Colon cancer is the third most common cancer worldwide. Vastly different rates between countries, migrants quickly assuming the rates of the host country, and major changes in rates within populations over short periods of time, suggest that environmental and lifestyle factors are important in its aetiology. Ecological studies have shown that fat, meat, fibre, and fruit and vegetable consumption vary consistently with rates of colon cancer across countries. However, large prospective cohort studies and secondary prevention trials of recurrent adenomas have not demonstrated robust consistent associations, particularly with fibre and fruit and vegetable intake. Identifying specific constituents of food amenable to preventive interventions is difficult using traditional epidemiological methods. Case-control studies are subject to recall and selection bias. Cohort studies have problems with residual confounding, poorly understood interactions, and co-linearity of nutrients and vitamins, making it impossible to identify their separate effects. Primary prevention trials are possible, but likely to be very long term.

One specific component of diet which may protect against colon cancer is folate, a B vitamin found in fresh fruit and vegetables. Evidence from randomized controlled trials demonstrates that folic acid, the synthetic and more bioavailable form of natural folate, protects against neural tube defects when taken in the peri-conceptual period. Folic acid lowers homocysteine, a possible risk factor for cardiovascular disease. Dietary folate has been consistently associated with a reduced risk of colorectal carcinoma and adenomas in both case-control and cohort studies. However, confounding by other components of folate-rich foods or by multivitamin supplements cannot be excluded.

Folate, a methyl donor, plays an important role in one-carbon metabolism, a series of interrelated biochemical reactions involved in DNA synthesis and methylation of DNA, RNA, and proteins. There are two plausible carcinogenic mechanisms for how sub-optimal folate status could pre-dispose to colon cancer. Firstly, folate is present in plasma as 5-methyltetrahydrofolate (5-methylTHF), a co-factor and methyl donor for the remethylation of homocysteine to methionine. Methionine, an essential dietary amino acid, is then converted to s-adenosylmethionine (SAM), a universal methyl donor involved in DNA methylation and several other biological methylation reactions (Figure 1). Sub-optimal folate status results in DNA hypomethylation which interferes with gene expression and impairs DNA repair. Secondly, the intracellular form of folate, 5,10-methylenetetrahydrofolate (5,10-methyleneTHF), donates a methyl group to uracil converting it to thymine. If folate is deficient, uracil, the alternative pyrimidine nitrogenous base usually found in RNA, replaces the normal thymine of DNA. Inclusion of uracil leads to DNA ‘breaks’ and instability. Both DNA hypomethylation and DNA ‘breaks’ are common in colon cancer.

Genetic studies of polymorphisms involved in folate metabolism allow us to examine colon cancer in individuals who are randomly predisposed to low folate status or who are ‘folate sensitive’ by chance alone. The enzyme methylenetetrahydrofolate reductase (MTHFR) metabolizes the conversion of 5,10-methyleneTHF to 5-methylTHF. The gene that codes for MTHFR is located on chromosome one and has several alleles. In one common polymorphism of the MTHFR gene, MTHFR C677T, a cytosine to thymine transition at position 677 results in an alanine to valine substitution in the MTHFR amino acid
sequence.\textsuperscript{22} Those with the homozygote genotype (MTHFR 677TT), about 10–15% of most Caucasian populations, have reduced enzyme activity which results in higher plasma homocysteine and lower circulating plasma folate relative to heterozygotes or those with the wild genotype. Because individuals are exposed to homozygous status by chance, the association between genetic status and colon cancer is less likely to be confounded.

Several studies have looked at the association between MTHFR C677T and colon cancer. Two large cohort studies, the US physicians study\textsuperscript{23} and the Health Professionals Follow-up Study,\textsuperscript{24} and a large multi-centre case control study\textsuperscript{25} all showed a 20–50% decreased risk of colon cancer with homozygous status (MTHFR 677TT) in comparison to either wild type (MTHFR 677CC) or heterozygotes (MTHFR 677CT) and wild type combined. This is in the opposite direction to what one might expect. In all three studies the protective effect was strengthened in those with high dietary folate. High methionine or low alcohol consumption also strengthened this effect. These studies also demonstrated an increased risk of colon cancer of between 30% and 80% in those with a ‘methyl-deplete’ diet i.e. low folate, low methionine, and high alcohol.

A methyl-deplete diet is one where the supply of methyl groups is poor. As well as low dietary folate, low dietary methionine will also result in reduced s-adenosyl methionine (SAM), the major methyl donor for DNA methylation (Figure 1). Alcohol has been associated with an increased risk in colon cancer in cohort studies.\textsuperscript{26} One of the possible mechanisms is by inactivating MTHFR or methionine synthetase, again resulting in a reduction of methionine and SAM with consequent DNA hypomethylation. Distinguishing the individual effects of the three components of a methyl-deplete diet—low folate, low methionine, and high alcohol—is not straightforward. They may not be independent of one another and their separate effects are more likely to interact in some way rather than be simply additive.

