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# HYPERVITAMINOSIS B12 – IS IT A SIGNIFICANT PARAMETER IN THE CONTEXT OF CANCER? – REVIEW PAPER

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**ABSTRACT**

**Introduction and Objective**
Vitamin B12 plays an important role in hematopoiesis, the synthesis of myelin sheaths and the DNA methylation process. Food products rich in vitamin B12 include meat, offal, eggs, fish, and fermented plants. Hypervitaminosis B12 is serum level of this vitamin exceeding the reference range. Causes of this condition include liver or kidney failure, autoimmune diseases, infections, excessive supplementation, improper diet and malignant neoplasms.
**Materials and Methods**
The aim of our paper is analyzing studies about relationship between hypervitaminosis B12 and cancer disease. All articles are available in Google Scholar database in English, full-text online and free of charge. The phrase used for the search was 'Vitamin B12 cancer'.
**Results**
Conclusions drawn by analyzed studies. Oncologic patients exhibit higher average levels of vitamin B12. Hypervitaminosis B12 adversely impacts survival time in patients with diagnosed cancer. Prolonged hypervitaminosis is more frequently associated with the future occurrence of malignant neoplasms compared to temporarily elevated levels. During cancer regression, vitamin B12 levels normalize. Increased mortality among patients with hypervitaminosis B12 is observed both in oncologic and internal medicine patients.
**Conclusions**
The diagnosis of hypervitaminosis B12 should not be marginalized. Detailed diagnostics should be implemented to find its cause. In the future, monitoring the level of vitamin B12 may prove helpful in cancer prevention and in assessing the effectiveness of anticancer treatment. The detailed connections between vitamin B12 and the occurrence of malignant tumors are still unclear and require further scientific research.

**KEYWORDS**
Vitamin B12, Hypervitaminosis B12, Cancer, Colorectal Cancer, Solid Tumor

**CITATION**

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**Introduction - history of discovery, role of vitamin $B_{12}$, causes of hypervitaminosis $B_{12}$**

Vitamin $B_{12}$ (cobalamin) was first isolated from liver tissue and cultures of the fermenting bacterium Streptomyces griseus in 1948 by a team of scientists, including Rickes, Brink, Koniuszy, Wood, and Folkers. However, its discovery began over 20 years earlier. In the 1920s, George Hoyt Whipple pioneered a novel approach to treating anaemia in dogs by enriching their diet with large quantities of animal liver, which led to significant health improvements. Similarly, in 1926, dietary liver extracts were introduced to patients suffering from pernicious anaemia (Addison–Biermer disease), a condition caused by vitamin $B_{12}$ deficiency. It was achieved by George Richards Minot and William Parry Murphy (Smith, 1950). Together with George Hoyt Whipple, they were recognized and honored with the Nobel Prize in Physiology or Medicine in 1934 for their contributions to the treatment of pernicious anaemia. Vitamin $B_{12}$ belongs to the group of exogenous, water-soluble vitamins and contains a central cobalt atom in its structure. It exists in its active forms as methylcobalamin and 5′-deoxyadenosylcobalamin, serving as coenzymes for vitamin $B_{12}$-dependent reactions. Additionally, it is found in its inactive forms, including cyanocobalamin and hydroxocobalamin. Vitamin $B_{12}$ is stored in the human body, primarily in the liver and kidneys, with reserves lasting for several years. It is abundant in animal-derived products such as kidneys, liver, meat, eggs, dairy, and fish. The highest concentration of vitamin $B_{12}$ is found in animal offal and meat, more than 10 µg per 100 g of wet weight. In fish, eggs, and dairy products, the content is significantly lower, ranging between 1–10 µg per 100 g of wet weight (Romain, Sviri, Linton, Stavvan & van Heerden, 2016). Fermented plant-based products can also serve as a source of vitamin $B_{12}$. It is an essential component of hematopoiesis. Additionally, vitamin $B_{12}$ plays an essential role in myelin sheath formation and neurotransmitter synthesis (Starostka-Tatar & Łabuz-Roszak, 2023). It ensures chromosomal structural stability and is involved in DNA synthesis. Moreover, it performs an important role in DNA methylation, which is particularly significant in carcinogenesis and embryogenesis. Vitamin $B_{12}$ also functions as a coenzyme for methyltransferase. It is indispensable in the remethylation of homocysteine to methionine, thereby facilitating DNA methylation (Karapiperi, Gousis & Papaioannidou, 2010). In 2015, the European Food Safety Authority (EFSA) published a report on reference intake values for cobalamin. The summary established a standardized daily intake recommendation for adults, set at 4 µg/day, while also considering biomarkers of cobalamin status, such as methylmalonic acid (MMA) and homocysteine levels in biochemical blood tests. For pregnant women, the recommended intake is 4.5 µg/day, and for lactating mothers, it is 5 µg/day. Among children, the intake guidelines range from 1.5 µg/day for infants aged 7–11 months to 4 µg/day for adolescents aged 15–17 years (EFSA Journal, 2015). The preferred reference range for serum vitamin $B_{12}$ is 148–740 pmol/L (200–1000 ng/L).

