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Review

Vitamin D Receptor Polymorphism and Cancer: An Update

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Abstract. *Background: Vitamin D mediates its action via vitamin D receptor (VDR) and is involved in a wide variety of biological processes including regulation of cell proliferation and differentiation in normal tissue and apoptosis, and cell adhesion in tumor cells. The study of genetic variations in VDR may elucidate the association of vitamin D levels, its metabolism, and VDR polymorphism with various diseases and cancer. The association of VDR polymorphism with cancer has been reported; however, the literature lacks critical analyses of the studies in last 3 years. Materials and Methods: A systematic search of PubMed database (2015 through mid-2017) was conducted to provide a comprehensive overview of this clinical arena. Results: Studies on the association of VDR polymorphisms FokI, BsmI, TaqI, and ApaI and cancer have suggested the involvement of VDR polymorphism in tumorigenesis. Conclusion: The inconsistent results and lack of the studies in some cancer types warrant additional research.*

Vitamin D is involved in a wide variety of biological processes including bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation. Vitamin D has a substantial function in overall human health, including cancer occurrence (1). Vitamin D regulates cellular differentiation and proliferation in normal tissue and regulates proliferation, apoptosis, and cell adhesion at the tumor cell level. It also modifies tumor angiogenesis, invasion, and metastasis along with decreasing oxidative DNA damage (2). Vitamin D mediates its biological action *via* the vitamin D receptor (VDR) (3). VDR is a steroid intracellular hormone receptor which binds to 1, 25(OH)2 D and interacts with vitamin D receptor response elements (VDRE) of the target genes to produce various biological effects (4). The *VDR* gene lies on the long arm of chromosome 12 (12q12-14) and has approximately 200 single nucleotide polymorphisms (SNPs) (5). The most common allelic variants studied includes a start codon polymorphism *Fok*I (T/C) in exon II, *Bsm*I (A/G) and *Apa*I (C/A) polymorphisms in the intron between exon VII and IX and a TaqI (T/C) variant in exon IX (6). The most commonly studied *VDR* polymorphisms include *Fok*1 (rs2228570), *Apa*1 (rs7975232), *Bsm*1 (rs1544410), *Bgl*1 (rs739837), and restriction fragment length polymorphisms rs7975232 (G/T substitution), rs1544410 (A/G substitution), and rs739837 (G/T substitution) (7). Since vitamin D acts through VDR, studying genetic variations in *VDR* may elucidate the association of altered vitamin D levels and metabolism, *VDR* polymorphism, and cancer. This systemic review focused on pooling the case–control studies and meta-analyses performed in the past 3 years (2015-mid 2017) for the association of *VDR* polymorphism and cancer.

Materials and Methods

A systematic search of the PubMed database (January 2015 through mid-2017) of the National Library of Medicine was performed using the following Medical Subject Headings: cancer, vitamin D, *VDR* polymorphism, tumor, breast cancer, female reproductive tract cancer, prostate cancer, skin cancer, gastrointestinal tract, esophageal cancer, colorectal cancer, urinary tract cancer, pediatric tumors, hematologic cancer. We included articles that examined and described the *VDR* polymorphisms in relation to risk and incidence of cancer. Articles that were not written in English, conference abstracts and studies not performed on humans were excluded.

VDR Polymorphism and Cancer

VDR SNPs within the gene coding for VDR may influence cancer risk (8). Numerous investigations have analyzed *VDR*-affiliated SNPs; however, their general association with

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Key Words: Vitamin D, VDR polymorphism, breast cancer, prostate cancer, gastrointestinal tract cancer, urological cancer, hematological cancer, pediatric cancer, review.

