Effect of vitamins and minerals' supplementation on mammographic breast density

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Abstract: Background: Vitamins and minerals supplements' intake are increasingly used among premenopausal and postmenopausal females. The effect of these supplements on the occurrence of breast cancer is unclear.
Material and Methods: We studied the effect of vitamins and minerals intake on mammographic breast density, through a cross sectional study, carried out on premenopausal and postmenopausal women who came for screening at King Abdul-Aziz University Hospital. The study included 100 women, ranging between 30 and 70 years, who completed a self administrated questionnaire covering personal information, family, medical history, lifestyle data (practices towards vitamin-mineral intake, physical activity), as well as a food frequency questionnaire. In addition, weight, height, fat percentage were measured. **Results**: 77% of women with dense breast, 56% of those with heterogonous breast and 55% of those with fatty breast were current users of vitamins and minerals ' supplements. Among them, only 8% with dense breast, opposite to 50% with fatty breast were current users of vitamin D and calcium. The study revealed a significant inverse association between mammographic breast density, and body mass index and percentage of total body fat (r= - 0.21** , r= - 0.20** respectively). We also detected a positive association between physical activity (metabolic equivalent) and mammographic breast density (r= 0.057*).
Conclusion: There was a positive association between intake of vitamins- minerals and breast density; while the association with the intake of vitamin D and calcium was negative. High body mass index and fat percentage were protective against increased breast density.
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Key words: breast density; vitamins; minerals; supplements; body mass index; fat percentage; physical activity

1. Introduction

Breasts are made up of fatty tissue, fibrous tissue, and glandular tissue. (1) Women have dense breast tissue (as seen on a mammogram) when they have more glandular and fibrous tissue and less fatty tissue. (2)

Breast density changes over a woman's lifespan, usually decreasing with age, but a certain proportion of women have dense breast tissue that remains extremely dense throughout life (3). Other factors affecting breast density are weight, (4) menopausal status(5), parity and age at first birth, (6), family history(7), hormonal use(8), and previous breast biopsy (5). However, breast density is identified consistently as an independent risk factor of breast cancer (9).

Classification of breast density :

Breast density is classified using the BI-RADS (American College of Radiology Breast Imaging Reporting and Data System) scoring method, into four different categories:

- BI-RADS type 1: the breast is almost entirely of fat. Glandular tissue is less than 25%.
- BI-RADS type 2: there are scattered fibro glandular tissues, ranging from 25%-50% of the breast.
- BI-RADS type 3: 'heterogeneously dense', the fibrous tissue is prevalent throughout the breast (1%-75% of the breast tissue), but not clustered together.
- BI-RADS type 4: glandular and fibrous tissue are greater than 75%(10).

Over the past decade, vitamin and mineral supplements 'use has increased, for the purpose of health maintenance. However, controversy surrounds their safety (11).

2. Materials and Methods

We conducted a cross sectional study. Target population was adult and older adult women aging between 30 and 70 years, who came for screening at Radiology department, mammogram center at KAUH, Jeddah.

Among a sample of 105, we excluded women taking hormone medication, including oral contraceptives or hormone replacement therapy within 3 months of the mammography, those who used tamoxifen or raloxifene within 3 months , pregnant women , those with a history of breast surgery (reduction or implants), or cancer at any site.

In addition, we excluded women with known pituitary, thyroid, adrenal, hepatic, or renal disease.

Before conducting the study, an official approval was obtained from the KAUH ethical committee.

First, a member of the research team explained to each woman the contents of the questionnaire, after this each respondent was handed a questionnaire, and was asked to complete it while waiting in the room.

Bias was minimized by that the respondent could ask for clarification, at the same time that there was no interviewer bias; in addition, we assured the respondent about anonymity and confidentiality, and that her participation was voluntary.

The questionnaire comprised the following data :

1- Use of vitamins minerals ' supplements:

Women were asked about the intake, frequency, and duration of vitamins and minerals supplements.

