

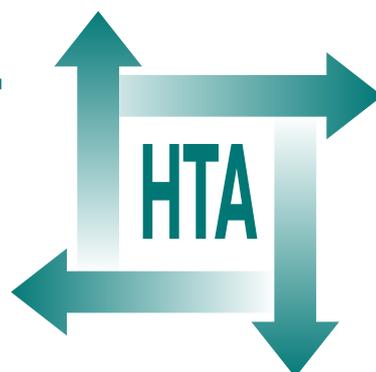
Chemoprevention of colorectal cancer: systematic review and economic evaluation

K Cooper, H Squires, C Carroll,
D Papaioannou, A Booth, RF Logan,
C Maguire, D Hind and P Tappenden



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Abstract

Chemoprevention of colorectal cancer: systematic review and economic evaluation

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Background: Colorectal cancer (CRC) is the third most common cancer in the UK: incidence increases with age, median age at diagnosis being over 70 years. Approximately 25% of cases occur in individuals with a family history of CRC, including 5% caused by familial adenomatous polyposis (FAP) or hereditary non-polyposis CRC (HNPCC). Most develop from adenomatous polyps arising from the intestine lining. Individuals with these polyps undergo polypectomy and are invited for endoscopic surveillance. Screening via faecal occult blood testing has been rolled out across the UK.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of drug and micronutrient interventions for the prevention of CRC and/or adenomatous polyps. Interventions considered include: non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and cyclo-oxygenase-2 (COX-2) inhibitors; folic acid; calcium; vitamin D and antioxidants (including vitamin A, vitamin C, vitamin E, selenium and beta-carotene). Chemoprevention was assessed in the general population, in individuals at increased risk of CRC, and in individuals with FAP or HNPCC.

Data sources: A systematic review identified randomised controlled trials (RCTs) assessing drug and nutritional agents for the prevention of CRC or adenomatous polyps. A separate search identified qualitative studies relating to individuals' views, attitudes and beliefs about chemoprevention. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, DARE, NHS-EED (NHS Economic Evaluation Database), HTA database, Science Citation Index, BIOSIS previews and the Current Controlled Trials research register were searched in June 2008. Data were extracted by one

reviewer and checked by a second.

Review methods: The synthesis methods used were systematic review and meta-analysis for RCTs and qualitative framework synthesis for qualitative studies. A health economic model was developed to assess the cost-effectiveness of chemoprevention for two populations with different levels of risk of developing CRC: the general population and an intermediate-risk population.

Results: The search identified 44 relevant RCTs and six ongoing studies. A small study of aspirin in FAP patients produced no statistically significant reduction in polyp number but a possible reduction in polyp size. There was a statistically significant 21% reduction in risk of adenoma recurrence [relative risk (RR) 0.79, 95% confidence interval (CI) 0.68 to 0.92] in an analysis of aspirin versus no aspirin in individuals with a history of adenomas or CRC. In the general population, a significant 26% reduction in CRC incidence was demonstrated in studies with a 23-year follow-up (RR 0.74, 95% CI 0.57 to 0.97). Non-aspirin NSAID use in FAP individuals produced a non-statistically significant reduction in adenoma incidence after 4 years of treatment and follow-up and reductions in polyp number and size. In individuals with a history of adenomas there was a statistically significant 34% reduction in adenoma recurrence risk (RR 0.66, 95% CI 0.60 to 0.72) and a statistically significant 55% reduction in advanced adenoma incidence (RR 0.45, 95% CI 0.35 to 0.58). No studies assessed the effect of non-aspirin NSAIDs in the general population. There were no studies of folic acid in individuals with FAP or HNPCC. There was no significant effect of folic acid versus placebo on adenoma recurrence (RR 1.16, 95% CI 0.97 to 1.39) or advanced adenoma incidence in individuals with a history of adenomas. In the general population there was no significant effect of folic acid on risk of CRC (RR 1.13, 95% CI

0.77 to 1.64), although studies were of relatively short duration. Calcium use by FAP patients produced no significant reduction in polyp number or disease progression. In individuals with a history of adenomas there was a statistically significant 18% reduction in risk of adenoma recurrence (RR 0.82, 95% CI 0.69 to 0.98) and a non-significant reduction in risk of advanced adenomas (RR 0.77, 95% CI 0.50 to 1.17). In the general population there was no significant effect of calcium on risk of CRC (RR 1.08, 95% CI 0.87 to 1.34), although studies were of relatively short duration. There were no studies of antioxidant use in individuals with FAP or HNPCC, and in individuals with a history of adenomas no statistically significant differences in relative risk of adenoma recurrence were found. In the general population there was no difference in incidence of CRC (RR 1.00, 95% CI 0.88 to 1.13) with antioxidant use compared with no antioxidant use. Twenty studies reported qualitative findings concerning chemoprevention. People are more likely to use NSAIDs if there is a strong perceived need. Perceptions of risk and benefit also influence decision-making and use. People have fewer concerns about using antioxidants or other supplements, but their perception of the benefits of these agents is less well-defined. The model analysis suggested that the most cost-effective age-range policy in the general population would be to provide chemoprevention to all individuals within the general population from age 50 to 60 years. The use of aspirin in addition to screening within the general population is likely to result in a discounted cost per life-year gained of around £10,000 and a discounted cost per quality-

adjusted life-year (QALY) gained of around £23,000 compared with screening alone. In the intermediate-risk group the most economically viable age-range policy would be to provide chemoprevention to individuals following polypectomy aged 61 to 70 years. Calcium is likely to have a discounted cost per QALY gained of around £8000 compared with screening alone. Although aspirin in addition to screening should be more effective and less costly than screening alone, under the current assumptions of benefits to harms of aspirin and calcium, aspirin is expected to be extendedly dominated by calcium.

Limitations: Whilst a number of studies were included in the review, the duration of follow-up was generally insufficient to detect an effect on cancer incidence. Given the uncertainties and ambiguities in the evidence base, the results of the health economic analysis should be interpreted with caution.

Conclusions: Aspirin and celecoxib may reduce recurrence of adenomas and incidence of advanced adenomas in individuals with an increased risk of CRC and calcium may reduce recurrence of adenomas in this group. COX-2 inhibitors may decrease polyp number in patients with FAP. There is some evidence for aspirin reducing the incidence of CRC in the general population. Both aspirin and NSAIDs are associated with adverse effects so it will be important to consider the risk–benefit ratio before recommending these agents for chemoprevention. The economic analysis suggests that chemoprevention has the potential to represent a cost-effective intervention, particularly when targeted at intermediate-risk populations following polypectomy.



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Glossary and list of abbreviations

Glossary

Adenomatous polyp/adenoma Growth arising from the lining of the intestine, which may or may not develop into colorectal cancer. There are three types of adenomas according to histology: tubular, tubulovillous and villous. Tubular adenomas are the most common and have a tube-like structure. Villous adenomas are the least common and have a 'frilly' or cauliflower-like structure. Tubulovillous adenomas are a mix between the two. Villous adenomas are the most likely to become cancerous, followed by tubulovillous adenomas.

Advanced adenoma see High-risk or advanced adenoma.

Antioxidant Antioxidants prevent oxidation of molecules in the body, thereby reducing the number of free radicals. Free radicals are molecules with an unpaired electron, which are highly reactive and may cause damage to cells (oxidative stress) which may contribute to progression of various diseases, including tumour development. However, free radicals are also essential for various biological processes, including removal of damaged cells. The antioxidants examined in this review include vitamin A, vitamin C, vitamin E, selenium and beta-carotene.

Chemoprevention The use of natural or laboratory-made substances to prevent a disease such as cancer.

Colorectal cancer Malignant neoplasm arising from the lining of the large intestine (colon or rectum).

Cost-effectiveness The relationship between cost and effectiveness of an intervention, often expressed as the incremental cost per quality-adjusted life-year (QALY).

Cyclo-oxygenase-2 (COX-2) inhibitors Cyclo-oxygenase is an enzyme that converts arachidonic acid to prostaglandins. Cyclo-oxygenase-2 is elevated in colorectal adenomas and cancers, and may play a role in colorectal tumour growth and development. Cyclo-oxygenase-2 inhibitors are a subset of non-steroidal anti-inflammatory drugs (NSAIDs) that specifically inhibit cyclooxygenase-2.

Dominated (simple) Where a given treatment alternative is less effective and more expensive than its comparator.

Dominated (extended) Where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next most effective comparator.

Effectiveness The extent to which an intervention works in clinical practice.

Endoscopic surveillance Examination of the colon and rectum at regular intervals to check for adenomas and colorectal cancer in people at increased risk (e.g. those who have had a previous adenoma).

Familial adenomatous polyposis (FAP) FAP is caused by a mutation in the adenomatous polyposis coli gene and accounts for approximately 1% of all colorectal cancers. Individuals with FAP develop hundreds of polyps in the colon and, by the age of 40 years, most will have developed colorectal cancer unless they have surgery to remove the colon.

General population or 'low risk' for colorectal cancer For the purposes of this assessment, 'general population' refers to individuals with no increased risk for colorectal cancer. This population is also referred to as 'low-risk'.

continued

Hereditary non-polyposis colorectal cancer (HNPCC) HNPCC (also called Lynch syndrome) is caused by a dominantly inherited alteration in one of a number of DNA mismatch repair genes, and accounts for approximately 2–5% of all colorectal cancers. HNPCC also conveys a higher risk of certain other cancers. People with HNPCC develop colorectal adenomas at an earlier age than the general population. The onset of colorectal cancer in these patients is typically earlier than that for the general population.

High-risk or advanced adenomas Adenomas that are either ≥ 1 cm or have villous or tubulovillous features or severe dysplasia.

‘High risk’ for colorectal cancer For the purposes of this assessment, ‘high risk’ refers to individuals at high risk for colorectal cancer because of the genetic syndromes familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC).

Incidence The rate of occurrence of an outcome during a specified time period.

‘Intermediate risk’ for colorectal cancer For the purposes of this assessment, ‘intermediate risk’ refers to individuals at increased risk for colorectal cancer because of a personal history of adenomatous polyps, personal or family history

of colorectal cancer, or inflammatory bowel disease.

Low-risk adenomas Adenomas that are < 1 cm and non-villous/tubulovillous without severe dysplasia.

Meta-analysis A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.

Natural history The progression of a disease over time.

Non-steroidal anti-inflammatory drugs (NSAIDs) A class of anti-inflammatory drugs, which includes aspirin as well as cyclooxygenase-2 inhibitors such as celecoxib.

Relative risk (risk ratio) Ratio of the probability of an event occurring in a treatment group relative to a control group. The terms ‘relative risk’ (used in the text) and ‘risk ratio’ (shown on the forest plots) are interchangeable.

