Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0098

The relationship between serum vitamin B12 level and fibroadenoma in adolescent female patients: a retrospective case-control study[a]

Melda Berber Hamamcı*[1], Şule Yeşil[2], Semih Ergişi[3], Ceren Kılcı[4]
Ali Fettah[2], Gürses Şahin[2]

[1]Division of Pediatric Oncology, Department of Pediatrics, Faculty of Medicine, Ankara University, Ankara, Turkiye
[2]Department of Pediatric Hematology and Oncology, Ankara Etlik City Hospital, Ankara, Turkiye
[3]Department of Methodology, Turkish Statistical Institute, Ankara, Turkiye
[4]Division of Pediatric Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Başkent University, Ankara, Turkiye

Cite this article: Berber Hamamcı M, Yeşil Ş, Ergişi S, Kılcı C, Fettah A, Gürses Ş. The relationship between serum vitamin B12 level and fibroadenoma in adolescent female patients: a retrospective case-control study. *J Curr Hematol Oncol Res.* 2026;4(4):140-145. doi:10.51271/JCHOR-0098

***Corresponding Author:** Melda Berber Hamamcı, meldaberber@hotmail.com

Received: 09/07/2026 ◆ **Accepted**: 19/08/2026 ◆ **Published**: 13/11/2026

ABSTRACT

Aims: This study aimed to investigate serum vitamin B12 levels in adolescent female patients diagnosed with fibroadenoma and to evaluate whether a significant difference exists between fibroadenoma patients and healthy controls.

Methods: This retrospective case-control study was conducted between 2018 and 2023. A total of 46 adolescent female patients diagnosed with fibroadenoma based on ultrasonographic (USG) evaluation in accordance with ACR guidelines, with histopathological confirmation in eight cases (17%), and 46 age- and gender-matched controls were included. Hematological parameters were analyzed alongside serum vitamin B12 levels. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of fibroadenoma. A decision tree model was additionally constructed to define clinically meaningful threshold values.

Results: The mean serum vitamin B12 level was significantly lower in the fibroadenoma group compared to controls (304.54±79 pg/ml vs. 407±137 pg/ml; p<0.001). Among fibroadenoma patients, 88.9% had vitamin B12 levels below 300 pg/ml. The proportion of patients with vitamin B12 levels exceeding 340 pg/ml was 18.9% in the fibroadenoma group versus 81.1% in controls, a statistically significant difference (p=0.019). Multivariate logistic regression identified low serum vitamin B12 level as an independent predictor of fibroadenoma. Decision tree analysis confirmed vitamin B12 as the primary discriminating variable, with red cell distribution width (RDW) emerging as a secondary node.

Conclusion: To our knowledge, this is the first study to investigate serum vitamin B12 levels in adolescent patients with fibroadenoma. The significantly lower vitamin B12 levels observed in fibroadenoma patients compared to controls suggest a potential role of vitamin B12 in the pathogenesis of this benign breast lesion. The identified 300 pg/ml threshold suggests that serum vitamin B12 may serve as a simple and accessible biomarker for fibroadenoma risk stratification in adolescents. Prospective multicenter studies incorporating functional B12 markers such as homocysteine and methylmalonic acid are needed to validate these findings

Keywords: Fibroadenoma, vitamin B12, adolescent, benign breast disease

[a]This study was presented as an oral presentation at the 45th Pediatrics Days, 24th Pediatric Nursing Days, and 1st Pediatric Dietetics Days, İstanbul, April 25–28, 2023.

INTRODUCTION

Fibroadenoma is the most common benign breast neoplasm in adolescents and young adult females. These lesions account for approximately 68% of all breast masses and 44–94% of biopsy-evaluated breast lesions in this age group.[1] The etiology of this lesion, characterized by simultaneous proliferation of stromal and epithelial components, is thought to involve increased estrogen sensitivity, local growth factors, and hormonal variables. Although fibroadenomas are classified as benign lesions, the potential for malignant transformation in cases containing proliferative epithelial changes should not be overlooked. Dupont et al.[2] reported that the risk of invasive breast cancer was 2.17-fold higher in females with fibroadenoma compared to controls, rising to 3.10 in complex fibroadenoma. In the systematic review by El-Wakeel and Umpleby,[3] fibroadenoma with atypical changes was reported to carry a 0.12–0.3% risk of malignant transformation.

