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ORIGINAL PAPER

BsmI but not FokI polymorphism of *VDR* gene is contributed in breast cancer

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Abstract There is growing evidence of a malignancy-protective role for vitamin D in breast cancer. The effects of vitamin D are mediated via the vitamin D receptor (VDR) which is encoded by *VDR* gene. Several SNPs on *VDR* gene has attracted research interest, although the magnitude of the impact of *VDR* allelic variations on breast cancer has been controversial. In the present study, we focused on the distribution of *VDR* FokI and BsmI polymorphisms in Iranian breast cancer patients. A case–control study was conducted on 296 samples including 140 breast cancer patients and 156 age matched control women. Restriction fragment length polymorphism (RFLP) analysis was performed for BsmI and FokI genotyping. Randomly selected PCR products were subjected to sequencing to verify the RFLP results. A significantly increased risk of breast cancer was observed with BsmI bb or even Bb genotype (OR 2.39, CI 1.17–4.85 and OR 2.28, CI 1.16–4.47, respectively). Nevertheless, statistically significant association between FokI genotypes and breast cancer risk was not observed. This study lends support for an increased risk of breast cancer associated with the *VDR* BsmI polymorphism.

Keywords Vitamin D receptor · Breast cancer · Single nucleotide polymorphism · RFLP

We observed an increased risk of breast cancer associated with the *VDR* BsmI polymorphism in Iranian patients. This is the first report with this regard.

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Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide. It is responsible for 16 % of all and 22.9 % of invasive female cancers (http://www.who.int/cancer/detection/breastcancer/en/index1.html). Despite lots of investigation on the molecular pathogenesis of breast cancer, the predisposing biological processes are still not well characterized [1]. In most cases, genetic alterations of the pathways controlling growth, differentiation, apoptosis, or genomic repair lead to the malignancy [2]. Most of these changes are mediated through transcriptional-regulatory elements [3].

Data are accumulating regarding the protective role of vitamin D in various types of cancers [4]. In vitro studies revealed that vitamin D enhanced the differentiation and apoptosis of cancer cells in culture [5] including mammary glands [6]. The effects of vitamin D are mediated via the vitamin D receptor (VDR) which is expressed in most cell

types, including breast tissues [7]. VDR belongs to nuclear receptor superfamily with a well-known role of transcriptional-regulatory factor [8]. It has been shown that breast tumors which express more VDR have better prognosis [9]. Animal model study exhibits enhanced growth and branching of breast tissue in VDR knockout mice [10].

The gene encoding the VDR is mapped on the long arm of chromosome 12 (12q12–14) composed of 9 exons, with an alternatively spliced promoter region [11, 12]. A series of polymorphisms in the *VDR* gene were reported to be linked to various biological processes [13]. FokI restriction enzyme can identify a variable site (rs2228570) in exon 2 of the gene [14]. The alteration made by a C/T transition (ACG to ATG) at the translation initiation sites and results in three amino acids longer proteins [15]. BsmI polymorphism which is located at the 3′ end of the gene apparently does not change the translated protein and has no known function on VDR [13]. This G → A polymorphism is located on intron 8 and is linked in a haplotype with variable-length polyA sequence within the 3′-untranslated region that has an impact on VDR mRNA stability [16].

Polymorphisms of the *VDR* gene are also associated with some pathological situations including osteoporosis [17, 18]. Although the impact of these allelic variation on breast cancer is still controversial [15, 19–21]. Recently, it has been shown that the ATG genotype at FokI site enhanced aggressive breast cancer via a poor response to vitamin D treatment [22]. In the present study, we focused on the distribution of *VDR* FokI and BsmI polymorphisms in Iranian breast cancer patients compared to healthy population.

Subjects and methods

A case–control study was conducted to investigate association of the two *VDR* gene polymorphisms with the risk of breast cancer. The breast cancer patients ($n = 140$) were randomly selected from patients who referred to three different breast cancer clinics. Diagnosis criteria and managements of the centers were similar and based on the standard international guidelines. All patients were diagnosed with ductal carcinoma. Histopathology reports were reviewed, and personal information such as age and menopausal status was obtained from their hospital records. The age of the patients at the time of breast cancer diagnosis was assigned. Also, 156 volunteer women participated in the study as normal controls. They were healthy women without family history of breast cancer who have referred to state-run health care services for routine mother and baby examinations. Each patient contributed to the study signed a written consent approved by the ethics committee of the Iran National Science Foundation (INSF).