Screening Screening for colorectal cancer has been rolled out to 99% of the UK population aged 60–69 years, and is currently being extended to people aged up to 74 years. Cancers and large adenomas are identified via faecal occult blood testing which tests for blood in the stool. Individuals with a positive result are invited for endoscopic investigation.

List of abbreviations

A&E	accident and emergency (department)	NICE	National Institute for Health and Clinical Excellence
APACC	Association pour la Prévention par Aspirine du Cancer Colorectal (study)	NPCT	Nutritional Prevention of Cancer Trial
APC	Adenoma Prevention with Celecoxib (study)	NPS	National Polyp Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (study)	NSAID	non-steroidal anti-inflammatory drug
BNF	<i>British National Formulary</i>	PHS	Physicians' Health Study
CAM	complementary and alternative medicine	PreSAP	Prevention of Sporadic Adenomatous Polyps (study)
CAPP	Colorectal Adenoma/carcinoma Prevention Programme (study)	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (standard)
CARET	The Beta-Carotene and Retinol Efficacy Trial	PSA	probabilistic sensitivity analyses
CEAC	cost-effectiveness acceptability curve	QALY	quality-adjusted life-year
COX-2	cyclo-oxygenase-2	QUOROM	Quality of Reporting of Meta-analyses (standard)
CRC	colorectal cancer	RCT	randomised controlled trial
DFMO	difluoromethylornithine	RD	absolute risk difference
FAP	familial adenomatous polyposis	RR	relative risk
FOBT	faecal occult blood test	SEER	Surveillance, Epidemiology and End Results (database)
GP	general practitioner	SELECT	Selenium and Vitamin E Cancer Prevention Trial
HMIC	Health Management Information Consortium	SU.VI. MAX	SUpplementation en Vitamines et Minéraux AntioXydants (study)
HNPCC	hereditary non-polyposis colorectal cancer	TIA	transient ischaemic attack
HOPE-TOO	Heart Outcomes Prevention Evaluation – The Ongoing Outcomes (study)	TNM	tumour, node, metastasis (staging system)
HPS	Heart Protection Study	ukCAP	United Kingdom Colorectal Adenoma Prevention (study)
HRQoL	health-related quality of life	UK-TIA	United Kingdom Transient Ischaemic Attack aspirin trial
ICER	incremental cost-effectiveness ratio	WACS	Women's Antioxidant Cardiovascular Study
LYG	life-year gained	WAFACS	Women's Antioxidant and Folic Acid Cardiovascular Study
LYS	life-year saved		
MeSH	Medical Subject Headings		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). Colorectal cancer is the third most common cancer in the UK, with approximately 32,000 new cases annually in England and Wales. Incidence increases with age, the median age at diagnosis being over 70 years. Environmental factors such as diet, exercise, obesity, smoking and alcohol intake are thought to affect the risk of developing colorectal cancer. Approximately 25% of colorectal cancers occur in individuals with a family history of the disease, including 5% caused by the genetic syndromes familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC). Risk is also higher in individuals with inflammatory bowel disease. The 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. It is thought that most colorectal cancers develop from adenomatous polyps arising from the lining of the intestine. Most adenomas are asymptomatic and do not develop into cancer, with approximately one-third of the population developing at least one adenoma by the age of 60 years. Indirect evidence suggests that adenomas may be present for 10 years or more before malignancy develops. Colorectal cancer screening via faecal occult blood testing has been rolled out across the UK. Individuals in whom adenomatous polyps are identified undergo polypectomy (removal of polyps) and are invited for endoscopic surveillance, i.e. repeat examinations at regular intervals. Studies have assessed the effect of various interventions in preventing colorectal cancer.

Objectives

This assessment evaluates the clinical effectiveness and cost-effectiveness of drug and micronutrient interventions for the prevention of colorectal cancer and/or adenomatous polyps in populations at differing risks for developing colorectal cancer. The interventions considered include: non-steroidal anti-inflammatory drugs (NSAIDs),

including aspirin and cyclo-oxygenase-2 (COX-2) inhibitors; folic acid; calcium; vitamin D and antioxidants (including vitamin A, vitamin C, vitamin E, selenium and beta-carotene). Chemoprevention is assessed in the following population groups: (1) general population (or individuals with no increased risk for colorectal cancer); (2) individuals at increased risk of colorectal cancer because of a personal history of adenomatous polyps, personal or family history of colorectal cancer, or inflammatory bowel disease; and (3) individuals with FAP or HNPCC.

Methods

A systematic review was undertaken to identify randomised controlled trials (RCTs) assessing drug and nutritional agents for the prevention of colorectal cancer and/or adenomatous polyps. A separate literature search was undertaken to identify qualitative studies relating to individuals' views, attitudes and beliefs about chemoprevention, to explore issues of expected compliance and other issues of implementation. The following electronic databases were searched for RCTs of clinical effectiveness: MEDLINE, Medline In-Process, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, DARE, NHS-EED (NHS Economic Evaluation Database), HTA database, Science Citation Index, and BIOSIS previews. The Current Controlled Trials research register was also searched; this includes the Medical Research Council trial register, UK Clinical Research Network, and the archives of the National Research Register. Searches were undertaken in June 2008. Data were extracted by one reviewer and checked by a second reviewer. The quality of included randomised trials was assessed using criteria based on recommendations from the Centre for Reviews and Dissemination. Qualitative studies were appraised using criteria from relevant critical appraisal checklists. The synthesis methods used were systematic review and meta-analysis for RCTs and qualitative framework synthesis for qualitative studies.

A health economic model was developed to assess the cost-effectiveness of chemoprevention for two populations with different levels of risk of developing colorectal cancer: (1) the general population (starting chemoprevention at age 50); (2) men and women at an intermediate risk of colorectal cancer due to previous polyps (starting chemoprevention at age 61). The model simulates the disease natural history of colorectal cancer and the impact of chemoprevention upon that natural history within a UK service pathway that includes screening, surveillance, diagnosis, treatment and follow-up. The results are presented in terms of the incremental cost per life-year gained and the incremental cost per quality-adjusted life-year (QALY) gained. The analysis adopted a UK NHS perspective and all costs and outcomes were discounted annually by 3.5%. There is considerable uncertainty associated with the analysis, particularly around the estimated effectiveness of chemoprevention over time. The results of the analysis should therefore be interpreted with caution.

Results

Summary of clinical effectiveness results

The search for RCTs of chemopreventive agents identified 116 references relating to 44 relevant RCTs: 10 RCTs of aspirin, nine RCTs of non-aspirin NSAIDs, six RCTs of calcium and/or vitamin D, six RCTs of folic acid, and 19 RCTs of antioxidants (six RCTs covered more than one intervention type). The search also identified a number of systematic reviews, which were screened to check for additional studies. In addition, six ongoing studies were identified.

Aspirin

Individuals with FAP or HNPCC Aspirin (600 mg/day) in a single study of FAP patients produced no statistically significant reduction in polyp number but a possible reduction in polyp size (however, data so far were only available in abstract form for 133 patients followed for 1 year). Aspirin (600 mg/day) was also assessed in a single study of HNPCC carriers ($n = 746$ analysed); at 2.5 years of follow-up, no statistically significant reduction was reported for adenoma incidence [relative risk (RR) 1.03, 95% confidence intervals (95% CI) 0.75 to 1.41] or colorectal cancer incidence (RR 0.87, 95% CI 0.39 to 1.96), but after 4 years of follow-up there was a significant reduction in time to first HNPCC cancer (hazard ratio 0.62, 95% CI 0.41 to 0.96).

Individuals with a history of adenomas or colorectal cancer Four studies (all good quality; $n = 2692$) assessed aspirin (81–325 mg/day) in individuals with a history of adenomas (three studies) or history of colorectal cancer (one study) with a follow-up of 3 years in three of the studies. There was a statistically significant 21% reduction in the relative risk of adenoma recurrence (RR 0.79, 95% CI 0.68 to 0.92) in the analysis of aspirin versus no aspirin (in two studies, 50% of participants in both arms also received folic acid), and a similar result was obtained when comparing aspirin alone versus placebo alone. The incidence of advanced adenomas was also significantly reduced when comparing aspirin versus no aspirin (RR 0.66, 95% CI 0.51 to 0.84; this was no longer significant when comparing aspirin alone vs placebo alone). Aspirin combined with folic acid produced a non-statistically significant reduction in adenomas and advanced adenomas.

General population (individuals at no increased risk of colorectal cancer) Of the four studies of aspirin in the general population, two large studies of good quality administered a relatively low dose of aspirin (100–325 mg every other day) with a treatment and follow-up duration of 5–10 years. Two smaller studies, one of reasonable quality and one unblinded and of slightly lower quality, administered a higher dose of aspirin (300–1500 mg/day) for 1–7 years with follow-up to 23 years. Analysis of all four studies ($n = 69,535$) showed no effect on colorectal cancer over the first 10 years of follow-up (RR 1.01, 95% CI 0.84 to 1.21). However, analysis of the two smaller, higher-dose studies ($n = 7588$) demonstrated a significant 26% reduction in colorectal cancer incidence over the full 23-year follow-up period (RR 0.74, 95% CI 0.57 to 0.97). An even greater reduction was observed when analysing years 10–19 only (RR 0.61, 95% CI 0.43 to 0.88).

Adverse effects Aspirin is associated with an increased risk of upper gastrointestinal toxicity, including nausea and dyspepsia, peptic ulcers and gastrointestinal bleeding, as demonstrated in the larger studies included here and in a review that collated systematic reviews of adverse effects of aspirin. Higher aspirin doses are associated with greater risk of toxicity. In the context of cardiovascular disease, a recent meta-analysis suggested that aspirin may reduce the risk of myocardial infarction and ischaemic stroke but increase the risk of haemorrhagic stroke and internal bleeding. Therefore, the benefits of aspirin may outweigh the risk of harm in individuals

at higher risk of cardiovascular disease but not necessarily in primary prevention.

Non-aspirin NSAIDs

Individuals with FAP or HNPCC A small study of sulindac in patients with the FAP genotype ($n = 41$) reported a non-statistically significant reduction in adenoma incidence after 4 years of treatment and follow-up. Five studies of NSAIDs (sulindac, celecoxib or tiracoxib, $n = 10$ to $n = 77$ per study, quality low-to-reasonable, treatment and follow-up 4–12 months) in FAP patients with existing adenomas demonstrated reductions in polyp number and size, some of which were statistically significant.

Individuals with a history of adenomas Two studies of good quality assessed celecoxib (400 mg/day) in individuals with a history of adenomas ($n = 2618$) with treatment and follow-up of 3 years. There was a statistically significant 34% reduction in the relative risk of adenoma recurrence (RR 0.66, 95% CI 0.60 to 0.72) and a statistically significant 55% reduction in the relative risk of advanced adenoma incidence (RR 0.45, 95% CI 0.35 to 0.58).