Vitamin B12 is an essential vitamin that plays a critical role in one-carbon metabolism, DNA synthesis, and methylation pathways.[4] As a cofactor of methionine synthase,

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

it supports the biosynthesis of S-adenosylmethionine (SAM), the principal methyl group donor for DNA, RNA, and histone methylation. It has been proposed that B12 deficiency may predispose rapidly dividing tissues such as the breast to proliferative changes through homocysteine accumulation, DNA strand breaks, aberrant methylation of tumor suppressor genes, and genomic instability.[4,5] During adolescence, the rapid rise in estrogen levels increases the proliferative capacity of the breast gland; vitamin B12 deficiency at this stage may, through its role as a critical cofactor in DNA methylation and synthesis, create the epigenetic milieu that supports cellular proliferation.

Existing studies have examined the relationship between vitamin B12 and breast gland pathology predominantly in the context of invasive breast cancer.[6-10] Although inconsistent findings have been reported in prospective studies and meta-analyses, the relationship between serum B12 levels and the presence of benign breast lesions such as fibroadenoma has not yet been investigated. To our knowledge, no study has directly examined the association between serum vitamin B12 level and fibroadenoma. This gap in the literature is clinically significant, particularly given the adolescent population. Considering that vitamin B12 deficiency is highly prevalent in adolescents and that the breast gland in this age group is especially sensitive to hormonal stimuli, investigation of this relationship carries considerable clinical and biological importance.

In this context, exploring the potential role of vitamin B12 in fibroadenoma pathogenesis during adolescence is of value both for elucidating biological mechanisms and for identifying clinical risk markers. Accordingly, this study aimed to investigate the association between serum vitamin B12 levels and fibroadenoma in adolescent female patients, and to evaluate the independent predictive role of serum vitamin B12 in fibroadenoma risk through logistic regression and decision tree analyses.

METHODS

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 27.11.2024, Decision No: AEŞH-BADEK-2024-1132). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective case-control study was conducted at a tertiary referral center. The fibroadenoma group was drawn from the department of pediatric surgery, and the control group was selected from the pediatric oncology outpatient clinic.

Medical records of adolescent female patients aged 10–19 years who presented to our clinic between 2018 and 2023 and were diagnosed with fibroadenoma based on ultrasonographic (USG) evaluation of a palpable breast mass were retrospectively reviewed. According to American College of Radiology (ACR) guidelines, USG is recommended as the primary imaging modality for the evaluation of palpable breast masses in females under 30 years of age, owing to its low radiation risk and high diagnostic accuracy.[11] Accordingly, diagnoses in our study were based on USG evaluation performed by experienced radiologists in accordance with the BI-RADS classification system. Cases with non-fibroadenoma diagnoses such as cyst, lipoma, or axillary lymphadenopathy were excluded. In eight patients (17%), additional histopathological confirmation was obtained, and pathology results were fully concordant with the USG diagnosis.

A total of 92 patients were included: 46 patients diagnosed with fibroadenoma (fibroadenoma group) and 46 age-matched controls with no breast pathology (control group). The control group comprised adolescent girls who presented to the outpatient clinic with lymphadenopathy during the same period, had no detectable breast pathology, and were not receiving vitamin B12 supplementation.

This approach was adopted to ensure retrospective access to documented serum vitamin B12 measurements, as vitamin B12 is systematically included in the standard haematological and biochemical panel for patients presenting to the Pediatric Oncology outpatient clinic at our institution. The following methodological advantages support the validity of this control group: (i) both groups were followed at the same tertiary referral center during the same study period under comparable socioeconomic conditions, minimising institutional confounding; (ii) the control group was rigorously selected by applying the same exclusion criteria used for the patient group, including known haematological disease, chronic inflammatory conditions, metabolic disorders, malignancy, and vitamin B12 supplementation; and (iii) the mean serum B12 level in the control group (408±138 pg/ml) was within the normal reference range, confirming that these individuals were metabolically representative of a healthy adolescent population.