We received cancer group samples either as whole blood or frozen peripheral blood mononuclear cells (PBMCs). Extraction of DNA was carried out using DNA genomic kit (QIAamp Mini kit, Qiagen). Peripheral blood sample (2 mL) was obtained from each subject in the control group. DNA extraction performed according to the standard salting out protocol. The concentration and quality of the DNA was measured using NanoDrop® ND-1000 spectrophotometer at 260 and 280 nm. DNA samples with the A260/A280 ratios of more than 1.7 were selected for analysis. DNA Sample aliquots were stored at −20 °C, and fresh working solutions (10–40 ng/μL) were prepared immediately before each experiment. Specific PCR primers were designed and verified using single nucleotide polymorphisms (SNPs) database (dbSNP 129; http://www.ncbi.nlm.nih.gov/projects/SNP/) and BLAST website (http://blast.ncbi.nlm.nih.gov/Blast.cgi) (Table 1).

Genomic DNA was amplified by PCR according to the following program: an initial denaturation step for 5 min at 94 °C then 30 amplification cycles of : denaturation at 95 °C for 30 s, annealing at 59 °C for 30 s, and extension at 72 °C for 30 s. Final extension was allowed to proceed for 5 min at 72 °C.

For BsmI and FokI genotyping, restriction fragment length polymorphism (RFLP) analysis was performed. Each PCR product was digested with the appropriate restriction endonuclease as recommended by the manufacturer's instruction (Fermentas, Cinaclon, Iran). The digested products were separated by electrophoresis on 2 % agarose gels and were visualized by ethidium bromide staining under short-wave UV light. In the case of cutting by the enzymes, alleles were indicated by b and f, whereas undigested alleles were assigned as B and F, respectively. Randomly selected PCR products were subjected to sequencing to verify the RFLP results.

Statistical methods

The collected data were loaded on statistical analysis software SPSS V.16. The data were analyzed using conditional logistic regression along with 95 % confidence intervals (CIs) in a 2×2 table. Chi-square test was selected to weigh up the null hypothesis (H0) among the groups. The p values less than 0.05 were considered to be statistically significant.

Results

Subject's data

Patients mean age was 45.44 ± 10.61, and Controls mean age was 42.64 ± 9.67 years. The age ranges were 30–72

Table 1 The sequence of the primers and their PCR–RFLP product characteristics

Primer name	Sequence	PCR product length (bp)	Digested fragments (bp)
BsmI-F	CCTCACTGCCCTTAGCTCTG	290	181 and 109
BsmI-R	TCTCACCTCTAACCAGCGGA		
FokI-F	CTGGCACTGACTCTGGCTCT	204	50 and 154
FokI-R	GGGCTCACCTGAAGAAGCCT		

and 30–67 years for the case and control groups, respectively. Controls were matched also by menopausal status, parity, and breast feeding experience.

Histopathology reports of the patients' tumors showed 78.5 % strong and 12.6 % week estrogen receptor expression (ER^+). Progesterone receptor expression was strong in 54 % and weak in 17 % of PR^+ patients. The Her2 overexpression was detected in 38 % of the breast tumors.

Genotyping and statistics

The desired fragments of BsmI and FokI containing amplicons were revealed after restriction enzyme digestion (Fig. 1). The allele frequencies of the two SNPs are summarized in Table 2. There was no major deviation from the expected Hardy–Weinberg equilibrium in control samples.

BsmI

The b allele of BsmI polymorphism was detected in 62.5 % of the patients versus 54 % of the controls. The relative frequency of BsmI minor allele was 0.37 which is comparable to the reports from other populations in whom *VDR* BsmI polymorphism showed an ethnicity-related variation with a highest rate in Caucasian (0.41) and the lowest rate in Japanese American (0.14) [23].

