. Furthermore, after adjusting for age (continuous) and ethnicity in the model, the breast cancer ORs were still non-significant.

Table 1: Background characteristics between cases and controls.

Characteristics	Total (N=693) n (%)	Cases (N=231) n (%)	Hospital Controls (N=462 n (%)	P value	Total (N=462) n (%)	Cases (N=231) n (%)	Population Controls (N=231) n (%)	P value	Total (N=924) n (%)	Cases (N=231) n (%)	Overall Controls (N=693) n (%)	P value
Vitamin D status												
Sufficient (>75 nmol/L)	85 (12.3)	23 (10.0)	62 (13.4)	0.19	43 (9.3)	23 (10.0)		0.631	105 (11.4)	23 (10.0)	82 (11.8)	0.437
Nonsufficient (<75 nmol/L)	608 (87.7)	208 (90.0)	400 (86.6)		419 (90.7)	208 (90.0)	211 (91.3)		819 (88.6)	208 (90.0)	611 (88.2)	
Age(mean)	54.20 (6.76)	54.00 (6.89)	54.25 (6.70)	<0.001*	51.78 (6.4)	54.00 (6.89)	50.07 (5.31)	<0.001*	52.82 (6.61)	54.00 (6.89)	52.32 (6.49)	<0.001*
Age(years)												
<50	216 (31.2)	69 (29.9)	147 (31.8)	0.602	183 (39.6)	69 (29.9)	114 (49.4)					
<0.001*	330 (35.7)	69 (29.9)	261 (37.7)	0.032*								
>50	477 (68.8)	162 (70.1)	315 (68.2)		279 (60.4)	162 (70.1)	117 (50.6)		594 (64.3)	162 (70.1)	432 (62.3)	
Ethnicity												
Malay	237 (34.2)	87 (37.7)	150 (32.5)	0.072	231 (50.0)	87 (37.7)	144 (62.3)	<0.001*	381 (41.2)	87 (37.7)	294 (42.4)	0.249
Chinese	285 (41.1)	99 (42.9)	186 (40.3)		162 (35.1)	99 (42.9)	63 (27.3)		348 (37.7)	99 (42.9)	249 (35.9)	
Indian	171 (24.7)	45 (19.5)	126 (27.3)		67(14.5)	45 (19.5)	22 (9.5)		193(20.9)	45 (19.5)	148 (21.4)	
Other	2 (0.4)	0 (0.0)	0 (0.0)		2 (0.4)	0 (0.0)	2 (0.9)		2 (0.2)	0 (0.0)	2 (0.3)	
Education												
No education	63 (9.1)	11 (4.8)	52 (11.3)	<0.001*	11 (2.4)	11 (4.8)	0 (0.0)	<0.001*	63 (6.8)	11 (4.8)	52 (7.5)	<0.001*
Primary	79 (11.4)	54 (23.4)	25 (5.4)		54 (11.7)	54 (23.4)	0 (0.0)		79 (8.5)	54 (23.4)	25 (3.6)	
Secondary	335 (48.3)	92 (39.8)	243 (52.6)		92 (19.9)	92 (39.8)	0 (0.0)		335 (36.3)	92 (39.8)	243 (35.1)	

