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Folic acid with and without aspirin in the chemoprevention of colorectal cancer: a systematic review

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Background

- Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and rectum)
- It is the third most common cancer in the UK, with approximately 32,000 new cases annually in England and Wales
- Overall 5-year survival rate for colorectal cancer in England and Wales is approximately 50%, but varies according to the stage of disease at diagnosis (Cancer Research UK, 2008)
- It is thought that most colorectal cancers develop from adenomatous polyps arising from the lining of the intestine
- Individuals in whom adenomatous polyps are identified undergo polypectomy (removal of polyps) and are invited for endoscopic surveillance



Background

- This review is part of a report evaluating the clinical effectiveness of several drug and micronutrient interventions for the prevention of colorectal cancer and/or adenomatous polyps in populations at differing risks for developing colorectal cancer
- The included interventions are: NSAIDs (non-steroidal anti-inflammatory drugs), including aspirin and cyclooxygenase-2 (COX-2) inhibitors; calcium; vitamin D; and antioxidants (including vitamin A, vitamin C, vitamin E, selenium and beta-carotene) and **folic acid**



Background

- Why folate?
 - Low folate diet has been associated with an increased risk of colorectal neoplasia (Giovannucci 2002)
 - Mechanisms: Folic acid may have an effect on DNA damage and repair (Kim 2004a, Choi & Mason, 2002)
- Research Question:
 - Is folic acid / folate effective at reducing recurrence of colorectal adenomas or occurrence of colorectal cancer in at risk populations or in the general population?



Inclusion Criteria

Population	Adults with Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colorectal Cancer (HNPCC), OR a history of colorectal adenomas OR general population
Intervention	Folic acid with or without other agents
Comparator	Placebo or agents other than folic acid
Outcome	Recurrence of adenomas, advanced adenomas, or occurrence of colorectal cancer
Study design	Randomised controlled trial



- A literature search was performed to identify relevant research:
 - 8 databases were searched for published and unpublished trials: Cochrane Library, MEDLINE, PreMEDLINE, CINAHL, EMBASE, Web of Science, Biological Abstracts and Research Registers
- The reference lists of relevant studies were searched for further papers
- Clinical experts were contacted to enquire about any relevant papers that may have had been missed



Results

- Literature search produced 3,785 citations, of which 6 satisfied the inclusion criteria:
 - No RCTs examined folic acid in individuals with FAP or HNPCC
 - 3 RCTs examined folic acid in populations with a history of adenomas
 - 3 RCTs examined folic acid in general populations, with low risk of colorectal cancer
- All 6 RCTs were identified from the search of electronic databases



History of adenomas

Study	Population & age	Intervention	Control	Treat- ment duration	Follow- up
Jaszewski 2008	History of adenomas, but not FAP or HNPCC Age 18-80 years eligible	Folic acid 5mg/d (N=80)	Placebo 5mg/d (N=97)	3 years	3 years
Logan 2008 (ukCAP trial: United Kingdom Colorectal Adenoma Prevention)	History of adenomas, but not FAP or HNPCC Age <75 years eligible (mean 58, range 28-75)	Folic acid 0.5mg/d (N=234) Folic acid 0.5mg/d + Aspirin 300mg/d (N=236)	Placebo only (N=233) Aspirin 300mg/d (N=236)	3 years	3 years
Cole 2007 (Aspirin / Folate Polyp Prevention Study)	History of adenomas, but not FAP or HNPCC Age 21-80 years eligible (mean 57 or 58 in all groups)	Folic acid 1mg/d only (N=170) Folic acid 1mg/d + Aspirin 81mg/d (N=175) Folic acid 1mg/d + Aspirin 325mg/d (N=171)	Placebo only (N=169) Aspirin 81mg/d (N=169) Aspirin 325mg/d (N=167)	3 years	3 years



Results

- Jaszewski 2008 did not report event data (only mean numbers of adenomas) and was therefore excluded from meta-analysis. The meta-analysis included only 2 RCTs (Logan 2008; Cole 2007)
- Cole 2007 reported follow-up data for two intervals (years 1-3 and years 4-8). Only the results from the first interval (3 years follow-up) are presented here, because only 607 of 1021 randomised patients (59%) agreed to be followed up beyond 3 years, and only 501 patients (49%) agreed to continue taking study medications beyond 3 years



Results

- Two studies (Logan 2008 and Cole 2007) compared:
 - folic acid (0.5-1.0mg/day) versus placebo alone (749 participants in analysis);
 - folic acid (0.5-1.0mg/day) with aspirin (81-325mg/d) with placebo alone (916 participants in analysis)
 - folic acid (0.5-1.0mg/day) with and without aspirin (81-325mg/d) with placebo with or without aspirin (1,840 participants in analysis)
- Meta-analysis showed no statistically significant effect on either the relative or absolute risk of adenoma or advanced adenoma recurrence, or colorectal cancer, for folic acid with or without aspirin



