heart defects, and some cancers may be reduced by high dietary folate, is confirmed, what further avoidable costs will be incurred while we delay this important public health measure?

Our current health system is unsustainable. Costs are increasing and this is exacerbated by an ageing population, with high needs for health care and supportive care. We must contain costs. As well as constantly looking for innovative ways to deliver health services effectively, we must take every opportunity to prevent disease. Folic acid fortification of the food supply offers one such opportunity.

The government has a responsibility, on behalf of the whole community, to spend taxpayer dollars wisely. Proceeding with the implementation of New Zealand (Mandatory Fortification of Bread with Folic Acid) Food Standard 2007, originally gazetted for implementation on 27 September 2009, is one wise way of ensuring that health care costs are reduced, and that as we age there will be healthy young people to contribute to the economy and support our care.

References

1. Trends in spina bifida by race/ethnicity: United States 1995–2005. Centers for Disease Control and Prevention. National Center for Health Statistics http://www.cdc.gov/features/dsSpinaBifidaTrends/
2. Folic acid and prevention of spina bifida and anencephaly. Centers for Disease Control and Prevention. MMWR 2002;51 (No. RR-13)
3. Botto LD, Lisi A, Robert-Gnansia E, Erickson JD, Vollset SE, Mastroiacovo P et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: Are the recommendations working? Br Med J. 330(7491):571;2005.
4. Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. Br Med J. 2009;338:b1673.
5. Scientific Advisory Committee on Nutrition. Summary of Report to CMO on folic acid and colorectal cancer risk—October 2009 http://www.sacn.gov.uk/reports_position_statements/reports/summary_of_report_to_cmo_on_folic_acid_and_colorectal_cancer_risk_-_october_2009.html
6. Mason JB. Dickstein A. Jacques PF. Haggarty P. Selhub J. Dallal G. Rosenberg IH. 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(7):1325–1329
7. Stevens VL. Rodriguez C. Pavluck AL. McCullough ML. Thun MJ. Calle EE. Folate nutrition and prostate cancer incidence in a large cohort of US men. Am J Epidemiol. 2006;163(11):989–96.
8. Yang Q, Bostick RM, Friedman JM, Flanders WD. Serum folate and cancer mortality among U.S. adults: Findings from the third national health and nutritional examination survey linked mortality file. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1439–47.

John D Potter MBBS PhD, Member and Senior Advisor, Fred Hutchinson Cancer Research Center and Professor of Epidemiology, University of Washington, Seattle WA, USA
jpotter@fhcrc.org

NO

Despite some benefits, folic acid fortification of the food supply is likely, overall, to be deleterious to the health of New Zealanders. There is clear epidemiologic evidence that folate is associated with a reduced risk of colorectal neoplasia.[1] Furthermore, there are plausible mechanisms that involve folate, both in the provision of bases essential to DNA synthesis and repair and in the synthesis of *S*-adenosylmethionine, the universal methyl donor.[2] Although the centrality of the first mechanism is established in practice (antifolates are effective chemotherapeutic agents[3]), the role of folate in DNA methylation[4] (normal and abnormal) remains to be clarified.

Folate is essential in early embryonic development, particularly neural tube closure: higher folate levels and folate supplements are beneficial.[5] Higher folate intake reduces plasma homocysteine levels, plausibly lowering risk of coronary heart disease (CHD).

This constellation of established and predicted benefits informed the call for fortification of food with folate, so that the benefits can be universally and passively achieved. However, data suggest that fortification may be harmful to the population overall, even in the face of specific benefit to some groups.