To analyze the correlation between BsmI SNP and breast cancer risk, the BB genotype was assigned as reference genotype according to the previous studies [15, 24, 25]. When the other two genotypes were compared with the reference genotype, a significantly (p value = 0.01) increased risk of breast cancer was observed with both BsmI bb and Bb genotypes (Table 3). The corresponding odds ratio was 2.39 (CI 1.17–4.85) for BsmI bb and 2.28 (CI 1.16–4.47) for BsmI Bb genotype. This data suggests that the b allele may contribute in susceptibility to breast cancer, either in heterozygote or homozygote state. There were no association between BsmI SNP and tumor characteristics including ER, PR, and HER2 status.

Table 2 *VDR* BsmI and FokI allele frequency in patients and controls

	Breast cancer (n = 140)		Controls (n = 156)	
	Breast cancer (%)	Frequency	Controls (%)	Frequency
VDR BsmI alleles				
B	37.5	0.37	46	0.46
b	62.5	0.62	54	0.54
VDR FokI alleles				
F	72.5	0.72	72.1	0.72
f	27.5	0.27	27.8	0.28

FokI

The relative frequency of FokI minor allele was 0.27 and 0.28 in patients and controls, respectively (Table 2). These values were lower than most of the previously published data. The reported minor allele frequency of FokI exhibits very slight variation within populations, with a few exceptions [23]. In our study, statistical analysis for cancer predisposing effect of FokI revealed no significantly increased risk in patients with FokI ff genotype compared to the control group (OR 0.83, CI 0.36–1.92). Also, the analysis of FokI heterozygous genotype demonstrates no association between this genetic variation and breast cancer

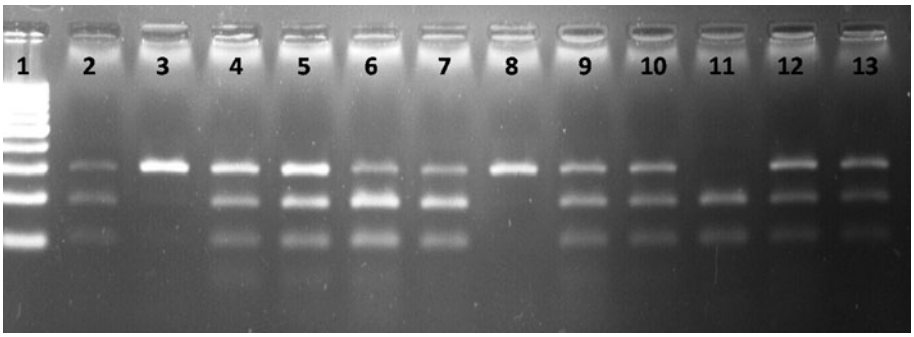

Fig. 1 Electrophoresis results of BsmI restriction enzyme digestion on 2 % agarose. *Lanes 3* and *8* BB genotype, *lane 11* bb genotype, and the other *lanes* Bb heterozygotes

Table 3 Odds ratios for the association of breast cancer with *VDR* gene BsmI and FokI polymorphisms

	Controls (%)	Cases (%)	Odds ratio[a] (95 % CI)	*p* value
BsmI				
bb	48 (30.6)	51 (35.4)	2.39 (1.17–4.85)	0.01
Bb	72 (46.3)	73 (53.1)	2.28 (1.16–4.47)	0.01
BB	36 (23.1)	16 (11.5)	1 (reference)	–
FokI				
ff	15 (9.6)	11 (7.8)	0.83 (0.36–1.92)	0.66
Ff	57 (36.5)	55 (39.4)	1.09 (0.67–1.77)	0.71
FF	84 (53.9)	74 (52.8)	1 (reference)	–

CI confidence interval

[a] Odds ratio adjusted for age, menopausal status, parity, and breast feeding experience

in Iranian patients (OR 1.09, CI 0.67–1.77). There was no correlation between *VDR* FokI and patients clinical findings or tumor specification.

