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Folic acid and breast cancer

IH Kunkler
Consultant and part time Senior Lecturer in Clinical Oncology, Western General Hospital, University of Edinburgh, Edinburgh, Scotland

ABSTRACT Folic acid plays a key role in cell synthesis and repair. Dietary supplementation with folate before conception reduces the risk of neural tube defects such as anencephaly and spina bifida. Most of the published literature suggests that plasma folate levels are inversely associated with the risk of breast cancer. The mechanisms by which folate deficiency contributes to carcinogesis are unclear. On balance most of the scientific evidence suggest that folic acid has a protective role against the development of breast cancer.

KEYWORDS Breast cancer, carcinogesis, folic acid

LIST OF ABBREVIATIONS Neural tube defects (NTD), odds ratio (OR)

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Correspondence to ***IH Kunkler, Department of Clinical Oncology, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU***

tel. ***+44 (0)131 537 2214***

fax. ***+44 (0)131 537 2216***

e-mail ***I.Kunkler@ed.ac.uk***

FOLIC ACID AND HEALTH

Folic acid is a B vitamin which plays an important role in cell synthesis and repair. Leafy vegetables, fruits and animal protein are all rich sources of folic acid, but folic acid is easily destroyed by prolonged cooking. Total body stores of folate are quite small and deficiency can occur within weeks leading mainly to megaloblastic anaemia. Folate stores in the body are best reflected in the folate concentrations in red blood cells. Folate can also be measured in the plasma, but plasma concentrations can change rapidly and do not accurately reflect body stores. Natural folates in foods lose their activity relatively rapidly over a period of days or weeks because of their chemical instability. In contrast, synthetic folic acid is virtually completely stable for months or years. This means that synthetic folate provides a much more reliable source of dietary intake than naturally occurring folates.

FOLIC ACID PLAYS AN IMPORTANT ROLE IN PREVENTING BIRTH DEFECTS

There is good evidence that dietary supplementation with folate before conception and during the first trimester reduces the risk of NTDs. It is between the seventeenth and thirtieth day after conception or four to six weeks after the first day of the last menstrual period that the neural tube forms in the embryo and then closes. Neural tube defects occur when the neural tube fails to close properly leaving the brain and spinal cord exposed to amniotic fluid. Anencephaly and spina bifida are the commonest NTDs. Current advice is that women should receive 400 mcg (0·4 mg) of folic acid per day before they become pregnant.

FOLIC ACID PREVENTING OR CAUSING BREAST CANCER?

Most of the published evidence shows that plasma folate concentrations are inversely associated with the risk of developing breast cancer. Folate deficiency may lead to DNA damage. An example is the misincorporation of uracil into DNA and the development of single and double-strand chromosomal breaks in DNA.[1] These defects may result in a reduced DNA repair capacity. Three large prospective epidemiological studies, the Nurses' Health Study,[2] the Iowa Women's Health Study,[3] and the Canadian National Breast Screening Study[4] have demonstrated that low dietary folate carries an increased risk of breast cancer. In the Nurses' Health Study,[2] of 121,700 female registered nurses aged between 30 and 55 years, the multivariate OR for breast cancer risk from low folate was 0·73 (95% CI, 0·50–1·07) for the highest versus lowest quintile.

The mechanisms by which folate deficiency might stimulate carcinogenesis are unclear. However, folate deficiency is known to reduce the methylation of dUMP to dTMP, causing imbalance in the dNTP pool and excessive misincorporation of uracil into DNA during DNA repair and replication. The base excision repair pathway is responsible for repairing uracil in DNA. Single strand breaks are created by the excision of uracil by uracil DNA glycosylase. Where folate is deficient, excision repair and uracil misincorporation occur due to thymidine deficiency.

