

Assessment of studies thought to suggest
associations between folic acid and
cancers of the colon and breast

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European Food Safety Authority / Swedish National
Food Administration Scientific Meeting on Folic Acid
Uppsala, Sweden
21 January 2009

THE LANCET

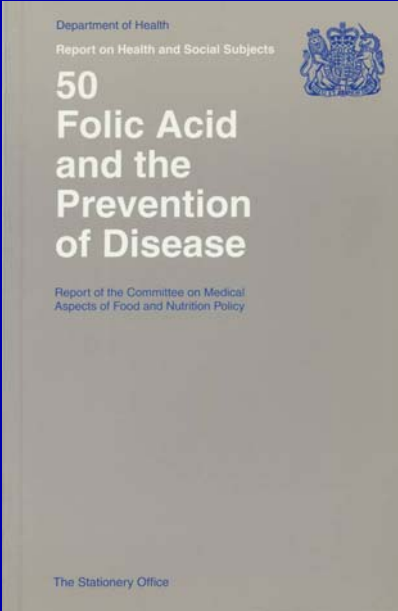
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No 8760

**Prevention of neural tube defects:
Results of the Medical Research Council Vitamin
Study**

MRC VITAMIN STUDY RESEARCH GROUP



Department of Health
Report on Health and Social Subjects

50
Folic Acid
and the
Prevention
of Disease

Report of the Committee on Medical
Aspects of Food and Nutrition Policy

The Stationery Office

“On scientific, medical and public health grounds, the committee concluded that universal folic acid fortification of flour at 240 µg/100 g in food products as consumed would have a significant effect in preventing NTD-affected conceptions and births without resulting in unacceptably high intakes in any group in the population.”

- COMA Report, 2000

Presentations/images/011/FACover.png

Countries with mandatory fortification of flour with folic acid in place or agreed

Argentina	El Salvador	Mexico	Surinam
Australia	Fiji	Morocco	Trinidad and Tobago
Bahrain	Ghana	New Zealand	Turkmenistan
Barbados	Grenada	Nicaragua	Uruguay
Belize	Guadalupe	Oman	USA
Bolivia	Guatemala	Palestine, Occupied Territory	Venezuela
Brazil	Guyana	Panama	Yemen
Canada	Haiti	Paraguay	
Chile	Honduras	Peru	
Colombia	Indonesia	Puerto Rico	
Costa Rica	Iran	Qatar	
Cote d'Ivoire	Iraq	Saudi Arabia	
Cuba	Jamaica	South Africa	
Dominican Republic	Jordan	St. Vincent	
Ecuador	Kuwait	Sudan	

52 Countries

No EU country has fortified

NEWS HEADLINES > REGULATION


FSA finally agrees to recommend folic acid fortification

By Jess Halliday, 18-May-2007

The board of the UK's Food Standards Agency yesterday agreed unanimously to recommend mandatory fortification of some foods with folic acid, but whether it is bread or flour is still up for debate.

The decision, which was made at an open board meeting in London, comes as no great surprise since the FSA's Scientific Advisory Committee on Nutrition (SACN) gave a positive recommendation at the end of last year. The agency subsequently launched its final consultation, and received around 200 responses from stakeholders.

18 May 2007

 LIVE BBC NEWS CHANNEL

The latest study follows a letter to the Food Standards Agency from Sir Liam Donaldson, the Chief Medical Officer of England, requesting further expert consideration of **two recent studies linking folic acid to bowel cancer** before the government gives the final go-ahead for mandatory fortification.

“ We challenge the underlying scientific premise behind this consensus ”

Dr Sian Astley
Institute of Food Research

But the Food Standards Agency said fortification was safe.

30 October 2007

Time trends relating to folic acid fortification and incidence of colorectal cancer in the USA and Canada

Hypothesis

A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis

Joel B. Mason,^{1,2} Aaron Dickstein,² Paul F. Jacques,¹ Paul Haggarty,³ Jacob Selhub,¹ Gerard Dallal,¹ and Irwin H. Rosenberg^{1,2}

¹Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University; ²Tufts University School of Medicine, Boston, Massachusetts; and ³Rowett Research Institute, University of Aberdeen, Aberdeen, United Kingdom

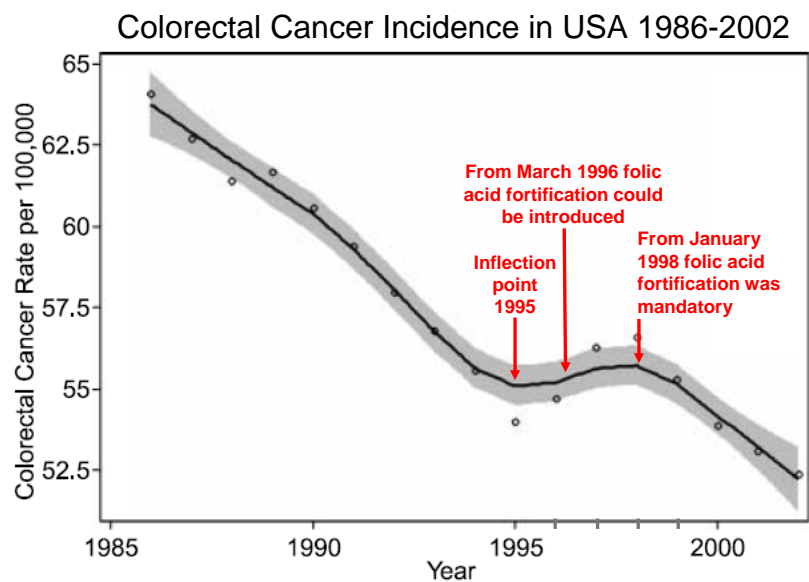
Mason et al. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(7):1325-1329.