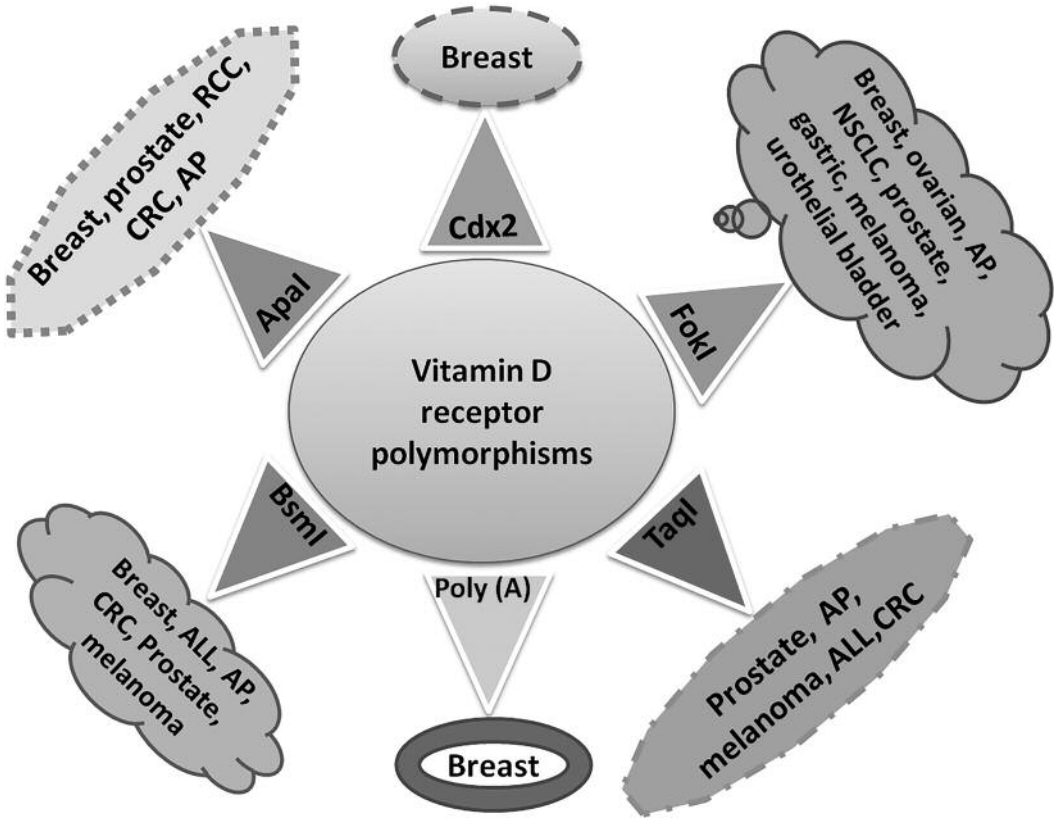

Figure 1. *Vitamin D receptor (VDR) polymorphisms associated with increased risk of cancer. The presence of these polymorphisms is associated with an increased risk of cancer. However, these relationships may vary with age, ethnicity, and race as discussed in the text. ALL: Acute lymphoblastic leukaemia, AP: adenomatous polyposis, CRC: colorectal cancer, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma.*

carcinogenesis remains controversial. Significant associations between *VDR* polymorphisms and breast (*Fok*1, *Bsm*1, *Apa*1), prostate (*Fok*1, *Bsm*1, *Taq*1), colorectal (*Fok*1, *Bsm*1, *Taq*1) and skin cancer (*Fok*1, *Bsm*1, *Taq*1) have been reported (9). For instance, the *CDX2* polymorphism (SNP - rs11568820) of the *VDR* gene has been associated with cancer susceptibility amid varied results. Various researchers have conducted the meta-analysis to establish the viable association between *VDR* polymorphism and cancer risk (10-22). A meta-analysis including 25 separate studies totaling 34,018 individuals published prior to March 2015 for *CDX2* polymorphism association with cancer conducted by Dai *et al*. demonstrated that in the homozygous model, *CDX2* mutations were significantly associated with an increased cancer risk of colorectal and ovarian cancer, particularly in African–American but not in Caucasians or Asians (10). Data-analysis of dominant, homozygous and recessive comparison models yielded a significant association between cancer risk and *CDX2* mutations in African–Americans. Stratifying the data by cancer types showed a strong association between *VDR CDX2* polymorphisms and an amplified risk of colorectal and ovarian cancer (10). Gandini *et al*. analysed the association between VDR polymorphisms (*Fok*1, *Bsm*1, *Taq*1, *Apa*1, and *Cdx2*) and various types of cancer such as ovarian cancer, renal cell carcinoma, thyroid carcinoma, hepatocellular carcinoma (HCC), sarcoma, skin (melanoma and non-melanoma skin cancer), bladder cancer, non-Hodgkin's lymphoma, leukaemia, oesophageal adenocarcinoma (EAC), head and neck and oral squamous cell carcinoma including 79 independent studies, for a total of 52427 cases and 62225 controls (9). The study concluded that significant associations exist between VDR polymorphisms and prostate (*Fok*1, *Bsm*1, *Taq*1), breast (*Fok*1, *Bsm*1, *Apa*1), colorectal (*Fok*1, *Bsm*1, *Taq*1) and skin cancer (*Fok*1, *Bsm*1, *Taq*1) (Figures 1 and 2).

A meta-analysis between *VDR* polymorphism including *Cdx2* (rs11568820), *Fok*I (rs2228570), *Bsm*I (rs1544410), *Apa*I (rs7975232), and *Taq*I (rs731236) and the risks for female reproductive cancer such as breast, ovarian, cervical, endometrial, uterine and vaginal cancer, found an increased risk of developing breast and ovarian cancers with *Fok*I polymorphism and reduced risk with *Bsm*I polymorphism (19). A meta-analysis for the association between *VDR*