The following exclusion criteria were applied: (i) history of haematological disease; (ii) chronic inflammatory disease; (iii) metabolic disorder (including thyroid dysfunction and diabetes mellitus); (iv) known malignancy; (v) regular vitamin B12 supplementation at the time of blood sampling; (vi) incomplete laboratory records at the time of diagnosis.

Serum vitamin B12 (pg/ml), haemoglobin (Hb, g/dl), mean corpuscular volume (MCV, fL), and red cell distribution width (RDW) values at the time of diagnosis were retrieved from the hospital information management system. All blood samples were collected by standard venous access and analysed at the same institution's biochemistry laboratory. Age at the time of laboratory testing was also recorded.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. As variables did not follow a normal distribution, non-parametric tests were used for group comparisons. Comparisons between the fibroadenoma and control groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Data are presented as mean±standard deviation (SD) and median (interquartile range, IQR).

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of fibroadenoma. To eliminate scale effects arising from different units of measurement and to improve comparability of effect sizes, z-score standardisation was applied to all continuous variables prior to logistic regression. Results are reported as odds ratios (OR) with 95% confidence intervals (95% CI).

A decision tree analysis (CHAID method) was performed to identify clinically meaningful threshold values for serum vitamin B12 levels. This method identifies statistically significant split points based on the Chi-square statistic without requiring parametric distributional assumptions. A p value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 92 adolescent female patients were included, comprising 46 with fibroadenoma and 46 age-matched controls. Demographic characteristics and laboratory values for both groups are presented in Table 1.

Table 1. Comparison of demographic and laboratory variables between the fibroadenoma and control groups (Mann-Whitney U test).

Variable	Control group (n=46)	Fibroadenoma group (n=46)	p value
Age at examination (years)			0.700
Mean±SD	14.15±3.29	14.78±1.86	
Median (IQR)	15.23 (11.01–16.81)	15.00 (13.67–16.00)	
Range	5.75–19.20	10.00–18.00	
Vitamin B12 (pg/ml)			<0.001
Mean±SD	408±138	305±79	
Median (IQR)	369 (324–430)	298 (254–326)	
Range	254–879	204–590	
Haemoglobin (g/dl)			0.400
Mean±SD	12.91±1.27	12.98±1.36	
Median (IQR)	13.20 (12.25–13.50)	13.40 (12.53–13.70)	
Range	9.00–15.10	9.20–14.80	
MCV (fL)			0.110
Mean±SD	82±6	83±7	
Median (IQR)	83 (79–86)	85 (81–88)	
Range	58–90	66–95	
RDW (%)			0.200
Mean±SD	14.06±1.70	13.86±1.77	
Median (IQR)	13.65 (13.00–14.58)	13.25 (12.73–14.48)	
Range	11.20–18.90	11.90–19.70	

n: Number, SD: Standard deviation, IQR: Interquartile range, MCV: Mean corpuscular volume, RDW: Red cell distribution width. p<0.05 was considered statistically significant.

No statistically significant difference was found between the groups with respect to age at examination. Mean age was 14.78±1.86 years in the fibroadenoma group (median: 15.00, IQR: 13.67–16.00, range: 10.00–18.00) and 14.15±3.29 years in the control group (median: 15.23, IQR: 11.01–16.81, range: 5.75–19.20) (p=0.700). This finding confirms successful age-matching between the two groups.

Serum vitamin B12 levels were significantly lower in the fibroadenoma group compared to controls (p<0.001). Mean vitamin B12 was 305±79 pg/ml (median: 298, IQR: 254–326) in the fibroadenoma group versus 408±138 pg/ml (median: 369, IQR: 324–430) in controls. The median difference of 71 pg/ml between groups is both clinically and statistically meaningful.

