RESEARCH COMMUNICATION

Association of Serum Level of 25 Hydroxy-Vitamin D with Prognostic Factors for Breast Cancer

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Abstract

Background and aim: In recent years, there has been considerable interest in whether vitamin D inhibits breast cancer development. Experimental studies have shown that vitamin D promotes cell differentiation and retards or terminates proliferation of breast cancer cells. However, there is little evidence supporting the association of vitamin D and prognosis of breast cancer. Methods and Materials: In this analytic-descriptive study, 119 female patients with histological proven breast cancer were recruited in Tabriz oncology clinics in a 15-month period of time. History of chemotherapy, radiotherapy or receiving vitamin D/Ca supplements and presence of other malignancies were exclusion criteria. Serum level of 25 hydroxy vitamin D (25(OH)D) was measured in all patients. Results: One hundred and nineteen patients with a mean age of 50.4±12.6 (26-76) years were enrolled in the study. Metastasis was present in 21.8% of the cases. Stage of tumor was I, II, III and IV in 11, 56, 26 and 26 patients, respectively. The Tumor grade was low in 37 cases, intermediate in 46 cases, and high in 36 cases. The P53, Ki-67, HER2, ER and PR were positive in 30.3%, 49.6%, 17.6%, 61.2% and 55.5% of the patients, respectively. The mean serum level of 25(OH)D was 15.7±17.8 (4-122) ng/ml, deficient in 66 cases, insufficient in 36 cases and normal level in 17 cases. The median level of 25(OH)D was lower in the P53+ group in a borderline trend (17.3 vs. 13.6 ng/ml; p=0.07). The median level of 25(OH)D was significantly higher in the patients with metastasis, as well (27.7 vs. 12.0 ng/ml; p=0.03). There was no significant association between the serum level of 25(OH)D and other studied parameters. Conclusion: Based on our findings, there may be an association between the serum level of 25(OH)D and prognosis of breast cancer.

Keywords: Breast cancer - vitamin D - prognosis - Iran

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Introduction

Breast cancer is one of the major public health problems in the world. It is the most frequent cancer and second cause of cancer related death in women in the United States (DeVita, 2008). In Iran its frequency is 17.4 cases in 100,000 people (Montazeri et al., 2008). Breast cancer is a heterogeneous disease and develops in interaction of hereditary and environment risk factors, that causes some changes in breast cancer cells (DeVita, 2008).

According to the literature, vitamin D deficiency is a risk factor for developing breast Cancer (John et al., 1999; Cui and Rohan 2006; Robien et al., 2007; Abbas et al., 2008; 2009; Gissel et al., 2008; Goodwin, 2009). The anticancer effect of vit D has been well demonstrated in different cells as well as normal and malignant breast cells. In vitro studies have shown vit D can inhibit the cell growth of other malignant cells beside breast cancer such as melanoma, prostate, colon, ovary and myeloid leukemia (Freedman and Goodwin ,2009).

Vit D exerts its anti carcinogenesis effect by inducing cell differentiation and proliferation, inhibiting and regulating cell growth and apoptosis. This effect is mediated by its active metabolite, 1.25 (OH) vit D, through binding to the Vit D receptor (VDR), that is present in almost all tissues including both normal and malignant breast cells. Even though the other metabolite of vit D like 25 (OH) vit D is biologically inactive but circulating 25 (OH) vit D is an excellent biological marker of the availability of vit D from the diet and sunlight exposure. The effect of vit D is not demonstrated clearly

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as prognostic factor in Breast Cancer (Goodwin, 2009). A prospective study by Freedman et al, has been shown that low vit D level at diagnosis has significant correlation with distant disease free survival, metastasis and overal survival independent of age, body mass index (BMI), insulin, tumor size, node status, estrogen receptor status and grade. In one study it was show on postmenopausal women who intake more than 800 IU/d versus less than 400 IU/d total vit D have lower risk of developing breast cancer. This relation is stronger among women with negative estrogen or progesterone receptor (Robien et al., 2007).

