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ORIGINAL PAPER

Serum calcium levels are elevated among women with untreated postmenopausal breast cancer

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Abstract
Objective Reports of an association between primary hyperparathyroidism in women and risk of breast cancer suggest an etiologic role for high serum calcium. However, data on the association between serum calcium levels and breast cancer in women without clinical hyperparathyroidism are limited.
Methods We conducted a hospital-based case–control study among postmenopausal women in Fargo, ND. Cases were women aged 65 and older with newly diagnosed, histologically confirmed breast cancer. Controls were aged 65 and older without clinical cancer who were seen at the same hospital.
Results We obtained data on 190 white cases and 172 white controls. Primary hyperparathyroidism (an abnormally high calcium level confirmed by an abnormally high serum PTH) was found in 3/190 cases and in 0/172 controls ($p = 0.25$). After excluding the women with primary hyperparathyroidism, the mean calcium levels among cases was 9.6 mg/dL (range, 7.5–11.0, SD = 0.47) vs. 9.4 mg/dL (7.7–10.5, 0.43) among the controls ($p < 0.0001$). Comparing women in the top with women in the bottom tertile of serum calcium, the multivariable-adjusted odds ratio (OR) for breast cancer was 5.21 (95% CI: 2.59–10.48). There was no relationship between serum calcium and tumor size or stage.
Conclusion The distribution of serum calcium levels among postmenopausal women with incident breast cancer was shifted significantly toward the right. These findings are consistent with an effect of early breast tumors on calcium homeostasis. However, the lack of association between serum calcium levels and tumor size or stage supports the hypothesis that subclinical hyperparathyroidism may increase the risk for breast cancer.

Keywords Breast cancer · Postmenopausal · Epidemiology · Serum calcium · Primary hyperparathyroidism

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Introduction

Breast cancer is the most commonly diagnosed cancer among United States (US) women with an estimated 192,569 new cases diagnosed in 2009. Mortality from breast cancer ranks second only to lung cancer with 40,470 breast cancer deaths predicted in 2009 [1]. Risk for breast cancer increases with age, with 78% of all breast cancers occurring in women of more than 50 years of age and 86% of breast cancer deaths occurring in this age group [2]. Established risk factors for breast cancer explain only about 13% of breast cancer incidence among women in the US [3]. Thus, the causes of most cases of breast cancer remain unknown.

A growing body of epidemiologic literature, ranging from case series to prospective cohort studies, implicates the calcium/parathyroid hormone axis in breast cancer [4, 5]. Numerous studies have shown an increased risk of breast cancer among women diagnosed with primary hyperparathyroidism [6, 7]. For example, Nilsson and colleagues conducted a record linkage study within the National Swedish Registry using persons subjected to parathyroid adenomectomy. They observed a standardized incidence ratio (SIR) of 1.44 (95% CI: 1.25–1.62) for breast cancer [8]. These findings raise the possibility that high serum calcium and/or high serum calcium and parathyroid hormone, increase the risk of breast cancer. There are few data available on the association between breast cancer and serum calcium among women who are not clinically hypercalcemic. Because serum calcium levels are commonly recorded during routine physical examinations, we examined these in a case–control study of incident breast cancer in relation to serum calcium levels in Fargo, North Dakota.

Methods

We performed a retrospective analysis of medical charts of patients newly diagnosed with breast cancer between January 2004 and December 2008. Cases were identified from the cancer registry of Meritcare hospital, North Dakota, USA. Controls were identified from the primary care database of the same hospital. This facility serves the Fargo Metropolitan Area comprising all of Cass County, North Dakota and Clay County, Minnesota. Meritcare hospital covers the entire population in the area. The population base of this area, according to the 2006 estimate (http://en.wikipedia.org/wiki/North_Dakota), is approximately 240,000. The majority (95%) of the population served in this area is white. Service area spans 250 miles west to east. The North Dakota Cancer Registry releases annual cancer statistics when the registry's data is estimated to be 95% complete for any given cancer-reporting year. Blue Cross Blue Shield of North Dakota is the largest provider of health care coverage in the state.

