



Position Statement on Folate and Reducing Cancer Risk

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Key Messages

Folate is a water soluble B-vitamin present naturally in foods such as wholemeal bread, legumes, green leafy vegetables (for example broccoli, lettuce and cabbage) and liver that is essential for biochemical and physiological processes in the body.

Mandatory folic acid fortification of wheat flour for bread making purposes commenced in Australia from September 2009 to reduce the incidence of neural tube defects. New Zealand has delayed the decision to require mandatory folic acid fortification of bread until 2012 and allowed voluntary fortification of bread with folic acid from September 2009. Voluntary fortification of certain foods with folic acid has been permitted in New Zealand and Australia since January 1996.

There is *probable* evidence that foods containing folate **reduce** the risk of pancreatic cancer and *limited suggestive* evidence that they reduce the risk of oesophageal and bowel cancer. Cohort studies suggest that a high dietary folate intake may **reduce** the risk of post-menopausal breast cancer, particularly for women with a family history of breast cancer.

There does not appear to be any significant association between folate intake and the risk of lung cancer, and *limited* evidence *suggests* there is no association between folate intake and ovarian, stomach and prostate cancer.

A small number of recent studies, while inconclusive, suggest that high doses of folic acid as a supplement may **promote** the progression of undiagnosed premalignant and malignant lesions of the bowel. While dietary folate (even from foods fortified with folic acid) may have no adverse effects, some studies suggest that the combined impact of folic acid from supplements and fortification could promote pre-existing adenomas.

Based on current evidence, the benefits of folic acid fortification for reducing the incidence of neural tube defects outweigh any potential increased risk of cancer. Therefore, the Cancer Society of New Zealand and Cancer Council Australia are not opposed to mandatory fortification of foods with folic acid. However, careful monitoring of emerging evidence on any adverse effects of folic acid fortification, particularly cancer incidence, is required.

The Cancer Society of New Zealand and Cancer Council Australia support the respective government guidelines for food and nutrition (New Zealand Food and Nutrition Guidelines and Australian Dietary Guidelines) and recommend people obtain their nutritional requirements from whole foods, such as fruits, vegetables, breads and cereals rather than individual nutrients in a supplement form.

Due to conflicting/uncertain advice around risk it is recommended that people with existing bowel adenomas and those with an increased risk of developing bowel adenomas should **avoid** taking nutritional supplements that contain high dose (greater than 1mg (1000µg) per day) folic acid.

Background

Folate is a water soluble B-vitamin that is present naturally in foods such as wholemeal bread, legumes, green leafy vegetables (for example broccoli, lettuce and cabbage) and liver (Table 1).

Table 1. Dietary sources of folate per 100g of food^{1,2}

Food	Folate (µg)	Food	Folate (µg)
Marmite	2000	Avocado	66
Weet-Bix®	333*	Broccoli, boiled	53
Liver	290	Wholemeal bread (New Zealand)	36
Red kidney beans, cooked	122	Lettuce, raw	34
Wholemeal bread (Australia)	120	Cabbage, steamed	20
Peanuts	110	Banana	10
Kidney	75	Beef lasagna	6

* Voluntarily fortified by manufacturers

Folate is the generic name for a class of compounds that have similar chemical structures and nutritional properties.¹ Folic acid is the more stable synthetic form used in food fortification, but is rarely found in foods or the body. Instead, folate in nature is typically found as one of several types of tetrahydrofolate.¹

Naturally occurring folates are very unstable and rapidly lose their activity in foods over a period of days or weeks. Approximately 50 to 75 percent of the original folate values are lost through food harvesting, storage, processing and preparation.¹ Bioavailability varies widely depending on the food source and preparation method.³

Folate is essential for biochemical and physiological processes in the body including DNA synthesis, fertility, foetal development and the prevention of anaemia.^{1,4} Consuming enough folic acid substantially decreases the risk of neural tube defects in babies.⁵

Rationale

Despite a number of initiatives over the past decade designed to increase folic acid intake among women of child-bearing age, most women are not having enough folic acid to reduce the risk of neural tube defects.⁵

Voluntary fortification of certain foods with folic acid up to a maximum of 50 percent of the Recommended Dietary Intake has been permitted in New Zealand and Australia since January 1996 to help prevent neural tube defects. Foods that have been voluntarily fortified include some biscuits, breakfast cereals, breads, cereal flours, pasta, fruit and vegetable juices, soy beverages and yeast extracts.