2- Assessment of other variables

Body height was measured to the nearest 0.1 cm with the subject's standing without shoes. Body weight in light clothes was measured to the nearest 0.1 kg. Body mass index was calculated as body weight (kilograms) divided by the square of body height (meters), body fat was evaluated by bioelectrical impedance analysis (BIA) . Age at menarche, number of full pregnancies, age at first childbirth, and family history of breast cancer were self-reported in the lifestyle questionnaire.

3-Dietary assessment

Dietary habits were assessed using a self-administered food frequency questionnaire (FFQ); when necessary, forms were reviewed with the participant to ensure the clarity of answers. The original questionnaire was shown to have an acceptable validity (r = 0.4; $p < 0.05$) against 24-hour diet recall using a convenient sample of 10 females in the pilot test. It was a 3-pages structured questionnaire consisting of the following sections: consumption frequency and number of portion sizes of 4 items of milk and dairy product; 7 of carbohydrate rich food items; 7 of protein rich food items; 7 of vegetables food items; 10 of fruits items and beverages; 5 of added fats and 5 of sweet items. The food and beverage items were selected as foods commonly consumed in Saudi Arabia.

4. Physical activity assessment

The questionnaire was designed to collect information on frequency, duration and intensity of variety of light-, moderate- and vigorous-intensity physical activities during a typical (usual) week. Moderate-intensity physical activity included activities such as brisk walking, recreational swimming, and moderate-intensity recreational sports as volleyball, table tennis. Vigorous-intensity physical activity and sports included activities such as stair climbing, jogging, and vigorous-intensity sports. All physical activities were assigned metabolic equivalent (MET) values based on the compendium of physical activity[12].Moderate-intensity recreational sports were assigned an average MET value equivalent to 4 METs. Vigorous-intensity sports were assigned an average MET value equivalent to 8 METs. To measure the participants' levels of physical activity, we used the total METs-min per week and the METs-min per week spent in each of the moderate- and vigorous-intensity physical activity[13].

For ease of statistical analysis, we categorized breast density results into: dense, fatty, and heterogenous (which grouped both BI-RADS type 2 and type 3

Statistical analysis:

Statistical analysis was performed using the SPSS package version 16.

Descriptive statistics:

At the end of the study, data obtained were coded, tabulated, and presented by arithmatic mean and standard deviation, or by percentage frequency in case of categorical variables.

Analytical statistics:

Data were analysed using Chi square (x^2) , ANOVA test, and correlation coefficients 'tests

3. Results

An increase in breast density was observed as intake of vitamins and minerals supplements progressed from never, to past, to current use (though statistically insignificant (*p*= 0.36) (Figure 2)

The intake of calcium and / or vitamins D supplements was 50% among those with fatty breast, 9.09 %among those with heterogonous breast, and 8% among those with dense breast (Figure3). On the other hand, 25% those with fatty breast, 59.09% those with heterogonous breast, and 28%those with dense breast were taking other types of vitamins and minerals supplements (*p*= 0.00).

By far, we observed a significant difference in breast density according to physical activity (Figure 4), where11.1% of those with fatty breast, 5.41% of those with heterogonous breast , and16.13% of those with dense breast were doing vigorous exercise, while 58.33% of those with fatty breast , 40.54% of those with heterogeneous breast and 32.26% of those with dense breast were not doing any type of exercise (*p*=0.04). The highest prevalence of educational level among those with fatty breast belonged to the elementary educational group; while the highest prevalence of educational level among those with dense breast belonged to the highly educated women (*p*=0.05) (Figure 5).

There was a significant difference between means of age, BMI, and fat percentage, and metabolic equivalent for fatty, heterogeneous and dense breast (*p*= 0.01*, 0.001**, 0.009 and 0.035***respectively) (Table II); while there was no significant difference between means of dietary intake of food groups among the three groups of breast density (Table IV). Mean age, BMI, and fat percentage for fatty breast were significantly higher than those of heterogeneous , and dense breast . (Table III).