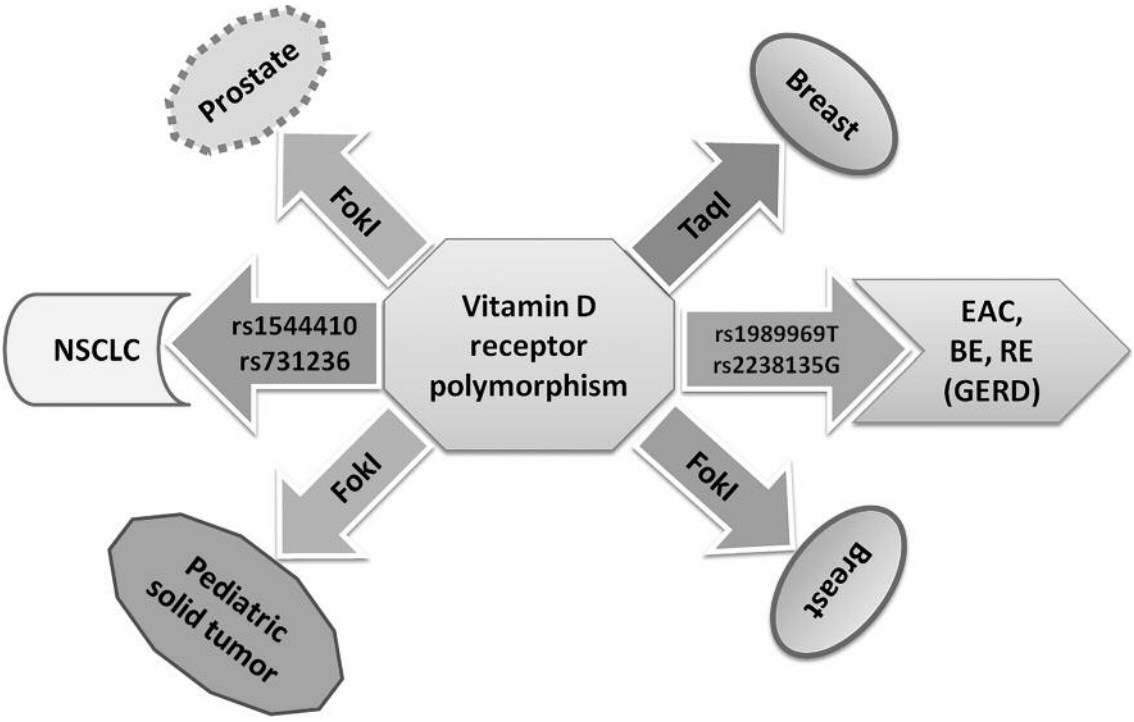

Figure 2. *Vitamin D receptor (VDR) polymorphisms associated with reduced risk of cancer. The presence of these polymorphisms is associated with a reduced risk of cancer. However, these relationships may vary with age, ethnicity, and race as discussed in the text. BE: Barrett's oesophagus, EAC: oesophageal adenocarcinoma; GERD: gastro-oesophageal reflux disease, RE: reflux oesophagitis; NSCLC: non-small cell lung cancer.*

polymorphism (*Taq*I, *Apa*I, and *Cdx2*) and the risk of basal cell carcinoma, colorectal cancer, EAC, hepatocellular carcinoma, head and neck cancer, non-Hodgkin lymphoma, oral squamous cell carcinoma, renal cell carcinoma, squamous cell carcinoma, and thyroid carcinoma found *Cdx2* gg *versus* GG to be associated with a significantly increased risk for all cancer types and TaqI was associated with significantly increased risk for colorectal cancer (21) (Figures 1 and 2). Significant variations in frequency were also existent between diverse ethnic groups. *VDR* genotypes may have more significance when grouped with specific haplotypes, or when linked to additional gene polymorphisms involved in the vitamin D pathway, or when stratified by different tumor type or patient background (21). Nevertheless, there are clear intersections between the ability of VDR to function properly and carcinogenesis in a number of indications. This section focuses on the effect of *VDR* polymorphisms in the entire gastrointestinal tract – where vitamin D-related patient management strategies hold much promise.

Female Reproductive Tract Cancer

VDR polymorphism has been associated with cancer of the female reproductive including breast, ovarian, cervical, endometrial, uterine, and vaginal cancer (19). Increased expression of *VDR* has been found in breast cancer and inversely related to aggressive tumor characteristics, including large tumor size, hormonal receptor (HR) negativity, triple-negative subtype [estrogen-receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative], and expression of proliferative marker Ki-67 (23). Similarly, various case–control studies suggested that the association between *VDR* polymorphism and risk of breast cancer may depend on race and ethnicity. Furthermore, these studies also showed inconsistent results, some suggesting the association of *VDR* polymorphism with breast cancer, while others suggested a lack of association (3, 19, 24-31). No association between *VDR* polymorphisms and breast cancer risk was found, however, modification of this relationship was observed with the menopausal status in Europeans (*VDR* rs4328262 and rs11168292) and East Asians (*VDR* rs11168287). Furthermore, heterogeneity by tumor subtype was also seen for rs1544410, rs7967152 and rs2239186 *VDR* polymorphisms in Europeans (30). These case–control and meta-analysis studies suggest that *VDR* polymorphism may be associated with increased risk of breast cancer (Table I). However, Shaikh *et al*. reviewed the impact of *VDR* gene polymorphisms *Fok*1, *Bsm*1, *Taq*1, *Apa*1

Table I. *Vitamin D receptor (VDR) polymorphisms and female genital tract cancer.*

