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Vitamin B12 and Cancer: A Systematic Review of the Evidence for both Protective and Promotional Effects

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Abstract

Background and Aim: DNA synthesis and cellular metabolism depend on vitamin B12. Emerging research indicates that excessive supplementing may raise the risk of cancer, even as moderate doses may offer protection against some malignancies. The preventive and promoting effects of vitamin B12 on cancer are assessed in this systematic study. The aim of the study is to synthesise existing evidence to clarify the complex association between Vitamin B12 intake, serum levels, and cancer risk.

Methods: Clinical trials and observational studies published in English were found by a thorough search of major scientific databases. Only abstracts, in vitro experiments, and animal studies were not included. Four of the 300 articles that were screened satisfied the requirements for eligibility. Serum B12 levels, dietary intake, supplementation, and cancer-related outcomes were also examined. The OHAT technique was used to evaluate the risk of bias.

Results: A higher incidence of colorectal and total cancer was linked to high-dose supplementation (≥500 μg/day). Serum B12 levels in cancer patients were significantly higher (>800 pg/mL) and were correlated with tumor stage. On the other hand, a decreased risk of colorectal cancer was associated with a sufficient dietary B12 consumption from natural food sources. A lower risk of oesophageal precancerous lesions was likewise linked to higher levels of transcobalamin II and serum B12**.**

Conclusion: There are two connections between vitamin B12 and cancer. While avoidable long-term high-dose supplementation may raise the risk of cancer, maintaining appropriate physiological levels is advantageous. Until a clinical deficiency is established, dietary sources should be given priority.

Keywords: Vitamin B12, Cobalamin, Cancer risk, Supplementation, Serum B12 levels, Colorectal cancer; Esophageal precancerous lesions; Transcobalamin II; Dietary intake

Introduction

Vitamin B12 (cobalamin) is a water-soluble vitamin that is essential for metabolism [1]. Cobalamins are substances having vitamin B12 action since vitamin B12 contains the element cobalt [2]. The forms of vitamin B12 that are biologically active are methyl cobalamin and 5-deoxyadenosylcobalamin. However, after being transformed into methyl cobalamin or 5-deoxyadenosylcobalamin, two more forms—hydroxy cobalamin and cyanocobalamin—become physiologically active[2,3] Animals need it because they use it as a cofactor in the creation of DNA and in the metabolism of amino acids and fatty acids[4] It plays a crucial role in the production of myelin in the neurological system and in the development of red blood cells in the bone marrow of the circulatory system[1,5]. Of all the vitamins, vitamin B12 is the most chemically complicated[6] and the only one that people need to get from foods or supplements produced from animals[1,7]. Vitamin B12 can only be synthesized by certain bacteria and archaea[8]. Foods rich in vitamin B12 encompass meat, shellfish, liver, fish, poultry, eggs, and dairy items[1]. Due to malnutrition vitamin B12 deficits are more prevalent in middle- and lower-developed nations and are particularly detrimental to young children, pregnant women, and the elderly[9] The loss of gastric intrinsic factor (IF), which is necessary for absorption to take place and must be attached to a food supply of vitamin B12, is the most frequent cause of vitamin B12 insufficiency in developed nations[10] Because acid exposure releases protein-bound vitamins, age-related decreases in stomach acid production (achlorhydria) are the second key reason[8] For the same reason, patients on proton-pump inhibitors and long-term antacid therapy[11] and Antacids such as H2 blockers are at increased risk[12.]

Although its role in human health is quite well established, there is a lot of interest among scientists about its relation with cancer risk and progression in recent years. This complex and nuanced area of research is the double-sided impact of Vitamin B12 on cancer: possible prevention and potential promotion risks[13] .On the one hand, it has been observed that sufficient amounts of Vitamin B12 and other B vitamins reduce risks of specific cancers, like breast and cervical cancers,

by supporting healthy cellular functions and DNA repair mechanisms[13]. On the contrary, however, new evidence is emerging about the role of high doses of Vitamin B12 supplementation in increasing the risk of cancers, specifically colorectal and lung cancers, as well as its association with plasma B12 levels in malignancies[14]. This systematic review intends to give a detailed insight into the intricate relationship of Vitamin B12 with cancer. This review will integrate evidence for Vitamin B12's role in cancer promotion and prevention, analyse underlying mechanisms of association, and balance implications for clinical practice and public health. Contrary to past reviews that considered only either the oncogenic or protective actions of Vitamin B12, our work offers a nuanced and balanced review of data. By integrating these apparently conflicting conclusions, our review provides a better overall picture of the intricate Vitamin B12 and cancer relationship to inform future studies, clinical practice, and public health policy decision-making.

