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Vitamin D Gene Pathway Polymorphisms and Risk of Colorectal, Breast, and Prostate Cancer

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vitamin D, VDR, SNP, gene-diet interaction, cancer

Abstract

Higher vitamin D exposure is hypothesized to prevent several cancers, possibly through genomic effects modulated by the vitamin D receptor (VDR), and autocrine/paracrine metabolism of the VDR's ligand, 1α,25-$(OH)_2$-vitamin D. Herein we review the background and evidence to date on associations between polymorphisms in *VDR* and selected genes in the vitamin D pathway in relation to colorectal, breast, and prostate cancer. Although most studies to date have examined only a few *VDR* polymorphisms, more are beginning to comprehensively investigate polymorphisms in the *VDR* as well as in other vitamin D pathway genes, such as the vitamin D–binding protein gene (*Gc*) and *CYP27B1* and *CYP24A1*, which code for enzymes that, respectively, synthesize and degrade 1α,25-$(OH)_2$-vitamin D. Currently, there is no strong, consistent epidemiologic evidence for substantial influences of single variants in vitamin D pathway genes on risk for colorectal, breast, or prostate cancer, but promising leads are developing.

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INTRODUCTION

Overview

International incidence rates of colorectal, breast, and prostate cancer vary approximately 10-, 7-, and 40-fold, respectively, and immigrants from low-risk to high-risk countries acquire approximately the rates of their adopted countries within one to two generations, emphasizing the almost overwhelming influence of environment on the etiology of these diseases. In contrast, results from genome-wide association scan (GWAS) studies suggest that, aside from a few classic, high-penetrance, low-prevalence genetic variants (e.g., BRCA1 or those resulting in familial adenomatous polyposis or hereditary nonpolyposis colon cancer), genetic variation in specific genes alone likely does not substantially contribute to risk for these cancers (64, 132, 146). On the other hand, it is clear that persons with certain ancestries appear to be at greater risk than those with other ancestries when they adopt Western diets and lifestyles that vary from their ancestral ones (e.g., black-white differences in invasive prostate cancer in the United States). Taken together, these observations suggest that the primary influence of genetic variation on risk for these cancers is as modifiers of risk from environmental/lifestyle factors. It is also possible that cumulative risk from multiple variants of multiple genes may substantially affect risk for some individuals, either from these genetic profiles alone or in interaction with environmental/lifestyle factors.

Recently, vitamin D, long known to play an integral role in maintaining calcium homeostasis and skeletal health, has been linked to the prevention of several chronic diseases, including common cancers such as colorectal, breast, and prostate cancer (46). However, to date, most studies of vitamin D–related genes and risk for cancer have primarily investigated main effects of a few variants of these genes alone, and few have investigated these variants, alone or in combinations, as modifiers of associations of vitamin D exposure with cancer. Herein we review the background and evidence to date on associations between polymorphisms in *VDR* and selected genes in the vitamin D pathway in relation to colorectal, breast, and prostate cancer. Because of the strong biologic rationale for genotype-environment interaction, we also review published data on diet, particularly vitamin D status or intake, as a modifier of risk associated with these polymorphisms.

Vitamin D Metabolism

The primary hypothesized protective effects of vitamin D against cancer involve recently elucidated, autocrine/paracrine functions of vitamin D rather than its more well-known classical endocrine functions for calcium homeostasis and bone metabolism. The classical endocrine functions of vitamin D are reviewed extensively in standard texts, but since some of this background applies to the autocrine/paracrine functions of the vitamin, a brief summary is provided here. There are two precursors to

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"vitamin D" (traditionally used as a collective term for vitamins D_2 and D_3), provitamin D_3 and provitamin D_2 (58) (**Figure 1**). Provitamin D_3 (7-dehydrocholesterol) is synthesized in the skin, where, when exposed to UVB radiation, it is converted to vitamin D_3. Vitamin D_3 is also found naturally in fatty fish and fish oil and, in many countries, including the United States, is added to milk and some cereals. Provitamin D_2 (ergosterol) is present only in plants. Vitamin D and multivitamin supplements can contain either or both forms. Vitamin D is transported by proteins (about 88% of which are a specific $alpha_1$ globulin, vitamin D–binding protein [VDBP or vitamin D–binding globulin], and about 11%–12% are albumin; about 0.03% is free) through the circulation to the liver, where it is hydroxylated at the 25 position to 25-OH-vitamin D [25(OH)D]. This reaction is catalyzed by one or more enzymes with 25-hydroxylase activity, including CYP27A1, CYP2D6, CYP2R1, CYP2C11, CYP3A4, CYP2D25, and CYP2J3. Vitamin D metabolites can also be taken up or sequestered and stored in adipose tissue (143). 25(OH)D can be stored in the liver or enter the circulation and be transported throughout the body. Since 25-hydroxylation is not tightly regulated, 25(OH)D levels reflect overall vitamin D status from combined dietary and sunlight sources. When serum calcium levels fall, parathyroid hormone (PTH) is released and, in the kidney, stimulates a CYP27B1-catalyzed second hydroxylation of 25(OH)D to 1α,25-$(OH)_2$-vitamin D [$1,25(OH)_2D$, which is 100- to 1000-fold more potent than 25(OH)D], which is then released into the circulation to increase calcium absorption from the gut, resorption from bone, and reabsorption from the kidneys through both passive and vitamin D receptor (VDR)-mediated mechanisms to restore blood calcium concentrations (**Figure 1**). The enzyme 24-hydroxylase [also known as 24(OH)ase or CYP24] initiates the degradation of $1,25(OH)_2D$; in fact, the major inducer of 24(OH)ase is $1,25(OH)_2D$, thus promoting its own inactivation and limiting its biologic effects.

More recently, autocrine/paracrine functions of vitamin D and their potential relevance to cancer prevention have become clearer via discoveries that (*a*) more than 36 cell types not involved with calcium metabolism are abundantly endowed with CYP27B1, CYP24, and the VDR, and produce, respond to, and degrade $1,25(OH)_2D$ [which is not released into the circulation because its synthesis is balanced with its degradation (41)]; and (*b*) there are vitamin D response elements (VDREs) on more than 200 genes that appear to be modulated, at least in part, by $1,25(OH)_2D$, and to a lesser extent by 25(OH)D, influencing cell functions in a cell- and tissue-specific manner (34, 144). $1,25(OH)_2D$ is thought to act locally through genomic and nongenomic mechanisms (59, 79, 96, 110). Nongenomic effects, or rapid responses (59, 79, 96), may work through a plasma membrane receptor and second messengers involved in regulating various cell activities, including cell cycle control. Genomic effects are mediated via binding to the nuclear VDR (**Figure 2**). $1,25(OH)_2D$, a relatively small, lipophilic molecule that easily penetrates the cell membrane, is taken up by the cell by simple diffusion, and binds to the VDR. The VDR then binds to target DNA sequences as a heterodimer with the retinoid X receptor (RXR), recruiting a series of coactivators resulting in the induction of target gene expression. As summarized in **Figure 2**, genomic autocrine/paracrine functions of vitamin D identified to date include roles in regulating cell proliferation, differentiation, apoptosis, growth factor signaling, and immunomodulation. Other potential functions include protection against oxidative stress, bile acid and xenobiotic metabolism, cell adhesion, DNA repair, and angiogenesis.

COMMON GENETIC POLYMORPHISMS IN THE VITAMIN D PATHWAY

Although the vitamin D "pathway" can be defined many ways, we include in our review polymorphisms associated with the *VDR* gene,

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the vitamin D–binding protein gene (*Gc*), and genes that code for enzymes that initiate formation (*CYP27B1*) and degradation (*CYP24A1*) of $1,25(OH)_2D$, the natural ligand for the VDR. Other genes, including the retinoic acid receptor (*RXR*), the multiple genes involved in synthesizing vitamin D in the skin or 25-hydroxylation in the liver, or genes involved in the synthesis of many other interrelated growth and risk factors involved in carcinogenesis, are not considered here.

The Vitamin D Receptor Gene (*VDR*)

By far the most well studied gene in the vitamin D pathway, *VDR*, encodes for the VDR, a nuclear transcription regulating factor that belongs to the steroid hormone superfamily of receptors. Nuclear receptors integrate hormonal, dietary, and other extracellular signals into cell-fate decisions via regulation of gene expression and repression of a host of common gene targets (133). The *VDR* gene, located on chromosome 12q13, spans over 100 kb (136) and contains six promoter regions, alternatively spliced untranslated exons 1a–1f, and eight protein-coding exons 2 to 9 (**Figure 3**) (116). The DNA-binding domain of the VDR peptide, encoded by exons 2 to 4, is responsible for high-affinity interaction with the VDRE in target genes. The ligand-binding domain encoded by exons 6 to 9 is responsible for $1,25(OH)_2D$ binding (116).

More than 470 single-nucleotide polymorphisms (SNPs) have been discovered on the human *VDR* gene, but most have low allele frequencies. To date, only a few *VDR* SNPs have been extensively studied in relation to cancer (**Table 1**), and a limited number of studies have examined risk by linkage disequilibrium (LD) block (116). One commonly studied polymorphism, identified by the *Fok1* restriction enzyme (*rs10735810*, also known as *rs2228570*), is in exon 2 of the promoter region of *VDR*. The presence of this site ("*f*") allows protein translation to begin from the first initiation codon rather than from the second ("*F*"), resulting in a protein that is three amino acids longer. The longer protein (*f* allele) is a less active transcriptional activator (133, 137).

Three SNPs located near the 3′ region, historically identified by their restriction endonuclease cleavage sites (*Taq1*, *Bsm1*, *and Apa1*), have been examined extensively in relation to bone disease (148) and cancer (133, 137). These polymorphisms include an intronic G→A replacement (*Bsm1*, *rs1544410*, *G = b*), an intronic C→A replacement (*Apa1 rs7975232*, *C = a*), both between exons 8 and 9, and a T→C replacement in exon 9 (*Taq1 rs731236*, *T = T*) that results in a synonymous change at codon 352 (isoleucine). Although not functional, these SNPs are strongly linked with a poly(A) microsatellite repeat in the 3′ untranslated region. The poly(A) microsatellite repeat contains a variable number of 12 or more alleles; because the population distribution of the number of these alleles is bimodal, individuals can be classified as having short (A13-A17) or long (A18-A24) nucleotides. The poly(A) sequence

Table 1 Common *VDR* SNPs, gene positions, and putative risk alleles

SNP name	Position on *VDR*	DbSNP reference	Gene position	Major allele	Putative risk allele[a]
Fok1	Exon 2	*rs10735810 (aka rs2228570)*	C/T 30875	C (F)	f
Cdx2	Block C2	*rs11568820*	G/A 1229	G	G
Bsm1[b]	Block B	*rs1544410*	G/A 64922	G (b)	b
Apa1	Block B	*rs7975232*	C/A 63935	A (A)	a
Taq1	Block B	*rs731236*	T/C 65013	T (T)	T
Poly(A)[b]	3′ UTR	*rs17878969*	Microsatellite repeat	A_{18}-A_{24}	L

[a]Putative risk haplotype: bL, baTL.
[b]D′ *Bsm1* and *Poly(A)*: Whites, 0.96; African Americans, 0.53; Hispanics, 0.77; Japanese Americans, 0.90; Chinese, 0.77 (67).

in the 3′ UTR region of genes is thought to be important in post-transcriptional control of gene expression (32), either by altering mRNA stability or the interaction of the mRNA with the translational apparatus, with the long genotype resulting in greater mRNA instability.

One of the earliest studies to examine the distribution of *VDR* polymorphisms by race/ethnicity (67) described the haplotype frequencies of the *BsmI* and *Poly(A)* genotypes as follows: Among African Americans all four haplotypes (*bS*, *BS*, *bL*, *BL*) were expressed, among non-Hispanic Caucasian individuals only haplotypes *BS* and *bL* ("risk" haplotype) were commonly expressed, and among Asians only the *bL* haplotype was commonly expressed. The *BS* and *bL* haplotypes were most commonly found among their sample of Hispanics. The authors proposed that all four haplotypes were originally present, but only a subset of African alleles persisted after the races diverged (67). LD in the *BsmI* and *Poly(A)* markers is not complete; thus, two markers are probably not interchangeable for evaluating putative disease loci in association studies (67, 137). **Table 1** provides information on LD for these two SNPs. Others have extended the linkage analysis to include *Apa1* and *Taq1* SNPs to identify *baTL* and *BAtS* haplotypes (127), with the former being the putative high-risk haplotype.