No statistically significant differences were found between the groups with respect to haemoglobin, MCV, or RDW (p=0.400, p=0.110, and p=0.200, respectively). All intergroup comparisons are summarised in Table 1.

In univariate logistic regression analysis after z-score standardisation, vitamin B12 demonstrated a statistically significant and strong inverse association with fibroadenoma (OR=0.22, 95% CI: 0.08–0.46, p<0.001). This finding indicates that each one SD increase in vitamin B12 level reduces the odds of fibroadenoma by approximately 78%.

In the multivariate logistic regression model including all variables, vitamin B12 remained a significant independent predictor of fibroadenoma (OR=0.17, 95% CI: 0.06–0.39, p<0.001). Age, haemoglobin, MCV, and RDW were not statistically significant in either model (all p>0.05). Results of both analyses are presented together in Table 2.

Table 2. Univariate and multivariate logistic regression analysis results for fibroadenoma (after z-score standardisation)

Variable	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age at examination	1.27	0.84–1.96	0.262	0.92	0.53–1.54	0.700
Vitamin B12	**0.22**	**0.08–0.46**	**<0.001**	**0.17**	**0.06–0.39**	**<0.001**
Haemoglobin	1.05	0.70–1.60	0.804	0.73	0.34–1.49	0.400
MCV	1.24	0.82–1.93	0.321	1.47	0.66–3.45	0.400
RDW	0.89	0.58–1.34	0.574	0.98	0.53–1.79	>0.900

OR: Odds ratio, CI: Confidence interval, MCV: Mean corpuscular volume, RDW: Red cell distribution width. Each OR reflects the effect of a one standard deviation increase in the corresponding variable on the probability of fibroadenoma. Bold: statistically significant variable.

Decision tree analysis (CHAID method) identified serum vitamin B12 as the primary and strongest discriminating variable based on Chi-square split points. This finding is concordant with the logistic regression results.

At the root node, the vitamin B12 threshold was determined to be 300 pg/ml. Of the 27 patients with vitamin B12 levels below 300 pg/ml, 24 (88.8%) had fibroadenoma. In the 28 patients with vitamin B12 between 300 and 340 pg/ml, this rate decreased to 53.6% (15 patients), while it fell to 18.9% in those with levels above 340 pg/ml (Figure). These findings indicate a clear dose-response relationship between serum vitamin B12 level and fibroadenoma risk.

At the second level of analysis, RDW emerged as a secondary determinant within the subgroup with vitamin B12 <340 pg/ml. Fibroadenoma was identified in 15 of 16 patients (93.75%) with vitamin B12 <340 pg/ml and RDW ≤13.8%. Subgroup results from the decision tree analysis are summarised in Table 3.

DISCUSSION

In this retrospective case-control study, serum vitamin B12 level was found to be independently and significantly

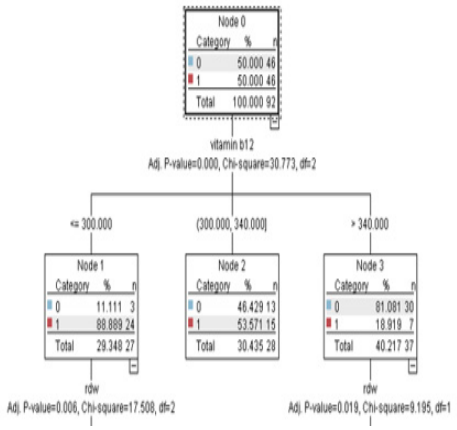


Figure. Decision tree model illustrating the discrimination of fibroadenoma and control groups by serum vitamin B12 levels. The root node is split at 300 pg/ml and 340 pg/ml as primary threshold points. 0: control group; 1: fibroadenoma group.

