Clinics in Oncology

Case Report
Published: 31 Dec, 2024

High Plasma Level of Vitamin B12 (Cobalamin [Cbl]) Associated with Early Breast Cancer (EBC) Diagnosis: A Case Report

Sharif Kullab[1], Yahya Al-Imamah[1], Mohammed Ghandour[1], Ahmed Jamal[1], Muath Abu Hilal[1] and Frederique Penault-Llorca[2]*

[1]Department of Oncology, King Saud University (KSU), Riyadh, Saudi Arabia

[2]Centre Jean Perrin (CJP), Clermont-Ferrand France, France

Abstract

Measurement of plasma vitamin B12 or Cobalamin (Cbl) is requested frequently in routine blood tests. Incidental findings of elevated levels of plasma Cbl are not uncommon, but they remain underestimated. However, it can be associated with serious medical situations such as underlying non-malignant or malignant disease. Such association with non-malignant disease is widely described and understood. Nonetheless, its relationship with underlying cancer conditions is still not well defined and not completely clear.

We report an incidental finding of persistent elevated plasma levels of Cbl. Investigation of this clinical situation leads to Breast Cancer (BC) diagnosis at an early stage. Treatment of this patient's breast cancer was characterized by a progressive decrease and then normalization of her plasma Cbl level.

Some retrospective and prospective studies support the relationship between BC and a high plasma level of Cbl. However, the mechanism of action and the real relation are still poorly understood and encompass several other risk factors, mainly genetic and nutritional factors.

Keywords: Breast Cancer (BC); High/elevated plasma level of vitamin B12 (Cobalamin [Cbl]); Early Breast Cancer (EBC)

OPEN ACCESS

Correspondence:
Sharif Kullab, Department of Oncology, King Saud University (KSU), Riyadh, Saudi Arabia, Tel: +966566383043;

Received Date: *11 Dec 2024*
Accepted Date: *30 Dec 2024*
Published Date: *31 Dec 2024*

Citation:
Sharif Kullab, Yahya Al-Imamah, Mohammed Ghandour, Ahmed Jamal, Muath Abu Hilal, Frederique Penault-Llorca. High Plasma Level of Vitamin B12 (Cobalamin [Cbl]) Associated with Early Breast Cancer (EBC) Diagnosis: A Case Report. Clin Oncol. 2024; 9: 2119.

ISSN: 2474-1663

Abbreviations

BC: Breast Cancer; BU: Breast Ultrasound; EBC: Early Breast Cancer; ER: Estrogen Receptor; Cbl: Cobalamin; CRP: C-Reactive Protein; CT: Chemotherapy; HC: Haptocorrin; HCC: Hepatocellular Carcinoma; HER-2: Human Epidermal Growth Factor Receptor-2; HT: Hormonal Treatment; IHC: Immunohistochemistry; ILC: Invasive Lobular Carcinoma; LVI: Lymphovascular Invasion; MRI: Magnetic Resonance Imaging; MRM: Modified Radical Mastectomy; MTHFR: Methylenetetrahydrofolate Reductase; OR: Odd Ration; PI: Perineural Invasion; PLP: pyridoxal 5-phosphate; PR: Progesterone Receptor; RS: Recurrence Score; RT: Radiotherapy; SBR: Scarf Bloom Richardson; SLN: Sentinel Lymph Node; TCB: Transcobalamin; US: Ultrasound

Introduction

BC is the most diagnosed cancer and the leading cause of cancer death among females [1,2]. The etiology of BC is complex and results from a combination of lifetime reproductive events, genetics, dietary, and lifestyle factors [3].

Out of screening cases, the most common presenting symptoms are, usually, a breast lump finding on auto palpation, followed by no lump breast symptoms (e.g., nipple abnormalities and breast pain) and non-breast symptoms (e.g., back pain and weight loss) [4,5]. It is almost rare to have the diagnosis of BC upon non-symptomatic blood investigation.

High plasma Cbl level is defined by a rate above 950 pg/ml (701 pmol/l), which corresponds, by biological standards, to the upper limit of biological normality in the absence of any sign and/ or clinical anomalies [6]. This has been reported in cases of high dietary intake, liver diseases, kidney diseases, hematological disorders, and rarely solid tumors, like breast cancer. We report a case of incidental finding of isolated high plasma Cbl level, which has been investigated and led to the diagnosis of EBC.

