

A descriptive study of vitamin D and other nutritional factors in breast cancer patients in Saudi Arabia

Nora A. AlFaris, MS, PhD, Nora M. Alkehayez, MS, PhD, Fatema I. Almushawab, MD, SCHS-GS, AbdulRbman N. Al Naeem, MD, PhD, Nadia D. AL-Amri, MD, PhD, Ebtisam S. Almudawah, MD, PhD.

ABSTRACT

الهدف: تقييم دور مستوى فيتامين (د) في السيرم والعوامل التغذوية الأخرى عند النساء المصابات بسرطان الثدي في السعودية.

الطريقة: تم اختيار 500 امرأة تتراوح أعمارهن بين 20 و 60 سنة (250 مريضة بسرطان الثدي و 250 ضابطة) من مدينة الملك سعود الطبية ومدينة الملك فهد الطبية (الرياض، المملكة العربية السعودية) بين مايو 2015 ويونيو 2016. وفي هذه الدراسة المقطعية تم تقدير ضغط الدم، وتركيز فيتامين (د) في البلازما، الكالسيوم. تم استخدام سجل غذاء 3 أيام لتقييم تناول الغذاء.

النتائج: كان متوسط العمر الانحراف المعياري 43.9 ± 7.5 ، وكان 45.7 ± 7.8 سنوات للضابطة وسرطان الثدي على التوالي. وكان متوسط مؤشر كتلة الجسم 31.2 ± 7.0 كجم / م² المريضات و 30.7 ± 7.6 كجم / م² للضابطة. أكثر من 80% من المشاركات مستويات فيتامين د لديهم غير كافية (< 75.0) نانومول / لتر. كان متوسط تناول من الكوليسترول منخفض معنويا عند العينة الضابطة (233.1 ± 75.1 مجم) مقارنة بمريضات سرطان الثدي (257.2 ± 84.8 مجم). لوحظ وجود ارتباط عالي بين كثافة الثدي وأعراض نقص فيتامين (د). كما لوحظ وجود ارتفاع معنوي في مدى الاحساس بالتنميل عند المريضات بالمقارنة بالضابطة وكانت الاحساس بأعراض نقص فيتامين (د) الأخرى، مثل تقلصات العضلات، وآلام مزمنة، وزيادة الوزن، مرتفع معنويا عند الضابطة.

الخلاصة: نظرا لا انتشار نقص فيتامين د عند السعوديات من الصعب تحديد دوره بسرطان الثدي. يرتبط معدل الإصابة بسرطان الثدي في السعودية بتقدم العمر وارتفاع تناول من الكوليسترول. التنميل قد يكون عرض لسرطان الثدي.

Objectives: To assess the role of serum vitamin D and other nutritional factors in women with breast cancer in Saudi.

Methods: A total of 500 women (250 patients with breast cancer and 250 controls) aged 30-60 years were recruited from King Saud Medical City and King Fahad Medical City, Riyadh, Saudi Arabia, between May 2015 and June 2016. In this cross-sectional study, blood pressure, plasma concentrations of vitamin D, and calcium levels were evaluated. A 3-day dietary record was used to assess dietary intake.

Results: The mean body mass index was 31.2 ± 7.0 kg/m² for the breast cancer group and 30.7 ± 7.6 kg/m² for the control group. More than 80% of the participants had insufficient vitamin D levels (< 75.0 nmol/L). The mean cholesterol intake was significantly ($p=0.001$) lower in the control group (233.1 ± 75.1 mg) than in the breast cancer group (257.2 ± 84.8 mg). Breast density was found to be significantly associated with vitamin D deficiency-symptoms. Severe paresthesia was also significantly associated with breast cancer. The incidence of other vitamin D deficiency-symptoms was significantly higher in the control group.

Conclusion: Due to prevalence of vitamin D deficiency in Saudi Arabia, it is difficult to determine the relationship to breast cancer. The incidence of it is associated with old age and high cholesterol intake, and paresthesia may be a symptom of breast cancer.

*Saudi Med J 2018; Vol. 39 (6): 564-571
doi: 10.15537/smj.2018.6.21902*

From the Nutrition and Food Science (AlFaris, Alkehayez), Princess Nourah bint Abdulrahman University, from the Department of Surgical Oncology (AlMushawab), from the Medical Imaging Administration, Women's Imaging Department (Al Naeem), King Fahad Medical City; and from the Department of Radiology (AL-Amri), from the Day Surgery Unit (Almudawah), King Saud Medical City, Riyadh, Kingdom of Saudi Arabia

Received 31st January 2018. Accepted 16th May 2018.