The study was approved by the Institutional Review Boards of the Hospital and the University of North Dakota.

Study design

Data collection

Information on age at diagnosis, family history of breast cancer, total serum calcium, use of calcium and vitamin D supplements, multivitamins use, and body mass index (BMI) [weight (kg)/height (m^2)] were collected. We also obtained data on smoking status (self-reported), alcohol use (self-reported), age at first pregnancy, age at menarche and menopause, parity, history of hysterectomy, hormonal replacement therapy use (defined as ever/never), type of hormonal replacement therapy use, stage of breast cancer at diagnosis (TNM), tumor size, hormonal receptors status, and mammography use within the last 2 years. Information was obtained for the period within 1 year prior to diagnosis for cases and prior to the physical examination for controls.

The inclusion criteria for cases were women with incident, histologically confirmed breast cancer as a primary site with cancer diagnosed between 2004 and 2008 using a pathology report present in the medical records, aged 65 and older, and date of the laboratory tests within a year prior to the diagnosis of breast cancer median (range): 20 (0–360) days. The proportion of cases that had calcium levels collected at time of diagnosis was approximately 24%. The exclusion criteria included diagnosis of any cancer other than primary breast cancer and diagnosis outside the study period. The inclusion criteria for controls were women who had an annual physical examination between 2004 and 2008 at the same hospital as cases, aged 65 and older, without any cancer seen at the same hospital as cases, and date of laboratory tests within a year of the annual physical examination median (range): 17 (0–358) days. We excluded women with a history of conditions that are associated with a derangement in the calcium-parathyroid axis, including chronic kidney disease or glomerular filtration rate (GFR) < 60, lithium therapy, sarcoidosis, and previous history of primary hyperparathyroidism. Because of the small number of patients who were not Caucasian (<6% of residents of Fargo-Moorhead are non-Caucasian), the study was restricted to Caucasians.

Age at menopause was defined as age at last menstrual period for women with natural menopause or age when estrogen use was initiated for women who had a hysterectomy with ovarian conservation.

Study population

Eligible cases were 293 white women with confirmed breast cancer who had had no other cancer. The following women were excluded: 47 women had missing values for serum calcium, 14 previous malignancy, 4 history of parathyroid disease, 7 chronic kidney disease or abnormal GFR, 2 with sarcoidosis, 29 lithium or thiazide diuretic use, which left 190 cases. Controls were selected from 218 white women with no history of cancer who had an annual physical examination at the same hospital. The following women were excluded: 19 women had missing values for serum calcium, 5 for previous malignancy, 2 for history of parathyroid disease, 4 chronic kidney disease or abnormal

GFR, and 16 lithium or thiazide diuretic use, which left 172 controls.

Statistical analysis

Unadjusted mean values were calculated for all continuous variables and frequency distributions were calculated for all categorical variables. We compared cases and controls on demographic, reproductive and other variables using Wilcoxon signed-rank test or *t*-test for continuous variables and with chi-square test for categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression. Multivariable logistic regression included terms for age at diagnosis, family history of breast cancer, BMI, hormonal therapy use, age at menarche, age at menopause, and parity. All p values are two-sided. All two-way interactions involving serum calcium were assessed. Tests for interaction were assessed by introducing a multiplicative term between the two variables for: (age, BMI, and estrogen) in the multivariable model using a Wald test. Statistics were performed using SAS (SAS Institute, Cary, NC; Version 9.1.3 Users Guide). All statistical tests were two-tailed with $p < 0.05$ considered to be significant.