Comments on the Mason et al hypothesis paper

Bayston, Russell, Wald, and Hoffbrand.
Lancet 2007;370:2004.

Mason, Cole, Baron, Kim and Smith.
Lancet 2008;371:1335.

Bayston, Russell, Wald, and Hoffbrand.
Lancet 2008;371:1335-1336.



Plot taken from: Mason et al. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(7):1325-1329.

Trends in serum folate after food fortification in California

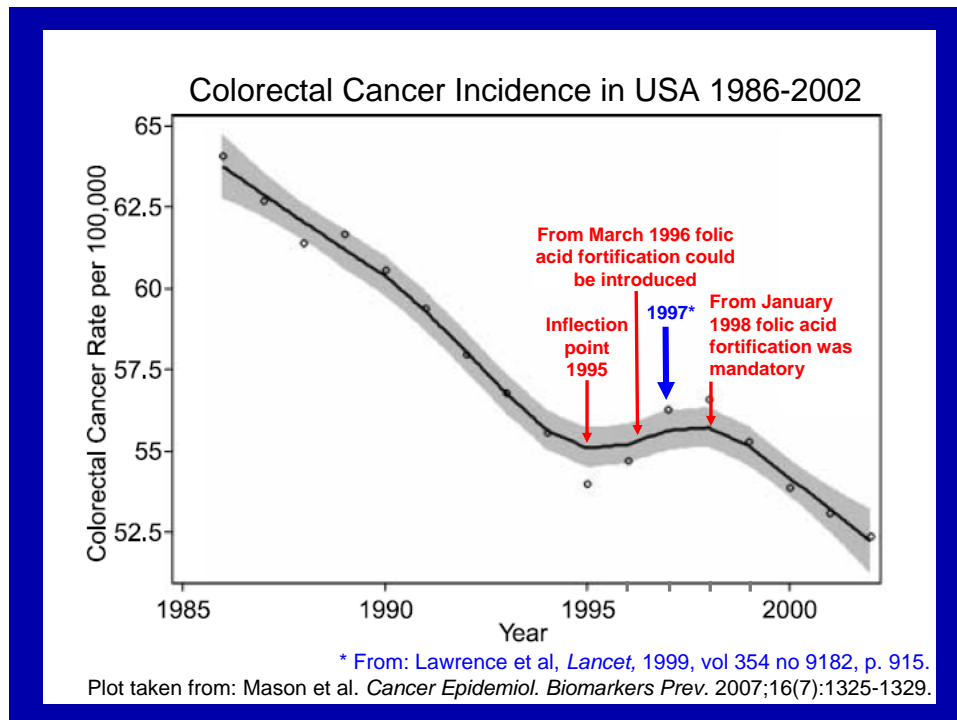
Year	No. of tests	% Test results < 2.7 ng/ml
1994	14493	1.3
1995	14750	1.3
1996	17642	1.3
1997	22805	0.6
1998	22662	0.3

Lawrence et al, *Lancet*, 1999, vol 354 no 9182, p. 915

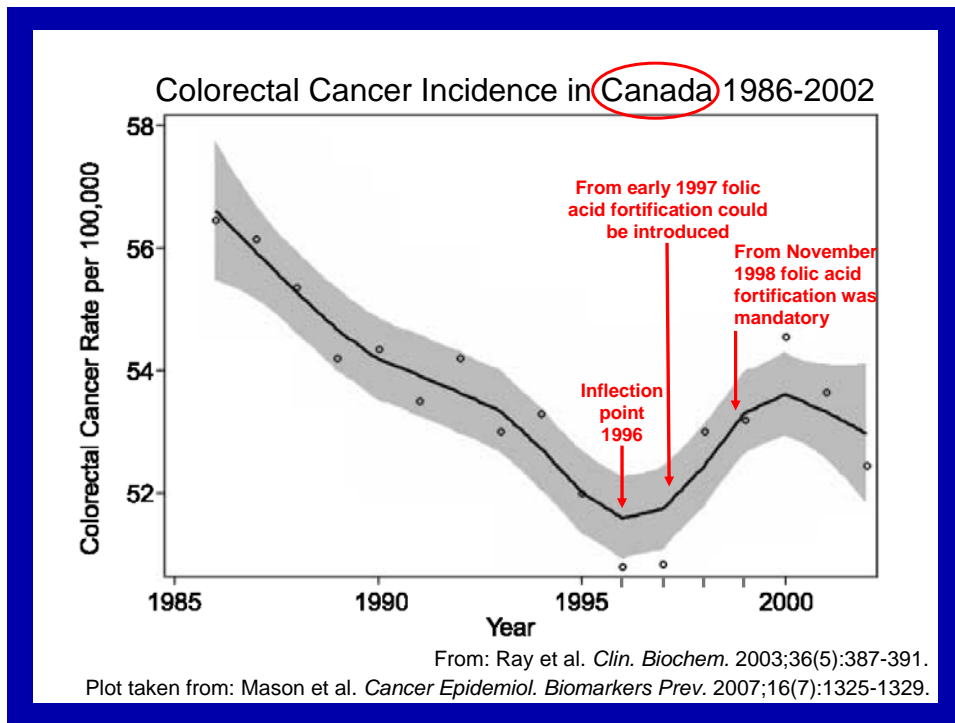
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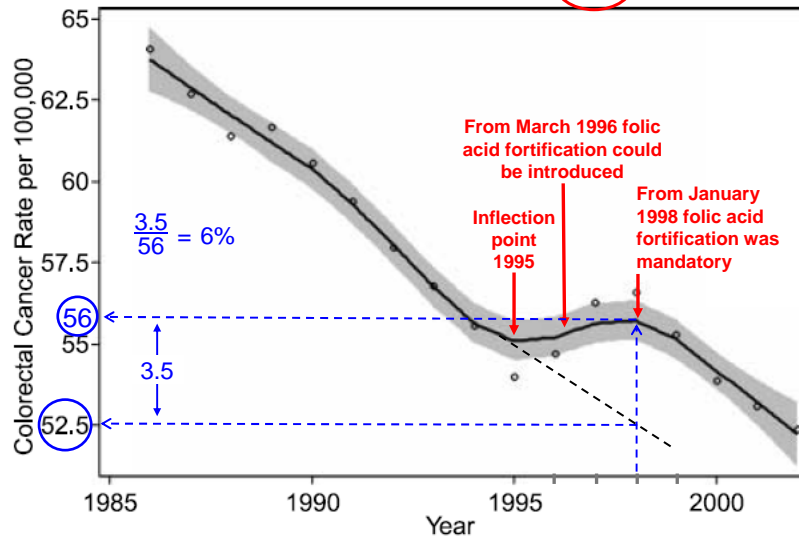
Fortification cannot have caused an increase in the incidence of colorectal cancer if the increase in cancer rates occurred before the introduction of fortification.