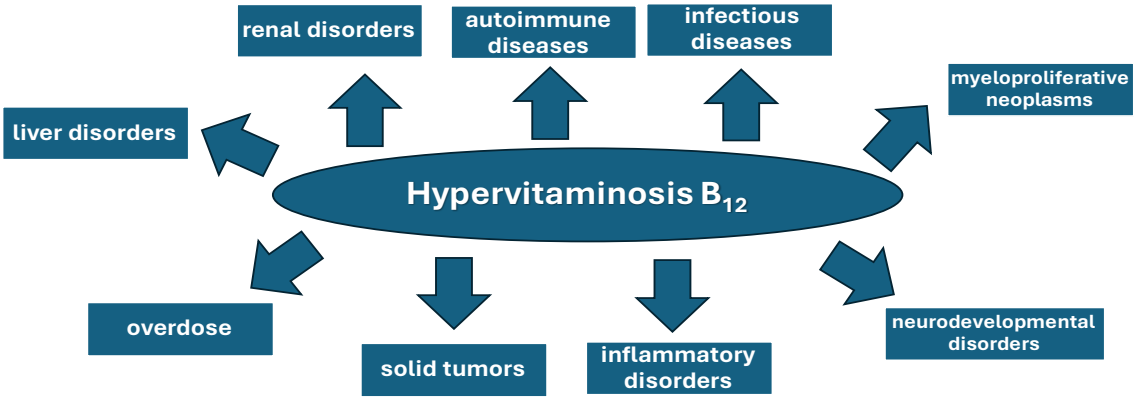


***Fig. 1.*** *Causes of hypervitaminosis $B_{12}$ (Kyriazi, 2024).*

**Methodology**

In recent years, studies have been published demonstrating that elevated vitamin $B_{12}$ levels may be associated with solid tumors. The aim of our study is analyzing of scientific reports relationship between hypervitaminosis $B_{12}$ and oncologic diseases. The review includes articles sourced from the Google Scholar database. This paper was conducted using the phrase "Vitamin B12 cancer." All articles included in this study are available in English, in full online versions, free of charge. The selection criteria were limited to studies published since 2015.