Cdx2. Situated in exon 1e, *Cdx-2* modulates specific transcription of *VDR* gene expression. The *Cdx2 A* allele results in increased binding of the *Cdx-2* protein in vitro and increased transcriptional activity of *VDR* in Caco-2 colon cancer cell lines (39). In another study, the *Cdx-2* binding element with the *G* allele was associated with significantly lower transcriptional activity and somewhat lower bone mineral density than that of the *A* allele (10). The *Cdx2* SNP is in linkage with a *GATA3* SNP, which is a G to A substitution further in the promoter region upstream of the exon 1a transcription start site (54). A base change in this polymorphism leads to a change in protein-DNA complex formation (116).

VDR blocks. Nejentsev et al. (94) developed high-resolution SNP, haplotype, and LD maps of the *VDR* gene region in five population samples and identified three extensive LD blocks, termed A, B, and C (see **Figure 3**), with identical patterns in all four European groups examined. The LD blocks identified demonstrate intrablock but little interblock LD. In an African population, two additional LD-breaking spots were apparent. The variable LD observed among European and Gambian populations potentially explains some of the variation in rates of vitamin D–related cancers by race/ethnicity (94).

1,α-Hydroxylase (*CYP27B1*)

CYP27B1 encodes for 1,α (OH)ase, which resides in the inner mitochondrial membrane where it hydroxylates 25(OH)D at the 1α position to form 1,25-$(OH)_2$D, the natural VDR ligand. *CYP27B1* is located on chromosome 12q13.1-q13.3, spans 4.8 kb, and contains nine exons. Although four nonsynonymous SNPs have been identified, all are uncommon. Holick et al. (57) evaluated tag SNPs from *CYP27B1* with $r^2 \geq 0.8$ with common genetic variants [minor allele frequency >5% in Caucasians (57)] and identified three tag SNPs. An earlier study that sequenced the gene also identified three noncoding SNPs (55). To date, there is limited evidence as to whether polymorphisms of *CYP27B1* affect gene function.

24-Hydroxylase (*CYP24A1*)

24(OH)ase, a member of the cytochrome P450 superfamily of enzymes, is encoded by the *CYP24A1* gene, located on chromosome 20q13. The gene is 20.5 kb long and contains 12 exons. It contains four nonsynonymous SNPs, all with low allele frequency. Using HapMap data and the criteria of $r^2 \geq 0.8$ with common genetic variants (minor allele frequency >5% in Caucasians), 20 tag SNPs were selected by Holick et al. (57). Whether any of the identified SNPs have functional effects is unclear. Roff & Wilson (112) describe a functional

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SNP in the *CYP24A1* promoter that results in lower expression of CYP24A1 protein. This mitochondrial enzyme initiates the degradation of $1,25(OH)_2D$, the physiologically active form of vitamin D, by hydroxylation of the side chain. By regulating the level of active vitamin D, this enzyme plays a role in calcium homeostasis. Presumably, because of its important role in vitamin D metabolism and blood calcium homeostasis, major alterations in vitamin D hydroxylation activity would lead to serious illness and may have been selected against through evolution. However, if certain genotypes influence primarily autocrine/paracrine vitamin D metabolism, alterations may still occur that have minimal influence on circulating calcium levels. Because 24(OH)ase may lead to abrogation of the growth control mediated by $1,25(OH)_2D$, *CYP24*, the gene that produces this enzyme, is considered a candidate oncogene (6, 90, 103).

Vitamin D–Binding Protein (*Gc*)

The protein encoded by the *Gc* gene belongs to the albumin family, together with human serum albumin and alpha-fetoprotein. Located on chromosome 4q11-q13, the *Gc* gene is 42.5 kb long and contains 13 exons and at least six nonsynonymous SNPs, two with relatively common frequency (*rs7041* and *rs4588*). The vitamin D–binding protein (DBP) greatly facilitates vitamin D actions by carrying vitamin D metabolites to various sites of action, and polymorphic DBP proteins differ in their affinity for $1,25(OH)_2$ D (102). The DBP may also have a role in inflammation and the immune system (76). Ezura et al. (38) characterized a C/T polymorphism at position −39 in the *Gc* promoter region that was strongly linked to bone mineral density. Kidd et al. (73) identified two of three SNPs in the *Gc* promoter region with functional effects on transcription factor binding sites. Recent studies have shown that allelic variation in the *Gc* gene is associated with DBP and serum 25(OH)D concentrations as well as higher affinity of the DBP to vitamin D metabolites (37, 77).

VITAMIN D GENE PATHWAY SINGLE-NUCLEOTIDE POLYMORPHISMS AND CANCER RISK

Colorectal Cancer

Background. Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death among both men and women in the United States (7). Although colorectal cancer screening can detect and remove adenomatous polyps, and therefore prevent most cancers, fewer than 50% of men and women in the United States age 50 and older are screened annually (8). Prevention of the disease through lifestyle modification, including engaging in regular physical activity, avoiding tobacco, and making changes in diet, can reduce the risk of colorectal cancer (108). A diet pattern low in red and processed meat and high in fruits and vegetables (and their components, such as fiber, and carotenoids) has been associated with lower risk of the disease (142). Higher circulating 25(OH)D concentrations have been fairly consistently associated with a lower risk of colorectal cancer (49), and calcium supplementation reduces adenoma recurrence (11, 17), especially among individuals with better 25(OH)D status (50). Calcium and vitamin D have antiproliferative and prodifferentiation effects in vitro, and some evidence suggests that the two nutrients act together to control colon epithelial cell proliferation (30).

Vitamin D, acting at least in part through binding with the VDR, is thought to protect against colorectal cancer via several distinct and complementary mechanisms. It reduces mutation and promotes safer patterns of cell cycle events in colon crypt cells, and it improves expression of various genes regulating the normal structure and function of the colon crypt. These effects are likely modulated through colon tissue autocrine/paracrine synthesis of $1,25\text{-}(OH)_2D$. In addition, the secondary bile acid, lithocholic acid (LCA), can also activate the VDR, inducing expression in vivo of CYP3A4, a cytochrome P450 enzyme

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that detoxifies LCA in the intestine and liver (85). Such increased bile acid detoxification leads to reduced colonocyte DNA mutation, cell damage, compensatory hyperproliferation, and inflammation.

VDR genotypes and colorectal cancer risk. To date, approximately a dozen studies have examined selected *VDR* SNPs in relation to risk of colorectal cancer (40, 72, 93, 100, 104, 124–127, 129, 131, 141). The largest studies to date include several publications from a combined case-control dataset from the state of Utah, the Kaiser Permanente Medical Care Program of northern California, the Twin Cities metropolitan area of Minnesota (93, 124–127, 129), and a recently published large case-control study in Scotland (131) (**Supplemental Table 1**; for all **Supplemental Material**, follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**). Several studies investigated potential interactions between *VDR* SNPs and calcium and vitamin D intakes or status.

The most commonly examined *VDR* SNPs were *Fok1* and *Bsm1* from the 5′ promoter region and 3′ flanking region, respectively. Out of eight studies that examined variants in the *Fok1* SNP in relation to colorectal cancer (93, 100, 104, 126, 127, 129, 131, 141), two observed a significant inverse association with the *Fok1 ff* genotype and colorectal cancer risk (93, 104), one observed a significant increase in risk associated with the *Fok1 FF* genotype (100), and in another study (129), two haplotypes that included the *Fok1 F* allele were associated with significantly increased risk. Thus, four of the seven studies observed a similar association with the *Fok1* SNP.

Specifically, in two analyses of data from all three participating states from the aforementioned combined case-control study, the *FokI Ff* genotype was associated with a 10% nonsignificant reduction in colorectal cancer risk [odds ratio (OR) 0.90, 95% CI 0.80–1.02], whereas the *ff* genotype was associated with a somewhat more pronounced decreased risk (OR 0.81, 95% CI 0.68–0.96) (93). The common haplotype *bLF*, containing the *BsmI b*, *Poly(A)* long *(L)* and *FokI F* alleles, was associated with a slightly increased risk of colon cancer (OR 1.13, 95% CI 1.01–1.26) as was the rare *BLF* haplotype (OR 2.26, 95% CI 1.36–3.78) (129). In a population-based study of *VDR* genotypes and colorectal cancer conducted in South Korea (104), colorectal cancer patients (n = 190) who underwent surgical treatment for colorectal cancer at a large medical center in Seoul were compared to 318 healthy controls with no history of colorectal cancer. Colorectal cancer risk was significantly lower among those with the *FokI ff* genotype (compared to *FF*) (OR 0.35, 95% CI 0.19–0.65). In a case-control study conducted in Kentucky, Ochs-Balcom et al. (100) observed an increased risk associated with having the *Fok1 FF* genotype (OR = 1.87, 95% CI 1.03–3.38) and haplotypes associated with this genotype. In contrast, in a nested case-control study (n = 217 cases, 890 controls) in a cohort of Singapore Chinese, *VDR FokI Ff* and *ff* polymorphisms were associated with moderately higher colorectal cancer risk: ORs 1.51 (95% CI 1.00–2.29) and 1.84 (95% CI 1.15–2.94), respectively (141). This positive association was stronger among individuals with lower dietary calcium intake (p interaction = 0.07) (141). However, a large Scottish case-control study observed the opposite: the overall association with the *ff* genotype was null, but it was slightly positive (but not statistically significant) among individuals with higher dietary calcium intake (p interaction = 0.006) or vitamin D intake (p interaction = 0.06).

Supplemental Material

Polymorphisms in the 3′ end of the *VDR* gene were not associated with colorectal cancer in the studies that examined SNPs in this region (40, 72, 100, 104, 126, 127, 129, 131). The exception is that the *Apa aa* allele was associated with a more than twofold increased colorectal cancer risk in a population-based case-control study in Korea (104), but not in a hospital-based case-control study in Russia (40) or a case-control study in Scotland (131), the only other studies to examine the *Apa1* SNP.

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Despite the absence of associations of colorectal cancer with individual SNPs located in the *VDR* 3′ region, analyses from the large multicenter U.S. case-control study support a possible lower risk of colorectal cancer associated with the *SS* genotype of the *Poly(A)* repeat and haplotypes associated with this genotype (126, 127, 129). In an analysis that included the Utah and California sites, the *Poly(A) SS* genotype and the *BsmI or Poly(A) (SSBB)* diplotypes were moderately inversely associated with risk [ORs 0.79 (95% CI 0.56–0.96) and 0.82 (95% CI 0.69–0.98), respectively], although the results for *BsmI* alone were null (126). There was also some evidence of an interaction between calcium intake and *Bsm1/Poly(A)* diplotypes for rectal but not colon cancer (126). The common haplotype *bLF*, containing the *Bsm1 b*, *Poly(A) L*, and *Fok1 F* alleles, was associated with a slightly increased risk of colon cancer (OR = 1.13, 95% CI 1.01–1.26) as was the rare *BLF* haplotype (OR 2.26, 95% CI 1.36–3.78) (129). Therefore, there is some indication that the *Poly(A)* variants may influence risk of colorectal cancer, but that individual 3′ SNPs may not predict risk when not included in haplotypes. In addition, these genotypes and haplotypes may interact with dietary calcium or vitamin D to influence risk for colorectal cancer, but the limited studies to date do not paint a clear picture.