Observation

Our case is related to a 46-year-old premenopausal woman who was following up with a hematology clinic for her thalassemia minor. She is free, otherwise, from any other medical illnesses. Her routine lab test, using a local hospital kit, showed an elevated plasma Cbl level on consecutive exams, ranging between 842 and 1144 pmol/L, over 16 months.

On her physical examination, there were no skin changes bilaterally, and both nipples were normal without discharges. On palpation of the right breast, there was a palpable mass of approximately one to 1.5 cm. Examination of the contralateral breast and both axillary and supraclavicular area was unremarkable. Other parameters of physical examination were also free of any significant findings.

Etiological studies were carried out in order to explain the persistently high level of Cbl, and couldn't find any primary etiology: there was no notion of high dietary intake, no associated liver or kidney disease, no other significant hematological disorders, and all other blood test results were within normal ranges.

In order to complete her investigation, a diagnostic mammogram was carried out, and it showed dense breasts with asymmetry seen in the upper aspect of both breasts without underlying suspicious mass or microcalcification. Breast Ultrasound (US) was done and showed the right breast, 5 cm from the nipple, an irregular heterogeneous, mainly hypoechoic mass with mild vascularity on color Doppler measuring 2.3 × 1.2 × 2 cm. No abnormality was seen otherwise on the mammogram or US at the contralateral breast and on both axillary areas. Given diffuse and bilateral breast densities, breast Magnetic Resonance Imaging (MRI) was done and confirmed the findings of breast US without any other suspicious lesion.

US-guided true-cut biopsy was carried out targeting the right breast mass, and the reading was in favor of Invasive Lobular Carcinoma (ILC), Grade II, Scarf Bloom Richardson Score (SBR) of 6: (tubular formation: 3, nuclear pleomorphism: 2 and mitotic index: 1), ki-67 (10%), without Perineural Invasion (PI) or Lymphovascular Invasion (LVI). Immunohistochemistry (IHC) test showed an intense positivity of both Estrogen Receptor (ER) and Progesterone Receptor (PR) status of around 95%, 3+, Allred 8, without amplification of human epidermal growth factor receptor 2 (Her-2).

Other radiological investigations, in terms of CT scans of chest-abdomen-pelvis and bone scans, did not find any distant disease.

The patient underwent a Modified Radical Mastectomy (MRM) of her right breast with the Sentinel Lymph Node (SLN) technique. The final histopathology report confirmed the findings of true cut biopsy, and the disease was of stage IIA: pT2 pN0 (sn), Luminal subtype. To estimate her potential need for adjuvant Chemotherapy (CT), a genomic test using an Oncotype Dx - Recurrence Score (RS) test was run. The RS result was 7%, in favor of low-risk profile disease, without indication of CT.

The patient was started on tamoxifen-based adjuvant Hormonal Treatment (HT) without an indication of Radiotherapy (RT).

Since surgery, the patient underwent a series of vitamin B12 blood tests that showed a progressive normalization. This was confirmed on her last visit, which was almost 22 months post-surgery; see (Figure 1) and (Table 1).

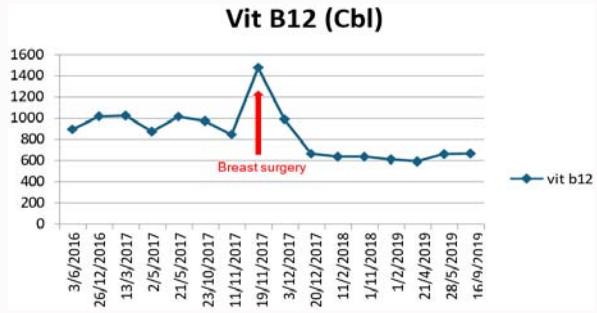

Figure 1: Series of patient vitamin B12 level.

Table 1: Series of patient's vitamin B12 level.