From September 2009, mandatory folic acid fortification requires Australian millers to add folic acid to wheat flour for bread-making purposes.⁵ This means most bread in Australia will contain 120µg of folic acid per 100g bread (approximately three slices of bread).⁵

New Zealand has delayed the decision to require mandatory fortification of bread with folic acid until 2012 and allowed voluntary fortification of bread with folic acid from September 2009. However, the New Zealand standard has been amended to provide permission for manufacturers to voluntarily fortify bread with folic acid from September 2009.

The fortification of wheat flour for bread making purposes in Australia is expected to reduce the number of neural tube defect-affected pregnancies by up to 14 percent, or between 14 to 49 pregnancies per year.⁵ Evidence suggests that the increase in folic acid due to mandatory fortification is safe for the whole population.⁵ However, concerns have been raised about the potential risk of cancer from increased folic acid.

The Cancer Society of New Zealand and Cancer Council Australia have an important role to play in determining the association between nutritional factors and cancer, and promoting advice to the community about how to reduce cancer risk. The purpose of this position statement is to evaluate and summarise the evidence linking folate and folic acid with cancer risk.

Evidence from Major Reviews of the Epidemiological Literature

In 2003, an expert report by the World Health Organization (WHO) observed that there was *possible/insufficient* evidence that a high intake of folate from diet or vitamin supplements decreased the risk of cancer.⁶

The World Cancer Research Fund (WCRF) released a comprehensive report on food and the prevention of cancer in 2007 which found there was *probable* evidence that foods containing folate reduced the risk of pancreatic cancer and *limited suggestive* evidence that they reduced the risk of oesophageal and bowel cancer.⁷

Evidence from Epidemiological Studies

Additional details on epidemiological studies can be seen in the summary evidence table document.

Bowel Cancer

WCRF identified nine cohort studies investigating dietary folate and two cohort studies investigating serum folate in relation to bowel cancer risk.⁷ Out of the nine cohort studies investigating dietary folate, seven reported a decreased risk of bowel cancer in the highest intake groups (statistically significant in one) and two reported a non-significant increased risk.⁷ Meta-analysis on four cohort studies showed a significantly decreased risk of 26 percent.⁷ One study of serum folate levels reported a significantly decreased risk for bowel cancer, while the other showed a non-significant decreased risk for colon cancer and non-significant increased risk for rectal cancer.⁷

Similarly a meta-analysis on five cohort studies found that high versus low dietary folate decreased the risk of bowel cancer by 25 percent, which was significant.⁸ The association between folate intake and cancer risk was slightly stronger for colon cancer than for rectal cancer, although only three cohort studies presented results for colon and rectal cancer separately.⁸ Separate meta-analysis on three cohort studies found there was no association between total folate (from dietary and supplement sources) and bowel cancer.⁸

The larger reduction in risk associated with dietary folate compared with total folate intake in this study was unexpected, and the authors concluded that more data is required to establish whether dietary or total folate is more strongly related to bowel cancer risk.⁸ The association between dietary folate and bowel cancer risk may be subject to greater confounding by other dietary factors.⁸

In the Netherlands cohort study on diet and cancer, dietary folate was not associated with colorectal or colon cancer risk in men and women.⁹ However, for rectal cancer, the effect of folate on cancer risk appears to be different for men and women.¹⁰

A nested case-control study within the Nurses' Health Study and Health Professionals Follow-up Study found high plasma folate levels were associated with a significant reduced risk of death from bowel cancer.¹¹

Overall, the evidence from prospective studies suggests there is a protective effect between folate intake and bowel cancer risk. Further research is required to establish the precise nature of association between dietary and supplemental folate intake.

