

The Correlation of Plasma 25-Hydroxyvitamin D with Risk of Colorectal Cancers in Asian Population

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Abstract: *Recently, it has been found that vitamin D deficiency links to highly prevalent chronic illnesses, such as cardiovascular disease, diabetes mellitus and cancer. Colorectal cancer is the third most prevalent cancer and the fourth most common cause of cancer mortality worldwide with increasing incidence in Asian countries. Western-based population studies has stated that there is an inverse relationship between plasma 25(OH)D and risk of colorectal cancer. Despite the increase on colorectal cancer incidence and low vitamin D status in Asian countries due to lifestyle change, very few Asian-population based studies on vitamin D and colorectal cancer have been conducted. We have aimed to evaluate articles that assessed the correlation of plasma 25(OH)D with risk of colorectal cancers in Asian population. The search for studies was conducted using Medline via Pubmed. Overall, 646 potential articles were identified, and after screening, 2 articles met eligible criteria for inclusion. Evidence suggest that plasma 25(OH)D levels may have inverse relationship with colorectal cancer, but specifically rectal cancer, rather than colon cancer in both women and men. There is still a very high need in the future for high-quality studies that assess the correlation of plasma 25(OH)D to the risk of colorectal cancer in Asian population.*

Keywords: 25-Hydroxyvitamin D, vitamin D deficiency, colorectal cancer

1. Background

Vitamin D deficiency is a worldwide problem.(1) Vitamin D deficiency may be overlooked in Asian countries, due to assumption the deficiency is unlikely to occur in regions with plentiful sunshine.(2)In India, despite the sun exposure, it is estimated 70% of the population is vitamin D deficient.(2) Nimthapong et al stated that in Southeast Asian countries, vitamin D deficiency is common. (2) Sari et al conduct a cross-sectional on 156 healthy women in North Sumatera, and found that 95% of samples is vitamin D deficient.(3) Recently in Asian countries, prevalence of vitamin D deficiency is increasing due to increasingly indoor lifestyles and efforts to minimize sun exposure by using sunscreens and other sun avoidance strategies.(4)

The biologically active form of vitamin D is 1,25-dihydroxycholecalciferol[1,25-(OH)₂D] or calcitriol, which is a steroid hormone that can activate vitamin D receptor which regulates the transcription of vitamin D responsive genes.(5,6) However, serum 25(OH)D is regarded as the best indicator of vitamin D status in individuals without kidney disease, because it has longer biological half-life than 1,25-(OH)₂D, circulates in much higher concentrations and reflects the total production of vitamin D from both endogenous and exogenous sources, including exposure to Ultraviolet B (UVB) radiation and intake of various dietary forms.(5)

In the past, vitamin D deficiency has always been associated with bone health, for example rickets and growth retardation in children and accelerates osteomalacia and osteoporosis in adults.(4,7,8) Recently, it has been found that the effect of vitamin D deficiency is more than that, it links to highly prevalent chronic illnesses, such as cardiovascular disease, diabetes mellitus and cancer. (4, 8)

Colorectal cancer is the third most prevalent cancer and the fourth most common cause of cancer mortality worldwide.(9,10) The incidence rate of colorectal cancer has increased in some Asian countries, which have undergone dramatic lifestyle changes.(11) In Korea, cancer incidence has steadily increased by 4.7% annually from 1999 to 2010.(11)In Japan, the mortality of colorectal cancer has sharply increased after the second world war and it is among the highest level in the world.(10)

Ordenez-Mena et al did a cohort involving 873 subjects and stated that higher plasma 25(OH)D concentration significantly lower cancer incidence, which is an interesting cancer prevention strategy.(12) Epidemiological studies suggest that high vitamin D intake may lower the risk of colorectal cancer.(9) Despite the increase on colorectal cancer incidence and low vitamin D status in Asian countries, very few Asian-population based studies on vitamin D and colorectal cancer have been conducted. In recent meta-analysis, Ekmekcioglu et al stated that there is an inverse association between 25(OH)D levels and colorectal cancer,(13) and other case-control studies are inline with this result,(14–16)but with a very limited number of Asian studies, it is hard to say whether the association was also applied to Asian populations. Choi et al conducted meta-analysis and stated that there is inverse association between 25(OH)D levels and colorectal adenoma in both western and Asian population, but not for colorectal cancer.(11)

Objective

We have aimed to evaluate articles that have assessed the correlation of plasma 25(OH)D with risk of colorectal cancers in Asian population.

