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Review Article

# VDR Gene SNPs in Gastrointestinal Tumors

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**Abstract**

GI tumors until now remain the major health problem in the world. The numerous risk factors are related to the development of GI tumors. Vitamin D is a multifunctional hormone with functions including immunomodulation or antioxidants to several intracellular like gene regulation, signal transduction, proliferation, and invasion of cancer cells. Among the risk factors, the genetic risk factor plays an important role in susceptibility to GI tumors. However, the association between genetic variants and GI tumors remains unclear. In particular, revealing the suitable genetic biomarkers for GI may provide a new opportunity to diagnose mentioned tumors. Specifically, To determine cancer susceptibility via single-nucleotide polymorphism (SNPs). This article reviews the association of gastrointestinal tumors (esophageal, gastric, colon, liver, gallbladder, and pancreatic tumors) with VDR single nucleotide polymorphisms.

## INTRODUCTION

Vitamin D is classically known for calcium and phosphate regulation for the mineralization of the skeletal system. However, vitamin D is a multifunctional hormone from functions including immunomodulation or antioxidants to several intracellular like gene regulation, signal transduction, proliferation, and invasion of cancer cells [1]. Studies have shown that the active form of Vitamin D, 1,25-dihydroxy vitamin D3 (VD3) is associated with inducing differentiation and cell cycle arrest in many malignant cancers such as breast, prostate, colon, skin, brain, and even in myeloid leukemia [2]. VD3 has also been shown to reduce proinflammatory stresses and function as an antiproliferative [3]. The Vitamin D receptor (VDR) gene is located on Chromosome 12q13.1. Vitamin D binds to VDR and retinoid X receptor (RXR) to form a complex that translocates to the cell nucleus and binds to the Vitamin D Response Element (VDRE), and regulates various transcriptions of genes [4]. Common VDR gene polymorphisms are FokI (exon 2, rs2228570), TaqI (exon 9, rs731236), BsmI (intron 8, rs1544410), and ApaI (intron 8, rs7975232).In this article, we review the association of various Gastrointestinal cancers, such as esophageal, gastric, colon, liver, gallbladder, and pancreatic, with VDR polymorphisms in various genetic and environmental backgrounds and ethnicities.

Vitamin D Receptor (VDR) is often considered a protective factor that prevents the development of tumors in the body. This hypothesis can mainly be explained due to the three significant effects of the VDR gene. First, when two novel epilogues were utilized to inhibit to cancer cells' growth in vitro and in vivo, it was found that these epilogues increased the activity of Cycle-dependent kinase inhibitors (CKI) which in turn stop the proliferation of the cell cycle at G0 and G1 stage [5]. Furthermore, the EB1089 analog of VD reduced the multiplication and increased the levels of damage to the mitochondria and apoptosis via increased expression of Bax and decreased levels of Bcl-2 and Bcl-Xl gene in gastric cancer cells via the mitochondrial-dependent apoptotic pathway [6]. Similarly, 1,25(OH)2-dihydroxy vitamin D3 (1,25(OH)2D3) inhibits cyclin D1, which is controlled via β-catenin, thus preventing the hyperproliferation of the epidermal cells on exposure to Ultraviolet radiation [7]. All in all, we can conclude that any changes/polymorphisms in the VDR gene, primarily related to the function or expression of the gene, could play a very significant role in the development of any gastrointestinal malignancy. Therefore, detecting these Single Nucleotide Polymorphisms (SNPs) needs to be extensively studied to identify the pathogenesis, prognosis, and therapeutic management of patients diagnosed with cancers due to VDR gene polymorphisms.