*Address correspondence and reprint request to: Dr. Nora A. AlFaris, Nutrition and Food Science, Princess Nourah bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia.
E-mail: naalfaris@pnu.edu.sa
ORCID ID: orcid.org/0000-0002-9135-5725*

Breast cancer is a major cause of cancer-related death and has been identified as a public health issue worldwide.¹ This cancer type accounts for 25.8% of all newly diagnosed cancer cases among women and was the most diagnosed malignancy in 2012 in Saudi Arabia.² Al-Amri et al³ reported that breast cancer is the most commonly diagnosed malignancy among women in Saudi Arabia, and the Saudi Cancer Registry has recently revealed a consistent increase in the incidence of breast cancer in Saudi Arabian women in recent years.² Moreover, the incidence and mortality rates of breast cancer has reportedly increased not only in high-income countries like Saudi Arabia, but also in low- to middle-income countries.⁴

Many factors such as population growth, aging, lifestyle changes, poor nutrition, lack of physical activity, and urbanization play potential roles in the pathophysiology of breast cancer.⁴⁻⁷ Moreover, age at menarche, age at menopause, and family history of a first-degree relative with breast cancer are substantiated risk factors for breast cancer.^{8,9}

Epidemiological studies have supported a link between low serum 25-hydroxyvitamin D (25[OH]D) concentrations and adverse health conditions in the general population.^{10,11} Vitamin D deficiency and insufficiency are common health problems in the Middle East including Saudi Arabia, where this deficiency or insufficiency has been reported in 81% of different populations.¹² In Saudi Arabia, more than 30% of young healthy women are reported to be vitamin D deficient despite the presence of high UV sunlight throughout the year.^{13,14} While many studies have focused on the relationship between vitamin D and the incidence of breast cancer, only a few have investigated the potential relationship between serum 25(OH)D status and cancer survival.¹⁵ Vitamin D plays a role in reducing the risk of many cancer types, including those of the breast, stomach, colon, and prostate.¹⁶ Several experimental studies have also confirmed the role of vitamin D in reducing the risk of breast cancer.^{17,18} Vitamin D, has been shown to regulate the expression of genes regulating cell proliferation, differentiation, and apoptosis via its receptor in the mammary tissue.¹⁹ Wong et al,²⁰ found an increased

risk of cancer-related death among women with serum 25(OH)D concentrations of less than 64.0 nmol/L, though they did not report an increase in cancer incidence per se.

Therefore, this study aimed to assess the prevalence of vitamin D deficiency and other potentially important risk factors, such as lifestyle factors, dietary intake, and socioeconomic factors, in patients with newly diagnosed breast cancer and compare this data with that obtained from healthy controls. Our findings may help identify the potential risk factors that may have contributed to the increase in the incidence of breast cancer in Saudi Arabia; further, our findings may guide the implementation of methods for the early detection of vitamin D deficiency in clinical practice and aid in appropriate management for improving the health outcomes of low-resource patients.

Methods. Study design and participants. Previously, the focus was primarily on the prevalence of vitamin D deficiency in cancer patients. The aim of this study is to find the role of nutrients and socioeconomic characteristics in patients newly diagnosed with breast cancer and in comparison to a control group of women without breast cancer.

A total of 500 women were recruited from King Saud Medical City (n=159) and from King Fahad Medical City (n=341) (Riyadh, Saudi Arabia) between May 2015 and June 2016 based on the following inclusion criteria: age 20-60 years, living in Saudi Arabia, and with no prior diagnosis of any medical disorder that interferes with the vitamin D status (such as thyroid disease). Patients with a history of any type of cancer were excluded. A cross-sectional study design was used to evaluate serum levels of vitamin D and other nutritional factors associated with risk of breast cancer among those who visited the surgical clinic at King Saud Medical City and King Fahad Medical City, Riyadh, Saudi Arabia for follow-up examinations. Of the 500 included women, 250 were newly diagnosed with breast cancer and were included in the breast cancer group, while the remaining 250 had no prior history of any type of cancer and were included in the control group.

All study participants provided informed written consent in their native language prior to enrollment. This study was conducted according to the principles of the Helsinki Declaration, and the study design was approved by the Institutional Review Boards of King Saud Medical City and King Fahad Medical City (Riyadh, Saudi Arabia). Breast density was measured using mammography and was classified into 4 categories: low, mild, moderate, and high.²¹

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. This study was funded by the King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia (AT-34-50)