Recently, Slattery et al. (124) found no association between the *Cdx2* polymorphism and risk of colon or rectal cancer in a large, combined case-control study. However, inclusion of the putative high-risk *Cdx2 (A)* allele with the *bLF* haplotype was associated with a greater increased risk of colon (OR = 2.45, 95% CI 1.38–4.38) but not rectal cancer (124). Although the *bLFA* haplotype was relatively uncommon in white (6.5%) and Hispanic (6%) participants, it was much more common in African Americans (41%) and Asians (33%), raising questions about ethnic-specific genetic risk factors (124). Unfortunately, this study was too small for meaningful analyses stratified by racial/ethnic groups. A population-based case-control study of 250 cases and 246 controls from Kentucky also observed a greater than twofold increased risk of colorectal cancer among individuals with the *Cdx2 AA vs. GG* genotype (100). In the only study to examine interactions between diet and the *Cdx2* polymorphism, Slattery et al. (124) observed no interaction between dietary calcium or vitamin D and the *Cdx2* polymorphism.

VDR genotypes and colorectal adenoma risk. None of the eight studies that examined associations between *VDR* polymorphisms and risk of colorectal adenoma observed a statistically significant association with colorectal adenoma risk (18, 48, 50, 63, 69, 74, 105, 106). Most included more than 200 cases (63, 69, 74, 105, 106). An advantage of the adenoma studies was that they were endoscopy based (18, 48, 50, 69, 74, 106). In one colonoscopy-based case-control study of incident, sporadic, colorectal adenoma in North Carolina, the *VDR Tru9I* polymorphism variant *u* allele was associated with a modest but not statistically significant decreased risk for adenoma: ORs were 0.88 (95% CI 0.17–4.55) and 0.69 (95% CI 0.40–1.25) for the *Uu* and *uu* genotypes, respectively (48). In the same population, there was no evidence for an association with the *VDR BsmI* polymorphism (18). Two similarly designed case-control studies found weak, nonsignificant lower colorectal adenoma risk among participants with *VDR FokI Ff* or *ff* genotypes (69, 106). In another similarly designed case-control study (74), relative to the *VDR BsmI bb* genotype, neither the *Bb* nor the *BB* genotype was strongly associated with risk of colorectal adenomas. A case-control study of colorectal adenoma nested within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (n = 239 cases, 228 controls) found no evidence for associations with *VDR TaqI* genotypes (105). In a cohort analysis of the Calcium Polyp Prevention Study, there was no evidence for an association of *VDR TaqI* or *FokI* genotypes with adenoma recurrence (50).

These adenoma studies, although decidedly null overall for genotype associations, observed some interactions with dietary intake of vitamin D, calcium, or dairy products. In one study, participants in the lowest tertile of vitamin D

intake who had the *BB* genotype were at lower risk (OR 0.24, 95% CI 0.08–0.76) of colorectal adenoma than those in the highest tertile of vitamin D intake who had the *bb* genotype ($p_{interaction} = 0.09$) (74). A similar, nonsignificant association was observed for calcium intake. In the U.K. Colorectal Adenoma Prevention Trial (63), risk of recurrent adenoma was significantly lower with higher intake of dairy products, but that risk did not differ by *Cdx2*, *Fok1*, *Bsm1*, or *Taq 1* genotype. However, a significant interaction ($p = 0.02$) between the *Apa1 aA or AA* genotype and dairy intake was noted, suggesting that there was lower risk of recurrence among individuals with a higher-dairy diet who also had the *Apa1 aA* or *AA* genotype (63). However, the findings from the five other studies that examined interactions between dietary calcium, vitamin D, and *VDR* SNPs were null (18, 48, 50, 69, 106).

Summary. The available human studies of *VDR* and colorectal cancer do not suggest that *VDR* polymorphisms strongly, independently influence colorectal cancer risk. Although four of seven studies suggest lower colorectal cancer risk associated with the *VDR Fok1 ff* genotype, findings across studies and study designs are inconclusive for the *Fok1* SNP. The preponderance of published studies used a retrospective case-control design, possibly because of smaller numbers of incident colorectal cancer cases relative to breast and prostate cancers in the reported prospective cohort studies. Interestingly, the evidence for a role of vitamin D and calcium (as main exposures) in carcinogenesis appears to be strongest for colorectal compared to other cancers. Thus, one might expect associations with *VDR* SNPs to emerge with colorectal cancer, if they exist. It may be that polymorphisms of *VDR* (and other genes in the vitamin D pathway) modify risk related to vitamin D or calcium exposure. Although some studies reviewed suggest such an interaction, data are insufficient to draw any conclusions on gene-diet interactions and colorectal cancer. In summary, there have been no reported epidemiologic studies of polymorphisms of *CYP27B1*, *CYP24A1*, or *Gc* in relation to risk for colorectal neoplasms, and currently there is neither strong nor consistent evidence that genetic variation in *VDR* plays a role in colorectal carcinogenesis, overall or in interaction with vitamin D or other exposures.

Breast Cancer

Background. Although breast cancer death rates have declined in recent years, breast cancer remains the most common cancer diagnosed, and it is the second cause of cancer deaths in women (7). Risk factors include positive family history, high breast tissue density, long menstrual history (menstrual periods that begin early and end late in life), reproductive factors (e.g., nulliparity, late age at first birth), hormone replacement therapy, regular alcohol consumption, low physical activity, and high BMI and weight gain during adulthood (for postmenopausal breast cancer). Apart from energy imbalance, few dietary risk factors have been consistently associated with risk of the disease (142).

Breast cancer rates are higher in areas of the United States with lower overall UVB exposure, raising the possibility that vitamin D may play a role in breast cancer etiology (44). In support of this hypothesis, epidemiologic studies have observed lower breast cancer risk with greater self-reported (75) and measured (71) sun exposure. The association between dietary and supplemental sources of vitamin D with breast cancer risk has been inconsistent (113), potentially because the typical doses of vitamin D intake have comparatively less impact on 25(OH)D concentrations compared to sun exposure. Circulating 25(OH)D reflects integrated input of vitamin D from sun exposure and diet over several weeks, and thus represents a better measure of vitamin D status. In some (1, 14, 43, 81) but not all (42) studies, greater circulating 25(OH)D concentrations were associated with lower breast cancer risk. This metabolite is thought to be relevant because 25(OH)D provides substrate for tissue-specific synthesis of the VDR ligand (97).

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There is biologic support for a role of vitamin D and the VDR in breast cancer prevention. The VDR is present in all major cell types of mouse mammary gland and is upregulated during puberty, pregnancy, lactation, and involution (reviewed in 139). MMTV-neu mice lacking *VDR* exhibit abnormal mammary ductal morphology characterized by dilated, distended ducts containing dysplastic epithelial cells (147). *VDR* gene dosage also appears to influence age-related changes in ductal morphology and oncogene-induced tumorigenesis of the mammary gland in vivo. Results from animal models of breast cancer show that treatment of tumor-bearing animals with vitamin D analogues can lead to inhibition of tumor progression or regression of established tumors (reviewed in 80). $1,25(OH)_2D$ transcriptionally downregulates the estrogen receptor, further desensitizing cells to estrogen-driven proliferation. Dysregulation of vitamin D signaling [due to lack of $1,25(OH)_2D$, mutations in the VDR, or disruption of VDR target genes] would lead to unopposed proliferation of undifferentiated cells, which may predispose to transformation (139).

Vitamin D pathway genotypes and breast cancer. The polymorphic *VDR* was first observed in human breast cancer cells 30 years ago (36). To date, at least 18 studies have evaluated associations between polymorphisms in *VDR* and other vitamin D pathway genes; most examined *VDR 5′ FokI* and *3′ Bsm*I polymorphisms (**Supplemental Table 2**).

The *FokI* genotype, which results in a longer, less transcriptionally active *VDR*, has been examined in at least nine studies (3, 19, 23, 31, 52, 66, 71, 86, 87), with two observing increased risk associated with the *ff* genotype (23, 87). In a nested case-control study of Caucasian women, the *FokI ff* genotype was associated with a 34% higher breast cancer risk in 1234 cases and 1676 controls (23). However, such an association has not been reported in other, mostly smaller studies of Caucasian women (3, 19, 31, 52, 71, 86), Latina women (66), or African American women (71). However, in a large, pooled analysis from six cohorts (including two previously analyzed populations; 23, 86), a statistically significant 16% increased breast cancer risk was observed for women with the *ff* (*vs FF*) genotype (87). When the previously published study that reported a positive association (23) was excluded from the pooled analysis, the risk was still increased but no longer statistically significant (87). In this large pooled analysis, associations with the *FokI* SNP were slightly stronger for localized invasive cases (OR = 1.23, 95% CI 1.08–1.41) and did not vary by ER/PR tumor type or menopausal status (**Figure 4**). No interactions between dietary vitamin D intake (86) or blood levels of 25(OH)D (1, 14, 52) and *Fok1* genotypes have been observed. The large pooled analysis found a borderline interaction between dietary calcium intake, *Fok1*, and breast cancer risk using data collected from six international cohorts. However, subanalyses may lead to chance findings and should be interpreted cautiously. Although calcium is well recognized to influence endocrine vitamin D metabolism (117), and dietary calcium may protect against local $1,25(OH)_2D$ degradation through direct intestinal mucosal contact (30), the regulation of vitamin D metabolizing enzymes is likely tissue specific and may not pertain to breast carcinogenesis (92).

Ten studies have examined the *Bsm1* SNP in the 3′ end of the *VDR* gene in relation to breast cancer risk (19, 20, 23, 52, 60, 66, 81, 86, 87, 134). The *BsmI bb* genotype is linked with a longer *Poly(A)* microsatellite repeat, which may produce more unstable *VDR* mRNA. Initial case-control studies of the *BsmI* polymorphism (*rs1544410*) suggested that variation at this site may play an important role in breast cancer risk (19, 52, 81, 114) (**Supplemental Table 2**). However, several other individual studies observed no association with the *Bsm1* SNP (20, 23, 60, 66, 86). In a study of pre- and postmenopausal Caucasian and African American women, Trabert et al. (134) observed a higher breast cancer risk for the *BsmI bb* genotype only among postmenopausal Caucasian women. A recent pooled analysis of data from six cohorts

with more than 5000 cases observed no overall association between the *BsmI bb* SNP and breast cancer, regardless of race or menopausal status (87), indicating little support for an association of this SNP with breast cancer. However, consistent with several of the earlier, smaller case-control studies of the *BsmI bb* genotype in which a higher risk of advanced or metastatic breast cancer was observed (19, 52, 81), the pooled analysis found a lower risk of advanced breast cancer with the *BsmI BB* SNP in all races combined (OR = 0.74, 95% CI 0.60–0.92, p trend = 0.015) (87) (**Figure 4**). Although the results remained significant when limited to Caucasians (OR = 0.77, 95% CI 0.61–0.97, p trend = 0.045), confounding by population stratification is still a potential concern, particularly since there may be racial/ethnic differences in breast cancer survival (25, 109). Case-series studies have also suggested that the *BsmI bb* genotype is associated with poorer prognosis (114, 118). In animal models, hypothesized mechanisms for better prognosis with more favorable vitamin D status involve modulation of cell cycle progression, apoptosis, and cell signaling leading to reduced tumor invasiveness and angiogenesis (28).

Results from studies that explored interactions between the *Bsm1* SNP and vitamin D intake or status and breast cancer risk have been mixed. Dietary or total vitamin D intake did not modify the association between vitamin D pathway genotype and breast cancer risk in one U.S. study (86). In a British case-control study in which blood was drawn after diagnosis, the higher risk of breast cancer associated with the *bb* genotype was more pronounced among those with a low level of circulating 25(OH)D (81); the OR for having a *bb* genotype and being in the lowest quartile of plasma 25(OH)D was 6.82 (2.57–17.1), whereas the main effect ORs were, for the *bb* genotype alone, 2.02 (1.03–3.97), and for being in the lowest quartile of 25(OH)D alone, 5.83 (2.31–14.7) (81). However, an interaction was not observed in a U.S.-based nested case-control study (23). Calcium intake modified associations between *Bsm1* and other 3′ *VDR* SNPs and breast cancer risk in one study (86), but this was not replicated in the larger pooled analysis (87).