Date	Vitamin B12 level (pmol/L)
Pre-Surgery	
03-06-2016	894
26-12-2016	1014
13-03-2017	1024
02-05-2017	873
21-05-2017	1013
23-10-2017	970
11-11-2017	842
12-11-2017	**Surgery: MRM + SLN**
Post-Surgery	
19-11-2017	1476
03-12-2017	986.4
20-12-2017	661
17-01-2018	635.5
11-02-2018	634.8
01-11-2018	608
01-02-2019	590
21-04-2019	660
28-05-2019	663
16-09-2019	627

Discussion

Cbl is an essential nutrient involved in body metabolism and cell division. Daily intake of 2 to 5 µg, together with efficient absorption, transportation, and transformation, is needed to maintain health [7]. Cbl, as well as other vitamin B subtypes, such as vitamin B9 (Folate) and vitamin B6 (Pyridoxine), are involved in our metabolism, where they play important roles in DNA synthesis and methylation, which are linked to carcinogenesis [8-10].

Elevated plasma Cbl levels have been associated with several non-malignant diseases, including liver, renal, autoimmune, infectious diseases, and alcoholism [11-13]. However, the association between elevated plasma Cbl levels and cancer is poorly understood.

Most studies on normal or low Cbl levels in relation to cancer have been negative [14-17]. On the other hand, the relation between high plasma levels of Cbl and solid neoplasms has been suggested in some retrospective and prospective studies.

It was first described and documented by Carmel, et al. in 1975 and

1977 [18,19]. Several studies have since supported this observation. The carcinomas most frequently involved are Hepatocellular Carcinoma (HCC) and secondary liver tumors. Elevated Cbl levels have been reported, to a lesser extent, in breast cancer, colon cancer, gastric cancer, and pancreatic tumors [20-22].

In some old series, approximately half of the patients with HCC presented with high plasma Cbl [23]. In patients with liver metastases, the frequency of high plasma Cbl is estimated at 30% to 40%, with Cbl levels sometimes reaching extreme thresholds [24-26].

In a retrospective epidemiological study of Chiche, et al. [6] 23% of patients with high plasma Cbl had a previously unknown solid cancer in 73% of cases, which was still at a non-metastatic stage in 80% of cases.

The association between high plasma Cbl and malignant disease has also been demonstrated by Jammal, et al. [27] in another retrospective trial, with an Odd Ratio (OR) of 1.8 for all cancers combined, 2.9 for metastatic tumors, 3.3 for HCC, 4.7 for other primary hepatic tumors and 6.2 for neoplasms with liver metastases.

We know that high plasma levels of Cbl involve three essential pathophysiological mechanisms. These mechanisms are a direct increase in plasma cobalamin by excess intake or administration, a direct increase in plasma cobalamin by liberation from an internal reservoir, an increase in Transcobalamin (TCB) *via* excess production or lack of clearance, and a quantitative deficiency or lack of affinity of TCB for Cbl [6,18,20,24,27-30].

In liver tumors, the primary mechanisms implicated in the genesis of elevated plasma Cbl are the decrease in hepatic clearance of the Haptocorrin (HC) - Cbl complex and high plasma levels of TCB due to excess degradation of hepatocytes. The decrease in hepatic clearance is thought to be due to poor hepatic vascularization and the reduction in the number of HC receptors on the surface of tumor hepatocytes [6,20].

In other solid tumors, high plasma Cbl is thought to be mainly related to an excess synthesis of TCB by the tumor or an increase in HCs due to the induction of hyperleukocytosis [6,20,25].

From a prognostic point of view, the correlation observed in some cases between the size of certain tumors, particularly of the liver, and the degree of elevation of Cbl has suggested plasma Cbl levels as a possible tumor marker for poor prognosis [31,32]. High plasma Cbl level was also shown to be a predictor factor for mortality in advanced stages and in terminally ill cancer patients. In addition, Creactive Protein (CRP) was the most important prognostic factor in such populations with elevated plasma Cbl levels. This combination of high plasma Cbl level and CRP allowed us to define a new prognostic index that can distinguish different levels of mortality risk [33,34].

When it comes to BC, the situation is quite different, mainly in the early stages. Regarding the association between high plasma levels of Cbl and BC, two questions need to be addressed to help the understanding of the causality and/or the effect of this association:

Is an elevated plasma Cbl level resulting from the cancer disease directly or indirectly a paraneoplastic syndrome?