University												
/College	192 (27.7)	50 (21.6)	142 (30.7)		281 (60.8)	50 (21.6)	231 (100.0)		423 (45.8)	50 (21.6)	373 (53.8)	
Unknown	24 (3.5)	24 (10.4)	0 (0.0)		24 (5.2)	24 (5.2)	0 (0.0)		24 (2.6)	24 (10.4)	0 (0.0)	
***Menopausal Status**												
Pre-menopause	202 (29.1)	79 (34.2)	123 (26.6)	0.039*	NA	NA	NA	NA	NA	NA	NA	NA
Post-menopause	491 (70.9)	152 (65.8)	339 (73.4)		NA	NA	NA		NA	NA	NA	
***OCP Used**												
No	515 (74.3)	144 (62.3)	371 (80.3)	<0.001*	NA	NA	NA	NA	NA	NA	NA	NA
Yes	144 (20.8)	53 (22.9)	91 (19.7)		NA	NA	NA		NA	NA	NA	
Unknown	34 (4.9)	34 (14.7)	0 (0.0)		NA	NA	NA		NA	NA	NA	
***HRT Used**												
No	562 (81.1)	187 (81.0)	375 (81.2)	<0.001*	NA	NA	NA	NA	NA	NA	NA	NA
Yes	97 (14.0)	10 (4.3)	87 (18.8)		NA	NA	NA		NA	NA	NA	
Unknown	34 (4.9)	34 (14.7)	0 (0.0)		NA	NA	NA		NA	NA	NA	
BMI (kg/m2)												
Normal (18.5 – 22.9)	165 (23.8)	52 (22.5)	113 (24.5)	0.056	105 (22.7)	52 (22.5)	53 (22.9)	0.033*	218 (23.6)	52 (22.5)	166 (24.0)	0.077
Underweight (<18.5)	29 (4.2)	6 (2.6)	23 (5.0)		7 (1.5)	6 (2.6)	1 (0.4)		30 (3.2)	6 (2.6)	24 (3.5)	
Overweight (23.0-27.4)	241 (34.8)	72 (31.2)	169 (36.6)		167 (36.1)	72 (31.2)	95 (41.1)		336 (36.4)	72 (31.2)	264 (38.1)	
Obese (>27.5)	258 (37.2)	101 (43.7)	157 (34.0)		183 (39.6)	101 (43.7)	82 (35.5)		340 (36.8)	101 (43.7)	239 (34.5)	
BMI, median	25.8 (5.25)	26.3 (5.52)	25.3 (5.08)	0.23	26.1 (5.17)	26.3 (5.52)	26.0 (4.8)	0.484	25.9 (5.14)	26.3 (5.52)	25.6 (4.9)	0.264
BFA	37.2 (7.64)	36.7 (7.88)	37.6 (7.49)	0.477	34.4 (8.62)	36.7 (7.88)	32.19 (9.03)	0.006*	36.3 (8.2)	36.2 (7.6)	35.9 (8.2)	0.908
Vitamin D concentration (nmol/L) Median	45.45 (22.55)	42.42 (22.5)	45.96 (22.5)	0.286	42.36 (21.5)	42.42 (22.5)	42.30 (20.5)	0.158	44.14 (22.0)	42.42 (22.5)	44.30 (21.9)	0.192

OCP: Oral Contraceptive; HRT: Hormone Replacement Therapy; BMI: Body Mass Index; BFA: Body Fat Analysis.
*Population Controls were excluded from the chi-square test

Table 2: The differences in characteristics of the participants by serum 25(OH)D level.

Characteristics	Overall (N) n (%)	Sufficient (≥75 nmol/L) n (%)	Nonsufficient (<75 nmol/L) n (%)	*P* value
Age(years)				
<50	330 (35.7)	15 (14.3)	315 (38.5)	<0.001**
≥50	594 (64.3)	90 (85.7)	504 (61.5)	
Ethnicity				
Malay	381 (41.2)	30 (28.6)	351 (42.9)	0.001**
Chinese	348 (37.7)	58 (55.2)	290 (35.4)	
Indian	193 (20.9)	17 (16.2)	176 (21.5)	
Education				
No education	63 (6.8)	10 (9.5)	53 (6.5)	0.793
Primary	79 (8.5)	10 (9.5)	69 (8.4)	
Secondary	335 (36.3)	37 (35.2)	298 (36.4)	
University/College	423 (45.8)	45 (42.9)	378 (46.2)	
Unknown	24 (2.6)	3 (2.9)	21 (2.6)	
***Menopausal status**				
Premenopause	202 (29.1)	5 (5.9)	197 (32.4)	<0.001**
Postmenopause	491 (70.9)	80 (94.1)	411 (67.6)	
***OCP used**				
No	515 (74.3)	66 (77.6)	449 (73.8)	0.737
Yes	144 (20.8)	15 (17.6)	129 (21.2)	
Unknown	34 (4.9)	4 (4.7)	30 (4.9)	
***HRT used**				
No	562 (81.1)	58 (68.2)	504 (82.9)	0.001**

