Folic acid and colorectal cancer: unwarranted fears

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Abstract

Question Some of my female patients are afraid of taking folic acid because they "fear cancer." What is the evidence for this?

Answer Theoretical evidence in experimental models is sharply contrasted by 3 recent meta-analyses of randomized and observational studies. Women planning to become pregnant should supplement with the folate dose they need to prevent neural tube defects.

Résumé

Question Certaines de mes patientes ont peur de prendre de l'acide folique par «crainte du cancer». Y a-t-il des données scientifiques à cet effet?

Réponse Les données théoriques dans des modèles expérimentaux contrastent vivement avec celles de 3 récentes méta-analyses d'études aléatoires et observationnelles. Les femmes qui prévoient une grossesse devraient prendre la dose de supplément d'acide folique nécessaire pour prévenir des anomalies du tube neural.

After years of speculation about whether folic acid might prevent neural tube defects (NTDs), 2 randomized control studies published in the early 1990s confirmed beyond a doubt the protective effect of this B vitamin against these devastating malformations.[1,2]

In 1998 the United States and Canada fortified flour with 140 mg of folate per 100 g of flour, resulting in a dramatic decrease in the incidence of NTDs.[3] In 2001 Wald et al found that, based on published studies on the relationship between folic acid doses and resultant serum concentrations, the recommended folic acid dose of 0.4 mg/d did not provide protective levels against NTDs in many women.[4] The reference values were derived from the breakthrough Irish study that correlated red blood cell folate levels with protective effects.[5] Wald et al suggested that up to 5 mg/d of folate was needed to ensure protection of 90% of the population.[4] Their prediction was corroborated in Ontario, where despite flour fortification, 40% of pregnant women in 2005 had red blood cell folate levels below the protective level of 900 nmol/L.[6]

The Motherisk Program has further shown poor compliance with folic acid prenatal vitamin supplements among women of reproductive age, even in the context of voluntary drug studies.[7] In 2007 the Society of Obstetricians and Gynaecologists of Canada and Motherisk initiated changes to practice guidelines, identifying women who would benefit from 5 mg/d of folic acid before conception and until the end of the first trimester.[8]

However, in parallel to this initiative, publications appeared in the literature suggesting that excessive folate intake might confer an increased risk of cancer, with most attention focused on colorectal cancer. The evidence has come mostly from in vitro work and experimental animal data, promoting the "dual effect" of folate on tumour cells, suggesting that at low folate levels, folate supplementation decreases cancer risk, and at high exposure levels in the context of precancerous cells, the risk might increase.[9,10]

This message has increased the levels of anxiety and confusion among pregnant women and their health care professionals. The fact that theoretical risks after prolonged use are not relevant to short-term use in pregnancy has provided little comfort.

Randomized and observational studies

By 2011, a large number of studies that reported on thousands of patients have addressed the question of whether folic acid intake in the prepregnancy period increases the risk of subsequent colorectal cancer. Moreover, this issue has been systematically reviewed in several meta-analyses published in 2011.

In general, 2 types of meta-analyses have been conducted:

- analysis of randomized trials, in which rates of colorectal cancer or adenomas were compared among people who received or did not receive daily doses of folic acid as an intervention; and
- analysis of observational studies, in which rates of colorectal cancer were compared among people

based on different rates of intake of folic acid from foods, supplements, and combined.

Analysis of randomized trials. Two meta-analyses were published almost simultaneously in 2011.[11,12] They included 5 and 3 studies, respectively. In all accepted studies, the rates of colorectal cancer were compared among those receiving or not receiving folic acid. Overall, more than 1000 patients were included in these studies.

Both meta-analyses found very similar results. Exposure to folic acid from 0.5 to 5 mg/d and for up to 6 years was not associated with increased risk of recurrence or occurrence of colorectal adenoma or cancer (odds ratio 1.09, 95% confidence interval [CI] 0.93 to 1.29, and odds ratio 0.78, 95% CI 0.49 to 1.24, respectively). The study with perhaps the most dramatic results was reported after the time limit of the 2 meta-analyses. It examined patients with colorectal cancer in remission who were randomized to receive 1 mg/d of folic acid or placebo for up to 6.5 years. Those randomized to folic acid did not exhibit increased risk of recurrence (relative risk 0.82, 95% CI 0.59 to 1.13); in fact, in those with low folate levels, the folic supplementation resulted in protective effects.[13] Therefore, even in the patients most likely to be affected by the proposed negative effects of folate, the vitamin did not increase the risk even at high doses given during 6.5 years.

Analysis of observational studies. Kennedy and colleagues systematically reviewed and analyzed all observational studies.[14] Observational studies that defined levels of folate intake and incidence of colorectal cancer in adults were included. Out of 6427 references, 27 studies met the inclusion criteria, including thousands of subjects. The summary risk estimate for case control studies comparing high versus low total folate intake was 0.85 (CI 95% 0.74 to 0.99), with no significant heterogeneity among studies. Similarly, for cohort studies, the results of the summary risk estimate for high versus low dietary folate intake was 0.92 (CI 95% 0.81 to 1.05), with no significant heterogeneity. These results suggest that higher folate intake levels offer a reduction in the risks of developing colorectal cancer. These data can serve to help reassure women planning to become pregnant and encourage them to increase folic intake during the preconception period to levels sufficient to prevent NTDs.

Thus, a very large body of evidence from both randomized trials and observational studies has failed to show increased risk of colorectal cancer associated with prolonged exposure to folate. When this negative overall result is put in the context of the short exposure during the periconceptional period, this unproven risk is further nullified.

Conclusion

In the context of pregnancy, we believe that it is irresponsible to scare pregnant women out of taking folic acid at the doses appropriate for them. Any mention of cancer risk can elicit strong responses, even when not evidence-based.[15] In the case of appropriate folic acid intake before pregnancy, the current risk-benefit equation confers tremendous fetal benefit versus no evidence of maternal cancer risk. We believe this is the way physicians should practise in 2011.

Competing interests

Dr Koren is a consultant for 2 companies that produce folic acid, Bayer Inc and Duchesnay Inc.

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Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**.

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