Two American studies of MTHFR C677T and colorectal adenoma, although both statistically underpowered, showed similar baseline trends to the colon cancer studies and support the ‘methyl-deplete’ hypothesis.\textsuperscript{27,28} Although the Nurses Health Study showed a protective effect of dietary folate with colon cancer\textsuperscript{27} they showed an increased risk of adenoma of about 30% in homoygotes (MTHFR 677TT), even when their folate status was high.\textsuperscript{29} A Norwegian study showed a high baseline risk of adenoma with homozygous status, a doubling of this risk in those with low folate intake and a slightly protective effect in those with a high folate intake.\textsuperscript{30}

Homoygous status (MTHFR 677TT) usually indicates low circulating folate (5-methylTHF) so a baseline increase in colon cancer risk in this group might be expected. In an apparent paradox, several of these studies show a baseline protective effect\textsuperscript{23-25,28} and others an increased risk.\textsuperscript{27,29,30} In fact, although circulating folate (5-methylTHF) tends to be low, the pool of intracellular 5,10-methyleneTHF is increased or ‘backed up’ because of the reduced activity of MTHFR. The extent to which this happens depends on folate nutrition. The studies that have shown a protective effect, regardless of folate status, are all studies of North American populations. One likely explanation is that the population being studied has optimum folate nutrition either through diet alone, fortification of common foods, or multivitamin supplements. This was recently illustrated in a large meta-analysis of MTHFR C677T and coronary heart disease (CHD)\textsuperscript{31} where homozygosity was associated with a 14% increase in CHD risk in European populations but not in North American populations.

This effect of MTHFR 677TT—protective if folate nutrition is adequate—may be applicable to other forms of cancer, particularly cancers of rapidly proliferating cells such as acute leukaemias. One case-control study of adult acute lymphocytic leukaemia (ALL) showed a protective effect of both MTHFR 677TT (odds ratio [OR] = 0.23, 95% CI: 0.06–0.81) and homozygosity of another polymorhism of MTHFR, A1298C. However, overall the number of cases was small, with only one case of ALL homozygous for MTHFR A1298C and each estimate was adjusted for the other polymorphism.\textsuperscript{32} Another case-control study showed a protective effect of MTHFR 677TT and 1298CC against particular molecular sub-types of ALL in children.\textsuperscript{33} An Australian case-control study showed a protective effect of maternal folate or iron supplementation during pregnancy against childhood ALL (OR = 0.37, 95% CI: 0.21–0.65). The authors state that this was not an a priori hypothesis and did not describe MTHFR status in the parents or children.\textsuperscript{34}

Marugame et al.,\textsuperscript{35} in this month’s International Journal of Epidemiology, have replicated the results of previous studies of colorectal adenoma and folate. They found a slightly increased baseline crude OR of adenoma in middle-aged pre-retirement soldiers associated with TT genotype (OR = 1.4, 95% CI: 0.72–2.73), an adjusted OR of adenoma of 2.13 (95% CI: 0.82–5.54) associated with low serum folate status and a decreased OR of adenoma in those with high serum folate (OR = 0.58, 95% CI: 0.21–1.61).

There has been one other study of adenoma and MTHFR C677T in a screened asymptomatic population, but this analysis was confined to only 48 high-risk adenomas.\textsuperscript{30} Studies based on screening a consecutive series are less likely to have ascertainment bias and more likely to have disease-free controls. Studies based on cases which are either symptomatic or ascertained through voluntary screening may not reflect the true population burden of disease, and could be an odd mixture of severe cases and those who are health conscious, with a substantial ‘clinical iceberg’. Also, there is no guarantee that the comparison group is disease-free. The estimate of effect in such a study could be exaggerated or diluted. This is not the case with Marugame’s paper.

There is consistent evidence that MTHFR C677T homozygous genotype reflects ‘folate sensitivity’. When folate nutrition is adequate, the risk of colon cancer or adenoma is reduced. When it is inadequate, there is an increase in risk especially if combined with a ‘methyl-deplete’ diet. The main problem with this evidence is not the lack of consistency—direction and magnitude of effect have been fairly consistent—but the lack of statistical power. Larger studies of MTHFR, folate, and colorectal cancer and adenomas are needed. If these findings are replicated in large studies, then increasing folic acid consumption in a 10–15% sub-set of the population could have substantial impact on colon cancer and adenoma incidence. How could this be achieved in a way that is acceptable to everyone? Unlike other population health promotion interventions, it is relatively cheap and easy to increase the whole population consumption of
folate by fortifying flour with folic acid. In order to reduce the incidence of neural tube defects in the US, fortification of grain products with folic acid became obligatory in 1998. It is still voluntary in the UK and other countries where there is concern about masking vitamin B<sub>12</sub> deficiency in the elderly and removing choice and consent from the individual. The alternative is voluntary screening for susceptible individuals, with the healthiest most likely to benefit. For the moment in the UK, public health policy on nutrition and cancer is confined to the national ‘five-a-day’ programme to increase fruit and vegetable consumption.

References