Yes	97 (14.0)	23 (27.1)	74 (12.2)	
Unknown	34 (4.9)	4 (4.7)	30 (4.9)	
BMI (kg/m²)				
Normal (18.5–22.9)	218 (23.6)	22 (21.0)	196 (23.9)	0.07
Underweight (<18.5)	30 (3.2)	6 (5.7)	24 (2.9)	
Overweight (23.0–27.4)	336 (36.4)	47 (44.8)	289 (35.3)	
Obese (≥27.5)	340 (36.8)	30 (28.6)	310 (37.9)	
BMI (kg/m²) median (IQR)	25.9 (5.14)	25.2 (4.73)	26.0 (5.18)	0.586
BFA median (IQR)	36.3 (8.20)	35.5 (8.19)	36.5 (8.20)	0.7

OCP: Oral Contraceptive; HRT: Hormone Replacement Therapy; BMI: Body Mass Index; BFA: Body Fat Analysis.
*Population controls were excluded from the chi-square test and logistic regression analysis for these variables.
[a]The chi-square test was used to look at the association between serum 25(OH)D status.

Table 3: Difference in Serum 25(OH)D level between cases and controls using cutoff points of 75, 50 and 44 nmol/L.

Characteristics	Vitamin D level (Serum 25(OH)D)(nmol/L)	Total (N = 924) n (%)	Cases (N = 231) n (%)	Overall controls (N=693) n (%)	P value
<50 years old	Sufficient (≥75 nmol/L)	15 (4.5)	2 (2.9)	13 (5.0)	0.46
	Nonsufficient (<75 nmol/L)	315 (95.5)	67 (97.1)	248 (95.0)	
	Sufficient (≥50 nmol/L)	83 (25.2)	15 (21.7)	68 (26.1)	0.463
	Nonsufficient (<50 nmol/L)	247 (74.8)	54 (78.3)	193 (73.9)	
	Sufficient (≥44 nmol/L)[a]	118 (35.8)	23 (33.3)	95 (36.4)	0.637
	Nonsufficient (<44 nmol/L)[a]	212 (64.2)	46 (66.7)	166 (63.6)	
≥50 years old	Sufficient (≥75 nmol/L)	90 (15.2)	21 (13.0)	69 (16.0)	0.362
	Nonsufficient (<75 nmol/L)	504 (84.8)	141 (87.0)	363 (84.0)	
	Sufficient (≥50 nmol/L)	307 (51.7)	81 (50.0)	226 (52.3)	0.615
	Nonsufficient (<50 nmol/L)	287 (48.3)	81 (50.0)	206 (47.7)	
	Sufficient (≥44 nmol/L)[a]	346 (58.2)	89 (54.9)	257 (40.5)	0.316
	Nonsufficient (<44 nmol/L)[a]	248 (41.8)	73 (45.1)	175 (40.5)	

The chi-square test was used to look at the association between serum 25(OH)D status.
[a]The vitamin D cutoff was based on the median Vitamin D obtained in this study.

Table 4: Crude and multivariate adjusted odds ratios (ORs) for age groups by different serum 25(OH) vitamin D levels (75, 50 and 44 nmol/L cutoff points).