The 3′ polymorphisms are hypothesized to be linked to a functional SNP, such as the *Poly(A) L* variant. The *Poly(A) LL* genotype was associated with a higher risk of breast cancer in three (19, 52, 66) of six (19, 52, 66, 86, 134, 138) studies. Generally, breast cancer associations with the *b* allele corresponded to associations with the *Poly(A) L* allele, when both were measured within a study (19, 52, 86, 134). One exception was in a study of Latinas, where the *BB* genotype was associated with increased risk of breast cancer, and the *Poly(A) LL* genotype was also positively associated with higher risk (66). As previously noted, linkage disequilibrium between the *BsmI* and *Poly(A)* genotypes varies by ethnicity, which underscores the point that examination of single SNPs will not reflect similar LD across populations studied and may explain heterogeneous findings in the literature (94, 116, 137).

The *ApaI* and *TaqI* SNPs, as previously noted, are in variable LD with the *BsmI* and *Poly(A)* genotypes. Four studies of *ApaI* (31, 60, 86, 122) and nine studies of the *Taq1* SNP (3, 20, 33, 60, 71, 82, 86, 95, 122) yielded inconsistent associations with breast cancer. In a small Australian study (31), the *a* allele and the *aT* haplotype were associated with higher breast cancer risk, a finding that was consistent with the higher risk hypothesized for the *baTL* haplotype. In contrast, a Finnish study reported a significant inverse association with the *a* allele, which was stronger among women with a positive family history of breast cancer (OR = 0.73) (122). In a case-series of 183 women with breast cancer, Schoendorf et al. (118) reported a higher risk of metastases to the bone in those with the *ApaI AA* or *TaqI tt* genotype. These discordant findings may be due to different influences of VDR SNPs on different stages of breast carcinogenesis, or they may be due to chance.

Relatively few studies have examined *VDR* genotype–breast cancer associations by ethnicity. In analyses within the racial/ethnic subgroups in the multiethnic cohort (87), the

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Fok1 ff genotype was associated with highest risk among Japanese American women (OR = 1.63, 95% CI 1.07–2.49); however, the *p* for heterogeneity across racial/ethnic subgroups was not statistically significant (p = 0.31) (87). Japanese American women with the *BsmI B* allele were at comparatively lower breast cancer risk, although numbers of cases were small and the p for heterogeneity across racial/ethnic groups was borderline (p = 0.08). Neither *BsmI* nor *FokI* SNPs were associated with risk for breast cancer in African American women in either of the two studies that reported results for this racial group (87, 134).

Of other *VDR* SNPs examined, the *Bgl1 BB* genotype, which lies 303 base pairs downstream of the stop codon, was associated with a 63% lower risk of advanced breast cancer (OR = 0.37, 95% CI 0.18–0.76) in a subgroup of women with medium pigmentation (71). It is unclear why this subgroup would be singled out, but the group with constitutive medium pigmentation comprised 25% of the Caucasian and 68% of the Hispanic women studied. No other studies of breast cancer have reported on this SNP. In another study, the *Cdx2* SNP was not associated with breast cancer risk (3).

Other genes in the vitamin D pathway. Two common vitamin D–binding protein gene (*Gc*) exon 11 nonsynonymous SNPs, *rs4588* and *rs7041*, were recently examined in relation to 25(OH)D and $1,25(OH)_2D$ concentrations (37, 77) and breast cancer risk (2, 86). The *rs4588* SNP *C* allele was associated with higher circulating levels of both metabolites in three study centers that examined Hispanic and African American populations in the United States, whereas the *rs7041* SNP *T* allele was associated with lower levels of 25(OH)D (37). However, neither SNP was associated with postmenopausal breast cancer risk in one study (86), nor was an interaction with vitamin D or calcium intake observed in that study. Another study described differences in vitamin D metabolites according to three alleles in the vitamin D–binding protein gene (*Gc*), *Gc1s*, *Gc1f*, and *Gc2*, that produce known, common phenotypes (77). The phenotypes that result from combinations of the two nonsynonymous single-nucleotide polymorphisms, *rs4588* and *rs7041*, on the *Gc* gene were examined in relation to breast cancer risk (2). Abbas et al. (2) observed a lower breast cancer risk associated with the *Gc2–2* allele, which corresponded to the *rs7041 TT* and *rs4588 AA* genotypes (versus the *rs7041 GG* and *rs4588 CC* genotypes). Adjustment or stratification by 25(OH)D status did not change the results. Although the *Gc2–2* allele is associated with lower circulating levels of 25(OH)D, the Gc2 protein is converted to GcMAF by deglycosylation. GcMAF is a potent activator of macrophages, which may have antitumorigenic properties (2). Given the functional effects of these common SNPs and their potential importance in carcinogenesis, additional studies involving these these SNPs and their associated proteins are needed.

Other than SNPs in the *Gc* gene, one study examined the association between a SNP in the *CYP24A1* gene (86), a synonymous A→G SNP in exon 4 (*rs2296241*). No main effect or interaction with dietary calcium or vitamin D intake was observed (86).

Summary. The small but statistically significant associations between *FokI* and *BsmI* and breast cancer in the largest studies to date suggest that vitamin D and its receptor may impact breast cancer risk in humans. However, these associations were not strong, and those for *BsmI* were limited to advanced tumors. Furthermore, associations appear to vary by ethnic subgroups, but this has been understudied. New evidence on functional polymorphisms in the vitamin D–binding protein gene will likely lead to more research into the potential importance of vitamin D binding in relation to carcinogenesis. Additional research on the association between genotypes and tumor progression, and the roles of genotypes and gene-environment interactions among various racial-ethnic groups, is warranted.

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Prostate Cancer

Background. Prostate cancer is the leading cancer diagnosed among men, accounting for 25% of incident cancers annually (7). Following death from lung cancer, it is the second cause of cancer death among men (7). Few risk factors for prostate cancer have been identified and include age, race/ethnicity, and family history of prostate cancer. African American men and Jamaican men of African descent have the highest prostate cancer incidence rates in the world. Dietary factors associated with lower risk include foods containing lycopene and selenium (142). In addition, some studies suggest that death from prostate cancer increases with obesity (111). Ecological studies show a latitudinal gradient in prostate cancer occurrence, supporting a hypothesis relating the disease to vitamin D status (119). However, findings from epidemiologic studies of dietary vitamin D and blood 25(OH)D in relation to prostate cancer risk do not suggest that high levels are necessarily associated with lower risk (5, 84, 89, 107, 135). On the contrary, higher circulating plasma 25(OH)D may be associated with greater risk of aggressive prostate cancer (5, 89).

Vitamin D metabolizing enzymes are present in prostate tissue (121). In a study using prostate epithelial cells, local synthesis of $1,25(OH)_2D$ was found to be independent of PTH and calcium (145), indicating that endocrine regulation of $1,25(OH)_2D$ and local synthesis are independent. With prostate cancer progression, local 1α-hydroxylase activity is reduced and eventually becomes nonexistent (22, 61, 140). Because prostate cancer cells lose hydroxylation capabilities but retain the VDR, circulating $1,25(OH)_2D$ and exogenous administration may play a more important role in inhibiting prostate tumor progression (89, 120).

High dietary calcium and dairy product intake was associated with a higher risk of prostate cancer (4, 47), especially aggressive prostate cancer, in some (47) but not all (4) observational studies that have investigated the possible association. A proposed mechanism is the downregulation of $1,25(OH)_2D$ by higher levels of dietary calcium or dairy products (45). This hypothesis is supported by a recent study relating higher serum calcium [which would also suppress circulating $1,25(OH)_2D$ synthesis] to increased risk of fatal prostate cancer (123). However, studies in animal models found that calcium and suppression of circulating $1,25(OH)_2D$ did not affect prostate tumor development or growth (92). Although a secondary analysis from a randomized, double-blind, placebo-controlled clinical trial of supplemental calcium and colorectal adenoma recurrence found no evidence for higher risk of overall prostate cancer (12), the number of cases was small and the study could not examine aggressive prostate cancer.

Vitamin D pathway genotypes and prostate cancer. Approximately 30 studies have reported on associations between vitamin D pathway genotypes and risk of prostate cancer (9, 13, 15, 16, 21, 24, 26, 27, 29, 51, 53, 56, 57, 62, 65, 68, 70, 73, 78, 83, 84, 88, 89, 91, 98, 99, 101, 115, 128, 130) (**Supplemental Table 3**). A meta-analysis of 14 studies published by Ntais et al. (98) in 2003 concluded that four common polymorphisms (*BsmI*, *TaqI*, *Poly(A)* repeat, and *FokI*) in *VDR* are unlikely to be major determinants of prostate cancer susceptibility on a population-wide basis. Associations were null regardless of whether individuals were of European, Asian, or African descent, and whether genotypes were treated as recessive (including heterozygotes) or dominant (by allele) (98). The meta-analysis did not examine whether these polymorphisms were related to clinicopathological attributes. A subsequent meta-analysis in 2006 by Berndt et al. (13) included 10 studies that were published after the initial meta-analysis of Ntais et al. (98). The results of the second meta-analysis concurred with the first (and in addition reviewed the *ApaI* SNP) and found no associations with these *VDR* polymorphisms in codominant, recessive, or dominant models (13). Subsequent studies of *VDR* polymorphisms and prostate cancer risk have found generally similar null results overall

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(56, 57, 70, 78, 89). Finally, recently available GWAS data do not link prostate cancer risk with the 12q12-q14 chromosomal region that encompasses the *VDR* gene (35, 132).

Interactions between VDR genotypes and vitamin D status. More studies have evaluated potential interactions between vitamin D status and vitamin D–pathway genotypes and risk for prostate cancer than for the other cancers reviewed; therefore, additional attention is given here to findings in this area. Studies that reported interactions of genotype or haplotype with vitamin D assessed vitamin D exposure using estimated UV exposure (16, 70, 115) or circulating levels of vitamin D metabolites (78, 89). A U.K. case-control study found no association overall for three *VDR* SNPs; however, among men who reported a greater number of hours/year of UVR exposure, the homozygote variant genotype for the *Cdx2 (AA)* and *Fok1 (ff)* SNPs were associated with higher prostate cancer risk (16). John et al. (70) reported statistically significant, approximately 50% reduced risk of advanced prostate cancer among those with the high-activity allele genotypes, *FokI FF* or *Ff*, *TaqI tt*, and *BglI BB*, and nonsignificant lower risk among those with *Cdx2 AG* or *AA* genotypes, but only in the presence of high sun exposure. The authors speculated that low vitamin D status might mask the relative importance of these genotypes in relation to prostate cancer risk. Rukin et al. (115) found a nonsignificant lower risk of prostate cancer only among men with the *Fok1 C (F)* allele who also had very low UV exposure. These investigators also found statistically significant lower risk among men with Block C SNPs in the 5′ end of the *VDR* gene who also had a history of very low estimated UV exposure during adulthood.

In a nested case-control study from the Physicians' Health Study, Li et al. (78) found that neither the *FokI* SNP nor plasma 25(OH)D were independently associated with overall or aggressive prostate cancer risk. However, men with low plasma 25(OH)D combined with the *Fok ff* genotype had a 2.5-fold increased prostate cancer risk compared with those who had greater than the median plasma 25(OH)D levels and the *FokI F* allele. Another study of male health professionals observed no main effect associations of *FokI*, *BsmI*, or *Cdx2 VDR* SNPs or their related haplotypes with overall prostate cancer risk; however, two haplotypes (*Afb* and *AFB*) relative to *AFb* were associated with a significantly lower risk of aggressive prostate cancer (89). These authors also observed interactions between the *Cdx2 A* allele and both 25(OH)D and $1,25(OH)_2D$ status, such that the *A* allele was associated with lower risk of poorly differentiated prostate cancer in a low 25(OH)D environment, but higher risk in a low $1,25(OH)_2D$ environment. The authors speculated that low $1,25(OH)_2D$ may be more relevant for prostate cancer (89). Additional studies will be needed to tease apart whether circulating levels of vitamin D metabolites interact with *VDR* genotypes to affect risk for prostate cancer.