Table 3. Distribution of fibroadenoma by serum vitamin B12 threshold values according to decision tree analysis (CHAID method)

Vitamin B12 subgroup	No. of patients (n)	Fibroadenoma (n)	Fibroadenoma rate (%)
B12<300 pg/ml	27	24	88.8%
300≤B12 < 340 pg/ml	28	15	53.6%
B12≥340 pg/ml	37	7	18.9%
B12<340 pg/ml and RDW ≤ 13.8%*	16	15	93.75%

n: Number, RDW: Red cell distribution width. *Subgroup showing co-occurrence of B12 <340 pg/ml and RDW ≤13.8%

associated with the presence of fibroadenoma in adolescent female patients. Mean serum vitamin B12 was markedly lower in the fibroadenoma group than in controls (305±79 pg/ml vs. 408±138 pg/ml; p<0.001), and this association persisted as an independent predictor in both univariate (OR=0.22, 95% CI: 0.08–0.46) and multivariate logistic regression analyses (OR=0.17, 95% CI: 0.06–0.39). Decision tree analysis further identified vitamin B12 as the primary discriminating variable, revealing that values below 300 pg/ml were associated with a marked increase in fibroadenoma risk. To our knowledge, this is the first study to evaluate serum vitamin B12 level specifically in the context of fibroadenoma in adolescent female patients, and this constitutes the primary novelty of our work.

Fibroadenoma is a benign breast tumour composed of stromal and epithelial components and represents the most common breast lesion in adolescents and young adult females.[1] Its etiology is thought to involve hormonal, nutritional, and metabolic variables. Although classified as a benign lesion, fibroadenoma has been shown to be associated with long-term breast cancer risk. Dupont et al.[2], in a retrospective cohort study of 1,835 fibroadenoma patients, reported a 2.17-fold increase in invasive breast cancer risk compared to controls, rising to 3.10 in complex fibroadenoma and to 3.88 in the presence of proliferative disease in adjacent parenchyma. El-Wakeel and Umpleby's[3] systematic review emphasized that fibroadenoma with atypical changes carries a 0.12–0.3% potential for malignant transformation, with this risk persisting for more than 20 years after diagnosis. These findings underscore the clinical importance of investigating underlying metabolic variables in fibroadenoma and support the biological rationale of our study.

The majority of existing studies have examined the relationship between vitamin B12 and invasive breast cancer rather than benign breast disease, with inconsistent results. Wu et al.[6], in a prospective nested case-control study using the Washington County serum bank, reported an approximately fourfold increase in breast cancer risk among postmenopausal females in the lowest quintile of serum B12 (matched OR=4.00, 95% CI: 1.05–15.20). Lajous et al,[8] in a case-control study of 475 breast cancer patients and 1,391 controls, found that the odds of breast cancer were approximately 68% lower in the highest quintile of vitamin B12 intake compared to the lowest (OR=0.32, 95% CI: 0.22–0.49). In contrast, Houghton et al.[9] found no significant association between plasma B12 and breast cancer risk in their prospective analysis within the Nurses' Health Study. Zeng et al.[10] likewise found no significant effect of vitamin B12 intake on breast cancer risk in a meta-analysis of 27 studies (RR=0.99, 95% CI: 0.94–1.04). Essén et al.[12] also reported no significant association between serum B12 and breast cancer risk in the prospective Swedish AMORIS cohort. By contrast, Haghighat et al.[13] reported that serum B12 levels were significantly higher in breast and colon cancer patients than in controls and correlated positively with tumour stage; this may reflect a divergence in cobalamin metabolism in invasive malignancies, biologically distinct from the low B12 profile seen in benign lesions such as fibroadenoma.

The inconsistencies across studies may be attributable to differences in study design, population characteristics (age, menopausal status, ethnicity), the use of dietary intake rather than serum B12 as the primary metric, and, most importantly, the fundamental biological differences between fibroadenoma and invasive breast cancer. The present study contributes to filling this gap in the literature by being the first to examine this association specifically in an adolescent population with fibroadenoma.

