Vitamin D and gastric cancer: A systematic review and meta-analysis

Xi Zhao (1032075378@qq.com)

Research article

Keywords: Stomach Neoplasm, Vitamin D, Meta-analysis

Posted Date: November 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1067367/v1

Abstract

Object:

To explore the correlation between serum vitamin D level and the occurrence and pathological grade of gastric cancer.

Data sources:

Search the PubMed, Embase, Web of Science, Cochrane,Chinese Journal Full-text Database (CNKI), Wanfang Science and Technology Journal Full-text Database, Chinese Science and Technology Journal Full-text Database (VIP), Chinese Biomedical Literature Database (CBM), All articles about the correlation between serum vitamin D levels and gastric cancer published before July 2021.

Results:

10 trials with 1159 cases of gastric cancer patients and 33387 cases of normal control patients were analyzed. The serum vitamin D level of the gastric cancer group(15.56±7.46ng/ml) was lower than the control group (17.60±1.61ng/ml), and the difference was statistically significant (MD=-8.28, 95%CI: -14.32~-2.23, P <0.00001). The patients with gastric cancer clinical stage III/IV(16.19±8.04ng/ml) is lower than that of patients with stage I/II (19.61±9.61ng/ml), and the patients with low differentiation of gastric cancer is (17.5± 9.5ng/ml) is lower than that of well or moderately differentiated patients (18.04±7.92ng/ml), and the patients with lymph node metastasis (19.41±8.63ng/ml) is lower than that of patients without lymph node metastasis (20.65± 7.96ng/ml), the difference is statistically significant;

Conclusions:

Vitamin D levels are negatively correlated with the occurrence of gastric cancer. Vitamin D levels are significantly correlated with different clinical stages, degrees of differentiation and lymph node metastasis, suggesting that low vitamin D levels may be a predictor of poor prognosis in gastric cancer.

Introduction

Gastric cancer is the fifth most common cancer and the third most common cause of cancer death in the world[1]According to statistics, there were about 1 million newly diagnosed cases of gastric cancer in 2018[2],Approximately 784,000 people died of stomach cancer[1].There are 319,000 newly diagnosed cases of gastric cancer and 390,000 cases died of gastric cancer in China [3].The incidence and mortality of gastric cancer have plummeted in recent years, partly due to wider population screening and increased awareness of the treatment of Helicobacter pylori infection[3].But cancer is still a major health problem in my country. Although interventions have been take to reduce the burden of cancer, the first task is to identify possible risk factors related to cancer risk[4].Therefore, we urgently need predictors of early gastric cancer that are easy to identify, obtain, and improve.

Recently, the role of vitamin D in gastric cancer has been gradually explored. Vitamin D is a precursor of the steroid hormone calcitriol. It mainly binds to vitamin D receptors to regulate gene expression, thereby inhibiting the growth of gastric cancer cells[5, 6].It is known that vitamin D has the effects of inhibiting proliferation, promoting apoptosis, inhibiting inflammation and angiogenesis[6],Recently it has been discovered that it can also overcome the resistance of chemotherapy drugs by reversing or reducing EMT (epithelial-mesenchymal transition) and cancer cell stemness[7].There is currently no human randomized controlled trial to clearly support the beneficial effects of vitamin D, but some clinical research results strongly indicate that vitamin D deficiency will increase the incidence of cancer, and supplement vitamin D may a economical and safe method to reduce the incidence of cancer and improve the prognosis of cancer [8].This study collects relevant clinical studies, conducts systematic reviews and Meta analysis to clarify the correlation between serum vitamin D levels and the occurrence of gastric cancer and different clinicopathological characteristics, and provide relevant evidence for the role of vitamin D in the primary prevention and long-term prognosis of gastric cancer.

1. Methods

1.1 Inclusion and Exclusion criteria

Inclusion criteria: ①All articles related to vitamin D and gastric cancer published before July 2021, the language type is limited to English and Chinese, including cross-sectional studies, case-control studies; ②At least one parameter required by this research can be extracted, Including the serum vitamin D levels of the experimental group and the control group, the serum vitamin D levels of patients with different clinical grades, degrees of differentiation, and distant metastasis; ③hematological indicators of all subjects were collected before radiotherapy, chemotherapy or surgery;

Exclusion criteria: ①Repetitive literature, literature review, graduation thesis, case report, etc.; ②Animal experiments or basic research; ③Documents for which the full text cannot be obtained; ④Documents for which the required data is not available or cannot be obtained; ⑤Do not clearly state the status of vitamin D supplementation before obtaining serological specimens.

