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Review Article

VITAMIN D RECEPTOR POLYMORPHISMS AND LUNG CANCER: BIOLOGICAL RATIONALE, EPIDEMIOLOGICAL SIGNALS, AND TRANSLATIONAL IMPLICATIONS – A NARRATIVE REVIEW

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ABSTRACT

This narrative review integrates mechanistic biology with population evidence to appraise when and why vitamin-D receptor (VDR) polymorphisms associate with lung cancer risk and outcomes. Using a structured narrative review approach to searching, screening, and data extraction across major databases, we included human observational studies (case–control/cohort), pooled analyses, and lung-specific functional experiments, focusing on incidence/risk, stage, overall/progression-free survival, and effect modification by smoking and Vitamin D axis status. A coherent, context-dependent signal emerges: TaqI (rs731236) shows the most reproducible susceptibility association, stronger in Asian ancestry, smokers, and non-small-cell lung cancer (NSCLC), while BsmI (rs1544410) and, in some settings, ApaI (rs7975232) tend to be protective; FokI (rs2228570) contributes to risk in certain populations and carries a pathway-level survival signal. Lung-specific evidence that ligand-activated VDR represses histidine-rich calcium-binding protein, curbing proliferation, migration, and xenograft growth, provides a credible mechanistic bridge from genotype to phenotype. However, heterogeneity in genotyping platforms and quality control, incomplete Hardy–Weinberg reporting, small or imbalanced cohorts, variable adjustment (smoking intensity, histology, stage), and sparse contemporaneous 25-hydroxyvitamin D and environmental data limit causal inference and impede quantitative synthesis in survival analyses. Taken together, the current data support cautious, genotype-aware research use of the vitamin-D axis rather than routine clinical testing. Priority next steps include adequately powered, multi-ancestry cohorts with harmonized genotyping and pre-specified covariates, standardized rsID-anchored genetic models, integrated vitamin-D/environmental measures, pathway-wide analyses across VDR–CYP27B1–CYP24A1–CYP2R1–GC, and prospective validation of genotype-augmented risk scores and NSCLC prognostic tools to test true translational utility.

Keywords: Vitamin D receptor, Polymorphism, Lung cancer, Non-small-cell lung cancer, Genetic susceptibility, Vitamin D pathway, Translational implications.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, with about 2.5 million new cases and 1.8 million deaths in 2020. Tobacco smoking remains the dominant risk factor (implicated in ~85% of cases), but other contributors, including environmental exposures and genetic susceptibility, also play significant roles [1-4]. In recent years, the Vitamin D pathway has attracted attention as a potential modifier of lung cancer risk and progression, beyond the traditional risk factors of smoking and pollution. Vitamin D's active form (1,25-dihydroxyvitamin D [1,25(OH)2D]) exerts its effects through the Vitamin D receptor (VDR), a ligand-activated transcription factor that regulates genes involved in cell proliferation, differentiation, angiogenesis, and apoptosis [5-9]. Especially, epidemiological studies have linked higher Vitamin D status to reduced risk of several cancers (including lung cancer), and experimental models show that Vitamin D can suppress lung tumor growth and metastasis. These observations suggest a prima facie protective role of Vitamin D signaling in lung carcinogenesis [10-16].

The *VDR* gene itself is polymorphic, and several common variants are known to alter VDR function or expression. For example, a promoter polymorphism (Cdx2, rs11568820) can influence *VDR* gene transcription, while a coding variant in exon 2 (FokI, rs2228570) alters the receptor's translation start site and protein length [17-20]. It is biologically plausible that such germline variants, by modulating the strength or efficiency of VDR signaling, could impact the development and behavior of lung cancers. Indeed, VDR is expressed in lung tissue, and its activation triggers anti-proliferative and pro-differentiation pathways that would intuitively counter tumorigenesis. Correlative clinical data further underscore this point: for instance, higher VDR expression in lung tumors has been associated with improved patient survival. This raises the question of whether inherited differences in VDR (i.e., polymorphisms) translate into measurable differences in lung cancer risk or outcomes [5,21,22].