Bowel Adenoma Recurrence

A meta-analysis of three studies found that there was no significant difference in the relative risk of adenoma recurrence in populations with a history of adenomas, although there was a non-significant increased recurrence of adenomas in populations taking supplemental folic acid.¹² However, an additional meta-analysis where follow-up was conducted over three to five years showed that while there was no significant effect on recurrence overall, there was a significantly increased risk of developing advanced colorectal adenomas beyond the three year follow-up in groups taking folate supplementation.¹³

Further analysis of the Aspirin/Folate Polyp Prevention Study found no evidence that folic acid supplementation was beneficial in reducing the risk of new adenomas, even among individuals with low baseline folates (measured as dietary folate, total folate, red blood cell folate and plasma folate).¹⁴

In addition, the Polyp Prevention Trial, a randomised controlled trial (RCT) looking at the effects of a high-fibre, low-fat, high fruit and vegetable diet on the recurrence of bowel cancer adenomas found no significant associations between dietary folate and total folate intake and any adenoma recurrence, multiple adenoma recurrence and advanced adenoma recurrence.¹⁵

In contrast, a double-blind RCT of folic acid supplementation in the form of a cereal supplement containing folic acid (140µg) and wheat bran found a significantly decreased risk of bowel adenoma recurrence with higher plasma folate levels.¹⁶ Further stratification by multi-vitamin use showed no positive or negative effect on risk of adenomas.¹⁶ Analysis of the same study looking at dietary folate and total folate intake showed there was a significantly decreased risk of bowel adenoma recurrence with total folate intake, but no association with dietary folate.¹⁷ The authors noted that higher than recommended intakes of total folate may be required to confer a protective effect.¹⁷

However, while folate intakes from diet (even once fortified with folic acid) may have no negative effects, some studies suggest that the combined impact of folic acid from supplements and fortification could have a negative effect on pre-existing adenomas.^{3,18}

An RCT conducted among participants of the prospective cohort studies, the Health Professionals Follow-Up Study and the Nurses' Health Study, who had a history of previous adenoma, did not find an overall protective effect of folic acid supplementation on adenoma recurrence.¹⁹ Folic acid supplementation may be beneficial among those with lower folate concentrations at baseline. Incidence of at least one recurrent adenoma was not significantly associated with folic acid supplementation.¹⁹ Among participants with low plasma folate concentrations at baseline, and predominantly those with a high alcohol intake, those randomly assigned to receive folic acid experienced a decrease in adenoma recurrence, whereas for subjects with high folate concentrations at baseline, supplemental folic acid had no significant effect.¹⁹

A recent critical review concluded that folate appears to have a dual effect depending on the timing and dose of folate intervention.³ In normal bowel mucosa, folate deficiency appears to predispose it to neoplastic changes, while moderate levels of folic acid suppress and high supplemental doses enhance the development of cancer.³ When bowel neoplasms already exist, folate supplementation may have a promoting effect on tumour progression.³

Lung Cancer

A meta-analysis on eight cohort studies found no significant association between dietary folate and total folate intake and lung cancer risk.²⁰ However, a subsequent study suggests that there may be a link between increased folate intake and an increase in lung cancer.³⁹ It is, therefore, unclear at this time what, if any, association there may be between folate intake and lung cancer.

Postmenopausal Breast Cancer

In the Malmo Diet and Cancer cohort study, a high dietary folate and total folate intake were associated with a significantly lower risk of postmenopausal breast cancer.²¹ Similarly in the French E3N Cohort Study, high dietary folate intake was associated with significantly decreased risk of postmenopausal breast cancer.²²

In the Iowa Women's Health Study, low dietary folate intake was associated with a significantly increased risk of postmenopausal breast cancer for women with a family history of breast cancer.²³ However, there was no association between low dietary folate intake and breast cancer risk in women with no family history.²³ When alcohol consumption was also considered, women with a family history of breast cancer who consumed more than 4g per day of alcohol had a slightly higher risk.²³ Therefore, low folate intake was primarily a risk factor among women with a family history of breast cancer and this was exacerbated by alcohol consumption.²³

These studies suggest that higher levels of dietary folate decrease the risk of post menopausal breast cancer, particularly in women with a family history of breast cancer.

Breast Cancer

A meta-analysis of cohort studies found that dietary folate (n=8 studies), total folate (n=6) and blood folate levels (n=3) were not associated with the risk of breast cancer.²⁴

Another meta-analysis of cohort studies also found no association between dietary folate intake (n=9) and supplements containing folate (n=3) and breast cancer risk.²⁵

In addition, an RCT among female health professionals found that the risk of breast cancer was not affected by a supplement containing 2.5mg (2500µg) folic acid.²⁶

Therefore there appears to be no association between dietary folate and total folate intake and breast cancer risk.