1.2 Search strategy

We search database of PubMed, Embase, Web of Science, Cochrane, and chinese database before July 2021. The search terms mainly include: "vitamin D", "gastric cancer", "Stomach Neoplasm", etc. The search languages are limited to Chinese and English. In addition, a manual search was conducted from the references of the subject-related articles to expand the search scope.Take Embase which has the most documents as an example, the search terms are as follows.((((((((((((((((((("Stomach Neoplasm") OR "Neoplasms, Stomach") OR "Gastric Neoplasms") OR "Gastric Neoplasm") OR "Neoplasm, Gastric") OR "Neoplasms, Gastric") OR "Cancer of Stomach") OR "Stomach Cancers") OR "Gastric Cancer") OR "Cancer, Gastric") OR" Cancers, Gastric") OR "Gastric Cancers") OR "Stomach Cancer") OR "Cancer, Stomach') OR" Cancers, Stomach") OR "Cancer of the Stomach") OR "Gastric Cancer, Familial Diffuse")) AND ((((((vitamin

D) OR ((((((Ergocalciferols) OR Calciferols) OR Vitamin D 2) OR Vitamin D2) OR "D2, Vitamin") OR Ergocalciferol)) OR ((((((Cholecalciferol) OR Calciol) OR "(3 beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol) OR Vitamin D 3) OR Vitamin D3) OR Cholecalciferols)) OR ((((((((((((((((((((((((((((((Calcitriol) OR 1 alpha,25-Dihydroxyvitamin D3) OR 1 alpha,25 Dihydroxyvitamin D3") OR "D3, 1 alpha,25-Dihydroxyvitamin") OR "1,25-Dihydroxyvitamin D3") OR "1,25 Dihydroxyvitamin D3") OR" D3, 1,25-Dihydroxyvitamin") OR" 1 alpha,25-Dihydroxycholecalciferol") OR "1,25-Dihydroxycholecalciferol") OR "1,25 Dihydroxycholecalciferol") OR "Bocatriol) OR Calcijex") OR "Calcitriol KyraMed") OR" KyraMed, Calcitriol") OR "Calcitriol-Nefro") OR "Calcitriol Nefro") OR Decostriol) OR "MC1288") OR "MC-1288") OR "MC 1288") OR Osteotriol) OR Renatriol) OR Rocaltrol) OR Silkis) OR Sitriol) OR Soltriol) OR Tirocal) OR '20-epi-1alpha,25-dihydroxycholecaliferol") OR "1,25-dihydroxy-20-epi-Vitamin D3') OR "1,25 dihydroxy 20 epi Vitamin D3") OR" D3, 1,25-dihydroxy-20-epi-Vitamin") OR "1,25(OH)2-20epi-D3") OR "1 alpha, 25-dihydroxy-20-epi-Vitamin D3"))))

1.3 Literature quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the eight case-control studies included. NOS includes 3 aspects, selection, comparability, and exposure or results. The total score is 9 points. The total score of included studies is ≥6 points, which is considered high quality[9].The research scores included in this study are all ≥6 points, and the total average score is 8 points.Evaluation of 2 cross-sectional studies using the cross-sectional study evaluation criteria recommended by the Agency for Healthcare Research and Quality (AHRQ)[10],The full score is 11 points, and the two studies are 9 points[11]and 8 points[12],both of which are high-quality articles. The scoring results are shown in Table1.

1.4 Data collection

According to the inclusion and exclusion criteria, the first author's name, publication time, research location, number of cases and parameters (including patient age and gender, smoking and drinking history, gastric mucosal tissue type, lymph node metastasis, and pathological grading are recorded). The data was independently extracted by the two authors(Zhao X,Wang J), and the differences were resolved through discussion. When the extracted serum vitamin D concentration unit is inconsistent, it is uniformly adjusted to ng/ml.

1.5 Statistical method

The RevMan5.4 provided by the Cochrane Library's official websiteand and Stata 14 statistical software were used for Meta analysis, and the Q statistic test and I^2 test were used to analyze the heterogeneity of the included studies. If there is significant heterogeneity between the studies ($P< 0.1$, $I^2 \geq 50\%$), then analyze the source of heterogeneity. Obvious clinical heterogeneity is processed by subgroup analysis or sensitivity analysis that eliminates each study to determine the potential source of heterogeneity. After excluding the factors that obviously affect the heterogeneity, the combined analysis between the research

results adopts the random effects model analysis; if the heterogeneity is not significant, the fixed effects model analysis is adopted. All measurement data use mean difference (MD) as the effect indicator, and each effect size is given its 95% confidence interval (CI). Draw a forest map and compare the count data among multiple groups by single factor analysis. The difference of P<0.05 is statistically significant. The Egger test was used to evaluate publication bias. When P<0.1, it was considered statistically significant, there was publication bias.

2. Result

2.1 Basic characteristics and quality evaluation

793 related documents were first detected, and 27 duplicate documents were found. After reading the title and abstract, 746 articles were excluded. After reading the full text, 10 articles were finally included[11–20],The screening flowchart is shown in Figure 1. Including 1159 cases of gastric cancer patients, 33387 cases of normal control patients. The literature screening process and results are shown in Figure 1. Including 8 case-control studies[13–20],2 cross-sectional studies[11, 12].All come from India, Iran, Turkey, South Korea,China and other Asian countries. The basic characteristics and the quality evaluation of the literature are shown in Table 1.