Discussion

The susceptibility and modifier genes play a major role in developing malignancies in concert with environmental factors. In this respect, impact of sunlight exposure, diet vitamin D, and *VDR* polymorphisms in breast cancer pathogenesis have attracted much interest worldwide. The effects of Vitamin D on proliferation and differentiation of several cancer cell lines have been demonstrated [26, 27]. Because this vitamin acts via VDR, the study of *VDR* gene SNPs can elucidate important factors in environmental exposure and breast cancer.

VDR FokI cause a longer protein with a reduced activity [28]. In vitro study has shown that FF(CC) genotype promotes gene transcription by interaction with transcription factor IIB [29]. Using MCF-7 breast cancer cells, a recent study revealed that FF genotype promotes vitamin D anti cancer function by different approaches such as regulation of estrogen receptor-α expression [22].

The distribution of two *VDR* gene SNPs, FokI and BsmI, has been extensively investigated in breast cancer patients. However, the reported results regarding both polymorphisms are controversial. Two comprehensive case–control study provided evidence that ff(TT) genotype of FokI was associated with a higher breast cancer risk [30, 31]. Nevertheless, there are other reports that have not supported this correlation, and in contrast, some researches even showed lower risk of breast malignancy in the subjects with ff genotype [19, 32–34]. Meta-analyses assessments have demonstrated that FokI ff genotype is linked to susceptibility to breast cancer [35, 36].

In our study, 140 Iranian breast cancer patients were analyzed for *VDR* gene BsmI and FokI polymorphisms. No statistically significant association was observed between FokI ff genotype and the predisposition to malignancy development. Although, in our study, the distribution of FokI minor allele mildly differs from other studies, but BsmI minor allele distribution showed the same pattern as most of the previous reports.

BsmI SNP is an intronic polymorphism, which is linked to polyA variants in a haplotype. Epidemiological studies assessing correlation of this SNP to breast cancer have reported controversial results [15, 24, 30, 37–40]. Since BsmI has various geographical distributions [23], the selected subjects and controls have a great impact on the results by population stratification. Most of the studies which were performed on Caucasian women reported increased risk of breast cancer with the BsmI bb(GG) genotype [15, 23, 37, 38]. Whereas, BsmI BB(AA) genotype was correlated to breast cancer among Hispanic [19] and Taiwanese population [20]. Both reports demonstrated diverse allele frequencies compared to the Caucasian population. We observed approximately twofold increased risk of breast cancer in carriers of BsmI b allele in either homozygote or heterozygote state. The BsmI exhibits strong linkage disequilibrium with other polymorphisms, located at the 3′ untranslated region (3′ UTR) of the *VDR* gene. This haplotype may affect mRNA stability and processing as well as regulation of *VDR* transcription and translation [41, 42].

In summary, the present study demonstrated that Iranian women with the BsmI Bb or bb genotype were at twice higher risk for breast cancer. To our knowledge, this is the first report regarding Iranian patients and may be applied for prevention and early intervention strategies in this population.

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Conflict of interest None.

References

1. Fang L, Barekati Z, Zhang B, Liu Z, Zhong X. Targeted therapy in breast cancer: what's new? Swiss Med Wkly. 2011;141:w13231.
2. Wu PE, Shen CY. 'Hide-then-hit' to explain the importance of genotypic polymorphism of DNA repair genes in determining susceptibility to cancer. J Mol Cell Biol. 2011;3:59–65.
3. Delgado MD, Leon J. Gene expression regulation and cancer. Clin Transl Oncol. 2006;8:780–7.
4. Krishnan AV, Swami S, Feldman D. Vitamin D and breast cancer: inhibition of estrogen synthesis and signaling. J Steroid Biochem Mol Biol. 2010;121:343–8.

