Routledge
Taylor & Francis Group

Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

Serum Vitamin D Levels and Risk of Liver Cancer: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies

Yonggui Zhang , Xuefeng Jiang , Xiangjun Li , Mihnea-Alexandru Găman , Hamed Kord-Varkaneh , Jamal Rahmani , Ammar Salehi-Sahlabadi , Andrew S Day & Yan Xu

To cite this article: Yonggui Zhang , Xuefeng Jiang , Xiangjun Li , Mihnea-Alexandru Găman , Hamed Kord-Varkaneh , Jamal Rahmani , Ammar Salehi-Sahlabadi , Andrew S Day & Yan Xu (2020): Serum Vitamin D Levels and Risk of Liver Cancer: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies, Nutrition and Cancer, DOI: 10.1080/01635581.2020.1797127

To link to this article: https://doi.org/10.1080/01635581.2020.1797127

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2020.1797127

Taylor & Francis
Taylor & Francis Group

REVIEW

Serum Vitamin D Levels and Risk of Liver Cancer: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies

Yonggui Zhang[a], Xuefeng Jiang[a], Xiangjun Li[b], Mihnea-Alexandru Găman[c,f], Hamed Kord-Varkaneh[d], Jamal Rahmani[d], Ammar Salehi-Sahlabadi[d], Andrew S Day[e], and Yan Xu[a]

[a]Department of Gastroenterology, China-Japan Union Hospital of Jilin University, Changchun, China; [b]Department of Experimental Pharmacology and Toxicology, School of Pharmaceutical Science, Jilin University, Changchun, China; [c]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [d]Department of Clinical Nutrition and Dietetics, Student Research Committee, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [e]Department of Paediatrics, University of Otago, Christchurch, New Zealand; [f]Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania

ABSTRACT

Data regarding the relationship between serum vitamin D levels and the risk of liver cancer are conflicting. Therefore, we performed a systematic review and dose–response meta-analysis of all available data of cohort studies on the association of 25-OH-vitamin-D levels with the risk of hepatocellular carcinoma. We conducted a systematic search in PubMed-MEDLINE, Scopus, Cochrane and Web of Science databases for prospective observational studies conducted on the general population from inception to May 2019. Six studies provided data from 6357 participants. According to the pooled HR, the subjects with the highest serum concentrations of vitamin D had a 47% lower risk of liver cancer *vs.* the subjects with the lowest serum concentrations of vitamin D (pooled HR: 0.53, 95% CI: 0.41–0.68; $P < 0.001$). There was no significant heterogeneity among the studies ($P = 0.431$, $I^2 = 0.0$). The pooled HR from the random-effects dose-response model indicated an indirect significant linear association between vitamin D and the risk of liver cancer (coef = −0.017, $P < 0.001$). However, there was no significant nonlinear dose-response association between serum vitamin D and the risk of liver cancer (coef = −0.0001, $P = 0.342$). The evidence from this meta-analysis suggests that there may be an inverse relationship between serum vitamin D levels and the risk of liver cancer.

ARTICLE HISTORY
Received 13 December 2019
Accepted 23 June 2020

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer (1) and the third leading cause of death attributed to cancer worldwide (2). The predominant risk factor for HCC development is cirrhosis which is a result of chronic viral hepatitis, obesity, steatosis, diabetes mellitus and/or alcohol abuse (3–6). The cumulative risk for HCC development is 5 to 30% within 5 years in patients with cirrhosis (1). HCC is often diagnosed in an advanced stage. Curative HCC treatment is only available in the early stages of the disease, when there is a preserved liver function, and involves surgical resection and liver transplantation (7,8). However, there is no curative treatment option for the intermediate or severe HCC stages (9).

Studies have shown that vitamin D deficiency can contribute to carcinogenesis and influence the course of several infectious diseases, including those affecting the liver (10–13). Furthermore, vitamin D has multiple functions in the human body and presents anti-proliferative, pro-apoptotic, differentiating, anti-angiogenic and anti-invasive effects which can be of aid in cancer prevention (14). The biosynthesis of active vitamin D occurs in the liver (hydroxylation to 25-OH-vitamin-D). Vitamin D levels in the body can be measured by dosing serum 25-OH-vitamin-D (15) which is a crucial modulator of bone growth and remodeling (16).

Inverse correlations have been reported between serum vitamin D values and the levels of systemic inflammation in the body (17). This might be related to the fact that vitamin D levels inversely correlate with the expression of Toll-like receptors in monocytes (17). Patients with HCC have an increased incidence of 25-OH-vitamin-D deficiency which

CONTACT Yan Xu zrlxuyan@sina.com Department of Gastroenterology, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China.
Supplemental data for this article can be accessed at https://doi.org/10.1080/01635581.2020.1797127.

corresponds to the severity of the liver dysfunction present in these patients (18). Studies have shown that tumor cell growth can be inhibited by increasing the expression of vitamin D receptors (19) or by the direct use of vitamin D or of its analogues on HCC cell lines (20). Recent prospective studies have reported a significant association between reduced levels of serum vitamin D and an increased risk of liver cancer (21–24). However, this association is not universally recognized (25). Aside from genetic and epidemiological studies, there is no available meta-analysis to clarify this issue. Therefore, we performed a systematic review and dose–response meta-analysis of all available data from cohort studies on the association of 25-OH-vitamin-D levels with the risk of HCC.