Polymorphisms in other vitamin D pathway genes. Several studies examined whether polymorphisms in other genes in the vitamin D pathway are associated with prostate cancer risk. Hawkins et al. (55) sequenced the *CYP27B1* gene in 32 case and control samples and found six common SNPs, three of which were examined in relation to prostate cancer risk in 245 cases and 434 controls; no associations were observed. All of the identified SNPs were found to be in the noncoding regions of the gene, suggesting that *CYP27B1* sequence variants are unlikely to be strongly related to prostate cancer risk. In addition, no associations were observed when cases were stratified by a Gleason score ≤ 6 or ≥ 7 (55). Kidd et al. (73) observed no association with two novel SNPs in the vitamin D–binding protein gene (*Gc*). In a comprehensive analysis of the *VDR*, *CYP27B1*, and *CYP24A1* genes, Holick et al. (57) found that tag SNPs in the *CYP27B1* and *CYP24A1* genes were not associated with prostate cancer risk in a case-control study that included 630 cases and 565 controls. The null findings from these studies are consistent with the findings from the GWAS, which found no significant

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associations for the *CYP27B1* or *CYP24A1* genes (35, 132).

Summary. Common polymorphisms of genes in the vitamin D pathway do not appear to be related to prostate cancer risk in the studies published to date. However, studies that quantified and stratified on UVR exposure or circulating vitamin D metabolite concentrations found associations in various subgroups. The stratified analyses are difficult to interpret because genotype associations either appear enhanced or muted in the presence of low or high UVR exposure or $1,25(OH)_2D$ or 25(OH)D concentrations. Because stratified analyses increase the potential for type 1 error, these findings should be considered hypothesis generating and need to be replicated in studies with larger sample sizes. In addition, a greater understanding of the relationship between circulating and tissue-specific vitamin D metabolites is needed.

FUTURE DIRECTIONS

Fine mapping of the genes involved in vitamin D metabolism and their surrounding areas of the human genome may yet uncover important gene variants that independently influence the risk of colorectal, breast, prostate, and other cancers. Future studies may also identify important phenotypic variations resulting from polymorphisms in these genes, using in vitro, animal, and proteomic or metabolomic approaches. Future epidemiologic studies must also carefully examine linked polymorphisms in a way that will not obscure potential associations between genotype and phenotype. More emphasis is needed on evaluating polymorphisms, alone or in combinations, as modifiers of risk from relevant environmental/lifestyle exposures. Much larger studies using more powerful statistical approaches and software will be required to examine the multitude of potential gene-gene and gene-exposure interactions (many which may realistically involve greater than two-way interactions). In large pooled analyses, extra attention should be given to the collection and harmonization of covariate and dietary data across these studies to minimize between-study heterogeneity and potential for measurement error.

SUMMARY

Studies of common polymorphisms in *VDR* and other genes in the vitamin D pathway do not provide evidence for substantial influences of single variants on risk of colorectal, breast, or prostate cancer. These findings are generally consistent with available GWAS data on these cancers. Furthermore, with some exceptions, functionality of genetic variation in this pathway is not well understood. The changing rates of colorectal, breast, and prostate cancer observed in migrant studies, in addition to recent GWAS study data, suggest that if vitamin D pathway gene variants influence risk, they may act largely as modifiers of risk from environmental/lifestyle factors. It is possible that associations with *VDR* genotypes may only be observed in the presence of low or high vitamin D status and may be more apparent or relevant in the setting of other environmental or dietary extremes. Most studies of vitamin D–related genes and cancer risk have primarily investigated main effects of a few variants of these genes alone. Few studies have investigated vitamin D–related gene variants, either alone or in combination, as modifiers of associations of vitamin D exposure and status on cancer risk; for those that have, results have been inconsistent.

Some "signals" did appear in our review of this literature that are worth noting. The largest studies to date suggest that the *Fok1 ff* genotype may be associated with lower risk for colorectal cancer but increased risk for breast cancer; however, these associations were neither strong nor entirely consistent. The *BsmI bb* genotype may be associated with higher risk of advanced breast cancer, but replication of these findings in additional human studies of various designs is needed. The variable linkage disequilibrium of common polymorphisms in *VDR* by ethnicity underscores the need to examine linked tag SNPs or haplotypes with disease risk among different racial/ethnic groups. The evidence for a

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role of genetic variation in other genes in the vitamin D pathway (e.g., *CYP27B1*, *CYP24A1*, *Gc*) is limited, but the recent discovery of functional *Gc* gene variants holds promise for future research in this area. In conclusion, very large studies with carefully collected data on vitamin D status and other environmental factors are needed to fully understand the role of genetic variation in the vitamin D pathway on cancer risk.

DISCLOSURE STATEMENT

For the past three years, Roberd Bostick has been a principal investigator and a co-investigator of NCI-funded grants related to vitamin D as a possible chemopreventive agent against colorectal neoplasms.

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LITERATURE CITED

1. Abbas S, Chang-Claude J, Linseisen J. 2008. Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. *Int. J. Cancer* 124:250–55
2. Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, et al. 2008. The Gc2 allele of the vitamin D binding protein is associated with a decreased postmenopausal breast cancer risk, independent of the vitamin D status. *Cancer Epidemiol. Biomarkers Prev.* 17:1339–43
3. Abbas S, Nieters A, Linseisen J, Slanger T, Kropp S, et al. 2008. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. *Breast Cancer Res.* 10:R31 (EPub ahead of print)
4. Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, et al. 2007. Dairy products, calcium intake, and risk of prostate cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol. Biomarkers Prev.* 16:2623–30
5. Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, et al. 2008. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J. Natl. Cancer Inst.* 100:796–804
6. Albertson DG, Ylstra B, Segraves R, Collins C, Dairkee SH, et al. 2000. Quantitative mapping of amplicon structure by array CGH identifies CYP24 as a candidate oncogene. *Nat. Genet.* 25:144–46
7. American Cancer Society. 2008. *Cancer Facts & Figures 2008*. Atlanta, GA: Am. Cancer Soc.
8. American Cancer Society. 2008. *Colorectal Cancer Facts & Figures 2008–2010*. Atlanta, GA: Am. Cancer Soc.
9. Andersson P, Varenhorst E, Söderkvist P. 2006. Androgen receptor and vitamin D receptor gene polymorphisms and prostate cancer risk. *Eur. J. Cancer* 42:2833–37
10. Arai H, Miyamoto KI, Yoshida M, Yamamoto H, Taketani Y, et al. 2001. The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene. *J. Bone Miner. Res.* 16:1256–64
11. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, et al. 1999. Calcium supplements for the prevention of colorectal adenomas. *N. Engl. J. Med.* 340:101–7
12. Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, et al. 2005. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol. Biomarkers Prev.* 14:586–89
13. Berndt SI, Dodson JL, Huang WY, Nicodemus KK. 2006. A systematic review of vitamin D receptor gene polymorphisms and prostate cancer risk. *J. Urol.* 175:1613–23
14. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, et al. 2005. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 14:1991–97
15. Blazer DG, Umbach DM, Bostick RM, Taylor JA. 2000. Vitamin D receptor polymorphisms and prostate cancer. *Mol. Carcinog.* 27:18–23
16. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, et al. 2004. Polymorphisms in the vitamin D receptor gene, ultraviolet radiation, and susceptibility to prostate cancer. *Environ. Mol. Mutagen.* 43:121–27

17. Bonithon-Kopp C, Kronborg O, Giocosa A, Rath U, Faivre J. 2000. Calcium and fibre supplementation in the prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 356:1300–6
18. Boyapati SM, Bostick RM, McGlynn KA, Fina MF, Roufail WM, et al. 2003. Calcium, vitamin D, and risk for colorectal adenoma: dependency on vitamin D receptor BsmI polymorphism and nonsteroidal anti-inflammatory drug use? *Cancer Epidemiol. Biomarkers Prev.* 12:631–37
19. Bretherton-Watt D, Given-Wilson R, Mansi JL, Thomas V, Carter N, Colston KW. 2001. Vitamin D receptor gene polymorphisms are associated with breast cancer risk in a UK Caucasian population. *Br. J. Cancer* 85:171–75
20. Buyru N, Tezol A, Yosunkaya-Fenerci E, Dalay N. 2003. Vitamin D receptor gene polymorphisms in breast cancer. *Exp. Mol. Med.* 35:550–55
21. Chaimuangraj S, Thammachoti R, Ongphiphadhanakul B, Thammavit W. 2006. Lack of association of VDR polymorphisms with Thai prostate cancer as compared with benign prostate hyperplasia and controls. *Asian Pac. J. Cancer Prev.* 7:136–39
22. Chen TC, Wang L, Whitlatch LW, Flanagan JN, Holick MF. 2003. Prostatic 25-hydroxyvitamin D-1alpha-hydroxylase and its implication in prostate cancer. *J. Cell Biochem.* 88:315–22
23. Chen WY, Bertone-Johnson ER, Hunter DJ, Willett WC, Hankinson SE. 2005. Associations between polymorphisms in the vitamin D receptor and breast cancer risk. *Cancer Epidemiol. Biomarker Prev.* 14:2335–39
24. Cheteri MB, Stanford JL, Friedrichsen DM, Peters MA, Iwasaki L, et al. 2004. Vitamin D receptor gene polymorphisms and prostate cancer risk. *Prostate* 59:409–18
25. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, et al. 2005. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J. Natl. Cancer Inst.* 97:439–48
26. Chokkalingam AP, McGlynn KA, Gao YT, Pollak M, Deng J, et al. 2001. Vitamin D receptor gene polymorphisms, insulin-like growth factors, and prostate cancer risk: a population-based case-control study in China. *Cancer Res.* 61:4333–36
27. Cicek MS, Liu X, Schumacher FR, Casey G, Witte JS. 2006. Vitamin D receptor genotypes/haplotypes and prostate cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 15:2549–52
28. Colston KW, Hansen CM. 2002. Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. *Endocr. Relat. Cancer* 9:45–59
29. Correa-Cerro L, Berthon P, Haussler J, Bochum S, Drelon E, et al. 1999. Vitamin D receptor polymorphisms as markers in prostate cancer. *Hum. Genet.* 105:281–87
30. Cross HS. 2007. Extrarenal vitamin D hydroxylase expression and activity in normal and malignant cells: modification of expression by epigenetic mechanisms and dietary substances. *Nutr. Rev.* 65:S108–12
31. Curran JE, Vaughan T, Lea RA, Weinstein SR, Morrison NA, Griffiths LR. 1999. Association of a vitamin D receptor polymorphism with sporadic breast cancer development. *Int. J. Cancer* 83:723–26
32. Day DA, Tuite MF. 1998. Post-transcriptional gene regulatory mechanisms in eukaryotes: an overview. *J. Endocrinol.* 157:361–71
33. Dunning AJ, McBride S, Gregory J, Durocher F, Foster NA, et al. 1999. No association between androgen or vitamin D receptor gene polymorphisms and risk of breast cancer. *Carcinogenesis* 20:2131–35
34. Ebert R, Schütze N, Adamski J, Jakob F. 2006. Vitamin D signaling is modulated on multiple levels in health and disease. *Mol. Cell Endocrinol.* 248:149–59
35. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, et al. 2008. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat. Genet.* 40:316–21
36. Eisman JA, Martin TJ, MacIntyre I, Moseley JM. 1979. 1,25-dihydroxyvitamin-D-receptor in breast cancer cells. *Lancet* 2:1335–36
37. Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, et al. 2008. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans. *J. Clin. Endocrinol. Metab.* 93:3381–88
38. Ezura Y, Nakajima T, Kajita M, Ishida R, Inoue S, et al. 2003. Association of molecular variants, haplotypes, and linkage disequilibrium within the human vitamin D-binding protein (DBP) gene with postmenopausal bone mineral density. *J. Bone Miner. Res.* 18:1642–49