5. James SY, Williams MA, Kelsey SM, Newland AC, Colston KW. The role of vitamin D derivatives and retinoids in the differentiation of human leukaemia cells. Biochem Pharmacol. 1997;54:625–34.
6. Eisman JA, Macintyre I, Martin TJ, Frampton RJ, King RJ. Normal and malignant breast tissue is a target organ for 1,25-(0H)2 vitamin D3. Clin Endocrinol (Oxf). 1980;13:267–72.
7. Townsend K, Banwell CM, Guy M, Colston KW, Mansi JL, Stewart PM, Campbell MJ, Hewison M. Autocrine metabolism of vitamin D in normal and malignant breast tissue. Clin Cancer Res. 2005;11:3579–86.
8. Kato S. The function of vitamin D receptor in vitamin D action. J Biochem. 2000;127:717–22.
9. Colston KW, Berger U, Coombes RC. Possible role for vitamin D in controlling breast cancer cell proliferation. Lancet. 1989;1:188–91.
10. Zinser G, Packman K, Welsh J. Vitamin D(3) receptor ablation alters mammary gland morphogenesis. Development. 2002;129:3067–76.
11. Labuda M, Fujiwara TM, Ross MV, Morgan K, Garcia-Heras J, Ledbetter DH, Hughes MR, Glorieux FH. Two hereditary defects related to vitamin D metabolism map to the same region of human chromosome 12q13-14. J Bone Miner Res. 1992;7:1447–53.
12. Miyamoto K, Kesterson RA, Yamamoto H, Taketani Y, Nishiwaki E, Tatsumi S, Inoue Y, Morita K, Takeda E, Pike JW. Structural organization of the human vitamin D receptor chromosomal gene and its promoter. Mol Endocrinol. 1997;11:1165–79.
13. Morrison NA, Yeoman R, Kelly PJ, Eisman JA. Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci U S A. 1992;89:6665–9.
14. Gross C, Eccleshall TR, Malloy PJ, Villa ML, Marcus R, Feldman D. The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postmenopausal Mexican-American women. J Bone Miner Res. 1996;11:1850–5.
15. Guy M, Lowe LC, Bretherton-Watt D, Mansi JL, Peckitt C, Bliss J, Wilson RG, Thomas V, Colston KW. Vitamin D receptor gene polymorphisms and breast cancer risk. Clin Cancer Res. 2004;10:5472–81.
16. Ingles SA, Haile RW, Henderson BE, Kolonel LN, Nakaichi G, Shi CY, Yu MC, Ross RK, Coetzee GA. Strength of linkage disequilibrium between two vitamin D receptor markers in five ethnic groups: implications for association studies. Cancer Epidemiol Biomarkers Prev. 1997;6:93–8.
17. Jorgensen HL, Scholler J, Sand JC, Bjuring M, Hassager C, Christiansen C. Relation of common allelic variation at vitamin D receptor locus to bone mineral density and postmenopausal bone loss: cross sectional and longitudinal population study. BMJ. 1996;313:586–90.
18. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, Sambrook PN, Eisman JA. Prediction of bone density from vitamin D receptor alleles. Nature. 1994;367:284–7.
19. Ingles SA, Garcia DG, Wang W, Nieters A, Henderson BE, Kolonel LN, Haile RW, Coetzee GA. Vitamin D receptor genotype and breast cancer in Latinas (United States). Cancer Causes Control. 2000;11:25–30.
20. Hou MF, Tien YC, Lin GT, Chen CJ, Liu CS, Lin SY, Huang TJ. Association of vitamin D receptor gene polymorphism with sporadic breast cancer in Taiwanese patients. Breast Cancer Res Treat. 2002;74:1–7.
21. Anderson LN, Cotterchio M, Cole DE, Knight JA. Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among Caucasian women in Ontario. Cancer Epidemiol Biomarkers Prev. 2011;20:1708–17.
22. Alimirah F, Peng X, Murillo G, Mehta RG. Functional significance of vitamin D receptor FokI polymorphism in human breast cancer cells. PLoS ONE. 2011;6:e16024.
23. McKay JD, McCullough ML, Ziegler RG, Kraft P, Saltzman BS, Riboli E, Barricarte A, Berg CD, Bergland G, Bingham S, Brustad M, Bueno-de-Mesquita HB, Burdette L, Buring J, Calle EE, Chanock SJ, Clavel-Chapelon F, Cox DG, Dossus L, Feigelson HS, Haiman CA, Hankinson SE, Hoover RN, Hunter DJ, Husing A, Kaaks R, Kolonel LN, Le Marchand L, Linseisen J, McCarty CA, Overvad K, Panico S, Purdue MP, Stram DO, Stevens VL, Trichopoulos D, Willett WC, Yuenger J, Thun MJ. Vitamin D receptor polymorphisms and breast cancer risk: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18:297–305.