Data collection. Sociodemographic characteristics, including age at marriage, educational level, occupation, monthly income, sun exposure, and parity was collected using a questionnaire. Dietary data were also collected, and included information regarding the consumption of foods containing vitamin D, such as fish, yogurt, and cheese. Details such as types and amounts of food, preparation methods, and serving size of each item were collected by asking the participants to recall what they had consumed within a 3-day period (24-hour dietary recall) retrospective. Daily intake of vitamin D for each participant was estimated by using Food Processor for Windows (version 7.71; ESHA Research, Inc., Salem, OR, USA). A daily vitamin D intake of a minimum of 600 IU (15.0 µg) was considered adequate based on the dietary reference intakes for women.²²

To measure plasma vitamin D levels, blood samples were collected after a 12-hours fasting period. The samples were centrifuged at 2,000 rpm for 20 minutes to separate the plasma, which was then stored at -70°C for later analysis. Roche Elecsys vitamin D3 assay (Roche Diagnostics GmbH, Mannheim, Germany), using a Cobas e601 immunoassay analyzer was used to estimate plasma vitamin D3 levels. Measured vitamin D levels were then classified as sufficient (>75.0 nmol/L), insufficient (50.0-75.0 nmol/L), or deficient (<50.0 nmol/L).²³

Statistical analyses. Continuous variables are presented as mean ± SD, while categorical variables are

presented as frequencies and percentages. Participants were categorized according to vitamin D status and differences between variables were evaluated using the Student's t-test (for comparing variables between 2 groups) or the analysis of variance method (for comparing variables among 3 or more groups). The Chi-square test was used to analyze the relationship between 2 categories (variables). Statistical Package for the Social Sciences for Windows, software version 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Statistical significance was defined as $p < 0.05$.²⁴

Results. The baseline characteristics of the participants (age, body weight, body mass index [BMI], blood pressure, plasma vitamin D and calcium levels, vitamin D and calcium intake and supplementation, and percentage of recommended dietary intake) are presented in Table 1. The mean age ± SD in the overall cohort was 40.4 ± 11.0 years. The average BMI indicated obesity, with the mean BMI being 30.7 ± 7.6 kg/m² in the control group versus 31.2 ± 7.0 kg/m² in the breast cancer group. Systolic blood pressure was high in both groups at 135.0 ± 13.0 in the breast cancer group and 133.0 ± 14.0 mm Hg in the control group. By contrast, diastolic blood pressure was within normal limits. The mean vitamin D concentration of the entire study population indicated insufficiency, with 57.4% of women classified as vitamin D deficient. In

Table 1 - Baseline characteristics of all study participants (N=500).

Characteristic	Participants		P-value
	Control (n=250)	Breast cancer (n=250)	
Age (years), mean ± SD	43.9 ± 7.5	45.7 ± 7.8	0.011*
Weight (kg), mean ± SD	75.5 ± 17.0	77.0 ± 15.6	0.302
Body mass index (kg/m²), mean ± SD			0.514
Normal: 18.5 - 25	30.7 ± 7.6	31.2 ± 7.0	
Obese: 30 - 35			
SBP (mmHg), mean ± SD	133.0 ± 14.0	135.0 ± 13.0	0.093
Normal: 120			
DBP (mmHg), mean ± SD	72.8 ± 13.1	71.7 ± 9.9	0.306
Vitamin D (nmol/L), mean ± SD	52.8 ± 32.4	49.7 ± 31.0	0.307
Vitamin D, n (%)			0.816
Deficient (<50.0 nmol/L)	140 (28.0)	147 (29.4)	
Insufficient (50.0-75 nmol/L)	55 (11.0)	52 (10.4)	
Sufficient (>75.0 nmol/L)	55 (11.0)	51 (10.2)	
Calcium (mmol/L), mean ± SD	2.3 ± 0.1	2.3 ± 0.5	0.188
Vitamin D supplement, n (%)	121 (48.4)	130 (52.0)	0.421
Calcium supplement, n (%)	66 (26.4)	68 (27.2)	0.840
Age at menopause (years), mean ± SD	46.6 ± 6.4	48.7 ± 5.2	0.022*
Age at menarche (years), mean ± SD	13.0 ± 1.9	12.9 ± 1.8	0.610

* $p < 0.05$ (Chi-square test for categorical data, Student's t-test for continuous data)

DBP - diastolic blood pressure, SBP - systolic blood pressure

addition, the data showed that there was no relationship between breast cancer diagnosis and blood vitamin D levels ($p=0.816$). Moreover, >80% of the patients with breast cancer and the controls had insufficient vitamin D levels (<75.0 nmol/L). Approximately 50% of the participants reported taking vitamin D supplements, and >25% reported taking calcium supplements. The mean \pm SD age at menarche was 13.0 ± 1.9 years in the control group and 12.9 ± 1.8 years in the breast cancer group. The mean \pm SD age at menopause was lower in the control group (46.6 ± 6.4 years) than that in the breast cancer group (48.7 ± 5.2 years) (Table 1).