Materials and Methods

Search Strategy

A literature search of prospective cohort studies examining the relationship between serum vitamin D levels and risk of liver cancer was performed in PubMed/MEDLINE, Scopus, Cochrane and Web of Science databases from inception to May 2019. Search strings of "vitamin D" AND "liver cancer" without restrictions were used to retrieve articles from related databases. Details of the search strategy are provided in Supplementary Table 1. In addition, an e-mail alert service was activated to discover new articles. The reference lists of the selected original papers were also scrutinized. This systematic review and meta-analysis was constructed according to the Meta-analysis Of Observational Studies in Epidemiology guidelines (MOOSE) (26).

Inclusion Criteria

Studies were eligible for inclusion if they met the following criteria: 1) authors reported the association between vitamin D levels and liver cancer; 2) the papers used a prospective cohort study design; 3) the studies investigated appropriate estimates such as the hazard ratio (HR), risk ratio (RR), or odd ratio (OR) and the corresponding 95% confidence intervals (CI) were reported; or if the studies presented data required for deriving these results. Studies were excluded if they involved subjects from the general population diagnosed with cancer or if they were editorials, review papers, non-human studies, In Vitro research, case reports, ecological studies, or letters without adequate data.

Data Extraction and Quality Assessment

Two independent authors (AS and HKV) screened the studies based on the inclusion criteria by title and abstract. The full-texts of the selected studies were evaluated for inclusion using the mark specific criteria. Disagreements were resolved through conversation with a third author (AH). Two review authors (AS and HKV) independently extracted the relevant information. Data about the authors, study location, year of publication, study design, cohort name, age, gender, number of participants, follow-up duration, confounding factors, summary estimates and 95% CIs of liver cancer incidence were extracted from the included articles. Data from fully adjusted models with different exposure categorizations where presented were used for the meta-analysis. The quality of all the eligible studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS). The studies were divided into "low quality" (scores of 0-6) and "high quality" (scores of 6.5-9) (27).

Statistical Analysis

The DerSimonian and Laird random-effects model was used to synthesize risk estimates of liver cancer incidence (28). Risk estimates were calculated assuming the lower category as the reference category. When authors did not report this data, the median or mean in each vitamin D category was used as the reference category. Between-study heterogeneity was assessed using the Cochran's Q test and I^2 statistic. The significance level for heterogeneity was set at alpha $P < 0.1$. Potential curvilinear association between vitamin D and risk of liver cancer was estimated using restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of the distribution (29). We performed the linearity curve of the meta-analysis by examination of the null hypothesis that the coefficient of the second spline was equal to zero. $P < 0.05$ was considered as statistically significant. The most common methods used to identify publication bias in meta-analyses, such as funnel plots, Egger's test and Begg's test, were used. All statistical analyses were conducted using the STATA 14.0 (Stata 14.0 Statistical Software, College Station, TX, USA) statistical software.

Results

Literature Search

A flow diagram of the study selection process is shown in Supplementary Figure 1. The results of the