A growing number of observational studies have examined VDR polymorphisms in relation to lung cancer, yielding some intriguing signals but also inconsistencies. Several case–control studies and meta-analyses report significant associations for certain VDR variants, such as FokI, BsmI, ApaI, TaqI, and Cdx2, with lung cancer susceptibility or prognosis [5,23-26]. For example, some pooled analyses have suggested that the *TaqI* and *FokI* risk alleles confer higher lung cancer risk in specific populations, whereas variants like *BsmI* or *Cdx2* might be linked to lower risk in others. Likewise, particular genotypes of VDR have been associated with differences in overall survival (OS) or disease-free survival in lung cancer cohorts. However, the results across studies have not been uniform or conclusive [27,28]. Discrepancies likely stem from varied study designs and populations, including differences in ethnic allele frequencies, smoking exposure, tumor histology, and sample size, as well as methodological limitations (e.g., some studies lacked comprehensive genotyping quality control

or did not account for Vitamin D levels. Consequently, despite the biological rationale and scattered positive findings, it remains unclear when and why VDR variants meaningfully influence lung cancer risk or progression [10-13,23].

In light of these knowledge gaps, the present narrative review aims to integrate mechanistic biology, population data, and methodological considerations to determine under what conditions VDR polymorphisms are associated with lung cancer, and what the practical implications might be. By synthesizing evidence on the biological functions of VDR, the epidemiological patterns (and variability) of VDR variant associations, and the quality of the supporting data, we seek to clarify the context-dependent impact of VDR genetics on lung cancer.

SEARCH, SELECTION, AND EXTRACTION OF DATABASE

We conducted a structured narrative review designed to balance breadth and interpretability in a heterogeneous literature. PubMed, Scopus, and Web of Science were searched from inception using controlled vocabulary and free-text terms combining "vitamin D receptor"/VDR, polymorphism/genotype, lung cancer/non-small cell lung cancer (NSCLC)/small cell lung cancer, and single nucleotide polymorphism (SNP)-specific rsIDs (rs2228570/FokI, rs1544410/BsmI, rs7975232/ApaI, rs731236/TaqI, rs11568820/Cdx2). Reference lists of eligible articles were hand-searched. We included human observational studies (case–control or cohort); meta-analyses/umbrella reviews were consulted for context; and mechanistic lung-focused studies were retained to anchor biological plausibility. We excluded non-human studies, non-VDR genetics, and reports with inadequate data. Two reviewers independently screened records and extracted data using a standardized form; discrepancies were resolved by consensus. Extracted items included design, setting, ancestry, genotyping platform/QC, Hardy–Weinberg equilibrium (HWE) in controls, genotype counts and models, covariate adjustment (age, sex, smoking, stage, and histology), and whether 25-hydroxyvitamin D (25(OH)D) was measured.

BIOLOGICAL RATIONALE AND MECHANISTIC EVIDENCE

Vitamin D signaling is biologically well-positioned to influence lung carcinogenesis. The active metabolite 1,25(OH)2D binds the VDR, a ligand-activated transcription factor that dimerizes with retinoid X receptor (RXR) and regulates vitamin-D-response-element (VDRE)-bearing genes involved in proliferation, differentiation, apoptosis, deoxyribonucleic acid (DNA) repair, epithelial integrity, and immune modulation [29-33]. Canonical downstream pathways include upregulation of cyclin-dependent kinase inhibitors (e.g., p21, p27) and stress-response genes (e.g., GADD45a), with parallel dampening of pro-inflammatory signaling; collectively, these programs provide a mechanistic basis for anticancer effects across epithelial tissues [29,34-36]. Functionally, common VDR polymorphisms can plausibly shift this transcriptional program: FokI (rs2228570) alters the translation start site and hence receptor isoform activity; Cdx2 (rs11568820) modifies promoter activity; and BsmI (rs1544410)/ApaI (rs7975232), located in the 3′ region, are linked to mRNA stability and haplotypes features that could tune VDR abundance or responsiveness to ligand [17,37-39].

Lung-specific experimental evidence substantiates this plausibility. In human lung cancers, VDR expression is reduced while histidine-rich calcium-binding protein (HRC) is increased; activation of VDR by Vitamin D directly represses HRC through VDRE binding on the HRC promoter, thereby curbing proliferation, migration, and tumor growth. The study triangulated across human tissues, H460 NSCLC cells (with CRISPR/Cas9 knockout and VDR overexpression), and xenograft models, showing that HRC knockdown synergizes with Vitamin D while HRC overexpression attenuates Vitamin D effects [40]. Although this program does not interrogate germline SNPs, it delivers a causal molecular pathway, VDR then HRC that explains how variation in VDR signaling capacity could translate into aggressive tumor phenotypes in the lung [40].