As shown in Table 2, 40.8% of the patients with breast cancer and 35.4% of the controls were married. The proportion of participants who were married was significantly lower in the control group than that in the breast cancer group, and the proportion of participants who were married at age ≤ 18 years was higher in the breast cancer group than that in the control group (20% versus 18.9%). The proportions of the participants who were married at age 18-30 years were similar between the control group and breast cancer group (28.4% and 28.9%). More than 70% of the participants (36% of the controls and 37.6% of the patients with breast cancer) had >3 children. Table 2 shows that most patients with

breast cancer (27.4%) had a low income. By contrast, the proportions of participants with low, moderate, and high income in the control group were higher than those of participants in the breast cancer group. The proportion of participants in the control group who attained a university level education was higher (18.4%) than that of the patients with breast cancer (12.6%), although most participants in both groups had a low education status.

As shown in Table 3, a low proportion of patients with breast cancer (22.4%) was exposed to sunlight. Of those who were exposed to sunlight, the exposure in most controls (37.4%) and patients with breast cancer (37.9%) was before 10:00 am and between 10:00 am and 3:00 pm, with 29% of patients with breast cancer being exposed to sunlight for >15 minutes daily compared to 22.9% in controls. The sites of exposure were mainly hands and face devoid of sun block. As shown in Table 3, more than two-thirds of the participants (68%) did not do any sport, and 67.8% of the participants who played a sport did not identify the location at which the sport was played. The proportion of participants who practiced sports was lower in the breast cancer group than that in the control group.

Table 2 - Socioeconomic characteristics of all study participants (N=500).

Characteristic	Participants		Total	P-value
	Control (n=250)	Breast cancer (n=250)		
Marital status, n (%)				0.034*
Married	177 (35.4)	204 (40.8)	381 (76.2)	
Single	26 (5.2)	13 (2.6)	39 (7.8)	
Divorced	27 (5.4)	19 (3.8)	46 (9.2)	
Widowed	20 (4.0)	14 (2.8)	34 (6.8)	
Age at marriage (years), mean \pm SD				0.409
≤ 18	87 (18.9)	92 (20.0)	179 (38.8)	
18-30	131 (28.4)	133 (28.9)	264 (57.3)	
>30	6 (1.3)	12 (2.6)	13 (2.8)	
Number of children, n (%)				0.719
≤ 3	54 (12.4)	61 (14.0)	115 (26.4)	
>3	157 (36.0)	164 (37.6)	321 (73.6)	
Duration of breast feeding (months), n (%)				0.065
≤ 6	87 (20.9)	75 (18.0)	162 (39.0)	
7-11	33 (7.93)	24 (5.8)	57 (13.7)	
12-24	78 (18.6)	106 (25.5)	184 (44.2)	
Did not breast feed	8 (1.9)	5 (1.2)	13 (3.1)	
Income (SR), n (%)				0.015*
Low <4,000	141 (28.2)	169 (33.8)	310 (62.0)	
Middle 4,001-10,000	71 (14.0)	45 (9.0)	116 (23.2)	
High >10,000	38 (7.6)	36 (7.2)	74 (14.8)	
Education, n (%)				0.005*
Below high school	158 (31.6)	187 (37.4)	345 (69.0)	
High school or above	92 (18.4)	63 (12.6)	155 (31.0)	

* $p < 0.05$ (Chi-square test for categorical data; Student's t-test for continuous data)

SR - Saudi Riyal (US\$1.0 = 3.75 SR).

The mean ± SD daily intake of vitamin D was similar between the control group (304.8 ± 129.75) and the breast cancer group (307.1 ± 143.3) (Figure 1). Both groups received approximately 50% of their recommended daily intake of vitamin D (recommended daily intake of vitamin D for women, 600 IU). The highest mean intake of vitamin D was from dairy products, followed by animal protein, fat, and oil sources. The lowest mean intake of vitamin D was from vegetable and fruit sources (Figure 1).

The mean daily nutrient intakes of the participants are shown in Table 4. The mean ± SD carbohydrate intake was higher in the breast cancer group (91.8±31.6 g) than that of the control group (89.45 ± 30.7 g). Meanwhile, the mean daily intake values of proteins and lipids (unsaturated and saturated fatty acids) were similar between the 2 groups. Table 4 shows that the mean daily intake value of cholesterol was significantly higher in the breast cancer group than that in the control group (*p*=0.001). The mean intake values

Table 3 - Lifestyle factors assessed in all study participants (N=500).

