

Long term dietary folate decreased risk of colon cancer in women

Giovanucci E, Stampfer MJ, Colditz GA, et al. *Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study*. *Ann Intern Med* 1998 Oct 1;129:517-24.

Question

Is folate intake from diet or dietary supplements associated with a decreased risk of colon cancer in women?

Design

Population based cohort study of women in the Nurses' Health Study with 14 years follow up.

Setting

USA.

Participants

88 756 female registered nurses who were 30-55 years of age in 1976 (baseline). Exclusion criteria were cancer other than non-melanoma skin cancer before 1980, ulcerative colitis, familial polyposis syndrome, implausible high or low scores for total energy intake, missing data on food frequency questionnaires between 1980 and 1992, or incomplete information on aspirin or multivitamin use in 1980.

Assessment of risk factors

Nurses completed postal questionnaires at baseline and every 2 years thereafter. Food frequency questionnaires included information on 61 foods and beverages, vitamin and mineral supplements, and brands and types of breakfast cereals and multivitamin products. For analysis, nurses were divided into quartiles based on folate intake in 1980 (≤ 200 , 201-300, 301-400, and > 400 $\mu\text{g}/\text{d}$) with the lowest concentration given a relative risk (RR) of 1.0. Folate use was divided into total, dietary, and supplemental. Baseline data included information on age, weight and height (body mass index), smoking history, physical activity, aspirin use, colonoscopy or sigmoidoscopy, parental

history of colorectal cancer, and postmenopausal hormone use. Analyses were adjusted for baseline variables as well as consumption of red meat, alcohol, fibre, and total energy intake.

Main outcome measures

Reported cases of colon or rectal cancer confirmed by blinded assessment of hospital records and pathology reports.

Main results

During follow up, 655 cases of confirmed colorectal adenocarcinoma were reported (442 in the colon, 143 in the rectum, and 70 at undetermined sites). Women in the highest quartile of total folate use had a decreased risk of colon cancer (RR 0.69, 95% CI 0.52 to 0.93, p for trend 0.01). Analyses adjusted for combinations of baseline variables did not change this result substantially. Multivitamin use for > 15 years lowered the risk of colon cancer (RR 0.25, CI 0.13 to 0.51—this means there were 15 instead of 68 new cases of colon cancer per 10 000 women aged 55-69 years). It also lowered the risk of proximal colon cancer (RR 0.16, CI 0.06 to 0.52) and distal colon cancer (RR 0.37, CI 0.15 to 0.90), but not rectal cancer (RR 1.27, CI 0.67 to 2.46).

Conclusions

Folate intake from diet or dietary supplements was associated with a decreased risk of colon cancer in women. Long term use of dietary supplements containing folate resulted in the lowest risk.

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A modified version of this abstract appears in ACP Journal Club.

Commentary

This is an interesting, large, long term cohort study of women who were nurses. Giovanucci *et al* noted that this was an observational study rather than a randomised study. Establishing firm evidence that the resulting decrease in the rates of colon cancer is solely attributable to folate intake is therefore difficult. Also, data on folate intake were based on self report and were not validated. Strenuous statistical analysis of the data indicated that folate may be an important factor in the reduction of colon cancer in these women.

One of most interesting findings about dietary intake is that the most substantial results were in groups of women who

took multivitamin supplements, regardless of their dietary folate intake. The authors had difficulties in ascertaining high folate concentrations using dietary data alone because of the low bioavailability of folate from dietary sources. Few of the women were thought to have frank folate deficiency, and none of the 180 women in a test sample had a clinical deficiency of folate. This limits the generalisability of the findings. If the results of the study are proved in the long term, folate may have the potential to have a large effect on the health of many people.

The duration of high folate intake must also be noted, even in those women who used multivitamin supplements; no benefit

was shown for colon cancer after 4 years of use, trends were shown in the 5-9 and 10-14 year groups, but after 15 years, the risk of colon cancer was markedly lower.

These results indicate that randomised controlled trials are needed to clearly understand how folate concentrations are associated with colon cancer. Until then, we have some indication that increasing folate in the diet either by multivitamin supplements or fortified cereals may have long term benefits.

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