2.2 Statistical analysis

2.2.1 Comparison of serum vitamin D levels between gastric cancer group and healthy control group

Among the included 10 studies, only 7 studies[11–17]compared the serum vitamin D levels of the gastric cancer experimental group and the normal control group, compared 730 cases of gastric cancer with 33387 cases of normal individuals, and conducted Meta on 7 studies. Significant heterogeneity was found during analysis (I^2=99%, P<0.00001). We found that there was no significant difference in heterogeneity among subgroups of different vitamin D determination methods and publication years (before or after 2018). After sensitivity analysis, it was finally found that there was no significant change in the heterogeneity after excluding any one of the studies. The analysis showed that the vitamin D level of the gastric cancer group was significantly lower than that of the normal group, and the difference was statistically significant [MD=-8.28,95%CI(-14.32~-2.23), P=0.007], as shown in Figure 2.

2.2.2 Vitamin D and clinical stage

Six studies[12, 14, 17–20]reported the serum vitamin D levels of patients with different clinical stage of gastric cancer. A total of 650 patients with gastric cancer were analyzed, including 429 patients with stage III/IV and 221 patients with stage I/II. The results It shows that there is significant heterogeneity (I^2=80%, P=0.0002). After submitting each study one by one, it is found that there is no heterogeneity (I^2=0%, P=0.89) after excluding Li Qiang’s research. Consider that Li Qiang's research subjects are elderly

men aged 62-83, and the sample size is small. Finally not included in Li Qiang's research.The results showed that the vitamin D level of patients with satge III/IV was lower than that of patients with stage I/II, and the difference was statistically significant [MD=-3.57,95%CI(-4.21~-2.92), P<0.00001],As shown in Figure 3.

2.2.3 Vitamin D and degree of differentiation

Six studies[12, 13, 17–20]reported a total of 677 patients with differently differentiated gastric cancer patients with serum vitamin D levels, the results suggests severe heterogeneity (I^2=80%, P=0.0002), sensitivity analysis suggests There is no significant improvement in heterogeneity after excluding any one study. The serum vitamin D level of poorly differentiated or other differentiated gastric cancer patients was significantly lower than that of well or moderately differentiated gastric cancer patients, the difference was statistically significant [MD=-2.59, 95%CI(-4.85~-0.66), P=0.03], As shown in Figure 4.

2.2.4 Vitamin D and lymph node metastasis and distant metastasis

Three studies[18–20]reported a total of 404 cases of gastric cancer, including 191 cases of N0/N1 gastric cancer and 213 cases of N2/N3 gastric cancer. The analysis showed that there was no heterogeneity (I^2=0%, P=0.72), The serum vitamin D level of patients with lymph node metastasis N2/N3 is lower than that of patients with N0/N1, the difference is statistically significant (MD=-0.55, 95%CI (-0.77~-0.32), P<0.00001), as shown in Figure 5. 4 studies [17-20] reported 392 patients with gastric cancer, including 62 patients with gastric cancer with distant metastasis and 330 patients with gastric cancer without distant metastasis, the difference was not statistically significant [MD=-2.57,95%CI (-6.73~1.58), P=0.23]. In addition, we also analyzed the differences in serum vitamin D levels in age, gender, smoking, drinking, and time of onset (whether more than four months), and the results showed no statistical significance.

2.2.5 Publication bias and sensitivity analysis

We performed Egger test to evaluate publication bias on 7 articles[11–17]that included control of gastric cancer and normal patients, and finally found that there was no obvious publication bias (P=0.395);We included 6 articles on different clinical stage of gastric cancer patients[12, 14, 17–20], and the Egger test to evaluate publication bias, no obvious publication bias was found (P=0.685). Evaluation of 6 articles with different degrees of differentiation [12, 13, 17–20]found the difference was statistically significant (P=0.055),suggesting publication bias. As shown in Figure 6.

3. Discussion

Vitamin D is a fat-soluble vitamin. The two main active forms are vitamin D3 (ergocalciferol) and vitamin D2. Vitamin D3 is the only form of vitamin D that naturally occurs in animals. It can be exposed to sunlight by 7-dehydrocholesterol in the skin Produced, the synthesis of vitamin D3 in the skin is the most important source of vitamin D, but vitamin D2 and vitamin D3 have no biological activity, and both must pass the action of 25-hydroxylase in the liver and 1,25-dihydroxylase in the kidney Later, synthesis of 1,25

(OH) 2D3 (calcitriol)[6].Calcitriol is a potent steroid hormone, which is involved in regulating gene expression in most tissues after binding to vitamin D receptors[8] .

The current anti-tumor research of vitamin D mainly includes the effect on cancer cell apoptosis and proliferation. Recently, it has also been found that vitamin D also has a certain effect on tumor microenvironment and drug resistance of chemotherapy. Studies have shown that $1,25(OH)_2D_3$ can re-encode the cancer-associated fibroblasts (CAF) genes to reduce the malignant phenotype of colon cancer and directly inactivate CAF to achieve the prevention andprotection of colon cancer.It can also affect immune cells and endothelial cells by stimulating CAF to secrete signal factors [21].Vitamin D may participate in the resistance of multiple drugs through different mechanisms, but the existing molecular mechanisms mainly involve reversing or reducing the epithelial-mesenchymal transition (EMT) and the inhibition of cancer cell stemness. EMT is a cellular program that makes tumor cells have other characteristics of malignant tumors, such as decreased apoptosis. The latest research has found that it can cause tumors to develop resistance to chemotherapy, radiotherapy and immunotherapy[7].Therefore, a large number of studies have proposed that inhibition of EMT can effectively improve tumor drug resistance. Studies have shown that after long-term use of the EGFR inhibitor erlotinib to treat non-small cell lung cancer, EMT has occurred. Treatment with 1,25(OH)2 D3 can reverse EMT and restore sensitivity,it is through inhibition of TGF-β Caused by EMT induction of cancer cells [22].In addition, by inhibiting the expression of LCN2 and phosphorylation of Nf-kB, oral cancer cells can be sensitized to cisplatin again [23].In in vitro studies, we found that human colorectal cancer cells treated with vitamin D analogue PRI-2191 and imatinib significantly down-regulated the expression of stemness-related genes, indicating that vitamin D plays a key role in controling to initiate cancer recurrence of residual colon cancer cells [24].