General population (or individuals at no increased risk of colorectal cancer) No studies assessed the effect of non-aspirin NSAIDs in the general population.

Adverse effects The two celecoxib trials in individuals with a history of adenomas were terminated early because of an increased risk of serious cardiovascular events, which was statistically significant in one of the studies. A published review of systematic reviews of adverse effects also demonstrated increased risk of serious cardiovascular events with COX-2 inhibitors, the risk being greatest in patients with pre-existing cardiovascular risk factors. Two COX-2 inhibitors, rofecoxib and valdecoxib, were recently withdrawn from use as the result of concerns about their cardiovascular toxicity; a study of rofecoxib was therefore excluded from this review. COX-2 inhibitors may also increase the risks of hypertension and renal toxicity. NSAIDs can also cause upper gastrointestinal toxicity, although the risk is lower for COX-2 inhibitors than for some other types of NSAID.

Folic acid

Individuals with FAP or HNPCC There were no studies of folic acid in individuals with FAP or HNPCC.

Individuals with a history of adenomas Two studies of folic acid presented relevant data for individuals with a history of adenomas (dose 0.5–1.0 mg/day; $n = 1840$). Both were of good quality and had treatment and follow-up durations of 3 years. Both were 2×2 factorial studies in which 50% of participants in both arms also received aspirin. There was no significant effect of folic acid versus placebo on adenoma recurrence (RR 1.16, 95% CI 0.97 to 1.39). The results were similar when comparing folic acid (with or without aspirin) versus no folic acid (with or without aspirin). There was no significant effect on advanced adenoma incidence.

General population (or individuals at no increased risk of colorectal cancer) Three studies assessed folic acid plus B vitamins in populations with no increased baseline risk of colorectal cancer ($n = 11,062$); the dose was 2.5 mg/day in two studies (one good quality, one reasonable) and 20 mg/day in one study (low-to-reasonable quality). There was no statistically significant effect on the relative risk of colorectal cancer (RR 1.13, 95% CI 0.77 to 1.64). However, the duration of follow-up was 5 to 7 years, which may not be long enough to detect an effect on cancer incidence.

Adverse effects No studies reported any difference in serious adverse event rates between the folic acid and placebo groups (except for one study reporting a higher incidence of non-colorectal cancer in the folic acid group, thought to be the result of the higher baseline rate of prostate cancer in that group).

Calcium and/or vitamin D

Individuals with FAP or HNPCC One small low-quality study assessed calcium in patients with adenomas due to FAP ($n = 28$), and reported no significant reduction in polyp number or progression at 6 months.

Individuals with a history of adenomas Two good-quality studies of calcium (1200–2000 mg/day) in individuals with a history of adenomas ($n = 1186$) demonstrated a statistically significant 18% reduction in the risk of adenoma recurrence after 3–4 years of follow-up (RR 0.82, 95% CI 0.69 to 0.98) and a non-significant reduction in the risk of advanced adenomas (RR 0.77, 95% CI 0.50 to 1.17).

General population (or individuals at no increased risk of colorectal cancer) Two studies assessed

calcium (1000–1500 mg/day) plus vitamin D (400–1100 IU/day) in populations with no increased baseline risk of colorectal cancer (one good quality, one low-to-reasonable quality; $n = 37,016$). There was no significant effect on the relative risk of colorectal cancer (RR 1.08, 95% CI 0.87 to 1.34). However, the duration of follow-up was 4–7 years, which may be insufficient to detect an effect on cancer incidence.

Adverse effects No study reported any serious adverse events associated with calcium and/or vitamin D.

Antioxidants

Individuals with FAP or HNPCC There were no studies of antioxidants in individuals with FAP or HNPCC.

Individuals with a history of adenomas There were six studies of antioxidants (including vitamins A, C and E, beta-carotene or selenium) in individuals with a history of adenomas ($n = 1706$) with treatment and follow-up durations of 2–5 years. Doses and combinations varied between studies, as did study quality. No statistically significant differences in relative risk of adenoma recurrence were demonstrated, either when all antioxidants were analysed together (RR 0.78, 95% CI 0.54 to 1.14) or when specific combinations were assessed separately.

General population (or individuals at no increased risk of colorectal cancer) There were 12 studies of antioxidants in populations with no increased risk of colorectal cancer ($n = 148,922$), with treatment follow-up durations between 5 and 12 years. Study quality was variable. Across the nine studies comparing antioxidants to no antioxidants, there was no difference in incidence of colorectal cancer (RR 1.00, 95% CI 0.88 to 1.13). The single study that assessed the effect of antioxidants on adenoma incidence in the low-risk population also did not demonstrate a statistically significant effect. Of 14 discrete analyses for different combinations of antioxidants in the low-risk population, one study reported a statistically significant increase in relative risk of adenoma incidence in participants receiving vitamin E or vitamin E plus beta-carotene; however, this should be interpreted with caution because of the large number of analyses undertaken.

Adverse effects Reported side effects of antioxidants in the included studies were pruritus (vitamins

A, C, E), epistaxis (vitamin E), a statistically significant increase in the risk of haemorrhagic stroke (vitamin E), alopecia and dermatitis (selenium), yellowing of the skin and belching (beta-carotene). Other reviews have shown that antioxidants did not reduce gastrointestinal cancer incidence (beta-carotene and vitamin A possibly increasing the risk), and that vitamin A, vitamin E and beta-carotene may increase overall mortality. Observational studies have shown possible detrimental effects of antioxidant supplements on cardiovascular mortality, prostate cancer and lung cancer.

Summary of qualitative findings on views, attitudes and beliefs

A literature search identified 20 studies reporting on individuals' views, attitudes and experiences relating to taking the various agents that may be used for chemoprevention. Both personal and external factors may affect people's decisions to use NSAIDs or supplements such as antioxidants, vitamins or minerals. People are more likely to use NSAIDs if there is a strong perceived need, principally determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also may influence the process of decision-making and use: there are greater perceived risks or side effects associated with NSAIDs than dietary supplements, and individuals who are required to take NSAIDs tend to weigh up the balance of benefits against risks and to modify their use of the agent accordingly. People have fewer concerns about using antioxidants or other supplements, but their perception of the benefits of these agents is less well-defined. They would like more information and advice from health professionals, but their use of these supplements tends to be governed more by input from family, friends, alternative therapists and the media.

Summary of cost-effectiveness results

General population results

The model analysis suggests that the most cost-effective age-range policy would be to provide chemoprevention to all individuals within the general population from age 50 to 60 years. This analysis suggests that the use of aspirin chemoprevention in addition to screening within the general population is likely to result in a discounted cost per life-year gained of around

£10,000 and a discounted cost per QALY gained of around £23,000 compared with screening alone. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that screening plus aspirin chemoprevention results in more net benefit than screening alone is expected to be around 80%. All other age policies assessed for the general population resulted in an incremental cost-effectiveness ratio that was greater than £30,000 per QALY gained. This analysis is, however, subject to considerable uncertainty because of a paucity of evidence, particularly around the long-term effectiveness and long-term adverse events associated with aspirin chemoprevention. Although there was no evidence of other chemopreventive agents being effective, and hence potentially cost-effective, within the general population, this may be because of the relatively short-term follow-up of the trials.

Intermediate-risk group results

The model analysis suggests that the most economically viable age-range policy would be to provide chemoprevention to individuals following polypectomy aged 61 to 70 years. This model analysis suggests that calcium chemoprevention is expected to have a discounted cost per QALY gained of around £8000 compared with screening alone. Although aspirin chemoprevention in addition to screening is expected to be more effective and less costly than screening alone, under the current assumptions of benefits to harms of aspirin and calcium, aspirin is expected to be extendedly dominated by calcium. Between thresholds of £10,000 and £100,000 per QALY gained, the probability that calcium chemoprevention produces the greatest level of net benefit is between 50 and 60%. Similarly, there is an estimated 20–30% probability that aspirin chemoprevention would be the most economically attractive option over these willingness-to-pay thresholds. There are no trials directly comparing aspirin and calcium, and because the quality of the trials of each agent is variable, the trial populations vary and the follow-up is relatively short, it is not possible to ascertain which of aspirin or calcium would be most effective or cost-effective within this intermediate-risk population. The model also suggests that the incremental cost-effectiveness of chemoprevention following polypectomy increases (becomes less favourable) as the chemoprevention start age increases. The results should be interpreted with considerable caution because of uncertainty in the model parameters.

Discussion

The majority of studies were of reasonable quality in terms of randomisation, blinding and allocation concealment. Some studies excluded a relatively large percentage of participants from the analysis of adenoma recurrence because this outcome could only be assessed in participants who underwent a follow-up colonoscopy. Approximately 60–100% of patients across studies were compliant with the majority of study medications, although some studies selected the most compliant participants during a run-in phase, which may have increased estimates of compliance relative to the general population. There was some heterogeneity in results, possibly as a result of differences in the duration of treatment and follow-up, sample sizes, differing doses and combinations of agents, and compliance rates.

The development of an adenoma into colorectal cancer may take an average of 10–15 years. Therefore, it is unclear whether interventions given for a relatively short duration can interrupt this sequence, and how long the follow-up duration of a trial would need to be to detect an effect on colorectal cancer incidence. For example, studies of aspirin use within the general population showed no effect on colorectal cancer over the first 10 years of follow-up but demonstrated a significant effect over years 10–19 (although this analysis was partly confounded by differing doses and durations of treatment). It is possible that, of the interventions included here, only aspirin was assessed over sufficient follow-up durations to detect an effect on colorectal cancer incidence. The majority of studies in individuals with a history of adenoma could not provide robust data on colorectal cancer incidence because of the relatively small number of participants and relatively short follow-up durations, as compared with those studies undertaken in the general population.

There is a marked disparity between the available evidence from clinical trials and the data requirements to populate a health economic model. The clinical trials do not provide evidence concerning the point at which chemoprevention begins to take effect relative to the start of treatment or the nature of this effect (whether this is gradual or constant). The relative risk associated with the incidence of polyps or cancers predicted by the clinical trials is assumed to be constant because of the lack of data to the

contrary, implying that chemoprevention offers no cumulative protection. It is not clear whether a protective effect continues when the interventions are stopped, although it appears likely that there will be a delay between any preventive effect on adenoma formation and later effects on colorectal cancer incidence. Moreover, within the model it is assumed that chemoprevention will continue to be taken for 10 or 20 years. However, the treatment duration in the majority of trials is considerably shorter than 10 or 20 years, hence the effectiveness of taking chemoprevention over this longer time frame is not known. These assumptions are likely to have an important impact on the cost-effectiveness results, particularly around the age at which to start and stop taking chemoprevention. Future clinical trials should focus on addressing questions concerning the optimal treatment duration, frequency, start age, end age and dose of chemoprevention.