THE ABERDEEN STUDY

More recently, Charles *et al.*[5] reported a study from Aberdeen, Scotland, of folate supplementation in pregnancy which suggested an increase in breast cancer

risk in women receiving oral supplements of folic acid. These authors report on a trial in 2,928 women. They were randomly allocated between 1966–67 to folate tablets in six colours, two of which contained 0·2 mg and 5 mg of folate respectively. The trial was double-blinded. At each patient's booking visit, blood was taken for serum folate. Information was collected on maternal age, parity, gestation, weight and blood pressure. The data was linked to the Aberdeen and neonatal databank for information on smoking and maternal height. Causes of death were ascertained by linkage to the NHS Central Registry in Edinburgh.

Follow-up to September 2002 showed that 210 women had died. Of these deaths 40 were from cardiovascular disease and 31 from breast cancer. For women randomised to the higher 5 mg dose of folate, all-cause mortality was one fifth higher and deaths due to breast cancer were doubled. For the lower 0·2 mg folic acid dose all-cause mortality was 18% higher, and breast cancer mortality was 50% higher. How can the findings of the Aberdeen study be reconciled with the bulk of the literature which suggests that folic acid has a protective effect against breast cancer? It should be noted that the 5 mg dose used in the one arm of the Aberdeen study was >10 times higher than the currently recommended dose of (0·4 mg). However, even in patients receiving less than the current recommended dose to reduce NTDs, the breast cancer mortality was increased. The authors acknowledge that these observations could be chance findings; the number of breast cancer deaths is small, the confidence limits wide. In addition, they admit that they had no specified hypothesis that folate supplements in pregnancy would increase the risk of cancer.

CRITICISMS OF THE ABERDEEN STUDY

The Aberdeen study has been criticised on a number of counts.[7] First, the trial is not a randomised trial since the treatments were given sequentially. Secondly, it was not really double-blind since the colours of the tablets corresponding to specific doses of folic acid could be known to the trialists. Only in the 5 mg folic acid group was cancer mortality statistically significantly increased (p=0·02). Statistical significance at the 0·05 level was not reached for breast cancer mortality for either the 0·2 mg (p=0·35) or 5 mg (p=0·10) doses of folic acid. It could well be that the observation of a relationship between folic acid supplementation and increased breast cancer mortality could be due to well recognised phenomenon of multiple testing for statistical associations.

HOW DO THE FINDINGS IN THE ABERDEEN STUDY FIT WITH THE OTHER PUBLISHED LITERATURE?

These findings contrast with the Nurses' Health Study[2] in which the highest plasma folate levels (>14 ng/ml) had a 27% lower risk of breast cancer than did women with a lowel level (<6·4 ng/ml). A higher level of protection against breast cancer was found in women who regularly drank alcohol (one drink per day or more). A particularly strong inverse association between serum folate and risk of breast cancer was found in women drinking at least 15 g/day of alcohol. Women with the highest folate levels had an 89% lower risk of breast cancer than did women with low levels. Alcohol is known to antagonise the action of folate. It might therefore increase an individual's requirement for folate.

The Canadian Breast Screening study[4] suggested that dietary intake of folate might be associated with a reduced risk of breast cancer at comparatively high levels of alcohol, especially in postmenopausal women. The authors acknowledge their findings could be due to chance. However in a prospective study a US group found no evidence of a protective association between higher concentrations of folate and subsequent breast cancer.[5]

SHOULD PATIENTS WISHING TO BECOME PREGNANT TAKE FOLIC ACID SUPPLEMENTS?

In the light of the methodological and analytical limitations of the Aberdeen study, it is premature to conclude that folic acid supplements really increase the risk of breast cancer. There is more evidence that folic acid may prevent rather than promote breast cancer. More studies are needed. In the meantime, women should be encouraged to take folic acid supplements at the recommended dosage of 400 mcg/day since the benefits in reducing NTDs are unequivocal.

KEYPOINTS

- It is well established that folic acid supplementation reduces the risk of neural tube defects.
- Most of the evidence suggests that folic acid contributes to preventing breast cancer rather than causing it.
- The apparent association between taking high doses of folic acid and increased risk of dying from breast cancer may be a chance finding. Further studies are needed.
- Women contemplating pregnancy should take folic acid supplements to reduce the risk of neural tube defects in the developing child.
- More studies are needed.

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