Materials and Methods

Study Design

A systematic review of observational studies, clinical trials, and experimental studies was conducted to investigate the role of Vitamin B12 in cancer promotion and prevention, evaluating its potential benefits and risks.

Search Strategy

This systematic review investigates the relationship between Vitamin B12 and cancer, examining its potential role in cancer promotion and prevention. A comprehensive literature search was conducted using major databases, including PubMed, Google Scholar, Science Direct, and Research Gate, to identify relevant studies published in English.

Eligibility Criteria

Inclusion criteria

- This study includes clinical trials
- It consists of full-length text articles from web engine such as pub-med, google scholar, science direct and research gate.
- It elaborates the articles on the effects of vitamin b12 in cancer promotion and prevention
- Publications over the years

Exclusion criteria

- Articles published in other languages
- Only abstracts available
- Animal studies
- In-vitro studies

Search Engines

- PubMed
- Google scholar
- Research gate
- Elsevier Science Direct
- Wiley Online library

Figure 1: Flow chart showing the number of studies identified, screened, assessed for eligibility, excluded and included in the systematic review.

Prisma Flowchart:

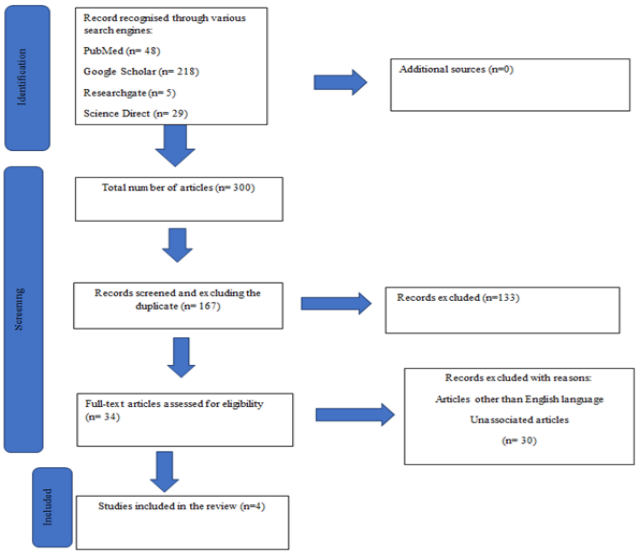

Table 1: Characteristics of the Interventions in the Included Studies.

Sn.	Author name	Year	Patient selection	Duration	Intervention
1	Sadaf Oliai Araghi, Jessica Jong, Suzanne Boon-van Dijk, and colleagues	2019	The study included 2,919 elderly individuals aged 65 years and older with elevated plasma homocysteine concentrations	Participants received the supplementation for a duration of 2 to 3 years.	The intervention group received daily oral supplementation of 400 µg of folic acid and 500 µg of vitamin B12, while the control group received a placebo.
2	Ivana Banjari and Sanja Kožić,	2018	The study was conducted on 200 healthy adults aged between 18 and 75 years, par ticipants had to be omnivores	The study was conducted over a period of two months, specifically during April and May 2013	Observational study assessing dietary intake of vitamin B12 and its sources, such as milk, dairy, and fish, in relation to diet and lifestyle characteristics associated with CRC risk.
3	Gholamreza Haghighat, Ali Khajeh-Mehrizi, and Hamed Ranjbar	2023	The study involved 140 patients diagnosed with colon or breast cancer and 140 healthy individuals matched for age, gender, and socioeconomic status	The study was carried out during a one year and 2 month period , specifically from April 2019 to June 2020.	according to the study, blood vitamin B12 levels were higher in 32.9% of cancer patients (above 800 pg/ml) than in the control group (10.0%). Furthermore, serum vitamin B12 levels and tumor stage were significantly positively correlated.
4	Da Pan, Ming Su, Dengfeng Xu, Yuanyuan Wang, Han Gao, James Daniel Smith, Jihan Sun, Xin Wang, Qingyang Yan, Guang Song, Yifei Lu, Wuqiong Feng, Shaokang Wang, and Guiju Sun.	2021	The study included 100 cases of esophageal precancerous lesions (EPL) and 100 healthy controls, matched by gender, age (±2 years), and villages, from a high-risk area in Huai'an, China.	The study was conducted over a 3-day period, during which duplicate diet samples were collected.	This was an observational case–control study. Researchers analyzed dietary intake of vitamin B12 and cobalt, plasma cobalt levels, and serum levels of vitamin B12 and transcobalamin II (TC II). They found that higher serum levels of vitamin B12 and TC II were significantly associated with reduced EPL risk

Table 1 presents the characteristics of the studies included in the systematic review. All four studies examined the role of Vitamin B12 in relation to various health conditions. However, the studies differed in terms of patient age, sample size, and the Duration of Outcome Assessment.