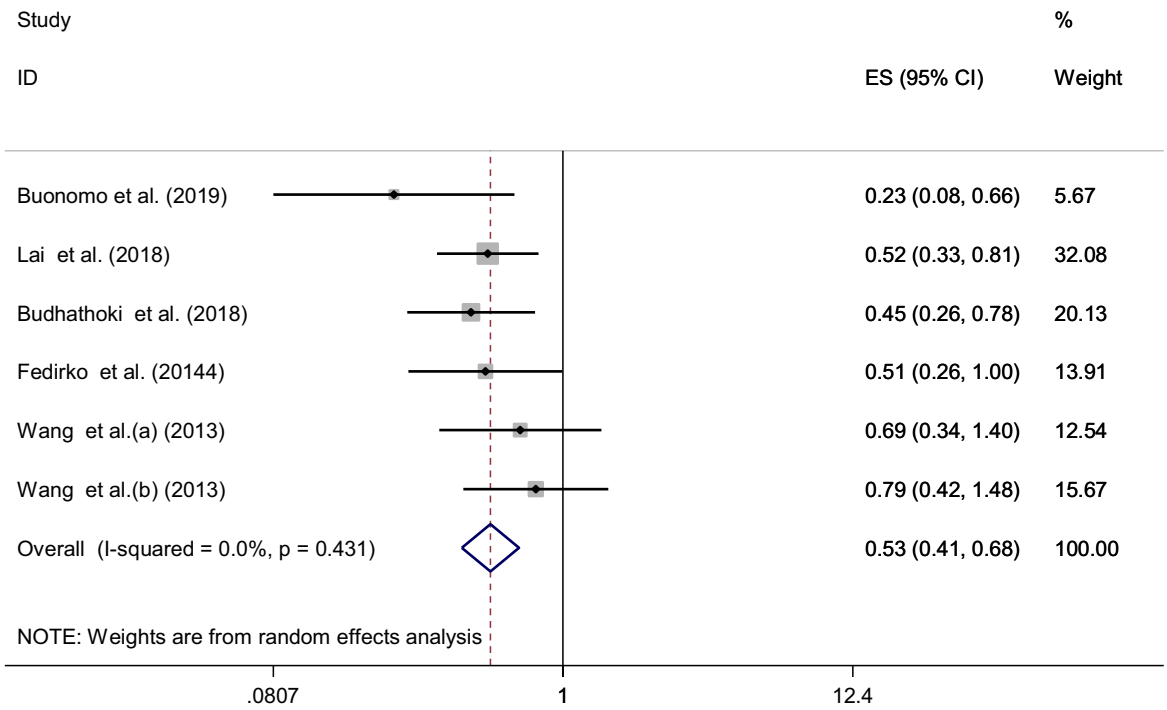

Figure 1. The forest plot of the highest category of vitamin D vs. the lower category of vitamin D and risk of liver cancer.

systematic search strategy yielded 156 records. 56 duplicates and 136 irrelevant articles were excluded after title and abstract screening. After full-text examination, 15 studies were excluded because they did not meet the inclusion criteria. Five articles with six studies were eligible for inclusion (21–25).

Study Characteristics and Quality Assessment

The characteristics of the population are provided in Table 1. Three studies were conducted in Europe (21,22,24) and three in Asia (23,25). Studies were published between 2013 and 2018. The mean age of the participants was 57.83 years and the mean duration of the follow-up was 17 years. Two studies involved men only (22,25), one study involved women only (25) and three studies included participants from both genders (21,23,24). The participants included in these studies did not have a prior diagnosis of liver cancer at baseline. All the studies were of high quality with NOS scores ranging from 7 to 9 (Supplementary Table 2). Four studies had a score of 9 (22–25) and one had a score of 7 (21). Case and control groups were selected from the same community. Serum 25-OH-vitamin D levels were measured in all studies.

Main Results of the Meta-Analysis

Six studies provided data from 6357 participants (21–25). According to the pooled HR (95% CI), the subjects with the highest serum concentrations of vitamin D had a 47% lower risk of liver cancer *vs.* the subjects with the lowest serum concentrations of vitamin D (pooled HR: 0.53, 95% CI: 0.41-0.68; $P < 0.001$) (Figure 1). There was no significant heterogeneity among the included studies ($P = 0.431$, $I^2 = 0.0$).

Dose-Response Analysis

The dose-response relationship between serum vitamin D levels and the risk of liver cancer was explored. The pooled HR from the random-effects dose-response model indicated a significant indirect linear association between serum vitamin D levels and the risk of liver cancer (coef $= -0.017$, $P < 0.001$) (Figure 2). However, there was no significant non-linear dose-response association between vitamin D levels and the risk of liver cancer (coef -0.0001, $P = 0.342$) (Figure 3).

Publication Bias and Sensitivity Analyses

The funnel plots of liver cancer incidence are shown in Figure 4. There was no significant publication bias among the studies. The Begg's test was not significant for the risk of liver cancer ($P = 0.523$). The Egger's regression test was also not significant for the risk of liver cancer ($P = 0.573$). According to the sensitivity analysis, the exclusion of a single study did not lead to a change in the overall result (Supplementary Figure 2).

Table 1. Baseline characteristics of included studies in the meta-analysis.

Studies	Author	Year	Country	Follow-up duration	Gender (1-women, 2-men, 3-both)	Patients, n	Cohort name	Age at baseline
1	Buonomo et al. (21)	2018	Italy	9 months	3	345	–	68
2	Lai et al. (22)	2018	Finland	25 years	2	629	**ATBC**	57
3	Budhathoki et al. (23)	2015	Japan	15.9 years	3	4044	Japan Public Health Center-based	53
4	Fedirko et al. (24)	2015	European countries	18 years	3	276	EPIC	59
5	Wang et al.(a) (25)	2013	China	22 years	1	490	Linxian Nutrition Intervention Trials	55
6	Wang et al.(b) (25)	2013	China	22 years	2	573	Linxian Nutrition Intervention Trials	55