The results of the study showed that the serum vitamin D level of patients with gastric cancer was lower than that of the normal individual. It can be seen that adequate vitamin D levels have a certain preventive effect on the occurrence of gastric cancer. In the study of gastric cancer patients of different clinical stages, it was found that the serum vitamin D level of patients with stage III/IV gastric cancer was significantly lower than that of patients with stage I/II. It can be seen that vitamin D has a certain effect on the prognosis of gastric cancer. There are 2 studies[18, 19]analyzing the survival data of patients with gastric cancer, and the results suggest that patients with high vitamin D levels have a longer survival time for patients with lower levels.The result of Wang,X,L[18]suggests that the median survival time of patients with vitamin D>20ng/ml is 52.4±4.98 months, and that of ≤20ng/ml is 29.8±5.15 months. Li,Q's research [19] showed that the progression-free survival period of gastric cancer patients with vitamin D greater than 20ng/ml was 19 months (95%CI: 14.1~23.8 months), and the progression-free survival period of patients ≤20ng/ml was 10 months. Months, (95%CI: 7.8~12.1 months), the difference is statistically significant.Therefore, vitamin D levels may affect the survival of patients with gastric cancer, but there are few studies reporting related outcomes, a large number of clinical studies are still needed to confirm.

Although some studies suggest that vitamin D is likely to play a role in neoadjuvant treatment or even in chemotherapy prevention[18],existing studies have not confirmed that vitamin D supplementation can improve the occurrence and prognosis of tumors. Urashima, M first proposed that vitamin D supplementation does not improve the 5-year recurrence-free survival rate of patients with gastrointestinal tumors[25].Interestingly, the research team found that vitamin supplementation in high-grade differentiation, signet ring cell carcinoma, and squamous cell carcinoma D cannot improve the relapse-free survival (RFS), but vitamin D supplementation can improve RFS in poorly differentiated cancers [26].At the same time, they found that low levels of bioavailable 25-hydroxyvitamin D (vitamin D that is not bound to vitamin D binding protein) gastric cancer patients with vitamin D supplementation can significantly improve 5-year RFS[27].

It is undeniable that this study has certain limitations: the sample size of each study is small, and some studies only include 3 documents, which may be biased; Egger test results included in this article may have publication bias in some indicators of the study, consider most published articles are positive results, and negative results may be missed; different determination methods of serum vitamin D levels in the included studies may also bias the results; vitamin D levels are affected by the intensity of ultraviolet rays, although the studies included are all in Asia, but the effects of ultraviolet radiation intensity and sunshine duration at different latitudes are not considered. Therefore, we need to design more rigorous randomized controlled studies to verify the final results.

In summary, there is a certain correlation between the serum vitamin D level and the occurrence of gastric cancer. The reduction of vitamin D increases the risk of gastric cancer. The serum vitamin D level is an independent predictor of gastric cancer. At the same time, vitamin D levels are significantly related to different clinical stages, degrees of differentiation, and lymph node metastasis. Therefore, serum vitamin D levels may be an important factor in the prevention and prognosis of gastric cancer.There is no obvious correlation between the patient's age, gender, smoking and drinking history, onset time and distant metastasis.Paying attention to serum vitamin D levels may become a clinical trend and make a certain contribution to the early detection and treatment of gastric cancer. However, according to the quality and sample size of the included articles, we need more rigorously designed, meticulous, high-quality, large-sample prospective randomized controlled studies to verify this conclusion.

4. Declarations

1Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2) Consent to publish

Not applicable.

3) Availability of data and materials

This publication is supported by multiple datasets, which are openly available at locations cited in the reference section. Additional data for this article have been provided as supplementary files. There is no additional unpublished data.

4、Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

5、Funding

This work was supported by the Science and Technology Program of Liaoning Province（2019-ZD-0913）.

6、Author Contributions

(I) Conception and design: Zhao X,Wang J,Ying L
(II) Administrative support: Ying L.
(III) Provision of study materials or patients: Zhao X,Ying L.
(IV) Collection and assembly of data: Zhao X,Wang J.

(V) Data analysis and interpretation:Zhao X,Wang J.
(VI) Manuscript writing: Zhao X,Wang J,Ying L.

(VII) Final approval of manuscript: Zhao X,Wang J,Ying L.

References

[1] Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020. 396(10251): 635-648.