Signals from observational human research align with this axis. Higher circulating 25(OH)D associates with better OS and progression-free survival (PFS) across cancers, and in the lung-cancer subset, the FokI (rs2228570) risk allele tracks with worse OS, supporting the clinical relevance of VDR activity and its inherited modulation [17,41,42]. In resected NSCLC, seasonality, a proxy for sunlight/vitamin-D exposure, co-varied with outcomes, and TaqI (rs731236) TT and combined TaqI/FokI risk genotypes predicted poorer postsurgical survival, suggesting that both axis status and receptor genotype may shape prognosis [43,44]. At the same time, Vitamin D replacement dose alone (without genotype) did not improve chemotherapy response or survival in advanced disease, a caution that status ≠ genotype and that late-stage biology may be less modifiable by supplementation in isolation [45,46].

Genetic data provide additional mechanistic coherence. A small Chinese case–control study reported haplotypes spanning FokI/ApaI/Cdx2 associated with lung cancer incidence, consistent with the idea that function-linked promoter/start-codon/3′ variants can act in combination to alter effective VDR signaling [47]. More broadly, reviews and meta-analyses emphasize that VDR-pathway effects are context-dependent, varying by ancestry (linkage disequilibrium [LD] and allele frequency), exposure history (notably smoking), and tumor subtype features that are biologically plausible for a receptor integrating environmental and immuno-epithelial cues [48,49]. Importantly, genotype may also shape axis status: In healthy adults, carriers of the FokI risk allele exhibited lower 25(OH)D, hinting at genetically influenced set-points or feedback within the vitamin-D/VDR system [50]. Together, these observations of molecular repression of a pro-tumorigenic target by VDR [40], survival benefits with higher 25(OH)D and adverse outcomes with functional VDR alleles [17], genotype-season interactions in surgical cohorts [43], and haplotypic susceptibility signals outline a biologically coherent pathway in which VDR activity, tuned by ligand availability and germline variation, plausibly modifies lung-cancer behavior [47].

Two boundary conditions follow from the evidence. First, axis-level modifiers beyond VDR, such as CYP27B1, CYP24A1, GC, and CYP2R1, may influence lung-cancer outcomes and interact with VDR genotypes, reinforcing the need for pathway-wide analyses in prognostic modeling [48]. Second, findings across cancers caution against naïve generalization: pooled "tobacco-related" analyses suggest variant-specific directions (e.g., a protective TaqI t allele overall), underlining tissue specificity and the importance of lung-focused syntheses [51]. Methodologically, many cohorts lack standardized genotyping QC, Hardy–Weinberg checks, or contemporaneous 25(OH)D measurement, and some signals derive from small or imbalanced samples, limitations that justify a measured translational stance and motivate replication in multi-ancestry NSCLC cohorts with pre-specified adjustment for smoking intensity, histology, and stage [43,47,48].

Genotype–status interaction model for the VDR axis. Beyond the principle that status ≠ genotype, accumulating signals suggest these dimensions interact. Observational data indicate that FokI (rs2228570) risk-allele carriers can have lower circulating 25(OH)D set-points, implying that germline variation may tune axis tone upstream of tumor biology (Tuncel et al., 2019) [21]. Mechanistically, VDR is a ligand-activated transcription factor whose activity depends on both receptor properties (e.g., FokI-dependent isoform transactivation) and ligand availability; moreover, VDR participates in feedback over the vitamin-D pathway (e.g., transcriptional control of CYP24A1 and interactions with CYP27B1/GC) (Thorne and Campbell, 2008; Pineda-Lancheros et al., 2023) [14,19]. We therefore posit a circular model: (i) VDR genotype influences receptor function and may shift steady-state 25(OH)D through pathway feedback or correlated variants; (ii) circulating 25(OH)D in turn modulates tissue-level VDR activity, amplifying or dampening the same genotype's phenotypic effect; and (iii) external modifiers (season/latitude, smoking, GC variants) perturb this loop [17,43]. In practical terms, the same genotype may be low-impact when 25(OH)D is sufficient (near-saturated receptor)

yet deleterious under low 25(OH)D (ligand-limited transactivation), or vice-versa for variants affecting receptor efficiency. This framework parsimoniously explains ancestry- and exposure-specific results and argues that studying genotype or status in isolation is insufficient. Future risk and survival analyses should co-measure 25(OH)D with genotype, pre-specify genotype×25(OH)D interaction terms (with flexible modeling of 25(OH)D), adjust for season/latitude, body mass index, smoking intensity, and vitamin D-binding protein gene (GC), stratify by ancestry/LD blocks and extend to trans-ethnic fine-mapping and eQTL colocalization within lung tissue [17,43].