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39. Fang Y, van Meurs JB, Bergink AP, Hofman A, van Duijn CM, et al. 2003. Cdx-2 polymorphism in the promoter region of the human vitamin D receptor gene determines susceptibility to fracture in the elderly. *J. Bone Miner. Res.* 18:1632–41
40. Flugge J, Krusekopf S, Goldammer M, Osswald E, Terhalle W, et al. 2007. Vitamin D receptor haplotypes protect against development of colorectal cancer. *Eur. J. Clin. Pharmacol.* 63:997–1005
41. Fraser DR. 1995. Vitamin D. *Lancet* 345:104–7
42. Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, et al. 2008. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol. Biomarkers Prev.* 17:889–94
43. Freedman DM, Looker AC, Chang SC, Graubard BI. 2007. Prospective study of serum vitamin D and cancer mortality in the United States. *J. Natl. Cancer Inst.* 99:1594–602
44. Garland FC, Garland CF, Gorham ED, Young JF. 1990. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev. Med.* 19:614–22
45. Giovannucci E. 1998. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control* 9:567–82
46. Giovannucci E. 2005. The epidemiology of vitamin D and cancer incidence and mortality: a review. *Cancer Causes Control* 16:83–95
47. Giovannucci E, Liu Y, Stampfer MJ, Willett WC. 2006. A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol. Biomarkers Prev.* 15:203–10
48. Gong YL, Xie DW, Deng ZL, Bostick RM, Miao XJ, et al. 2005. Vitamin D receptor gene Tru9I polymorphism and risk for incidental sporadic colorectal adenomas. *World J. Gastroenterol.* 11:4794–99
49. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, et al. 2007. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am. J. Prev. Med.* 32:210–16
50. Grau MV, Baron JA, Sandler RS, Haile RW, Beach ML, et al. 2003. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J. Natl. Cancer Inst.* 95:1765–71
51. Gsur A, Madersbacher S, Haidinger G, Schatzl G, Marberger M, et al. 2002. Vitamin D receptor gene polymorphism and prostate cancer risk. *Prostate* 51:30–34
52. Guy M, Lowe LC, Bretherton-Watt D, Mansi JL, Wilson RG, et al. 2004. Vitamin D receptor gene polymorphisms and breast cancer risk. *Clin. Cancer Res.* 10:5472–81
53. Habuchi T, Suzuki T, Sasaki R, Wang L, Sato K, et al. 2000. Association of vitamin D receptor gene polymorphism with prostate cancer and benign prostatic hyperplasia in a Japanese population. *Cancer Res.* 60:305–8
54. Halsall JA, Osborne JE, Potter L, Pringle JH, Hutchinson PE. 2004. A novel polymorphism in the 1A promoter region of the vitamin D receptor is associated with altered susceptibility and prognosis in malignant melanoma. *Br. J. Cancer* 91:765–70
55. Hawkins GA, Cramer SD, Zheng SL, Isaacs SD, Wiley KE, et al. 2002. Sequence variants in the human 25-hydroxyvitamin D3 1-alpha-hydroxylase (CYP27B1) gene are not associated with prostate cancer risk. *Prostate* 53:175–78
56. Hayes VM, Severi G, Padilla EJ, Eggleton SA, Southey MC, et al. 2005. Genetic variants in the vitamin D receptor gene and prostate cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 14:997–99
57. Holick CN, Stanford JL, Kwon EM, Ostrander EA, Nejentsev S, Peters U. 2007. Comprehensive association analysis of the vitamin D pathway genes, VDR, CYP27B1, and CYP24A1, in prostate cancer. *Cancer Epidemiol. Biomarker Prev.* 16:1990–99
58. Holick MF. 1999. Vitamin D. In *Modern Nutrition in Health and Disease*, ed. ME Shils, JA Olson, M Shike, AC Ross, pp. 329–45. Philadelphia, PA: Lippincott Williams and Wilkins
59. Holick MF. 2007. Vitamin D deficiency. *N. Engl. J. Med.* 357:266–81
60. Hou M, Tien Y, Lin G, Chen C, Liu C, et al. 2002. Association of vitamin D receptor gene polymorphism with sporadic breast cancer in Taiwanese patients. *Breast Cancer Res. Treat.* 74:1–7
61. Hsu J, Feldman D, McNeal JE, Peehl DM. 2001. Reduced 1 alpha hydroxylase activity in human prostate cancer cells correlates with decreased susceptibility to 25 hydroxyvitamin D3-induced growth inhibition. *Cancer Res.* 61:2852–56
62. Huang SP, Chou YH, Wayne Chang WS, Wu MT, Chen YY, et al. 2004. Association between vitamin D receptor polymorphisms and prostate cancer risk in a Taiwanese population. *Cancer Lett.* 207:69–77

63. Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, et al. 2008. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int. J. Cancer* 123:586–93
64. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, et al. 2007. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat. Genet.* 39:870–74
65. Ingles SA, Coetzee GA, Ross RK, Henderson BE, Kolonel LN, et al. 1998. Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. *Cancer Res.* 58:1620–23
66. Ingles SA, Garcia DG, Wang W, Nieters A, Henderson BE, et al. 2000. Vitamin D receptor genotype and breast cancer in Latinas. *Cancer Causes Control* 11:25–30
67. Ingles SA, Haile RW, Henderson BE, Kolonel LN, Nakaichi G, et al. 1997. Strength of linkage disequilibrium between two vitamin D receptor markers in five ethnic groups: implications for association studies. *Cancer Epidemiol. Biomarkers Prev.* 6:93–98
68. Ingles SA, Ross RK, Yu MC, Irvine RA, La Pera G, et al. 1997. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. *J. Natl. Cancer Inst.* 89:166–70
69. Ingles SA, Wang J, Coetzee GA, Lee ER, Frankl HD, Haile RW. 2001. Vitamin D receptor polymorphisms and risk of colorectal adenomas. *Cancer Causes Control* 12:607–14
70. John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. 2005. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res.* 65:5470–79
71. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. 2007. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multi-ethnic population. *Am. J. Epidemiol.* 166:1409–19
72. Kadiyska T, Yakulov T, Kaneva R, Nedin D, Alexandrova A, et al. 2007. Vitamin D and estrogen receptor gene polymorphisms and the risk of colorectal cancer in Bulgaria. *Int. J. Colorectal Dis.* 22:395–400
73. Kidd LC, Paltoo DN, Wang S, Chen W, Akereyeni F, et al. 2005. Sequence variation within the 5′ regulatory regions of the vitamin D binding protein and receptor genes and prostate cancer risk. *Prostate* 64:272–82
74. Kim HS, Newcomb PA, Ulrich CM, Keener CL, Bigler J, et al. 2001. Vitamin D receptor polymorphism and the risk of colorectal adenomas: evidence of interaction with dietary vitamin D and calcium. *Cancer Epidemiol. Biomarkers Prev.* 10:869–74
75. Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. 2007. Vitamin D and reduced risk of breast cancer: a population-based case-control study. *Cancer Epidemiol. Biomarkers Prev.* 16:422–29
76. Laing CJ, Cooke NE. 2005. Vitamin D-binding protein. In *Vitamin D*, ed. D Feldman, JW Pike, FH Glorieux, pp. 117–34. New York: Academic
77. Lauridsen AL, Vestergaard P, Hermann AP, Brot C, Heickendorff L, et al. 2005. Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. *Calcif. Tissue Int.* 77:15–22
78. Li H, Stampfer MJ, Hollis JB, Mucci LA, Gaziano JM, et al. 2007. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med.* 4:e103
79. Lips P. 2006. Vitamin D physiology. *Prog. Biophys. Mol. Biol.* 92:4–8
80. Lowe L, Hansen CM, Senaratne S, Colston KW. 2003. Mechanisms implicated in the growth regulatory effects of vitamin D compounds in breast cancer cells. *Recent Results Cancer Res.* 164:99–110
81. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, 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* 41:1164–69
82. Lundin A, Soderkvist P, Eriksson B, Berman-Jungestrom M, Wingren S. 1999. Association of breast cancer progression with a vitamin D receptor gene polymorphism. *Cancer Res.* 59:2332–34
83. Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, et al. 2001. Prostate cancer risk: associations with ultraviolet radiation, tyrosinase and melanocortin-1 receptor genotypes. *Br. J. Cancer* 85:1504–9
84. Ma J, Stampfer MJ, Gann PH, Hough HL, Giovannucci E, et al. 1998. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol. Biomarkers Prev.* 7:385–90
85. Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, et al. 2002. Vitamin D receptor as an intestinal bile acid sensor. *Science* 296:1313–16

Annu. Rev. Nutr. 2009.29:111-132. Downloaded from www.annualreviews.org
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86. McCullough ML, Stevens VL, Diver WR, Feigelson HS, Rodriguez C, et al. 2007. Vitamin D pathway gene polymorphisms, calcium intake, and risk of postmenopausal breast cancer. *Breast Cancer Res.* 9:R9. doi: 10.1186/bcr642
87. McKay JD, McCullough ML, Ziegler RG, Kraft P, Saltzman BS, et al. 2009. Vitamin D receptor polymorphisms and breast cancer risk: results from the NCI Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiol. Biomarkers Prev.* 18:297–305
88. Medeiros R, Morais A, Vasconcelos A, Costa S, Pinto D, et al. 2002. The role of vitamin D receptor gene polymorphisms in the susceptibility to prostate cancer of a southern European population. *J. Hum. Genet.* 47:413–18
89. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Hollis BW, Giovannucci E. 2007. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. *Prostate* 67:911–23
90. Mimori K, Tanaka Y, Yoshinaga K, Masuda T, Yamashita K, et al. 2004. Clinical significance of the overexpression of the candidate oncogene CYP24 in esophageal cancer. *Ann. Oncol.* 15:236–41
91. Moon S, Holley S, Bodiwala D, Luscombe CJ, French ME, et al. 2006. Associations between G/A1229, A/G3944, T/C30875, C/T48200 and C/T65013 genotypes and haplotypes in the vitamin D receptor gene, ultraviolet radiation and susceptibility to prostate cancer. *Ann. Hum. Genet.* 70:226–36
92. Mordan-McCombs S, Valrance M, Zinser G, Tenniswood M, Welsh J. 2007. Calcium, vitamin D and the vitamin D receptor: impact on prostate and breast cancer in preclinical models. *Nutr. Rev.* 65:S131–33
93. Murtaugh MA, Sweeney C, Ma KN, Potter JD, Caan BJ, et al. 2006. Vitamin D receptor gene polymorphisms, dietary promotion of insulin resistance, and colon and rectal cancer. *Nutr. Cancer* 55:35–43
94. Nejentsev S, Godfrey L, Snook H, Rance H, Nutland S, et al. 2004. Comparative high-resolution analysis of linkage disequilibrium and tag single nucleotide polymorphisms between populations in the vitamin D receptor gene. *Hum. Mol. Genet.* 13:1633–39
95. Newcomb PA, Kim H, Trentham-Dietz A, Farin F, Hunter D, Egan KM. 2002. Vitamin D receptor polymorphism and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 11:1503–4
96. Norman AW. 2006. Minireview. Vitamin D receptor: new assignments for an already busy receptor. *Endocrinology* 147:5542–48
97. Norman AW. 2008. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am. J. Clin. Nutr.* 88:491–99S
98. Ntais C, Polycarpou A, Ioannidis JP. 2003. Vitamin D receptor gene polymorphisms and risk of prostate cancer: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 12:1395–402
99. Oakley-Girvan I, Feldman D, Eccleshall TR, Gallagher RP, Wu AH, et al. 2004. Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor. *Cancer Epidemiol. Biomarkers Prev.* 13:1325–30
100. Ochs-Balcom HM, Cicek MS, Thompson CL, Tucker TC, Elston RC, et al. 2008. Association of vitamin D receptor gene variants, adiposity and colon cancer. *Carcinogenesis* 29:1788–93
101. Onen IH, Ekmekci A, Eroglu M, Konac E, Yesil S, Biri H. 2008. Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer. *Exp. Biol. Med. (Maywood)* 233:1608–14
102. Pani MA, Regulla K, Segni M, Hofmann S, Hufner M, et al. 2002. A polymorphism within the vitamin D-binding protein gene is associated with Graves' disease but not with Hashimoto's thyroiditis. *J. Clin. Endocrinol. Metab.* 87:2564–67
103. Parise RA, Egorin MJ, Kanterewicz B, Taimi M, Petkovich M, et al. 2006. CYP24, the enzyme that catabolizes the antiproliferative agent vitamin D, is increased in lung cancer. *Int. J. Cancer* 119:1819–28
104. Park K, Woo M, Nam J, Kim JC. 2006. Start codon polymorphisms in the vitamin D receptor and colorectal cancer risk. *Cancer Lett.* 237:199–296
105. Peters U, Hayes RB, Chatterjee N, Shao W, Schoen RE, et al. 2004. Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. *Cancer Epidemiol. Biomarkers Prev.* 13:546–52
106. Peters U, McGlynn KA, Chatterjee N, Gunter E, Garcia-Closas M, et al. 2001. Vitamin D, calcium, and vitamin D receptor polymorphisms in colorectal adenomas. *Cancer Epidemiol. Biomarkers Prev.* 10:1267–74