[2] Arnold M, Abnet CC, Neale RE, et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology. 2020. 159(1): 335-349.e15.

[3] Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics. Cancer Commun (Lond). 2019. 39(1): 22.

[4] Cao M, Li H, Sun D, Chen W. Cancer burden of major cancers in China: A need for sustainable actions. Cancer Commun (Lond). 2020. 40(5): 205-210.

[5] Carlberg C, Muñoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol. 2020 .

[6] Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev. 2016. 96(1): 365-408.

[7] Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019. 20(2): 69-84.

[8] Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014. 14(5): 342-57.

[9] 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): 603-5.

[10] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015. 8(1): 2-10.

[11] Kwak JH, Paik JK. Vitamin D Status and Gastric Cancer: A Cross-Sectional Study in Koreans. Nutrients. 2020. 12(7).

[12] Kevin A, Anandhi A, Lakshminarayanan S, Sureshkumar S, Kamalanathan S. Association between serum 25-hydroxy Vitamin D level and gastric adenocarcinoma-A cross sectional study. Przeglad GastroenterologicznyPrz. Gastroenterol.. 2021. 16(2): 155.

[13] Zeng Y, Chu Y, Sun J. Relationship Between Serum 25-(OH) D3, Ca2+ and Gastric Carcinoma. Cancer Research on Prevention and Treatment. 2015. (04): 369-372.

[14] Bao AY. Clinical Significance of Serum 25-Hydroxyvitamin D Level of Gastric Cancer Patients. Journal of Modern Laboratory Medicine. 2016. 0(2).

[15] Eom SY, Yim DH, Kim DH, et al. Dietary vitamin D intake and vitamin D related genetic polymorphisms are not associated with gastric cancer in a hospital-based case-control study in Korea. J Biomed Res. 2018. 32(4): 257-263.

[16] Durak Ş, Gheybi A, Demirkol Ş, et al. The effects of serum levels, and alterations in the genes of binding protein and receptor of vitamin D on gastric cancer. Molecular Biology ReportsMol. Biol. Rep.. 2019. 46(6): 6413.

[17] Hedayatizadeh-Omran A, Janbabaei G, Alizadeh-Navaei R, Amjadi O, Izadi JM, Omrani-Nava V. Association between pre-chemotherapy serum levels of Vitamin D and clinicopathologic findings in gastric cancer. Caspian Journal of Internal MedicineCaspian J. Int. Med.. 2020. 11(3): 290.

[18] Wang XL, Fan CG, Yang LI, Guo-Li LI. Correlations between serum 25(OH) vitamin D levels and the prognosis of advanced gastric cancer patients with neoadjuvant chemotherapy. Parenteral & Enteral Nutrition. 2019. 26(1).

[19] LI Qiang SUY, Wei-Guo R. Clinical significance of serum 1,25-(OH)2D3 level in elderly patients with gastric cancer. Chin J Mult Organ Dis Elderly. 2014. 13(5).

[20] Ren C, Qiu M-Z, Wang D-S, et al. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. J Transl Med. 2012 : 16.

[21] Ferrer-Mayorga G, Gómez-López G, Barbáchano A, et al. Vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. Gut. 2017. 66(8): 1449-1462.

[22] Liu C, Shaurova T, Shoemaker S, Petkovich M, Hershberger PA, Wu Y. Tumor-Targeted Nanoparticles Deliver a Vitamin D-Based Drug Payload for the Treatment of EGFR Tyrosine Kinase Inhibitor-Resistant Lung Cancer. Mol Pharm. 2018. 15(8): 3216-3226.

[23] Huang Z, Zhang Y, Li H, et al. Correction: Vitamin D promotes the cisplatin sensitivity of oral squamous cell carcinoma by inhibiting LCN2-modulated NF-κB pathway activation through RPS3. Cell Death Dis. 2020. 11(3): 190.

[24] Kotlarz A, Przybyszewska M, Swoboda P, et al. Imatinib inhibits the regrowth of human colon cancer cells after treatment with 5-FU and cooperates with vitamin D analogue PRI-2191 in the downregulation of expression of stemness-related genes in 5-FU refractory cells. J Steroid Biochem Mol Biol. 2019. 189: 48-62.

[25] Urashima M, Ohdaira H, Akutsu T, et al. Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers: The AMATERASU Randomized Clinical Trial. JAMAJAMA. 2019. 321(14): 1361.

[26] Yonaga H, Okada S, Akutsu T, Ohdaira H, Suzuki Y, Urashima M. Effect modification of vitamin D supplementation by histopathological characteristics on survival of patients with digestive tract cancer: Post hoc analysis of the AMATERASU randomized clinical trial. NutrientsNutrients. 2019. 11(10).

[27] Urashima M, Okuyama M, Akutsu T, Ohdaira H, Kaji M, Suzuki Y. Effect of vitamin D supplementation on survival of digestive tract cancer patients with low bioavailable 25-hydroxyvitamin d levels: A post hoc analysis of the AMATERASU randomized clinical trial. CancersCancers. 2020. 12(2).