Results

Participants were 190 women with newly diagnosed breast cancer and 172 without breast cancer. Women newly diagnosed with breast cancer were slightly but significantly older than controls (median age [range]: 75 (65–94) vs. 71 (65–93); $p = 0.0001$). Breast cancer patients had a higher prevalence of family history of breast cancer (39 vs. 27%, respectively; $p = 0.02$) (Table 1). They were also more likely to be overweight or obese (75 vs. 65%; $p = 0.02$). The majority of cases (85%) were diagnosed at an early stage (i.e., stage 1 or 2) breast cancer (Table 2). Most cases (81%) had an estrogen receptor positive and progesterone receptor positive (69%). Women who used hormonal replacement therapy had a significantly increased risk for breast cancer (OR = 2.12, 95% CI: 1.21–3.70).

We defined primary hyperparathyroidism as a total serum calcium greater than 10.2 mg/dL and a serum intact PTH greater than 72 (the upper limit of the reference ranges at our hospital) or a PTH that was inappropriately high in the presence of an abnormal serum calcium. PTH was not routinely obtained for all patients but was obtained in several instances because of clinical suspicion of primary hyperparathyroidism.

Three of the 190 cases would be considered to have prevalent primary hyperparathyroidism vs. 0/172 controls

Table 1 Distribution of 190 cases of newly diagnosed breast cancer and 172 controls according to demographic and clinical characteristics between 2004 and 2008

Variables	Cases		Controls	
	n	%	*n*	%
Age at diagnosis (years)				
65–74	93	49	118	68
75–84	71	37	46	27
85–94	26	14	8	5
Median (range)	75 (65–94)		71 (65–93)	
Body mass index				
Normal	44	23	60	34
Overweight	66	35	61	36
Obese	76	40	50	29
Missing values	4	2	1	1
Median (range)	29 (17–63)		27 (17–47)	
Smoking status				
Never	124	65	122	71
Past	51	27	38	22
Current	14	7	11	6
Missing	1	1	1	1
Alcohol use				
Never	117	61	80	46
Past	–	–	1	1
Current	70	37	90	52
Missing	3	2	1	1
Age at first pregnancy (years)				
<20	36	19	37	22
20–24	43	23	60	35
25–29	43	23	23	13
≥30	2	1	–	–
Missing	66	34	52	30
Age at menarche (years)				
≤11	27	14	41	24
12-13	64	34	73	43
≥14	42	22	35	20
Missing	57	30	23	13
Age at menopause (years)				
<47	36	19	27	16
47–51	57	30	85	49
52–55	28	15	45	26
≥56	8	4	4	2
Missing	61	32	11	7
Parity	($n = 164$)		($n = 154$)	
0	22	12	15	9
1–2	48	25	52	30
3–4	70	37	67	39
≥5	46	24	35	20
Missing	4	2	3	2

Table 1 continued

Variables	Cases		Controls	
	n	%	*n*	%
History of hysterectomy				
No	109	57	108	63
Yes	70	37	57	33
Missing	11	6	7	4
Family history of breast cancer				
No	108	57	115	67
Yes	75	39	47	27
Missing	7	4	10	6
Type of hormonal therapy	($n = 63$)		($n = 45$)	
Never	78	41	106	70
Estrogen	33	17	28	19
Progesterone	1	1	–	–
Estrogen and progesterone	20	10	17	11
Other	9	5	–	–
Missing	49	25	21	12
Total serum calcium level (mg/dl)	9.6 (7.5–11.1)		9.3 (7.7–10.5)	
Dose of calcium supplement use				
Never	14	7	38	22
≤1,000	48	25	63	37
>1,000–1,500	57	30	60	35
>1,500	7	4	11	6
Missing	64	34	–	–
Dose of Vitamin D supplement use	($n = 83$)		($n = 108$)	
Never	23	12	64	37
≤400	62	33	73	42
>400–800	13	7	18	11
>800	8	4	17	10
Missing	84	44	–	–
Multivitamins use				
No	53	28	53	31
Yes	135	71	119	69
Missing	2	1	–	–
Mammography use within 2 years				
No	34	18	18	10
Yes	140	74	154	90
Missing	16	8	–	–

($p = 0.25$). These included two women with PTHs that were beyond the reference range (160 and 73) and one woman with a PTH of 63 that was abnormally elevated in the context of an elevated serum calcium of 11.1 mg/dL. After excluding the three women with primary hyperparathyroidism, the mean calcium levels among cases was 9.6 mg/dL (range, 7.5–11.0, SD = 0.47) vs. 9.4 mg/dL (7.7–10.5, 0.43) among the controls ($p < 0.0001$). The distribution of serum calcium among the cases and controls was normally distributed.