Annu. Rev. Nutr. 2009.29:111-132. Downloaded from www.annualreviews.org
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107. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. 2004. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. *Cancer Causes Control* 15:255–65
108. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. 2000. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control* 11:579–88
109. Porter PL, Lund MJ, Lin MG, Yuan X, Liff JM, et al. 2004. Racial differences in the expression of cell cycle–regulatory proteins in breast cancer. *Cancer* 100:2533–42
110. Reichrath J, Lehmann B, Carlberg C, Varani J, Zouboulis CC. 2007. Vitamins as hormones. *Horm. Metab. Res.* 39:71–84
111. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, et al. 2007. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol. Biomarkers Prev.* 16:63–69
112. Roff A, Wilson RT. 2008. A novel SNP in a vitamin D response element of the CYP24A1 promoter reduces protein binding, transactivation, and gene expression. *J. Steroid Biochem. Mol. Biol.* 112:47–54
113. Rohan T. 2007. Epidemiological studies of vitamin D and breast cancer. *Nutr. Rev.* 65:S80–83
114. Ruggiero M, Pacini S, Aterini S, Fallai C, Ruggiero C, Pacini P. 1998. Vitamin D receptor gene polymorphism is associated with metastatic breast cancer. *Oncol. Res.* 10:43–46
115. Rukin NJ, Luscombe C, Moon S, Bodiwala D, Liu S, et al. 2007. Prostate cancer susceptibility is mediated by interactions between exposure to ultraviolet radiation and polymorphisms in the 5′ haplotype block of the vitamin D receptor gene. *Cancer Lett.* 247:328–35
116. Rukin NJ, Strange RC. 2007. What are the frequency, distribution, and functional effects of vitamin D receptor polymorphisms as related to cancer risk? *Nutr. Rev.* 65:S96–101
117. Sanchez M, de la Sierra A, Coca A, Poch E, Giner V, Urbano-Marquez A. 1997. Oral calcium supplementation reduces intraplatelet free calcium concentration and insulin resistance in essential hypertensive patients. *Hypertension* 29:531–36
118. Schondorf T, Eisberg C, Wassmer G, Warm G, Becker M, et al. 2003. Association of the vitamin D receptor genotype with bone metastases in breast cancer patients. *Oncology* 64:154–59
119. Schwartz GG. 2005. Vitamin D and the epidemiology of prostate cancer. *Semin. Dial.* 18:276–89
120. Schwartz GG. 2008. Vitamin D and intervention trials in prostate cancer: from theory to therapy. *Ann. Epidemiol.* 19:96–102
121. Schwartz GG, Whitlatch LW, Chen TC, Lokeshwar BL, Holick MF. 1998. Human prostate cells synthesize 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3. *Cancer Epidemiol. Biomarkers Prev.* 7:391–95
122. Sillanpää P, Hirvonen A, Kataja V, Eskelinen M, Kosma VM, et al. 2004. Vitamin D receptor gene polymorphism as an important modifier of positive family history related breast cancer risk. *Pharmacogenetics* 14:239–45
123. 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.* 17:2302–5
124. Slattery ML, Herrick J, Wolff RK, Caan BJ, Potter JD, Sweeney C. 2007. CDX2 VDR polymorphism and colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* 16:2752–55
125. Slattery ML, Murtaugh M, Caan B, Ma KN, Wolff R, Samowitz W. 2004. Associations between BMI, energy intake, energy expenditure, VDR genotype and colon and rectal cancers (United States). *Cancer Causes Control* 15:863–72
126. Slattery ML, Neuhausen SL, Hoffman M, Caan B, Curtin K, et al. 2004. Dietary calcium, vitamin D, VDR genotypes and colorectal cancer. *Int. J. Cancer* 111:750–56
127. Slattery ML, Yakumo K, Hoffman M, Neuhausen S. 2001. Variants of the VDR gene and risk of colon cancer. *Cancer Causes Control* 12:359–64
128. Suzuki K, Matsui H, Ohtake N, Nakata S, Takei T, et al. 2003. Vitamin D receptor gene polymorphism in familial prostate cancer in a Japanese population. *Int. J. Urol.* 10:261–66
129. Sweeney C, Curtin K, Murtaugh MA, Caan BJ, Potter JD, Slattery ML. 2006. Haplotype analysis of common vitamin D receptor variants and colon and rectal cancers. *Cancer Epidemiol. Biomarkers Prev.* 15:744–49

Annu. Rev. Nutr. 2009.29:111-132. Downloaded from www.annualreviews.org
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130. Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, Bell DA. 1996. Association of prostate cancer with vitamin D receptor gene polymorphism. *Cancer Res.* 56:4108–10
131. Theodoratou E, Farrington SM, Tenesa A, McNeill G, Cetnarskyj R, et al. 2008. Modification of the inverse association between dietary vitamin D intake and colorectal cancer risk by a FokI variant supports a chemoprotective action of vitamin D intake mediated through VDR binding. *Int. J. Cancer* 123:2170–79
132. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, et al. 2008. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat. Genet.* 40:310–15
133. Thorne J, Campbell MJ. 2008. The vitamin D receptor in cancer. *Proc. Nutr. Soc.* 67:115–27
134. Trabert B, Malone KE, Daling JR, Doody DR, Bernstein L, et al. 2007. 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.* 9:R84. doi:10.1186/ber1833
135. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, et al. 2004. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int. J. Cancer* 108:104–8
136. Uitterlinden AG, Fang Y, Van Meurs JBJ, Pols HA, Van Leeuwen JP. 2004. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 338:143–56
137. Uitterlinden AG, Fang Y, van Meurs JBJ, Pols HAP. 2005. Genetic vitamin D receptor polymorphisms and risk of disease. In *Vitamin D*, ed. D Feldman, JW Pike, FH Glorieux, pp. 1121–57. New York: Academic
138. Wedren S, Magnusson C, Humphreys K, Melhus H, Kindmark A, et al. 2007. Associations between androgen and vitamin D receptor microsatellites and postmenopausal breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 16:1775–83
139. Welsh J, Wietzke JA, Zinser GM, Smyczek S, Romu S, et al. 2003. Impact of the vitamin D3 receptor on growth-regulatory pathways in mammary gland and breast cancer. *J. Steroid. Biochem. Mol. Biol.* 83:85–92
140. Whitlatch LW, Young MV, Schwartz GG, Flanagan JN, Burnstein KL, et al. 2002. 25-Hydroxyvitamin D-1alpha-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer. *J. Steroid Biochem. Mol. Biol.* 81:135–40
141. Wong HL, Seow A, Arakawa K, Lee HP, Yu MC, Ingles SA. 2003. Vitamin D receptor start codon polymorphism and colorectal cancer risk: effect modification by dietary calcium and fat in Singapore Chinese. *Carcinogenesis* 24:1091–95
142. World Cancer Research Fund/American Institute for Cancer Research. 2007. *Food, Nutrition, and the Prevention of Cancer: a Global Perspective*. Washington, DC: Am. Inst. Cancer Res.
143. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. 2000. Decreased bioavailability of vitamin D in obesity. *Am. J. Clin. Nutr.* 72:690–93
144. Yee YK, Chintalacharuvu SR, Lu J, Nagpal S. 2005. Vitamin D receptor modulators for inflammation and cancer. *Mini Rev. Med. Chem.* 5:761–78
145. Young MV, Schwartz GG, Wang L, Jamieson DP, Whitlatch LW, et al. 2004. The prostate 25-hydroxyvitamin D-1 alpha-hydroxylase is not influenced by parathyroid hormone and calcium: implications for prostate cancer chemoprevention by vitamin D. *Carcinogenesis* 25:967–71
146. Zanke BW, Greenwood CM, Rangrej J, Kustra R, Tenesa A, et al. 2007. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat. Genet.* 39:989–94
147. Zinser GM, Welsh J. 2004. Vitamin D receptor status alters mammary gland morphology and tumorigenesis in MMTV-neu mice. *Carcinogenesis* 25:2361–72
148. Zmuda JM, Cauley JA, Ferrell RE. 2000. Molecular epidemiology of vitamin D receptor gene variants. *Epidemiol. Rev.* 22:203–17

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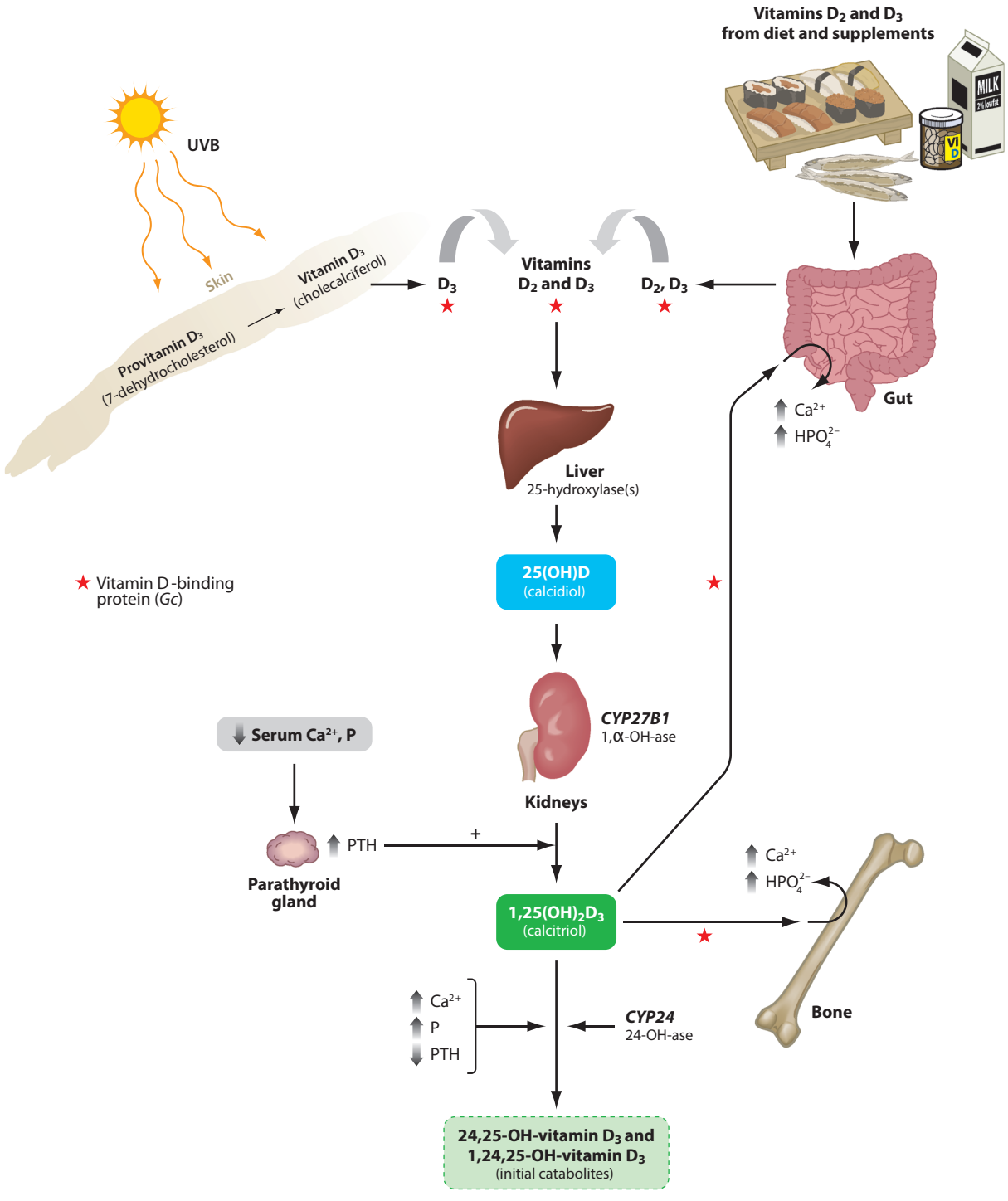