Table

Table 1 The basic characteristics and the quality evaluation.* Evaluat by AHRQ evaluation standard.HPLC（high-pressure liquid chromatography),RIA(radioimmunoassay),ECLI(Electro-Chemiluminescence Immunoassay)

Name	Country	Year	Study type	Test	Gastric cancer		Conrol		NOS AHRQ*
					n	Mean±SD	n	Mean±SD	
Zeng, Y[13]	China	2014	case-control study	ELISA	118	15.42±4.91	68	37.33±14.32 14.32	9
Bao,A,Y[14]	China	2016	case-control study	ECLI	101	10.12±5.78	99	18.12±7.36	10
Eom SY[15]	Korea	2018	case-control study	ELISA	72	17.1±8.9	91	20±6.5	9
Durak, Ş[16]	Turkey	2019	case-control study	HPLC	77	11±6	84	16±6	9
Hedayatizadeh-Omran, A[17]	Iran	2020	case-control study	ELISA	50	26.86±14.6	50	31.72±13.4	9
Kwak JH[11]	Korea	2020	Cross- sectional study	RIA	218	17.4±0.59	32901	17.5±0.1	9*
Kevin, A[12]	India	2021	Cross- sectional study	-	94	13.83±5.97	94	29.15±4.13	8*
Wang,X,L[18]	China	2019	case-control study	ELISA	167	18.94±9.47	-	-	7
Li□Q[19]	China	2014	case-control study	ELISA	65	18.26±4.13	-	-	8
Chao Ren[20]	China	2012	case-control study	ELISA	197	19.94±9.47	-	-	6

