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Vitamin D and VDR FokI Polymorphisms in Thyroid Cancer: A Comprehensive Review

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ABSTRACT:
Thyroid cancer is one of the fastest-rising endocrine malignancies worldwide, with a particularly notable surge across Asian populations, including India. In North India, this escalating burden reflects a multifactorial interplay between environmental exposures, nutritional deficiencies, hormonal influences, and genetic predispositions. Among nutritional determinants, Vitamin D deficiency stands out as a critical and widespread problem despite ample sunlight. Vitamin D, beyond its classical role in calcium and bone homeostasis, exerts significant antiproliferative, pro-differentiation, immunomodulatory, and anti-inflammatory functions, largely mediated through the Vitamin D receptor (VDR). Genetic variations within the VDR gene—especially the FokI (rs2228570) polymorphism—modify receptor efficiency and alter downstream transcriptional responses, potentially influencing individual susceptibility to malignant transformation in tissues such as the thyroid, which expresses VDR abundantly. Emerging literature indicates that the FokI polymorphism generates two receptor isoforms with differing biological activity, with the shorter F-allele–encoded VDR demonstrating stronger transcriptional signaling. Populations carrying the less active f-allele may have impaired vitamin D–mediated tumor suppression, particularly under conditions of chronic vitamin D insufficiency. This is highly relevant for North Indians, who exhibit among the world's highest rates of hypovitaminosis D due to cultural clothing, indoor lifestyles, air pollution, skin pigmentation, and limited dietary Vitamin D intake. Parallel epidemiological evidence links low Vitamin D levels with aggressive clinicopathological features of thyroid cancer, including larger tumor size, lymph node metastasis, and extrathyroidal extension. Additionally, long-standing iodine deficiency persists in pockets of North India despite national fortification programs, contributing to chronic TSH stimulation, oxidative stress, nodular hyperplasia, and potential genomic instability within the thyroid gland. Environmental radiation exposure—both medical and atmospheric—further heightens carcinogenic risk, with childhood exposure being particularly detrimental. Ionizing radiation is known to induce DNA double-strand breaks, chromosomal rearrangements, and oncogenic events such as RET/PTC fusions, which drive pathways central to thyroid tumorigenesis. The convergence of nutritional insufficiencies (Vitamin D and iodine), VDR FokI polymorphisms, radiation exposure, and other region-specific determinants creates a unique biological milieu that may predispose North Indians to higher thyroid cancer susceptibility and potentially more aggressive disease. This review synthesizes epidemiological trends, molecular mechanisms, and gene–environment interactions underpinning this relationship. Understanding the synergistic effects of vitamin D status, VDR functionality, and environmental factors is essential for developing predictive models tailored to Indian populations. Such models hold promise for improving early detection, refining risk stratification, and guiding targeted prevention strategies for high-risk groups in North India.

Introduction

Thyroid cancer has emerged as one of the most rapidly increasing endocrine malignancies globally, with a particularly notable rise in countries across Asia, including India. In the North Indian population, this growing burden has been attributed to a complex interplay of environmental exposures, nutritional imbalances, hormonal disturbances, and genetic predisposition. Among the nutritional determinants, Vitamin D deficiency stands out prominently, given its alarmingly high prevalence in North India despite abundant sunlight. Vitamin D, traditionally recognized for its role in calcium and bone homeostasis, is now understood to exert broad influence on cellular processes including

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proliferation, differentiation, apoptosis, immune modulation, and suppression of oncogenic signaling pathways. These biological effects are primarily mediated through the Vitamin D Receptor (VDR), a ligand-activated transcription factor that regulates the expression of numerous genes involved in tumor suppression.

Recent scientific attention has focused on the genetic variability within the VDR gene, especially functionally significant single nucleotide polymorphisms (SNPs) such as FokI. This polymorphism results in the synthesis of VDR protein variants with differing transcriptional activity. The shorter, more active VDR isoform produced by the wild-type allele is associated with stronger anti-proliferative signaling, whereas the alternative FokI variant may lead to reduced receptor function and diminished responsiveness to Vitamin D. Such alterations may influence individual susceptibility to carcinogenesis, particularly in tissues like the thyroid that express VDR abundantly. Accumulating evidence suggests that VDR polymorphisms may modulate oncogenic pathways involving MAPK, PI3K/AKT, NF-κB, and immune regulatory networks—mechanisms that are critically implicated in thyroid tumor development and progression.