Or whether such an elevated level of Cbl might be a risk factor for cancer.

Several factors have been suggested to influence the association between B vitamins and the risk of BC, including menopausal status, alcohol consumption, Nutrient interactions, and Methylenetetrahydrofolate Reductase (MTHFR) gene polymorphisms [35-41].

Biomarkers of folate and Cbl and BC risk have been studied in some prospective trials. These biomarkers were not found to be significantly associated with BC. Furthermore, A marginally positive association was found between vitamin B12 status and BC risk in women consuming above the median level of alcohol (ORQ4-Q1=1.26; 95% CI 1.00- 1.58; Ptrend=0.05). Vitamin B12 status was also positively associated with BC risk in women with plasma folate levels below the median value (ORQ4-Q1=1.29; 95% CI 1.02-1.62; Ptrend=0.03). Overall, folate and vitamin B12 status was not clearly associated with BC risk in prospective cohort studies [42-45].

The largest reported study was conducted by Arendt, et al. [46] and reported in 2013, based on a large cohort of patients referred for plasma Cbl measurement. In this study, 333,667 patients without prevalent cancer and not receiving Cbl treatment were identified. Six percent had Cbl levels greater than the upper reference limit in this trial (≥601 pmol/L). Cancer risk increased with higher Cbl levels and was highest during the first year of follow-up. The risks were particularly elevated in the case of hematological neoplasia and smoking or alcohol-related cancers, most substantially for persons with Cbl levels greater than 800 pmol/L [46].

A prospective trial examined the association of plasma B vitamins and metabolites with the risk of BC among predominantly premenopausal women. A higher plasma level of vitamin pyridoxal 5- phosphate (PLP; the principal active form of B6), homocysteine, cysteine, and cysteinylglycine were not associated with the risk of BC overall. In contrast, a significant positive association between plasma levels of Cbl and risk of BC overall was observed. Among these cases of BC, a significant positive correlation with invasive, ER+/PR+, and luminal A tumors was observed [47].

Conclusion

Vitamin B12 or Cbl is crucial for our metabolism. A high plasma level of Cbl is clearly associated with some non-malignant diseases. However, its association with solid tumors is still poorly understood.

Several prospective studies have suggested a potential role of Cbl in breast carcinogenesis. This association is not supported in other prospective studies. The potential deleterious effect of high Cbl status in combination with other risk factors for BC is still not clear and deserves further investigations and prospective trials.

Some combined mathematical modalities, using the level of Cbl and CRP, might represent a prognostic index, which helps to distinguish different levels of mortality risk in advanced stages.

BC is not commonly exhibited with isolated elevated Cbl, especially at early stages. Incidental high Cbl level should not be underestimated as it may indicate early stages of malignancies. Extensive clinical examination, as well as baseline and specific investigations in such cases, is warranted and needs to include malignancies workup, mainly in cases of persistence of increased plasma Cbl level. In all cases, monitoring the Cbl level after the treatment of putative underlying etiologies remains necessary to confirm the causality link.

References

1. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women:

Burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444-57.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

3. Hankinson SE, Colditz GA, Willett WC. The lifelong interplay of genes, lifestyle, and hormones. Breast Cancer Res. 2004;6(5):213-8.

4. Koo MM, von Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. Cancer Epidemiol. 2017;48:140-6.

5. Walker S, Hyde C, Hamilton W. Risk of breast cancer in symptomatic women in primary care: A case-control study using electronic records. Br J Gen Pract. 2014;64(629):e788-93.

6. Chiche L, Jean R, Romain F, Roux F, Thomas G, Canavese S, et al. Clinical implications of high cobalamin blood levels for internal medecine. Rev Med Interne. 2008;29(3):187-94.

7. Nielsen MJ, Rasmussen MR, Andersen CBF, Nexø E, Moestrup SK. Vitamin B 12 transport from food to the body's cells - A sophisticated, multistep pathway. Nat Rev Gastroenterol Hepatol. 2012;9(6):345-54.