Characteristics	Vitamin D level (serum 25(OH)D)(nmol/L)	Cases (N = 231) n (%)	Overall Controls (N = 693) n (%)	Crude OR (95% CI)	*P* value	[a]Adjusted OR (95% CI)	*P* value
<50 years old	Sufficient (≥75 nmol/L)	2 (2.9)	13 (5.0)	1 [Ref]		1 [Ref]	
	Nonsufficient (<75 nmol/L)	67 (97.1)	248 (95.0)	1.756 (0.387-7.973)	0.466	1.704 (0.371-7.825)	0.493
	Sufficient (≥50 nmol/L)	15 (21.7)	68 (26.1)	1 [Ref]		1 [Ref]	
	Nonsufficient (<50 nmol/L)	54 (78.3)	193 (73.9)	1.268 (0.672-2.394)	0.463	1.293 (0.681-2.456)	0.433
	Sufficient (≥44 nmol/L)	23 (33.3)	95 (36.4)	1 [Ref]		1 [Ref]	
	Nonsufficient (<44 nmol/L)	46 (66.7)	166 (63.6)	1.145 (0.653-2.005)	0.637	1.2 (0.679-2.121)	0.53
≥50 years old	Sufficient (≥75 nmol/L)	21 (13.0)	69 (16.0)	1 [Ref]		1 [Ref]	
	Nonsufficient (<75 nmol/L)	141 (87.0)	363 (84.0)	1.276 (0.754-2.159)	0.363	1.486 (0.867-2.548)	0.15
	Sufficient (≥50 nmol/L)	81 (50.0)	226 (52.3)	1 [Ref]		1 [Ref]	
	Nonsufficient (<50 nmol/L)	81 (50.0)	206 (47.7)	1.097 (0.764-1.574)	0.615	1.299 (0.883-1.911)	0.185
	Sufficient (≥44 nmol/L)	89 (54.9)	257 (40.5)	1 [Ref]		1 [Ref]	
	Nonsufficient (<44 nmol/L)	73 (45.1)	175 (40.5)	1.205 (0.837-1.734)	0.317	1.446 (0.978-2.136)	0.064

[a]The multivariate logistic regression model was adjusted for age (continuous) and for ethnicity. Other ethnicity was excluded from the analysis.

Discussion

The current study revealed that there was no significant association between different serum 25(OH)D levels (cut off values of 75, 50 and 44 nmol/L) and the risk of breast cancer. Notably, only 11.4% of the participants had a sufficient (≥75 nmol/L) level of serum 25(OH)D. When the data was stratified by age, the analyses showed that among those aged <50 years only 4.5% and among those aged ≥50 years only 15.2% had sufficient serum 25(OH)D. The median (IQR) serum 25(OH)D level in this study was 44.138 ± 22.05; the older (≥50) and the postmenopausal groups had more sufficient serum 25(OH)D compared to the younger and the premenopausal groups ($p < 0.001$). These findings are in line a previous study that found a low prevalence of sufficient vitamin D level among Malaysian women [16] despite Malaysia having abundant sunlight throughout the year and being located near the equator.

The previous study also reported a mean serum 25(OH)D level of 36.2 ± 13.4 nmol/L among Malay female employees of a public university in Kuala Lumpur, Malaysia and that age is negatively associated with the serum 25(OH)D level, where older participants have a higher 25(OH)D level [16]. The results of the current study are in agreement with this existing evidence because they showed that a greater proportion of older individuals had a sufficient serum vitamin D.

These findings on the vitamin D are in contrast with the epidemiology of breast cancer in Malaysia. Among Malaysian women, both the incidence and survival of breast cancer seems to have relationship with ethnicity, independent of stage, tumour pathology and treatment factors [26]. The Chinese have the highest age-standardized incidence rate of breast cancer, followed by the Indian and the Malay ethnic groups. In the current study, a greater proportion of the Chinese participants had sufficient serum 25(OH)D as compared to the Malay and Indian participants ($p = 0.001$). Most of the Malaysia-based studies conducted among men, women, and teenage groups have found that the Chinese ethnic group commonly has the highest vitamin D level as compared to the Malay and Indian ethnic groups [16,17,27]. In addition, one of these studies reported that over 47% of female secondary school students in three states in Malaysia have vitamin D deficiency (with a mean vitamin D level of 53 ±15 nmol/L). The study found that the Malay and Indian female participants had a significantly higher vitamin D deficiency compared to the Chinese [17]. This may be due to cultural differences, where Malay and Indian women tend to wear clothes that conceal more of the body as compared to their Chinese counterparts. Thus, the darker pigmentation of the Indian and Malay women due to sun exposure might have add on this observation. Subjects with darker skin pigmentation have a lower 25(OH)D level after exposure to UVB radiation because melanin is absorbed and competes with 7-dehydrocholesterol for UVB photons [28,29]. The racial divergence in vitamin D status identified in the current study has also been observed in Western multiracial populations as well. For example, a study conducted in the United States found that a suboptimal vitamin D level (<50 nmol/L) is most common in African Americans, followed by Hispanics and non-Hispanic whites aged 20 years and above [30].

