Scientific Advisory Committee on Nutrition

Folic acid and colorectal cancer risk: Review of recommendation for mandatory folic acid fortification

SUMMARY

Process

1. In October 2007, the Chief Medical Officer requested advice from the Scientific Advisory Committee on Nutrition (SACN) on potential adverse effects of folic acid on colorectal cancer risk.

2. A working group (WG) comprising members of SACN and experts in cancer and cancer epidemiology, was set up to take this work forward. The main studies considered by the WG were: Cole *et al* (2007)[1]; Mason *et al* (2007)[2]; and confidential results[3] of a meta-analysis of randomised controlled trials on the effects of B vitamins (including folic acid) on risk of cardiovascular disease (CVD), which also reported effects on cancer.

3. The study by Cole *et al* (2007) and the B-vitamin meta-analysis were also considered by the Committee on Carcinogenicity (COC). A paper by Figueiredo *et al* (2009)[4] reporting secondary findings regarding prostate cancer incidence from the study by Cole *et al* (2007) was also considered by the COC.

4. The discussions and conclusions of the WG and the COC were considered by the full SACN Committee in June 2009.

Consideration of the evidence

5. The study by Cole *et al* (2007) was a double-blind randomised controlled trial in the USA which investigated the potential of folic acid supplementation (1 mg/d) with or without aspirin for prevention of new colorectal adenomas in persons with a recent history of colorectal adenomas. The results from this study suggest that folic acid at doses in excess of 1 mg/day may increase the risk of developing multiple/advanced adenomas and consequently increase colorectal cancer risk in people with existing premalignant colorectal adenomas, a previous history of colorectal adenomas, or older people who are at increased risk of developing colorectal adenomas.

6. The paper by Mason *et al* (2007) is an ecological study highlighting a temporal association between folic acid fortification and an increase in colorectal cancer incidence in the USA and Canada. An improvement in cancer screening was considered as a possible explanation for the increase in colorectal cancer incidence; however, the available data were insufficient to confirm

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[1] Cole BF *et al.* Folic acid for the prevention of colorectal adenomas. *JAMA.* 2007; 297: 2351-2359.

[2] Mason JB *et al.* A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. *Cancer Epidemiol Biomarkers Prev.* 2007; 16: 1325-29.

[3] The full results of the B-vitamin trials will remain confidential until they are published by the researchers.

[4] Figueiredo *et al.* Folic acid and risk of prostate cancer: Results from a randomized clinical trial. *J Natl Cancer Inst.* 2009; 101:432-435.

this possibility. The WG agreed that there was no clear explanation for the increase in colorectal cancer incidence at around the same time as the introduction of folic acid fortification and that increased rates of colorectal cancer screening, higher intakes of folic acid at the time of fortification, or other factors, could have been responsible.

7. The meta-analysis of 35,603 individuals from seven randomised controlled trials of B-vitamins and CVD risk, which also collected data on cancer outcomes, found that folic acid did not have a statistically significant effect on cancer incidence in men or women. However, the possibility that folic acid might be associated with increased cancer risk cannot be excluded as the meta-analysis had limited statistical power to detect an effect of folic acid on cancer risk. It is unlikely that a study with a large enough sample size to have sufficient statistical power to detect an effect of folic acid on cancer risk is achievable.

8. The study by Figueiredo *et al* (2009) which examined prostate cancer occurrence in the trial by Cole *et al* (2007) reported that men in the folic acid supplemented group (1 mg/d) were at greater risk of developing prostate cancer compared to those in the placebo group. The COC noted that the analysis was based on a small number of cases which could lead to spurious results. This publication was not considered to alter the weight of evidence.

9. After consideration of all the evidence, the majority view of the WG was that the new evidence did not provide a substantial basis for changing SACN's original recommendation for mandatory folic acid fortification. It was agreed that in the event of fortification, concerns about cancer risk should be addressed by careful monitoring of emerging evidence on any adverse effects of folic acid fortification. One member of the WG thought that it was unsafe to proceed with mandatory folic acid fortification because of uncertainties in relation to cancer risk.

10. At its meeting in April 2009, the COC agreed with the decision of the WG to support SACN's previous recommendation for mandatory folic acid fortification together with controls on voluntary fortification. The Committee also agreed that it would be prudent to monitor emerging evidence of any adverse effects of folic acid fortification.

11. At the full SACN meeting in June 2009, the Committee agreed that there were still uncertainties regarding folic acid and cancer risk; SACN's original recommendation had taken this into account by trying to limit exposure to high intakes. The majority of Members supported the previous recommendation to introduce mandatory fortification alongside controls on voluntary fortification. However, it was agreed that the recommendation should be amended to include precautionary advice on consumption of supplements containing folic acid by those at greater risk of developing colorectal adenomas and those with existing premalignant adenomas. One SACN Member did not support mandatory folic acid fortification because of the uncertainties regarding folic acid and cancer risk (the same person who did not support mandatory folic acid fortification on the WG).