### VDR gene SNPs in Gastric Cancer

Gastric cancer (GC) is the third leading cause of cancer deaths worldwide due to delayed diagnosis, usually during terminal stages. It is one of the most aggressive cancer with a poor prognosis and low survival [8]. Hence investigating factors influencing the development of gastric cancer is essential to reduce mortality and improve prognosis. Vitamin D demonstrates as an independent prognostic factor of gastric cancers. This is shown in studies performed on 197 gastric patients, 57.9% were deficient in Vitamin D levels, 34% were insufficient, and 8.1% were sufficient. Patients with high levels of Vitamin D demonstrated a higher survival rate compared to patients with lower levels (P=0.018). Studies showed that high Vitamin D

levels were statistically significant associated with a lower risk of esophageal cancer and stomach cancer. This study's analysis also demonstrated that an increase of 25 nmol/L in predicted VD3 levels for digestive cancers was associated with a reduction in incidence and mortality of about 43% and 45%, respectively. The strongest inverse association of Vitamin D levels and the risk of cancer was for oral/ pharyngeal cancers [9].

Cong et al. demonstrated that VDR Fokl polymorphism (rs10735810) showed an increased risk of GC development in the Chinese Han Population. Alterations in Allele occur when ATG nucleotide becomes replaced with ACG in the start codon resulting in allele change from 'f' to 'F'. In this study, 187 patients and 212 healthy controls were studied. The frequency of f allele was higher in patients (51.6%) compared to healthy controls (43.6%). This f allele in Fokl polymorphism is associated with an increased risk of GC development (Ff+ff), along with higher levels of C reactive protein (CRP) compared to FF genotype and highly undifferentiated GC($p<0.05$), resulting in poor prognosis and high mortality due to GC [10]. Thus early detection of high-risk patients carrying an allele can help reduce mortality and improve outcomes. Surprisingly, F allele proves to be a protective allele in the development of GC. Similar results were obtained among Kurdish population from western Iran. This case-control study investigated 99 gastric cancer patients and 100 healthy controls. Results showed a positive correlation between Fokl polymorphism and the risk of GC development ($p=0.021$). In addition, other polymorphisms such as Taq1, ApaI, and BsmI failed to show any statistical significance in predisposing to GC compared to healthy controls [11].

In other studies, TaqI polymorphism was related to the risk of GC. Parsamanesh et al. investigated 69 GC patients and 100 healthy individuals from the south Khorasan population of Iran. Genotyping for both FokI and TaqI was performed. TC genotype of TaqI polymorphism showed statistical significance in predisposing to cancer development ($P=0.002$) compared to the control group. However, this population failed to show associations with FokI phenotypes [12]. Another study observed that polymorphisms in both FokI and TaqI were not associated with risk; however, independently deficient levels of VD3 (<10ng/ml) showed a fourfold higher predisposing and development risk of GC., The frequency of t allele was increased in patients with advanced stages of GC [13].

Bsml polymorphism also showed a strong association with GC. A case-control study carried out in the Kashmiri population reported that BsmI polymorphism was higher in Preobese GC patients (P value=0.001) and in patients with no family history of any gastrointestinal malignancy (P value=0.014), concluding that Bsml polymorphism in patients with High BMI was strongly associated with increased risk however Apal and Taql were not [14].

Wen et al., reported an interesting correlation between the expression of VDR in normal, precancerous, and cancerous gastric cells. VDR expression was significantly lower in cancerous gastric cells (57.61%) (P value=0.001). Moreover, between cancerous cells, increased number of VDR was found in well-differentiated tissues compared to poorly differentiated cancerous tissue and in small-sized tumors (<5cm) (P value=0.016 and P value =0.009 respectively). Hence, the expression of VDR can serve as an essential prognostic factor for GC [15].

