REVIEW ARTICLE

Translational Health Reports. 2026; 2(1): 8
https://doi.org/10.22034/thr.2025.236687

The Impact of Serum 25-Hydroxyvitamin D and Genetic Factors on Liver Cancer Risk: An Updated Review and Mendelian Randomization Analysis

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Article history:

Received: 13 Oct 2025
Accepted: 6 Dec 2025
Available online: 14 Dec 2025

Keywords:

Serum 25-Hydroxyvitamin D
Genetic Factors
Liver

Abstract

Background: Liver cancer, mainly hepatocellular carcinoma (HCC), presents a major global health challenge with high mortality. While established risk factors such as viral hepatitis and alcohol consumption are widely recognized, there is growing interest in modifiable factors like vitamin D (VD) deficiency. Observational studies indicate a link between low serum 25-hydroxyvitamin D (25(OH)D) and increased liver cancer risk, though confounding factors and reverse causality complicate causal conclusions.
Objectives: This review aims to integrate current findings on the relationship between serum 25(OH)D and liver cancer risk, critically assess causality using Mendelian randomization (MR) evidence, and explore mechanistic insights from genetic research.
Methods: A narrative literature review was conducted using PubMed and Google Scholar, focusing on epidemiological studies, MR analyses, and mechanistic research published up to 2025. Search terms included "25-hydroxyvitamin D," "liver cancer," "hepatocellular carcinoma," "Mendelian randomization," and "genetic polymorphisms."
Results: Case-control and cohort studies consistently show that liver cancer patients have significantly lower serum 25(OH)D levels compared to healthy individuals. MR studies, using genetic variants in *DHCR7*, *CYP2R1*, and *VDR* genes as instrumental variables, strongly indicate a causal protective effect of higher 25(OH)D concentrations on liver cancer risk. For example, alleles associated with increased 25(OH)D, such as those in *DHCR7* (rs12785878) and *VDR* (rs2228570), correlate with a 20-30% reduction in liver cancer odds. These findings are supported by biological mechanisms, including VD's anti-proliferative, pro-apoptotic, and anti-inflammatory actions mediated through the VDR receptor in liver cells.
Discussion: The alignment of epidemiological and genetic evidence reinforces the likely causal, protective role of vitamin D in liver cancer. Genetic polymorphisms offer a means to reduce confounding, providing more robust evidence than observational data alone. Future research should emphasize large-scale randomized controlled trials of VD supplementation in high-risk groups and further investigation of gene-environment interactions.

Cite this article as: Priyadarshini P. The Impact of Serum 25-Hydroxyvitamin D and Genetic Factors on Liver Cancer Risk: An Updated Review and Mendelian Randomization Analysis. Transl Health Rep. 2026; 2(1):8. https://doi.org/10.22034/thr.2025.236687.

Introduction

Liver cancer is the third most common cause of cancer-related deaths worldwide, with HCC representing most cases [1]. Incidence and mortality rates are highest in East Asia and Sub-Saharan Africa, largely due to hepatitis B virus (HBV) infection and dietary aflatoxin exposure [2,3]. Despite improvements in detection and treatment, outcomes remain poor, often because of late diagnosis and limited treatment options in advanced stages [4,5].

Known risk factors for HCC include chronic HBV and hepatitis C virus (HCV) infections, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and cirrhosis from various causes [6,7]. However, not all

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cases are explained by these factors, suggesting a role for other modifiable risks [8]. In recent years, vitamin D—a fat-soluble secosteroid—has gained attention for its potential role in cancer development [9]. Beyond its traditional role in calcium and phosphate balance, VD displays anti-proliferative, pro-differentiation, anti-inflammatory, and pro-apoptotic properties in diverse cell types [10,11].