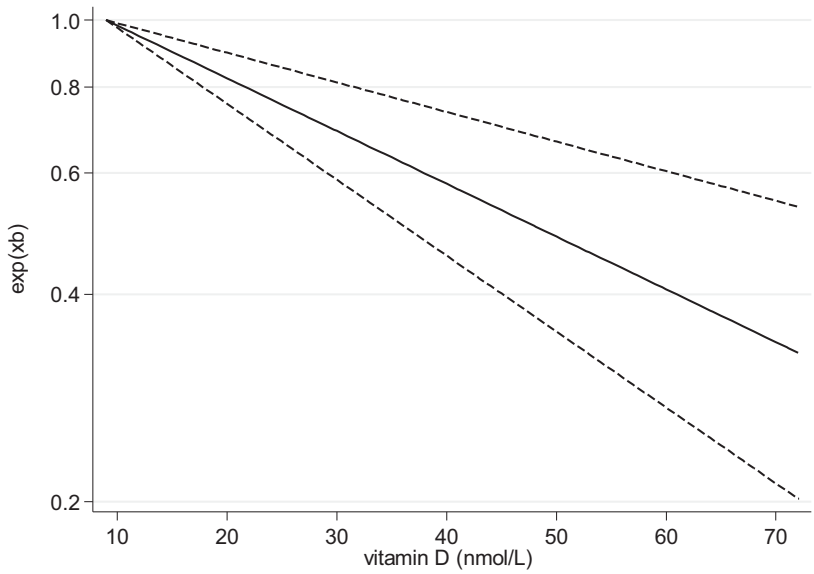

Figure 2. Linear dose-response relationship between serum vitamin D and risk of liver cancer.

Discussion

The overarching aim of this systematic review and dose-response meta-analysis of cohort studies was to investigate the association between serum vitamin D levels and the risk of liver cancer. This meta-analysis found a significant, direct association between low serum vitamin D levels and the risk of liver cancer.

According to the American Cancer Society, an estimate of 42,030 patients will be diagnosed with liver cancer, and 31,780 will succumb to the disease in the United States in 2019 (30). Hepatocellular carcinoma will account for 75% of these reported cases (30). The incidence and mortality of liver cancer has increased worldwide, with a 3% increase per year in incidence during the 2005-2016 period and a 2.4% increase per year in mortality during the 2007-2016 period (30). Since the 1980s, the incidence rate has tripled and the mortality rate has doubled (30). In both sexes, liver cancer has had the most rapid increase in incidence of all diagnosed cancers (30).

Hepatocellular carcinoma is the most common form of liver cancer encountered in clinical practice and risk factors for this neoplasm include: age, chronic viral infections (hepatitis B or hepatitis C, HCV-HIV co-infection), male gender, genetic factors, exposure to aflatoxin B_1, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, alcohol consumption, smoking, obesity, type 2 diabetes mellitus, metabolic syndrome, a previous diagnosis of renal cell carcinoma or Non-Hodgkin's lymphoma in the liver, and hereditary hemochromatosis (30–36). Prevention is of utmost importance, with preventive strategies including vaccination against HBV infection, reducing alcohol intake and body mass index, smoking cessation, adoption of healthy dietary habits (30–34). The signs and symptoms of liver cancer are generally non-specific (abdominal pain, jaundice, loss of appetite, weight loss or liver enlargement) and may only be present in the advanced stages of the disease, making this neoplasm a silent killer. Treatment options include surgery in early stages of the disease, liver transplantation, embolization, tumor ablation, and, for advanced stages of the disease, chemotherapy and/or immunotherapy (30,33).

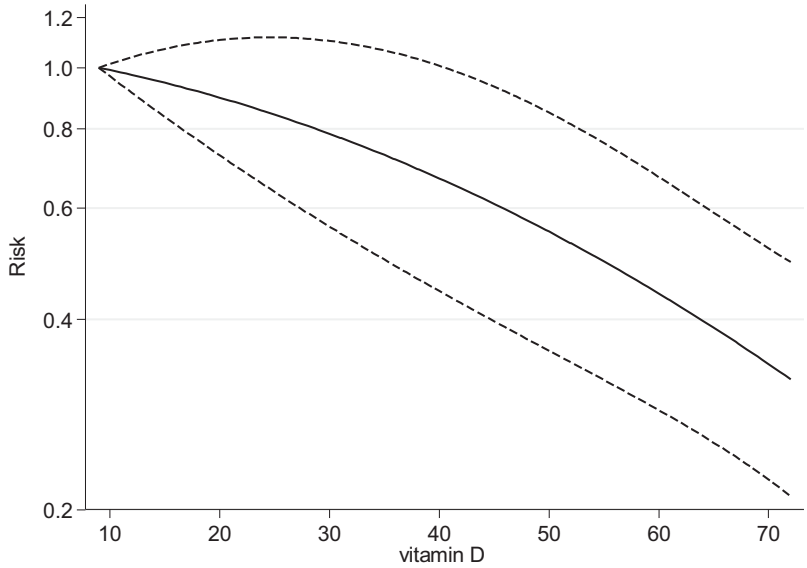

Figure 3. Non-liner dose-response relationship between serum vitamin D and risk of liver cancer.