The analysis of the harms resulting from the use of chemoprevention is limited by the paucity of evidence. The economic analysis assumes that the excess harms associated with chemoprevention are constant over time and by age, that their impact upon quality of life is no longer than 3 months and that there is no negative impact of chemoprevention upon mortality; hence harms may be slightly underestimated within the model. In addition, the economic analysis does not assess the possible impact of chemoprevention upon forms of cancer other than colorectal cancer (e.g. prostate or stomach cancers). In this sense, there are questions concerning the appropriateness of the boundary assumed around the model. This in turn points towards a methodological requirement for developing a modelling framework for modelling public-health interventions.

Given the uncertainties in the evidence base and ambiguities concerning the implementation of potential chemoprevention policy, the results of the health economic analysis should be interpreted with caution.

Conclusions

Implications for service provision

Aspirin and celecoxib may reduce recurrence of adenomas and incidence of advanced adenomas in individuals with an increased risk of colorectal cancer because of a history of adenomas, and COX-2 inhibitors may decrease polyp number in patients

with FAP. There is some evidence for aspirin reducing the incidence of colorectal cancer in the general population, although this effect was only observed in studies of at least 300 mg/day aspirin with a follow-up duration greater than 10 years. There is an absence of long-term follow-up data for lower doses of aspirin or for other NSAIDs. Both aspirin and NSAIDs are associated with adverse effects so it will be important to consider the risk–benefit ratio for each population before these agents can be recommended for chemoprevention. It will be important for health professionals to explain and clarify this balance to patients for any agents that are recommended. Calcium may also reduce adenoma recurrence in individuals with a history of adenomas. However, studies of calcium plus vitamin D in the general population did not demonstrate a significant effect on colorectal cancer, although follow-up durations were relatively short. Folic acid and antioxidants (vitamins A, C, E, beta-carotene and selenium) were not shown to reduce adenoma or colorectal cancer incidence, and recent studies have questioned the potential harms as well as benefits of these agents when given as dietary supplements.

The economic analysis presented here suggests that chemoprevention has the potential to represent a cost-effective intervention when targeted at the intermediate-risk populations following polypectomy, given levels of cost-effectiveness currently considered acceptable by NHS policy-makers. Within the general population, the most favourable cost-effectiveness ratio for chemoprevention is between £20,000 and £30,000 per QALY gained for individuals aged 50–60 years. These findings should be interpreted with caution given the uncertainties in the current evidence base.

Suggested research priorities

Some interventions (aspirin, NSAIDs and calcium) had a statistically significant effect in reducing adenoma recurrence in individuals with a history of adenoma. Further research would be useful to investigate the longer-term risk–benefit balance for potentially effective chemopreventive agents, e.g. whether there is a dose level that gives a significant benefit without unacceptable toxicity, necessary treatment durations required, whether an effect on colorectal cancer can be demonstrated, and for how long the benefits are maintained after the intervention is stopped. Larger studies that follow up participants over long time periods (e.g. 20 years) and assess

colorectal cancer incidence as an outcome would be valuable. Also, studies in which participants take these interventions for longer durations (e.g. 10 years or more) would be valuable in assessing the risk–benefit balance associated with long-term chemoprevention. Within the general population, even for studies with relatively short treatment duration, long-term follow-up is essential if the primary outcome is colorectal cancer incidence. Of the chemopreventive interventions included in this review, it is likely that only aspirin has so far been trialled over a sufficient follow-up duration to assess the effect on colorectal cancer incidence.

It would be informative to test combinations of chemopreventive agents for which effectiveness

has been demonstrated individually (e.g. aspirin and calcium within the intermediate-risk population). It will also be important to test newer chemopreventive agents that have not yet been assessed in RCTs (e.g. preliminary reports have suggested possible chemopreventive effects of curcumin and omega-3 fatty acids). It may also be clinically useful to undertake trials in higher-risk patients for whom endoscopic surveillance is not sufficiently effective, e.g. patients with ulcerative colitis. Finally, it would be useful to consider the relative benefit of chemoprevention when compared with, e.g., action to increase compliance with screening programmes. Very few of these suggested research priorities will be addressed by current ongoing trials.

Chapter I

Background

Description of health problem

Colorectal cancer

Colorectal cancer (CRC) is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon, rectum). Approximately two-thirds of CRCs occur in the colon and one-third in the rectum.

Epidemiology and incidence

Colorectal cancer is more common in developed countries than developing countries.¹ The age-standardised incidence of CRC in England in 2006 was 54 per 100,000 in males and 34 per 100,000 in females,² and the equivalent figures for Wales in 2007 were 62 per 100,000 in males and 40 per 100,000 in females (*Table 1*).³ The incidence of colon cancer is similar in males and females (39 and 36 per 100,000 respectively in England in 2006),² whereas the incidence of rectal cancer is higher in males (22 per 100,000 in males and 13 per 100,000 in females). Colorectal cancer is the third most common cancer in the UK, with

approximately 32,000 new cases annually in England and Wales in 2006–7.^{2,3}

Incidence of CRC increases with age. The incidence in England in 2006 was less than 6 per 100,000 in both men and women below the age of 40 years, rising to approximately 20–25 per 100,000 in people aged between 45 and 49 years. In people aged over 75 years, the annual incidence was over 300 per 100,000 for men and over 200 per 100,000 for women.² The median age at diagnosis is over 70 years for both colon and rectal cancer patients.^{2,3}

Aetiology, pathology and prognosis

Aetiology

Colorectal cancer is thought to result from a complex interaction between inherited susceptibility and environmental factors, as indicated by genetics⁴ and experimental⁵ and epidemiological⁶ studies. Approximately 75% of patients have neither a clear family history nor any known predisposing condition.⁷ Observational

TABLE 1 Colorectal cancer incidence in England and Wales

Number of new cases	Age bands (years)					All males	All females	All cases
	0–44	45–54	55–64	65–74	75+			
England (2006 data from 2008 report)²								
Colon cancer	537	1069	2973	5292	9172	9752	9291	19,043
Rectal cancer	299	870	2237	3282	4315	6723	4280	11,003
Colorectal cancer	836	1939	5210	8574	13,487	16,475	13,571	30,046
Wales (2007 data from 2009 report)³								
Colon cancer	26	79	262	399	651	751	666	1417
Rectal cancer	22	60	178	243	297	491	309	800
Colorectal cancer	48	139	440	642	948	1242	975	2217
England and Wales								
Colon cancer	563	1148	3235	5691	9823	10,503	9957	20,460
Rectal cancer	321	930	2415	3525	4612	7214	4589	11,803
Colorectal cancer	884	2078	5650	9216	14,435	17,717	14,546	32,263

Source: Office for National Statistics 2008² and Welsh Cancer Intelligence and Surveillance Unit 2009.³

studies suggest that development of CRC may be related to environmental factors including the following: high calorie intake, high consumption of red meat (especially if overcooked), high consumption of saturated fat, low consumption of fruit, vegetables and fibre, high alcohol intake, obesity, cigarette smoking, and a sedentary lifestyle.⁸

A family history of CRC (particularly with relatives diagnosed under the age of 45 years) is associated with an increased risk of developing CRC.⁹ Approximately 20% of CRCs occur in individuals who have a clear family history of the disease but for whom no specific disease-causing mutations can be identified.^{10,11} Risk of CRC is also higher in patients with a personal history of inflammatory bowel disease, with cancer risk increasing with increased duration and severity of the condition.¹²

Approximately 5% of cases are associated with one of two genetic syndromes, familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome). FAP accounts for approximately 1% of all CRCs and is caused by a mutation in the adenomatous polyposis coli gene.¹³ Individuals with FAP develop hundreds of polyps in the colon and, by the age of 40 years, most will have developed CRC unless they have surgery to remove the colon.⁸ HNPCC accounts for approximately 2–5% of all CRCs¹⁴ and is caused by a dominantly inherited alteration in one of a number of DNA mismatch repair genes; HNPCC also conveys a higher risk of certain other cancers.¹⁴ People with HNPCC may develop CRC at an early age, but it is less often preceded by the growth of multiple polyps. People with HNPCC develop colorectal adenomas at an earlier age than the general population, and these adenomas have more villous components, are more dysplastic, and progress more rapidly to invasive CRC (over 2–3 years rather than approximately 10 years).^{11,15} The diagnosis of HNPCC is set out by the Amsterdam II criteria¹⁶ (at least three family members with CRC or HNPCC-related cancers, at least two generations affected, one person under 50 years of age at the time of diagnosis, and exclusion of FAP).

Pathology

Colorectal cancer includes malignant growths from the mucosa of the colon and rectum. Cancer cells may eventually spread to nearby lymph nodes

(local metastases) and subsequently to more remote lymph nodes and other organs in the body (distant metastases), the most frequent site of metastasis being the liver. The pathology of the tumour is usually determined by analysis of tissue taken from a biopsy or surgery.

It is thought that most CRCs develop from adenomatous polyps (growths) arising from the lining of the intestine.^{17,18} Colorectal adenomas are common in older age groups, with approximately one-third of people developing at least one adenoma by the age of 60 years.¹⁹ Most adenomas are asymptomatic and do not develop into cancer. Indirect evidence suggests that adenomas may be present for 10 years or more before malignancy develops.^{20,21} The size and number of adenomas, as well as their histological type and presence of epithelial dysplasia, is thought to affect the risk of development to CRC.

Colorectal cancer stage can be described using the modified Dukes' staging system (based on postoperative findings) or the more precise Tumour, Node, Metastases (TNM) staging system, based on the depth of tumour invasion (T), lymph node involvement (N) and metastatic spread (M) assessed preoperatively by radiological examination (*Table 2*). In the UK, approximately 11% of patients are diagnosed at TNM stage I, 32% at stage II, 26% at stage III (lymph node involvement), and 30% at stage IV (metastatic disease).²² It is estimated that around 30% of patients present with metastatic disease and a further 20% may eventually develop metastatic disease.²² Metastatic disease often develops first in the liver, but metastases may also occur at other sites including the lungs.

Prognosis

The treatment, prognosis and survival rate depend to a large extent on the stage of disease at diagnosis. The overall 5-year survival rate for CRC in England and Wales is approximately 50%.²³ Approximate 5-year survival rates for the various stages of CRC, estimated in European clinical guidance from 2005, are shown in *Table 2*.²⁴ For the 80% of patients who receive surgery to remove the primary tumour, approximately 40% will remain disease-free in the long term.⁸ In 20–30% of cases, the disease is too far advanced at initial presentation for curative intervention to be possible; many of these patients die within a few months.⁸

TABLE 2 Five-year survival rates for colorectal cancer, by stage at diagnosis

TNM status	Stage	Modified Dukes' stage	5-year overall survival
T <i>in situ</i> N0 M0	0	–	Likely to be normal
T1 N0 M0	I	A	>90%
T2 N0 M0	I	B1	85%
T3 N0 M0	IIa	B2	70–80%
T4 N0 M0	IIb	B3	
T1–2 N1 M0/T2 N2 M0	III	C1	25–60%
T3 N1 M0/T3 N2 M0	III	C2	
T4 N1 M0	III	C3	
Any T any N M1	IV	D	5–30%

Reproduced from Van Cutsem and Kataja,²⁴ with permission of Oxford University Press.