Table 2 Distribution of 190 cases of newly diagnosed breast cancer according to clinical characteristics between 2004 and 2008

Variables	Cases	
	n	%
Stage of breast cancer at diagnosis		
I	99	58
II	45	27
III	22	13
IV	3	2
Missing	21	11
Tumor size (cm)		
≤2	120	63
>2	53	28
Missing	17	9
Hormonal receptor status of tumor		
ER		
Positive	155	81
Negative	24	13
Missing	11	6
PR		
Positive	130	69
Negative	48	25
Missing	12	6

However, relative to the distribution of serum calcium for the controls, the distribution for the cases was significantly shifted toward the right (Fig. 1).

Comparing women in the top with women in the bottom tertile of serum calcium, the multivariable-adjusted odds ratio (OR) for incident breast cancer was 5.21 (95% CI: 2.59–10.48) (Table 3). These findings were not affected by the removal of women with more advanced disease (stage IV). Similar findings were observed when the results were stratified by estrogen use and for +ER tumors and for +PR tumors (data not shown). There was no apparent relationship between serum calcium level and tumor size or stage (Table 4).

Discussion

The central finding of this paper is that, compared to non-cancer controls, the distribution of serum calcium among postmenopausal women with incident, untreated breast cancer was shifted significantly to the right and their mean serum calcium was modestly, but significantly higher (9.6 vs. 9.4, $p < .0001$). Compared with women in the lowest tertile of total serum calcium, women in the highest tertile had a multivariate-adjusted odds ratio of 5.21 (95% CI: 2.59–10.48).