Considering the high prevalence and importance of breast cancer and its relation with vit D level, we conducted this study to determine any correlation of breast cancer prognostic factors with serum level of vitamin D in women with breast cancer, meanwhile to evaluate the vitamin D level in breast cancer patient in our studied community at diagnosis.

Materials and Methods

Subjects and Methods

In a descriptive-analytic study 119 newly diagnosed women with breast cancer were enrolled during 2009-2011 in Hematology and Oncology research center of Tabriz University of Medical Sciences. Inclusion criteria were: women with histologicaly confirmed Breast Cancer by two pathologists at first presentation. Exclusion criteria included: concurrent other malignancy, history of radiotherapy, chemotherapy or surgery, intake of calcium or vitamin D supplements. All patients signed informed consent, referred to laboratory for obtaining blood sample to measure 25 (OH) Vit D levels by chemiluminance method. Hydroxy vit D level classified in three groups: 1- deficient:<10ng/dl; 2- insufficient:10-30ng/dl; 3- normal:>30ng/dl Clinical stage of cancer and performance status were evaluated by physician after physical examination and Para clinic surveys. Histologic grade and status of ER, PR, HER2, Ki-67, and P53 were determined through IHC staining by pathologist. Number of lymph node involvement was evaluated after surgery or sentinel node evaluation. Demographic information was obtained by research staff through interview with patient.

Statistical Analysis

All data described by mean+/_ standard deviation, frequency and percentage, using version 15 SPSS, Mann –Whitney U,T test and Spearman correlation index (rho). Probability values of less than 0.05 were considered significant.

Results

One hundred and nineteen patients with a mean age of 50.4±12.6 (26-76) years were enrolled in the study. The mean serum level of 25(OH) D was 15.7±17.8 (4-122) ng/ml, deficient in 66 cases, insufficient in 36 cases and normal level in 17 cases. The relation of 25 (OH) Vit D level with age, tumor size, patient performance status was not statistically significant (p=0.91, rho=0.01, p=0.74, p=0.80 respectively). The relation of median value of serum 25 (OH) vitamin D to variables is shown in table 1. The median level of 25 (OH) vitamin D was significantly higher in metastatic patients compared to non metastatic patients. (27.7 vs. 12.0 ng/ml; p=0.03). The median level of 25 (OH) vitamin D in patients without mutation of p53 was higher than patients with p53 negative mutation, but this difference was not statistically significant (17.3 vs. 13.6 ng/ml; p=0.07). The studied variables relation regarding serum normal level of 25 (OH) vit D is shown in Table 2.

Table 1. Comparison of Variables Investigated based on Serum 25-Hydroxy Vitamin D Level

Variable		Normal	Insufficient	Deficient	P value
Number of involved lymph nodes					
	0	5 (29.4)	12 (33.3)	26 (39.4)	0.17
	1-3	6 (35.3)	13 (36.1)	9 (13.6)	
	4-9	4 (23.5)	5 (13.9)	18 (27.3)	
	≥10	2 (11.8)	6 (16.7)	13 (19.7)	
Stage	I	2 (11.8)	3 (8.3)	6 (9.1)	0.33
	II	4 (23.5)	19 (52.8)	33 (50.0)	
	III	4 (23.5)	6 (16.7)	16 (24.2)	
	IV	7 (41.2)	8 (22.2)	11 (16.7)	
Grade	Low	4 (23.5)	16 (44.4)	17 (25.8)	0.33
	Intermediate	3 (17.6)	12 (33.3)	31 (47.0)	
	High	10 (58.8)	8 (22.2)	18 (27.3)	
Metastases		7 (41.2)	8 (22.2)	11 (16.7)	0.09
P53+		3 (17.6)	7 (19.4)	26 (39.4)	0.05
Ki-67+		9 (52.9)	19 (52.8)	31 (47.0)	0.82
HER2+		2 (11.8)	7 (19.4)	12 (18.2)	0.73
ER+		10 (58.8)	25 (29.4)	39 (59.1)	0.56
PR+		8 (47.1)	21 (58.3)	37 (56.1)	0.74