Age was positively correlated with fat % (r= 0.24 *), number of pregnancies (r=0.34**), and negatively correlated with breast density, educational level and contraceptive pills 'use (r= -0.22** , r - 0.91* and r= -0.71* respectively)

Body mass index was strongly positively correlated with fat % (r= 0.51**), number of pregnancies (r= 0.22*) and negatively correlated with breast density and educational level (r=-0.21**, r=-0.16* respectively)

Fat% was negatively correlated with breast density and educational level (r= -0.20** and r= 0.60* respectively). Use of contraceptive pills was negatively correlated with family history of breast cancer (r= -0.23*), and age (-0.17*)

Breast density was negatively associated with menopausal status (-0.27*), age (-0.22**), BMI (-0.21**), Fat%(-0.20**), and positively correlated with positive family history of breast cancer (0.29**), and educational level (r= 0.29**)

Educational level was negatively correlated with age at menarche (r=-0.16*), BMI (-0.16*), body fat%(-0.16*), and positively correlated with positive family history of breast cancer(r=0.21*), and breast density (0.29**) (Table V).

Table I: Distribution of the whole sample according to anthropometrical measurements, and gynecological history

Variables	Minimum	Maximum	Mean ± SD
Age in years	32.00	82.00	49.12 ± 9.01
Wt in Kg	41.60	118.50	75.0 ± 14.76
Ht in cm	142.00	176.00	155.9 ± 6.51
BMI	18.73	48.49	30.9 ± 5.94
Fat %	21.00	49.90	39.65 ± 6.59
Age at menarche	9.00	18.00	12.97 ± 1.45
Number of pregnancies	0.00	12.00	4.5± 2.5
Age at first child birth	14.00	40.00	21.8 ± 5.03

Figure 1: Distribution of the whole sample according to menopausal status

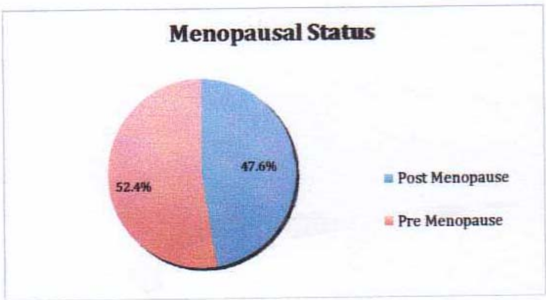
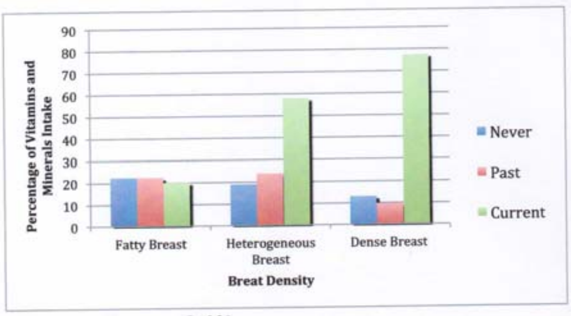
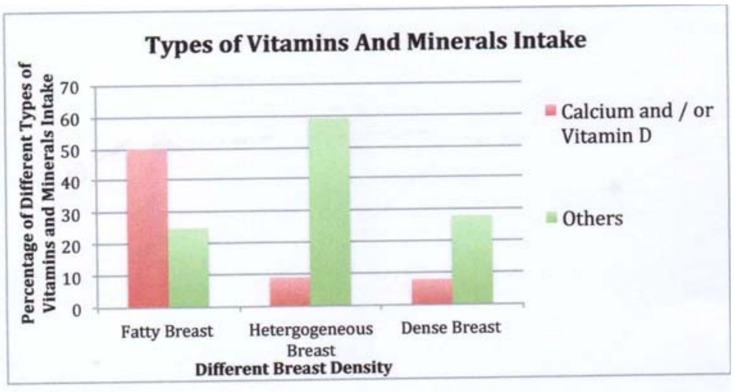


Figure 2: Distribution of results of mammography according to vitamins and minerals ' intake