RISK STUDIES (CASE–CONTROL/META-ANALYSES)

Anchoring our synthesis, Duan *et al*. meta-analyzed 15 case studies spanning Asian and Caucasian cohorts and found increased lung-cancer risk with TaqI (rs731236), strongest in Asians and in NSCLC with amplification among smokers; FokI (rs2228570) also conferred elevated risk in Asians, whereas BsmI (rs1544410), ApaI (rs7975232; particularly in Asians), and Cdx2 (rs11568820) generally showed protective directions. To preserve interpretability amid heterogeneity in controls, call rates, and model specification, we retain per-study genetic models, effect-allele coding, HWE status, and genotyping QC as reported. Single-center signals provide context: A Turkish surgical series observed higher NSCLC risk for TaqI TT and for combined TaqI/FokI risk genotypes, and a small Chinese case–control study suggested haplotypic susceptibility across FokI/ApaI/Cdx2; given small samples, group imbalances, and incomplete QC, these are treated as supportive rather than definitive. Finally, by separating risk odds ratios from prognosis hazard ratios (HRs) and harmonizing rsIDs while retaining RFLP aliases, we minimize endpoint conflation and maintain cross-study comparability [23,43,47].

PROGNOSIS STUDIES (OS/PFS IN NSCLC)

Table 1 synthesizes NSCLC survival (OS/PFS) signals from three evidence streams: a focused NSCLC review, a pathway-level survival meta-analysis, and a single-center surgical cohort. In the review, adverse associations recur for TaqI (rs731236), ApaI (rs7975232), and BsmI (rs1544410), with cohort-specific effects for FokI (rs2228570) and mixed findings for Cdx2 (rs11568820); heterogeneous platforms/QC and inconsistent covariate sets prevented formal pooling. At the pathway level, the FokI risk allele tracked with worse OS in the lung- cancer subset, while in resected NSCLC, combined TaqI/FokI risk genotypes independently predicted poorer postsurgical OS after adjustment for nodal stage and season. To avoid endpoint conflation, Table 1 reports HR-based estimates only, annotates adjustment for stage/histology/smoking, and flags the absence of contemporaneous 25(OH)D; overall, signals are biologically plausible yet heterogeneous, warranting replication with standardized genotyping/QC and pre-specified adjustment [17,43,48].

MECHANISTIC/BIOLOGICAL RATIONALE (NO GERMLINE GENOTYPING)

In lung tissues, NSCLC cells, and xenografts, 1,25-$(OH)_2$D–activated VDR binds VDREs in the HRC promoter, represses HRC, and suppresses proliferation, migration, and tumor growth demonstrated through reverse-transcription quantitative polymerase chain reaction (RT-qPCR), Western blot, immunohistochemistry, CRISPR knockout, VDR overexpression, and VDRE-luciferase. Although germline variants were not tested, this VDR-HRC program aligns with the adverse survival signal for functional FokI in lung-cancer subsets, supporting VDR pathway involvement and motivating genotype-aware prognostic work with attention to axis activity, microenvironment, and exposure (Tables 2 and 3) [17,40].

VARIANT-SPECIFIC EPIDEMIOLOGICAL SIGNALS (RISK)

Across VDR loci, the most reproducible susceptibility signal is for TaqI (rs731236): A 15-study meta-analysis reported higher lung-cancer risk for the T allele/TT genotype, amplified in Asians and in NSCLC, with a TT with smoking interaction. A Turkish single-center series echoed this pattern (TT and combined TaqI/FokI risk genotypes), while several loci showed protective trends BsmI (rs1544410) and Cdx2 (rs11568820) overall, and ApaI (rs7975232, AA) and BsmI (AA) in Asian strata; in contrast, FokI (rs2228570) increased risk in Asians. A small Chinese case–control study suggested susceptibility haplotypes spanning FokI/ApaI/Cdx2, but it remains hypothesis-generating given the size and reporting limits. For context only, a pooled analysis across tobacco-related cancers found the TaqI t allele protective, including a lung subgroup underscoring tissue specificity and the need for lung-focused syntheses. Taken together, TaqI (risk) and FokI (risk in Asians) are the clearest candidates, whereas BsmI/ApaI/Cdx2 more often show ancestry-dependent protection [23,43,47,51].