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Figure 1

"Classical" role of vitamin D in calcium homeostasis. Vitamin D is synthesized in the skin from provitamin D_3 (7-dehydrocholesterol) and is also obtained through dietary and supplemental sources (vitamins D_2 and D_3). Vitamin D is transported through the circulation bound to vitamin D–binding protein (DBP) to the liver, where it is hydroxylated at the 25 position to 25-OH-vitamin D [25(OH)D], the major circulating form. This reaction is catalyzed by one or more cytochrome P_{450} enzymes with 25-hydroxylase activity. Alternatively, vitamin D metabolites can be stored in adipose tissue. During periods of calcium deprivation, serum ionized calcium (Ca^{2+}) levels decline, and parathyroid hormone (PTH) or low phosphorus (P) stimulates a second hydroxylation of 25(OH)D catalyzed by 1α(OH)ase to form $1,25(OH)_2D$. $1,25(OH)_2D$ produced in the kidneys increases calcium absorption from the gut, calcium resorption from bone and tubular reabsorption from the kidneys, through both passive and vitamin D receptor (VDR)-mediated mechanisms, to restore blood calcium concentrations. When Ca^{2+}, P, and parathyroid hormone levels stabilize, $1,25(OH)_2D$ is degraded by 24-OH-ase to initial catabolites through a feedback loop. Genes are italicized adjacent to relevant proteins.

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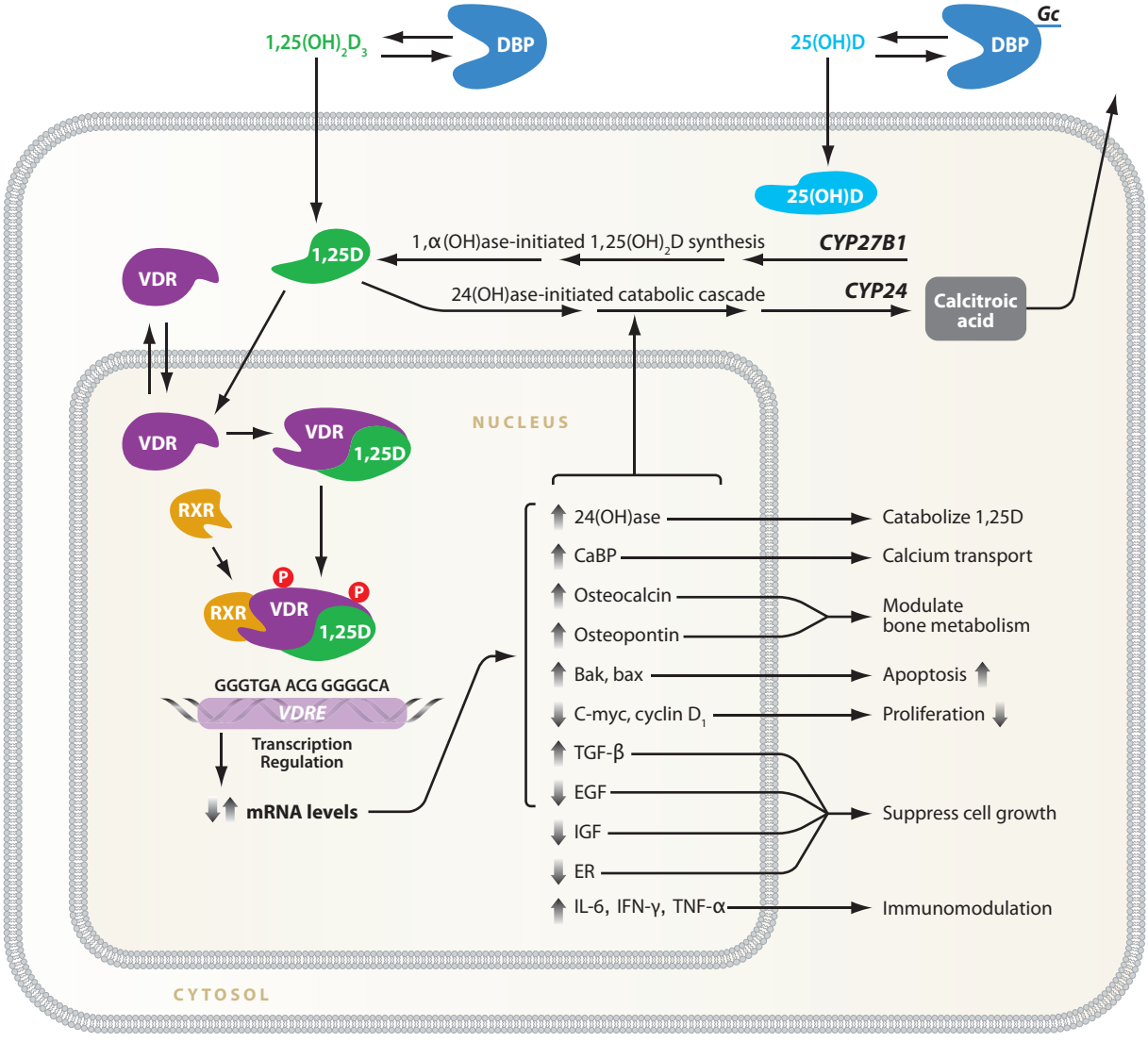

Figure 2

Proposed mechanism of action of vitamin D receptor (VDR) and $1,25(OH)_2D$ in target cells. $1,25\text{-}(OH)_2D$ is a relatively small, lipophilic molecule that easily penetrates the cell membrane, is taken up by the cell by simple diffusion, and binds to the VDR. Because many nonendocrine tissues possess 1α(OH)ase and 24(OH)ase, local synthesis and degradation of $1,25(OH)_2D$ is also thought to occur in an autocrine/paracrine manner. 25(OH)D can also bind to the VDR, but with 100- to 1000-fold lower magnitude. The VDR complex then binds to target DNA sequences as a heterodimer with the retinoid X receptor (RXR), recruiting a series of coactivators, resulting in the induction of target gene expression. More than 200 genes contain vitamin D response elements (VDREs) and influence a wide array of functions. Examples of genes with VDREs related to carcinogenesis include those involved in regulating cell proliferation, differentiation, apoptosis, and modulation of growth and inflammatory factors. Genes are italicized adjacent to relevant proteins. Modified from Holick (58).

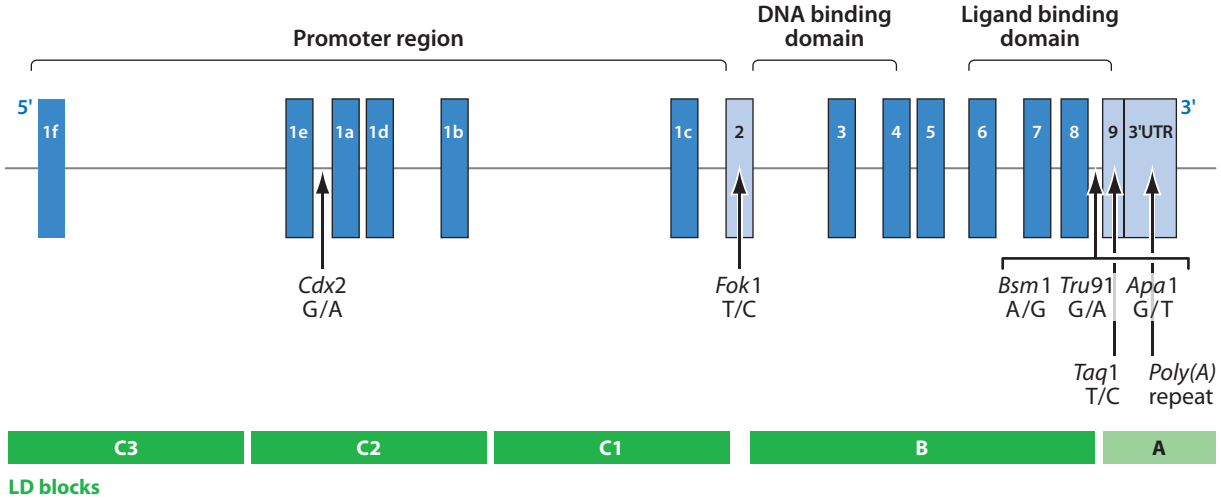

Figure 3

Vitamin D receptor gene (*VDR*). The gene is located on chromosome 12q13 and is <100 Kb long. It contains eight protein-coding exons 2–9, six untranslated exons 1a–1f, and several promoter regions. The most commonly examined single-nucleotide polymorphisms to date are identified above, most in the 3′ end of the gene. Linkage disequilibrium (LD) is strong within LD blocks, but there is little LD between blocks (94). Modified from Rukin et al. (116).

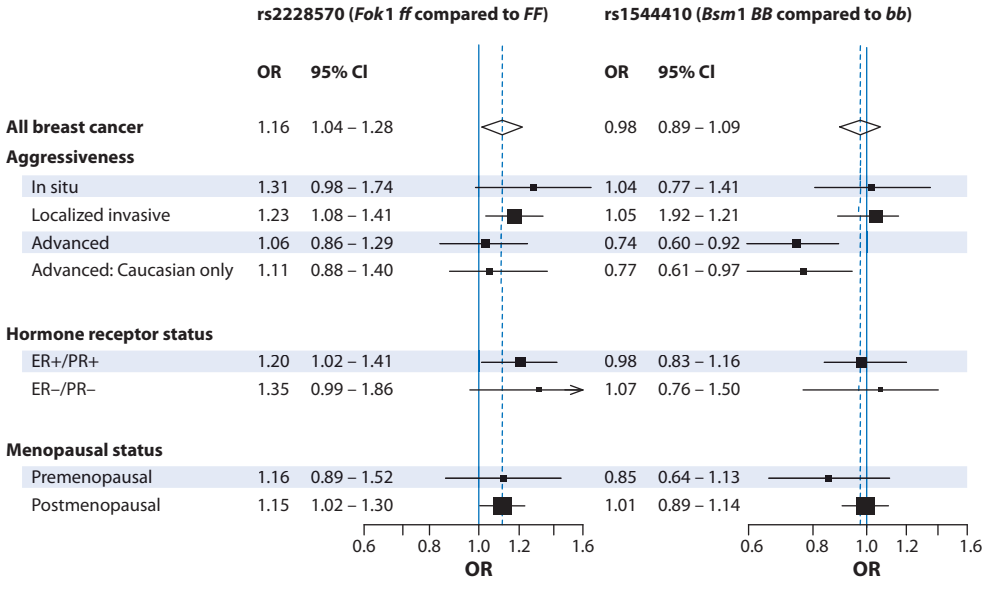

Figure 4

Risk of breast cancer by tumor characteristics and menopausal status for rs2228570 (*Fok1*) and rs1544410 (*Bsm1*). Odds ratios (OR) and 95% confidence intervals (CI) were calculated by conditional logistic regression and compared subjects homozygous for the less common variant (*ff* and *BB*, respectively) to subjects homozygous for the more common variant (*FF* and *bb*, respectively). The overall OR is represented by the diamond and the dashed line.

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Errata

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