**Results**

**Serum levels of vitamin $B_{12}$ in patients with colon cancer and breast cancer**

Ghazaleh Haghighat with a team of researchers, conducted a study aimed at evaluating serum vitamin $B_{12}$ levels in patients with colon cancer and breast cancer, comparing them to healthy people. For this purpose, a research group was selected, consisting of patients diagnosed with colorectal cancer or breast cancer. The control group comprised healthy people with no oncological history, who were family members of the patients from the research group. To eliminate false results, participants who took medications that affected vitamin $B_{12}$ levels or were diagnosed with diseases that caused fluctuations in its levels were excluded from the study. The study included a total of 280 participants, with 140 members in the research group and 140 in the control group. Among those in the research group, 87 were diagnosed with breast cancer and 53 had colon cancer. The upper reference limit for serum vitamin $B_{12}$ was set at 800 pg/mL. Nearly 80% (220 participants) had serum levels of vit.$B_{12}$ below the upper reference limit. In the research group, 46 participants had elevated vitamin $B_{12}$ levels, compared to only 10 individuals in the control group. The mean serum $B_{12}$ level was significantly higher in the research group compared to the control group ($p=0.001$). However, no statistically significant difference in vitamin $B_{12}$ levels was observed between breast cancer patients and colon cancer patients ($p=0.8$). Using Pearson's correlation coefficient, a positive correlation was confirmed between the advanced stage of cancer and increased serum levels of vit. $B_{12}$ ($p=0.001$) (Haghighat, Khajeh-Mehrizi & Ranjbar, 2023).

**Serum levels of vitamin $B_{12}$ in colon cancer patients**

In 2015, Nai-Hui Sun and co-authors published the results of a meta-analysis aimed at assessing the relationship between vitamin $B_{12}$ intake, serum $B_{12}$ levels and the risk of colorectal cancer. The meta-analysis included 17 studies, of which 14 examined vitamin $B_{12}$ intake, while 3 investigated serum $B_{12}$ levels in patients diagnosed with colorectal cancer. A nonlinear statistically significant relationship was identified between vitamin $B_{12}$ intake and colorectal cancer risk ($p=0.026$). The risk decreased when daily vitamin $B_{12}$ intake exceeded 12.85 μg/day. Additionally, the findings indicate no statistically significant association between

serum vitamin $B_{12}$ levels and colorectal cancer incidence (p=0.219). An increase of 150 pmol/L in serum B12 levels did not elevate colorectal cancer risk (Sun et al., 2015).

In 2020, Hatim Boughanem and colleagues presented their study on global DNA methylation in relation to serum vitamin $B_{12}$ levels in patients with colorectal cancer. The study included 80 patients, divided into two groups. The first group consisted of patients with serum vitamin $B_{12}$ levels below the 25th percentile representing 24% of the study population. The second group included patients with serum vitamin $B_{12}$ levels exceeding the 25th percentile comprising 76% of participants. The 25th percentile threshold was 261 pg/mL. DNA samples were collected from peripheral blood mononuclear cells (PBMCs), tumor cells, adjacent non-cancerous tissues and visceral adipose tissue. In patients from the second group, a reduction in DNA methylation was observed in both analyzed cell types. The aim of the study was to investigate the association between LINE-1 (long interspersed nuclear element-1) methylation in patients divided into two groups. Pearson's correlation coefficient was used to analyze the relationship. LINE-1 methylation in tumor cells was significantly lower in patients from the second group compared to those in the first group (p=0.023). There was no significant difference in LINE-1 methylation between malignant tumor cells and healthy adjacent cells in both groups. However, it was demonstrated that LINE-1 methylation in tumor cells was markedly reduced compared to healthy adjacent cells in patients from the second group (p<0.001). Analysis of LINE-1 methylation in DNA extracted from peripheral blood mononuclear cells (PBMCs) showed results consistent with those observed in cancer cells. Patients in the second group exhibited lower LINE-1 methylation compared to those in the first group (p=0.046). In contrast to the previously analyzed tissues, no differences in LINE-1 methylation were observed in visceral adipose tissue among patients in both groups. A reduction in LINE-1 methylation in colorectal cancer cells was associated with worse prognosis, compared to those with higher methylation levels (Boughanem et al., 2020).