Type of study	Cancer type	Number of study subjects	Polymorphism under study	Outcome of the study
Case–control study (3)	Breast	60 Egyptian female patients with breast cancer and 60 age matched healthy control females	*Bsm*I (A/G)	B Allele or Bb genotype of *VDR* may be a susceptibility risk factor for breast cancer development.
Meta-analysis (16)	Breast	Two case–control studies (1,526 cases and 2,058 control in premenopausal group) and five studies (7,738 cases and 10,453 control in postmenopausal group)	*Fok*I	*Fok*I polymorphism is a risk factor for breast cancer in post-menopausal women but not in premenopausal women.
Meta-analysis (17)	Breast	Four prospective case–control studies (case/control: 270/554; 6473/8397; 6355/8149; 500/500)	*Fok*1, *Bsm*1, *Taq*1, and *Apa*1	No significant association between *Fok*1, *Bsm*1, *Taq*1, *Apa*1 polymorphism, and breast cancer risk in the general as well as Caucasian population.
Meta-analysis (19)	Breast	Six ovarian cancer studies (13 individual studies involving 4107 cases and 6661 controls) and 29 breast cancer studies (38 individual studies involving 16,453 cases and 22,044 controls)	*Cdx2*, *Fok*I, *Bsm*I, *Apa*I, *Taq*I	*Fok*I and *Bsm*I *VDR* gene polymorphisms may be significantly associated with gynecological cancer.
In vitro study (20)	Breast	ER-positive (MCF7 and T-47D) and ER-negative (MDA-MB-231, SUM 159PT, SK-BR-3, BT549, MDA-MB-468, HCC1143, BT20 and HCC1954), human breast cancer cell lines	Cdx2	*Cdx2* polymorphism is associated with breast cancer and may be a potential biomarker for vitamin D treatment in breast cancer.
Case–control study (24)	Breast	130 Post-menopausal breast cancer cases aged 49 to 65 years and 100 controls aged 50 to 72 years	*Bsm*I-rs1544410, *Apa*I-rs7975232, *Taq*I-rs731236 *Fok*I-rs10735810	Significantly increased risk of breast cancer among carriers of BsmI bb genotype and ApaI aa genotype.
Case–control study (25)	Breast	261 Blood samples, 134 women with breast cancer and 127 controls	poly(A)	Poly (A) variant L allele is associated with risk of breast cancer in females of northern Iran.
Case–control study (26)	Breast	60 Females with breast cancer and 30 healthy controls of matched age	*Bsm*1 (rs1544410)	No association with breast cancer risk.
Case control study (27)	Breast	264 Subjects (103 cases and 161 controls)	*Cdx2*	Non-significant association between *Cdx2* and breast cancer, however the GG genotype increases the risk of developing cancer in southern Pakistan.
Case–control study (28)	Breast	463 Genetically enriched female breast cancer cases with known BRCA1/2 status and 1,012 controls	*Bsm*I (rs1544410), *Fok*I (rs2228570)	*Bsm*I polymorphism may be associated with increased breast cancer risk in Pakistani women negative for *BRCA1/2* germline mutations.
Population-based case–control study (29)	Breast	967 Incident breast cancer cases and 993 controls	*Taq*I, *Bsm*I, *Apa*I	*Taq*I (rs731236) was significantly associated with 26% risk reduction
Case–control study (30)	Breast	1037 Cases and 1050 controls	rs4328262, rs11168292, rs11168287, rs1544410, rs7967152, rs2239186	No association between *VDR* polymorphism and breast cancer. Relationship may change with menopausal status.
Case-control study (31)	Breast	Blood samples from 95 cancer and 71 healthy individuals	*Fok*I and *Bsm*I	Protective effect of the *Fok*I polymorphism and no association of *Bsml* in breast cancer in West Azerbaijan Province, Iran.
Case–control study (33)	Breast	50 Healthy donors from indigenous black Tanzanian and a Caucasian Italian population and 35 Caucasian and 18 African patients with breast cancer	A1012G, *Cdx2* and *Fok*1	Significantly higher frequency of AA *Cdx2* and CC *Fok*1 in Africans.
Case–control study (34)	Ovarian	245 patients and 465 healthy controls	*Fok*I (rs2228570)	*Fok*I is a risk factor for ovarian cancer in non-carriers of *BRCA1/BRCA2* mutations in the Polish population.
Case–control study (35)	Ovarian	100 Controls and 100 patients	*Fok*I, *Taq*1	*Fok*I might be a risk factor for the development of ovarian cancer.

ER: Estrogen receptor; BRCA1/2: breast cancer susceptibility gene 1/2.

Table II. *Vitamin D receptor (VDR) polymorphisms and prostate cancer.*

Type of study	Number of study subjects	Polymorphism under study	Outcome of the study
Meta-analysis (11)	27 Eligible studies included 12,276 cases and 13,506 controls	*Taq*I	*Taq*I genotypes TT and TT/Tt were significantly higher in the advanced prostate cancer and is associated with the risk in Asians.
Meta-analysis (13)	27 Case–control studies with 10,486 cases and 10,400 controls	*Fok*I	Overall-no significant association. Significant association in Caucasian population
Meta-analysis (18)	9,720 Patients and 9,710 controls	*Fok*I	Increased risk of developing prostate cancer in Caucasian population.
Meta-analysis (22)	10 Studies involving 4979 cases and 4380 controls (*Cdx2*) and 11 studies involving 2837 cases and 2884 controls (*Apa*l)	*Cdx2*, *Apa*I	*Cdx2* and *Apa*I polymorphisms were not associated with prostate cancer.
Case–control study (41)	Peripheral blood of 342 patients: 132 PC, 41 BPH and 169 young healthy volunteers	*Fok*I, *Bsm*I, *Apa*I, *Taq*I	*VDR* polymorphism has a genotype-phenotype association with prostate cancer.
Case–control study (42)	124 Jordanian prostate cancer patients and 100 healthy volunteers	*Fok*1	No significant association
Case–control study (43)	446 AA men aged 35 to 93 years and 379 control from AAPCA and Vitamin D and Prostate Cancer Risk in AA Men Study	rs731236, rs7975232, rs731236, rs1544410, rs3782905, rs1544410, rs2239185	Significant association between *VDR* polymorphism and prostate cancer risk in African-American men.
Case–control study (44)	7,666 Patients and 8,073 controls	*Bsm*I	*Bsm*I polymorphism may be related to prostate cancer in Caucasian descendants.
Case–control study (45)	Blood DNA sample from 50 patients and 79 age-qualified controls	*Fok*I, *Bsm*I, *Apa*I and TaqαI	A and B alleles of the *VDR Apa*I and *Bsm*I loci are associated with risk of prostate cancer.

AA: African-American, AAPCA: African-American Sporadic Prostate Cancer Study; BPH: benign prostate hypertrophy.

and poly(A) on development of breast cancer from 1996 to 2015 and suggested that due to the inconsistent results of various studie, no conclusive evidence associates the risk of breast cancer with *VDR* polymorphism (32). Similarly, the inconsistent results of the studies shown in Table I suggest the need for further research.