Significance in terms of ill-health (burden of disease)

Colorectal cancer is a significant cause of mortality. The age-standardised mortality rate for CRC in the UK in 2006 was 18 per 100,000 population.²³ Colorectal cancer is also a significant cause of morbidity and may affect quality of life as a result of the disease itself and its treatment. Treatment of CRC has significant cost implications for the NHS. Prevention of CRC, for example through screening, also has significant associated costs.

Symptoms

Common symptoms of CRC or large polyps are abdominal pain, rectal bleeding, persisting change in bowel habit, and anaemia; more advanced tumours are likely to cause weight loss, nausea and anorexia, and abdominal pain. The early symptoms are common in the general population and can have a variety of other causes. In some patients, symptoms do not become apparent until the cancer is far advanced.⁸

Current service provision

A conceptual model of the current bowel cancer service for England has been previously developed as part of a bowel cancer simulation study to inform future priorities in service investment on behalf of the Department of Health (*Figure 1*).²⁵ This service pathways model was developed through consultation with current national guidelines on the management of bowel cancer,^{8,26}

relevant technology appraisals undertaken by the National Institute for Health and Clinical Excellence (NICE),^{27–31} associated literature on the treatment of bowel cancer,^{25,32} together with considerable clinical input from leading experts in the management of the disease. A condensed form of the conceptual model is described below.

Symptomatic presentation

Once an individual develops symptoms associated with CRC, there are a number of potential entry routes into the bowel cancer service. The most common route is symptomatic presentation either to a general practitioner (GP) or at an Accident and Emergency (A&E) Department. Around 71% patients present via their GP, 7% through A&E and 22% elsewhere in secondary care (Department of Health Waiting Times Database 2006).²⁵ Of those presenting to their GP, around 13% are referred as emergency episodes (Department of Health, personal communication).²⁵ Upon presentation, the patient would receive a general patient consultation and some form of investigation. Initial investigations before referral are likely to depend on the nature and severity of symptoms and may include the use of simple examinations such as per rectal examination, rigid sigmoidoscopy and proctoscopy. Patients with symptoms related to CRC may already be undergoing treatment for other conditions within a secondary-care setting and may be referred for colonoscopy. Individuals who are at high-risk of developing hereditary CRC may be identified through linkage (family history) analysis or genetic testing.²⁵

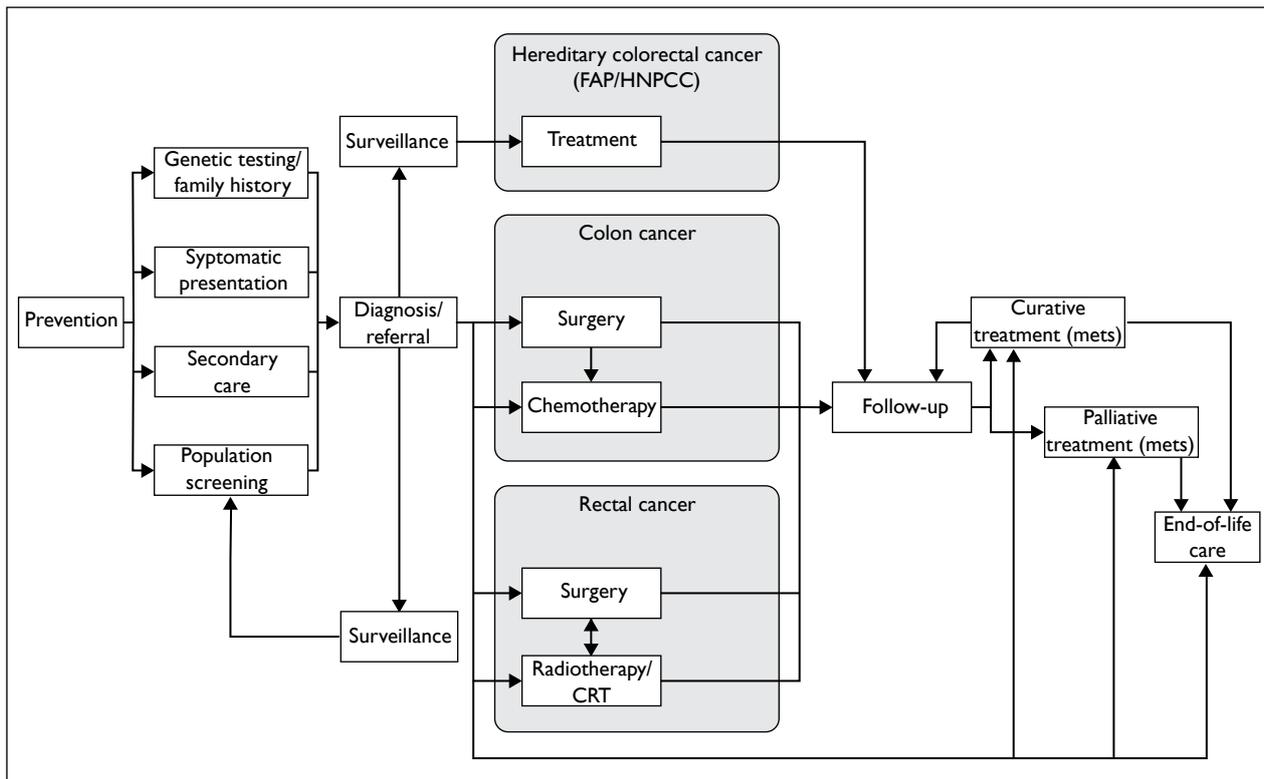


FIGURE 1 Conceptual model of the current bowel cancer service in England.³³

Screening and surveillance

Cancers and large adenomas may bleed, so their presence can be detected via faecal occult blood testing (FOBT; guaiac test) which tests for blood in the stool. Meta-analysis of four randomised controlled trials (RCTs) has shown that screening by FOBT reduced the risk of death from CRC by 16% overall, and by 23% [relative risk (RR) 0.77, 95% confidence interval (95% CI) 0.57 to 0.89] in those who were actually screened.³⁴ Colorectal cancer screening via FOBT has been rolled out across the UK for people aged 60–69 years, and is currently being extended to people aged up to 74 years. FOBT kits are sent out by post and can be undertaken by individuals in their own homes. Individuals with a negative FOBT result will be invited for repeat screening every 2 years, while those with a positive result will be invited for endoscopic follow-up.^{35,36}

Individuals in whom adenomatous polyps are identified may undergo polypectomy (removal of polyps) and may undergo endoscopic surveillance, i.e. repeat examinations at regular intervals. Guidelines published in 2002 advised that patients should undergo follow-up according to their risk level as follows:

- patients with one or two adenomas of < 1 cm diameter undergo either no repeat follow-up or 5-yearly follow-up until one negative examination
- patients with three or four adenomas of < 1 cm diameter or at least one adenoma > 1 cm undergo 3-yearly follow-up until two consecutive negative examinations
- patients with five or more adenomas or three or more adenomas at least one of which is ≥ 1 cm diameter undergo an examination after 12 months before returning to 3-yearly surveillance.¹⁹

Routine endoscopic surveillance is also recommended for other groups of patients who are considered to be at an increased risk of developing CRC, including patients with FAP, HNPCC (and their family members), ulcerative colitis or Crohn's disease.

Diagnostic investigations

Upon referral, diagnosis of CRC may involve the use of a variety of technologies depending on the symptoms present, the fitness of the patient and the results of previous investigations. These

may include haemoglobin checks, per rectal examination, proctoscopy, colonoscopy, flexible sigmoidoscopy, barium enema, computerised tomography, positron emission tomography, ultrasound, colonography, laparotomy with biopsy, X-ray and magnetic resonance imaging scans. Further tests may be undertaken to identify non-malignant colorectal disease, e.g. ulcerative colitis and Crohn's disease.²⁵ Endoscopic techniques include colonoscopy, which allows visualisation of the whole colon, and flexible sigmoidoscopy, which can reach far enough to detect approximately 60% of tumours.⁸ Colonoscopy is associated with some risks, including heavy bleeding (risk of approximately 1 in 150),³⁵ bowel perforation (estimated as 1 in 1500)³⁵ and, in very rare cases, death (estimated at 1 in 10,000).^{35,37}

Colorectal adenomas can be observed and removed by endoscopy before they become malignant. Approximately 90% of adenomas can be seen and removed during colonoscopy and approximately 70% during flexible sigmoidoscopy.

Treatment of colorectal cancer

In 2000, the NHS Executive published guidelines for the management of CRC in England and Wales; this guidance was updated in 2004.⁸ NICE has issued guidance on various chemotherapy regimens and biological agents for the treatment of metastatic CRC,³⁸⁻⁴⁰ as well as guidance on chemotherapy for adjuvant treatment of stage III colon cancer,⁴¹ and on laparoscopic surgery for CRC.⁴² In addition, a report on bowel cancer services was produced for the Department of Health in 2007.²⁵

Treatment of CRC may be curative or palliative depending on the location of the tumour and the degree to which the tumour has penetrated the bowel and spread to other organs in the body. Treatment options differ considerably for colon and rectal tumours. Curative treatment of colon cancer involves surgical resection; the majority of patients undergo open surgery, for example, left- or right-hemicolectomy. Surgery may be undertaken as an open procedure or laparoscopically. Patients may require a permanent or temporary stoma following resection. Patients with non-metastatic colon cancer may subsequently receive adjuvant chemotherapy using a variety of regimens (for example, 5-fluorouracil and folinic acid, capecitabine, oxaliplatin) either in an inpatient or outpatient setting.²⁵

Curative treatment of rectal cancer involves surgical resection, most commonly via anterior resection or abdominoperineal resection, depending on the location and fixity of the tumour. Surgical resection may be undertaken alongside total mesorectal excision and may be undertaken as either an open or laparoscopic procedure. Other adjuvant/neoadjuvant treatments include radiotherapy, chemotherapy and chemoradiation, each of which may be given according to a range of different regimens. Following surgical resection, patients may be followed up using a variety of diagnostic and imaging technologies including the use of ultrasound, carcinoembryonic antigen, magnetic resonance imaging, colonoscopy and computerised tomography scans. There is no currently accepted gold standard for the follow-up of patients with CRC, and schedules may differ considerably in terms of the modality and intensity according to local protocols.²⁵

Recurrence of CRC may be local or metastatic; however, local recurrence is less commonly reported in patients with colon cancer.