When considering the plausible mechanisms underlying the association between vitamin B12 and fibroadenoma, the vitamin's role in one-carbon metabolism is particularly prominent. Vitamin B12, as a cofactor of methionine synthase, catalyses the conversion of homocysteine to methionine from 5-methyltetrahydrofolate; this reaction maintains the methionine pool necessary for the biosynthesis of SAM, the principal methyl group donor for DNA, RNA, and histone methylation. Lyon et al.[4] emphasised that vitamin B12 in its methylcobalamin form is a critical component of the methionine cycle, and that disruption of this pathway may adversely affect DNA methylation regulation. Plazar and Jurdana[5] proposed that B12 deficiency increases homocysteine accumulation, which may lead to DNA damage and hypermethylation of tumour suppressor genes. Choi7 suggested that B12 deficiency may impair thymidine and purine synthesis, causing imbalances in the deoxyribonucleotide pool and ultimately resulting in DNA strand breaks. Taken together, these mechanisms suggest that B12 deficiency may predispose rapidly dividing tissues such as the breast to genomic instability; however, further studies are needed to elucidate the specific role of these mechanisms in fibroadenoma pathogenesis.

The absence of significant differences in haemoglobin, MCV, and RDW between the two groups is a noteworthy finding.

This suggests that patients in the fibroadenoma group did not present with clinically overt B12 deficiency, yet relatively lower serum B12 levels may be associated with breast gland pathology. This finding implies that serum B12 may exert biological effects at the tissue level without necessarily falling to levels that produce haematological changes, highlighting the need to assess functional B12 deficiency beyond standard haematological parameters. Vashi et al,[14] in a study of 316 cancer patients, emphasised that serum B12 alone may be insufficient to reflect metabolic deficiency, and that functional markers such as methylmalonic acid and homocysteine provide more reliable assessment of true B12 status.

Limitations

Several methodological limitations of this study must be acknowledged when interpreting its findings. The relatively small sample size (n=46 per group) may have limited the statistical power of the logistic regression model and the generalisability of the decision tree analysis; validation in larger samples is warranted. The fact that fibroadenoma diagnoses were based predominantly (83%) on USG findings, with histopathological confirmation in only eight patients (17%), represents a methodological limitation, although ACR guidelines recognise USG as the primary and sufficient diagnostic method in the adolescent age group.[11] Due to the retrospective design, functional B12 markers such as methylmalonic acid, homocysteine, folate, and vitamin B6 could not be measured, and Vashi et al.[14] have highlighted that serum B12 alone may be insufficient to reflect functional deficiency. The inability to control for potential confounders such as body-mass index, dietary habits, socioeconomic status, and menstrual irregularity due to the retrospective design limits the interpretation of the observed association, as does the single-centre nature of the study. However, the fact that the control group comprised patients followed at the same institution under comparable conditions partially mitigates the risk of selection bias. Despite these limitations, our study makes an original contribution to the literature as the first study to systematically evaluate serum vitamin B12 levels in adolescent patients with fibroadenoma. The findings suggest that serum vitamin B12 may be a candidate as a simple, low-cost, and accessible biomarker for fibroadenoma risk assessment. The 300 pg/ml threshold identified by decision tree analysis may represent a clinically meaningful cut-off value; nonetheless, prospective validation in larger cohorts is required before any clinical recommendation can be made.

The selection of the control group from patients presenting with lymphadenopathy to the pediatric oncology outpatient clinic warrants consideration as a potential source of selection bias. When lymphadenopathy is associated with underlying inflammation or other systemic pathology, it may theoretically influence B12 metabolism. However, individuals with known haematological disease, chronic inflammatory conditions, or malignancy were excluded through the application of predefined exclusion criteria. Furthermore, the mean serum B12 level in the control group (408±138 pg/ml) fell within the normal reference range, supporting the premise that these individuals were metabolically representative of a healthy adolescent population. Nevertheless, future prospective studies employing more homogeneous control groups recruited from general outpatient settings will be important in addressing this limitation.