Revised Recommendations

12. As previously recommended by the Committee on Medical Aspects of Food and Nutrition Policy (Department of Health, 2000[5]), all women who could become pregnant should take 400 μg/day folic acid as a medicinal or food supplement prior to conception and until the twelfth week of pregnancy. Women with a previous pregnancy affected by a neural tube defect (NTD) are advised to take 5 mg/day of folic acid prior to conception and until the twelfth week of pregnancy.

13. Individual long-term intakes of folic acid from fortified foods and supplements above the Guidance/Tolerable Upper Level (GL/UL)[6] per day for folic acid (1 mg/day for adults; lower amounts for children[7]) should be avoided. A proportion of the UK population[8] is currently exceeding the GL/UL per day due to consumption of foods fortified with folic acid on a voluntary basis and supplement use. The current risk posed by voluntary fortification of food with folic acid and supplement use in contributing to intakes above the GL/UL per day for folic acid needs to be addressed.

14. Mandatory fortification of flour with folic acid would improve the folate status of women most at risk of pregnancies affected by NTDs. It would also improve the folate status of other population groups in the UK. However, mandatory fortification, combined with the current practice of voluntary fortification of foods with folic acid and inappropriate supplement use, would increase the numbers in the population consuming levels of folic acid above the GL/UL per day. Therefore, mandatory fortification should only be introduced in the UK if it is accompanied by:
    - Action to restrict voluntary fortification of foods with folic acid;
    - measures for careful monitoring of emerging evidence on any adverse effects of long-term exposure to intakes of folic acid above the GL/UL per day; and
    - guidance on supplement use for particular population groups.

15. Mandatory fortification of flour[9] alongside restrictions on voluntary fortification will confer a more even distribution of folic acid intakes across the population compared to current voluntary fortification and supplement use. It will not lead to a substantial increase in the average population intake of folic acid but will reduce the risk of intakes exceeding the GL/UL and increase intakes of those currently consuming the lowest total folate intakes (from foods containing naturally occurring folates and foods fortified with folic acid).

16. The introduction of mandatory fortification will require: acquisition of new baseline data on folic acid intakes and blood folate concentration to ensure that mandatory fortification does not lead to an increase in folic acid intakes above the GL/UL and to permit monitoring of trends in future surveillance programmes; adoption of a sufficiently robust common standard analytical method for measurement of folate status at baseline and in all future surveillance studies; and establishment of suitable reference ranges to predict folate adequacy and deficiency.

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[5] Department of Health. *Folic acid and the prevention of disease.* Report on health and social subjects 50. London: TSO, 2000.

[6] In the UK, the Expert Group on Vitamins and Minerals set a GL of 1 mg/day of folic acid for adults. The GL is based on limited data and is an approximate indication of intakes that would not be expected to cause adverse effects. In the USA and Europe, a UL of 1 mg/d of folic acid was set for adults; the UL represents the highest level of daily nutrient that is likely to pose no risk to health.

[7] GLs were not set for children in the UK. ULs were set for children in the USA and Europe based on body weight. ULs for children, Europe: 4-6y, 300 μg/d; 7-10y, 400 μg/d; 11-14y, 600 μg/d; 15-17y, 800 μg/d. ULs for children, USA: 1-3y, 300 μg/d; 4-8y, 400 μg/d; 9-13y, 600 μg/d; 14-18y, 800 μg/d.

[8] Approximately 106,000 people.

[9] Careful consideration would need to be given to the issue of overage.

17. If mandatory fortification were introduced, all women who could become pregnant and those with a history of a previous NTD-affected pregnancy should continue to supplement their diet with 400 μg and 5 mg per day of folic acid respectively prior to conception and until the twelfth week of pregnancy.

18. There are no specific recommendations on folic acid supplementation for other population groups (i.e., children, women above child bearing age, and men) except on medical advice. For people who choose to take supplements, as a precaution, it would be advisable for those aged over 50 years not to consume supplements containing folic acid above the recommended nutrient intake (RNI)[10] for folate of 200 μg/day since the risk of developing colorectal adenomas/colorectal cancer increases after this age (Winawer *et al,* 1997[11]; American Cancer Society, 2008[12]). For people with a previous history of colorectal adenomas, folic acid supplementation should also not exceed 200 μg/day without medical guidance. This recommendation is relevant to current consumption patterns and those which would prevail if mandatory fortification were introduced.

19. Evidence on the benefits and hypothesised risks of folic acid should be reviewed after an appropriate period of time which should be no later than five years.

20. There are a number of uncertainties regarding the GL/UL per day set for folic acid which is based on limited data and relates to concerns regarding vitamin B_{12} deficiency. Further research is required on safe upper levels of folic acid intake in relation to other postulated risks, such as cancer.

21. More reliable diagnostic indices to identify vitamin B_{12} deficiency should be developed. The development of a clinical strategy to manage issues related to vitamin B_{12} is necessary irrespective of a decision on future mandatory fortification of flour with folic acid.

22. The prevalence of poor vitamin B_2 (riboflavin) status in the UK population needs to be addressed.

[10] The RNI represents the amount of a nutrient that that is sufficient to meet the requirements of 97.5% of the population.
[11] Winawer SJ *et al.* Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology.* 1997; 112:1060 and 1998; 114:625.
[12] American Cancer Society. *Cancer Facts & Figures 2008.* Atlanta: American Cancer Society; 2008.