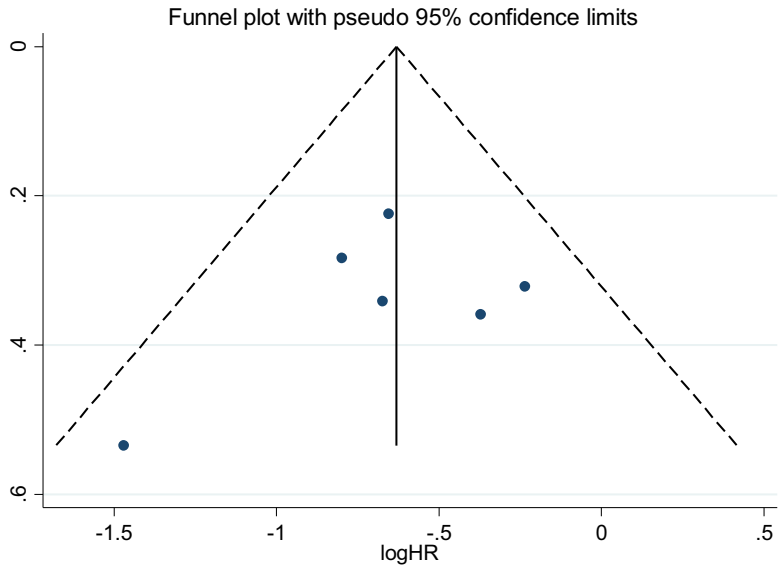

Figure 4. Funnel plot (with pseudo 95% CIs) of the log hazard ratio (HR) vs. the s.e. of the log hazard ratio (HR) for studies that investigated the liver cancer HR of participates in highest serum vitamin D compered to lowest.

The 5-year survival rate for localized stage disease is 31% and the relative 5-year survival rate is 18% (30). Thus, identifying and addressing risk factors is an important step in the prevention of liver cancer development. The results of the current meta-analysis show a direct association between low levels of serum vitamin D and the risk of liver cancer. Recent empiric studies have shown that vitamin D does not only play a key role in calcium and bone metabolism, but also possesses anti-inflammatory, immuno-modulatory, cardioprotective, antidiabetic, antimicrobial, antiapoptotic, antiproliferative, antimetastatic, antiangiogenic and antineoplastic properties (37–40).

Vitamin D deficiency or insufficiency has been widely associated with chronic liver disorders, such as viral hepatitis, alcoholic liver disease, liver cancer, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver fibrosis, cirrhosis and also autoimmune diseases of the liver (37,38,41). In both hepatocellular and cholangiocarcinoma, the high expression of the cytochrome P450 family 24 subfamily A member 1 gene (CYP24A1) resulted in a decrease in vitamin D levels and potentiated the proliferation of neoplastic cells, an effect which may be reversed when liver cancer cell lines are exposed to vitamin D (37,40,42,43).

In a recent study regarding the levels of circulating vitamin D and risk of total and site-specific neoplasms, Budhathoki et al. (39) reported an inverse association between vitamin D levels and the risk of cancer. Regarding site-specific malignancies, their report shows a strong association exists between vitamin D levels and the risk of liver cancer in Japanese patients. Results from The European Prospective Investigation into Cancer and Nutrition (EPIC) study have also confirmed this hypothesis: for a 10-nmol/L decrease in vitamin D levels, a 20% elevation in the risk of hepatocellular carcinoma was registered (40,44).

Vitamin D levels are also known to negatively correlate with the stages of hepatocellular carcinoma, with vitamin D deficiency also associated with mortality in patients with cirrhosis, with and without hepatocellular carcinoma (21,45). Gomes et al. (46) also reported a higher percentage of liver disorders ($P = 0.001$) and cancer ($P = 0.017$) among patients with vitamin D levels <12 ng/mL admitted to the intensive care unit, where, of the 71 patients involved, only 8.4% ($n = 6$) did not have vitamin D deficiency (vitamin D levels equal or >30 ng/mL) and 91.6% ($n = 65$) of the patients were diagnosed with vitamin D deficiency, with mean serum concentrations of vitamin D reported at 17.7 ± 8.27 (range 3.5–37.5) ng/mL.

Moreover, the vitamin D receptor is also involved in the normal physiology of the liver and, when affected, facilitates carcinogenesis. Its interaction with the retinoid X receptor, which is enhanced by sequestosome 1 (SQSTM1; also called nucleoporin p62 or simply p62), is involved in the prevention of liver cancer development. Its antineoplastic activity derives from its power to inhibit the activity of hepatic stellate cells and prevent liver fibrosis (47).

Hepatic stellate cells, in which the activity of p62 is reduced, are key players in the development of hepatocellular carcinoma (47). Loss of p62 in these cells, as demonstrated by Duran et al. (47), is responsible for a decreased interaction between the vitamin D receptor, highly expressed in hepatic stellate cells, and the retinoid X receptor which favors inflammation and fibrosis in the liver. Low-grade chronic inflammation has also been held accountable as a contributing factor to cancer development and hepatocellular carcinoma is no exception (40,47–49). Moreover, the crosstalk between the vitamin D receptor and the risk factors for developing hepatocellular carcinoma must to be taken into consideration as well. Barooah et al. (50) reported that, in patients with hepatitis C virus infection and hepatocellular carcinoma, there is an association between the development and severity of liver cancer and the presence of the bAt haplotype of the vitamin D receptor gene, as well as the vitamin D receptor ApaI CC genotype. However, they did not find an association between hepatocellular carcinoma and CYP2R1 or carrier globulin/binding protein gene polymorphisms (50).