Prostate Cancer

Prostate cancer is the most common malignant tumor in older men across the globe. The incidence of prostate cancer is increasing worldwide while ethnic origin, family history, hormonal status, dietary structure, age and low vitamin D levels are risk factors for prostate cancer (36, 37). Furthermore, studies have reported the association between *VDR* polymorphism with an increased risk of prostate cancer (36, 38). However, the results of various studies were disputable and contradictory (39, 40). Most of the studies found no association between *VDR* polymorphism and prostate cancer (13, 22), however, Nunes *et al*. found correlation between CC genotype (*Taq*I) with age (>58 years old), and GG (*Bsm*I) with lower prostate-specific antigen (PSA) levels (<10 ng/ml) (41). Aassociation between a significantly increased estimated chance of PSA <10 ng/ml with G allele (*Bsm*I) and 9.75-fold increased chance of patients with prostate cancer having a lower PSA level with GG/GG genotype (*Bsm*I/*Apa*I) was also found. Recently, various meta-analysis and case-control studies have been conducted to find a relation between *VDR* polymorphism (*Taq*I, *Fok*I, *Cdx2*, *Apa*I, *Bsm*I, rs731236, rs7975232, rs731236, rs1544410, rs3782905, rs1544410, and rs2239185) and risk of prostate cancer (11, 13, 18, 22, 41-44). *VDR* polymorphism *Folk*I, *Cdx2*, and *Apa*I were not found to have any association with an increased risk of prostate cancer. VDR polymorphism *Taq*I, *Bsm*I, rs731236, rs7975232, rs731236, rs1544410, rs3782905, rs1544410, and rs2239185 were found associated with increased risk of prostate cancer (Table II). However, the association varies with race (Asian, Caucasian, and African-American) and the genotype–phenotype-based relationship of VDR. Recently, a case–control study investigating the possible associations of *VDR* polymorphism (*FokI*, *BsmI*, *ApaI* and *TaqαI*), and the cytochrome *P-45017* alpha (*CYP17*) gene (the MspA1I locus) with prostate cancer among Lebanese men suggested that the overall polymorphism profile of every gene involved in prostate physiology is a better indicator than polymorphisms in individual genes (45).

Cancer of the Gastrointestinal Tract

An array of epidemiological studies have shown that vitamin D protects cells from carcinogenesis in several solid tumors;

however, recent elucidation concerning the possible deleterious effect of high vitamin D levels in the development of EAC has raised concern in this field. *VDR* polymorphism (rs10735810) representing to a T-to-C transition (ATG to ACG) in exon 2 of the *VDR* gene has been associated with gastric cancer in Chinese Han population (46). The role of *VDR* polymorphisms in relation to the risk of Barrett's oesophagus and EAC has been robustly investigated. Barrett's oesophagus is characterized by highly dysplastic columnar squamous epithelium near the gastro-oesophageal junction and has been deemed a precursor to EAC. Janmaat *et al*. in a meta-analysis found that *VDR* haplotype rs2238135G allele is associated with reduced oesophageal VDR expression and a reduced incidence of gastroesophageal reflux disease (GERD), Barrett's oesophagus and EAC (12). In another study, 15 haplotype SNPs of the *VDR* gene were analyzed in patients with GERD, Barrett's oesophagus or EAC paired with normal histological controls (12). The results demonstrated that there is higher *VDR* gene expression in tissue from Barrett's oesophagus compared to healthy control samples. A specific SNP was identified in the *VDR* gene and patients with this haplotype had a two-fold reduced risk of GERD, Barrett's oesophagus and EAC (12) (Table III). The mutated allele was found to cause the appearance of a GATA-1 binding site. GATA-1 turns off transcription, which could explain how the presence of a mutated *VDR* gene would suppress inflammation and rapid cell proliferation in that region (47). The relationship between vitamin D and oesophageal cancer is essentially the opposite to that seen in other cancerous conditions. Whereas abundant and highly functioning vitamin D/VDR pathways are seen to reduce cancer risk, the likelihood of oesophageal cancer and its affiliated precursor diseases is heightened with robust vitamin D pathway activity. Another meta-analysis also found a significant association of reduced risk of oesophageal cancer with *VDR* SNPs, suggesting that a dysfunctional vitamin D network is advantageous in oesophageal cancer (48). Understanding the mechanisms of action of the *VDR* haplotype in oesophageal cancer could be of clinical utility by identifying patients in whom vitamin D chemoprevention would be efficacious. One of the potential explanations for the inverse relationship seen between vitamin D and oesophageal cancer is that *VDR* has been recently characterized as a bile acid receptor in addition to its well-characterized role as a vitamin receptor. Reflux of bile acid into the most distal parts of the oesophagus is one of the pervasive causes of dysplastic progression into EAC (48, 49).