History of adenomas: event data

Analysis	Outcome	I:n	I:N	C:n	C:N
FA alone	Any adenoma	152	383	126	366
FA+/-aspirin	Any adenoma	366	933	311	907
FA + aspirin	Any adenoma	184	550	126	366
FA alone	Advanced adenoma	60	383	44	366
FA+/-aspirin	Advanced adenoma	109	933	94	907
FA + aspirin	Advanced adenoma	49	550	44	366
FA+/-aspirin	CRC	8	948	9	926

FA=folic acid; CRC=colorectal cancer; I:n=number of events in intervention group;
I:N=number of participants in intervention group; C:n=number of events in control group;
C:N=number of participants in control group



History of adenomas: risk of adenoma recurrence



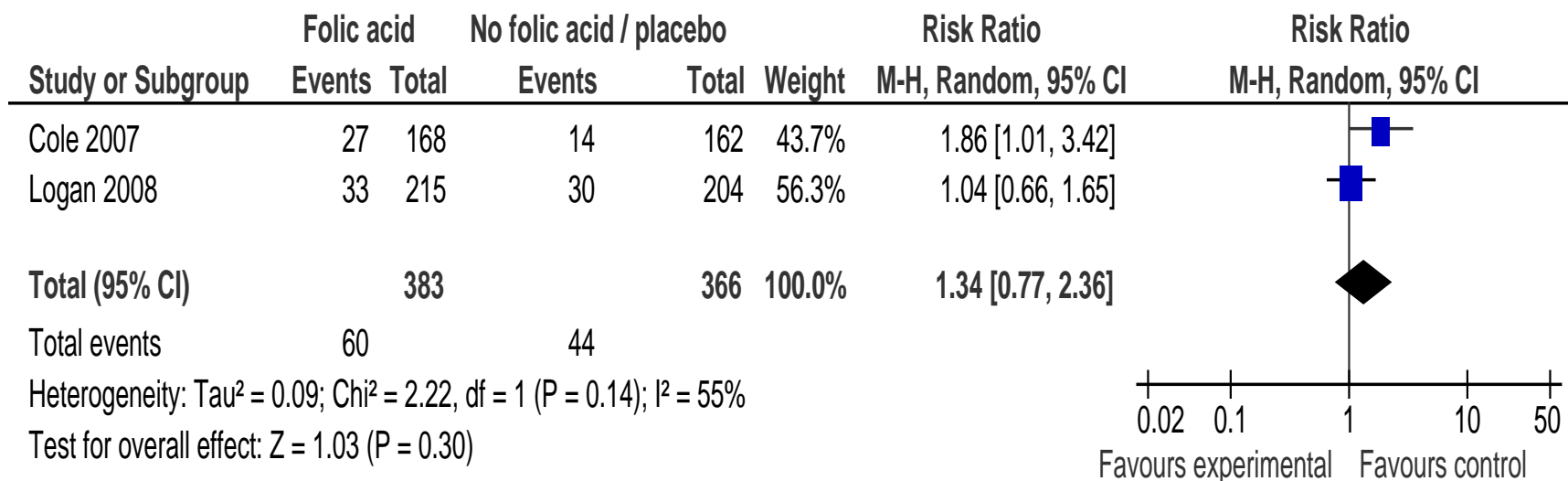
Analysis	Outcome	RR	UCI	LCI	I ² (%)
FA alone	Any adenoma	1.16	0.97	1.39	0
FA+/-aspirin	Any adenoma	1.05	0.93	1.18	0
FA + aspirin	Any adenoma	0.90	0.75	1.08	0
FA alone	Advanced adenoma	1.34	0.77	2.36	55
FA+/-aspirin	Advanced adenoma	1.13	0.84	1.51	21
FA + aspirin	Advanced adenoma	0.77	0.46	1.34	45
FA+/-aspirin	CRC	0.87	0.34	2.25	0

FA=folic acid; CRC=colorectal cancer; RR=relative risk; RD=absolute risk difference; LCI=lower 95% confidence limit; UCI=upper 95% confidence limit; I²=measure of heterogeneity



History of adenomas: risk of advanced adenoma

Folic acid alone versus placebo alone





Results

- Meta-analysis of Logan 2008 and Cole 2007 suggests possible increased risk of adenoma for populations with a history of adenomas taking folic acid
- The third, lower quality and smaller study (Jaszewski 2008; 94 participants in analysis) reported that the mean number of recurrent adenomas was significantly higher in the placebo group (OR=2.77, 95%CI=0.06-0.84, $p=0.025$).