Factor	Participants		P-value
	Control (n=250)	Breast cancer (n=250)	
Exposed to sunlight	102 (20.4)	112 (22.4)	0.816
<i>Period of exposure</i>			
Before 10:00 am	80 (37.4)	81 (37.85)	0.642
After 10:00 am	22 (10.2)	31 (14.5)	
<i>Long exposure (minutes)</i>			
<15	53 (24.8)	51 (23.8)	0.642
>15	49 (22.9)	61 (28.5)	
<i>Part of the body exposed</i>			
Face and hands	78 (36.5)	87 (40.7)	0.065
Other	24 (11.2)	25 (11.7)	
Uses sun block	43 (8.6)	35 (7.0)	0.197
Plays sport	87 (17.4)	64 (12.8)	0.170
<i>Place of sport</i>			
Outdoor	55 (39.0)	34 (24.1)	0.022*
Indoor	32 (22.7)	20 (14.2)	
<i>Duration of sport (hours)</i>			
<1	84 (59.6)	50 (35.5)	0.080
≥1	3 (2.1)	4 (2.8)	

Values are expressed as number and percentage (%)
**p*<0.05 (Chi-square test for categorical data; Student's t-test for continuous data)

Table 4 - Mean daily nutrient intakes of all study participants (N=500).

Nutrient†	Participants		P-value
	Control (n=250)	Breast cancer (n=250)	
Carbohydrate (g/d)	89.5 ± 30.7	91.8 ± 31.6	0.399
Protein (g)	42.6 ± 10.6	42.5 ± 10.9	0.923
Fat (g)	41.6 ± 15.5	42.0 ± 14.6	0.769
Saturated fatty acids (g)	19.9 ± 3.7	19.7 ± 3.9	0.622
Unsaturated fatty acids (g)	23.5 ± 8.9	22.7 ± 7.1	0.264
Cholesterol (mg)	233.1 ± 75.1	257.2 ± 84.8	0.001*
total calories/d	902.4 ± 236.9	914.9 ± 235.2	0.552
Fiber (g)	12.3 ± 1.5	12.2 ± 1.6	0.527
Vitamin A (µg/d)	214.9 ± 83.3	215.6 ± 92.4	0.926
Vitamin E (mg/d)	2.0 ± 2.4	1.8 ± 2.6	0.553
Vitamin D (IU/d)	319.2 ± 229.1	304.6 ± 146.5	0.396
Calcium (mg/d)	401.9 ± 182.9	388.9 ± 198.8	0.447
Phosphorus (mg/d)	251.4 ± 122.5	255.8 ± 124.1	0.695
Iron (mg/d)	2.2 ± 2.1	2.6 ± 2.9	0.143
Sodium (mg/d)	4.8 ± 2.5	4.7 ± 2.7	0.580
Potassium (mg/d)	2.7 ± 1.2	2.7 ± 1.5	0.659
Zinc (mg/d)	2.1 ± 0.8	2.1 ± 1.2	0.718
Magnesium (mg/d)	62.3 ± 57.5	69.7 ± 66.0	0.178

Values expressed as means ± SD.
**p*<0.05 (Chi-square test for categorical data; Student's t-test for continuous data).

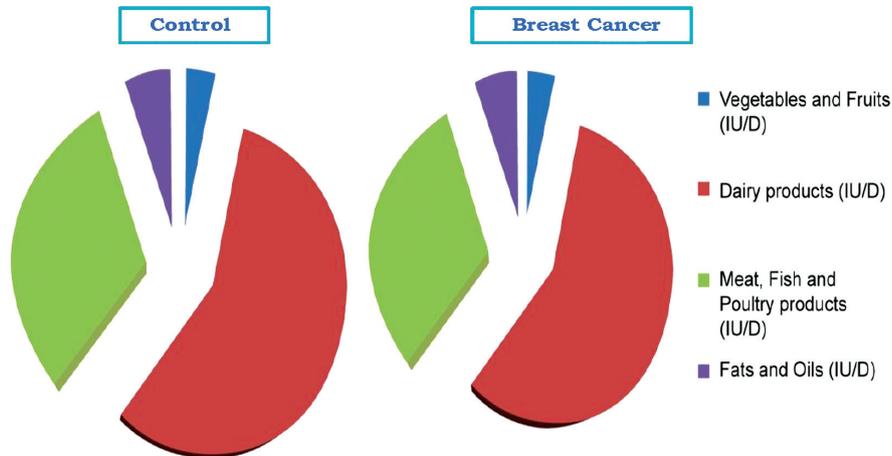


Figure 1 - Sources of vitamin D (IU/D) intake from 4 groups.