Table 1: Summary of variant-specific associations (risk and prognosis combined)

Variant (rsID; alias)	Putative function	Risk association (lung)	Prognostic association (NSCLC)	Overall strength of evidence*
TaqI (rs731236)	Synonymous exon 9/3′ region; tags BsmI/ApaI haplotypes; may affect mRNA stability through LD	Increased risk, strongest in Asians, NSCLC; smoking×TT interaction noted in primaries/meta	Adverse signals for risk genotypes across several cohorts (OS/PFS)	Moderate-strong: lung-focused meta+multiple cohorts; heterogeneity present
FokI (rs2228570)	Start-codon variant (shorter VDR isoform; altered transactivation)	Increased risk in Asians; direction outside Asian strata uncertain	Adverse OS in lung subset of pathway meta; cohort-specific within NSCLC review	Moderate: meta-level lung subset+cohort signals; ancestry-dependent
BsmI (rs1544410)	3′ region; LD with TaqI/ApaI; mRNA stability/haplotype effects	Protective overall (esp. AA in Asians)	Adverse OS reported in selected Asian/Spanish cohorts	Limited-moderate: mixed directions across endpoints; QC variability
ApaI (rs7975232)	3′ region; LD with BsmI/TaqI	Protective in Asians (AA, AA+Aa)	Adverse OS/PFS in several cohorts	Limited–moderate: ancestry-specific risk+cohort prognosis; heterogeneity
cd×2 (rs11568820)	Promoter variant (transcription factor binding; expression)	Protective in some risk models	Mixed (histology-specific, small Ns)	Limited: fewer lung-specific studies; inconsistent models

Consolidated variant-level signals (risk and prognosis) derived from the studies in Table 1. "Overall strength of evidence" is a qualitative synthesis based on number/size of lung-specific studies and consistency of direction. *Evidence grading (qualitative): Strong = ≥1 lung-focused meta and≥2 independent cohorts with consistent direction; Moderate=meta support or≥2 cohorts with some heterogeneity; Limited=single/very small cohorts or inconsistent findings. LD note: The BsmI-ApaI-TaqI trio belongs to a 3′ LD block with ancestry-dependent LD/haplotype structure; per-SNP associations may reflect haplotype tagging rather than the functional impact of a single marker. FokI (start codon) and Cd×2 (promoter) are generally independent of this block. NSCLC: Non-small cell lung cancer, OS: Overall survival, PFS: Progression-free survival, QC: Quality control, LD: Linkage disequilibrium, TT: Homozygous T-allele genotype

Table 2: Characteristics of included studies

First author (Year)	Design	Population/ Ancestry	Sample size (cases/ controls or cohorts)	Genotyped variants (focus)	Key findings (lung-focused)	Quality score (NOS/JBI)	Key limitations
Duan *et al*. (2020) [23]	Systematic review and meta-analysis of case–control risk studies	Asian and Caucasian	15 studies; ~4,732/4,337	VDR: FokI rs2228570, BsmI rs1544410, ApaI rs7975232, TaqI rs731236; GC rs7041/rs4588	↑Risk for TaqI (strongest in Asians/NSCLC; amplified in smokers); ↑Risk for FokI in Asians; BsmI/ApaI generally protective; Cd×2 protective in some models	NA (meta); primaries variably moderate	Between-study heterogeneity; variable HWE/ QC/covariate adjustment; limited 25(OH) D data
Pineda-Lancheros *et al*. (2023) [48]	Systematic review of NSCLC survival	China, USA, Spain (NSCLC I–IV)	6 cohorts	VDR: TaqI, BsmI, ApaI, FokI, Cd×2; pathway SNPs	Recurrent adverse OS/ PFS signals for TaqI/ ApaI/BsmI in selected cohorts	Reported variable; no unified score	Heterogeneous platforms, covariates; pooling not feasible; sparse 25(OH) D
Vaughan-Shaw *et al*. (2017) [17]	Systematic review and meta-analysis (survival across cancers; lung subset)	Multi-country (lung subset)	Multiple cohorts (lung subset size limited)	VDR panel; circulating 25(OH) D	FokI cohort-specific in lung subset, FokI associated with worse OS	NA (meta)	Cross-cancer pooling; lung subset small; heterogeneous adjustments
Turna *et al*. (2012) [43]	Surgical cohort (prognosis) with case–control subset (risk)	Turkey; resected NSCLC	Genotyped subset~62 NSCLC+75 controls	TaqI, FokI (PCR-RFLP)	Combined TaqI/FokI risk genotypes predicted poorer postsurgical OS (with nodal stage/ season); TaqI TT linked to NSCLC risk in subset	Not reported	Small genotyped subset; limited covariates; no 25(OH) D
Li *et al*. (2012) [47]	Case–control (risk)	China	67/72	FokI, BsmI, ApaI, TaqI, Cd×2	Haplotype spanning FokI/ApaI/Cd×2 associated with incidence (hypothesis-generating)	Not reported	Small, imbalanced; abstract-level effects; QC/HWE not detailed
Laczmanski *et al*. (2019) [51]	Meta-analysis of tobacco-related cancers (context)	Mixed; includes lung subgroup	Multi-site	TaqI (and others)	For context: Pooled t allele protective overall; lung subgroup also protective (tissue specificity caveat)	NA (meta)	Cross-cancer pooling; not lung-only; used for context (not core)
Elsalahaty *et al*. (2024) [5]	Systematic review and meta-analysis (risk)	Mixed	Multi-study	Vitamin-D pathway genes incl. VDR	Pathway variants associated with lung-cancer risk; supports VDR-axis relevance	NA (meta)	Heterogeneity; variable QC; gene-set breadth (not VDR-only)