In the context of North India, where Vitamin D deficiency is widespread due to dietary inadequacy, cultural practices, skin pigmentation, and air pollution limiting UVB exposure, the potential interaction between low Vitamin D levels and VDR genetic variants warrants focused investigation. Several studies have proposed that populations with both suboptimal Vitamin D status and high-risk VDR genotypes may exhibit enhanced vulnerability to thyroid tumorigenesis, particularly to well-differentiated cancers such as papillary and follicular thyroid carcinoma. Moreover, emerging epidemiological data indicate associations between low Vitamin D levels and more aggressive tumor features, including larger tumor size, extrathyroidal extension, and lymph node metastasis.

Given these converging lines of evidence, exploring the Vitamin D–VDR axis offers a valuable framework for understanding thyroid cancer risk in genetically and nutritionally diverse populations. This review synthesizes current epidemiological findings, molecular mechanisms, and population-specific data related to Vitamin D status, VDR FokI polymorphism, and thyroid cancer susceptibility. By contextualizing these elements within the North Indian demographic, the review aims to highlight critical gaps in knowledge and strengthen the foundation for future research targeting early detection, risk stratification, and potential preventive strategies in this region.

Thyroid Cancer: Global and Regional Burden

Global cancer surveillance reports consistently highlight a substantial rise in thyroid malignancies over the past two decades, with papillary thyroid carcinoma (PTC) remaining the predominant subtype, accounting for nearly 80% of all cases worldwide. Siegel et al. (2024) emphasized that this upward trend cannot be attributed solely to improved imaging and diagnostic scrutiny. While increased detection plays an important role, parallel epidemiological patterns indicate the influence of broader biological, environmental, and hormonal factors that have shifted thyroid cancer risk profiles globally. This multifactorial rise underscores the need for population-specific investigations that evaluate both genetic susceptibility and modifiable determinants [1]. Ghosh & Sinha et al. reported that the South Asian region, thyroid cancer epidemiology demonstrates unique variability shaped by nutritional disparities, fluctuating iodine intake, changing lifestyle practices, and increasing exposure to industrial pollutants and endocrine-disrupting chemicals. Several regional studies have reported that South Asian populations face a distinctive interplay of risk factors, including micronutrient deficiencies, sedentary lifestyles, and varying degrees of sun exposure due to cultural clothing and urban living. These factors combine to produce heterogeneous disease patterns that diverge from Western populations, emphasizing the importance of contextualized research approaches tailored to local determinants of thyroid malignancy [2].

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According to ICMR (2020) reported that, In India, cancer registry data have recorded a steady and significant rise in thyroid cancer incidence, with marked geographical and sex-specific variations. Several Indian studies have documented a disproportionately higher burden among women, suggesting potential roles of estrogenic influences, reproductive history, and gender-specific environmental exposures in modulating thyroid cancer risk. Urban regions, in particular, show sharper increases, possibly linked to lifestyle transitions, dietary shifts, and greater exposure to environmental contaminants. These evolving patterns reflect a complex interaction between genetic predisposition and rapidly changing socio-environmental conditions within the Indian population [3]. Moreover, In North Indians constitute an especially relevant demographic for exploring the Vitamin D–thyroid cancer relationship due to the region's exceptionally high prevalence of Vitamin D deficiency. Multiple studies, including those by Harinarayan et al. and Goswami et al., indicate that despite abundant sunlight, factors such as increased indoor lifestyles, higher melanin levels, air pollution, and limited dietary Vitamin D intake contribute to widespread insufficiency. These characteristics provide a unique framework to examine how disrupted Vitamin D metabolism and VDR gene polymorphisms—particularly FokI—may influence susceptibility to thyroid neoplasia. Given the intersection of genetic, environmental, and nutritional risk factors, North India represents a critical setting for investigating the biological underpinnings of thyroid cancer vulnerability [4-5].