Ovarian Cancer

In the Canadian National Breast Screening cohort study, higher dietary folate intake was associated with a non-significant decreased risk of ovarian cancer.²⁷ On stratification by alcohol consumption, women with a higher dietary folate intake that consumed 4g or more per day of alcohol had an even lower risk of ovarian cancer, but the association was still non-significant.²⁷ Dietary folate was not associated with ovarian cancer risk among women consuming less than 4g per day of alcohol.²⁷

Similar results were found in the Swedish Mammography cohort, where a higher dietary folate was associated with a non-significant decreased risk of ovarian cancer.²⁸ In this study there was no association between dietary folate and ovarian cancer risk in women consuming 20g or less per week (approximately two standard drinks) of alcohol.²⁸ However, the risk significantly decreased for women consuming more than 20 per week of alcohol.²⁸

The Nurses Health Study also found dietary folate intake was associated with a non-significant decreased risk of ovarian cancer.²⁹ However, there was no association between total folate intake and ovarian cancer risk.²⁹

There appears to be no significant association between ovarian cancer and dietary folate intake. Two studies suggest that a higher dietary folate intake may be more beneficial for ovarian cancer risk in women who consume more alcohol.

Pancreatic Cancer

The WCRF identified three cohort studies, two case control studies, and one ecological study which investigated folate from foods and/or supplements, and pancreatic cancer.⁷ One cohort study reported a statistically significant reduced risk for the highest intake groups (without specifying the source of the folate) when compared with the lowest.⁷ The second study reported no effect on risk in men and the third study reported a non-significant increased risk in women.⁷

One of the case-control studies reported a statistically significant reduced risk for the highest intake groups compared with the lowest with the other reporting a non-significant decreased risk in women and no effect in men.⁷ The ecological study showed a statistically significant decreased risk in areas of high folate risk.⁷ A systematic review and meta-analysis of cohort studies found a decreased risk of pancreatic cancer with increased dietary folate and total folate intake in one study but not the other two studies.³⁰ In a further review of two large Swedish Cohort Studies, increased folate intake from food sources (dietary folate) but not from supplements was associated with a reduced risk pancreatic cancer.³¹

In a combined analysis of two large US cohort studies, the Nurses Health Study and the Health Professionals Health Study, dietary folate intake was not associated with the risk of pancreatic cancer.³² There was also no influence of supplemental folate or total folate but similar to Larsson et al 2006b there was a non-significant inverse trend for folate from food sources for both cohorts.³²

Similar to the above two studies, a prospective nested case-control study found no significant relationship between plasma folate levels and pancreatic cancer. When multivitamin supplement users were excluded from the analysis, a modest inverse trend between plasma folate and pancreatic cancer was noted.³³

While the evidence is limited, it suggests a possible protective effect from folate from food sources but not from dietary supplements. It is possible that this effect is related to confounding from other nutrients present in foods.

Oesophageal Cancer

The WCRF identified ten case-control studies, eight of which investigated dietary folate and two which investigated red cell and/or plasma folate in relation to oesophageal cancer.⁷ All of the eight studies that investigated dietary folate reported decreased risk for the highest intake groups when compared with the lowest intakes.⁷ Two of these studies showed statistically significant results.⁷

One of the two red cell/plasma folate studies reported that cases with oesophageal cancer had significantly lower red blood cell folate levels and plasma folate than controls. The other reported that lower serum folate concentrations were associated with increased risk for squamous cell carcinoma of the oesophagus after controlling for age, gender and smoking. These studies were unsuitable for a dose-response meta-analysis.⁷

The WCRF concluded that although the available evidence is sparse, there is limited evidence which suggests folate protects against oesophageal cancer.⁷

Gastric Cancer

A meta-analysis on two cohort studies showed there was no association between dietary folate intake and stomach cancer risk,³⁰ while another cohort study found there was no association between plasma folate levels and stomach cancer risk.