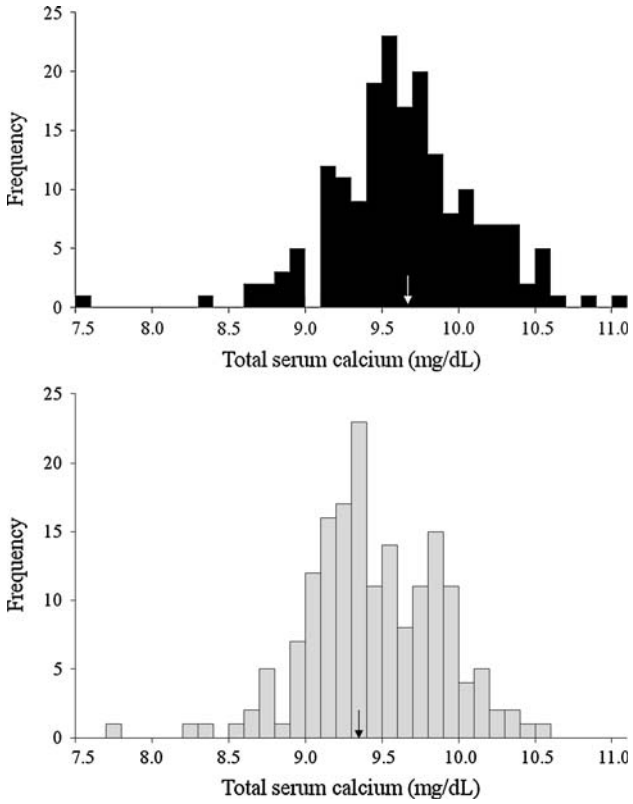

Fig. 1 Serum calcium levels (mg/dL) distribution among cases and controls

We found a higher prevalence of primary hyperparathyroidism among women with incident breast cancer, 3/190 vs. 0/170. A high prevalence of primary hyperparathyroidism in breast cancer has been reported by several investigators. For example, Mann et al. [22] recently reported a prevalence of 4%, approximately twice the expected rate, among breast cancer cases within 5 years of diagnosis. Similarly, Camacho et al. [9] compared 64 women with a history of treated breast cancer to a control group of 174 non-breast cancer patients. The prevalence of primary hyperparathyroidism was 4.7 vs. 1.7% among the controls ($p = 0.196$). Interestingly, these authors reported a higher prevalence of idiopathic hypercalciurea among cases (15.6 vs. 8.0%, $p = 0.085$). Idiopathic hypercalciurea is a disorder characterized by normocalcemia in the presence of a generalized increase in calcium turnover. Although the pathophysiology of idiopathic hypercalciurea is incompletely understood, one potential mechanism is parathyroid hyperfunction [10, 11].

Our results are similar to those of Fierabracci et al. who studied 100 women aged 28–80 with treated breast cancer, 102 healthy age-matched women and 60 age-matched women with differentiated thyroid cancer [12]. Seven of the 100 cases were diagnosed with primary hyperparathyroidism (i.e., a prevalence of 7%) vs. none of the normal or thyroid cancer controls ($p = 0.005$ and 0.04, respectively). After the patients with prevalent primary hyperparathyroidism were removed, the mean (±SD) values for serum calcium were 9.6 ± 0.5 mg/dL for the cases vs. 9.3 ± 0.5 for the normal and 9.2 ± 0.6 mg/dL for the thyroid cancer controls. Our findings are similar to those reported by Fierabracci et al. but differ in the important respect that the cases in our study were untreated.

Table 4 Serum calcium levels (mg/dL) distribution by breast cancer stage and tumor size

	Serum calcium levels (mean, SD, range)	*p* value
Stage of breast cancer ($n = 166$)		0.61
I ($n = 97$)	(9.55, 0.47, 7.5–10.5)	
II ($n = 44$)	(9.67, 0.45, 8.8–10.6)	
III ($n = 22$)	(9.57, 0.57, 8.7–11)	
IV ($n = 3$)	(9.57, 0.45, 9.1–10)	
Tumor size (cm) ($n = 170$)		0.46
≤2 ($n = 118$)	(9.59, 0.44, 8.3–11)	
>2 ($n = 52$)	(9.67, 0.42, 8.7–10.6)	

Table 3 Odds ratios (ORs) for 187 (excluding three women newly diagnosed with primary hyperparathyroidism) cases of newly diagnosed breast cancer and 172 controls by tertile of serum calcium levels between 2004 and 2008

	Tertile of serum calcium (median value)		
	Tertile 1 (≤9.2 mg/dL)	Tertile 2 (>9.2–9.6 mg/dL)	Tertile 3 (>9.6 mg/dL)
No. incident breast cancer (cases)	37	68	82
		OR, 95% CI	OR, 95% CI
Unadjusted ORs	Reference	2.26, 1.20–4.27	3.54, 1.91–6.59
Age-adjusted ORs	Reference	2.31, 1.20–4.45	4.39, 2.28–8.44
+Family history of breast cancer	Reference	2.46, 1.27–4.79	4.68, 2.40–9.12
+Hormonal therapy use	Reference	2.79, 1.38–5.65	5.21, 2.59–10.48

Age at diagnosis was included in the multivariable logistic regression as a continuous variable

Our findings add to a growing literature that implicates a subtle aberration in calcium among women with breast cancer. A central problem in this literature is in determining whether the higher levels of calcium in serum are a cause or a consequence of breast cancer. It is conceivable that our findings could be based on difference in health behaviors. For example, if cases increased their intake of calcium and vitamin D in order to prevent skeletal fracture, this might account for their higher serum calcium levels. However, multivitamins use was similar among cases and controls (71 vs. 69%). Use of calcium and vitamin D was actually more common among controls ($p = 0.07$ and 0.03, respectively). We also examined serum calcium levels by calcium intake. For all women who did not take calcium supplements, the mean serum calcium was 9.5 ± 0.42, which is identical to the serum calcium for women who reported taking more than 1,000 mg of calcium per day. This is consistent with the findings that calcium levels in serum generally are tightly controlled and are not correlated with levels of calcium in diet [13].