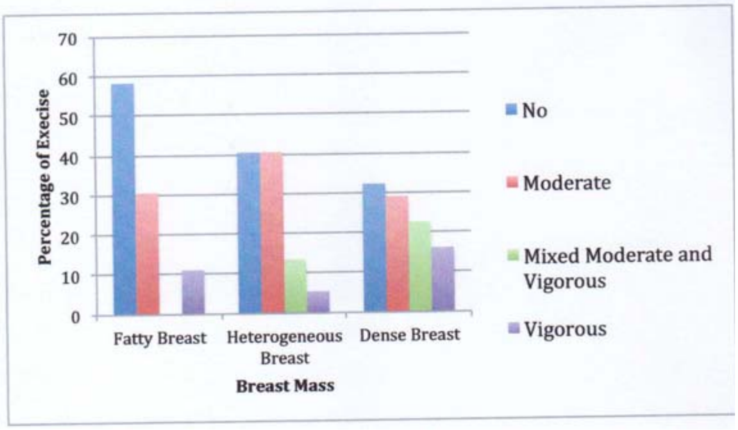
Chi square: 4.35 *p*= 0.36

Figure3: Distribution of results of mammography according to types of vitamins minerals intake:



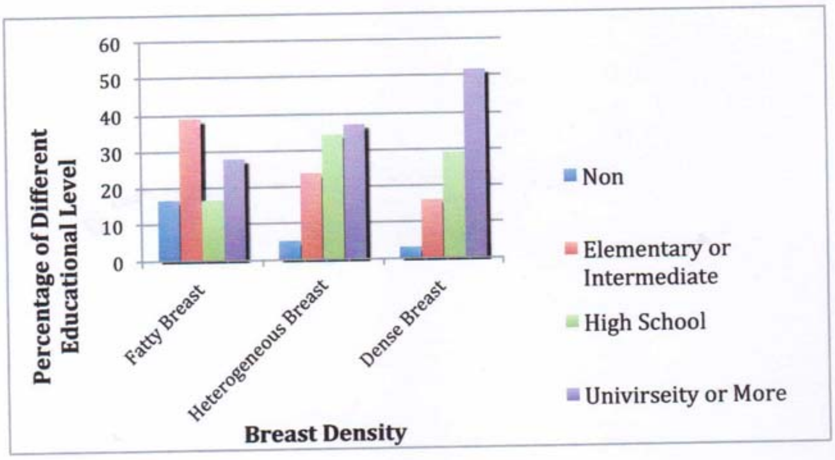
Chi square: 20.58 *p*= 0.00

Figure 4: Distribution of mammography results according to type of exercise:



Chi square: 12.96 *p*=0.04

Figure 5: Distribution of results of mammography according to educational level:



Chi square: 12.44 *p*=0.05

Table II: Comparison of demographics, anthropometrical and gynecological data between the three groups of breast density:

Variables	Mammography result	Mean ± SD	F	*P* value
Age	Fatty breast	52.7 ± 8.52	4.68	0.01*
	Heterogeneous breast	47.63 ± 9.6		
	Dense breast	46.8 ± 7.70		
BMI	Fatty breast	33.7± 5.40	7.89	0.001**
	Heterogeneous breast	28.6 ± 5.98		
	Dense breast	30.4 ± 5.3		
Fat %	Fatty breast	42.34 ± 4.97	4.95	0.009**
	Heterogeneous breast	38.1± 7.2		
	Dense breast	38.5 ± 6.7		
Age at menarche	Fatty breast	13.22 ± 1.5	2.76	0.068
	Heterogeneous breast	13.15 ± 1.4		
	Dense breast	12.5 ± 1.54		
Number of pregnancies	Fatty breast	5.14 ± 2.64	2.30	0.105
	Heterogeneous breast	3.92 ± 2.21		
	Dense breast	4.5 ± 2.5		
Age at first birth	Fatty breast	19.4± 6.40	0.42	0.66
	Heterogeneous breast	20.1 ± 8.02		
	Dense breast	21.06 ± 8.31		
Vitamins and minerals intake duration in months	Fatty breast	16.00 ± 11.6	1.12	0.332
	Heterogeneous breast	13.3 ± 13.7		
	Dense breast	20.84± 23.6		
Metabolic Activity	Fatty breast	188.3 ± 304.64	3.46	0.035*
	Heterogeneous breast	464.2 ± 685.63		
	Dense	607.81 ± 912.50		

