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Vitamin D3 and Breast Cancer

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Breast cancer, Vitamin D3, Deficiency of Vitamin D.

A B S T R A C T

The role of vitamin D3 deficiency in breast cancer has been extensively studied. An inverse relationship does exist between the vitamin D3 level and breast cancer risk. Many cancer treatment centers worldwide have included vitamin D3 supplement in their programs aiming at reduction of cancer recurrence and enhancing cancer response to chemotherapy and hormonal therapy. To find out differences in vitamin D3 levels in women with and without breast cancer**.** To establish the relation(if any) between vitamin D3 deficiency in breast cancer patients and estrogen, progesterone, and HER2 receptor status; and with TNM staging, tumor marker Ca 15-3, histopathological type, family history of breast carcinoma, and history of oral contraceptive pills usage. A case-control study was conducted among 212 patients with breast cancer and equal number of controls. The patients were attendants at Oncology Unit at Al-Sadr teaching hospital / Al-Najaf from December 1st, 2013 until October 1st, 2014. There is a statistically significant difference in vitamin D3 level between the two studied groups (cancer patients record lower levels)**.** Our patients are younger at the time of diagnosis and the deficiency in vitamin D is clear in breast cancer group. The study doesn't show any relation to estrogen, progesterone and HER2 receptors; there was no relation between vitamin D level and TNM staging, CA 15-3 marker, histopathological type of the tumor, family history or oral contraceptive pills usage.

Introduction

Evidence for the role of vitamin D in the development of various cancers including breast cancer has been accumulating in recent years (Giovannucci, 2005; Cui *et al*., 2006). Initial evidence suggesting the potential for vitamin D to reduce breast cancer risk and mortality arose from ecologic studies relating higher latitude, and therefore lower UVB, to increased breast cancer incidence and mortality (Vieth, 1999; Gorham *et al*.,), and from in vitro studies

showing anti-proliferativeand pro-apoptotic effects of 1,25(OH)2D in breast cancer cell lines (Bortman *et al*., 2002; Welsh *et al*., 2004). Ecological studies have associated high levels of sunlight exposure with low breast cancer incidence and mortality rates (Studzinski *et al*., 1995). Some found that vitamin D3 given at non-toxic doses significantly reduces the tumor proliferation.

Patients and Methods

In this case-control study, we compared vitamin D3 levels among 212 women newly diagnosed with breast cancer and 212 healthy women (as a control group). All cancer cases were collected from the Oncology Center of Al-Sadr Teaching Hospital in Najaf City during the period from Dec. 1st, 2013 to Oct. 1st, 2014. The age range was 20 to 80 years old for both groups with matched age groups.

Only women who were free from breast disease (benign or malignant) or other forms of cancer were enrolled in the control group, and consents were taken from the subjects.

In the cancer group, several parameters were taken into consideration including the type of breast cancer, TNM staging, presence of estrogen receptors, progesterone receptors, HER-2 status, family history of breast cancer, age of menarche, history of using contraceptive pills, and the level of tumor marker CA 15-3.

Elisa test was used to determine vitamin D3 level (The laboratory kit used is by Carolline Vangreveling. DIA source Immuno Assay S.A -2,rue du Bosquet -1348 Louvain La Neuve –Belgium –QC –Department – email QC@diasource.be).

Statistical analysis was done by using SPSS (statistical package for social sciences) version 20 in which we used independent sample T-test and ANOVA (analysis of variance) and Pearson correlation coefficient for numerical data; P value <0.05 was regarded a significant.

Results and Discussion

This study consists of 424 women, 212 (50%) have breast cancer while the others were healthy women. The comparison between the two groups had been shown in Table (1).

There was no significant difference of vitamins D level regarding the age group, but there was a significant difference regarding vitamin D level between the two groups where it is higher among healthy women.