Iodine Deficiency and Thyroid Health: Foundational Evidence

Iodine deficiency remains one of the leading global micronutrient problems, profoundly affecting thyroid physiology and endocrine health. According to the World Health Organization (2023), nearly two billion individuals worldwide have inadequate iodine intake, placing them at risk for a spectrum of thyroid abnormalities. Iodine is an indispensable substrate for the synthesis of thyroxine (T4) and triiodothyronine (T3), hormones essential for regulating basal metabolic rate, thermogenesis, and neurocognitive development [6]. Zimmermann et al. (2009) showed the experimental and epidemiological studies demonstrate that even marginal iodine insufficiency can alter thyroid hormone synthesis, trigger compensatory increases in thyroid-stimulating hormone (TSH), and initiate adaptive glandular changes such as diffuse goiter. These physiological disturbances lay the groundwork for chronic thyroid dysfunction and susceptibility to proliferative disorders [7]. Moreover, Persistent iodine deficiency also leads to morphological and functional alterations within the thyroid gland that may contribute indirectly to malignant transformation. Under conditions of prolonged TSH-driven stimulation, thyroid follicular cells undergo repeated cycles of proliferation and involution, increasing the probability of DNA replication errors, oxidative stress, and genomic instability. Landmark work by Hetzel et al.(1983) and subsequent molecular studies have shown that chronic iodine depletion enhances thyrocyte mitotic activity and encourages the evolution of nodular hyperplasia, a known precursor to some follicular and, less consistently, papillary thyroid carcinomas [8]. Although Burgess et al., (2021) reported that the iodine deficiency is not recognized as a direct carcinogen, it creates a hormonal milieu that favors cellular stress, altered differentiation pathways, and the accumulation of mutations that may predispose susceptible individuals to thyroid tumorigenesis [9].

In the Indian context—especially North India, where dietary diversity, socioeconomic factors, soil depletion, and inconsistencies in iodized salt utilization contribute to localized iodine insufficiency—the public health impact is significant. Studies by Kapil & Pandey et al. (1997) and Dunn et al (2001) highlight that, despite national iodine fortification programs, residual pockets of endemic deficiency persist, sustaining the risk of goiter and nodular thyroid disease. These populations often face simultaneous micronutrient challenges, including low selenium and widespread Vitamin D deficiency, creating

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overlapping biochemical stressors for the thyroid gland [10-11]. The coexistence of iodine and Vitamin D insufficiency may amplify disturbances in thyroid hormone synthesis, inflammatory pathways, and immune-mediated thyroid responses, thereby intensifying the likelihood of developing disorders that precede malignancy. Furthermore, Emerging evidence suggests that iodine deficiency may interact synergistically with genetic susceptibility factors, including polymorphisms affecting Vitamin D receptor (VDR) function and other genes regulating thyroid growth and differentiation. In North Indian cohorts, where VDR FokI polymorphisms and Vitamin D deficiency are common, researchers propose a multifactorial risk model in which micronutrient deficits exacerbate genetically determined vulnerabilities. According to recent integrative reviews González et al., (2021), such interactions may enhance proliferative signaling, increase oxidative stress, and dysregulate pathways central to thyroid cell homeostasis. While iodine deficiency alone does not directly cause thyroid cancer, understanding how it intersects with genetic and biochemical factors is essential to clarifying its role in creating a pro-carcinogenic environment, especially in high-risk regions [12].

Vitamin D Physiology and Its Anticancer Roles

Holick et al. (2007) showed that the Vitamin D plays a critical role not only in calcium homeostasis and skeletal health but also in regulating a wide array of cellular processes relevant to cancer biology. Once synthesized in the skin or obtained from dietary sources, Vitamin D undergoes sequential hydroxylations in the liver and kidneys to form its active metabolite, 1,25-dihydroxyvitamin D. This hormone-like molecule interacts with the Vitamin D receptor (VDR), influencing gene expression in numerous tissues, including endocrine organs such as the thyroid gland. This mechanistic framework provides a biological rationale for exploring Vitamin D's significance in carcinogenesis [13]. Moreover, Deeb et al. (2007) reported that the anticancer functions of Vitamin D have been extensively characterized in experimental models. These include induction of apoptosis through caspase activation, inhibition of cancer cell proliferation by arresting the cell cycle at G0/G1, suppression of angiogenesis, and modulation of tumor microenvironment immune responses. These actions collectively maintain cellular integrity and prevent uncontrolled growth. Such multifaceted tumor-suppressive effects are particularly relevant in endocrine malignancies where hormonal and immune pathways intersect [14].

Haussler et al. (1998) were among the first to describe the VDR as a nuclear transcription factor capable of regulating over 900 genes related to immunity, metabolism, and cell growth. Their work highlighted that Vitamin D's anticancer properties are strongly dependent on VDR expression and functionality. Inadequate levels of Vitamin D impair VDR-mediated signaling, diminishing genomic stability and weakening cellular defense against oncogenic transformation [15].