Characteristics of all included lung-focused studies and pathway reviews used in the synthesis. Where formal NOS/JBI scores were not reported in the sources, entries are marked "Not reported." Meta-analyses are listed once to prevent redundancy across tables. NSCLC: Non-small cell lung cancer, OS: Overall survival, PFS: Progression-free survival, HWE: Hardy-Weinberg equilibrium, QC: Quality control (genotyping), 25(OH) D: 25-hydroxyvitamin D

Table 3: Key mechanistic studies (VDR activity in lung cancer models)

First author (Year)	System/models	Core mechanism and assays	Main readouts	Relevance to VDR SNP effects	Key limitations
Liu *et al*. (2021) [5]	Human lung tissues; H460 NSCLC cells; BALB/c nude mouse xenografts	1,25-(OH) D–activated VDR binds VDREs in HRC promoter→HRC repression; methods: RT-qPCR, Western, IHC, CRISPR knockout, VDR over-expression, VDRE-luciferase	↓Proliferation/ migration; ↓xenograft growth; apoptosis modulation	Provides a causal VDR→HRC pathway plausibly modulated by VDR signaling capacity (context for functional variants like FokI)	No germline SNP analysis; no direct survival linkage

Mechanistic studies supporting the biological plausibility of VDR signaling in lung cancer. These do not genotype SNPs but anchor the genotype-to-phenotype narrative. VDRE: Vitamin-D response element, HRC: Histidine-rich calcium-binding protein, IHC: Immunohistochemistry, RT-qPCR: Reverse-transcription quantitative polymerase chain reaction

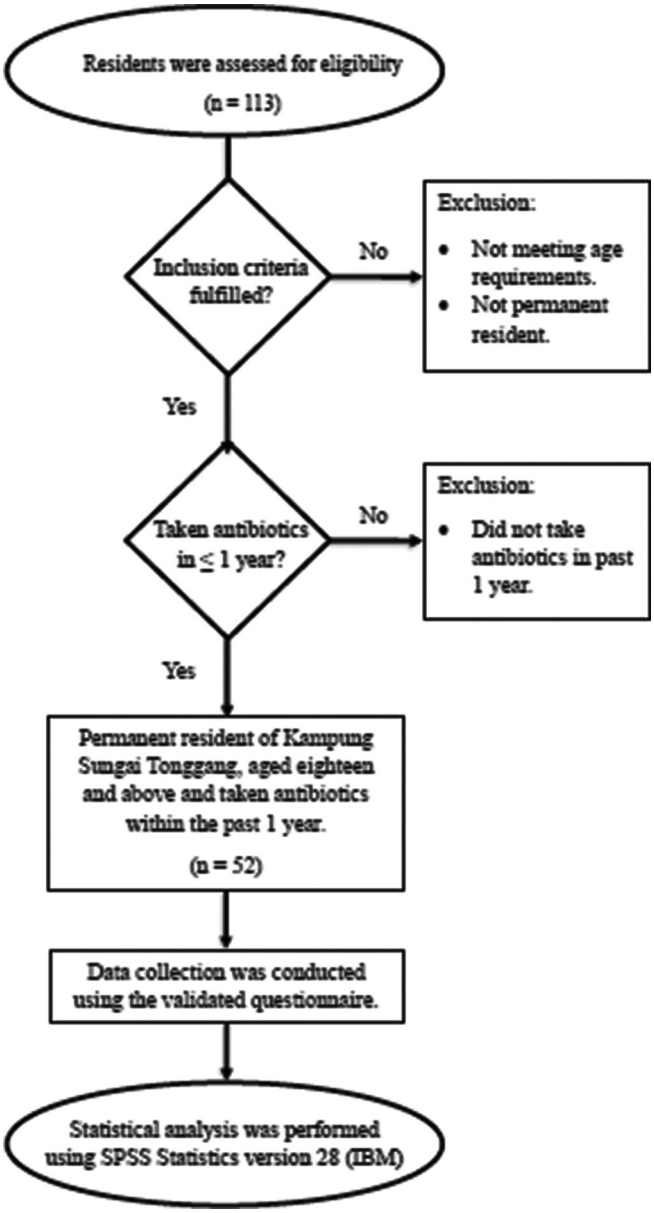

Fig. 1: The flow of the study

PROGNOSTIC SIGNALS (OS/PFS IN NSCLC)