**Serum levels of vitamin $B_{12}$ in patients with metastatic solid tumors**

In 2020, Hye Kyung Oh and colleagues conducted a retrospective study among patients at a university hospital in Seoul, South Korea. Clinical patient data were collected over nine years. The study included only adult patients diagnosed with solid malignant tumors with metastases and serum vitamin B12 levels > 211 pg/mL. The reference range for normal serum vit. $B_{12}$ was 211–911 pg/mL. Patients with disturbing the normal level of vitamin $B_{12}$ were excluded from the analysis. A total of 523 patients were included in the study and divided into two groups. The first group comprised patients with normal serum $B_{12}$ levels (302 participants). The second group consisted of patients diagnosed with hypervitaminosis $B_{12}$ (221 participants). Among oncologic patients in the first group, the largest proportion had lung cancer, whereas in the hypervitaminosis $B_{12}$ group, most had liver or biliary tract cancer. The highest serum $B_{12}$ levels were recorded in patients diagnosed with liver or biliary tract cancer, neurological malignancies, colorectal cancer, and lung cancer. Among patients with breast cancer, sarcomas or head and neck cancer, the mean serum vitamin $B_{12}$ level remained within the reference range. Differences between the two groups were analyzed, focusing on mortality rates over two time periods - 30 days and 90 days. In the first group, mortality rates were 10.6% at 30 days and 34.1% at 90 days, whereas in the second group, they were significantly higher at 38.9% and 63.8%, respectively. Patients in the second group more frequently experienced liver dysfunction, required parenteral nutrition and demonstrated worse general activity, as assessed using the ECOG scale. These differences were deemed statistically significant (p<0.001). Survival time also varied significantly between the two groups (p<0.001). Kaplan-Meier survival analysis showed a median survival time of 5.1 months in the first group versus 1.8 months in the second group. Further analysis examined survival differences excluding patients with liver metastases. Among patients with normal serum vitamin $B_{12}$ levels, the median survival time was 6.1 months, while for those with elevated $B_{12}$ levels, it was 2.1 months (p<0.001). Survival time was also compared excluding patients with infectious diseases. In the first group, survival was 6.8 months, while in the second group, it was 2.7 months. Overall, oncologic patients with active metastatic cancer and hypervitaminosis $B_{12}$ had significantly shorter survival times compared to those within the normal reference range (Oh, Lee, Eo, Yoon & Hans, 2017).

**Long-term elevated serum vitamin $B_{12}$ levels and the risk of developing cancer**

The relationship between persistently elevated serum vitamin $B_{12}$ levels and the occurrence of solid malignant tumors was examined by Valentin Lacombe and colleagues. The study selected adult patients who had two measurements of serum levels vit. $B_{12}$ at two time points. The minimum time interval between the first and second measurement was 1 month, and the maximum was 48 months. The observation period lasted

60 months after the first $B_{12}$ measurement. Elevated serum $B_{12}$ was defined as ≥1000 ng/L. Among participants with two correct $B_{12}$ measurements, a control group (344 people) was created through matching for sex, age, and number of measurements. The research group comprised patients who had at least one elevated serum $B_{12}$ measurement, but excluded participants with disorders causes of hypervitaminosis or hypovitaminosis. The research group was further divided into two subgroups. The first group included participants with hypervitaminosis at two time points, while the second group consisted of those who had hypervitaminosis at the first time point and a normalized serum value at the second time point. Among qualified patients, 344 of them had elevated $B_{12}$ levels in the first time point. Among them, 144 exhibited persistent hypervitaminosis at the second time point, while 200 showed normalization of their initially high $B_{12}$ levels upon the second measurement. Mortality in first subgroup (persistent hypervitaminosis $B_{12}$) was significantly higher compared to the control group and second subgroup ($p<0.001$). In first subgroup, the risk of developing a malignant tumor was statistically significantly increased compared to the control group, with a hazard ratio (HR) of 5.90 [95% CI 2.79–12.45] ($p<0.001$). However, this association was not observed in second subgroup (normalized $B_{12}$ levels at the second measurement), with an HR of 1.52 [95% CI 0.70–3.30], ($p=0.29$). The highest cancer incidence was observed in first subgroup (20.8%), followed by second subgroup (6.0%), and the lowest in the control group (3.8%). It was demonstrated that first subgroup had a significant statistical association with the development of cancer ($p<0.001$) and metastatic cancer ($p<0.001$) compared to the control group. No such association was found between second subgroup and the control group ($p=0.56$ and $p=0.38$). The study concluded that long-term hypervitaminosis $B_{12}$ may be associated with an increased future risk of malignancy, whereas temporarily elevated serum $B_{12}$ levels showed no such relationship (Lacombe et al., 2021).

