Association of Vitamin D Level with Clinicopathological Features in Breast Cancer

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Abstract

A population-based relationship between low vitamin D status and increased cancer risk is now generally accepted. However there were only few studies reported on prognostic impact. To determine the effect of low vitamin D on progression of breast cancer, we conducted a cross-sectional analysis of vitamin D levels and clinicopathological characteristics in 200 cases of breast cancer diagnosed during 2011-2012 at the National Cancer Institute of Thailand. Vitamin D levels were measured by high-performance liquid chromatography (HPLC). Clinical and pathological data were accessed to examine prognostic effects of vitamin D. We found that the mean vitamin D level was 23.0±6.61 ng/ml. High vitamin D levels (≥32 ng/ml) were detected in 7% of patients, low levels (<32 ng/ml) in 93% Mean vitamin D levels for stages 1-4 were 26.1±6.35, 22.3±6.34, 22.2±6.46 and 21.3±5.42 ng/ml respectively (P=0.016) and 24.1 and 21.3 ng/ml for lymph node negative and positive cases (P=0.006). Low vitamin D level (<32 ng/ml) was significantly found in majority of cases with advanced stage of the disease (P=0.036), positive node involvement (P=0.030) and large tumors (P=0.038). Our findings suggest that low and decreased level of vitamin D might correlate with progression and metastasis of breast cancer.

Keywords: Vitamin D - prognosis - breast cancer

Materials and Methods

Patients

In the present study peripheral blood was collected from two hundred cases of newly diagnosed breast cancer were evaluated for age, menopausal status, tumor stage, number of lymph node involvement, tumor size and

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vitamin D level at National Cancer Institute of Thailand. The study was approved by institutional review board and ethic committee.

Serum collection and determination of vitamin D level
Serum was isolated from peripheral blood after centrifugation and frozen at -80°C until measurement. Levels of vitamin D were determined by HPLC with UV detection (Neyestani et al., 2007).

Statistical analyses
Statistical analyses in this study were done using the SPSS 18.0 statistical software package (SPSS Inc., Chicago, IL, USA). The cut-off value of vitamin D level was 32 ng/L (Dawson-Hughes et al., 2005; Hart et al., 2006), used to groupings. The association between vitamin D levels and clinical pathological data of the patients was described with percentages and means, and the means were compared using t-test. Correlation between vitamin D levels and clinicopathological characteristics of the patients was evaluated using chi-square test. The results were considered statistically significant at P<0.05.

Results
In this study, mean vitamin D level was 23.02±6.61 ng/ml. High vitamin D levels (≥32 ng/ml) were detected in 14 patients (7%), while low levels (<32 ng/ml) in 186 cases (93%). They were significantly higher in post-menopause patients than pre-menopause cases (P=0.029; Table 1). Vitamin D was significantly inversely correlated with patients’ tumor stage (P=0.016), number of lymph node involvement (P=0.041) and tumor size (P=0.02; Table 1).

In addition, when compared vitamin D with clinicopathological parameters of the patients, we found that low vitamin D level (<32 ng/ml) was significantly mainly detected in cases with poor prognosis-high stage of the disease (P=0.036), positive-nodal involvement (P=0.030) and large tumor size (P=0.038)-as shown in Table 1.

Discussion
In this study, the majority of patients (93%) had low vitamin D levels (<32 ng/ml). These findings are similar to other reports that the majority of patients with breast cancer had low levels of vitamin D (Goodwin et al., 2009; Neuhouser et al., 2008). Our observation revealed that low levels of vitamin D were associated with advanced stage, positive-nodal involvement and large tumors, suggesting that the prognostic effect of vitamin D may be due to the aggressiveness of tumors in low vitamin D patients, consistent with a potential role of vitamin D in breast carcinogenesis. Low vitamin D levels in patients with breast cancer have been associated with increased risk of cancer and mortality (Freedman et al., 2007; Neuhouser et al., 2008; Goodwin et al., 2009; Mohr et al., 2014). Vitamin D levels have been reported to be significantly lower in women with locally advanced or metastatic breast cancer compared with women with early-stage disease (Palmiere et al., 2006). Metastasis is a complex, multistep process, during which circulating tumor cells (CTC) spread from the primary tumor mass, in the reversible epithelial-to mesenchymal transition (EMT) form, to the distant organs. Once distant organs are reached, these mesenchymal tumor cells reverse to an epithelial identity via mesenchymal-to-epithelial transition (MET) to regain the ability to proliferate (Vandewalle et al., 1993). The regulation of intracellular calcium in breast cancer may be important in modulating cell proliferation, differentiation, apoptosis and cytotoxicity, as well as contributing to mechanisms of action of anticancer agents. Vitamin D is intimately involved in maintaining cellular calcium homeostasis. The role of vitamin D in the regulation of intracellular calcium in the estrogen-receptor negative human breast