Vitamin D plays a crucial role in the pathogenesis of colorectal cancer and epidemiological research has put forth evidence that vitamin D plays a protective role against colorectal cancer (50). The role of polymorphisms of *VDR* and CYP27B2 and CYP24A1, which are involved in the production and suppression of vitamin D, have all been linked to colorectal cancer risk (51). Similarly, a randomized clinical trial conducted with 2259 patients for 41 SNPs of seven genes [VDR, gene encoding vitamin D-binding protein previously known as gc-globulin (*GC*), *7-dehydrocholesterol reductase (DHCR7), CYP2R1, CYP27B1, CYP24A1* and calcium-sensing receptor (*CASR*)] concluded that VDR genotype may influence the prevention of advanced colorectal adenomas with vitamin D_3 supplementation, suggesting the role of *VDR* in colorectal carcinoma (52). Another study in Japan found an association between common genetic variations in *VDR* and risk of colorectal cancer. The researchers selected 29 *VDR* SNPs and concluded a limited association existed between *VDR* polymorphism and risk of colorectal cancer (53). Furthermore, another cohort study suggested little effect of the variants in the *VDR* gene on the risk of colorectal cancer (54). Adenomatous polyps are the precursor for colorectal cancer and a study found *Fok*I to be associated with modified risk for adenomatous polyps in males and association of *Bsm*I/*Apa*I/*Taq*I haplotype in females (55). The inconsistent results for the association between *VDR* polymorphism and risk of colorectal cancer indicate the need for further research as well as epidemiological studies in larger cohorts (Table III).

Skin Cancer

The protective effect of vitamin D against ultraviolet radiation-induced DNA damage and skin cancer development and the protective role of vitamin D in reducing skin cancer have been discussed. However, the association between vitamin D and the risk of skin cancer, including melanoma and keratinocyte carcinoma, is still unclear. Vitamin D intake has been positively associated with risk of basal cell carcinoma and melanoma, while non-statistically significantly reducing the incidence of squamous cell carcinoma and melanoma (61, 62). The main risk factors associated with skin cancers are sun exposure and skin phototype, anticarcinogenic and procarcinogenic effects of vitamin D. Along with these factors, VDR polymorphism is also involved in the pathogenesis of skin cancer and may increase the susceptibility for malignancy (14). The association of *Fok*1, *Taq*1, *Apa*1, and *Bsm*1 polymorphisms with skin cancer including the studies up to 2014 has been discussed by Ombra *et al*. (63). Recent studies have suggested VDR polymorphism as a risk factor for skin malignancies (14, 15) (Table IV). A meta-analysis showed that *VDR* polymorphism is associated with the risk of keratinocyte cancer, while rs2228570, rs927650 and rs1544410 recessive genotypes are associated with a reduced risk of squamous cell carcinoma. *VDR* rs7975232 and rs739837 recessive genotypes were also associated with a reduced risk of basal cell carcinoma (14). Another study

Table III. *Vitamin D receptor (VDR) polymorphisms and cancer of the gastrointestinal tract*.

Type of study	Cancer type	Number of study subjects	Polymorphism under study	Outcome of the study
Case–control study (12)	EAC	858 Patients with GERD, BE or EAC and 202 healthy controls	rs1989969T/ rs2238135G	rs1989969T/rs2238135G is associated with two-fold lower risk of RE (GERD), BE, and EAC and lower VDR expression.
Case–control study (56)	ESCC	582 Patients with ESCC and 569 controls	rs2296241, rs11568820, rs4646536	rs11568820 is significantly associated with ESCC cancer.
Meta-analysis (21)	CRC	73 Independent studies including 35,525 cases and 38,675 controls	*Taq*I, *Apa*I, and Cdx2	*Taq*I associated with a significant increased risk for CRC.
Case–control study (46)	Gastric	187 Patients and 212 healthy controls	*Fok*I (rs10735810)	f Allele is associated with susceptibility to gastric cancer and F allele may be protective.
Case–control study (51)	CRC	152 Patients with CRC and 321 controls	*Bsm*I and *Apa*I	*Apa*I polymorphisms increase the risk of CRC.
Randomized control trial (52)	CRC	2259 Patients	rs7968585 rs731236	VDR genotype may affect adenoma treatment.
Case–control study (53)	CRC	356 CRC cases and 709 matched controls	rs2254210, rs1540339, rs2107301, rs11168267, rs11574113, rs731236, rs3847987 rs11574143	Limited association of *VDR* polymorphism with CRC.
Case–control study (54)	CRC	1,012 CRC cases and 1,080 controls	35 VDR variants	Little effect of *VDR* variants and risk of CRC.
Case–control study (57)	CRC	100 Patients with CRC and 100 healthy age- and gender-matched controls	*Bsm*I, *Fok*I, *Apa*I and *Taq*I	*Apa*I and *Bsm*I loci are significantly associated with CRC in elderly and female patients, respectively.
Hospital based study (55)	AP	Blood from 258 colonoscopy patients	Taql, *Apa*l, *Fok*I, *Bsm*I	Sex-specific relationship between these polymorphisms and risk for adenomatous polyp.
Case–control study (58)	Pancreatic	3,583 Pancreatic cancer cases and 7,053 controls	rs2239186, rs7967152, rs12721364	rs2239186 is associated with risk of pancreatic cancer but not significant.
Cohort analysis (59)	Pancreatic	493 Patients from five prospective US cohorts	30 SNPs	No significant association between *VDR* polymorphism and pancreatic cancer.
Case–control study (60)	HCC	35 Patients with HCC with HCV and 45 healthy controls	*Bsm*I (G/A) polymorphism (rs1544410)	No significant influence on susceptibility to HCC.

AP: Adenomatous polyp; BE: Barrett's esophagus, CRC: colorectal cancer; ESCC: esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; GERD: gastro-esophageal reflux disease, HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; RE: reflux esophagitis.

found an association of *Bsm*l polymorphism with melanoma in Europeans (15). Furthermore, a meta-analysis by Orlow *et al*. found a significant association between VDR polymorphism and melanoma-specific survival, however, no significant association was found between Breslow thickness, ulceration or mitosis, and *VDR* polymorphism (64). These results suggest the need for more research.

