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Folic acid, vitamin B6, B12, and breast cancer incidence

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Abstract

Breast cancer is the most common cancer in women, and its frequency is rising in countries with low and middle incomes. The influence of diet on mammary carcinogenesis has been clearly demonstrated in animal models. Inadequate folate intake has been associated with several cancers, and low levels of serum folate, vitamin B6, and vitamin B12 have been associated with increased breast cancer risk. The levels of folic acid, B6, and B12 in the plasma of 85 people with breast cancer were measured and compared with healthy people. A significant inverse trend was observed between folate intake (p-value=0.004) and vitamin B6 intake (p-value=0.0001) and breast cancer risk. Data from this study suggests that B vitamins, including folate, vitamin B-6, and vitamin B-12, may confer little or no reduction in overall risk of developing breast cancer..

INTRODUCTION

Various dietary factors have been hypothesized to be determinants of breast cancer, but few have been unequivocally associated with the disease (1). In contrast with most known risk factors for breast cancer, dietary factors are potentially modifiable, making their identification essential (2). Folate is a b vitamin essential for nucleotide biosynthesis, DNA replication, and methyl group supply, and thus for cell growth and repair (1). Folic acid is the synthetic form of folate used in vitamin supplements and fortified foods. Most epidemiological studies have found inverse associations between folate intake and the risk of colorectal cancer, although such associations have been inconsistent or absent for other cancers (3). Experimental evidence suggests that folate deficiency may promote initial stages of carcinogenesis, whereas high doses of folic acid may enhance the growth of cancer cells (4). Inadequate folate intake has been associated with several cancers, and low levels of serum folate, vitamin B6, and vitamin B12 have been associated with increased breast cancer risk (5). Diminished levels of these vitamins may result in the misincorporation of uracil into DNA, leading to chromosome breaks and disruption of DNA repair (6). Folate and vitamin B12 are involved in DNA methylation. Methionine synthase, a vitamin B12-dependent enzyme, catalyzes the transfer of a methyl group from methyltetrahydrofolate to homocysteine to form methionine and, eventually, S-adenosylmethionine, which is the universal methyl donor for methylation reactions (7). Deficient folate and vitamin B12 levels can reduce the availability of S-adenosylmethionine for DNA methylation and may thereby influence gene expression. Adequate vitamin B6 levels are important for the conversion of homocysteine into cysteine. Homocysteine is converted to cystathionine to form cysteine via the transsulfuration pathway, which is facilitated by two pyridoxal 5_-phosphate-dependent enzymes, cystathionine synthase and cystathionase (8). Inadequate levels of folate, vitamin B6, and vitamin B12 are primary determinants of high blood homocysteine levels, and high intracellular levels of pyridoxal 5_-phosphate can lead to decreased steroid hormone-induced gene expression (9). In this study, the levels of folic acid, B6, and B12 in the plasma of people with breast cancer were measured and compared with those levels in healthy people.

METHODS AND MATERIALS

Participants were enrolled in this population-based case-control study to assess the relationship between diet and breast cancer risk. The case group included 85 women with confirmed breast cancer and without previous treatment identified in 2018 to 2020 from among women aged 45 to 75 years who were attending gynecologic clinics for the biopsy of a breast lump. Controls were an age-stratified random

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sample of nurses. Blood samples were collected in both EDTA- and citrate-containing tubes from 170 women and stored at -70 °C. Plasma concentrations of folate and vitamin B-12 were measured using the IMMULITE 1000 immunoassay system. Plasma PLP, the major active form of vitamin B-6, was measured by an enzymatic procedure based on radioactive tyrosine and apo-enzyme tyrosine decarboxylase. Moreover, m2 tests were used for categorical variables, and t tests or Kruskal-Wallis tests were employed for continuous variables to compare cases and controls. Folate, vitamin B6, and vitamin B12 intakes were adjusted for total energy intake using the regression-residual method.

Results

The case group comprised 85 women with histologically confirmed breast cancer. No differences in the dietary intake of folate, vitamin B-6, and vitamin B-12 were seen between cancer patients and control subjects.

For the whole population, median folate, vitamin B6, and vitamin B12 intake was 310 ug/d, 1.27 mg/d, and 4.58 ug/d, respectively. For all women, the greater intake of folate, vitamin B6, and vitamin B12 was associated with a lower risk for breast cancer. However, a significant inverse trend was observed between folate intake (p-value=0.004) and vitamin B6 intake (p-value=0.0001) and breast cancer risk.

Table 1. Characteristics of breast cancer case patients and their matched control subjects at blood collection

Characteristic	Case (n=85)	Control (n=85)	P.value
Folate, ng/mL	7.0	7.8	0.004
Vitamin B6, pmol/mL	44.1	50.4	0.0001
Vitamin B12, pg/mL	417	416	0.182

DISCUSSION

Breast cancer is the most common cancer in women, and its frequency is rising in low- and middle-income countries (1). Approximately one in eight women worldwide will develop breast cancer during her lifetime, and breast cancer is the leading cause of cancer deaths among women. A number of risk factors have been identified in the pathogenesis of breast tumors; among these, a great number are linked to nutrition and lifestyle (e.g., alcohol consumption, obesity, and eating patterns) (11). The influence of diet on mammary carcinogenesis has been clearly demonstrated in animal models. Obesity induced by high-fat diets increases the risk of several cancers, including breast cancer in several animal species (12). On the contrary, soybean products act as cancer preventive agents in rodents and other animals. Epidemiological studies provide clear evidence of an association between breast cancer incidence, mortality, and dietary patterns or dietary constituents in humans, but frequently, there is a discrepancy between the studies on human populations and investigations performed in more controlled conditions, such as cellular or animal studies (13). Many other variables, such as race, age, menopausal status, onset of puberty, and the number of pregnancies, are also associated with diet and lifestyle in humans and act as confounding factors. Vitamin B6, also known as pyridoxine or pyridoxal phosphate, is an important component of folate metabolism. It is part of the pathway that produces a supply of methionine to serve as a main donor for active methyl groups and components for DNA synthesis and repair (14). It is hypothesized that the deficit or surplus of vitamin B6, as well as other B vitamins, may play a role in carcinogenesis and may, therefore, be a target for chemoprevention or antitumor activity. There is no evidence that dietary vitamin B12 alone reduces the risk of breast cancer (15). However, vitamin B12 may reduce the risk of breast cancer when taken with folate, vitamin B6, and methionine. Given its role as a modulator of DNA synthesis, repair, and methylation, folate was hypothesized to reduce the risk of breast cancer (16). The importance of these processes in cell growth and development led to investigations of the consequences of either low or high folate intake on cancer development. The results of several studies suggest that increased folate intake is associated with an increased prostate cancer risk but significantly reduced risks of esophageal, stomach, pancreatic, and colorectal cancers (17). However, data regarding the subsequent effects of folate intake on breast cancer are limited and inconclusive. A meta-analysis based on 9 prospective studies and 14 case-control studies suggested no clear association between the folate intake or blood folate levels and the risk of breast cancer; however, folate appeared to significantly counteract the increased risk of breast cancer associated with moderate or high levels of alcohol consumption (18). It is particularly important to clarify the optimal daily folate intake level with respect to the general population, as this level has yet not been definitively determined. Furthermore, additional unanswered questions remain, including whether associations differ according to follow-up duration or alcohol intake. The present results show significant associations between vitamin B6 and folate plasma levels and the risk of breast cancer. Data from this study suggests that B vitamins, including folate, vitamin B-6, and vitamin B-12, may confer little or

no reduction on the overall risk of developing breast cancer.

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