Figures

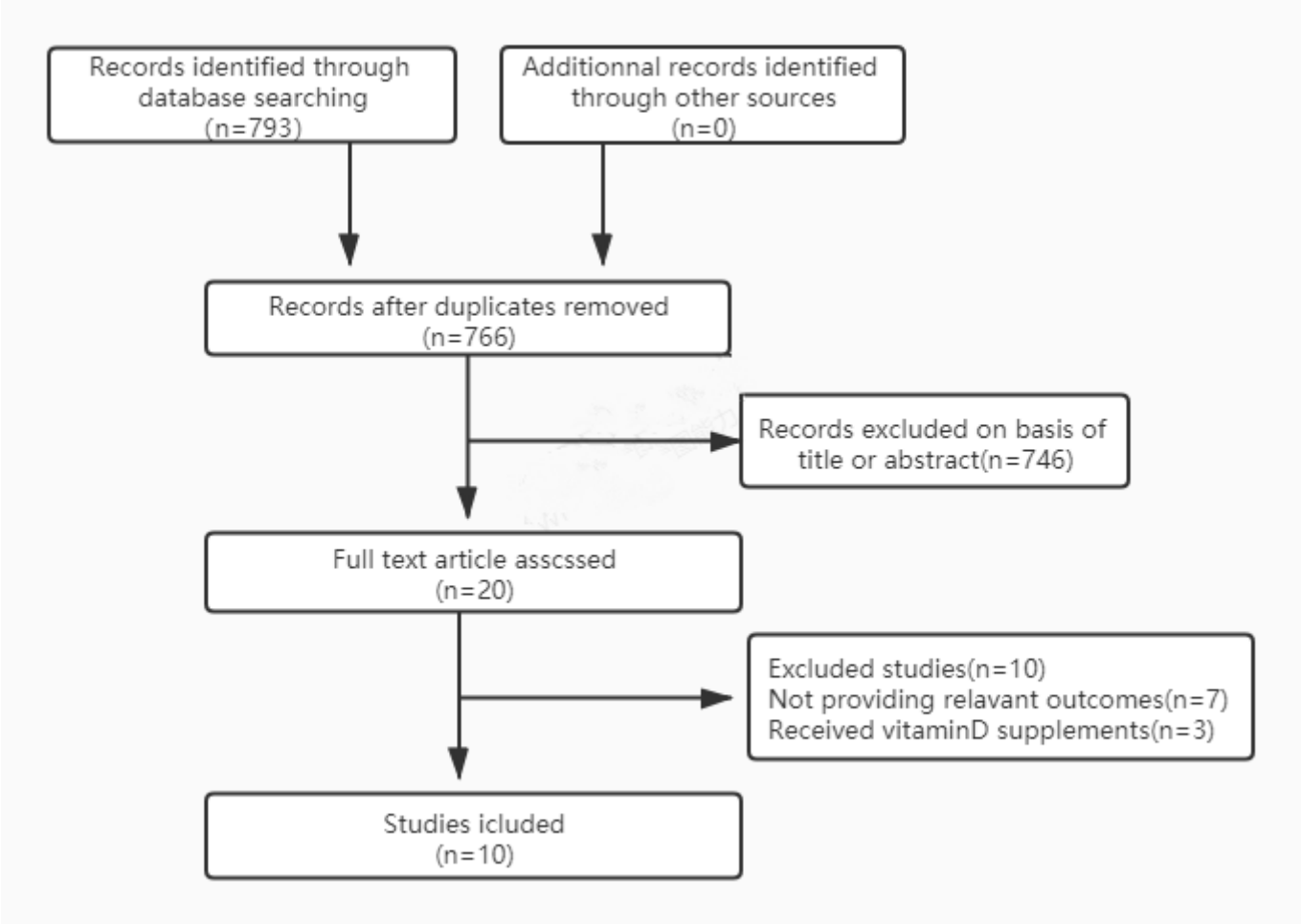

Figure 1

The literature screening process and results

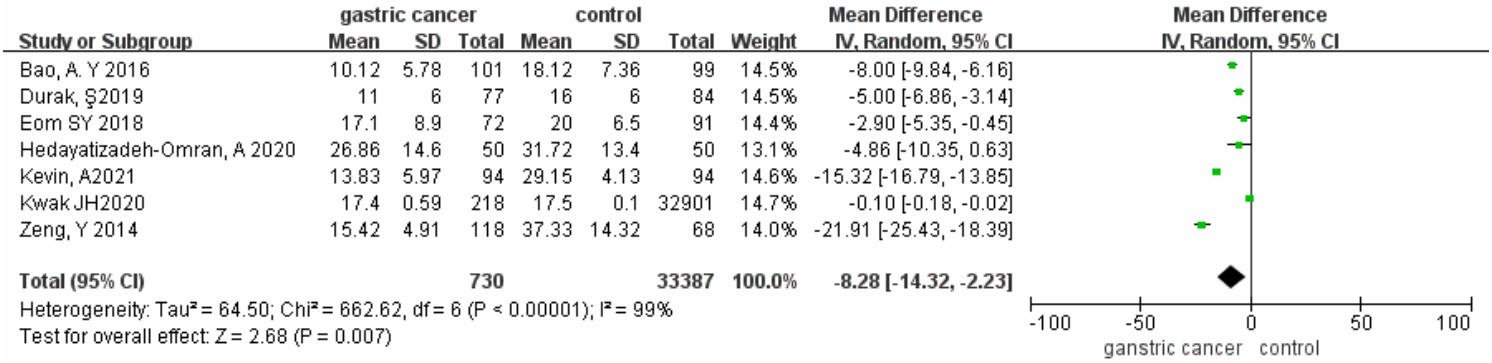

Figure 2

Serum vitamin D levels between gastric cancer group and healthy control group The analysis showed that the vitamin D level of the gastric cancer group was significantly lower than that of the normal group.

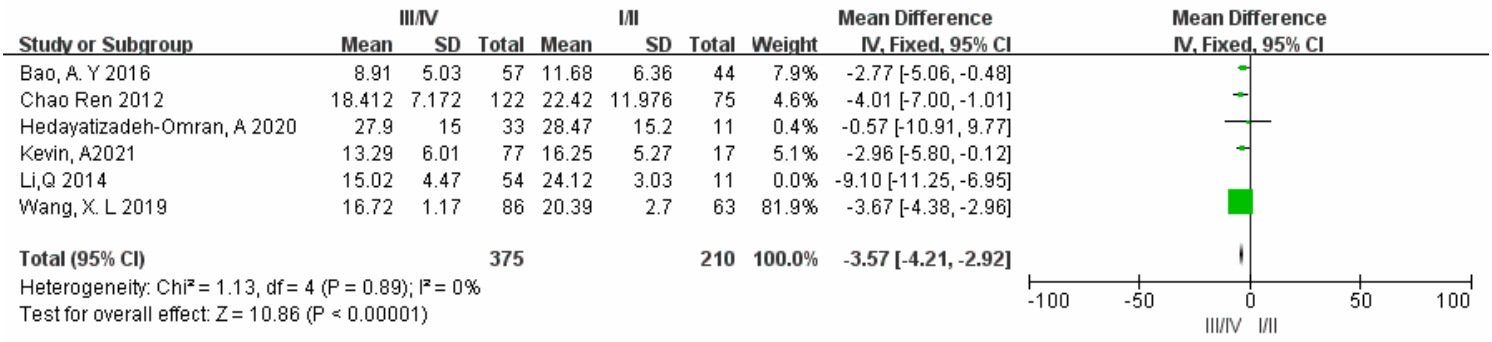

Figure 3

Serum vitamin D levels between different clinic stage. The vitamin D level of patients with satge III/IV was lower than that of patients with stage I/II

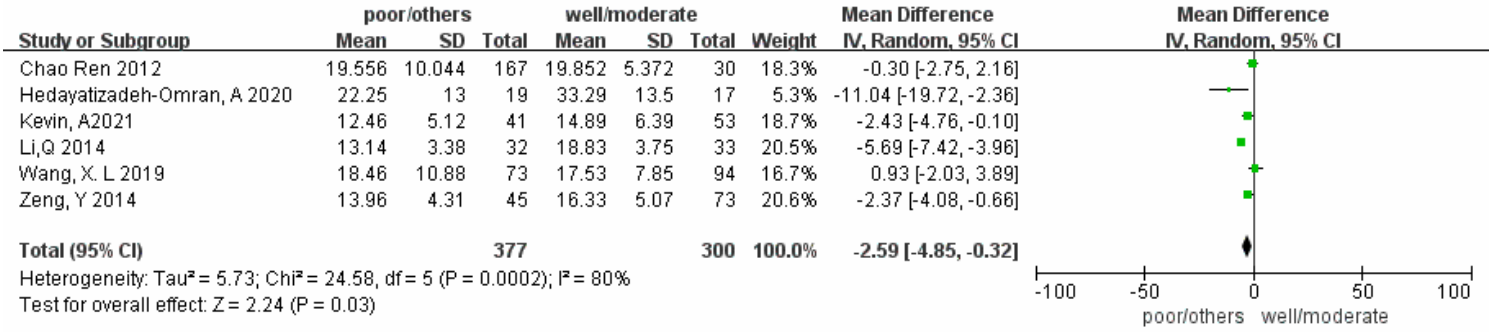

Figure 4

Serum vitamin D levels between different degrees of differentiation. The serum vitamin D level of poorly differentiated or other differentiated gastric cancer patients was significantly lower than that of well or moderately differentiated gastric cancer patients