Across NSCLC cohorts, prognostic associations concentrate on canonical VDR loci: TaqI (rs731236), ApaI (rs7975232), and BsmI (rs1544410) repeatedly show adverse OS/PFS signals, whereas FokI (rs2228570) is cohort-specific. At the pathway level, a survival meta-analysis reported poorer OS for FokI in the lung subset (HR 1.29; 95% confidence intervals 1.00–1.57), offering variant-specific external support. Single-center surgical data align directionally: combined TaqI/FokI risk genotypes independently predicted worse post-surgical OS alongside nodal status and season. Interpretation is constrained by under-reported platforms and call/error metrics, heterogeneous covariate adjustment (stage, histology, smoking), and absent contemporaneous 25(OH)D, which collectively inflated heterogeneity and prevented pooling in the NSCLC-focused review. Overall, TaqI/ApaI/BsmI associate with poorer survival in selected cohorts, FokI signals triangulate at pathway and single-center levels, Cdx2 (rs11568820) remains mixed, and replication with standardized genotyping/QC and pre-specified adjustment in multi-ancestry NSCLC cohorts is required (Table 1) [17,43,48].

INTEGRATIVE INTERPRETATION

Integrating the mechanistic and human data, VDR variation exerts a context-dependent influence on lung cancer, shaped by vitamin-D axis status and smoking. Biologically, VDR is a ligand-activated transcription factor orchestrating programs in proliferation, apoptosis, DNA repair, and immune modulation [29]; in lung models, Vitamin D-activated VDR directly represses HRC through VDRE binding, limiting proliferation, migration, and xenograft growth, linking receptor activity to actionable tumor phenotypes [40]. These signals accord with pathway-level survival evidence for the functional FokI variant [17]. Epidemiologically, TaqI (rs731236) confers a higher risk, strongest in Asian NSCLC and in smokers with TT-while FokI (rs2228570) increases risk in Asians; BsmI, ApaI, and Cdx2 more often show ancestry-dependent protection [23]. Single-center and haplotype findings are supportive yet small [43,47], and site-specificity is underscored by cross-cancer pooling [49,51]. Heterogeneity reflects both method (QC, imbalance) and biology: survival tracks with 25(OH)D, FokI relates to worse OS, seasonality associates with outcomes, and FokI carriers may have lower 25(OH) D [17,43,50]. Specifically, supplementation without genotype did not improve advanced-disease outcomes [45]. Collectively, the evidence supports pathway-wide, genotype-aware, multi-locus models tested with pre-specified QC in multi-ancestry NSCLC cohorts [48]. LD-aware interpretation. Differences in LD across populations mean that the 3′ VDR variants BsmI-ApaI-TaqI (often tightly correlated in Europeans) can tag different haplotypes and different putative causal sites across ancestries; consequently, an apparent “signal” at one marker in Europeans may not replicate at the same marker in East Asians even if the biological effect is conserved at the haplotype level. By contrast, FokI (start codon) and Cdx2 (promoter) lie outside the 3′ block and likely capture independent mechanisms. This LD context helps reconcile ancestry-specific results and supports haplotype/onditional analyses and trans-ethnic fine-mapping going forward.

TRANSLATIONAL IMPLICATIONS (MEASURED AND REALISTIC)

Translational use of VDR genetics should be deliberate and research-focused. A coherent mechanistic chain exists VDR, a ligand-activated transcription factor, modulates proliferation, apoptosis, DNA repair, and immune programs [29], and in lung models, vitamin D-activated VDR directly represses HRC, restraining tumor growth and migration [40], but the human evidence is conditional and methodologically variable. For risk, TaqI (rs731236) and, in Asians, FokI (rs2228570) function as risk modifiers rather than deterministic markers; a measured application is trial enrichment within high-risk cohorts to test added discrimination beyond age, pack-years, family history, and comorbidity, while small Chinese haplotype signals remain hypothesis-generating [23,47]. For prognosis, convergent yet heterogeneous data worse OS for FokI in a pathway meta-analysis and adverse OS/PFS patterns for TaqI/ApaI/BsmI in NSCLC cohorts support including genotype as covariates in multivariable Cox models rather than using them to direct therapy; single-center signals for combined TaqI/FokI risk genotypes warrant replication in larger, well-adjusted datasets [17,43,48]. On supplementation, separate status from genotype: correct frank Vitamin D deficiency for general health, but do not infer oncologic benefit absent genotype- and stage-aware RCTs, particularly since replacement alone did not improve chemotherapy response or survival in advanced disease without genotyping [45]. The practical path is pathway-wide modeling co-analyzing VDR with CYP27B1, CYP24A1, CYP2R1, and GC, with ancestry- and exposure-aware specifications, while resisting tissue-agnostic extrapolations that show direction flips for TaqI across “tobacco-related cancers” [23,48,49,51]. Methodological guardrails are essential: pre-specified genotyping QC and HWE checks; uniform rsID-anchored allele coding and explicit genetic models; adjustment for stage, histology, age/sex, smoking intensity (and season/latitude where relevant); and contemporaneous 25(OH) D measurement to decouple genotype from status [43,47,48]. In sum, deploy VDR genotyping to sharpen risk models, inform prognostic nomograms under validation,