Treatments of metastatic recurrence of CRC are typically palliative; however, hepatic resection and pulmonary resection may offer a chance of cure in a small proportion of patients. The mainstay of treatment for metastatic CRC involves chemotherapy; cytotoxic agents include 5-fluorouracil, capecitabine, oxaliplatin, irinotecan, tegafur with uracil, and mitomycin. Again, these may be given according to a variety of regimens across different lines of therapy. Cetuximab, a monoclonal antibody, has also been recommended for use within a specific subgroup of these patients. Supportive care may include a range of interventions for the alleviation of symptoms associated with the disease; this may include drug therapies such as antibiotics, analgesics, transfusions, corticosteroids, as well as localised radiation therapy and non-interventional therapies such as counselling and spiritual support.²⁵

Diagnosis and management of FAP patients

People who are FAP carriers are identified either through linkage analysis (family history) or genetic testing (direct mutation analysis) once they reach the age of around 12 years, or based on colonoscopic investigations undertaken because of symptomatic presentation. Genetic counselling may be required in families where FAP has been diagnosed. FAP patients in whom

malignant bowel tumours are not found are offered ongoing annual surveillance using flexible sigmoidoscopy from the age of 13–15 years. It is recommended that at the age of about 20 years, colonoscopic surveillance should be started, alternating between flexible sigmoidoscopy and colonoscopy thereafter. Following a diagnosis of CRC, or when the patient reaches the age of 25 without a diagnosis of cancer, FAP patients are offered prophylactic surgery to remove either the colon or both the colon and rectum. One surgical option is removal of the colon via colectomy followed by connection of the small intestine (ileum) to the rectum (ileorectal anastomosis). The other option is removal of the colon and rectum via proctocolectomy plus ileoanal pouch reconstruction. The choice of surgery depends on patient preference and the number and location of polyps or cancer. Following surgery, the patient will undergo surveillance of the small intestine (duodenum) via oesophagogastroduodenoscopy (6-monthly to 3-yearly depending on severity of duodenal polyposis). If the rectum is not removed, the patient will undergo surveillance of the rectum via flexible sigmoidoscopy every 6–12 months.^{11,25,43}

Diagnosis and management of HNPCC patients

As with FAP, HNPCC patients are identified either through family history or through symptom-driven colonoscopy. Diagnosis of HNPCC may be based on a detailed family history (with the aid of the Amsterdam II criteria¹⁶) together with molecular screening via microsatellite instability and immunohistochemistry techniques. Genetic counselling may be required in families where HNPCC has been diagnosed. HNPCC patients undergo surveillance colonoscopy every 2 years from the age of 25 or from 5 years younger than the youngest HNPCC-affected relative (whichever is earlier). This surveillance continues until either: the patient reaches the age of 75, or until the causative mutation in that family has been excluded. Following a diagnosis of CRC, or prophylactically, patients with HNPCC are offered either surgical removal of the bowel and rectum via proctocolectomy (plus ileoanal pouch), or surgical removal of the bowel via colectomy plus ileorectal anastomosis followed by surveillance of the rectum using flexible sigmoidoscopy at 1- to 3-yearly intervals (this option is more usual than proctocolectomy). As with FAP, the choice of surgery depends on patient preferences and the location of the tumour.^{11,25,43}

Current cost of colorectal cancer services

A 2007 report on CRC for the Department of Health estimated the total annual treatment costs in England to be approximately £1.1 billion, the largest component of which was the cost of diagnosis (accounting for 26.4% of the total cost), followed by the cost of follow-up (24.7% of the total cost). The mean cost per patient for colon cancer treatment was estimated at £8808, and the mean cost for rectal cancer treatment was estimated at £12,037. The additional cost of screening by FOBT for those aged 60–69 every 2 years was estimated to be £112.8 million in year 1.²⁵

Variation in services and uncertainty about best practice

The NICE CRC guidance from 2004 states that a national survey of NHS patients carried out in 1999–2000 (just before the publication of 2-week referral guidelines for CRC) found that 34% of patients with CRC had had an appointment with a hospital doctor within 2 weeks of visiting their GP with symptoms, but 37% had waited over 3 months for their first hospital appointment and 13% waited 7 or more months.^{8,44} In addition, referrals from GPs did not always adhere correctly to national guidelines in terms of whether or not to classify cases as urgent. The NHS bowel screening programme has been rolled out in England and Wales for people aged 60–69 years, and is currently being extended to people aged up to 74 years.³⁵

Description of technology under assessment

Summary of interventions

This study aims to assess various interventions for the prevention of CRC and/or adenomatous polyps in populations at differing risks for developing CRC. Decisions concerning the inclusion of interventions were taken through reference to clinical advice. The interventions included here are those which can be classed as a drug or a nutritional supplement. The assessment does not include whole-food interventions (such as fruit, vegetables, meat, fibre, garlic, green tea). Other agents such as curcumin⁴⁵ and omega-3 fatty acids⁴⁶ have also begun to be assessed for potential roles in chemoprevention, but were not included in this assessment because only preliminary data exist.

This study includes the following interventions: non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and cyclo-oxygenase-2 (COX-2) inhibitors; antioxidants (including vitamin A, vitamin C, vitamin E, selenium and beta-carotene); calcium, vitamin D and folic acid. Rofecoxib was explicitly excluded from the assessment because its licence has been revoked and it has been withdrawn from the market.⁴⁷

Mechanisms of action

The potential mechanisms of action of the various agents in terms of chemoprevention are as follows. One mechanism proposed for the chemopreventive effects of NSAIDs (including aspirin) is through the inhibition of COX-2. Cyclo-oxygenase is an enzyme required for the conversion of arachidonic acid to prostaglandins. Cyclo-oxygenase-1 is expressed in most tissues and produces prostaglandins which mediate normal physiological functions. Cyclo-oxygenase-2 is undetectable in most normal tissues but is elevated in colorectal adenomas and cancers. Animal models suggest that COX-2 may play a role in colorectal tumour growth and development, through its effects on apoptosis, cell migration, attachment, invasion and angiogenesis.^{48–50}

Oxidation of molecules can produce free radicals (molecules with an unpaired electron). Free radicals are highly reactive and at high levels may cause oxidative stress, i.e. damage to cells which may contribute to progression of various diseases, including tumour development. However, free radicals are also essential for various biological processes, including removal of damaged cells. Antioxidants prevent oxidation, thereby reducing the number of free radicals.^{51–54} Calcium is thought to bind fatty acids and bile acids within the lumen of the colon and rectum, inhibiting the fat-induced hyperproliferation of colon epithelial cells. Calcium also has a direct antiproliferative effect on cells, as well as promoting cellular differentiation and cell death (apoptosis).⁵⁵ Vitamin D has also been shown to inhibit cellular proliferation and promote differentiation and apoptosis.⁵⁵ Folate may have a role in tumour prevention through its involvement in metabolic pathways for DNA methylation and biosynthesis.⁵⁵

Licensed indications, cautions and contraindications

Aspirin

Aspirin is not currently licensed for cancer chemoprevention, although it is widely available

as an over-the-counter medication. Aspirin (acetylsalicylic acid) is licensed for relief of mild to moderate pain and/or pyrexia in adults (age 16 years and over), at an oral dose of 300–900 mg every 4–6 hours when necessary (maximum 4 g daily). Aspirin can also be used as an antiplatelet agent (as a single dose of 300 mg following an ischaemic event, and as a long-term treatment of 75 mg/day in people with, or at high risk of, cardiovascular disease). Aspirin and other NSAIDs are contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID. Aspirin should be avoided in individuals with severe hepatic impairment or severe renal impairment (creatinine clearance less than 10 ml/minute), and analgesic doses should be avoided if possible in the last few weeks of pregnancy. Aspirin should be used with caution in the elderly; in the event of concomitant use of drugs that increase risk of bleeding; and in individuals with glucose 6-phosphate dehydrogenase deficiency (aspirin at a dose greater than 1 g/day may increase the risk of acute haemolytic anaemia in these individuals). Adverse effects resulting from aspirin are reported to be generally mild.⁵⁶ However, there is an increased frequency of dyspepsia and gastrointestinal bleeding which is dose-related. Bronchospasm and skin reactions are also well-described. Further evidence on adverse effects of aspirin is described in Chapter 3; Results: aspirin.

Non-aspirin NSAIDs

In terms of non-aspirin NSAIDs, celecoxib is the only drug that is currently licensed for cancer chemoprevention by the European Medicines Agency. Celecoxib is licensed under the brand name Onsenal™ (Pfizer Ltd, Sandwich, Kent, UK) for the reduction in the number of adenomatous polyps in FAP patients, as an adjunct to surgery and further endoscopic surveillance.⁵⁷ In single doses, NSAIDs have analgesic activity comparable to that of paracetamol. In regular full dosage, NSAIDs have both a lasting analgesic and an anti-inflammatory effect and can therefore be used to treat continuous or regular pain associated with inflammation, e.g. in rheumatoid arthritis, some cases of advanced osteoarthritis, back pain and soft-tissue disorders. Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individuals' tolerance and response. About 60% of patients will

respond to any NSAID in terms of gaining relief from pain and inflammation, and those who do not respond to one may well respond to another. COX-2 inhibitors, NSAIDs which selectively inhibit COX-2 but not COX-1, have fewer gastrointestinal side effects than non-selective NSAIDs. Several other factors also influence susceptibility to gastrointestinal effects, and a NSAID should be chosen on the basis of the incidence of gastrointestinal and other side effects.⁵⁶

The NSAIDs should be used with caution in the elderly (because of the risk of serious side effects and fatalities), in allergic disorders (they are contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID), during pregnancy and breastfeeding, and in coagulation defects. Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment. In patients with renal, cardiac or hepatic impairment, caution is required because NSAIDs may impair renal function; the dose should be kept as low as possible and renal function should be monitored. All NSAIDs are contraindicated in severe heart failure. The COX-2 selective inhibitors (celecoxib, etoricoxib and parecoxib) are contraindicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate or severe heart failure, and should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with oedema for any other reason, and in patients with risk factors for heart disease. COX-2 selective inhibitors are associated with an increased risk of thrombotic events (e.g. myocardial infarction and stroke) and should not be used in preference to non-selective NSAIDs except when specifically indicated (i.e. for patients at a particularly high risk of developing gastroduodenal ulceration or bleeding) and after assessing cardiovascular risk. Non-selective NSAIDs may also be associated with a small increased risk of thrombotic events, particularly when used at high doses and for long-term treatment. The lowest effective dose of NSAID or COX-2 inhibitor should be prescribed for the shortest period allowing control of symptoms, and the need for long-term treatment should be reviewed periodically. Non-selective NSAIDs are contraindicated in patients with previous or active peptic ulceration and selective COX-2 inhibitors are contraindicated in active peptic ulceration.