**Discussion**

One of the main factors contributing to hypervitaminosis $B_{12}$ is liver failure. This condition is caused by an increased level of haptocorrin (a protein that protects vitamin $B_{12}$ from the acidic environment in the stomach), the release of stored vitamin $B_{12}$ from the liver due to liver damage or reduced synthesis of transcobalamin II (a protein responsible for providing vit. $B_{12}$ to enter cells) which falsely elevates $B_{12}$ levels in the bloodstream. Other organ disorder lead to hypervitaminosis $B_{12}$ is kidney failure. It may also result from an improperly balanced diet lacking the active form of vitamin $B_{12}$, leading to an accumulation of inactive forms of the vitamin, also falsely increasing its blood levels. Autoimmune diseases can contribute to hypervitaminosis $B_{12}$ through the production of autoantibodies against transcobalamin II. Cancer cells induce hypervitaminosis $B_{12}$ by increasing haptocorrin synthesis (Kyriazi, 2024). Over the past several years, studies have indicated a higher mortality rate among patients with hypervitaminosis $B_{12}$. In 2023, Luisana Molina-Pimienta and colleagues published an article investigating the mortality rate in internal medicine patients with elevated levels of vit. $B_{12}$. The results indicated increased mortality in these individuals. Moreover, clinicians did not interpret hypervitaminosis $B_{12}$ as an abnormal finding in clinical practice (Molina-Pimienta, Amado-Garzón, Salgado-Sánchez & Vásquez-Jiménez, 2023). Hypervitaminosis $B_{12}$ is strongly associated with patient mortality within six months and 48 months following initial hospitalization. These conclusions were presented in a study by Betül Türker and colleagues (Çavuşoğlu, Solmaz, Türker & Ataoğlu, 2024). The relationship between vitamin $B_{12}$ and cancer development remains unclear and controversial. Previously, excess vitamin $B_{12}$ in the bloodstream was considered a consequence rather than a cause of cancer progression, as secondary liver damage could occur due to metastasis. However, recent publications indicate that the risk of developing cancer is higher in patients with no prior oncologic history but with existing hypervitaminosis $B_{12}$. At present, there is insufficient evidence linking blood vitamin $B_{12}$ levels to specific malignant tumors. Nevertheless, considering the findings, normalizing vit. $B_{12}$ values during cancer treatment could potentially be used as an indicator of effective therapy response. Based on the presented research findings, hypervitaminosis $B_{12}$ is associated with poorer prognosis and increased mortality among patients, not just in oncology. Monitoring blood vitamin $B_{12}$ levels may be a valuable diagnostic tool for the prevention of cancer and other organ dysfunctions.

**Conclusions**

Elevated vitamin $B_{12}$ levels should be thoroughly examined and explained. The causes of hypervitaminosis $B_{12}$ include organ diseases, autoimmune disorders and cancer. Recent studies suggest an association between hypervitaminosis $B_{12}$ and an increased risk of cancer development. Hypervitaminosis $B_{12}$ may adversely affect prognosis in patients diagnosed with cancer. Effective anticancer treatment leading to tumor regression allows for the normalization of levels in the blood. During oncologic treatment, measuring $B_{12}$ levels in the blood can be using for monitoring therapy effectiveness. To thoroughly elucidate the relationship between vitamin $B_{12}$ and carcinogenesis, further scientific research is required.

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**Conflict of Interest Statement**
The authors reported no potential conflict of interest.

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