Table 5 - Association between breast density and symptoms of vitamin D deficiency

Vitamin D deficiency symptom	Breast density n (%)				Total	P-value
	Low	Mild	Moderate	High		
<i>Severe paresthesia</i>						
Control	18 (9.4)	22 (11.5)	17 (8.9)	15 (7.8)	82 (42.7)	-
Breast cancer	13 (6.8)	53 (27.6)	33 (17.2)	11 (5.7)	110 (57.3)	-
Total	31 (16.1)	75 (39.1)	60 (31.3)	26 (13.5)	192 (100.0)	0.028*
<i>Joint pain</i>						
Control	31 (9.4)	48 (14.6)	55 (16.7)	32 (9.7)	166 (50.5)	-
Breast cancer	19 (5.8)	74 (22.5)	50 (15.2)	20 (6.1)	163 (49.5)	-
Total	50 (15.2)	122 (37.1)	105 (31.9)	52 (15.8)	329 (100.0)	0.001*
<i>Chronic pain</i>						
Control	15 (23.8)	8 (12.7)	12 (19.1)	6 (9.5)	41 (65.1)	-
Breast cancer	6 (9.5)	3 (4.8)	10 (15.9)	3 (4.8)	22 (34.9)	-
Total	21 (33.3)	11 (17.5)	22 (34.9)	9 (14.3)	63 (100.0)	0.007*
<i>Increased weight</i>						
Control	15 (15.2)	12 (12.1)	19 (19.2)	14 (14.1)	60 (60.6)	-
Breast cancer	9 (9.1)	19 (19.2)	9 (9.1)	2 (2.0)	39 (39.4)	-
Total	24 (24.2)	31 (31.3)	28 (28.3)	16 (16.2)	99 (100.0)	0.004*

* $p < 0.05$ (Chi-square test for categorical data, Student's t-test for continuous data)

of calcium and vitamins E, D, and B12 were higher in the control group than that in the breast cancer group.

As shown in Table 5, breast density was significantly related with symptoms of vitamin D deficiency. A highly significant relationship between breast density and paresthesia was also observed ($p < 0.01$). Mild breast density was the most significant contributing factor for severe paresthesia, with 39.1% of participants having a mild breast density. A highly significant relationship was also observed between mild breast density and joint pain. Moderate to low breast density was more significantly related with chronic pain than high breast density. Data also revealed a significant relationship between breast density and increased weight.

As shown in Table 5, the breast density in the control group correlated significantly with muscle cramps, chronic pain, and increased weight ($p < 0.01$). Breast density was also found to be more significantly associated with severe paresthesia in the breast cancer group than in the control group.

Discussion. The mean age of patients with breast cancer was significantly higher than of the controls ($p < 0.05$). However, the mean age of these patients in the current study was 5-10 years lower than that reported in the Saudi Cancer Registry²⁵ and the study by Al Mulhim et al.²⁶ In addition to age, the World Health Organization,²⁷ also reported that other factors associated with breast cancer risk include late age at marriage, early menarche, late menopause, and long menstrual history. Our findings revealed a later age

at menopause in patients with breast cancer than in controls, which is in line with previous findings.²⁷

The results showed that the majority of patients with breast cancer had low income and educational level. By contrast, the control group had higher proportions of all categories for income and educational attainment compared to those in the breast cancer group. The higher educational status of the control group may reflect better knowledge of healthy dietary habits and awareness of risk of diseases such as breast cancer associated with poor diet. In connection to this, the incidence of breast cancer has been increasing in low- to middle-income countries. This increase is assumed to be caused by a combination of factors, such as population growth, lifestyle changes, aging, obesity, family history of malignancy, genetics, and delivering the first child after age 30 years.^{5,27,28}

Several studies have focused on the role of nutrients in breast cancer development and progression.^{29,30} It has been reported that breast cancer risk may be affected by specific dietary components and differences in dietary habits.³¹ A positive relationship between increased daily total fat consumption and risk of breast cancer has been proposed.³² According to Freedman et al.³³ and Mobarakeh et al.,³⁴ increased fat intake significantly affects the carcinogenesis pathway in mammary cells, and healthy dietary plans may be an appropriate strategy for breast cancer prevention. In the present study, differences in fat intake between the control group and breast cancer group were minimal and statistically insignificant, precluding an analysis of

the role of dietary fat in increasing the risk of breast cancer. The consumption of cholesterol in our study was significantly higher in the breast cancer group than that in the control group, which supports the findings of several previous studies, reporting high blood cholesterol as a risk factor for breast cancer.^{35,36} Moreover, the aggressiveness of breast tumors and disease progression have been reported to be linked to high plasma cholesterol levels.²⁹