Although it is preferable to avoid NSAIDs in patients with active or previous gastrointestinal ulceration or bleeding, and they should be withdrawn if gastrointestinal lesions develop; nevertheless, patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness.⁵⁶

Adverse events resulting from the use of NSAIDs include gastrointestinal discomfort, nausea, diarrhoea and occasionally bleeding and ulceration. Systemic as well as local effects of NSAIDs contribute to gastrointestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia. Those at risk of duodenal or gastric ulceration (including the elderly) who need to continue NSAID treatment should receive either a selective inhibitor of COX-2 alone, or a non-selective NSAID with gastroprotective treatment. Other side effects include hypersensitivity reactions (particularly rashes, angioedema, bronchospasm, headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity and haematuria). Blood disorders have also occurred. Fluid retention may occur (rarely precipitating congestive heart failure), and blood pressure may be raised. Renal failure may be provoked by NSAIDs, especially in patients with renal impairment. Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure. Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, eye changes, Stevens–Johnson syndrome and toxic epidermal necrolysis are other rare side effects. Induction of or exacerbation of colitis has been reported. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible.⁵⁶ Further evidence on adverse effects of NSAIDs is described in Chapter 3; Results: non-aspirin NSAIDs.

Folic acid

Folic acid is not currently licensed for cancer chemoprevention. According to the BNF, folic acid has few indications for long-term therapy because most causes of folate deficiency are self-limiting or will respond to a short course of treatment. In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy or antiepileptic drugs), daily folic acid supplementation for

4 months brings about haematological remission and replenishes body stores. For prophylaxis in chronic haemolytic states, malabsorption, or in renal dialysis, folic acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis. Folic acid supplements taken before and during pregnancy can reduce the incidence of neural tube defects. Women at a low risk of conceiving a child with a neural tube defect should be advised to take folic acid at a dose of 400 µg daily before conception (or from the point at which they suspect they are pregnant) until week 12 of pregnancy. Women at a high risk of conceiving a child with a neural tube defect (if either partner has a personal or family history of neural tube defects, if they have had a previous pregnancy affected by a neural tube defect, or if the woman has coeliac disease or another malabsorption state, diabetes mellitus, sickle-cell anaemia or is taking antiepileptic medicines) should be advised to take folic acid 5 mg daily and continue until week 12 of pregnancy. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B₁₂ is administered concurrently otherwise neuropathy may be precipitated. Folic acid may rarely cause gastrointestinal disturbances.⁵⁶

Calcium

Calcium is not currently licensed for cancer chemoprevention. Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy and lactation, because of increased demand, and in old age, because of impaired absorption. In osteoporosis, a calcium intake that is double the recommended amount reduces the rate of bone loss. If the actual dietary intake is less than the recommended amount, a supplement of as much as 40 mmol is appropriate. Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements. Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements. In severe acute hypocalcaemia or hypocalcaemic tetany, intravenous calcium may be given. Oral supplements of calcium and vitamin D may also be required in persistent hypocalcaemia. Calcium supplements should be used with caution in individuals with renal impairment, sarcoidosis or a history of nephrolithiasis, and calcium chloride should be avoided in respiratory

acidosis or respiratory failure. Contraindications include conditions associated with hypercalcaemia and hypercalciuria (e.g. some forms of malignant disease). Adverse effects may include gastrointestinal disturbances; bradycardia and arrhythmias.⁵⁶

Antioxidants

Antioxidants are not currently licensed for cancer chemoprevention. Antioxidants may be purchased as over-the-counter supplements. According to the *British National Formulary* (BNF), vitamin C therapy is essential for the prevention and treatment of scurvy, and may be required for other manifestations of vitamin C deficiency, especially in the elderly. It is rarely necessary to prescribe more than 100 mg daily except early in the treatment of scurvy. Deficiency of vitamin A is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption). Massive overdose of vitamin A can cause rough skin, dry hair, an enlarged liver, and a raised erythrocyte sedimentation rate and raised serum calcium and serum alkaline phosphatase concentrations. In view of evidence suggesting that high levels of vitamin A may cause birth defects, women who are (or may become) pregnant are advised not to take vitamin A supplements (including tablets and fish-liver oil drops), except on the advice of a doctor or an antenatal clinic; nor should they eat liver or products such as liver pâté or liver sausage.⁵⁶

The daily requirement of vitamin E has not been well defined but is probably approximately 3–15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestasis. In young children with congenital cholestasis, abnormally low vitamin E concentrations may be found in association with neuromuscular abnormalities, which usually respond only to the parenteral administration of vitamin E. Vitamin E should be used with caution in individuals with a predisposition to thrombosis, and may cause an increased risk of necrotising enterocolitis in neonates weighing < 1.5 kg. Vitamin E may cause diarrhoea and abdominal pain at doses > 1 g daily.

Selenium deficiency can occur as a result of inadequate diet or prolonged parenteral nutrition. A selenium supplement should be given only when there is good evidence of deficiency. Selenium may be administered orally or by intramuscular

injection or by intravenous injection, at a dose of 100–500 μg daily.⁵⁶

According to the BNF, the term vitamin D is used for a range of compounds that possess the property of preventing or curing rickets. They include ergocalciferol (calciferol, vitamin D₂), colecalciferol (vitamin D₃), dihydrotachysterol, alfacalcidol (1-hydroxycholecalciferol) and calcitriol (1,25-dihydroxycholecalciferol). Simple vitamin D deficiency can be prevented by taking an oral supplement of only 10 μg (400 units) of ergocalciferol (calciferol, vitamin D₂) or colecalciferol (vitamin D₃) daily. Vitamin D deficiency can occur in people whose exposure to sunlight is limited and in those whose diet is deficient in vitamin D. In these individuals, ergocalciferol or colecalciferol in a dose of 20 μg (800 units) daily by mouth can prevent vitamin D deficiency. Preparations containing calcium with colecalciferol are available for the management of combined calcium and vitamin D deficiency, or for those at high risk of deficiency. Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements. Elderly patients, especially those who

are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements. Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses, such as ergocalciferol tablets up to 1 mg (40,000 units) daily; the hypocalcaemia of hypoparathyroidism often requires doses of up to 2.5 mg (100,000 units) daily to achieve normocalcaemia.

Vitamin D requires hydroxylation by the kidney to its active form, therefore the hydroxylated derivatives alfacalcidol or calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of postmenopausal osteoporosis. Paricalcitol, a synthetic vitamin D analogue, is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. All patients receiving pharmacological doses of vitamin D and its analogues should have their plasma calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occur. Breastmilk from women taking pharmacological doses of vitamin D can cause

TABLE 3 Estimated acquisition costs of chemopreventive agent

Chemopreventive agent	Dose, cap size	Cost	Source
Aspirin	300mg, 100-tab pack	£4.71	BNF 57, 2009
Celecoxib	200mg, 30-cap pack	£21.55	BNF 57, 2009
Sulindac	200mg, 56-tab pack	£35.48	BNF 57, 2009
Tiracoxib	Unavailable	–	–
Vitamin A	Unavailable individually ^a	–	–
Vitamin C	500mg, 28 tab pack	£3.12	BNF 57, 2009
Vitamin E	100ml (500mg/5ml)	£25.08	BNF 57, 2009
Selenium	10-ml bottle ^b	£3.08	BNF 57, 2009
Beta-carotene	Unavailable individually ^c	–	–
Calcium	1.25g, 100-tab pack	£9.46	BNF 57, 2009
Vitamin D	500ng, 30-cap pack	£9.99	BNF 57, 2009
Folic acid	400 μg , 90-tab pack	£2.32	BNF 57, 2009

a Vitamin A is only available in combination with other vitamins. The acquisition cost of vitamin A 4000 units and vitamin D 400 units for an 84-cap pack is £3.14.

b Selenium appears to be unavailable in tablet form individually, but it is possible to obtain tablets of vitamins A, C and E in addition to selenium at a cost of 8p per cap (Boots online; www.boots.com). The dosing of selenium/each vitamin is not presented.

c 30 multivitamin tablets including beta-carotene are available at a cost of £7.99 (Boots online). The dosing of each vitamin is not presented.

hypercalcaemia if given to an infant. Vitamin D supplements are contraindicated in individuals with hypercalcaemia or metastatic calcification. Symptoms of overdosage of vitamin D include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo and raised concentrations of calcium and phosphate in plasma and urine.⁵⁶

Identification of important subgroups

The use of prophylactic interventions is assessed in various populations at differing risk of CRC. One subgroup is the general population (or individuals with no increased risk for CRC); this population is described in this assessment as the 'low-risk' subgroup. Another subgroup consists of individuals at an increased risk for CRC because of a personal history of adenomatous polyps, personal or family history of CRC, or inflammatory bowel disease; this population is described in this assessment as the 'intermediate-risk' subgroup. Finally, there are individuals who are at a high risk of CRC because of one of two genetic conditions, FAP or HNPCC;

this population is described in this assessment as the 'high-risk' subgroup.

Current usage in the NHS

Neither NICE nor the Association of Coloproctology of Great Britain and Ireland have made either a positive or a negative recommendation for chemoprevention in any subgroup of patients.^{8,26} Use of NSAIDs in FAP patients has been discussed in recent reviews.⁵⁸

Anticipated costs associated with intervention

The acquisition costs of the various interventions are described in *Table 3*. All the agents are self-administered in tablet form and do not require administration by a health-care professional. Aspirin is available over the counter, as are many of the antioxidants (either individually or as multivitamin tablets). It should be noted that combinations of antioxidants may result in lower acquisition costs than the sum of the individual antioxidants.

Chapter 2

Definition of the decision problem

Overall aims and objectives of assessment

The aim of this study is to assess the clinical effectiveness and cost-effectiveness of drug and micronutrient interventions for the prevention of CRC and adenomatous polyps in populations at differing risks for developing CRC.

Specifically, the objectives of the assessment are:

1. to conduct a systematic review of the published evidence on the clinical effectiveness and cost-effectiveness of agents for the prevention of CRC and adenomatous polyps
2. to use published data on epidemiology and compliance to model the expected benefits and harms of different chemoprevention agents in people with different baseline risks of developing CRC
3. to use decision-analytic modelling and probabilistic sensitivity analysis to assess the cost-effectiveness and cost-utility of chemoprevention agents in different risk groups
4. to identify areas in which further primary research would be valuable, based on the results of the systematic review and value-of-information analysis.

The rest of the report is organised as follows to address these aims and objectives. Chapter 3 describes the effectiveness reviews of each of the chemopreventive agents and Chapter 4 describes the qualitative review of chemopreventive use. Chapter 5 brings together the evidence from these reviews, together with information from the wider literature, to inform a health economic analysis of alternative chemoprevention options. A discussion of factors relevant to the NHS is presented in Chapter 6 and all the available evidence is discussed within Chapter 7. The conclusions of the analyses are presented within Chapter 8.