The hepatitis B virus also interacts with the vitamin D receptor, as shown by Gotlieb et al. (51) in a study conducted on HepG2 (hepatoma) and HepG.2.215 (HBV-infected hepatoma cells) cell lines (51). In hepatoma cells that were also HBV-infected, the expression of the vitamin D receptor was reportedly downregulated, and thus, the antiviral and immune functions of vitamin D (*via* stimulation of the expression of tumor necrosis factor α and antimicrobial host defense peptides) on HBV transcription and production was prevented. The findings of Gotleib et al. (51) might help elucidate the mechanisms exploited by the HBV virus to escape the immune system.

In spite of the promising results collected from preclinical studies regarding the myriad of effects of vitamin D, there remains equivocality regarding vitamin D supplementation in cancer patients. The Clinical Practice Guidelines of The Endocrine Society on the Evaluation, Treatment and Prevention of Vitamin D Deficiency (52), published in 2011, recommend the use of vitamin D supplementation only in patients with malabsorption or diagnosed with liver failure. With regard to screening, patients with liver disorders (either chronic or in severe stages) should be screened for deficiency in vitamin D levels and, if these levels are abnormal, vitamin D levels should be corrected until a healthy bone metabolism is guaranteed (49,52,53).

In preclinical models, Chen et al. (54) have evidenced that vitamin D deprivation is linked to a dysfunctional TGF-β pathway which in turn is associated with liver fibrogenesis and carcinogenesis. In human liver tissue affected by fibrosis/cirrhosis, low levels of vitamin D were associated with aberrant Smad3 signaling and activation of β-catenin. Vitamin D supplementation had opposite effects: it decreased β-catenin levels and restored the expression of TGF-β (54).

Limitations

Although the evidence from our meta-analysis suggests that there may be an inverse relationship between serum levels of vitamin D and the risk of liver cancer, further studies are needed to clarify this relationship. At this moment, it is premature to hypothesize that vitamin D supplementation might protect against the development of hepatic malignancies.

Conclusion

The evidence from this meta-analysis suggests that there may be an inverse relationship between vitamin D deficiency and risk of liver cancer. Prospectively, vitamin D may conceivably be useful as a therapeutic agent directed against liver cancer and other malignancies, however, further research of high-quality is evidently necessitated.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions to Manuscript

YZ and YX designed and conducted the research; XJ, XL and MG screened and extracted articles data; HK_V and JR executed statistical analysis; YZ, AS-S and ASD wrote the paper; YX and YZ had primary responsibility for final content. All authors read and approved the final manuscript.

References

1. El-Serag H. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118–1127. doi:10.1056/NEJMra1001683
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, et al. Cancer incidence and mortality worldwide: IARC CancerBase.11. Lyon (France): International Agency for Research on Cancer; 2012.
3. Dyal HK, Aguilar M, Bartos G, Holt EW, Bhuket T, Liu B, Cheung R, Wong RJ. Diabetes mellitus increases risk of hepatocellular carcinoma in chronic hepatitis C virus patients: a systematic review. Dig Dis Sci. 2016;61(2):636–645. doi:10.1007/s10620-015-3983-3
4. Hagström H, Tynelius P, Rasmussen F. High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. Gut. 2018; 67(8):1536–1542. doi:10.1136/gutjnl-2016-313622
5. Younes R, Bugianesi E. Should we undertake surveillance for HCC in patients with NAFLD? J Hepatol. 2018;68(2):326–334. doi:10.1016/j.jhep.2017.10.006
6. Suh B, Yun JM, Park S, Shin DW, Lee TH, Yang H-K, Ahn E, Lee H, Park JH, Cho B, et al. Prediction of future hepatocellular carcinoma incidence in moderate to heavy alcohol drinkers with the FIB-4 liver fibrosis index. Cancer. 2015;121(21):3818–3825. doi:10.1002/cncr.29577
7. Hepatology E. EASL–EORTC clinical practice guidelines: management of Hepatocellular Carcinoma. J Hepatol. 2012;56(4):908–943.
8. Sacco R, Gadaleta-Caldarola G, Galati G, Lombardi G, Mazza G, Cabibbo G. EASL HCC summit: liver cancer management. Future Oncol. 2014;10(7): 1129–1132. doi:10.2217/fon.14.68
9. Finkelmeier F, Kronenberger B, Köberle V, Bojunga J, Zeuzem S, Trojan J, Piiper A, Waidmann O. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma - a prospective cohort study . Aliment Pharmacol Ther. 2014;39(10):1204–1212. doi:10.1111/apt.12731
10. Manco M, Ciampalini P, Nobili V. Low levels of 25-hydroxyvitamin D3 in children with biopsy-proven nonalcoholic fatty liver disease. Hepatology. 2010; 51(6):2229. doi:10.1002/hep.23724
11. Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metabol Cardiovasc Dis. 2007;17(7):517–524. doi:10.1016/j.numecd.2006.04.002
12. Barchetta I, Angelico F, Del Ben M, Baroni MG, Pozzilli P, et al. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25 (OH) vitamin D levels in an adult population with normal serum liver enzymes. BMC Med. 2011;9(1):85.
13. Petta S, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology. 2010;51(4):1158–1167. doi:10.1002/hep.23489
14. Vanoirbeek E, Krishnan A, Eelen G, Verlinden L, Bouillon R, Feldman D, Verstuyf A. The anti-cancer and anti-inflammatory actions of $1,25(OH)_2D_3$. Best Pract Res Clin Endocrinol Metab. 2011;25(4):593–604. doi:10.1016/j.beem.2011.05.001
15. Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int. 2013; 33(3):338–352. doi:10.1111/liv.12106
16. Plum LA, DeLuca H. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov. 2010; 9(12):941–955. doi:10.1038/nrd3318
17. Kitson MT, Roberts S. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol. 2012;57(4):897–909. doi:10.1016/j.jhep.2012.04.033
18. Arteh J, Narra S, Nair S. sciences. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci. 2010;55(9):2624–2628. doi:10.1007/s10620-009-1069-9
19. Li Q, Gao Y, Jia Z, Mishra L, Guo K, Li Z, Le X, Wei D, Huang S, Xie K, et al. Dysregulated Krüppel-like factor 4 and vitamin D receptor signaling contribute to progression of hepatocellular carcinoma. Gastroenterology. 2012;143(3):799–810. e2. doi:10.1053/j.gastro.2012.05.043
20. Chiang KC, Yeh CN, Chen MF, Chen T. Hepatocellular carcinoma and vitamin D: a review. J Gastroenterol Hepatol. 2011;26(11):1597–1603. doi:10.1111/j.1440-1746.2011.06892.x
21. Buonomo AR, Scotto R, Zappulo E, Nerilli M, Pinchera B, Perruolo G, Formisano P, Nappa S, Gentile I. Severe vitamin D deficiency increases mortality among patients with liver cirrhosis regardless of the presence of HCC. In Vivo. 2019;33(1):177–182. doi:10.21873/invivo.11456
22. Lai GY, Wang J-B, Weinstein SJ, Parisi D, Horst RL, McGlynn KA, Männistö S, Albanes D, Freedman ND. Association of 25-hydroxyvitamin D with liver cancer