General population

- Only colorectal cancer was measured as an outcome (no adenoma data)
- Three studies of folic acid (2.5mg/day in two studies and 20mg/day in one study) in populations with no increased baseline risk of colorectal cancer demonstrated no statistically significant effect of folic acid on either the relative or absolute risk of colorectal cancer.
- The duration of follow-up was only 5 to 7 years, which may not be long enough to detect an effect on cancer occurrence.



General population



Study	Population & age	Intervention	Control	Treatment duration	Follow-up
Zhang 2008 (WAFACS)	Women with or at high risk of cardiovascular disease Age >40 years (mean 63 years)	Folic acid 2.5mg/d, Vitamin B6 50mg/d, Vitamin B12 1mg/d (N=2721) These participants were a subset of those in the WACS study, and were also receiving various combinations of vitamin C, vitamin E and beta-carotene	Placebo (N=2721)	7 years	7 years
Lonn 2006 (HOPE-TOO study)	History of vascular disease or diabetes or risk of atherosclerosis Age 55 years or older (mean 69 years)	Folic acid 2.5mg/d, Vitamin B6 50mg/d, Vitamin B12 1mg/d (N=2758) Some participants also received antioxidants.	Placebo (N=2764)	5 years	5 years
Zhu 2003	Patients with atrophic gastritis Age 28-77 years eligible (mean 55-57 years in all groups)	Folic acid 20mg/day for 1 year then 20mg twice weekly for 1 year; Vitamin B12 1mg/month for 1 year then 1mg every 3 months for 1 year (N=44)	Placebo (N=54) Beta-carotene (natural), 30mg/d for 1 year then 30mg twice/week for 1 year (N=61) Beta-carotene (synthetic), doses as above (N=57)	2 years	6 years



General population: risk of colorectal cancer



Analysis	Outcome	I:n	I:N	C:n	C:N
FA + B vitamins +/- antioxidants vs placebo +/-antioxidants	CRC	68	5523	60	5539
FA + B vitamins + antioxidants vs placebo +/-antioxidants	CRC	68	5479	59	5485

Analysis	Number of studies	RR	UCI	LCI	I ² (%)
FA + B vitamins +/- antioxidants vs placebo +/-antioxidants	3	1.13	0.77	1.64	7
FA + B vitamins + antioxidants vs placebo +/-antioxidants	2	1.15	0.82	1.63	42



All populations

- Adverse events:
 - No studies reported any difference in serious adverse event rates between the folic acid and placebo groups (except for Cole 2007 reporting a higher occurrence of non-colorectal cancer in the folic acid group, thought to be due to the higher baseline rate of prostate cancer in that group).



Discussion

- Two studies of folic acid (0.5-1.0mg/day) in individuals with a history of adenomas showed no statistically significant difference in the relative risk of adenoma recurrence or advanced adenoma recurrence, but with the event rates actually being slightly higher in the folic acid groups.
- Three studies of folic acid (2.5mg/day in two studies and 20mg/day in one study) in populations with no increased baseline risk of colorectal cancer demonstrated no statistically significant effect of folic acid on the relative risk of colorectal cancer, but with the rates being slightly higher in individuals receiving folic acid.



Discussion

- Why higher event rates?
 - Animal studies suggest that although folate may initially suppress cancer, it may also accelerate progression if pre-neoplastic lesions are present (eg. in at-risk populations with a history of adenomas) (Ulrich & Potter, 2006, Kim 2004b)
 - Addition of aspirin as an agent appears to moderate the possible adverse effect of folate (NSAIDs have been found to be effective at reducing the risk off adenoma recurrence [Cooper [forthcoming]; Dube 2007; Rostom 2007])



Limitations

- The meta-analysis for both at-risk and general populations only included the results of 2 and 3 trials respectively
- The quality of most studies was good, but some trials were comparatively weak (Jaszewski 2008; Zhang 2008; Zhu 2003)
- For the colorectal cancer outcome: duration of follow-up was 5 to 7 years, which may not be long enough to detect an effect on cancer occurrence.



Conclusion

- Folic acid does not appear to reduce the risk of adenoma recurrence or colorectal cancer in populations with a history of colorectal adenomas, or in general populations with no risk
- Folic acid may increase risk of adenoma recurrence in populations with a history of colorectal adenomas
- Caution must be exercised with these results as the number of studies is small



Included trials

- Cole et al (2007). Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 297(21):2351-59.
- Logan et al (2008). Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology* 134(1):29-38.
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