There was no significant relation between vitamin D level and estrogen receptor status of breast cancer women as shown in Table (2)

There was no significant relation between vitamin D level and progesterone receptor status of breast cancer women as shown in Table (3)

There was no significant relation between vitamin D level and HER2 status of breast cancer women as shown in Table (4).

There was non-significant very weak negative correlation between vitamin D and TNM staging and very weak non-significant correlation between CA 15-3 and vitamin D level as shown in Table (5)

There was no significant relation between vitamin D level and histopathological type of breast cancer women as shown in Table (6)

There was no significant relation between vitamin D level and family history of breast carcinoma as shown in Table (7).

There was no significant relation between vitamin D level and history of oral contraception as shown in Table (8).

It has been theorized for some time that there is an inverse correlation between breast cancer and vitamin D3. Many studies showed anti-carcinogenic properties of vitamin D3 and calcium. Some even further postulated the role of VDR (Vitamin D receptors) polymorphisms in the development of breast cancer (Yan Cui; Reimers *et al*., 2014).

Patients with optimal or adequate serum vitamin D3 levels have shown reduced risk for developing breast cancer, whether this is related to exogenous route (higher vitamin D intake) or endogenous route (vitamin D synthesis in the skin) (Jacobson *et al*., 1989).

Vitamin D and Calcium are metabolically interrelated, so in this study, the control group has been selected with normal calcium levels to eliminate Calcium's role.

For vitamin D3, plasma concentration of 25(OH)D (>20 ng/mL) is ≈1,000 times higher than that of 1,25(OH)2D (20-60 pg/mL). Circulating 25(OH)D concentration varies with dietary intake and exposure to sunlight and is considered to be the best indicator of vitamin D3 status. In contrast, the circulating concentration of 1,25(OH)2D is maintained in a relatively narrow range due to tight regulation by renal 1-α-hydroxylase. Various epithelial cells, such as those in the prostate, breast, and colon, have been shown to express vitamin D 1-α-hydroxylase. However, circulating 1,25 (OH)2D produced by these extra-renal tissues is undetectable in anephric condition. Circulating 1,25(OH)2D plays an important role in calcium homeostasis by participating in a feedback mechanism that maintains the level of calcium within its regulated range. In response to inadequate and decreased intake of calcium, increased production of 1,25(OH)2D leads to increased calcium absorption. And also, 1,25(OH)2D facilitates the cellular uptake of calcium from circulating blood (Newmark, 1994). The level of circulating 1,25(OH)2D varies inversely with that of calcium intake. It has been found that the addition of 1,25(OH)2D to mammary gland explants enhances calcium uptake into its functionally differentiated epithelial cells. Other studies shown, circulating levels of calcium influence the activity of renal 1-α-hydroxylase and thus the circulating concentration of 1,25(OH)2D. As a result, in normal physiologic states, vitamin D3 and calcium are metabolically interrelated and blood levels of both calcium and 1,25(OH)2D are maintained in relatively narrow ranges.

The biologically active form of vitamin D exerts its effects mainly through binding to nuclear vitamin D receptor (VDR) and further binding to specific DNA sequences, namely vitamin D response elements. Experimental studies have shown that 1,25(OH)2D can inhibit cellular proliferation, induce differentiation and apoptosis, and inhibit angiogenesis in normal and malignant breast cells. In rodent models, high intake of vitamin D has been shown to suppress high-fat diet-induced epithelial hyperproliferation and tumorigenesis of the mammary gland. Two distinct pathways of vitamin D biosynthesis and action have been proposed in mammary carcinogenesis, one involving 1,25(OH)2D and the other involving 25(OH)D. In the endocrine pathway, circulating 1,25(OH)2D reaches the breast tissue to exert its

anticarcinogenic effect. The other pathway is the autocrine/ paracrine pathway, in which circulating 25(OH)D reaches the breast tissue and is further catalyzed to 1,25(OH)2D by the 1- α -hydroxylase in the breasts. The locally produced 1,25(OH)2D may bind to VDR and therefore regulate cell proliferation, differentiation, and apoptosis.