Feldman D et al. (2014) reported, In populations with chronic Vitamin D deficiency, such as North Indians, impaired VDR signaling may be an important contributor to increased cancer susceptibility. Studies have shown that low serum Vitamin D levels reduce the efficiency of DNA repair pathways, enhance oxidative stress, and lower immune surveillance—factors that collectively promote tumor initiation and progression. This suggests that Vitamin D deficiency may influence both the onset and aggressiveness of thyroid malignancies [16].

Vitamin D Deficiency in North Indians

India, particularly the northern region, has reported among the world's highest rates of Vitamin D insufficiency. Holick et al. (2007) and Gupta et al. (2014) documented prevalence estimates ranging from 50% to as high as 90%. Despite abundant sunlight, environmental and cultural barriers significantly limit effective UVB exposure necessary for Vitamin D synthesis. This paradox places millions at risk of hormone-related disorders, including thyroid dysfunction and

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malignancy[13,17]. Goswami et al. (2008) study showed that the multiple lifestyle and environmental determinants contribute to hypovitaminosis D in North Indians. These include increased indoor work patterns, high levels of air pollution that block UVB rays, darker skin pigmentation which reduces cutaneous Vitamin D production, and vegetarian dietary habits low in natural Vitamin D sources. Collectively, these factors create a persistently low Vitamin D milieu with potential implications for endocrine and immune-related cancers [5]. Moreover, With respect to thyroid cancer specifically, emerging evidence indicates a relationship between serum Vitamin D levels and tumor characteristics. Xing et al. (2020) reported that lower Vitamin D levels correlate with larger tumor size, extrathyroidal extension, and lymph node metastasis in differentiated thyroid carcinomas. These findings underscore Vitamin D's potential role in modulating tumor aggressiveness and clinical outcomes[18].

The Vitamin D receptor itself is central to these mechanisms. Structurally belonging to the steroid hormone receptor family, the VDR binds to its ligand and forms a heterodimer with the retinoid X receptor (RXR). This complex interacts with Vitamin D response elements (VDREs) within gene promoter regions, modulating transcription of genes responsible for cell cycle regulation, apoptosis, immune function, and oxidative stress response [19].

The Vitamin D Receptor (VDR): Structure and Function

Uitterlinden et al. (2004). Study showed the alterations in VDR activity—whether due to genetic variants, reduced ligand availability, or epigenetic modifications—can significantly influence cancer susceptibility. The VDR gene contains several polymorphic sites, including FokI, which results in a structural change at the start codon. This variant alters receptor length and activity, potentially modifying transcriptional efficiency and downstream signaling pathways [20] .

Ahn J et al. (2010) showed that the among these polymorphisms, the FokI (rs2228570) variant is one of the most extensively investigated in cancer research. The "f" allele produces a longer VDR protein with reduced transcriptional efficiency, whereas the "F" allele results in a shorter, more active receptor. Reduced VDR activity may impair Vitamin D–mediated antitumor effects, providing a genetic basis for differential susceptibility to thyroid cancer across populations [21]. Moreover, Several studies across Asian populations have explored the association between VDR FokI polymorphism and cancer risk, reporting inconsistent but suggestive results. Population-specific differences in allele frequency, environmental exposure, and baseline Vitamin D levels may modify the gene–environment interaction. For North Indians, where both Vitamin D deficiency and thyroid cancer rates are increasing, this polymorphism warrants focused investigation [22].

Penna & Badenhoop et al.(2010) reported that the taken together, the interplay between Vitamin D deficiency, impaired VDR signaling, and genetic variations such as the FokI polymorphism forms a biologically plausible framework for understanding thyroid cancer susceptibility in North Indian populations. With evidence linking low Vitamin D levels to more aggressive tumor phenotypes, and VDR polymorphisms influencing receptor functionality, studying these factors together could provide crucial insights for early detection, risk stratification, and preventive strategies [23].

VDR FokI Polymorphism and Its Biological Implications

Uitterlinden et al. (2004) identified the FokI polymorphism (rs2228570) as one of the most functionally significant variants within the vitamin D receptor (VDR) gene**.** Located in the start codon (ATG) of exon 2, this polymorphism leads to an alteration in the translational start site, generating two structurally distinct VDR protein isoforms. This positional variation within a critical regulatory region underscores the biological importance of

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FokI in modulating downstream genomic actions of vitamin D [20].