Table 2: Characteristics of the Primary Outcome and Results of The Studies Included In The Systematic Review

Sn.	Author name	Year	Outcome	Result
1	Sadaf Oliai Araghi, Jessica Jong, Suzanne Boon-van Dijk, and colleagues	2019	Increased overall cancer incidence in the supplementation group. Increased risk of colon cancer in people taking vitamin B12 and folic acid	Compared to the placebo group, participants who took supplements experienced a noticeably higher incidence of cancer. Findings suggest a potential adverse effect of folic acid and vitamin B12 on cancer risk, particularly colorectal cancer.
2	Ivana Banjari and Sanja Kožić,	2018	Higher intake of vitamin B12, particularly from milk, dairy products, and fish, is associated with a low-risk diet and lifestyle in individuals at high risk for colorectal cancer (CRC)	Increased consumption of vitamin B12-rich foods correlates with dietary and lifestyle patterns that may reduce CRC risk.
3	Gholamreza Haghighat, Ali Khajeh-Mehrizi, and Hamed Ranjbar	2023	Higher serum vitamin B12 levels in colon and breast cancer patients. Increased prevalence of elevated vitamin B12 (>800 pg/ml) in cancer patients. Positive correlation between vitamin B12 levels and tumor stage	Mean serum vitamin B12: Patients – 380.4 ± 540.2 pg/ml, Controls – 278.0 ± 314.08 pg/ml. Elevated B12 (>800 pg/ml): Patients – 32.9%, Controls – 10%. Correlation with tumor stage: r = 0.49, P = 0.001.
4	Da Pan, Ming Su, Dengfeng Xu, Yuanyuan Wang, Han Gao, James Daniel Smith, Jihan Sun, Xin Wang, Qingyang Yan, Guang Song, Yifei Lu, Wuqiong Feng, Shaokang Wang, and Guiju Sun.	2021	Higher dietary cobalt and serum vitamin B12 levels linked to reduced risk of oesophageal precancerous lesions (EPL). Elevated serum transcobalamin II (TC II) associated with lower EPL risk.	Higher dietary cobalt intake significantly decreased EPL risk (p = 0.034). Increased serum vitamin B12 levels linked to lower EPL risk (p = 0.036). Elevated TC II levels correlated with reduced EPL risk (p = 0.046).

Table 2: Shows the outcome and result of the effectiveness of Vitamin B12 in the studies mentioned above. The outcome and results were significant, indicating that Vitamin B12 plays a crucial role in cancer risk and prevention. Higher serum Vitamin B12 levels were associated with increased risk in colon and breast cancer, whereas adequate dietary intake and elevated levels correlated with a reduced risk of oesophageal precancerous lesions and colorectal cancer.

Table 3: Bias Analysis of The Included Studies

Sn.	Author (Year)	Randomization	Allocation Concealment	Comparison Group	Confounding	Experimental Conditions	Blinding	Complete Outcome Data	Exposure Characterization	Outcome Assessment	Outcome Reporting	No Other Threats
1	Sadaf Oliai Araghi et al. (2019)											
2	Ivana Banjari and Sanja Kožić (2018)											
3	Gholamreza Haghighat et al. (2023)											

4	Da Pan et al. (2021)											

Legend

Low Risk	Some Concerns	High Risk

Table 3: Shows the Risk of bias in all the included studies based on the Office of Health Assessment and Translation (OHAT) Assessment tool

Discussion

The relationship between vitamin B12 and cancer is complex, with evidence suggesting both protective and promotional effects. Adequate B12 levels support DNA synthesis and repair, potentially reducing cancer risk by preventing genomic instability. However, some studies have linked high B12 levels—particularly from supplementation—to an increased risk of cancers such as lung and colorectal cancer. This paradox could be caused by changed methylation pathways or by B12 acting as a biomarker for cancers that already exist rather than as a cause. This relationship is further complicated by the interaction of coexisting nutritional levels, hereditary variables and B12 consumption.