| Variables | No. | %  | Mean | SD  | P | No. | %  | No. | %  | P  |
|-----------|-----|----|------|-----|---|-----|----|-----|----|----|---|
| All patients | 200 | 100 | 20.66 | 6.61 |   | 186 | 93  | 14  | 7  |    |    |
| Age, years |     |    |       |      |    |   |     |     |    |    |    |
| ≤ 50 | 105 | 52.5 | 22.06 | 5.91 | 0.029 | 102 | 97.14 | 3   | 2.86 | 0.016 |
| > 50 | 95  | 47.5 | 24.09 | 7.19 |   | 84  | 88.42 | 11  | 11.58 |    |    |
| Menopausal status |     |    |       |      |    |   |     |     |    |    |    |
| Pre | 105 | 52.5 | 22.06 | 5.91 | 0.029 | 102 | 97.14 | 3   | 2.86 | 0.016 |
| Post | 95  | 47.5 | 24.09 | 7.19 |   | 84  | 88.42 | 11  | 11.58 |    |    |
| Tumor stage |     |    |       |      |    |   |     |     |    |    |    |
| 1 | 35  | 17.5 | 26.05 | 6.35 | 0.016 | 29  | 82.86 | 6   | 17.14 | 0.036 |
| 2 | 95  | 47.5 | 22.25 | 6.34 |   | 89  | 93.68 | 6   | 6.32  |    |    |
| 3 | 56  | 28  | 22.17 | 6.46 |   | 55  | 98.21 | 1   | 1.79  |    |    |
| ≥4 | 4   | 2.5  | 21.3  | 5.42 |   | 5   | 100  | 0   | 0    |    |    |
| Lymph node |     |    |       |      |    |   |     |     |    |    |    |
| 0 | 74  | 51.39 | 24.12 | 6   | 0.006 | 69  | 93.24 | 5   | 6.76 | 0.03 |
| ≥1 | 70  | 48.61 | 21.33 | 6.06 |   | 69  | 98.57 | 1   | 1.43 |    |    |
| Tumor size (cm) | | | | | | | | | | |
| ≤2 | 50  | 38.76 | 24.12 | 5.88 | 0.02 | 46  | 92  | 4   | 8   | 0.038 |
| >2-5 | 70  | 54.26 | 21.11 | 6.14 |   | 70  | 100  | 0   | 0    |    |    |
| ≥5 | 9   | 6.98  | 20.88 | 3.12 |   | 9   | 100  | 0   | 0    |    |    |

SD, standard deviation
cancer cell line BT-20 was observed in a study which showed that voltage-insensitive Ca2+ channels (VICC) and the thapsigargin-sensitive endoplasmic reticulum Ca2+ stores are the principal pathways for Ca2+ entry and Ca2+ mobilization in the breast cancer cell line. Vitamin D rapidly increases Ca2+ influx through VICC and after a chronic treatment, depletes endoplasmic reticulum Ca2+ stores. Targeting of Ca2+ signaling mediated by VICC and endoplasmic reticulum Ca2+ stores may represent a novel approach to the treatment and chemoprevention of breast cancer (Sergeev et al., 1998).

Furthermore, vitamin D levels shortly after diagnosis were significantly lower in American women with local versus regional breast cancer. Recently, lower vitamin D concentration was found to be associated with poorer overall survival and distant disease-free survival in post menopausal breast cancer patients (Vrieling et al., 2011).