24. McCullough ML, Stevens VL, Diver WR, Feigelson HS, Rodriguez C, Bostick RM, Thun MJ, Calle EE. Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study. Breast Cancer Res. 2007;9:R9.
25. Trabert B, Malone KE, Daling JR, Doody DR, Bernstein L, Ursin G, Marchbanks PA, Strom BL, Humphrey MC, Ostrander EA. Vitamin D receptor polymorphisms and breast cancer risk in a large population-based case-control study of Caucasian and African-American women. Breast Cancer Res. 2007;9:R84.
26. Colston K, Colston MJ, Feldman D. 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. Endocrinology. 1981;108:1083–6.
27. Lointier P, Wargovich MJ, Saez S, Levin B, Wildrick DM, Boman BM. The role of vitamin D3 in the proliferation of a human colon cancer cell line in vitro. Anticancer Res. 1987;7:817–21.
28. Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene. 2004;338:143–56.
29. Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, Tavakkoli P, Galligan MA, Dang HT, Haussler CA, Haussler MR. The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. Mol Endocrinol. 2000;14:401–20.
30. Chen WY, Bertone-Johnson ER, Hunter DJ, Willett WC, Hankinson SE. Associations between polymorphisms in the vitamin D receptor and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2005;14:2335–9.
31. Sinotte M, Rousseau F, Ayotte P, Dewailly E, Diorio C, Giguere Y, Berube S, Brisson J. Vitamin D receptor polymorphisms (FokI, BsmI) and breast cancer risk: association replication in two case-control studies within French Canadian population. Endocr Relat Cancer. 2008;15:975–83.
32. Curran JE, Vaughan T, Lea RA, Weinstein SR, Morrison NA, Griffiths LR. Association of A vitamin D receptor polymorphism with sporadic breast cancer development. Int J Cancer. 1999;83:723–6.
33. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multiethnic population. Am J Epidemiol. 2007;166:1409–19.
34. Abbas S, Nieters A, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. Breast Cancer Res. 2008;10:R31.
35. Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis. 2009;30:1170–80.
36. Tang C, Chen N, Wu M, Yuan H, Du Y. Fok1 polymorphism of vitamin D receptor gene contributes to breast cancer susceptibility: a meta-analysis. Breast Cancer Res Treat. 2009;117:391–9.
37. Bretherton-Watt D, Given-Wilson R, Mansi JL, Thomas V, Carter N, Colston KW. Vitamin D receptor gene polymorphisms are associated with breast cancer risk in a UK Caucasian population. Br J Cancer. 2001;85:171–5.
38. Ruggiero M, Pacini S, Aterini S, Fallai C, Ruggiero C, Pacini P. Vitamin D receptor gene polymorphism is associated with metastatic breast cancer. Oncol Res. 1998;10:43–6.

39. Buyru N, Tezol A, Yosunkaya-Fenerci E, Dalay N. Vitamin D receptor gene polymorphisms in breast cancer. Exp Mol Med. 2003;35:550–5.
40. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, Colston KW. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer. 2005;41:1164–9.
41. Whitfield GK, Remus LS, Jurutka PW, Zitzer H, Oza AK, Dang HT, Haussler CA, Galligan MA, Thatcher ML, Encinas Dominguez C, Haussler MR. Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. Mol Cell Endocrinol. 2001;177: 145–59.
42. Ogunkolade BW, Boucher BJ, Prahl JM, Bustin SA, Burrin JM, Noonan K, North BV, Mannan N, McDermott MF, DeLuca HF, Hitman GA. Vitamin D receptor (VDR) mRNA and VDR protein levels in relation to vitamin D status, insulin secretory capacity, and VDR genotype in Bangladeshi Asians. Diabetes. 2002;51:2294–300.