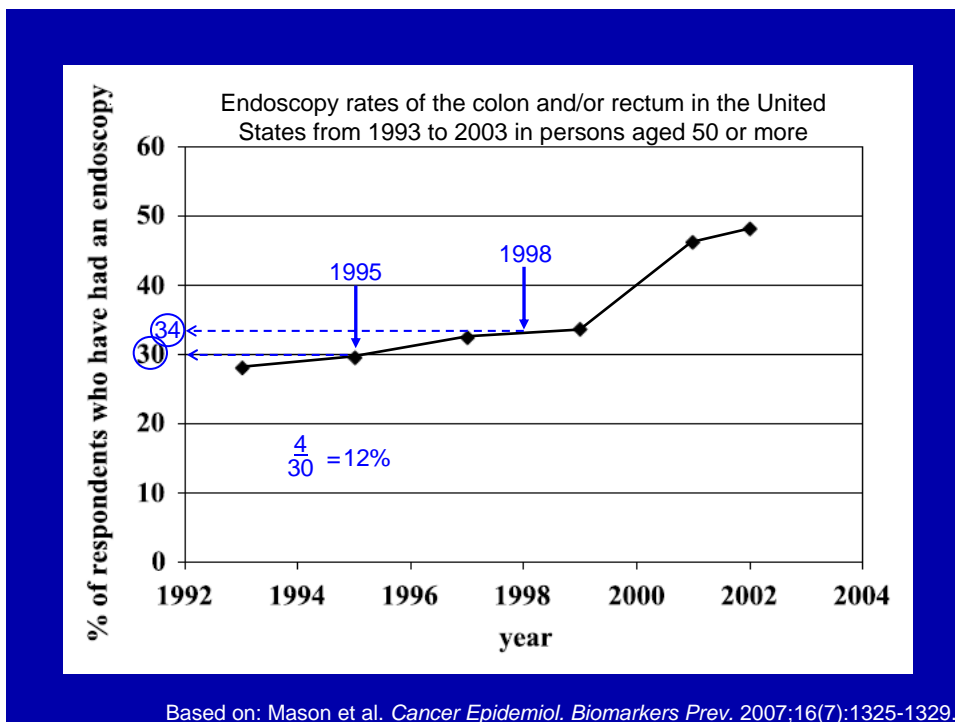
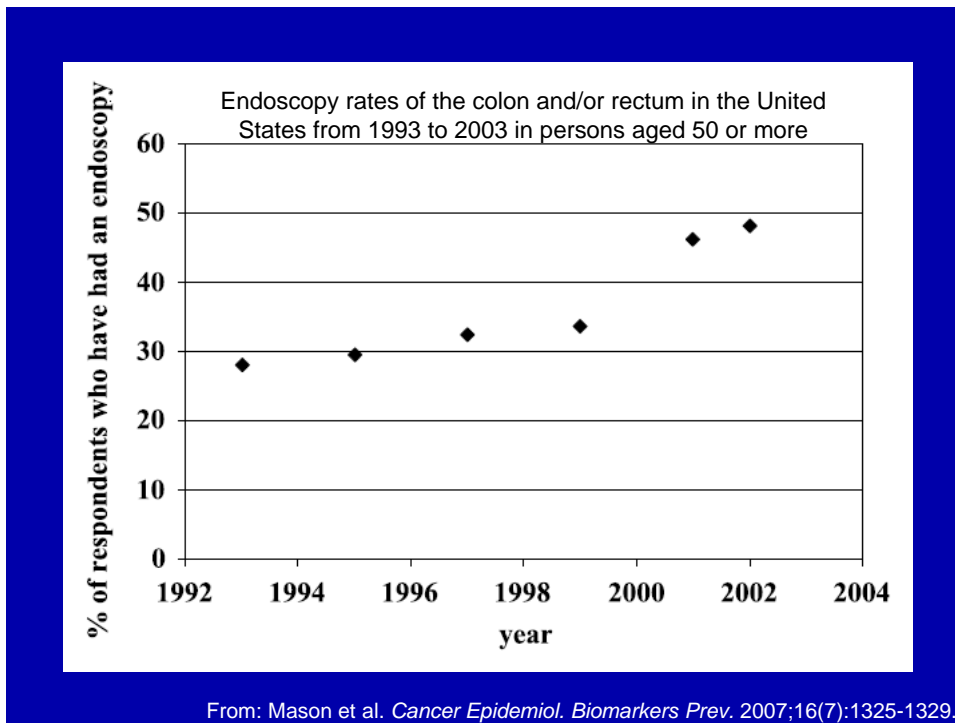
The same temporal sequence between the introduction of fortification and the rise in colorectal cancer is seen in Canada as in the United States.