Serum 25(OH)D is the primary indicator of VD status [12]. Many observational studies report an association between low 25(OH)D levels and increased risk of various cancers, including colorectal, breast, and prostate cancer [13,14]. For liver cancer, evidence suggests that VD deficiency is prevalent in HCC patients and may relate to poorer outcomes [15,16]. However, these observational studies are vulnerable to residual confounding—such as poor nutrition, limited sun exposure, and systemic inflammation—and reverse causality, where the disease itself lowers 25(OH)D levels [17,18].

Mendelian randomization has become a valuable epidemiological method for evaluating causal relationships [19]. By using genetic variants that affect modifiable exposures (e.g., 25(OH)D levels) as instrumental variables, MR can provide evidence less affected by confounding, as genetic alleles are randomly assigned at conception and generally unaffected by lifestyle or disease processes [20]. Genome-wide association studies have identified several single nucleotide polymorphisms in genes involved in VD synthesis (*DHCR7*), hydroxylation (*CYP2R1*, *CYP24A1*), and transport (*GC*) that are reliably linked to circulating 25(OH)D levels [21,22].

This review synthesizes current evidence on the association between serum 25(OH)D and liver cancer risk. It critically evaluates findings from observational studies and MR analyses, which use genetic instruments to infer causality. Additionally, it explores the biological mechanisms of VD's potential anti-cancer effects in the liver and discusses implications for future research and public health.

Methods

This narrative review involved a comprehensive search of PubMed and Google Scholar for relevant articles published through July 2024. Keywords and MeSH terms included: "Vitamin D," "25-hydroxyvitamin D," "Cholecalciferol," "Liver Cancer," "Hepatocellular Carcinoma," "HCC," "Risk," "Incidence," "Mendelian Randomization," "Genetic Polymorphism," "Single Nucleotide Polymorphism," "*VDR*," "*CYP2R1*," "*DHCR7*," and "*CYP24A1*."

Inclusion criteria were: (1) original research articles (case-control, cohort, cross-sectional, or MR studies); (2) review articles and meta-analyses providing foundational or synthesized evidence; (3) English-language publications. Exclusion criteria included: (1) editorials, conference abstracts without full data, and non-English publications; (2) studies not focused on liver cancer/HCC or not measuring/reporting on 25(OH)D or relevant genetic variants.

The initial search produced over 500 articles. Titles and abstracts were screened for relevance, and full texts of eligible papers were obtained. Reference lists of key articles were also manually searched. Data from selected studies were extracted and synthesized narratively, focusing on key themes: the epidemiological link between 25(OH)D and liver cancer, MR evidence for causality, the functional role of key genes, and underlying biological mechanisms.

Results

Epidemiological Evidence Linking 25(OH)D to Liver Cancer Risk

Multiple case-control studies consistently show that newly diagnosed HCC patients have significantly lower circulating 25(OH)D levels compared to healthy controls or individuals with chronic liver disease without HCC [23,24]. For instance, a large study by Chiang et al. found that VD deficiency (25(OH)D < 20 ng/mL) was an independent risk factor for HCC in patients with chronic HBV infection, even after adjusting for liver function and viral load [25]. Cohort studies, though fewer, support this inverse relationship. The Linxian Nutrition Intervention Trials observed that lower prediagnostic 25(OH)D levels were associated with increased liver cancer mortality [26].

Mendelian Randomization Evidence for a Causal Relationship

MR studies offer stronger, less confounded evidence. A two-sample MR analysis by Yuan et al., using genetic instruments from the SUNLIGHT consortium, found that a genetically predicted one-standard deviation increase in log-transformed 25(OH)D concentration was associated with a 43% reduction in HCC risk [27]. Another recent MR study confirmed this inverse causal relationship, identifying specific SNPs in *DHCR7* (rs12785878) and *CYP2R1* (rs10741657) as key contributors to this protective effect [28]. These results align with other MR investigations reporting consistent, directionally similar effects across different populations and genetic instruments [29,30].

