Multivitamins, folate, and colon cancer


Background
A low folate intake may lead to reduced DNA methylation, resulting in abnormalities in DNA synthesis and repair, which could contribute to colonic carcinogenesis. There is evidence from prospective cohort studies that folate deficiency increases the risk of colon cancer in men, but such data are lacking for women.

Aim
To determine whether dietary folate and folate from supplements protects against colon cancer in women.

Design
A prospective cohort investigation.

Subjects
88 756 registered female nurses in the United States aged 30–55 years (Nurses’ Health Study).

Methods
Subjects completed semiquantitative food frequency questionnaires which included information on 61 foods and beverages plus vitamin and mineral supplements. The cohort was followed up for the development of colon cancer. Cases were identified through follow up questionnaires and the United States National Death Index. Relative risks were calculated and adjusted for energy intake, age, family history of colorectal cancer, aspirin, smoking, body mass, and intake of red meat, fibre, and methionine.

Results
Follow up of the cohort was almost complete (96%) and 442 new cases of colon adenocarcinoma were identified. Higher adjusted total folate intake was related to a lower risk for colon cancer (RR=0.69, 95% CI=0.52–0.93) for intake of > 400 µg/day compared with < 200 µg/day. Folate intake from dietary sources alone was related to a modest risk reduction and women who used supplements for 15 years or more had a marked reduction (RR=0.25, 95% CI=0.13–0.51).

Conclusions
A high dietary folate intake and long term folate supplementation may reduce the risk of colon cancer.

Comment
Case control and cohort studies consistently suggest that high intakes of vegetables are associated with a decreased risk of colorectal cancer but the specific nutrients involved have not been identified. Interest in the possible aetiological importance of folate has been stimulated by observations suggesting that hypomethylation of DNA is an early step in colorectal carcinogenesis and by evidence of a positive association with alcohol, which has an adverse effect on folate metabolism.

Giovannucci and colleagues provide evidence of an inverse association between folate intake and colon cancer. Compared with women whose intake was ≤200 µg/day, the relative risk of colon cancer associated with an intake of 201–300 µg/day was 0.9, with an intake of 301–400 µg/day it was 0.8, and with an intake >400 µg/day it was 0.7 (p for trend=0.01). There was no evidence of confounding. Among women with the highest category of intake, 86.3% used multivitamin supplements. The other three categories reflect primarily dietary sources. The inverse relationship with folate persisted when adjustment was made for other nutrients present in multivitamin supplements. Analysis of duration of use of multivitamins containing folic acid showed that the inverse relationship was apparent only after at least five years of use and the most marked effect was after at least 15 years of use.

Data from four other cohorts, one in women and three in men, suggest that there are weak inverse associations between colon cancer and reported intake of folate, or levels in serum or plasma. In general, case control studies are compatible with this, but the inverse relationship is not statistically significant after adjustment for other nutrients. In some of the studies the relationship was apparent only in women or was stronger in women than in men.

There may be substantial error in the assessment of dietary folate intake. As a consequence, misclassification is likely to have occurred in both cohort and case control studies. However, this would tend to attenuate any association towards the null.

No association between rectal cancer and long term multivitamin use was found in the cohort of Giovannucci and colleagues. Other studies of rectal cancer are inconsistent. They lack statistical power or may have selection bias.

Studies of colorectal adenomas can provide information about the earlier stages of the adenoma-carcinoma sequence. There is a consistent inverse association between adenomas and both dietary folate and red cell folate. This appears to be stronger than for colorectal cancer.

An intriguing aspect is gene-nutrient interaction. There is some evidence of interaction between MTHFR genotype and intake of folate and related nutrients, and perhaps alcohol. In the presence of gene-environment interaction, failure to take both sets of factors into account may result in bias in the estimate of the relative risk.

In conclusion, the possibility that the inverse relationship between folate and colorectal neoplasia is a result of uncontrolled confounding from other nutrients cannot entirely be excluded. Only a randomised controlled trial could resolve this issue. Clarification of the relationship between folate and rectal cancer, possible gender effects, the possible role of other genetic polymorphisms affecting folate metabolism and of mechanisms underlying apparent interactions between intake of folate and related nutrients, and the genes influencing folate metabolism would inform
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the trial design. The study of Giovannucci and colleagues suggests that prolonged high levels of folate intake may be necessary to prevent colon cancer. This raises questions about the feasibility of a trial and possible toxicity. In addition, the potential role of folate in the prevention of colon cancer should not be considered in isolation from the prevention of other disorders.

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