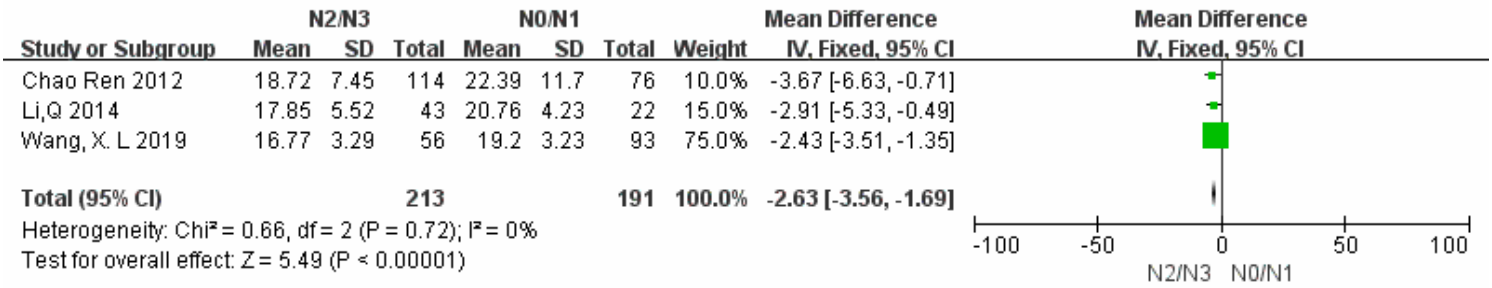

Figure 5

Serum vitamin D levels between lymph node metastasis. The serum vitamin D level of patients with lymph node metastasis N2/N3 is lower than that of patients with N0/N1

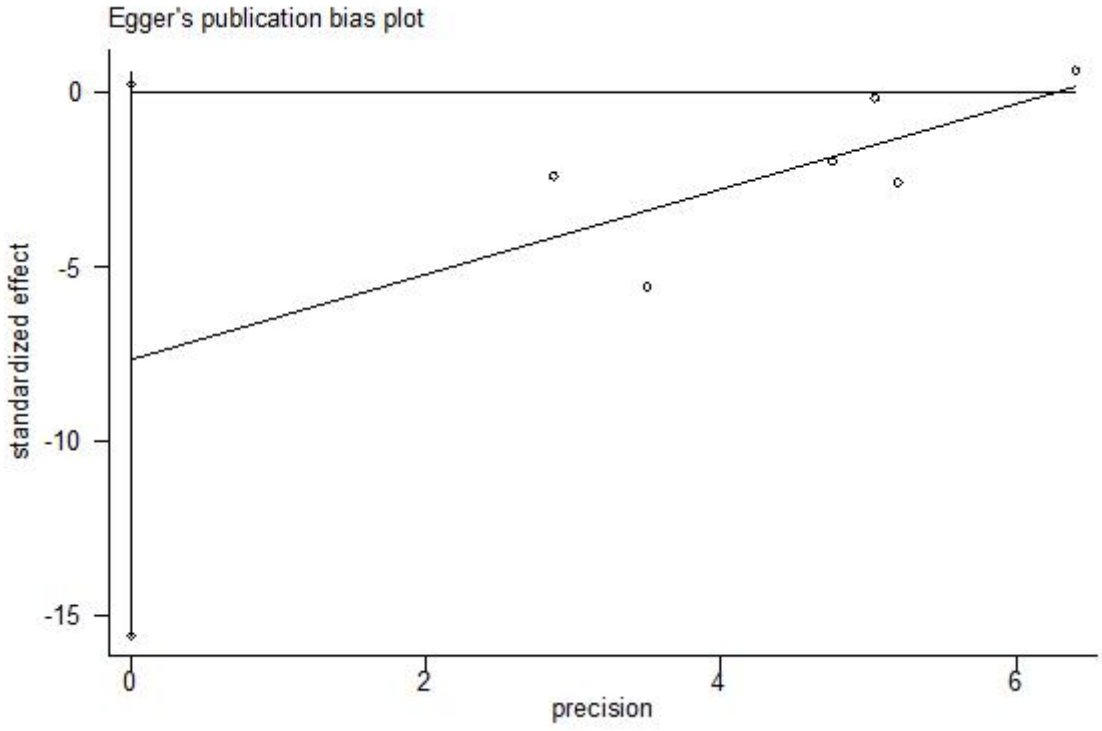

Figure 6

The publication bias. no obvious publication bias was found.