A cohort study by Levi *et al.,* (2001) reported that calcium intake from dairy foods was inversely associated with premenopausal breast cancer within strata of vitamin D intake.

A study by Grau *et al.,* (2003) showed that calcium supplementation lowered the risk of colorectal adenoma only among subjects with a high level of 25(OH)D and that 25(OH)D was inversely associated with the risk only among subjects who received calcium supplements.

Thorne (2008) and Deeb (2007) also suggested a possible association between vitamin D3 and cancer risk. In studies of cancer cells and of tumors in mice, vitamin D3 has been found to have several activities that might slow or prevent the development of cancer, including promoting cellular differentiation, decreasing cancer cell growth, stimulating cell death (apoptosis), and reducing tumor blood vessel formation (angiogenesis).

Paloma Ordóñez-Morán (2008) found that vitamin D3 can adjust almost everything in the cancer cell, from its genetic messaging to its cytoskeleton. It can switch genes on and off, and it can reduce cell division, and it can calm the cancer cells so that they settle rather than spread "It seems that vitamin D3 can actually return a cancer cell to a normal and healthy state… one pathway seems to control everything".

Zeichner (2014) found that vitamin D3 supplementation in patients with non-metastatic HER2+ breast cancer is associated with improved disease-free survival, and improvement during neoadjuvant chemotherapy.

In our study the mean age of breast cancer women was (50.6) years while in America the mean age at the time of breast cancer diagnosis was (61) years.

We found a significant difference regarding vitamin D3 level among the studied groups, where it is lower among breast cancer patients similar to what Reimers (2014) found. Reimers LL stated that breast cancer risk may be associated with specific vitamin D3-related polymorphisms, and genetic variation in the vitamin D3 pathway should be considered when designing potential intervention strategies with vitamin D supplementation.

There was no significant difference in the estrogen receptor status and the level of vitamin D3. Stephanie Scarmo (2013) could not find a relation between them too.

Similarly, for progesterone receptor status there was no significant difference between them and the level of vitamin D3. IA Kermani (2011) also could not find a relation between them.

There was no significant difference between HER-2 positive or negative status and the level of vitamin D3. IA Kermani (2011) also could not find a relation between the two groups. We found a non-significant very weak negative correlation between vitamin D3 and TNM staging, similar to what was found by IA Kermani (2011).

In our study, there was very weak non-significant correlation between CA 15-3 and

vitamin D3 level. However, no study discussing such correlation could be found.

Histopathological cancer types (ductal versus lobular) did not have significant difference in vitamin D3 level. Skaaby T (2014) found no statistically significant associations between vitamin D3 status and total or specific cancer.

Table.1 Vitamin D Level Comparison in Control and Cancer Groups

Sample	Total	Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean ±SE Vit. D3 level	Mean ±SE Age (years)
		No.	%	No.	%	No.	%		
Control (Healthy)	212	208	98.11	4	1.89	0	0.00	47.2±0.55	49.98±0.81
CA group	212	5	2.36	11	5.19	196	92.45	13.1±0.75	50.6±0.77
								P value <0.001	P value 0.583

Table.2 Vitamin D Levels Distribution According to Estrogen Receptors Status

ER	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean±SE
	No.	%	No.	%	No.	%	No.	%	
Positive	168	79.25	5	2.98	9	5.36	154	91.67	13.29±0.93
Negative	44	20.75	0	0.00	2	4.55	42	95.45	12.38±0.74
									P value 0.625

Table.3 Vitamin D Levels Distribution According to Progesterone Receptor Status

PR	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean±SE
	No.	%	No.	%	No.	%	No.	%	
Positive	171	80.66	5	2.92	7	4.09	159	92.98	12.57±6.3
Negative	41	19.34	0	0.00	4	9.76	37	90.24	12.10±5.67
									P value 0.664