Can the temporary increase in colorectal cancer incidence be explained?

Colorectal Cancer Incidence in **USA** 1986-2002

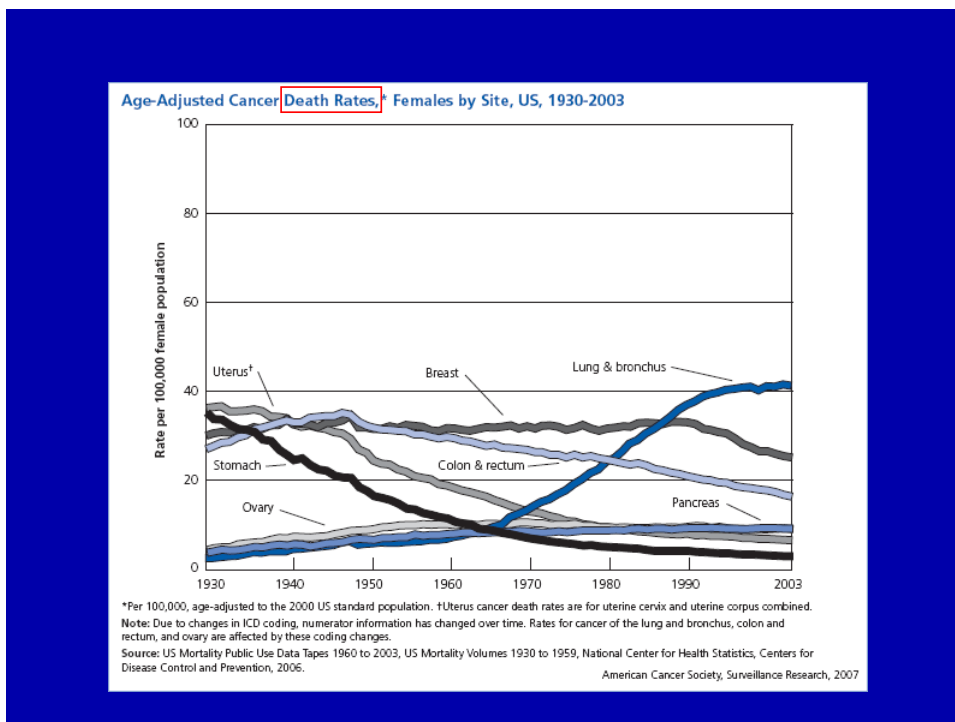
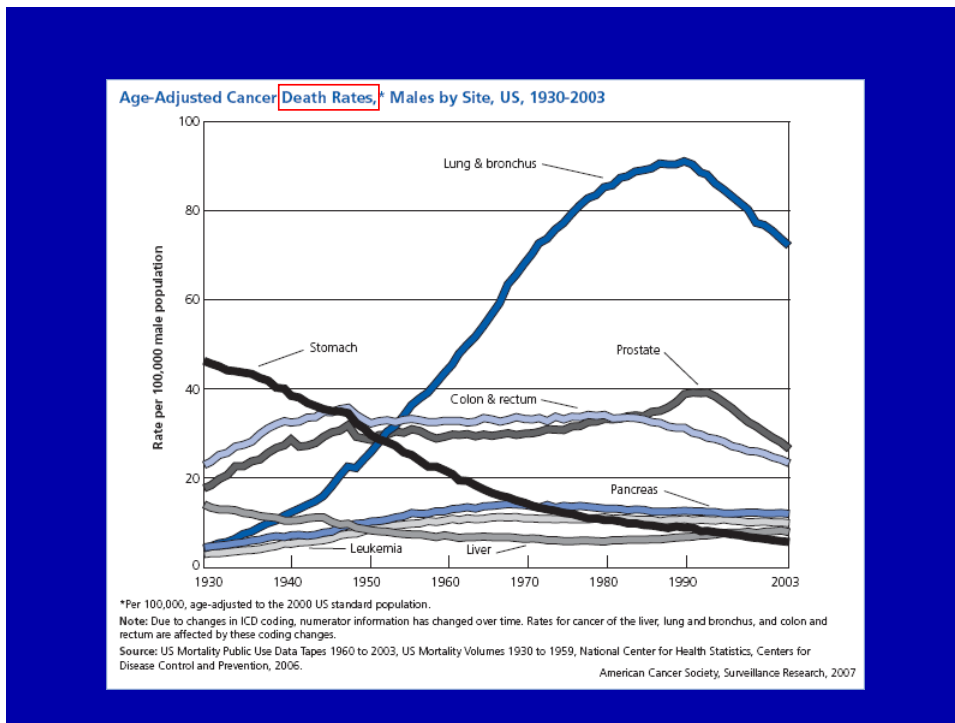