8. Scott JM, Weir DG. Folic acid, homocysteine and one-carbon metabolism: A review of the essential biochemistry. J Cardiovasc Risk. 1998;5(4):223-7.

9. Potischman N, Freudenheim JL. Biomarkers of nutritional exposure and nutritional status: An overview. J Nutr. 2003;133(3):873S-874S.

10. Nazki FH, Sameer AS, Ganaie BA. Folate: Metabolism, genes, polymorphisms and the associated diseases. Gene. 2014;533(1):11-20.

11. Arendt JFB, Nexo E. Unexpected high plasma cobalamin. Clin Chem Lab Med. 2013;51(3):489-96.

12. Zulfiqar AA, Sebaux A, Andrès E, Novella JL. Hypervitaminia B12: An Unknown Endocrine Marker. J Food Nutr Sci. 2015;3(2):32.

13. Serraj K, Mecili M, Housni I, Andrès E. Hypervitaminemia B12 (high level of cobalamin): Physiopathology, role and interest in clinical practice. Presse Med. 2011;40(12 pt 1):1120-7.

14. De Vogel S, Schneede J, Ueland PM, Vollset SE, Meyer K, Fredriksen Å, et al. Biomarkers related to one-carbon metabolism as potential risk factors for distal colorectal adenomas. Cancer Epidemiol Biomarkers Prev. 2011;20(8):1726-35.

15. Gibson TM, Weinstein SJ, Mayne ST, Pfeiffer RM, Selhub J, Taylor PR, et al. A prospective study of one-carbon metabolism biomarkers and risk of renal cell carcinoma. Cancer Causes Control. 2010;21(7):1061-9.

16. Schernhammer E, Wolpin B, Rifai N, Cochrane B, Manson JA, Ma J, et al. Plasma folate, vitamin B6, Vitamin B12, and homocysteine and pancreatic cancer risk in four large cohorts. Cancer Res. 2007;67(11):5553-60.

17. Vollset SE, Igland J, Jenab M, Fredriksen Å, Meyer K, Eussen S, et al. The association of gastric cancer risk with plasma folate, cobalamin, and Methylenetetrahydrofolate reductase polymorphisms in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2416-24.

18. Carmel R, Eisenberg L. Serum vitamin B12 and transcobalamin abnormalities in patients with cancer. Cancer. 1977;40(3):1348-53.

19. New T, Journal E. The New England Journal of Medicine ownloaded from www.nejm.org at COLUMBIA UNIV HEALTH SCIENCES LIB on September 2, 2010. For personal use only. No other uses without permission Copyright© 1986 Massachusetts Medical Society. 2010.

20. Andrès E, Serraj K, Zhu J, Vermorken AJM. The pathophysiology of elevated vitamin b12 in clinical practice. QJM. 2013;106(6):505-15.

21. Collin SM, Metcalfe C, Refsum H, Lewis SJ, Zuccolo L, Smith GD, et al. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010;19(6):1632-42.

22. Johansson M, Relton C, Ueland PM, Vollset SE, Midttun O, Nygård O, et al. Serum B Vitamin Levels and Risk of Lung Cancer. JAMA. 2010;303(23):2377-85.

23. Frémont S, Champigneulle B, Gérard P, Felden F, Lambert D, Guéant JL, et al. Blood transcobalamin levels in malignant hepatoma. Tumor Biol. 1991;12(6):353-9.

24. Arendt JFB, Nexo E. Cobalamin Related Parameters and Disease Patterns in Patients with Increased Serum Cobalamin Levels. PLoS One. 2012;7(9):e45979.

25. Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. Clin Biochem. 2003;36(8):585-90.

26. Gimsing P, Hippe E. Increased Concentration of Transcobalamin I in a Patient with Metastatic Carcinoma of the Breast. Scand J Haematol. 1978;21(3):243-9.

27. Jammal M, Deneuville T, Mario N, Tiev K, Tolédano C, Josselin-Mahr L, et al. High plasmatic concentrtion of vitamine B12: un indicator of hepatic disease or tumour. Rev Med Interne. 2013;34(6):337-41.