2. Methods

Data sources

The initial search was performed with the medical subject heading (MeSH) keywords “vitamin D AND colorectal cancer” using Medline via Pubmed database to identify articles eligible for this review. The limitations were: 1. English language 2. Publication date from January 1, 2007 to January 1, 2018 3. Full-text availability 4. Asian population. In the screening process, review articles and case-reports were excluded.

Study selection

To find the articles that met eligibility criteria, titles and abstracts were examined. Those articles which have evaluated plasma 25 (OH) Din patients with colorectal cancers were included. The following data for each eligible study were summarized; author, year, country, sex, study design, study dates, number of cases and controls, age, level of 25(OH)D, outcomes studied and applicable results.

Data extraction

This systematic review was performed in accordance with the PRISMA (Preferred reporting items for systematic

review and meta-analysis) statement.(17) Critical appraising of evidence was performed using the study quality assessment tools of national institutes of health, national heart, lung and blood institute (NHLBI). Studies with low risk of bias were determined as good quality, high risk of bias as poor quality and moderate risk of bias as fair quality.

3. Results

Study selection

Overall, 646 articles were identified through database searching using the MeSH keywords as previously described. One additional record was identified through reference list but it was already in our identified articles list. After duplicated removal, 646 records were screened. After screening, 631 records were excluded, including 14 articles which were published in other languages besides English, 100 articles using subject not human, 242 articles not available in full text, 267 articles not based on Asian population and 8 review articles. Eventually, 15 full-text articles have assessed for eligibility. Eleven articles did not measure vitamin D levels and two articles did not study colorectal cancer. At last, two studies were included in this systematic review (figure 1).

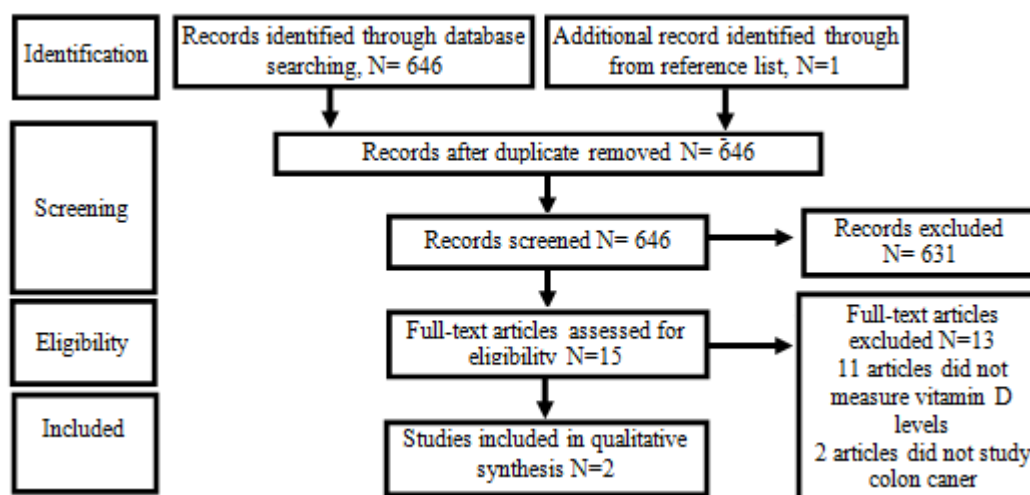


Figure 1: Study selection

Study characteristics

A total of two articles reporting 587 colorectal carcinoma and 862 controls were included in this systematic review. We included 2 case-control studies. One study was conducted in Japan and one study in China. All of the articles were conducted among men and woman, with primary outcome of colorectal carcinoma. Both of the studies were conducted among men and women and both have compared vitamin D levels with control groups. Evidence was mainly of fair quality.