Similarly, a nested case control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) found no association between plasma folate and gastric cancer risk.³⁴

The studies reviewed did not show a relationship between folate intake and gastric cancer.

Prostate Cancer

The American Cancer Society Cancer Prevention Study II Nutrition cohort study found no association between dietary folate or total folate intake and prostate cancer risk.³⁵ However, increases in dietary folate and total folate intake were associated with a non-significant decreased risk of advanced prostate cancer.³⁵

A nested case-control study within the Northern Sweden Health and Disease cohort also found that plasma folate was not associated with prostate cancer risk, although men with higher plasma folate levels who were followed up after five years or more had a significantly increased risk of prostate cancer.³⁶ Another nested case-control study within the European Prospective Investigation into Cancer cohort study found there was a non-significant increased risk of prostate cancer associated with plasma folate.³⁷

Prostate cancer occurrence was studied in the Aspirin/Folate Polyp Prevention Study, a placebo-controlled randomised trial of aspirin and folic acid supplementation for the chemoprevention of colorectal adenomas.³⁸ Participants were followed for a median of seven years. Among the 643 men who were randomly assigned to placebo or supplementation with folic acid, the estimated probability of being diagnosed with prostate cancer over a 10-year period was 9.7 percent in the folic acid group and 3.3 percent in the placebo group.³⁸ In contrast, baseline dietary folate intake and plasma folate in non-multivitamin users were inversely associated with risk of prostate cancer, although these associations did not attain statistical significance in adjusted analyses.³⁸ These findings highlight the potential complex role of folate in prostate cancer and the possibly different effects of folic acid-containing supplements versus natural sources of folate.³⁸

Overall, there appears to be no significant association between folate intake and prostate cancer risk.

All Cancers

Treatment with 0.8mg (800µg) per day of folic acid and 0.4mg (400µg) per day of vitamin B12 in an RCT was associated with significantly increased cancer incidence and cancer mortality after more than three years of follow up.³⁹ These findings were mainly driven by an increase in the incidence of lung cancer.³⁹

While this RCT provides important short-term data, the findings do not nullify the potential long-term benefits that folic acid fortification may have for health.⁴⁰ It is important that preventive interventions undergo long-term evaluation.⁴⁰

Potential Mechanisms of Action

Folate plays an essential role in DNA synthesis and replication.¹ Consequently, folate deficiency in tissues with rapidly replicating cells results in ineffective DNA synthesis.³ With cancer, where DNA replication and cell division are occurring at an accelerated rate, folate deficiency causes ineffective DNA synthesis and slows tumour growth.³

In normal tissues, folate deficiency appears to have the opposite effect. Folate deficiency appears to predispose normal tissues to neoplastic growth and supplementation suppresses this growth.⁵ Epidemiological evidence suggests an inverse relationship (in some cases dose-dependent) between folate status measured by either intake (dietary and supplemental) or biochemical measurements (blood levels of folate) and cancer risk.³ This relationship has been demonstrated in experimental studies for cancers of the bowel, lung, mouth, pharynx, oesophagus, stomach, pancreas, cervix, ovary and breast as well as neuroblastoma and leukaemia.³

In experimental research, folate administration prior to the development of cancer can prevent tumour development whereas folate supplementation once early lesions are established appears to increase the formation of tumours.¹⁸

Factors to Consider when Evaluating the Literature on Folate and Cancer Risk

Folate intake is typically measured in two ways, either as dietary folate (from foods) or as total folate (including dietary folate and folic acid from supplements). It is not always clear in epidemiological studies, particularly when dietary measures are derived from food frequency data, whether intake from supplements has been included in dietary assessments.

In addition, dietary sources of folate such as fruits, vegetables and wholegrain breads and cereals contain other nutrients such as fibre, vitamins and minerals which may have independent protective effects against cancer. Some studies have not controlled for these other nutrients, making it difficult to measure the impact of dietary folate intake on cancer risk.