Test used: One-way Anova
All reported P values are two-tailed.
* p <0.05
** p <0.01

Table III: Post hoc test result for One-Way anova test

Dependent variable	Mammography result	Mammography result	Mean	*P* value
Age	Fatty breast	Heterogeneous Dense	5.06 5.89	0.01* 0.01*
	Heterogonous breast	Fatty Dense	-5.06 0.83	0.01* 0.69
	Dense breast	Fatty Heterogeneous	-5.89 -0.83	0.01* 0.69
BMI	Fatty breast	Heterogeneous Dense	5.10 3.31	0.000*** 0.02*
	Heterogonous breast	Fatty Dense	-5.10 -1.79	0.000*** 0.19
	Dense breast	Fatty Heterogeneous	-3.31 1.79	0.02* 0.19
Fat %	Fatty breast	Heterogeneous Dense	4.28 3.88	0.005** .001**
	Heterogonous breast	Fatty Dense	-4.28 -0.39	0.005** 0.79
	Dense breast	Fatty Heterogeneous	-3.38 0.39	0.01* 0.79

Test used: LSD post Hoc test
All reported P values are two-tailed. * $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table IV: Comparison of dietary intake between the three groups of breast density:

Variables	Mammography result	Mean ± SD	F	*P* value
Percent calories From starch	Fatty breast	0.27 ± 0.1	0.79	0.46
	Heterogeneous breast	0.29 ± 0.11		
	Dense	0.29 ± 0.1		
Percent calories From sweets	Fatty breast	0.04 ± 0.03	0.88	0.42
	Heterogeneous breast	0.1 ± 0.06		
	Dense breast	0.04 ± 0.03		
Percent calories From added fats	Fatty breast	0.2± 0.07	0.92	0.41
	Heterogeneous breast	0.19 ± 0.08		
	Dense breast	0.17 ± 0.06		
Percent calories From milk and dairy products	Fatty breast	0.11 ± 0.06	1.82	0.17
	Heterogeneous breast	0.13 ± 0.08		
	Dense breast	0.14 ± 0.06		
Percent calories From MFP	Fatty breast	0.09 ± 0.05	0.43	0.65
	Heterogeneous breast	0.11 ± 0.05		
	Dense breast	0.11 ± 0.05		
Percent calories From legumes	Fatty breast	0.07 ± 0.08	0.32	0.73
	Heterogeneous breast	0.09 ± 0.12		
	Dense breast	0.08 ± 0.08		
Percent calories From fruits	Fatty breast	0.16 ± 0.08	0.19	0.83
	Heterogeneous breast	0.16 ± 0.07		
	Dense breast	0.15 ± 0.07		
Percent calories From vegetables	Fatty breast	0.05 ± 0.02	0.39	0.68
	Heterogeneous breast	0.05 ± 0.02		
	dense breast	0.05 ± 0.02		

Test used: One-way ANOVA
All reported *p* values are two-tailed.

Table V: Correlation coefficients of demographic, anthropometrical and gynecological history, and breast density:

5	Menopausal status	Age	BMI	Fat %	Age at menarche	Contra ceptive pills	Family history	Number of Pregnan cies	Educational level	Breast density on mammography
Menopausal status	1	0.64**	0.14	0.21*	-0.08	-0.17	-0.21*	0.17*	-0.19	-0.27*
Age	0.64**	1	0.06	0.24*	-0.11	-0.17*	-0.11	0.34**	-0.19*	-0.22**
BMI	0.14	0.06	1	0.51**	-0.01	-0.01	0.08	0.22*	-0.16*	-0.21**
Fat %	0.21*	0.24*	0.51**	1	0.06	0.02	0.02	0.19	-0.16*	-0.20**
Age at menarche	-0.08	-0.11	-0.01	0.06	1	0.01	0.02	-0.04	-0.16*	-0.13
Contraceptive pills	-0.17	-0.17*	-0.01	0.02	0.01	1	-0.23*	0.16	-0.06	0.05
Family History	-0.21*	-0.12	0.08	0.02	0.02	-0.23*	1	-0.16	0.21*	0.29**
Number of pregnancy	0.17*	0.34**	0.22*	0.19	-0.04	0.16	-0.16	1	-0.29	-0.10
Educational Level	-0.19	-0.19*	-0.196**	-0.16*	-0.16*	-0.06	0.21*	-0.29	1	0.29**
Breast density on mammography	-0.27*	-0.22**	-0.21**	-0.20**	-0.13	0.05	0.29**	-0.10	0.29**	1