incidence and chronic liver disease mortality in finnish male smokers of the ATBC study. Cancer Epidemiol Biomarkers Prev. 2018;27(9):1075–1082. doi:10.1158/1055-9965.EPI-17-0877
23. Budhathoki S, Hidaka A, Yamaji T, Sawada N, Tanaka-Mizuno S, et al. Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site specific cancers in Japanese population: large case-cohort study within Japan Public Health Center-based Prospective Study cohort. BMJ (Online). 2018;360:k671.
24. Fedirko V, Duarte-Salles T, Bamia C, Trichopoulou A, Aleksandrova K, Trichopoulos D, Trepo E, Tjønneland A, Olsen A, Overvad K, et al. Prediagnostic circulating vitamin D levels and risk of hepatocellular carcinoma in European populations: a nested case-control study. Hepatology (Baltimore, MD). 2014;60(4):1222–1230. doi:10.1002/hep.27079
25. Wang J-B, Abnet CC, Chen W, Dawsey SM, Fan J-H, Yin L-Y, Yin J, Major JM, Taylor PR, Qiao Y-L, et al. Association between serum 25(OH) vitamin D, incident liver cancer and chronic liver disease mortality in the Linxian Nutrition Intervention Trials: a nested case-control study. Br J Cancer. 2013;109(7):1997–2004. doi:10.1038/bjc.2013.546
26. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283(15):2008–2012. doi:10.1001/jama.283.15.2008
27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–605. doi:10.1007/s10654-010-9491-z
28. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. Stat Med. 2010;29(12):1282–1297. doi:10.1002/sim.3602
29. Harre FE, Jr Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst. 1988;80(15):1198–1202. doi:10.1093/jnci/80.15.1198
30. Cancer Facts & Figures. 2019. American Cancer Society 2019. updated 2019/06/04. Available from: https://amp.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html.
31. Ogunwobi OO, Harricharran T, Huaman J, Galuza A, Odumuwagun O, Tan Y, Ma GX, Nguyen MT. Mechanisms of hepatocellular carcinoma progression. World J Gastroenterol. 2019;25(19):2279–2293. [updated May 21PMC6529884]. 2019/06/01:[2279-93]. doi:10.3748/wjg.v25.i19.2279
32. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet (London, England). 2018;391(10127):1301–1314. doi:10.1016/S0140-6736(18)30010-2
33. Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol. 2017;34(2):153–159.
34. Marengo A, Rosso C, Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med. 2016;67:103–117. doi:10.1146/annurev-med-090514-013832
35. Gad MM, Al-Husseini MJ, Saad AM, Bazarbashi N, Al Obaid L. The risk of developing primary hepatocellular carcinoma following renal cell carcinoma; a seer-based study. Gastroenterology. 2019;156 (6):S-769. doi:10.1016/S0016-5085(19)38872-9
36. Chaker M, Saad AM, Al-Husseini MJ, Gad MM, Ruhban IA, Azmi AS. The risk of developing hepatocellular carcinoma following non-Hodgkin lymphoma. J Clin Oncol. 2018;36(15_suppl):e16141–e16141. doi:10.1200/JCO.2018.36.15_suppl.e16141
37. Mahendra A, Karishma BKC, Sharma T, Bansal N, Bansal R, et al. Vitamin D and gastrointestinal cancer. J Lab Phys. 2018;10(1):1. doi:10.4103/JLP.JLP_49_17
38. Khan S, Ali A, Khan S, Bakillah A, Damanhouri G, Khan A, Makki A, AlAnsari I, Banu N. Current therapies in alleviating liver disorders and cancers with a special focus on the potential of vitamin D. Nutr Metab (Lond)). 2018;15:13. doi:10.1186/s12986-018-0251-5
39. Budhathoki S, Hidaka A, Yamaji T, Sawada N, Tanaka-Mizuno S, et al. Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site specific cancers in Japanese population: large case-cohort study within Japan Public Health Center-based Prospective Study cohort. BMJ (Clinical Research ed). 2018;360:k671.
40. Louka ML, Fawzy AM, Naiem AM, Elseknedy MF, Abdelhalim AE, Abdelghany MA. Vitamin D and K signaling pathways in hepatocellular carcinoma. Gene. 2017;629:108–116. doi:10.1016/j.gene.2017.07.074
41. Chen E-Q, Shi Y, Tang H. New insight of vitamin D in chronic liver diseases. Hbpd Int. 2014;13(6):580–585. doi:10.1016/S1499-3872(14)60295-2
42. Kennedy L, Baker K, Hodges K, Graf A, Venter J, Hargrove L, Harris R, Harnish E, Meng F, Francis H, et al. Dysregulation of vitamin D3 synthesis leads to enhanced cholangiocarcinoma growth. Dig Liver Dis. 2013;45(4):316–322. doi:10.1016/j.dld.2012.12.012
43. Mondul AM, Weinstein SJ, Layne TM, Albanes D. Vitamin D and cancer risk and mortality: state of the science, gaps, and challenges. Epidemiol Rev. 2017;39(1):28–48. doi:10.1093/epirev/mxx005
44. Colombo M, Sangiovanni A. Vitamin D deficiency and liver cancer: more than just an epidemiological association? Hepatology. 2014;60(4):1130–1132. doi:10.1002/hep.27178
45. Wu D-B, Wang M-L, Chen E-Q, Tang H. New insights into the role of vitamin D in hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol. 2018;12(3):287–294. doi:10.1080/17474124.2018.1406307
46. Gomes TL, Fernandes RC, Vieira LL, Schincaglia RM, Mota JF, Nóbrega MS, Pichard C, Pimentel GD. Low vitamin D at ICU admission is associated with cancer, infections, acute respiratory insufficiency, and liver failure. Nutrition. 2019;60:235–240. doi:10.1016/j.nut.2018.10.018
47. Duran A, Hernandez ED, Reina-Campos M, Castilla EA, Subramaniam S, Raghunandan S, Roberts LR, Kisseleva T, Karin M, Diaz-Meco MT, et al. p62/SQSTM1 by binding to vitamin D receptor inhibits