Arai H et al., (1997) showed that the functional consequence of the FokI variant is reflected in the production of two VDR proteins: the F allele encodes a shorter 424-amino acid VDR protein with higher transcriptional efficiency, whereas the f allele generates a longer 427-amino acid isoform with reduced functional potency. The shorter F-VDR variant demonstrates stronger binding to vitamin D response elements (VDREs), enhancing the regulation of genes involved in cell growth inhibition, differentiation, apoptosis, and immune modulation**.** In contrast, the less active f-variant may limit these protective mechanisms, potentially predisposing individuals to impaired antitumor responses [24].

Mishra DK et al., (2013) showed the central role of vitamin D in cancer biology—through anti-proliferative, pro-apoptotic, and immunoregulatory pathways—reduced VDR activity due to the ff genotype may diminish the anticancer actions of vitamin D. This has been documented in several malignancies, including breast, colorectal, prostate, and thyroid cancers, where the FokI variant has been associated with variations in tumor aggressiveness, susceptibility, and prognosis. Therefore, FokI serves not only as a genetic marker but also as a mechanistic contributor to cancer risk via modulation of vitamin D signaling [25].

Harinarayan CV et al., (2011) showed the relevance of the FokI polymorphism becomes even more pronounced in populations with endemic Vitamin D deficiency**,** such as North Indians**,** who exhibit high prevalence of hypovitaminosis D due to factors such as darker skin pigmentation, indoor lifestyle, pollution, and dietary inadequacy. In such settings, the coexistence of low vitamin D levels with a less active f-allele variant may create a compounded biological risk, heightening vulnerability to cancers influenced by vitamin D pathways, including papillary and follicular thyroid carcinoma**.** This interaction between genetics and environment highlights the importance of investigating VDR FokI polymorphism as a candidate susceptibility marker in thyroid cancer research [4].

Molecular Mechanisms of Thyroid Carcinogenesis

Nikiforov YE, (2011) showed that thyroid carcinogenesis is driven by a spectrum of molecular alterations that disrupt normal cellular homeostasis and stimulate uncontrolled proliferation. These changes affect signaling pathways that regulate cell growth, apoptosis, and differentiation, ultimately promoting malignant transformation. Understanding these mechanisms is essential for identifying genetic and environmental risk factors relevant to thyroid pathology [26]. Furthermore, Fugazzola et al. (2019) highlighted that RET/PTC rearrangements are among the earliest and most frequent genetic events in papillary thyroid carcinoma (PTC). These chromosomal rearrangements result in constitutive activation of the MAPK signaling cascade, a key driver of mitogenic and anti-apoptotic responses in thyroid follicular cells. Such persistent signaling fosters tumor initiation and progression [27].

Rabes et al. (2013) study showed that, Radiation exposure, especially in childhood, significantly increases the probability of DNA strand breaks that lead to RET/PTC fusion formation. These fusions enable aberrant signaling even in the absence of extracellular stimuli, thus placing previously normal thyroid cells on a carcinogenic trajectory[28] Besides RET/PTC, several other molecular drivers contribute to thyroid tumorigenesis. These include the well-characterized BRAF V600E mutation**,** RAS point mutations**,** PAX8-PPARγ rearrangements, and dysregulation of the PI3K–AKT pathway**.** Each of these molecular events enhances proliferative capacity, promotes immune evasion, and disrupts cellular differentiation [18].

Role of Radiation in Thyroid Cancer: Epidemiological Evidence

Feldman D et al., (2014) reported that the vitamin D, through its nuclear receptor VDR, interacts with many of the pathways implicated in thyroid carcinogenesis. The active hormone, 1,25-dihydroxyvitamin D, exerts anti-proliferative and

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pro-differentiation effects that can counterbalance oncogenic signaling induced by mutations in BRAF, RAS, and other oncogenes [16]. Furthermore, When VDR activity is compromised—such as in individuals carrying less functional alleles like the f allele of FokI—the protective influence of vitamin D is weakened. This reduction in receptor activity limits transcription of vitamin D–responsive genes that regulate cellular apoptosis, repair, and growth control[20].