## VDR gene SNPs in Liver cancer

Hepatocellular Carcinoma (HCC) has multifactorial risks. Viral infections such as Hepatitis B (HBV), Hepatitis C (HCV) and alcohol consumption are amongst most common worldwide. Numerous studies have reported an association of HCC and VDR polymorphism. Falleti et al., conducted research in Italian population consisting of 80 HCC patients and 236 healthy controls. Patients carrying b/b genotype of BsmI and T/T genotype of TaqI had high susceptibility of HCC ($P<0.05$). Moreover, patients lacking the protective allele A-T-C were significantly associated with risk of HCC. Patients with alcoholic liver disease demonstrated that the presence of BAT A-T-C and G-T-T genotypes also showed a strong correlation. Hence, HCC patients with alcoholic liver showed a specific link to HCC development [16]. However, In Vietnamese population, TaqI, FokI, and BsmI polymorphism failed to show any association or clinical presentation in HCC patients. However, the frequency of ApaI AA genotype was higher in HCC patients compared to chronic HBV infective patients ($p=0.04$). In contrast, ApaI CA genotype showed no significant association [17].

Fok1 polymorphism is also linked to HCC development and prognosis. Peng et al., reported that in Chinese HCC and HBV patients, VDR Fok1 polymorphism was studied. TT/CC genotypes exhibited increased HBV-related HCC developmental risk in contrast to CC genotype, while VDR rs11568820, and rs3782905 showed no such association. Interestingly, patients with Vitamin D binding protein (DBP) rs7041 GG and GG/TG genotypes had higher HCC risk chances than the TT genotype. Suggesting that Fok1 and DBP rs7041polymorphisms were associated with increased risk in HBV related HCC patients in the Chinese population [18]. Likewise, Apa1 polymorphism has been shown as a possible independent biomarker for HCV cirrhosis-related HCC development. Raafat Rowida et al., reported that SNP such as Apa1 could solve a healthcare burden of HCV-related liver cirrhosis leading to HCC by predicting diagnosis and thus initiating early management. This study done in Egyptian population included 80 HCC patients with diagnosed HCV, 80 HCV cirrhotic patients with no HCC development, and 80 healthy controls. Results were as follows, Apa1 CC genotype was highly observed in HCC patients, about 75%, compared to cirrhotic patients (35%) and controls (20%) ($p<0.0001$). Moreover, patients with CC genotypes had severe Child-Pugh scores($P=0.027$) and Model for End-Stage Liver Disease (MELD) score ($P<0.05$). Suggesting a higher risk for poor prognosis in CC genotype patients [19].

## VDR gene SNPs in Esophageal Cancers

VDR polymorphism variations are associate with Esophageal Adenocarcinoma (EAC) and Barrett Esophagus (BE) development. Janmaat et al. studied this relation in 858 patients with reflux esophagitis (RE), EAC, or BE and 202 healthy controls. rs1989969T/rs2238135G was associated with two-fold reduced incidence risk of RE, EAC, and BE. BE patients carrying 2 copies of rs2238135 G allele were associated with 2.5 times reduced expression of VDR compared to patients having 2 copies of rs2238135 C allele ($p = 0.01$). Similarly, subjects carrying 2 copies

of T allele of rs1989969 showed a 2-fold reduced expression of VDR than patients carrying C allele. Consequently, establishing genetic variation with different risk frequencies. Furthermore, suggesting a potential benefit from Vitamin D chemotherapy in patients carrying higher frequency of rs1989969 T and rs2238135 G alleles [20]. On the contrary, Chang et al., reported that SNP rs2238135 showed no significant association with EAC in Ireland population-based case-control study. Chang et al., also analyzed rs2238139 (277+2550 C>T) and rs2107301 (277+3260 C>T) TT homozygotes, showing a statistically significantly lower risk for EAC development when compared to CC genotype [21].

Studies on the western population also reveal exciting outcomes. Trowbridge et al. reported that expression of VDR in the United States is significantly decreased with EAC dedifferentiation meaning low levels of VDR was observed in high-grade tumors. This could open scope for VDR expression levels as a marker for responsiveness to neoadjuvant therapy [22].

A metanalysis on VDR polymorphisms and risk of tobacco-related cancer (Esophageal, oral, neck, lung, liver, and head cancers) suggested that increased frequency of "t" allele of TaqI polymorphism reduced the occurrence of such cancers by 17% (p=0.0114, OR=0.83, 0.72-0.96 95% CI). FokI, BsmI and ApaI polymorphisms did not show any statistically significant association [23].