While some reports have implied a potential role for Vitamin D in the prevention of breast cancer, our data was not in agreement with this contention. In this study, there was no significant difference in the vitamin D levels between the breast cancer group and the control group. Though a majority of patients with breast cancer had insufficient levels of vitamin D, this observation may be attributed to the high prevalence of vitamin D deficiency and insufficiency in the general population in Saudi Arabia.^{37,38} However, Formiga et al³⁹ revealed in an observational study that low levels of 25(OH)D may be linked to several types of breast cancer. In contrast, epidemiological evidence suggests an inverse relationship between vitamin D deficiency and adverse health outcomes.⁴⁰ Our data showed significant associations between breast density and several symptoms of vitamin D deficiency. Women with mild to moderate breast density were more likely to develop symptoms of vitamin D deficiency, such as severe paresthesia, joint pain, and increased weight. Except for paresthesia, these symptoms were more noticeable in the control group than in the breast cancer group. Women with a low to moderate breast density were more likely to have chronic pain. McCullough et al⁴¹ indicated that high breast tissue density was a major risk factor for breast cancer. Al Mulhim et al²⁶ reported that the majority of patients with breast cancer had high breast density. Taken together, these findings imply that paresthesia may be one of the symptoms of breast cancer.

One limitation of this study; however, is that only information concerning vitamin D and calcium levels at one time point was available, and no information regarding exposure to sunlight across different seasons was provided. Another limitation is that plasma cholesterol levels were not measured, warranting further studies.

We evaluated the effect of education status, economic status, and vitamin D sufficiency on breast cancer risk in Saudi Arabian women. We additionally sought to identify possible predictive factors that may aid in disease detection. Our findings may help future studies to identify risk factors and develop recommendations

for maintaining healthy dietary and lifestyle patterns that will aid in disease prevention.

In conclusion, our findings highlight significant factors that may contribute to the risk of breast cancer. We show that low income, low education level, and high cholesterol intake are associated with increased risk of breast cancer. Thus, health policies focusing on the importance of the factors affecting women's health should be established to educate women and to prevent breast cancer. Information concerning women in Saudi Arabia may guide members of the health care team in implementing methods for the early detection of risk factors for breast cancer in clinical practice and aid in providing appropriate management tools to improve health outcomes in low-income patients.

Acknowledgment. *Authors would like to thank the King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia, for the financial assistance provided to conduct this research. Authors would like to thank Editage (www.editage.com) for English language editing.*

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108.
2. Bazarbashi S, Al Eid H, Minguet J. Cancer Incidence in Saudi Arabia: 2012 Data from the Saudi Cancer Registry. *Asian Pac J Cancer Prev* 2017; 18: 2437-2344.
3. Al-Amri FA, Saedi MY, Al-Tahan FM, Ali AM, Alomary SA, Arafa M, et al. Breast cancer correlates in a cohort of breast screening program participants in Riyadh, KSA. *J Egypt Natl Canc Inst* 2015; 27: 77-82.
4. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev* 2016; 25: 16-27.
5. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 1495-1506.
6. Shapira N. The potential contribution of dietary factors to breast cancer prevention. *Eur J Cancer Prev* 2017; 26: 385-395.
7. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. *Int J Cancer* 2014; 135: 2444-2452.
8. Howell A, Anderson AS, Clarke RB, Duffy SW, Evans DG, Garcia-Closas M, et al. Risk determination and prevention of breast cancer. *Breast Cancer Res* 2014; 16: 446.
9. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: Burden and trends. *Cancer Epidemiol Biomarkers Prev* 2017; 26: 444-457.
10. Arnsion Y, Gringauz I, Itzhaky D, Amital H. Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients. *QJM* 2012; 105: 633-639.
11. Fan C, Nieto FJ, Bautista LE, Fine JP. Vitamin D intake and cardiovascular mortality in the NHANES I epidemiological follow-up study cohort. *J Diet Suppl* 2012; 9: 79-89.