Urinary Tract Cancer

Vitamin D and VDR are involved in cell division, cell adhesion, and cell function. A normal renal function is necessary for vitamin D metabolism. The role of vitamin D, VDR, and retinoid-X-receptor in inhibition of cell proliferation and angiogenesis and induction of differentiation and apoptosis, and in the pathogenesis of renal cell carcinoma (RCC) has been discussed. Both low and high levels of circulating vitamin D have been associated with higher risk of death from any cause among RCC cases (66-68). This indicates that vitamin D levels may affect the pathogenesis of RCC and VDR might be involved in RCC carcinogenesis. Recent case–control studies by Yang *et al*. (66) and Pospiech *et al*. (69) suggest the association of increased risk of RCC with *VDR* polymorphism. There is experimental and epidemiological evidence that vitamin D has a protective role against bladder cancer, however, the causal relationship is unclear (2, 70, 71). Studying *VDR* polymorphisms may elucidate the causal relationship of bladder cancer. Recently,

Table IV. *Vitamin D receptor (VDR) polymorphisms and skin cancer.*

Type of study	Cancer type	Number of study subjects	Polymorphism under study	Outcome of the study
Case–control study and Meta-analysis (14)	SCC, BCC	1,124 Adults in 11-year follow-up. Associations with incidence of keratinocyte cancer	rs2228570, rs7975232, rs1544410, rs739837	rs2228570, rs1544410, and rs927650 are associated with a reduced risk of SCC and rs7975232 and rs739837 with a decreased risk of BCC
Meta-analysis (15)	Melanoma	11 Studies including 4,413 patients and 4,072 controls (all European).	*Fok*I, *Bsm*I, *Taq*I, *Apa*I, and EcoRV	*Bsm*I polymorphism is associated with susceptibility to melanoma in Europeans, *Bsm*I B allele may be a protective factor.
Multi-center population -based study of melanoma (64)	Melanoma	3566 Incident single and multiple primary melanoma.	rs7299460, rs3782905, rs2239182, rs12370156, rs2238140, rs7305032, *Bsm*I (rs1544410), *Taq*I (rs731236)	All significantly associated with melanoma-specific survival but not with Breslow thickness, ulceration or mitosis.
Meta-analysis (65)	Melanoma	10 studies including 4,961 melanoma patients and 4,605 controls.	*Apa*1, *Bsm*1, *Cdx2*, *Eco*RV, *Fok*1, and *Taq*1	*Fok*1 and *Bsm*1 may influence susceptibility to developing melanoma.

BCC: Basal cell carcinoma; SCC: squamous cell carcinoma.

Ben Fradj *et al*. suggest that ff genotype and f allele of FokI polymorphism are associated with increased risk of urothelial bladder cancer (70). Furthermore, the associations of *Apa*I, *Bsm*I, *Fok*1, and *Taq*1 polymorphisms with RCC and prostate cancer, *Fok*1 with bladder cancer, *VDR* in relation to testicular cancer and testicular germ cell tumors have been reviewed (2). The results of the studies reported in Table V suggest that *VDR* polymorphisms may be risk factors for urological cancer. However, due to the limited number of studies, the evidence for a clear association between urological cancer and *VDR* polymorphism is not concrete and more epidemiological studies needed.

Paediatric Tumors

Vitamin D plays a crucial role in regulating cellular homeostasis and proliferation. The role of vitamin D in the pathogenesis of various cancer types has been discussed in the literature as described above in relation to breast, prostate, gastric, and colorectal, *etc*. in adults. Vitamin D deficiency has been associated with increased prevalence of childhood cancer (72, 73). Vitamin D also plays a role in bone homeostasis and metabolism and its deficiency play a role in inflammation and the pathogenesis of osteoporosis and osteoarthritis (74). Furthermore, the association of osteosarcoma and Ewing sarcoma with a significantly higher frequency of the Ff genotype for the FokI polymorphism suggests the role of *VDR* polymorphism in bone tumors (75). In a pediatric population, no association of *VDR* polymorphism and Hodgkin's lymphoma was found (76). However, in the case of pediatric solid tumors, a weak association between CT and CC genotype of *Fok*I with reduced risk of pediatric solid cancer occurrence was reported (24). Moreover, the association of VDR polymorphic variant rs1544410 with minimal residual disease in pediatric B-cell precursor acute lymphoblastic leukaemia at day 15 suggests a prognostic value as well as the pathogenic role of this *VDR* polymorphism (77). Furthermore, the case–control studies in Table VI suggest that *VDR* polymorphism has an association with reduced pediatric solid tumors (*Fok*I), no association with Hodgkin's lymphoma, and may affect bone mineral density, patient height and overall survival. Vitamin D level and VDR expression may also serve as predictors for the occurrence and overall survival of solid tumors in the pediatric population (24, 75, 76, 78). The effects of *VDR* polymorphisms on tumourigenesis and other parameters indicate the need for deeper research into the role of *VDR* polymorphisms and their effects on vitamin D metabolism pertains to the human physiology.

Haematological Cancer

A study on the association of plasmablastic B-cell malignancies including plasmablastic lymphoma, subsets of multiple myeloma, and diffuse large B-cell lymphoma and *VDR* polymorphism found that the *Fok*1 polymorphism was associated with greater vitamin D3-dependent tumor growth inhibition. The findings of the study suggest the possible therapeutic benefit of the disruption of the VDR pathway

Table V. *Urinary tract cancer and vitamin D receptor (VDR) polymorphisms*.