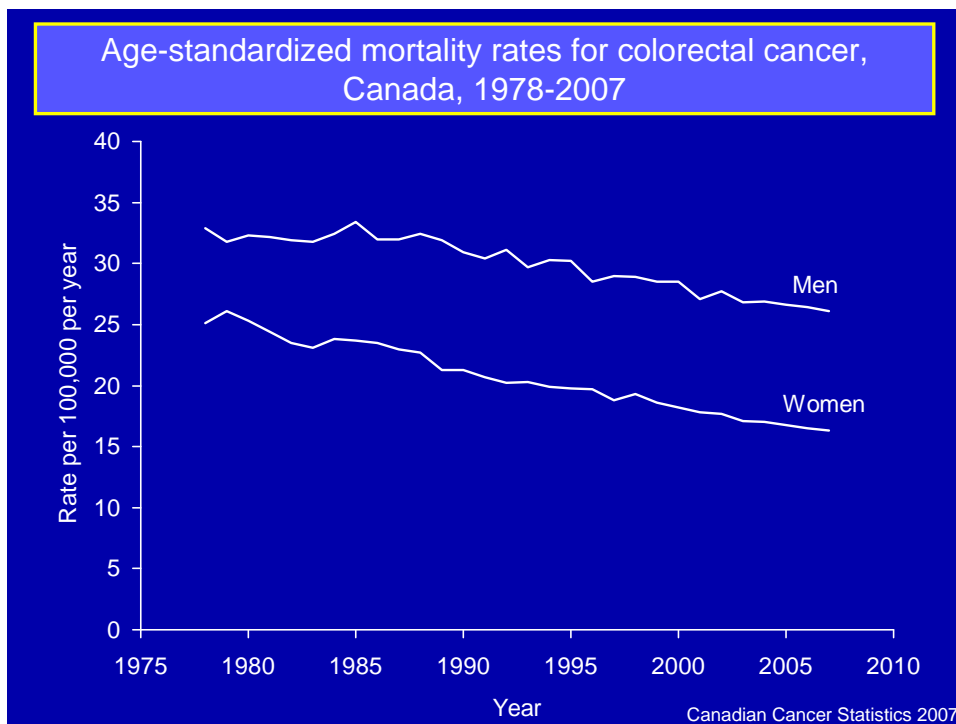
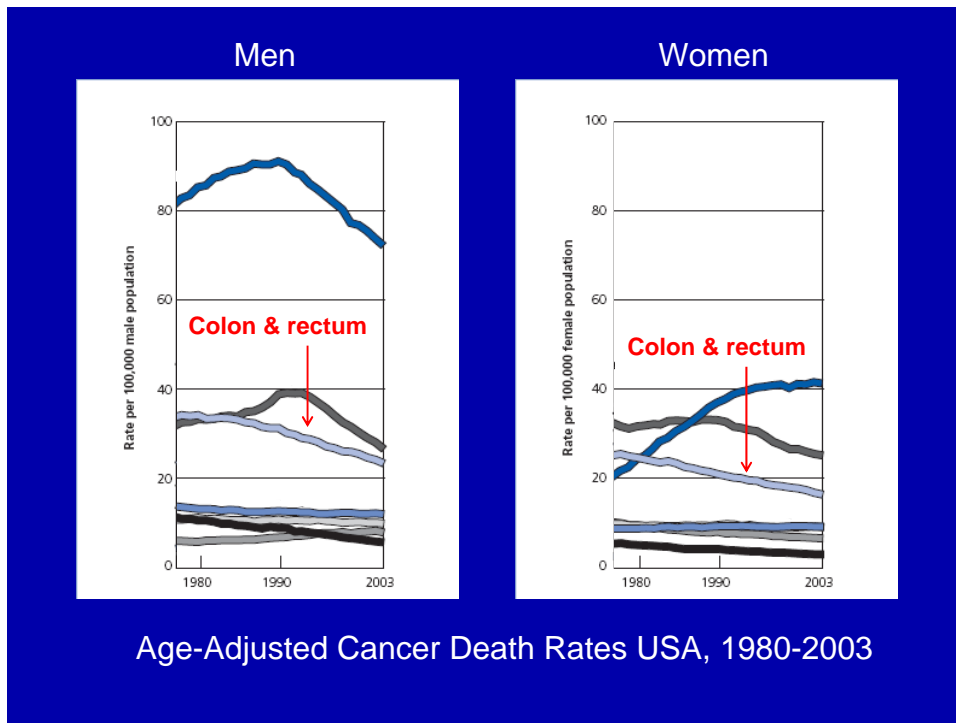
Plot taken from: Mason et al. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(7):1325-1329.



In the US, between 1995 and 1998, there was a 12% increase in endoscopic colorectal screening in persons aged 50 or more and a 6% rise in colorectal cancer incidence so screening could explain the increase in incidence.

Examination of trends in **mortality** as well as incidence





Since the beginning of the period covered by the introduction of fortification and the temporary increase in colorectal cancer incidence, there has been a continuous decrease in colorectal cancer mortality.

The temporary rise in colorectal cancer incidence could have two explanations:

1. Increase in exposure to a new cause
2. Earlier diagnosis from screening.

When screening for a cancer is increased there is an increased **incidence** of the cancer being screened for, because of earlier detection, without an increase in **mortality** from that cancer.

This was observed.

If an increase in incidence were due to an increased exposure to a cause of the cancer, there would be an increase in mortality from that cancer.

This was **not** observed.

We can therefore exclude folic acid fortification as a cause of the temporary increase in colorectal cancer incidence in the US and Canada.

The most likely explanation for the increase is colorectal cancer screening.