The Role of Key Vitamin D Pathway Genes

The MR approach relies on functionally relevant genetic variants. Important genes and their roles include:

DHCR7 (7-dehydrocholesterol reductase): Converts 7-dehydrocholesterol to cholesterol, reducing substrate for cutaneous VD synthesis. The T allele of rs12785878 near *DHCR7* is associated with lower 25(OH)D and higher liver cancer risk in MR analyses [31,32].

CYP2R1 (Vitamin D 25-hydroxylase): The main enzyme for 25-hydroxylation of VD. Loss-of-function mutations in *CYP2R1* are linked to low 25(OH)D levels, and SNPs like rs10741657 are used in MR studies of liver cancer [33,34].

VDR (Vitamin D Receptor): The nuclear receptor mediating most of VD's genomic actions. Polymorphisms such as *FokI* (rs2228570) and *TaqI* (rs731236) affect VDR function and have been associated with both 25(OH)D levels and liver cancer susceptibility in multiple studies [35,36].

CYP24A1 (24-hydroxylase): Initiates degradation of 25(OH)D and 1,25(OH)2D. While SNPs in *CYP24A1* (e.g., rs6013897) are associated with 25(OH)D levels, their link to liver cancer risk in MR studies has been less consistent, possibly due to its catabolic role [37,38].

Biological Mechanisms of Vitamin D in Hepatoprotection

Proposed mechanisms, supported by in vitro and in vivo models, are multifaceted:

Cell Cycle Arrest and Apoptosis: 1,25(OH)2D (calcitriol) induces G0/G1 cell cycle arrest in liver cancer cells by upregulating p21 and p27, and promotes apoptosis via intrinsic and extrinsic pathways [39,40].

Inhibition of Epithelial-Mesenchymal Transition (EMT) and Metastasis: VD signaling through VDR can suppress EMT, a key process for invasion and metastasis, by downregulating transcription factors like SNAIL and TWIST [41,42].

Anti-inflammatory and Immunomodulatory Effects: VD reduces pro-inflammatory NF-κB signaling and promotes a tolerogenic immune environment, countering chronic inflammation that drives liver cancer in conditions like NASH and viral hepatitis [43,44].

Inhibition of Angiogenesis: Calcitriol decreases expression of pro-angiogenic factors like VEGF in tumor cells, inhibiting new blood vessel formation needed for tumor growth [45,46].

Discussion

This review integrates evidence from multiple approaches, collectively suggesting that vitamin D status significantly influences liver cancer risk. The shift from observational correlations to causal inference via MR marks a key advancement in the field. Consistent MR findings [27,28,30] strongly indicate that low 25(OH)D is not just a marker of poor health in liver cancer patients but likely a contributing causal factor in disease development.

Using genetic proxies for 25(OH)D levels effectively addresses major limitations of observational studies. The random allocation of genotypes minimizes confounding, and the fixed nature of genetics eliminates reverse causality. Identifying specific SNPs in biologically relevant genes (*DHCR7*, *CYP2R1*, *VDR*) further supports the causal argument by directly linking genetic influences on VD metabolism to liver cancer risk [31,33,35].

Biological plausibility is strong, with extensive in vitro and animal model data showing that the VD/VDR axis acts as a tumor suppressor pathway in the liver [39,41,45]. These mechanisms align with cancer hallmarks, including sustained proliferation, evasion of growth suppression, and angiogenesis.

However, several considerations and future directions remain. First, while MR suggests causality, it does not quantify the effect size of lifelong genetic elevation in 25(OH)D, which may differ from supplementation effects in adulthood. Second, potential pleiotropy—where genetic instruments affect liver cancer risk through pathways independent of 25(OH)D—cannot be entirely excluded, though methods like MR-Egger regression can help detect and adjust for this [47]. Third, the relationship may be modified by the underlying liver environment; VD's protective effect might be stronger in specific contexts like NAFLD or viral hepatitis [25,48].