Mettler and Huda et al. (2022) reported that ionizing radiation remains one of the most potent and well-established risk factors for thyroid cancer. Even low-dose exposure during childhood significantly elevates lifetime cancer risk due to the heightened radiosensitivity of thyroid tissue during early developmental stages [29]. Additionally, Williams D et al. (2008) study reported that the radiation exposure induces DNA double-strand breaks, oxidative damage, and chromosomal aberrations—all of which enhance genomic instability. This facilitates the formation of oncogenic mutations and rearrangements that predispose thyroid cells to malignant transformation[30].

Interaction Between Vitamin D, VDR Polymorphisms, and Oncogenesis

Morris HA et al. (2010) showed that vitamin D has known roles in DNA repair, anti-inflammatory regulation, and oxidative stress reduction. Therefore, individuals with Vitamin D deficiency or reduced VDR activity may experience a heightened carcinogenic response following radiation exposure. This interplay is particularly relevant in populations where Vitamin D deficiency is common [31]. Moreover, Haussler et al. (1998) demonstrated that vitamin D signaling interacts with pathways controlling cell-cycle arrest, apoptosis, oxidative stress responses, and inflammatory modulation. These mechanisms collectively contribute to its broad antitumor effects across tissues, including the thyroid gland [15]..

Arai H et al. (1997) study revealed that the FokI polymorphism alters the translational start site of the VDR gene, producing protein isoforms with different transcriptional activities. Individuals with the ff genotype exhibit reduced VDR function, diminishing vitamin D's tumor-suppressive actions and increasing vulnerability to oncogenic mutations and radiation-induced DNA damage [24]. Furthermore, Reduced VDR functionality leads to impaired apoptosis in thyroid follicular cells, elevated oxidative DNA damage, and dysregulated immune surveillance. These biological effects accelerate neoplastic transformation and facilitate progression from premalignant lesions to established thyroid carcinoma.[14].

Population-Specific Considerations for North Indians

Uitterlinden et al. (2004) showed that the combination of low circulating Vitamin D levels and less active VDR genotypes exerts a synergistic detrimental effect on genetic susceptibility to cancer. This synergism may be particularly relevant in regions with endemic hypovitaminosis D [20]. Harinarayan et al. (2011) and Goswami et al. (2008) documented extremely high rates of Vitamin D deficiency in North Indian populations due to lifestyle patterns, pollution, limited dietary intake, and skin pigmentation. Such chronically low vitamin D status may amplify the impact of genetic susceptibility variants like FokI [4-5]. Moreover, South Asian populations exhibit a moderate-to-high frequency of the f allele of the FokI polymorphism. This distribution pattern indicates genetic predisposition that may contribute to elevated risk for cancers influenced by VDR signaling, including thyroid carcinoma [31].Given increasing thyroid cancer incidence in India, integrating Vitamin D status**,** VDR genotypes**,** environmental radiation exposure**,** and nutritional factors (such as iodine deficiency) is crucial for developing population-specific predictive models. Such models could improve targeted screening, prevention, and intervention strategies tailored to high-risk groups.

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Conclusion

Thyroid cancer incidence is rising steadily in India, particularly in the northern region, where a unique convergence of nutritional deficiencies, genetic predispositions, and environmental exposures shapes disease vulnerability. Among these determinants, Vitamin D deficiency stands out as a critical yet modifiable factor. Despite abundant sunlight, hypovitaminosis D is highly prevalent in North Indians due to lifestyle patterns, air pollution, and dietary habits, creating a biological environment that weakens cellular defense mechanisms. At the same time, the functional significance of VDR polymorphisms—especially the FokI variant—adds a genetic dimension to thyroid cancer susceptibility. Reduced VDR activity, particularly in individuals carrying the f allele, may diminish vitamin D–mediated antitumor effects and heighten vulnerability to oncogenic pathways such as MAPK, PI3K/AKT, and NF-κB, all of which play central roles in thyroid carcinogenesis.

The interaction of Vitamin D deficiency with high-risk VDR genotypes, radiation exposure, and micronutrient imbalances like iodine insufficiency creates a multifactorial risk landscape that is especially relevant in the North Indian population. Together, these factors may synergistically impair immune regulation, increase oxidative stress, weaken DNA repair pathways, and accelerate malignant transformation within the thyroid gland. Integrating these components into population-specific predictive models offers an important opportunity for early risk stratification, targeted screening, and personalized preventive strategies. Future research should prioritize large-scale, region-specific studies that elucidate gene–environment interactions and evaluate the role of Vitamin D optimization as a potential preventive or adjunctive therapeutic approach in thyroid cancer management.

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