Values are Pearson, Spearman, and Kendall's r correlation coefficients All report *p* values are 2 tailed
*: Correlation is significant at the 0.05 levels **: Correlation is significant ate the 0.01 levels

4.Discussion

It's well known that women with large body mass index tend to have large breasts with substantial amount of fatty (non dense tissue) as part of the whole body fat increase [14] .

Our study revealed an inverse association between mammography breast density, and body mass index and percentage of total body fat (r= -0.21**, r= -0.20** respectively)

These results were consistent with other studies, which found that the adult BMI was inversely associated with breast density, hence premenopausal breast cancer risk. [14]

Body size and mammographic density are each confounder of the association of the other with risk of breast cancer. It has been concluded that these two risk factors for breast cancer operate through separate pathways. Adipose tissue influences exposure to estrogen. It is the site in which androstenedione is converted by aromatization to estrogen. Furthermore, obesity is associated with lower levels of sex hormone–binding globulin, and so with higher levels of free, and biologically active, sex hormones. The effect of adipose tissue on estrogen production affects mainly postmenopausal women, but the effect of BMI on sex hormone–binding globulin levels affects both premenopausal and postmenopausal women [15] .

On the other hand, body fatness during youth is inversely associated with breast cancer risk in both pre- and postmenopausal women. Rapid adolescent growth may increase breast cancer risk; during this episode, girls with more body fat may have higher levels of sex hormones that could lead to earlier differentiation of breast tissue, resulting in cells less susceptible to malignant transformation [16] .

Physical activity is believed to reduce breast cancer risk; however, we detected a positive association between physical activity (metabolic equivalent) and mammographic breast density (r= 0.057).Our result was consistent with that detected by previous studies [17].

This could be explained by that the association between physical activity and breast cancer risk is unlikely to be mediated through an effect on mammographic breast density [18], especially that a yearlong randomized controlled trial, reported that physical activity had a favorable effect on reducing circulating sex hormone concentrations among overweight postmenopausal women [19].

Our study revealed a positive association between educational level and breast density(r= 0.29**). Indeed, a positive relationship between level of education and female breast cancer risk is well supported. Highly educated women tend to have lower body mass index, more frequent use of hormonal contraceptives, physical activity that may have an influence on density of the breast [20] .

Vitamin and mineral supplement and mammographic breast density

We observed that 77% of women with dense breast, 56% of those with heterogonous breast and 55% of those with fatty breast were current users of vitamins and minerals supplements. Similar results proved that the current use of multi vitamin and multi mineral in premenopausal women was associated with a significant higher mean mammographic breast density [21] .

In addition, we detected a significant difference in breast density, specifically according to intake of calcium and vitamin D supplements (p= 0.00).

Vitamin D and calcium supplements have been linked to cellular growth and differentiation in breast tissue and hence, may influence the amount of dense tissue in breast , it can be expected that an adequate vitamin D status is required to achieve the benefits of high calcium intake and *vice versa*. [22]. Moreover, vitamin D has been shown to suppress the proliferative activity of both 17β-estradiol and IGF-I, inhibit the antiapoptotic effect of IGF-I, and down-regulate the levels of estrogen receptors and IGF-I receptors [23].

Finally, limitations of our research work were time, and exclusion criteria, which resulted in a relatively small sample size. In addition, the retrospective nature of the study could result in recall bias , with a consequent lack of significant results where they should be significant .

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