Alternately, the higher levels of calcium among cases could be due to the pathophysiology of breast cancer. Approximately 30% of women with breast cancer develop hypercalcemia at some point in their disease. Typically, the hypercalcemia results from local osteolysis of bone. However, even early stage breast cancers may be associated with aberrations in calcium homeostasis that are caused by parathyroid hormone-related protein (PTHrP), the agent of humoral hypercalcemia of malignancy [14]. Serum levels of PTHrP, which are known to increase serum levels of calcium, are reported to increase with tumor size in both hematologic and solid tumors [23]. However, if the increase in serum calcium that we observed were due to PTHrP, it might be expected that serum calcium levels would increase with tumor size and stage, which was not observed. Camacho et al. [9] also observed no relationship between tumor size and stage. Moreover, Fierabracci et al. reported that the mean PTH was significantly higher in the breast cancer cases than among either control group. This suggests that the modestly higher mean serum calcium among the cases may be caused by a higher setpoint for serum calcium. To our knowledge, the only prospective study of breast cancer in relation to serum calcium levels is that of Almquist et al. [15] who examined a cohort of 7,847 women from the Malmo Preventive Project. Although there was no association between serum calcium levels and breast cancer overall, higher serum calcium was associated with a significantly increased risk of breast cancer among overweight postmenopausal women. A recent reanalysis of this cohort by Almquist et al. [16] showed that pre-diagnostic serum calcium levels were positively associated with increased tumor aggressiveness in premenopausal and/or overweight women.

We studied total serum calcium, which includes the fraction of calcium that is bound to albumin (about 40% of the total), to other ions (e.g., phosphate, about 10%), as well as the physiologically active, ionized fraction (about 50%). In normal individuals, total serum calcium is well-correlated with ionized calcium levels [17]. Conditions that alter the bound fraction of serum calcium, principally low albumin, can spuriously lower the value for total serum calcium. Lower levels of serum albumin have been reported in stage 4 breast cancer by many authors [18]. Although we had few cases with advanced disease, the effect of low albumin would be to lower the value of total serum calcium (i.e., a bias in the opposite direction of our findings).

We cannot rule out a causative role for PTHrP or other endocrine factors that were not measured in our study. However, our findings are consistent with a growing literature that suggests that calcium may play an etiologic role in breast cancer. Increases in serum calcium could increase breast cancer risk by several mechanisms. For example, the calcium-sensing receptor (CaR) is known to be expressed in the normal and cancerous human breast [19]. High calcium levels have been shown to activate the CaR and to stimulate protein kinases resulting in an increased proliferation of these cells. It is noteworthy that two prospective studies recently reported an increased risk for fatal prostate cancer among men with serum calcium levels that are high but within the normal range [20, 21].

Calcium is routinely available as part of the annual physical examination or possibly as a part of screening for osteoporosis or would be measured for suspected primary hyperparathyroidism. However, if serum calcium was measured because of suspected primary hyperparathyroidism, this would result in a higher prevalence of high serum calcium in the controls and would bias the results toward the null. In secondary hyperparathyroidism, the serum calcium is low but the major reason for secondary hyperparathyroidism is chronic kidney disease for which the patients were excluded. Finally, it is possible that we did not have enough power to detect associations between calcium level and tumor stage or size.

In summary, our case–control study of 190 cases and 172 controls found a small, but significantly higher mean serum calcium level among postmenopausal Caucasian women with newly diagnosed, untreated breast cancer. These data are consistent with several prospective cohorts showing an increased risk for breast cancer among women with primary hyperparathyroidism. Prospective studies are required to determine whether the altered distribution of serum calcium is a cause or a consequence of breast cancer.