Discussion

In this study serum level of 25 (OH) D was normal only in 14.3% of patients. 25 (OH) D levels were deficient in 55.5% and insufficient in 30.3% of patients. For first time, the protective effect of vitamin D against breast cancer development was suggested by Garland (1980). Shin et al revealed that consuming more than 1000mg Ca in a day in pre menopausal women decreases the risk of breast cancer up to 33% (Shin et al. , 2002). Lin et al showed inverse relation between calcium supplement consuming and breast cancer risk (Lin et al., 2007). In another study Rossi et al. (2009) compared the serum level of 25 (OH) D in 2569 women with breast cancer and 2588 control group. They showed 25 (OH) D level in patients was significantly lower than normal subject.

In Iran and other Middle East countries, the prevalence of vit D deficiency has been shown to be between 30-80% (Alagol et al., 2000; Azizi et al., 2000; Dawodu et al., 2003; Hashemipour et al., 2004), with female dominancy (Hashemipour et al., 2004). In spite of reported results in those studies, others reported some controversies about the relation between vitamin D deficiency and breast cancer risk (Simard et al., 1991; Frazier et al., 2003), so and based on multiple factors that may impact 25 (OH)D level, other randomized control trials looks to be necessary for resolving these controversies. In this study 25 (OH) D serum level in patient with P53 mutation was statistically

lower than patients without P53 mutation. In metastatic breast cancer patients serum vitamin D was significantly higher than patients without metastasis. The relation between serum 25 (OH)D level with tumor grade, stage, number of involved lymph nodes , hormone receptor, HER2 and ki-67 was not statistically significant. In review of the literature, few studies have been conducted about the correlation of prognostic factors in breast cancer and vitamin D deficiency. The results of these studies have been variable. Larsson et al. (2009) showed discordant correlation between calcium and vitamin D consuming only in estrogen and progesterone receptor negative breast cancer. We did not find significant association of 25(OH) D level with ER/PR status ,considering that their study compared breast tumor with healthy subjects, whereas we studied different groups of breast cancer patients. Goodwin et al. (2009) reported serum25 (OH) D level in breast cancer patients was not related to tumor stage, number of lymph node involvement and ER status.

In this study relation of 25 (OH) D level with P53 mutation indicates the role of vitamin D in improving breast cancer outcome. Several studies demonstrated that vitamin D in Breast Cancer can improve prognosis through apoptosis induction. On the other hand P53 gene is not able to inhibit apoptosis (Mathiasen et al., 1999).

Another finding in this study regarding the correlation of serum level of 25 (OH) D with metastasis was not consistent with previous studies. Nakagawa et al revealed that in animal model, 1, 25 (OH) D can prevent metastases in Lung Cancer (Nakagawa et al , 2005) , that is consistent with some other studies (Eisman et al., 1987; Haq et al., 1993 ; Colton et al., 1999; van den Bemd et al., 2000; Mantell et al., 2000;), But what really is the cause of such discrepancy.

Palmieri et al. (2006) showed that in advanced breast cancer regulating mechanisms of vitamin D metabolism has been broken down and paracrine effects of the tumor and 24 hydroxylase play a role in this regard. In the other hand in hypercalcemia of malignancy which is also common in breast tumor, serum level of parathormon is decreased. Thus vitamin D serum level and its metabolites are significantly decreased. However. in some cases the results have been inversed and for unexplained reasons, level of vitamin D metabolites has shown to be increased (Garland et al., 1990; Gorham et al., 1990; Van Weelden et al , 1998; John et al., 1999) .

In our study 21% of patients had metastases mainly in bone, which may be the reason of higher level of 25 (OH) D in metastatic patients. Overall based on current study there may be a link between serum 25 (OH) D level with some prognostic factors of breast cancer, but this relation is complex and requires further investigation. Our findings showed that there may be a correlation between the serum level of 25 (OH) D and breast cancer prognosis which needs further randomized studies to be done.

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