12. Al-Daghri NM. Vitamin D in Saudi Arabia: Prevalence, distribution and disease associations. *J Steroid Biochem Mol Biol* 2018; 175: 102-107.
13. Al-Turki HA, Sadat-Ali M, Al-Elq AH, Al-Mulhim FA, Al-Ali AK. 25-Hydroxyvitamin D levels among healthy Saudi Arabian women. *Saudi Med J* 2008; 29: 1765-1768.
14. El-Kaissi S, Sherbeeni S. Vitamin D deficiency in the Middle East and its health consequences for adults. In: Holick MF, editor. *Vitamin D: Physiology, Molecular Biology, and Clinical Applications*. 2nd ed. New York (NY): Humana Press; 2010. p. 495-503.
15. Villase-or A, Ballard-Barbash R, Ambs A, Bernstein L, Baumgartner K, Baumgartner R, et al. Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. *Cancer Causes Control* 2013; 24: 759-767.
16. Cheney CP, Thorand B, Huth C, Berger K, Peters A, Seifert-Klauss V, et al. The Association between serum 25-Hydroxyvitamin D and cancer risk: Results from the prospective KORA F4 Study. *Oncol Res Treat* 2018; 41: 117-121.
17. Welsh J, Wietzke JA, Zinser GM, Byrne B, Smith K, Narvaez CJ. Vitamin D-3 receptor as a target for breast cancer prevention. *J Nutr* 2003; 133 (7 Suppl): 2425S-2433S.
18. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1991-1997.
19. Welsh J. Vitamin D and breast cancer: insights from animal models. *Am J Clin Nutr* 2004; 80 (6 Suppl): 1721S-1724S.
20. Wong G, Lim WH, Lewis J, Craig JC, Turner R, Zhu K, et al. Vitamin D and cancer mortality in elderly women. *BMC Cancer* 2015; 15: 106.
21. Vachon CM, van Gils CH, Sellers TA, Ghosh K, Pruthi S, Brandt KR, et al. Mammographic density, breast cancer risk and risk prediction. *Breast Cancer Res* 2007; 9: 217.
22. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press; 2011.
23. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96: 1911-1930.
24. Larson R, Farber B. *Elementary Statistics: Picturing the World*. 5 Ed. Upper Saddle River (NJ): Prentice-Hall; 2012.
25. Saudi Cancer Registry. *Saudi Arabia Cancer Incidence Report 2012*. Riyadh, Saudi Arabia: Saudi Cancer Registry, 2015. [Accessed December 2017]. Available from: <http://www.chs.gov.sa/Ar/HealthRecords/CancerRegistry/CancerRegistryReports/>
26. Al Mulhim FA, Syed A, Bagatadah WA, Al Muhanna AF. Breast cancer screening programme: experience from Eastern province, Saudi Arabia. *East Mediterr Health J* 2015; 21: 111-119.
27. World Health Organization. *Breast cancer: prevention and control*. Geneva: World Health Organization; 2018. [Accessed 2018]. Available from: <http://www.chs.gov.sa/Ar/HealthRecords/CancerRegistry/CancerRegistryReports/> <http://www.who.int/cancer/detection/s/>
28. Beiler JS, Zhu K, Hunter S, Payne-Wilks K, Roland CL, Chinchilli VM. A case-control study of menstrual factors in relation to breast cancer risk in African-American women. *J Natl Med Assoc* 2003; 95: 930-938.
29. Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, et al. Role of cholesterol in the development and progression of breast cancer. *Am J Pathol* 2011; 178: 402-412.
30. Shapira N. The potential contribution of dietary factors to breast cancer prevention. *Eur J Cancer Prev* 2017; 26: 385-395.
31. Moorman PG, Terry PD. Consumption of dairy products and the risk of breast cancer: a review of the literature. *Am J Clin Nutr* 2004; 80: 5-14.
32. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst* 1990; 82: 561-569.
33. Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. *Cancer Res* 1990; 50: 5710-5719.
34. Mobarakeh ZS, Mirzaei K, Hatmi N, Ebrahimi M, Dabiran S, Sotoudeh G. Dietary habits contributing to breast cancer risk among Iranian women. *Asian Pac J Cancer Prev* 2014; 15: 9543-9547.
35. Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst* 2004; 96: 1152-1160.
36. Ferraroni M, Gerber M, Decarli A, Richardson S, Marubini E, Crastes de Paulet P, et al. HDL-cholesterol and breast cancer: a joint study in northern Italy and southern France. *Int J Epidemiol* 1993; 22: 772-780.
37. Al-Mogbel ES. Vitamin D status among Adult Saudi Females visiting Primary Health Care Clinics. *Int J Health Sci* 2012; 6: 116-126.
38. Alsuwadia AO, Farag YM, Al Sayyari AA, Mousa DH, Alhejaili FF, Al-Harbi AS, et al. Prevalence of vitamin D deficiency in Saudi adults. *Saudi Med J* 2013; 34: 814-818.
39. Formiga F, Ferrer A, Megido MJ, Boix L, Contra A, Pujol R. Octabaix study members. Low serum vitamin D is not associated with an increase in mortality in oldest old subjects: the Octabaix three-year follow-up study. *Gerontology* 2014; 60: 10-15.
40. Fan C, Nieto FJ, Bautista LE, Fine Jp, (2012). Vitamin D intake and cardiovascular mortality in the NHANES 1 epidemiological follow-up study cohort. *J Dietary Supplements* 2012; 9: 79-89.
41. McCullough ML, Stevens VL, Patel R, Jacobs EJ, Bain EB, Horst RL, et al. Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. *Breast Cancer Res* 2009; 11: R64.