Higher intake of folate prevents neural tube defects (NTDs): both clinical trials and subsequent implementation of fortification produced substantial reductions. For example, a British trial reported a greater than 70% decline in NTDs in the active arm compared with placebo;[5] other comparable data exist. Fortification of the US food supply produced a decline in NTDs of almost 20%, showing that, even in a free-living population, the benefits are detectable.[6]

Because of the substantial observational epidemiologic evidence of beneficial consequences of

higher folate on colorectal cancer (CRC) risk, a trial of folate in the secondary prevention of metachronous (second primary) polyps was undertaken. There was no benefit overall of 1 mg per day at either of the subsequent follow-up colonoscopies. Furthermore, at the second colonoscopy, there was a 1.7-fold (95% confidence interval: 1.0–2.8) increased risk of histopathologically advanced lesions and a 2.3-fold (1.2–4.4) increased risk of having at least three adenomas.[7] These are the polyp profiles with the highest risk of subsequent CRC. Thus, contrary to expectation, the risk of deleterious consequences was elevated.

In this same trial, the active arm showed a 2.6-fold (1.2–5.7) higher risk of prostate cancer even though (as for CRC) there was an inverse association between baseline dietary and plasma folate and subsequent prostate cancer in the participants in this trial.[8]

Other studies show no benefit of supplemental folate on other cancers. A combined analysis of two homocysteine-lowering trials using B-vitamins among 6837 CHD patients, after a median in-trial follow-up period of 39 months in the folate/vitamin B_{12} arm, has reported a higher risk of cancer incidence (hazard rate: 1.21; 95% confidence interval: 1.03–1.41), of cancer mortality (1.39; 1.07–1.81) and, after 88 months' median follow-up, a higher all-cause mortality (1.16; 1.03–1.30).[9] Thus, all three poor outcomes were more frequent with 0.8 mg of folic acid and 0.4 mg of vitamin B_{12} in patients with existing CHD in a country without folic acid fortification.[9]

On the basis of these existing data, what might be the impact on health and disease outcomes in New Zealand (NZ) of fortification of foods with folic acid? Current NTD rates in NZ are around three per thousand live births (and have declined markedly over the last decades).[10] Applying a very optimistic estimate (70% reduction, as in the British trial[5]), universal fortification might result in 14 fewer NTDs per year across NZ. More realistically (20% reduction, as with fortification in the US population), there would be four fewer NTDs each year. For the purposes of further discussion, I use the lower confidence bounds to specify risk rather than the hazard ratios. I assume that there will be a 20% higher risk (the data suggest 67–130%) of high-risk polyps among those with a tendency to form polyps (i.e. an extra 4000 higher-risk polyps against a total population prevalence of around 200 000 polyp carriers, of whom 10% normally have a higher risk of progression); of these 4000, I assume 10% will go on to CRC. For prostate cancer, I assume a 20% higher risk (a 2.6-fold higher risk was reported in the clinical trial above) in men over 50.

Among those over 50 with CHD, around 150 000 individuals,[11] I assume there will be a 3% increase

Table 1. Improvement in neural tube defect numbers and lower bound of predicted worsening in other specific disease outcomes following folic acid fortification of the New Zealand food supply

Outcome	Population at risk	Number at risk	Current number of cases/yr in NZ	Projected number of cases/yr in NZ following folic acid fortification*	Change in number of cases/yr in NZ
Neural-tube defects	Newborns	60,000/yr	20[10]	70% reduction – 6 20% reduction – 16	-14 -4
Colorectal cancer	Over 50s with Polyps	~200,000 prevalent cases, 20,000 of whom will have high-risk histology etc.	~12,500[14]	~12,900	+400
Prostate cancer	Men over 50	480,000 population	~14,000[14]	~16,800	+2,800
Serious outcomes in those with CHD	Over 50s with CHD	~150,000 prevalent cases[11]			
Cancer incidence			~12,000[14]	~12,360	+360
Total Mortality			~1000	~1030	+30

*See text for assumptions

in cancer incidence and a 3% increase in overall mortality. I assume no other beneficial or deleterious outcomes, although it seems possible that there may be some long-term reduction of CRC among those exposed from early in life to higher levels of folate[1,3] and there are, conversely, almost certainly problems associated with the masking of vitamin B_{12} deficiency among the elderly.[12]

Table 1 shows possible changes in health outcomes per year for NZ following mandated fortification with folic acid. The data suggest a rise in colorectal cancer (as already noted as a possible outcome in North America[13]) and in prostate cancer, and some increase in deleterious outcomes in those with existing CHD. The reduction of NTDs will be real but very small.