The most critical next step is conducting large-scale, well-designed randomized controlled trials to test whether VD supplementation reduces liver cancer incidence in high-risk populations, such as patients with compensated cirrhosis. Previous RCTs on VD supplementation for cancer prevention have shown mixed results, often lacking power for site-specific cancers like HCC [49,50]. Future trials should consider baseline VD status, genetic background, and liver disease etiology in their design.

From a public health perspective, maintaining adequate VD status through sensible sun exposure, diet, or supplementation is a low-cost, safe intervention with potential benefits beyond bone health. While awaiting definitive trial data, monitoring and correcting severe VD deficiency in patients with chronic liver disease is a prudent clinical practice.

Conclusion

In summary, evidence, particularly from Mendelian randomization studies, strongly supports a causal inverse relationship between serum 25-hydroxyvitamin D levels and liver cancer risk. Genetic research has not only strengthened causal inference but also highlighted

key genes in the vitamin D pathway that modulate this risk. Extensive biological data on VD's anti-proliferative, pro-apoptotic, and anti-inflammatory actions provide a solid mechanistic basis for these observations. While further research, especially intervention trials, is needed to translate findings into clinical practice, current evidence positions vitamin D sufficiency as a promising modifiable factor in the primary prevention of hepatocellular carcinoma.

Acknowledgment

The authors would like to express their appreciation to all those who helped us conduct this research.

Funding

None

Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
2. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Hepatology. 2021;73 Suppl 1(Suppl 1):4-13.
3. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology. 2019;156(2):477-491.e1.
4. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.
5. Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol. 2019;16(10):589-604.
6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
7. Marengo A, Rosso C, Bugianesi E. Liver Cancer: Connections with Obesity, Fatty Liver, and Cirrhosis. Annu Rev Med. 2016;67:103-117.
8. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women Have a Lower Risk of Nonalcoholic Fatty Liver Disease but a Higher Risk of Progression to Fibrosis: A Large Multicenter Study. Clin Gastroenterol Hepatol. 2023;21(4):1080-1088.e13.
9. Feldman D, Krishnan AV, Swami S, et al. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014;14(5):342-357.
10. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exp Mol Med. 2018;50(4):1-14.
11. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007;7(9):684-700.
12. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol. 2009;19(2):73-78.
13. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ. 2019;366:l4673.
14. Chandler PD, Chen WY, Ajala ON, et al. Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. JAMA Netw Open. 2020;3(11):e2025850.
15. Lai JC, Bikle DD, Lizaola B, et al. Total 25(OH) vitamin D, free 25(OH) vitamin D and markers of bone turnover in cirrhotics with and without synthetic dysfunction. Liver Int. 2015;35(9):2294-2300.
16. Stokes CS, Volmer DA, Grünhage F, et al. Vitamin D in chronic liver disease. Liver Int. 2013;33(3):338-352.
17. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014;2(1):76-89.
18. Manson JE, Bassuk SS. Vitamin D research and clinical practice: at a crossroads. JAMA. 2015;313(13):1311-1312.
19. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?. Int J Epidemiol. 2003;32(1):1-22.
20. Lawlor DA, Harbord RM, Sterne JA, et al. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133-1163.
21. Jiang X, O'Reilly PF, Aschard H, et al. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat Commun. 2018;9(1):260.
22. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010;376(9736):180-188.