28. Wu K, Helzlsouer KJ, Comstock GW, Hoffman SC, Nadeau MR, Selhub J. A prospective study on folate, B12, and pyridoxal 5'-phosphate (B6) and breast cancer. Cancer Epidemiol Biomarkers Prev. 1999;8(3):209-17.

29. Markman M. Cancer in women. J Women's Heal (Larchmt). 2019;28(2):236.

30. Stevens VL, McCullough ML, Sun J, Gapstur SM. Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr. 2010;91(6):1708-15.

31. De Batlle JD, Ferrari P, Chajes V, Park JY, Slimani N, McKenzie F, et al. Dietary folate intake and breast cancer risk: European prospective investigation into cancer and nutrition. J Natl Cancer Inst. 2015;107(1):367.

32. Lajous M, Romieu I, Sabia S, Clavel-chapelon F. Women breast cancer in a prospective study of French women. 2014;17(9):1209-13.

33. Geissbühler P, Mermillod B, Rapin CH. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. J Pain Symptom Manage. 2000;20(2):93-103.

34. Kelly L, White S, Stone PC. The B12/CRP index as a simple prognostic indicator in patients with advanced cancer: a confirmatory study. Ann Oncol. 2007;18(8):1395-9.

35. Zhang SM, Willett WC, Selhub J, Hunter DJ, Giovannucci EL, Holmes MD, et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. J Natl Cancer Inst. 2003;95(5):373-80.

36. Ericson U, Sonestedt E, Gullberg B, Olsson H, Wirfält E. High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmö Diet and Cancer cohort1-3. Am J Clin Nutr. 2007;86(2):434-43.

37. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, Johnson KA, Johnson C, Buys SS, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr. 2006;83(4):895-904.

38. Agnoli C, Grioni S, Krogh V, Pala V, Allione A, Matullo G, et al. Plasma riboflavin and vitamin B-6, but not homocysteine, folate, or vitamin B-12, are inversely associated with breast cancer risk in the european prospective investigation into cancer and nutrition-varese cohort. J Nutr. 2016;146(6):1227-34.

39. Kane SP, Murray-Lyon IM, Paradinas FJ, Johnson PJ, Williams R, Orr AH. Vitamin B12 binding protein as a tumour marker for hepatocellular carcinoma. Gut. 1978;19(12):1105-9.

40. Wheeler K, Pritchard J, Luck W, Rossiter M. Transcobalamin I as a "marker" for fibrolamellar hepatoma. Med Pediatr Oncol. 1986;14(4):227-9.

41. Matejcic M, de Batlle J, Ricci C, Biessy C, Perrier F, Huybrechts I, et al. Biomarkers of folate and vitamin B12 and breast cancer risk: report from the EPIC cohort. Int J Cancer. 2017;140(6):1246-59.

42. Zittoun J, Zittoun R, Marquet J, Sultan C. The Three Transcobalamins in Myeloproliferative Disorders and Acute Leukaemia. Br J Haematol. 1975;31(3):287-98.

43. Ericson UC, Ivarsson MIL, Sonestedt E, Gullberg B, Carlson J, Olsson H, et al. Increased breast cancer risk at high plasma folate concentrations among women with the MTHFR 677T allele. Am J Clin Nutr. 2009;90(5):1380-9.

44. Lildballe DL, Nguyen KQT, Poulsen SS, Nielsen HO, Nexo E. Haptocorrin as marker of disease progression in fibrolamellar hepatocellular carcinoma. Eur J Surg Oncol. 2011;37(1):72-9.

45. Nörredam K, Chainuvati T, Gimsing P, Hippe E, Viranuvatti V. Plasma cobalamin and transcobalamin in patients with primary carcinoma of the liver: A study from Thailand. Scand J Gastroenterol. 1983;18(2):229-32.

46. Arendt JFB, Pedersen L, Nexo E, Sørensen HT. Elevated plasma vitamin B12 levels as a marker for cancer: A population-based cohort study. J Natl Cancer Inst. 2013;105(23):1799-805.

47. Houghton SC, Eliassen AH, Zhang SM, Selhub J, Rosner BA, Willett WC, et al. Plasma B-vitamins and one-carbon metabolites and the risk of breast cancer in younger women. Breast Cancer Res Treat. 2019;176(1):191-203.