Interpretation of randomized trials of folic acid and the prevention of colorectal adenomas

Folic Acid for the Prevention of Colorectal Adenomas
A Randomized Clinical Trial

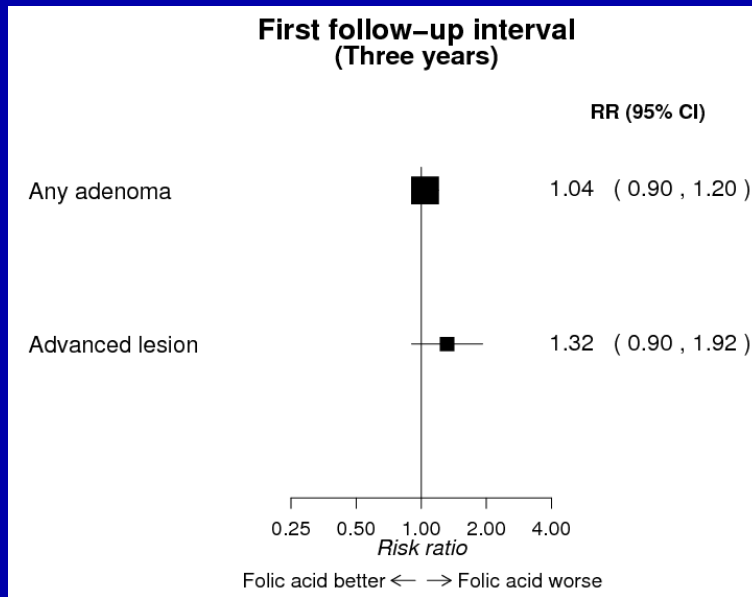
Bernard F. Cole, PhD
John A. Baron, MD

Context Laboratory and epidemiological data suggest that folic acid may have an antineoplastic effect in the large intestine.

1 mg/day folic acid vs. no folic acid

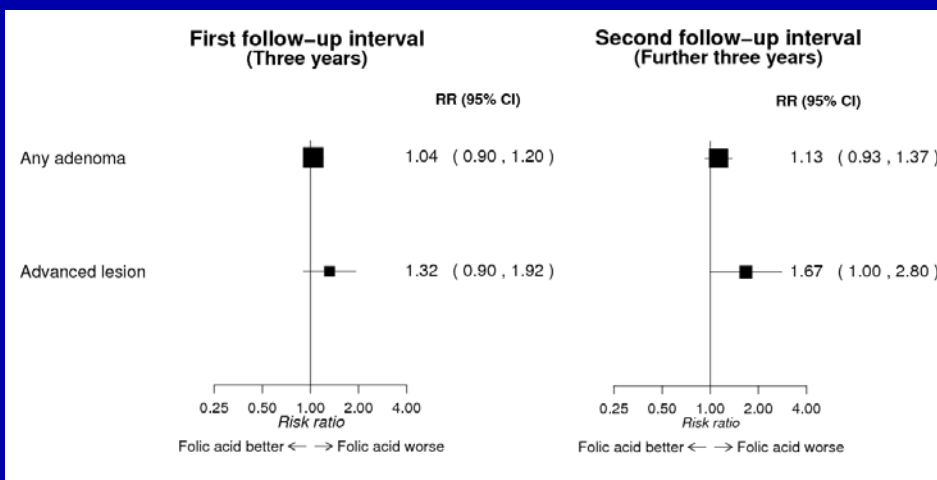
Cole et. al. *JAMA* June 6 2007; 297:21; 2351-59

Folic Acid for the Prevention of Colorectal Adenomas



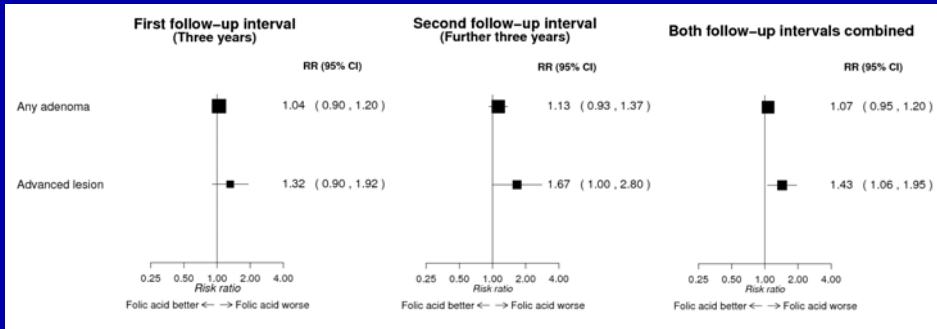
Adapted from Table 3 in Cole et. al. *JAMA* June 6 2007; 297:21; 2351-59

Folic Acid for the Prevention of Colorectal Adenomas



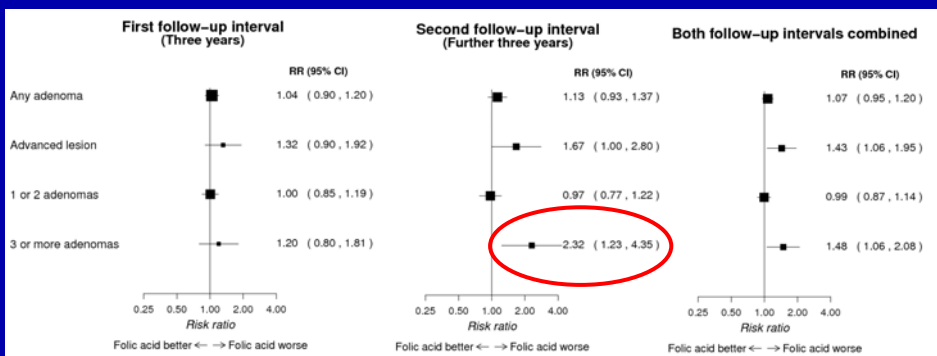
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Folic Acid for the Prevention of Colorectal Adenomas



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Folic Acid for the Prevention of Colorectal Adenomas