CONCLUSION

As a result, this study is the first, to our knowledge, to investigate the association between serum vitamin B12 levels and fibroadenoma in adolescent female patients. The significantly lower vitamin B12 levels and the 300 pg/ml threshold identified by decision tree analysis suggest that vitamin B12 may play a biologically meaningful role in fibroadenoma pathogenesis and may serve as a simple, accessible, and low-cost biomarker candidate for risk stratification in adolescents. Prospective, multicentre studies incorporating functional B12 markers such as homocysteine and methylmalonic acid are needed to validate these findings and establish evidence-based clinical recommendations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 27.11.2024, Decision No: AEŞH-BADEK-2024-1132).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: GŞ; Design: MBH, GŞ; Control: GŞ, ŞY; Resources: ŞY, AF; Materials: MBH, CK; Data Collection and/or Processing: MBH; Analysis and/or Interpretation: MBH, GŞ; Literature Review: MBH; Writing the Article: MBH; Critical Review: MBH, ŞY, SE, CK, AF, GŞ.

REFERENCES

1. Lee M, Soltanian HT. Breast fibroadenomas in adolescents: current perspectives. *Adolesc Health Med Ther.* 2015;6:159-163. doi:10.2147/AHMT.S55833
2. Dupont WD, Page DL, Parl FF, et al. Long-term risk of breast cancer in women with fibroadenoma. *N Engl J Med.* 1994;331(1):10-15. doi:10.1056/NEJM199407073310103
3. El-Wakeel H, Umpleby HC. Systematic review of fibroadenoma as a risk factor for breast cancer. *Breast.* 2003;12(5):302-307. doi:10.1016/S0960-9776(03)00123-1
4. Lyon P, Strippoli V, Fang B, Cimmino L. B vitamins and one-carbon metabolism: implications in human health and disease. *Nutrients.* 2020;12(9):2867. doi:10.3390/nu12092867
5. Plazar N, Jurdana M. Hyperhomocysteinemia and the role of B vitamins in cancer. *Radiol Oncol.* 2010;44(2):79-85. doi:10.2478/v10019-010-0022-z

6. 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):209-217.
7. Choi SW. Vitamin B12 deficiency: a new risk factor for breast cancer? *Nutr Rev.* 1999;57(8):250-253. doi:10.1111/j.1753-4887.1999.tb06952.x
8. Lajous M, Lazcano-Ponce E, Hernandez-Avila M, Willett W, Romieu I. Folate, vitamin B6, and vitamin B12 intake and the risk of breast cancer among Mexican women. *Cancer Epidemiol Biomarkers Prev.* 2006;15(3): 443-448. doi:10.1158/1055-9965.EPI-05-0532
9. Houghton SC, Eliassen AH, Zhang SM, et al. Plasma B-vitamin and one-carbon metabolites and risk of breast cancer before and after folic acid fortification in the United States. *Int J Cancer.* 2019;144(8):1929-1940. doi:10.1002/ijc.31934
10. Zeng J, Gu Y, Fu H, Liu C, Zou Y, Chang H. Association between one-carbon metabolism-related vitamins and risk of breast cancer: a systematic review and meta-analysis of prospective studies. *Clin Breast Cancer.* 2020;20(4):e469-e480. doi:10.1016/j.clbc.2020.02.012
11. Klein KA, Kocher M, Lourenco AP, et al. ACR Appropriateness Criteria palpable breast masses: 2022 update. *J Am Coll Radiol.* 2023;20(5S): S146-S163. doi:10.1016/j.jacr.2023.02.013
12. Essén A, Santaolalla A, Garmo H, et al. Baseline serum folate, vitamin B12 and the risk of prostate and breast cancer using data from the Swedish AMORIS cohort. *Cancer Causes Control.* 2019;30(6):603-615. doi:10.1007/s10552-019-01170-6
13. Haghighat G, Khajeh-Mehrizi A, Ranjbar H. Evaluation of serum vitamin B12 levels in patients with colon and breast cancer: a case-control study. *Int J Hematol Oncol Stem Cell Res.* 2023;17(4):240-244. doi:10.18502/ijhoscr.v17i4.13914
14. Vashi P, Edwin P, Popiel B, Lammersfeld C, Gupta D. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. *PLoS One.* 2016;11(1):e0147843. doi:10.1371/journal.pone.0147843