Table.4 Vitamin D Levels Distribution According to HER2 Status

HER	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean±SE
	No.	%	No.	%	No.	%	No.	%	
Positive	41	19.34	3	7.32	4	9.76	34	82.93	12.9±1.3
Negative	120	56.60	2	1.67	7	5.83	111	92.50	12.59±0.55
Equivocal +2	51	24.06	0	0.00	0	0.00	51	100.00	11.89±0.66
									P value 0.714

Table.5 Correlation between vitamin D and TNM staging

Staging	R	P value
T	-0.035	0.621
N	-0.129	0.069
M	-0.015	0.833
Ca 15-3	0.010	0.883

Table.6 Vitamin D Levels Distribution According to histopathological type

Histopathology	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean ±SE
	No.	%	No.	%	No.	%	No.	%	
Ductal	172	81.13	4	2.33	10	5.81	158	91.86	12.49±0.48
Lobular	40	18.87	1	2.50	1	2.50	38	95.00	12.44±0.92
									P value 0.969

Table.7 Vitamin D Levels Distribution According to Family History of Breast CA

Family History	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean ±SE
	No.	%	No.	%	No.	%	No.	%	
Positive	21	9.91	0	0.00	1	4.76	20	95.24	11±5.34
Negative	191	90.09	5	2.62	10	5.24	176	92.15	12.64±6.31
									P value 0.251

Table.8 Vitamin D Levels Distribution According to History of OCP

Contraceptive	Total		Optimal (30-100 ng/mL)		Insufficient (20-30 ng/mL)		Deficient (<20 ng/mL)		Mean ±SE
	No.	%	No.	%	No.	%	No.	%	
Positive	142	66.98	2	1.41	5	3.52	135	95.07	11.93±0.44
Negative	70	33.02	3	4.29	6	8.57	61	87.14	13.58±0.93
									P value 0.071

There was no significant difference between those with positive or negative family history of breast cancer in the level of vitamin D3.Tseng (2007) conclusion for women with a strong family history that were not associated with known cancer syndromes, dietary factors may be associated with a strong predictor of breast cancer risk. Since women with strong family history are often very motivated to change their lifestyle habits, further studies are needed to confirm whether changes in diet will change the breast density and the subsequent onset of breast cancer in these women.

Finally, there was no significant difference regarding the use of oral contraceptive and the level of vitamin D3. But there was no study that gave enough information about this parameter.

Conclusion

The deficiency in vitamin D3 is clear in breast cancer group .The study doesn't show any relation to estrogen, progesterone and HER2. There was no relation between vitamin D3 level and TNM staging, CA 15-3 marker, histopathological type of the tumor, family history or oral contraceptive pills usage.

Recommendations

Stressing the importance of treating vitamin D3 deficiency, and being a modifiable risk factor for breast cancer.

Extending the study in the future to include women with benign breast disease and precancerous conditions.

Increasing the availability of vitamin D3 kit in the general hospital.

References

American Cancer Society. Breast Cancer Facts & Figures 2011-2012. Atlanta: American Cancer Society, Inc.

Bortman, P., Folgueira, M.A., Katayama, M.L., Snitcovsky, I.M., Brentani, M.M. 2002. Antiproliferative effects of 1,25-dihydroxyvitamin D3 on breast cells: a mini review. *Braz. J. Med. Biol. Res.*, 35: 1 – 9.

Colditz, G.A., Frazier, A.L. 1995. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiol. Biomarkers Prev.*, 4: 567 – 71.

Colston, K.W., Hansen, C.M. 2002. Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. *Endocr. Relat. Cancer*, 9: 45 – 59.

Cui, Y., Rohan, T.E. 2006. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol. Biomarkers Prev.*, 15: 1427 – 37.

Deeb, K.K., Trump, D.L., Johnson, C.S. 2007. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nature Reviews Cancer*, 7(9): 684-700.

Giovannucci, E. 2005. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control*, 16: 83 – 95.