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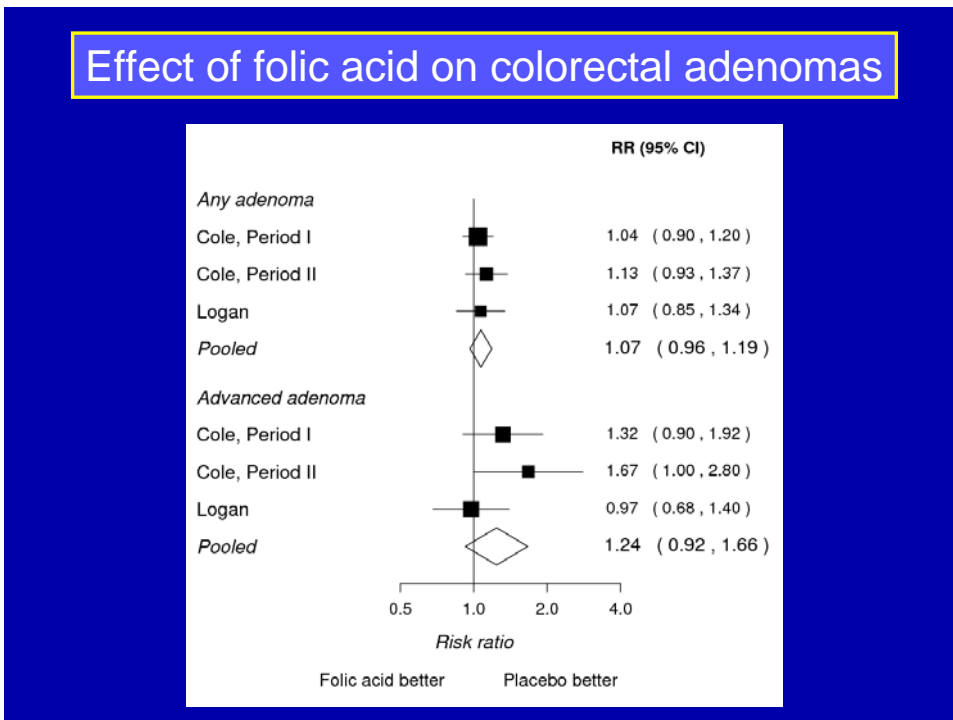
GASTROENTEROLOGY 2008;134:29-38

Aspirin and Folic Acid for the Prevention of Recurrent Colorectal Adenomas

RICHARD F. A. LOGAN,* MATTHEW J. GRAINGE,* VIC C. SHEPHERD,* NICHOLAS C. ARMITAGE,† and KENNETH R. MUIR* on behalf of the ukCAP Trial Group*

*Division of Epidemiology and Public Health, †Division of Surgery, University of Nottingham, University Hospital, Nottingham, United Kingdom

0.5 mg/day folic acid vs. no folic acid



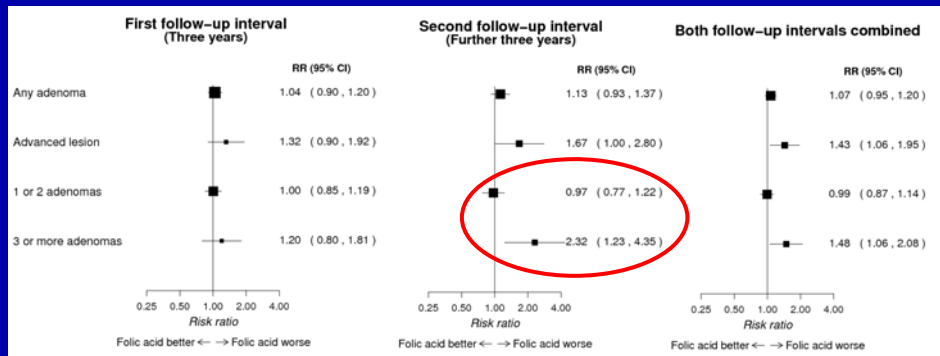
Interpretation of trial results in relation to colon cancer

1. Trial results related to adenomas not cancer, but adenomas are a reasonable indicator of cancer risk.
2. 1mg or 0.5mg of folic acid a day did not reduce colorectal adenoma risk, but neither did it increase it. Relative risk 1.07 (0.96, 1.19).

Interpretation of trial results in relation to colon cancer

3. The only hint of an increased adenoma risk is in a subset analysis in one study (Cole at al) relating to the incidence of three or more adenomas. This subset analysis was based on small numbers (30 folic acid, 13 no folic acid).
4. Subset analyses are prone to the effect of chance producing formally significant results.

Folic Acid for the Prevention of Colorectal Adenomas



Adapted from Table 3 in Cole et. al. *JAMA* June 6 2007; 297:21; 2351-59

Interpretation of trial results in relation to colon cancer

- The absence of an excess in people with 1 or 2 adenomas weighs against a causal explanation.

If folic acid genuinely caused adenomas then one would expect not only an increase in people with 3 or more adenomas but also in people with 1 or 2.

Percentage of people with 3+ adenomas in Cole et al

	Period 1	Period 2
Folic acid	9.4	9.9
No folic acid	7.8	4.3

6. The difference in Period 2 arises from a deficiency of people with 3+ adenomas in the no folic acid group, not an excess in the folic acid group, which suggests chance as the most likely explanation.

Summary of Cole et al and Logan et al

- No overall association between folic acid and adenomas in either trial alone or in both combined.
- A suggestion of an excess in a subgroup analysis (3+ adenomas) that, in spite of being statistically significant, could have arisen by chance.
- This is the likely explanation given that the increased relative risk arises from a deficit in the no folic acid group, not an excess in the folic acid group.
- The absence of an excess of one or two adenomas supports chance as the explanation.