Understanding the intricate connection between vitamin b12 and cancer risk is crucial, as is placing these results in the context of suggested supplementation regimens and intake levels. According to the NIH Office of Dietary Supplements (2021) and , as per the Institute of Medicine (1998) the Recommended Dietary Intake (RDI) for vitamin B12, is 2.4 µg/day for healthy adults, 2.6 µg/day for pregnant women, and 2.8 µg/day for lactating women. These values are predicted on preserving regular DNA synthesis, red blood cell generation, and metabolic activity.

In clinical and public health practice, oral supplementation in the range of 25–100 µg/day is considered safe and favorable, particularly for individuals at risk of deficiency—such as vegetarians, the elderly, or patients on long-term antacid therapy .Occasionally, moderate deficiency conditions or problems with absorption lead to the prescription of higher doses , between 250 to 500 µg/day. 1000 µg/day orally or via intramuscular injection is used in situation of severe deficiency or pernicious anemia, usually under medical care. Evidence currently indicates caution with extended high-dose use in people without a proven deficit, even though these dosages are beneficial in addressing deficiencies.

Notably, research has shown that prolonged high-dose supplementation (≥500 µg/day) may be linked to an elevated risk of cancer. In the B PROOF randomized controlled study, for example, those who received 400 µg of folic acid and 500 µg of vitamin B12 daily for two to three years experienced a considerably higher incidence of colorectal cancer than those who received a placebo. Additionally, serum vitamin B12 levels exceeding 800–1000 pg/mL have been observed more frequently in cancer patients and have shown a positive correlation with tumor stage in certain cancers such as colon and breast cancer. These findings raise concerns about excessive supplementation, particularly when not medically indicated.

Because of this, vitamin B12 supplements should be designed to maintain and restore physiological levels without causing long-term supraphysiologic blood concentrations, even though vitamin B12 is essential for good health. The safest course of action, according to available data, is to follow dietary consumption guidelines, favor food-based sources, and save high-dose

supplements for people who have clinically confirmed deficiencies or problems with absorption. This well-rounded approach can assist avoid the potential hazards of excessive intake while preventing issues connected to deficiencies.

To distinguish between the effects of dietary and supplementary B12, evaluate long-term results, and set precise upper intake criteria, more study is required. Until then, the best course of action for managing cancer risk and general health seems to be to maintain adequate—but not excessive—B12 levels.

Sadaf Oliai Araghi, Jessica Jong, Suzanne Boon-van Dijk, and colleagues (2019) reported that this combined supplementation was associated with an increased risk of overall cancer, particularly colorectal cancer. Specifically, 43 participants (3.4%) in the supplementation group developed colorectal cancer compared to 25 participants (2.0%) in the placebo group, resulting in a hazard ratio (HR) of 1.77 (95% CI, 1.08–2.90; P = 0.02). These findings suggest that folic acid and vitamin B12 supplementation may elevate the risk of colorectal cancer. The authors recommend further research to confirm these results and to evaluate whether such supplementation should be limited to individuals with a known deficiency or specific medical indication

Ivana Banjari and Sanja Kožić, (2018) examined the relationship between dietary and lifestyle factors and vitamin B12 intake in people with a higher risk of colorectal cancer (CRC). Higher vitamin B12 intake, especially from milk, dairy products, and fish, was linked to a low-risk diet and lifestyle in this population, according to the authors. In particular, 52.2% of participants had high-risk dietary and lifestyle traits; risk was much lower for women, those with lower BMIs, and those who lived in cities. The scientists came to the conclusion that eating more foods high in vitamin B12 is associated with dietary and lifestyle choices that may lower the risk of colorectal cancer.

Gholamreza Haghighat, Ali Khajeh-Mehrizi, and Hamed Ranjbar (2023) reported that patients with colon and breast cancer had significantly higher serum vitamin B12 levels compared to healthy controls. It was observed that 32.9% of cancer patients had elevated B12 levels (>800 pg/ml) versus 10% in the control group. A positive correlation was noted between serum B12 levels and tumour stage in patients with colon and breast cancer, suggesting that higher levels may be linked to cancer progression in these malignancies. The authors proposed that increased B12 levels could be due to tumour-related metabolic changes or liver involvement, but further research is needed to confirm its potential as a biomarker for cancer detection and progression.