In Malaysia, the Malay ethnic group has the lowest 5-year overall survival rate in breast cancer as compared to the Indian and Chinese ethnic groups [20]. In the current study, the Malay ethnic group had higher vitamin D deficiency as compared to the Indian and Chinese groups. Vitamin D has been proven to induce apoptosis and suppress cell proliferation in a variety of cancer cell models including breast cancer [3]. Studies on vitamin D and prognosis of our survivors can be a fine resource to recognize the associations between serum 25(OH)D levels and prognosis among different ethnic group in Malaysia.

Notably, the current study showed that there was no significant difference in cases and controls in terms of the mean serum 25(OH)D level. It also showed that there was no significant association between different serum 25(OH)D values and the risk of breast cancer even after stratifying the data by different cut off values. This study inconsistent with other Asian studies. For example, a significant inverse association was observed between the vitamin D level and breast cancer risk among Japanese women [14]. Another large Korean case-control study, found that there was an association with serum 25(OH)D deficiency and increased risk of breast cancer [15]. This discrepancy may be owing to exercise of different serum vitamin D cut off values and measurement method. In the Japan-based study, the daily intake of vitamin D was obtained from a food frequency questionnaire and the risk was compared based on four quartiles of vitamin D intake level. In the Korea-based study, ≥20 mg/mL was used as the cut off value and the data was stratified by menopausal and receptor (ER, PR Her2) status.

Many evidences, suggest that vitamin D deficiency is associated with an increased risk of development of breast cancer [3]. Preclinical studies in animal models and cell, plus some observational studies and minor interventional studies, support that vitamin D has anticancer effect [6]. However, the epidemiological studies are inconsistent because they report both positive and negative results and to date, no large-scale and long-term RCTs are available from which definitive conclusions can be drawn as to whether vitamin D can offer preventive and therapeutic benefits in respect of breast cancer [3,12].

Several limitations and strengths ought to be taken into account when interpreting the results. One of the limitations is the relatively small sample size. Nevertheless, need to consider the lower incidence of breast cancer in Malaysia than in Western countries. And we evaluated the associations with substantial statistical power. Secondly, the population of the current study was limited to women in the Klang valley, Malaysia. Thirdly, the current study measured the vitamin D level after the diagnosis of breast cancer. Thus, the participants might have altered their dietary or other behavioural habits, potentially causing differential misclassification in vitamin D status among cases and controls. The age groups were different between cases and controls. However, we attempted to control for bias by choosing the control population from two sources, i.e ., non-cancer patients from the same hospitals as the cases and population controls from the same city as the cases. The probable effects of confounding factors were considered by matching the participants by age and by statistically adjusting for ethnicity; however, the effect of residual confounding influences cannot be completely ruled out. Nevertheless, despite some shortcomings, according to the information we have, the current study is the first in a multiethnic Malaysian setting to have been conducted to determine the association between different serum 25 (OH)D level and breast cancer, and thus makes an important contribution to this area of research.

Conclusion

This case-control study showed that the serum 25(OH)D level was not associated with the risk of developing breast cancer.

Malaysian women had significant vitamin D deficiency despite the plentiful sunlight in Malaysia all year round. Hence supplementation with vitamin D may be useful for general health status rather than for the prevention of breast cancer. Further studies are needed to investigate the role of vitamin D in the prognosis of breast cancer among multiethnic Malaysian survivors.

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Declaration of Conflicting Interests

The authors have declared no conflict of interest.

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