Results of individual studies

We investigated the association between plasma 25(OH)D and the subsequent colorectal cancer incidence risk by a case-control study in The Japan Public Health Center-based Prospective Study, covering 375 newly diagnosed cases of colorectal cancer from 38,373 study subjects during 11.5-year follow-up after blood collection. Two controls were matched per case on sex, age, study area, date of blood draw, and fasting time. Otaniet al assessed the risk for

colorectal cancer, colon and rectal cancer to low plasma 25(OH)D. Plasma 25(OH)D was lower in rectal cancer cases than their controls (24.3 ng/mL vs 26.6 ng/mL in men ($p=0.0051$); 20.6 ng/mL vs 22.6 ng/mL in women ($p=0.093$)). It was found that plasma 25(OH) D was not associated with the risk of colorectal cancer and colon cancer in men or women, but low level plasma 25(OH)D is associated with rectal cancer risk in both men and women.(18)

Ying et al. conducted case-control study with 212 cases and 212 controls matched with age, gender and blood collection time. All subjects were from health assessment cohort population comprised routine physical examination of individuals who performed annually in Nanjing First Hospital from 2010 to 2012. The case group consisted of 212 colorectal cancer patients including 115 colon and 97 rectal cancer patients with ranging age from 37 to 83 years with median age 65 years old for cases and 63 years old for control. Plasma 25(OH)D was lower in colorectal cancer

cases than their controls (9.71 ng/mL vs 14.6 ng/mL ($p < 0.001$)). After adjusted with age and gender, and adjusted for BMI, smoking, drinking, history of diabetes and hypertension as well as either total 25(OH)D or Vitamin D Binding Protein (VDBP), the results revealed that there was a negative association between total 25(OH)D and the risk of colorectal cancers ($p = 0.027$).⁽⁹⁾

4. Discussion

Summary of evidences

Evidence suggest that plasma 25(OH)D levels may have inverse relationship with colorectal cancer, but specifically rectal cancer, rather than colon cancer in both women and men. Ma et al conducted systematic review including nine studies with approximately 1,000,000 participants from several countries.⁽¹⁹⁾ The pooled RRs of colorectal cancer for the highest versus lowest categories of vitamin D intake and blood 25(OH)D levels were 0.88 (95% CI, 0.80 to 0.96) and 0.67 (95% CI, 0.54 to 0.80), respectively. ⁽¹⁹⁾ It shows inverse relationship between plasma 25(OH)D to colorectal cancer.⁽¹⁹⁾ This results are in line with other systematic review studies.⁽¹³⁾ Song et al stated there is an 6% reduction in risk for colorectal cancer for each 1 ng/mL increase in plasma 25(OH)D, ⁽¹⁶⁾ and Garland et al stated that individuals with plasma 25(OH)D levels below 30 ng/mL had approximately twice the risk of colorectal cancer, with doubling of incidence for those with less than 20 ng/mL.⁽²⁰⁾ Plasma 25(OH)D status did not correlate with dietary vitamin D intake because over 90% of the vitamin D in the body comes from casual exposure to sunlight, hence the various result in studies assessing correlation vitamin D intake and colorectal cancer.^(18, 21)

Otani et al stated that high plasma 25(OH)D levels only lowers the risk of rectal cancer, and not colon cancer.⁽¹⁸⁾ This difference may derive from 1,25(OH)₂D receptor or Vitamin D receptor (VDR) expression between colon and

rectum.⁽¹⁸⁾ Vitamin D receptor also has some differences in genetic polymorphism by ethnic group. ⁽¹⁸⁾ BsmI B and short poly A alleles are more prevalent in Caucasians than in Japanese and may be protective against colorectal cancer.⁽¹⁸⁾ Asians may be more vulnerable to rectal cancer due to the low prevalence of this protective VDR genotype.⁽¹⁸⁾