Although, in the face of clear empirical evidence as a basis for making policy decisions, additional data on biology and pharmacology may be superfluous, two considerations are worth brief comment. First, cancer chemoprevention has a very poor track record, in part at least, because of the failure to take into account dose effects, differences in host biology, and the problematic use a single agents which, like single chemotherapeutic agents, may exert strong clonal selective pressure on existing cancers.[3,15] The second point is, in the specific case of folate, the usual form of this compound in the diet or plasma is not folic acid, which has a quite different biologic impact from that of polyglutamated folate.[3]

Conclusion

When balancing benefit and harm to the individual, the practising physician is focussed only on his/her patient. For an entire population, however, the benefits and risks may well accrue to different individuals and groups. If, in addition, the intervention is designed as a widespread, long-term preventive measure in a largely healthy population, avoidance of harm must be the primary consideration.

The fortification of food with folic acid has deleterious consequences that are much more frequent than benefits; even if only some deleterious consequences, in fact, occur in NZ, there does not have to be much harm to outweigh the tiny population benefit of preventing a very small number of NTDs, important though this is for the individuals who are directly affected. The benefits accrue to a different age group from those who experience the deleterious consequences. None of the individuals being treated by mass medication of this sort are being treated because they are ill and, perhaps most distressing, those who have existing conditions may actually experience the greatest degree of harm.

There is no justification for fortification of the NZ (or any other) food supply with folic acid.

References

1. Giovannucci E. Epidemiologic studies of folate and colorectal neoplasia: a review. J Nutr. 2002;132(suppl):2350–5S.
2. Choi SW, Mason JB. Folate and carcinogenesis: An integrated scheme. J Nutr. 2000;130:129–32.
3. Ulrich CM, Potter JD. Folate and cancer—timing is everything. JAMA. 2007;297:2408–9.
4. Laird PW. Cancer epigenetics. Hum Mol Genet. 2005;14: R65–76.
5. MRC Vitamin Study Research Group. Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. Lancet. 1991;338:131–7.
6. Honein MA, Paulozzi LJ, Mathews TJ, et al. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA. 2001;285:2981–6.
7. Cole BF, Baron JA, Sandler RS, et al; for the Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA. 2007;297:2351–9.
8. Figueiredo JC , Grau MV, Haile RW, et al. Folic acid and risk of prostate cancer: Results from a randomized clinical trial. J Nat Cancer Inst. 2009;101:432–5.
9. Ebbing M, MD, Bønaa KH, Nygård O, et al. Cancer incidence and mortality after treatment with folic acid and Vitamin B12. JAMA. 2009;302:2119–2126.
10. International Clearinghouse Centre for Birth Defects Surveillance and Research. Annual report 2008 (with data for 2006) ISSN 0743-5703 ICBDSR Centre. Available at: http://www.icbdsr.org/page.asp?p=10065&l=1 Accessed December 2009.
11. National Heart Foundation of New Zealand. General Statistics. Available at: http://www.nhf.org.nz/index.asp?pageID=2145831169 Accessed December 2009.
12. Skeaff M, Green T, Mann J. Mandatory fortification of flour? Science, not miracles, should inform the decision. N Z Med J. 2003;116:1–5.
13. Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, Rosenberg IH. 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;16:1325–9.
14. Hanna, S, Lewis C. Cancer incidence in New Zealand (1998–2002). In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M and Boyle P, editors (2007). Cancer incidence in five continents. Vol. IX. IARC Scientific Publications No. 160, Lyon, IARC. Available at: http://www-dep.iarc.fr/CI5-IX/PDF/Oceania/65540099T.pdf Accessed December 2009.
15. Potter, JD. Chemoprevention: Why do we keep getting it wrong? 2009 AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention Lecture, 100th AACR Meeting, Denver, CO, April, 2009.