Type of study	Cancer type	Number of study subjects	Polymorphism under study	Outcome of the study
Case–control study (66)	RCC	302 Patients and 302 healthy controls	*Taq*I, *Bsm*I, Cdx-2, *Apa*I, *Fok*I	*Apa*I genotypes may be associated with the increased risk and progression of RCC in Chinese Han population.
Case–control study (69)	ccRCC	167 Patients and 200 healthy controls	rs739837, rs731236, rs7975232, rs1544410	*VDR* polymorphism is associated with increased risk of ccRCC.
Case–control study (70)	UBC	200 unrelated Tunisian patients and 200 healthy controls	*Fok*I	ff Genotype and f allele were associated with increased risk of UBC in ever-smokers.

ccRCC: Clear cell renal cell carcinoma; RCC: renal cell carcinoma; UBC: urothelial bladder cancer.

Table VI. *Vitamin D receptor (VDR) polymorphisms and paediatric tumors*.

Type of study	Cancer type	Number of study subjects	Polymorphism under study	Outcome of the study
Case–control study (24)	Solid tumors	111 Pediatric patients and 787 adults as control	*Bsm*I (rs1544410; A>G), *Fok*I (rs 2228570; C>T), *Taq*I (rs731236; T>C), *Apa*I (rs 7975232; C>T) Cdx-2 (rs11568820; A>G)	*Fok*I was associated with lower risk of cancer.
Case–control study (76)	HL	95 Cases with 100 healthy controls	*Cdx2*, *Fok*1, *Bsm*1, *Apa*1, and *Taq*1	No association with HL.
Single-center study (78)	ALL	40 Newly diagnosed cases	*Bsm*I (rs1544410), *Apa*I (rs739837), *Taq*I (rs731236), *Cdx2* (rs11568820) *GATA* (rs4516035)	*Taq*I (Tt) was significantly correlated with high BMD in ALL and *Bsm*I (Bb) was related to higher BMD in ALL Egyptian paediatric population.

ALL: Acute lymphoblastic leukaemia; BMD: bone mineral density; HL: Hodgkin's lymphoma.

activity in order to enhance susceptibility to vitamin D treatment in these malignancies (79). Another study in a Chinese Han population on the association of *VDR* polymorphisms rs2228570 (*Fok*I) and rs731236 (*Taq*I) and multiple myeloma susceptibility including 113 patients and 117 healthy controls reported that rs2228570 TT genotype and mutant C allele of rs731236 are significantly associated with increased risk of multiple myeloma. The study concluded that the polymorphisms rs2228570 and rs731236 might be important genetic factors in the susceptibility to multiple myeloma (80). Esfahani *et al*. studied the association of VDR polymorphisms (*Fok*I, *Bsm*I, *Taq*I and *Apa*I) with acute myeloid leukaemia involving 133 patients and 300 controls and found a significant association between VDR polymorphism and acute myeloid leukaemia, and association of *Taq*I with complete remission (81).

Additional Cancer-related Interactions of *VDR* polymorphisms

Along with cancer of female genital tract, prostate, gastrointestinal tract, urological tumors, skin cancer, and pediatric tumors, *VDR* polymorphisms may also play a role in the carcinogenesis of lung and thyroid cancer. A case–control study including 426 patients with non-small cell lung cancer (NSCLC) and 445 controls from China studying *VDR* polymorphisms rs1544410 and rs731236 found a statistically significant relation between *VDR* polymorphism and reduction in NSCLC risk (82). Furthermore, the association of increased *VDR* mRNA expression with worse prognostic factors in papillary thyroid carcinoma suggests the role of VDR in thyroid cancer (83). Since vitamin D deficiency is associated with thyroid diseases and its

metabolism is regulated by thyroid hormone, *VDR* polymorphism may play a role in pathogenesis and prognosis of thyroid cancer (84). A recent meta-analysis found a clear and strong association between low levels of baseline vitamin D and poorer survival and an association between *VDR* genetic variants and survival [rs7975232 (*Apa*I) with progression-free survival; rs1544410 (*Bsm*I) with overall survival; and rs2228570 (*Fok*I) with overall survival] in lung cancer. However, from all the observational studies included in this meta-analysis, a causal relationship was not conclusively established (85).

Conclusion

The results of various studies suggest the crucial role of *VDR* polymorphism (mainly *Fok*I, *Apa*I, *Bsm*I, and *Taq*I) in tumorigenesis of various cancer types by affecting vitamin D metabolism and the cellular response to vitamin D. From the above-discussed studies, it is also obvious that the association between VDR polymorphism and tumorigenesis varies with age, sex, race and ethnicity. The results of these studies also suggest that studying *VDR* polymorphisms in order to strengthen our understanding of the vitamin D pathway could provide additional evidence for its protective therapeutic role against cancer development (33, 79). *VDR* polymorphisms might also serve as indicators for diagnosis, occurrence, and prognosis as well as survival in cancer (24, 64, 75-78, 83-85). There have been many epidemiological studies of breast, prostate and colorectal cancer, however, there are limited reports on the association of *VDR* polymorphism with lung, thyroid, oesophageal, ovarian, renal and hepatocellular carcinoma. These studies have shown the association of *VDR* polymorphism with increased risk of cancer, reduced risk of cancer, as well as no association. Thus, there is a need for more studies with larger cohorts in order to establish the significant associations and causal relationships between *VDR* polymorphism and cancer. Additionally, genetic variation in the vitamin D pathway should be considered when designing potential intervention strategies with vitamin D supplementation.

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