and stratify biomarker-guided trials, but do not alter screening thresholds or systemic therapy based on VDR genotype outside a trial.

LIMITATIONS AND FEATURE DIRECTIONS

Key constraints temper inference in this literature: We did not perform haplotype-based or conditional analyses across studies, and LD structures differ by ancestry; therefore, some per-SNP summaries may reflect tagging of causal haplotypes rather than variant-specific effects, underscoring the need for trans-ethnic fine-mapping and colocalization analyses. Heterogeneous genotyping platforms and call/error reporting, inconsistent Hardy–Weinberg checks, small or imbalanced single-center cohorts, and variable covariate adjustment (stage, histology, smoking intensity), coupled with absent contemporaneous 25(OH)D and season/latitude data; these issues, alongside endpoint conflation between risk and prognosis, explain the high between-study heterogeneity and why NSCLC-focused reviews could not pool estimates. Signals for TaqI/FokI (risk) and for FokI in pathway-level survival analyses arise from subsets and are ancestry- and context-dependent; haplotype findings remain hypothesis-generating; and vitamin-D replacement without genotype stratification did not improve advanced-disease outcomes, highlighting that axis "status" and genotype are distinct constructs. Future work should prioritize adequately powered, multi-ancestry NSCLC cohorts with pre-specified covariate sets; standardized genotyping and QC (with explicit HWE), uniform rsID-anchored genetic models, and contemporaneous 25(OH)D with environmental proxies; and pathway- wide, multi-locus analyses integrating VDR with CYP27B1, CYP24A1, CYP2R1, and GC, testing gene-environment and histology-specific interactions. Prospective validation of genotype-augmented risk models and prognostic nomograms, alongside genotype- and stage-aware biomarker-stratified trials of vitamin-D-axis modulation, are necessary before any clinical adoption.

CONCLUSION

VDR signaling plausibly shapes lung carcinogenesis, and common variants show context-dependent rather than universal effects. The most reproducible susceptibility signal is TaqI (rs731236), particularly in Asian ancestry, smokers, and NSCLC, while BsmI (rs1544410) and, in some settings, ApaI (rs7975232) trend protective; FokI (rs2228570) shows population-specific risk and a pathway-level survival signal. Lung- specific experiments demonstrating ligand-activated VDR repression of HRC provide a credible mechanistic bridge. Yet heterogeneity in study design, genotyping QC, ancestry mix, covariate handling, and sparse contemporaneous 25(OH)D/environmental data limits causal inference and precludes clinical use at present. Priority next steps are adequately powered, multi-ancestry cohorts with harmonized genotyping and pre-specified adjustments, standardized rsID-anchored models, integrated vitamin-D/status and environmental measures, and pathway-wide analyses spanning VDR, CYP27B1, CYP24A1, CYP2R1, and GC with explicit gene-environment and histology-specific tests. Only after prospective validation of genotype-augmented risk scores and NSCLC prognostic nomograms, and biomarker-stratified trials of vitamin-D- axis modulation, should clinical adoption be considered.

AUTHOR'S CONTRIBUTIONS

Gogineni Rajyalakshmi (GR): Conceptualization; Literature search; Data curation; Formal analysis; Writing original draft. Muniinathan Natarajan (MN): Methodology; Data extraction/verification; Visualization; Writing, review, and editing. M. Girija Menon (MGM): Clinical interpretation; Critical review; Supervision; Writing, review, and editing. A. Suresh Arumugam (ASA): Data curation; Tables/Figures; Writing, review, and editing. Kuppusamy Baskaran (KB): Conceptualization; Supervision; Project administration; Correspondence; Writing – review and editing; Guarantor.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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