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References

1. Cancer facts and figures (2009) American Cancer Society
2. American Cancer Society. Breast Cancer Facts & Figures (2005–2006) American Cancer Society, Inc., Atlanta
3. Colditz GA, Rosner B (2000) Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 152:950–964
4. Pal SK, Blazer K, Weitzel J, Somlo G (2009) An association between invasive breast cancer and familial idiopathic hyperparathyroidism: a case series and review of the literature. Breast Cancer Res Treat 115:1–5
5. Garner CN, Ganetzky R, Brainard J et al (2007) Increased prevalence of breast cancer among patients with thyroid and parathyroid disease. Surgery 142:806–813
6. Michels KB, Xue F, Brandt L, Ekbom A (2004) Hyperparathyroidism and subsequent incidence of breast cancer. Int J Cancer 110(3):449–451
7. Palmér M, Adami HO, Krusemo UB, Ljunghall S (1988) Increased risk of malignant diseases after surgery for primary hyperparathyroidism. A nationwide cohort study. Am J Epidemiol 127(5): 1031–1040
8. Nilsson IL, Zedenius J, Yin L, Ekbom A (2007) The association between primary hyperparathyroidism and malignancy: nationwide cohort analysis on cancer incidence after parathyroidectomy. Endocr Relat Cancer 14:135–140
9. Camacho PM, Dayal AS, Diaz JL et al (2008) Prevalence of secondary causes of bone loss among breast cancer patients with osteopenia and osteoporosis. J Clin Oncol 26(33):5380–5385
10. Worcester EM, Coe FL (2008) New insights into the pathogenesis of idiopathic hypercalciuria. Semin Nephrol 28(2):120–132
11. Evan RA, Hills E, Wong SP, Wyndham LE, Eade Y, Dunstan CR (1984) The pathogenesis of idiopathic hypercalciuria: evidence for parathyroid hyperfunction. Q J Med 53:41–53
12. Fierabracci P, Pinchera A, Miccoli P et al (2001) Increased prevalence of primary hyperparathyroidism in treated breast cancer. J Endocrinol Invest 24(5):315–320
13. Jorde R, Sundsfjord J, Bønaa A (2001) Determinants of serum calcium in men and women. The Tromsø study. Eur J Epidemiol 17:1117–1123
14. Wysolmerski JJ, Broadus AE (1994) Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. Annu Rev Med 45:189–200
15. Almquist M, Manjer J, Bondeson L, Bondeson AG (2007) Serum calcium and breast cancer risk: results from a prospective cohort study of 7, 847 women. Cancer Causes Control 18(6):595–602
16. Almquist M, Anagnostaki L, Bondeson L et al (2009) Serum calcium and tumour aggressiveness in breast cancer: a prospective study of 7847 women. Eur J Cancer Prev 18(5):354–360
17. Calvi LM, Bushinsky DA (2008) When is it appropriate to order an ionized calcium? J Am Soc Nephrol 19:1257–1260
18. Coates R, Clark WS, Eley W, Greenberg RS, Huguley CM Jr, Brown RL (1990) Race, nutritional status and survival from breast cancer. JNCI 82:1684–1692
19. Cheng I, Klingensmith ME, Chattopadhyay N et al (1998) Identification and localization of the extracellular calcium-sensing receptor in human breast. J Clin Endocrinol Metab 83(2): 703–707
20. Skinner HG, Schwartz GG (2008) Serum calcium and incident and fatal prostate cancer in the National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev 17(9): 2302–2305
21. Skinner HG, Schwartz GG (2009) A prospective study of total and ionized serum calcium and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev 18(2):575–578
22. Mann GB, Kang YC, Brand C, Ebeling PR, Miller JA (2009) Secondary causes of low bone mass in patients with breast cancer: a need for greater vigilance. J Clin Oncol 27(22):3605–3610
23. Nakamura Y, Bando H, Shintani Y, Yokogoshi Y, Saito S (1992) Serum parathyroid hormone-related protein concentrations in patients with hematologic malignancies or solid tumors. Acta Endocrinol (Copenh) 127(4):324–330