Contrary to the previous results, a cohort study was conducted by Wang et al. to 4208 men in Perth and found that plasma 25(OH)D did not predict incidence of colorectal cancer in aging man.⁽²²⁾ Several reasons for discrepancy in findings from these studies have been postulated, including length of follow-up, residual confounding and possibility of publication bias.⁽²²⁾

Multiple studies have tried to evaluate the possible mechanism vitamin D lower the risk of colorectal cancer. Song et al. stated after does case-control study 615 cases with 1209 controls, stated that circulating inflammatory markers, like C-reactive Protein (CRP), Interleukin-2 (IL-2) and Tumor Necrosis Factor (TNF) does not appear to account for the inverse association between plasma 25(OH)D and colorectal cancer.⁽²³⁾ Weinstein et al in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial based on 476 colorectal cases and 748 controls matched in age, sex race and date of serum collection stated that higher vitamin D lower colorectal cancer risk, but doesn't indicate a direct or modifying role of vitamin D Binding Protein (VDBP).⁽¹⁴⁾ It is said that vitamin D and its metabolites has several mechanism in reducing risk of cancer.^(20, 11, 24) Vitamin D has antiproliferative effect on colorectal cancer.⁽²⁵⁾ Other than that, vitamin D also inhibit cell proliferation, induced apoptosis by upregulating the pro-apoptotic proteins and down regulating anti-apoptotic protein. Vitamin D also has anti-angiogenesis effect on colorectal cancer.⁽²⁵⁾

Table 1: Summary of Evidences

First author, year	Contry (sex)	Study design	Study dates	No. of cases/ controls	Age (years)	25(OH)D levels in the highest and lowest categories	Outcomes studied	OR (95% CI)	Result	Quality
Otani, 2007 ⁽¹⁸⁾	Japan (M, W)	Case-control study	1990-2003	375/750	M: 56.9 years in cases and control; W: 56.5 years in cases and 56.4 years in control	M: > 32.1 ng/mL vs< 22.9 ng/mL; W: > 27.0 ng/mL vs< 18.7 ng/mL	Colorectal cancer, colon cancer, rectal cancer	1: M: Ref; W: Ref 2: M: 0.76 (0.42–1.4) W: 1.0 (0.55–1.9) 3: M: 0.76 (0.39–1.5) W: 1.2 (0.65–2.3) 4: M: 0.73 (0.35–1.5) W: 1.1 (0.50–2.3)	Lowest category of plasma 25(OH)D was associated with an elevated risk of rectal cancer in both men (OR:4.6 (1.0-20)) and women (OR: 2.7 (0.94-7.6)), compared with the combined category of the other quartiles	Fair
Ying, 2015 ⁽⁹⁾	China (M,W)	Case-control study	2010-2012	212/212	65 years in cases, 63 years in control, median	> 28.84 ng/mL vs< 7.29 ng/mL, range	First colorectal carcinoma	1.00 (ref); 0.62 (0.35-1.12); 0.67 (0.38-1.20); 0.53 (0.29-0.98)	Negative association between total 25(OH)D and the risk of colorectal cancer (P=0.027)	Fair

Limitations

There was very limited studies that study the correlation of plasma 25(OH)D to risk of colorectal cancer in Asian

population, therefore limiting the number of studies included in this systematic review.

5. Conclusion

This systematic review investigated its correlation of plasma 25(OH)D to risk of colorectal cancer in Asian population. Evidence suggests that plasma 25(OH)D levels may have an inverse relationship with colorectal cancer, but specifically rectal cancer, rather than colon cancer in both women and men. There is still a very high need in the future for high-quality studies that assess the correlation of plasma 25(OH)D to the risk of colorectal cancer in Asian population.

6. Footnotes

Conflict of Interest: The authors have declared that they had no conflict of interest.

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