Recommended Dietary Intake

The Recommended Dietary Intake of folate for adults in the Nutrient Reference Values for Australia and New Zealand is 400µg per day for men and women, and 600µg and 500µg for pregnant and lactating women respectively.⁴ The upper limit of folate intake is 1mg (1000µg) per day per day for all adult populations.⁴

Women planning to become pregnant should consume at least 400µg of folic acid per day to help reduce the risk of neural tube defects.⁵

Current Level of Intake in Adults

In New Zealand, the median intake of folate is 278µg per day in men and 212µg in women, with an estimated 1 percent and 13 percent of men and women having an inadequate intake respectively.⁴¹ For Australian adults, the median intake is 293µg for men and 225µg for women.⁴²

The main sources of folate in the diets of New Zealand adults are vegetables (18 percent), bread (13 percent), breakfast cereals (11 percent), fruits (8 percent) and potatoes and kumara (8 percent).⁴¹ In Australian diets, the main sources of folate for adults are bread and breakfast cereals (20 percent), vegetables (19 percent), milk (15 percent), cakes, pastries and cereal-mixed-dishes (9 percent), fruit and vegetable juices (9 percent) and fruit (5 percent).⁴²

Folic Acid Fortification

In June 2009, the Scientific Advisory Committee on Nutrition of the British Food Standards Agency and the Department of Health reviewed new evidence on folate and bowel cancer,⁴³ including publications from the Aspirin/Folate Polyp Prevention Study^{14,44} and an ecological study highlighting a temporal association between folic acid fortification and an increase in colorectal cancer incidence in the USA and Canada.⁴⁵

The British Scientific Advisory Committee on Nutrition concluded that the new evidence did not provide a substantial basis for changing the Committee's original recommendation to introduce mandatory fortification alongside controls on voluntary fortification.⁴³ However, the Committee agreed that concerns about cancer risk should be addressed by careful monitoring of emerging evidence on any adverse effects of folic acid fortification.⁴³

Similarly, Food Standards Australia and New Zealand (FSANZ) investigated the association between folate and cancer as part of the development of the proposal for mandatory folic acid fortification, and concluded that there was no apparent increase in cancer risk associated with higher folic acid intakes for the population as a whole.⁴⁶

FSANZ summarised their conclusions as:

Some studies suggest that an increase in folic acid intake may be protective of cancer, however, the evidence is not conclusive. Two large trials using much higher doses of folic acid than is proposed under mandatory fortification do not indicate a gradient of risk for total cancers. For the three specific cancer sites examined, the results of more recent studies do not alter the conclusion reached in earlier reviews (SACN, 2004; SACN, 2005; Sanjoaquin et al., 2005f) that there is no apparent increase in risk associated with higher folic acid intakes for the population as a whole. Although many of the studies suggest that some reduction in cancer might occur, most of these are observational and so might be affected by uncontrolled confounding by other factors.⁴⁶

Manufacturers must list folic acid in the ingredient list on the labels of foods that have been fortified with folic acid.⁵ Therefore, consumers will be able to identify fortified and unfortified products. Women planning to or who may become pregnant can, therefore, adjust their intake of folate appropriately, based on their intake of dietary folate from naturally occurring and fortified sources, and folic acid supplements.

Recommendations

Based on current evidence, the benefits of folic acid fortification for reducing the incidence of neural tube defects outweigh any potential increased risk of cancer. Therefore, the Cancer Society of New Zealand and Cancer Council Australia are not opposed to mandatory fortification of foods with folic acid. However, careful monitoring of emerging evidence on any adverse effects of folic acid fortification, particularly cancer incidence, is required.

The Cancer Society of New Zealand and Cancer Council Australia support the respective government guidelines for food and nutrition (New Zealand Food and Nutrition Guidelines and Australian Dietary Guidelines) and recommend people obtain their nutritional requirements from whole foods, such as fruits, vegetables, breads and cereals rather than individual nutrients in a supplement form.

People with existing bowel adenomas and those with an increased risk of developing bowel adenomas should avoid taking high-dose (above the upper limit of 1mg (1000µg) per day⁴) supplements that contain folic acid.

Future Research

There is a need for more studies that investigate the:

- difference between dietary folate and folic acid in terms of cancer risk.
- effect of mandatory fortification of foods with folic acid on future cancer incidence.

Acknowledgements

This position statement has been reviewed by:

- Craig Sinclair, Director, Cancer Prevention Unit, Cancer Council Victoria
- Professor Ian Olver, Chief Executive Officer, Cancer Council Australia
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Footnotes

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