23. Mi Y, Liu J, Zhang D. Association between serum vitamin D levels and the risk of liver cancer: a systematic review and meta-analysis. Nutr Cancer. 2021;73(7):1105-1113.
24. Fedirko V, Duarte-Salles T, Bamia C, et al. Prediagnostic circulating vitamin D levels and risk of hepatocellular carcinoma in European populations: a nested case-control study. Hepatology. 2014;60(4):1222-1230.
25. Chiang KC, Yeh CN, Chen MF, Chen TC. Hepatocellular carcinoma and vitamin D: a review. J Gastroenterol Hepatol. 2011;26(11):1597-1603.
26. Abnet CC, Chen Y, Chow WH, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol. 2010;172(1):94-106.
27. Yuan S, Larsson SC. Association of genetically predicted serum 25-hydroxyvitamin D status with liver cancer incidence and mortality. Am J Clin Nutr. 2022;116(1):63-68.
28. Zhang X, Guan L, Tian H, et al. Genetic predisposition to low vitamin D and risk of liver cancer: A Mendelian randomization study. J Nutr. 2023;153(4):1023-1030.
29. Geng T, Li L, Chen Z, et al. Causal Relationship Between Serum 25-Hydroxyvitamin D Levels and Liver Cancer: A Mendelian Randomization Study. Front Nutr. 2022;9:888089.
30. Wang N, Wang C, Chen X, et al. Vitamin D and cause-specific liver disease: a Mendelian randomization study. Hepatol Int. 2023;17(2):386-395.
31. Ahn J, Yu K, Stolzenberg-Solomon R, et al. Genome-wide association study of circulating vitamin D levels. Hum Mol Genet. 2010;19(13):2739-2745.
32. O'Brien KM, Sandler DP, Shi M, et al. Vitamin D and DNA methylation: a genome-wide analysis. Prev Med. 2017;99:247-256.
33. Ramos-Lopez E, Brück P, Jansen T, et al. CYP2R1 (vitamin D 25-hydroxylase) gene variants in primary biliary cirrhosis. Exp Clin Endocrinol Diabetes. 2008;116(3):154-159.
34. Thacher TD, Fischer PR, Singh RJ, et al. CYP2R1 mutations impairing vitamin D 25-hydroxylation cause vitamin D dependency rickets type 1B. J Bone Miner Res. 2015;30(2):193-199.
35. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006;371(1-2):1-12.
36. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K. Contribution of VDR polymorphisms to type 1 diabetes susceptibility: Systematic review of case-control studies and meta-analysis. J Steroid Biochem Mol Biol. 2014;143:240-249.
37. Nissen J, Rasmussen LB, Ravn-Haren G, et al. Common variants in CYP24A1 and DBPs are associated with circulating 25-hydroxyvitamin D concentrations. J Steroid Biochem Mol Biol. 2014;144 Pt A:207-214.
38. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis. 2009;30(5):769-776.
39. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol. 2012;57(4):897-909.
40. Sherman MH, Yu RT, Engle DD, et al. Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. Cell. 2014;159(1):80-93.
41. Bao A, Li Y, Tong Y, et al. Tumor-suppressive effect of vitamin D receptor in hepatocellular carcinoma. Acta Biochim Biophys Sin (Shanghai). 2021;53(10):1337-1347.
42. Zhang X, Jiang F, Li P, et al. 1,25-dihydroxyvitamin D3 inhibits the proliferation of hepatic stellate cells by downregulating the TGF-β/Smad signaling pathway. Mol Med Rep. 2015;12(3):3897-3903.
43. Kong M, Zhu L, Bai L, et al. Vitamin D deficiency promotes nonalcoholic steatohepatitis through impaired enterohepatic circulation in animal model. Am J Physiol Gastrointest Liver Physiol. 2014;307(9):G883-G893.
44. Gorman S, Judge MA, Hart PH. Immune-modifying properties of topical vitamin D: Focus on dendritic cells and T cells. J Steroid Biochem Mol Biol. 2010;121(1-2):247-249.
45. Mantell DJ, Owens PE, Bundred NJ, et al. 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. Circ Res. 2000;87(3):214-220.
46. Chung I, Han G, Seshadri M, et al. Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis in vivo. Cancer Res. 2009;69(3):967-975.
47. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512-525.
48. Barchetta I, Cimini FA, Cavallo MG. Vitamin D and Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD): An Update. Nutrients. 2020;12(11):3302.
49. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019;380(1):33-44.
50. Scragg R, Khaw KT, Toop L, et al. Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the Vitamin D Assessment randomized clinical trial. JAMA Oncol. 2018;4(11):e182178.