Gorham, E.D., Garland, F.C., Garland, C.F. Sunlight and breast cancer incidence.

Grau, M.V., Baron, J.A., Sandler, R.S., *et al*. 2003. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J. Natl. Cancer Inst.*, *9*5: 1765 – 71.18.

Holick, M.F. 2004. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am. J. Clin. Nutr*., 80: 1678–88S.

Jacobson, E.A., James, K.A., Newmark, H.L., Carroll, K.K. 1989. Effects of dietary fat, calcium, and vitamin D on growth and mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene in female Sprague-Dawley rats. *Cancer Res.*, 6300–3.

Kermani, I.A. 2011. Hematology and Oncology Research Center, Shahid Ghazi Tabatabai Hospital, and Physiology Department, Tabriz Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. *Asian Pac. J. Cancer Prev., 1*2(6): 1381-4.

Levi, F., Pasche, C., Lucchini, F., La Vecchia, C. 2001. Dietary intake of selected micronutrients and breast-cancer risk. *Int. J. Cancer*, 91: 260 – 3.

McCullough, M.L., Rodriguez, C., Diver, W.R., *et al*. 2005. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol. Biomarkers Prev.*, 14: 2898–904.

Newmark, H.L. 1994. Vitamin D adequacy: a possible relationship to breast cancer. *Adv. Exp. Med. Biol.*, 364: 109–14.14.

Paloma Ordóñez-Morán *et al*., RhoA–ROCK and p38MAPK-MSK1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells, *J. Cell Biol.*, 183(4): 697-710.

Reimers *et al*. 2014. Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk, *Cancer Causes Control.*

Saez, S., Falette, N., Guillot, C., Meggouh, F., Lefebvre, M.F., Crepin, M., William, L. 1993. McGuire Memorial Symposium. 1,25(OH)2D3 modulation of mammary tumor cell growth in vitro and in vivo. *Breast Cancer Res. Treat*, 27: 69–81.

Skaaby, T., Husemoen, L.L., Thuesen, B.H., *et al*. 2014. Prospective population-based study of the association between serum 25-hydroxyvitamin-D levels and the incidence of specific types of cancer. *Cancer Epidemiol. Biomarkers Prev.*, 23(7): 1220-9.

Stephanie Scarmo *et al*. 2013. Circulating levels of 25-hydroxyvitamin D and risk of breast cancer: a nested case-control study, *Breast Cancer Res.*, 15: R15.

Studzinski, G.P., Moore, D.C. 1995. Sunlight—can it prevent as well as cause cancer? *Cancer Res*., 55: 4014–22.

Thorne, J., Campbell, M.J. 2008. The vitamin D receptor in cancer. *Proceedings of the Nutrition Soc*., 67(2):115-127.

Tseng, M., Byrne, C., Evers, K.A., Daly, M.B. 2007. Dietary intake and breast density in high-risk women: a cross-sectional study, *Breast Cancer Res.*, 9(5): R72.

Vieth, R. 1999. Vitamin D supplementation, 25-hydroxyvitamin D concentrations

& safety. *Am. J. Clin. Nutr.*, 69: 842 – 56.

Welsh, J. 2004. Vitamin D and breast cancer: insights from animal models. *Am. J. Clin. Nutr.*, 80: 1721 – 4Sin the USSR. *Int. J. Epidemiol.*, 19: 820 – 4.

Yan Cui. Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Belfer 1301D, Bronx, NY 10461.

Zeichner, S.B., Koru-Sengul, T., Shah, N., Liu, Q., Markward, N.J., Montero, A.J., Glück, S., Silva, O., Ahn, E.R. 2014. Improved Clinical Outcomes Associated With Vitamin D Supplementation During Adjuvant Chemotherapy in Patients With HER2+ Non-metastatic Breast Cancer. *Clin. Breast Cancer*, pii: S1526-8209(14)00166-9. doi: 10.1016/j.clbc.2014.08.001.

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