An example of results from subset analysis

Deaths from all causes in two randomized trials of folic acid supplementation

	Folic acid	No folic acid
Cole et al	10	19
Logan et al	1	7
Combined	11	26

Relative risk 0.4 (p=0.02)

One might conclude that folic acid reduces all-cause mortality by about 60%; this would be misleading, but no more so than concluding that folic acid causes multiple adenomas.

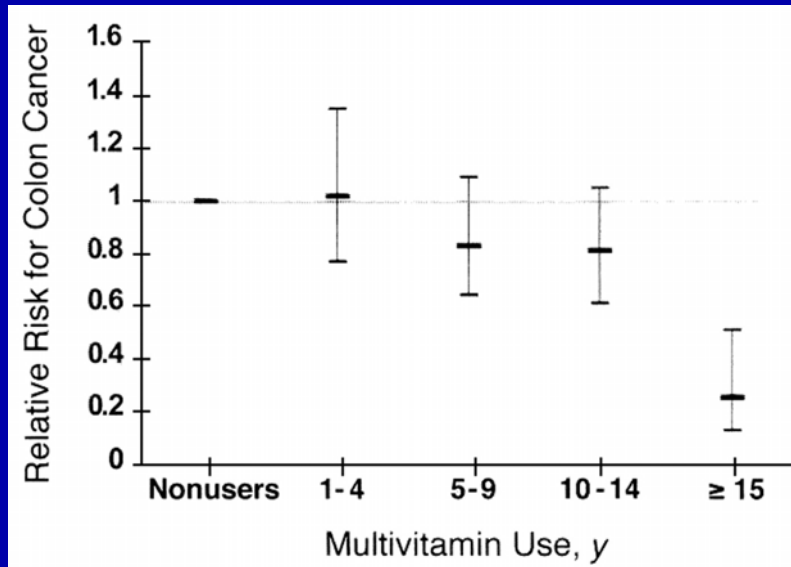
Bayston, Russell, Wald, and Hoffbrand. Lancet 2008;371:1335-1336.

The trend analyses and trial results do not provide **evidence** that folic acid fortification is a cause of colorectal cancer.

A large cohort study showed that long-term use of folic acid supplements is associated with a substantially decreased chance of colorectal cancer.

This suggests a benefit but on its own is insufficient evidence of a protective effect.

Colon cancer in women in the US Nurses' Health Study



Colon cancer relative risk according to years since the start of use of multivitamins containing folic acid

Giovannucci, E. et. al. Ann Intern Med 1998;129:517-524

Folic acid and breast cancer



Daily Express, 10 December 2004

Aberdeen folic acid supplementation trial

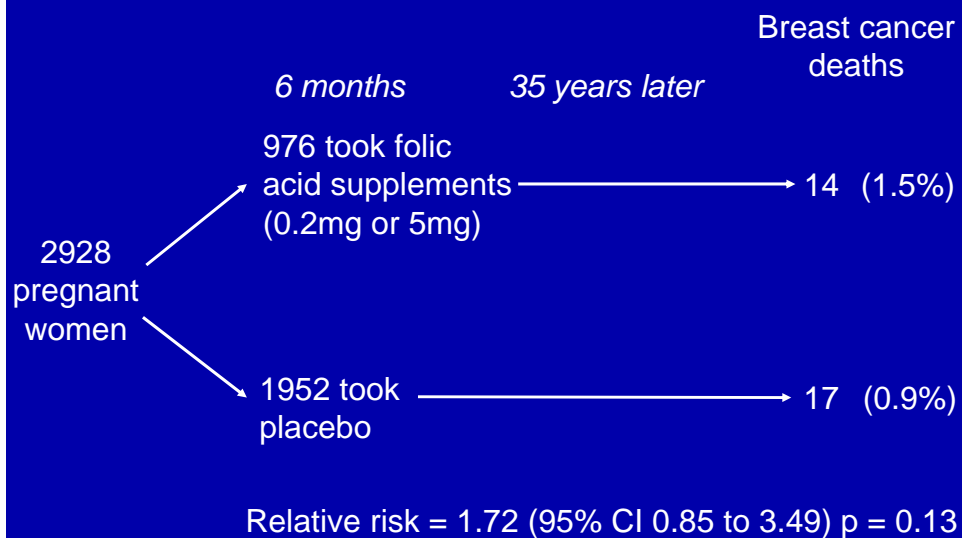
Conducted 1966-7.

2928 pregnant women randomised to take folic acid or placebo.

35 years later - trial data resurrected; all deaths by cause were identified up to 2002.

Charles D, Ness AR, Campbell D, Davey Smith G, Hall MH.
BMJ 2004;329: 1375-76.

Aberdeen folic acid supplementation trial



Aberdeen folic acid supplementation trial

The publication of the paper, particularly in a prominent journal such as the *BMJ*, raised concern even though the authors stated:

The increase in mortality from breast cancer associated with folic acid was probably chance, it was not statistically significant and the number of deaths was small.

The trial results are uninformative.

Aberdeen folic acid supplementation trial

Even if folic acid were a cause of breast cancer, it would be extremely unlikely to be apparent given a six-month exposure followed by an interval of thirty-five years.

Even a known carcinogen would not have been detectable.

If the women had smoked cigarettes for a 6-month period in their life 30 years ago, and had not smoked before or after, we would not expect any perceptible increase in lung cancer.

Conclusions

Detailed analyses of the studies thought to suggest links between folic acid and colon adenomas and between folic acid and breast cancer do not provide evidence of a causal association.

Such concerns should not delay the decision to introduce the fortification of flour with folic acid.

Public health risk assessment

On their own, hypotheses and associations do not provide evidence.

Population risk assessment should be based on evidence.

Otherwise almost any useful public health intervention would be stalled simply on the basis of hypothesis, speculation and possible associations.