Da Pan, Ming Su, Dengfeng Xu, Yuanyuan Wang, Han Gao, James Daniel Smith, Jihan Sun, Xin Wang, Qingyang Yan, Guang Song, Yifei Lu, Wuqiong Feng, Shaokang Wang, and Guiju Sun. (2021) revealed that a lower risk of developing EPL was linked to higher dietary cobalt intake, elevated transcobalamin II (TC II) concentrations, and elevated serum vitamin B12 levels. In particular, individuals who consumed more cobalt in their diet were at a considerably decreased risk of developing EPL (p for trend = 0.034). Likewise, elevated TC II concentrations (p for trend = 0.046) and elevated serum vitamin B12 levels (p for trend = 0.036) were associated with a lower risk of EPL. According to these results, oesophageal precancerous lesions may be prevented by having enough amounts of cobalt and vitamin B12. The study emphasizes how crucial these nutrients may be for preventing oesophageal cancer.

Noor JJ et al. (2025) demonstrated that certain dietary bioactive compounds, such as gingerol, exert anti-carcinogenic effects by suppressing cancer-promoting

signaling pathways and enhancing tumor-suppressor activity. In contrast, emerging evidence suggests that excessive intake or dysregulated metabolism of vitamin B12 may exert opposing molecular effects. Elevated vitamin B12 levels have been implicated in the activation of proliferative signaling pathways, altered one-carbon metabolism, and reduced apoptotic regulation, thereby potentially facilitating tumor initiation or progression in susceptible individuals. These observations underscore that dietary components differ substantially in their influence on intracellular signaling networks, with vitamin B12 excess under specific biological contexts potentially shifting the molecular balance toward cancer-promoting events.[27]

Highlights

Vitamin B12 shows both protective and promotional effects in cancer. Adequate levels support DNA synthesis and repair, reducing mutation risk, but excessive supplementation may promote cancer development through altered methylation or by reflecting pre-existing malignancies.

Only 10–20% of large supplement doses of vitamin B_{12} are actually absorbed due to intrinsic-factor-dependent pathways. As a result, elevated cellular uptake may not always be reflected in elevated blood levels. Age, gastrointestinal health, and medication use (e.g., PPIs, antacids) can all lower B_{12} bioavailability and affect how the body reacts to supplementation.

The recommended daily intake (RDI) of vitamin B12 is 2.4 µg for adults, 2.6 µg for pregnant women, and 2.8 µg for lactating women. For the prevention of deficiencies, oral supplementation of 25–100 µg/day are safe; for moderate deficiencies, 250–500 µg/day; and for severe deficiencies, 1000 µg/day (oral or IM) under supervision.

For people who are unable to sufficiently absorb vitamin B12 through the gastrointestinal tract, such as those with pernicious anemia, intrinsic factor deficiency, ileal disease or resection, chronic malabsorption syndromes, patients undergoing gastric or bariatric surgery, and those taking long-term protocol pump inhibitors or metformin-related therapy, parenteral supplementation is especially advised.

According to studies like the B-PROOF study (2019) and Haghighat et al. (2023), long-term consumption of ≥500 µg/day or serum levels above 800–1000 pg/mL has been linked to an increased risk of malignancies, including colorectal, breast, and lung cancer.

Natural food sources of vitamin B12, such as meat, fish, dairy eggs, and others, seem to be neutral or even preventive against the risk of cancer. Eating enough to meet the recommended daily intake of 2.4 µg for people, which can be obtained from meals like 100g of fish (2.5 µg) or 1-2 eggs (0.5-1.0 µg), supports appropriate cellular metabolism and DNA integrity.

On the other hand, excessive synthetic vitamin B12 supplementation has been linked in certain studies to an increased incidence of some cancer, particularly when paired with high folic acid intake. This calls for caution when using high-dose supplements over an extended period of time in people who do not have a proven deficit.

Gender-related differences in vitamin B12 intake and dietary habits were evident in the study by Banjari & Kožić (2018), which found that 52.2% of participants were in the high-risk diet/lifestyle group for colorectal cancer. Men made up a larger share of this risk group, while women showed significantly lower risk.

Conclusion

Although there is evidence of both protective and possibly promoting effects, the role of vitamin B12 in cancer is still being investigated. Excessive B12 levels, particularly from supplements, have been connected to an

increased risk of several malignancies, even though sufficient levels are necessary for DNA stability and cellular function. Uncertainty surrounds the processes underlying this connection, which could include reverse causality, metabolic changes, or methylation modifications. A balanced approach to B12 intake is advised in light of these issues, prioritizing food sources over high-dose supplements. Future studies should focus on long-term effects, genetic influences, and the distinction between natural and synthetic B12 sources to provide clearer guidance. Until more definitive evidence emerges, maintaining sufficient but not excessive B12 levels appears to be the most prudent strategy for overall health and cancer risk management.

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