hepatic stellate cell activity, fibrosis, and liver cancer. Cancer Cell. 2016;30(4):595–609. doi:10.1016/j.ccell.2016.09.004

48. Berceanu D, Bucur D, Diaconu C. Type 2 diabetes and liver disease: a frequent and harmful connection. Archiv Balkan Med Union. 2016;51(4):506–511.
49. Keane J, Elangovan H, Stokes R, Gunton J. Vitamin D and the liver—correlation or cause? Nutrients. 2018;10(4):496. doi:10.3390/nu10040496
50. Barooah P, Saikia S, Bharadwaj R, Sarmah P, Bhattacharyya M, Goswami B, Medhi S. Role of VDR, GC, and CYP2R1 polymorphisms in the development of hepatocellular carcinoma in hepatitis C virus-infected patients. Genet Test Mol Biomarkers. 2019;23(5):325–331. doi:10.1089/gtmb.2018.0170
51. Gotlieb N, Tachlytski I, Lapidot Y, Sultan M, Safran M, Ben-Ari Z. Hepatitis B virus downregulates vitamin D receptor levels in hepatoma cell lines, thereby preventing vitamin D-dependent inhibition of viral transcription and production. Mol Med. 2018;24(1):53. doi:10.1186/s10020-018-0055-0
52. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–1930. doi:10.1210/jc.2011-0385
53. Scaranti M, de Castro Júnior G, Hoff AO. Vitamin D and cancer: does it really matter? Curr Opin Oncol. 2016;28(3):205–209. doi:10.1097/CCO.0000000000000282
54. Chen J, Katz LH, Muñoz NM, Gu S, Shin J-H, Jogunoori WS, Lee M-H, Belkin MD, Kim S-B, White JC, et al. Vitamin D deficiency promotes liver tumor growth in transforming growth factor-β/Smad3-deficient mice through Wnt and toll-like receptor 7 pathway modulation. Sci Rep. 2016;6:30217. doi:10.1038/srep30217