### VDR gene SNPS in Gallbladder cancer

Gallbladder Cancer (GBC) is the most cancer of the digestive tract [24]. GBC patients are also victims of VDR polymorphisms influencing susceptibility. Li et al., conducted a study in Chinese population analyzing FokI, ApaI, BsmI, and TaqI polymorphisms with GBC risk. 291 GBC patients and 396 age and gender-matched healthy controls were studied. FokI TT polymorphisms were significantly increased in patients compared to controls (38.14 vs 22.73%, P < 0.001). Moreover, patients carrying higher frequency of CC and TC genotypes had greater Odds ratio (OR), suggesting that C allele is significantly associated with GBC incidence. ApaI, BsmI,TaqI polymorphisms did not show any statistically significant association [25].

### VDR gene SNPs in Pancreatic cancer

Pancreatic cancer is one the most aggressive and invasive malignancies. It generally presents with a poor prognosis; therefore, identifying its core cause is vital for the patients. Once such risk factors for developing pancreatic cancer are gene polymorphisms, particularly the Vitamin D Receptor (VDR) gene polymorphism, these VDR gene polymorphisms could profoundly affect the course and differentiation of cancer.

A case-control study was conducted in Asia to evaluate whether VDR gene polymorphisms were associated with pancreatic cancer; two specific polymorphisms were identified, namely rs2228570 and rs1544410. Histopathological analysis of the samples was conducted in patients diagnosed with pancreatic adenocarcinoma. Genotyping of the above two mentioned genes was done, and statistical analysis was performed. It was reported that the rs2228570 gene polymorphism, the genotype TT showed a significant increased likelihood of pancreatic cancer (univariate: OR= 3.02, 95 % CI=1.92–4.76, P<0.01), and the genotype with one T gene demonstrated similar results (univariate: OR=2.42, 95 % CI=1.72–3.42, P<0.01). Furthermore, the prevalence of T allele was higher in patients with pancreatic cancer (OR=1.869, 95 % CI=1.489– 2.347, P=0.0001). As for the rs2228570 gene polymorphism, the presence of one G gene loci will decrease the risk of pancreatic cancer (univariate: OR=0.63, 95 % CI=0.45–0.89). Overall, it was reported that the G allele could reduce the cancer risk (OR=0.76, 95 % CI=0.60–0.95, P=0.01). Thus, it was found that the rs2228570 polymorphism was related to the differentiation of cancer, and the rs1544410 polymorphism was associated with the TNM classification. These VDR gene polymorphisms are a potential risk factor for the development of pancreatic cancer. They could identify the susceptibility and prognosis for this condition and possibly guide the treatment for the patient [26].

### VDR gene SNPs in Colon Cancer

VDR SNPs may have some contribution to cancers. Colon cancer (CC) is a severe global health problem, among other gastrointestinal (GI) tumors. As already confirmed, genetic risk factors have a crucial contribution to CC. It is suggested that the VDR gene SNPs [27]. The SNP of rs11064124 in 12p13.31 revealed a higher risk of colon adenocarcinoma. It was also suggested that VDR interacts with two target gene promoters, causing the coactivation of CD9 and PLEKHG6 transcription in colon adenocarcinoma. VDR SNPs have been associated increase susceptibility to colorectal cancer [28]. The study by Messaritakis et al. (2020) confirmed the vital role of VDR SNPs in carcinogenesis, disease progression, and patients' survival in CRC. Furthermore, the same study indicated that the expressed VDR is associated with patients' survival [29].

The genetic variation at the VDR, particularly the FokI SNPs, is associated with CC risk [30]. Thus, studies suggest that VDR gene SNPs may significantly play a key role in GI cancer's predisposition and development [31-36].

## CONCLUSION

Thus, Based on the existing research, there is an association between VDR gene SNPs and GI tumors. We have thought that revealing associated VDR SNPs for GI tumors may use as a new opportunity in diagnosis and therapy.

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