Our findings provide the evidence that vitamin D may be used as a prognostic factor in patients with breast cancer. Although women with breast cancer will probably benefit in conditions of overall health from having high vitamin D levels, further investigation in larger studies is needed in recommending that vitamin D intake in patients with breast cancer be increased to high levels in order to improve breast cancer outcomes.

References

Ananthakrishnan AN, Cheng SC, Cai T, et al (2014). Association between reduced plasma 25-hydroxy vitamin D and increased risk of cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol, 12, 821-7.

Bao Y, Ng K, Wolpin BM, et al (2010). Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. Br J Cancer, 102, 1422-7.

Bolland MJ, Grey A, Gamble GD, et al (2011). Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women’s Health Initiative (WHI) limited-access data set. Am J Clin Nutr, 94, 1144-9.

Crew KD, Gammon MD, Steck SE, et al (2009). Association between plasma 25-hydroxyvitamin D and breast cancer risk. Cancer Prev Res (Phila), 26, 598-604.

Dawson-Hughes B, Heaney RP, Holick MF, et al (2005). Estimates of optimal vitamin D status. Osteoporos Int, 16, 713-6.

Freedman DM, Looker AC, Chang SC, et al (2007). Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst, 99, 1594-602.

Garland CF, Garland FC, Gorham ED, et al (2006). The role of vitamin D in cancer prevention. Am J Public Health, 96, 252-61.

Goodwin PJ, Ennis M, Pritchard KI, et al (2009). Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. J Clin Oncol, 27, 3757-63.

Gorham ED, Garland CF, Garland FC, et al (2007). Optimal vitamin D status for colorectal cancer prevention: a quantitative meta-analysis. Am J Prev Med, 32, 210-6.

Hart GR, Furniss JL, Laurie D, et al (2006). Measurement of vitamin D status: background, clinical use, and methodologies. Clin Lab, 52, 335-43.

Hatse S, Lambrechts D, Verstuyf A, et al (2012). Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. Carcinogenesis, 33, 1319-26.

Holick MF (2006). Vitamin D: its role in cancer prevention and treatment. Prog Biophys Mol Biol, 92, 49-59.

Larriba MJ and Munoz A (2010). Mechanisms of resistance to vitamin D action in human cancer cells. In: Holick MF, editor. Vitamin D physiology, molecular biology, and clinical applications. New York: Humana Press. pp. 325-33.

Lowe LC, Guy M, Mansi JL, et al (2005). Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer, 41, 1164-9.

Mehm SB, Gorham ED, Kim J, et al (2014). Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Res, 34, 1163-6.

Neuhouser ML, Sorensen B, Hollis BW (2008). Vitamin D insufficiency in a multietnic cohort of breast cancer survivors. Am J Clin Nutr, 88, 133-9.

Neyestani TR, Gharavi A, Kalayi A (2007). Determination of serum 25-hydroxy cholecalciferol using high-performance liquid chromatography: a reliable tool for assessment of vitamin D status. Int J Vitam Nutr Res, 77, 341-6.

Palmieri C, MacGregor T, Girgis S, et al (2006). Serum 25-hydroxyvitamin D levels in early and advanced breast cancer. J Clin Pathol, 59, 1334-6.

Sergeev IN, Rhoten WB (1998). Regulation of intracellular calcium in human breast cancer cells. Endocrine, 9, 321-7.

Vandewalle B, Hornez L, Lassalle B, et al (1993). Intracellular calcium and breast cancer growth and differentiation. Intern J Oncol, 2, 613-20.

Vrieling A, Hein R, Abbas S, et al (2011). Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast Cancer Res, 13, 74.

Yang J, Mani SA, Weinberg RA (2006). Exploring a new twist on tumor metastasis. Cancer Res, 66, 4549-52.

Yin L, Grandi N, Raum E, et al (2010). Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer, 46, 2196-205.

Yousef FM, Jacobs ET, Kang PT, et al (2013). Vitamin D status and breast cancer in Saudi Arabian women: case-control study. Am J Clin Nutr, 98, 105-10.