Decision problem

Population and relevant subgroups

The use of prophylactic interventions is assessed in the following populations:

- general population or individuals with no increased risk for CRC (described in this assessment as ‘low risk’)
- individuals at increased risk of CRC (described in this assessment as ‘intermediate risk’) because of:
 - history of adenomatous polyps
 - personal history of CRC
 - family history of CRC
 - inflammatory bowel disease
- individuals at high risk of CRC (described in this assessment as ‘high risk’) because of the following genetic conditions:
 - FAP
 - HNPCC.

Interventions

The scope of this study includes interventions that can be classed as drugs or nutritional supplements used as chemopreventive agents for CRC. The study excludes whole-food interventions (such as fruit, vegetables, meat, fibre, garlic, green tea). Decisions concerning the inclusion of interventions were taken through reference to clinical advice.

The following interventions are included in this assessment:

- aspirin
- non-aspirin NSAIDs (non-steroidal anti-inflammatory drugs), including COX-2 inhibitors
- folic acid
- calcium and/or vitamin D
- antioxidants: vitamin A, vitamin C, vitamin E, selenium and beta-carotene.

Relevant comparators

Studies were included if they compared the above interventions against placebo or some other chemopreventive agent.

Outcomes

Relevant outcomes include:

- incidence/recurrence of any adenoma
- incidence of advanced adenoma
- change in polyp burden, number and size (for secondary prevention trials in FAP/HNPCC patients in whom adenomas are already present)
- incidence of CRC
- compliance and discontinuation rates
- adverse effects
- health-related quality of life (HRQoL)
- cost-effectiveness and cost-utility.

It is thought that most CRCs develop from adenomatous polyps (growths) arising from the lining of the intestine.^{17,18} Therefore, adenoma incidence is used as an intermediate outcome in many trials of chemoprevention. The term

‘adenoma recurrence’ is used for studies in patients with a history of adenomas which were resected at baseline. Advanced adenomas are those which are thought to be of higher risk of developing into CRC, although there is some uncertainty about which properties are the greatest predictors of higher risk. Guidelines from 2002 advise that patients are at a higher risk if they have a higher number of adenomas or at least one adenoma with a diameter ≥ 1 cm, while there was uncertainty regarding the role of histology as a predictor of future risk.⁵⁹ In several chemoprevention trials, advanced adenomas have been defined as those which are large (≥ 1 cm) or have villous or tubulovillous features or severe dysplasia.⁶⁰⁻⁶⁴ Detection of CRC as an end point is likely to require trials with a larger sample size and a long follow-up duration because it is thought that adenomas may be present for 10 years or more before malignancy develops, and chemopreventive agents are thought to act mainly at the point of adenoma formation.^{20,21} However, it is possible that chemopreventive agents may also act at other points in the pathway, such as during the progression from adenomas to cancer.

Chapter 3

Assessment of clinical effectiveness

The methods for identifying and reviewing the clinical literature are described in this chapter. The number of included studies relating to all interventions is described and the clinical effectiveness results for each intervention are described in separate sections then discussed in the final section. Qualitative data on views and attitudes relating to chemoprevention are described in Chapter 4.

Methods for reviewing effectiveness

A systematic review of the clinical effectiveness of drug and nutritional agents for the prevention of CRC and/or adenomatous polyps was undertaken according to the general principles recommended in the Quality of Reporting of Meta-analyses (QUOROM) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements.^{65,66}

Identification of studies

The search strategy was comprised of two key elements: (1) systematic searches to identify RCTs that evaluate the clinical effectiveness of chemopreventive agents, and (2) systematic searches to identify qualitative studies relating to individuals' perceptions and experiences of compliance with chemopreventive agents.

Identification of RCTs of clinical effectiveness

The following strategies were used to identify RCTs assessing the clinical effectiveness of agents for chemoprevention of CRC and adenomatous polyps:

- searching of electronic databases
- contact with experts in the field
- handsearching of bibliographies of retrieved papers
- identification of relevant studies included in other high-quality systematic reviews of chemoprevention.

The following electronic databases were searched for RCTs of clinical effectiveness: MEDLINE 1950 to June 2008 (via Ovid), MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE 1980 to June 2008 (via Ovid), CINAHL 1982 to June 2008 (via Ovid), Cochrane Database of Systematic Reviews 1991 to June 2008 (via Wiley), Cochrane CENTRAL Register of Controlled Trials 1991 to June 2008 (via Wiley), DARE 1991 to June 2008 (via Wiley), NHS EED 1991 to June 2008 (via Wiley), HTA database 1991 to June 2008 (via Wiley), Science Citation Index 1900 to June 2008 (via ISI), BIOSIS previews 1985 to June 2008 (via ISI). The following research registers were searched: Current Controlled Trials (which includes the Medical Research Council trial register, UK Clinical Research Network, the archives of the National Research Register). Searches were undertaken in June 2008. Subject headings and free text terms were used. The MEDLINE search strategy is shown in Appendix 1. Three sets of search terms were combined:

- terms for CRC or adenomatous polyps AND
- terms for the relevant interventions AND
- a search filter to identify RCTs.

Searches were restricted to RCTs. For all interventions except calcium, searches were restricted to studies published from 2003 onwards because studies published up to 2002 could be identified from recent systematic reviews (Cochrane reviews or other high-quality reviews). For calcium, the search was not restricted by publication date (because the existing Cochrane review excluded studies of calcium combined with other interventions and studies giving less than 1000 mg/day of calcium, and we did not wish to apply these exclusions). Searches were not restricted by language.

Identification of qualitative studies on compliance and views about chemoprevention

A separate literature search was undertaken to identify qualitative studies relating to people's views, attitudes and beliefs about chemoprevention, to explore issues of expected compliance and

other issues of implementation for different types of chemopreventive agent in different risk populations. The search methods, analysis methods and results are described in Chapter 4 and the MEDLINE search strategy is shown in Appendix 1.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used to identify relevant studies.

Population and relevant subgroups

The use of prophylactic interventions is assessed in the following populations:

- general population or individuals with no increased risk for CRC (described in this assessment as ‘low risk’)
- individuals at increased risk of CRC (described in this assessment as ‘intermediate risk’) due to:
 - history of adenomatous polyps
 - personal history of CRC
 - family history of CRC
 - inflammatory bowel disease
- individuals at high risk of CRC (described in this assessment as ‘high risk’) due to the following genetic conditions:
 - FAP
 - HNPCC.

Interventions

The following interventions are included in this assessment (at any dose, alone or in combination):

- aspirin
- non-aspirin NSAIDs, including COX-2 inhibitors
- folic acid
- calcium and/or vitamin D
- antioxidants: vitamin A, vitamin C, vitamin E, selenium and beta-carotene.

Relevant comparators

Relevant comparisons include the following:

- trials comparing the intervention of interest with placebo or no intervention
- trials comparing the intervention of interest with another intervention not included in this assessment
- trials which have adopted a factorial design, whereby the intervention of interest is compared with placebo or no prophylaxis, and some of the participants in both the intervention and control arms also received

another intervention (which may be an intervention included in this assessment).

Approaches for analysing these different types of trial are described further (see Evidence synthesis methods).

Outcomes

Relevant outcomes include:

- incidence/recurrence of any adenoma
- incidence of advanced adenoma (generally defined as ≥ 1 cm in diameter, villous or tubulovillous, having severe dysplasia, or CRC)
- change in polyp burden, number and size (for secondary prevention trials in FAP/HNPCC patients in whom adenomas are already present)
- incidence of CRC
- compliance and discontinuation rates
- adverse events.

Study types

This review includes RCTs. Observational studies were excluded from the review because of the potential for bias through lack of randomisation. Dose-finding and administration studies without an alternative intervention or placebo control group were also excluded. Studies undertaken within low-risk and intermediate-risk populations (i.e. those assessing adenoma incidence and CRC incidence) were included only if they had a treatment and follow-up duration of at least 1 year. Studies undertaken within patients with FAP or HNPCC, which tended to assess other outcomes such as changes in polyp burden, were included irrespective of treatment and follow-up duration.

Screening references and data abstraction strategy

Titles and abstracts were screened by one reviewer and 10% of citations were double-checked by a second reviewer. A kappa of 0.76 was recorded for inter-rater reliability. Full papers were examined for inclusion by two reviewers. Data were extracted by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion.

Critical appraisal strategy

The quality of included randomised trials was assessed using criteria based on recommendations from the Centre for Reviews and Dissemination. The following criteria were used:

- What was the number (and percentage) of randomised patients excluded from the main analyses (< 5%, between 5 and 20%, or > 20%)?
- Was the study randomised and was the method described?
- Was allocation concealed and was the method described?
- Were the following blinded to treatment allocation: participants, caregiver and analyst?
- Were the study groups comparable at baseline?
- Were there any co-interventions or other factors that may influence outcome?

Evidence synthesis methods

For discrete and numerical outcomes, relative risk (risk ratio) and risk difference are reported with 95% confidence intervals. For continuous outcomes, weighted mean differences were calculated using the inverse variance and reported with 95% confidence intervals. The studies were appraised in terms of clinical validity and methodological heterogeneity to determine whether statistical pooling of trial data within a meta-analysis was appropriate. Where studies were meta-analysed, the more conservative random effects model was used to account for clinical and methodological variations between trials. Statistical heterogeneity was described using the *I*-squared statistic, and potential reasons for any heterogeneity were discussed. Forest plots are presented for all analyses where there was more than one relevant study and sufficient data to undertake a meta-analysis. Results for all analyses, including those of single studies, are presented in summary tables.

For studies that include more than one intervention, two types of comparison are analysed and presented:

- the intervention of interest alone versus placebo alone
- the intervention of interest (plus or minus any other intervention) versus placebo (plus or minus any other intervention).

Where trials assess a combination of more than one relevant intervention versus placebo (e.g. all the participants in one trial arm received vitamin C plus vitamin E and all the participants in the other arm received placebo), outcomes data were analysed as a combined intervention. The data contributed to the meta-analysis of (for example) all antioxidants versus placebo, and also to the meta-analysis of vitamin C plus vitamin E versus placebo, but did not contribute to the meta-analysis of vitamin C alone versus placebo.

Factorial trials assessing more than one intervention of the same 'intervention group' (as listed, see Inclusion and exclusion criteria, e.g. 'antioxidants' or 'NSAIDs') were analysed as follows. For example, a factorial trial may include the following arms: 25% of participants receive vitamin C, 25% receive vitamin E, 25% receive both vitamins, and 25% receive placebo alone. If the trial report presented separate data on all trial arms including the placebo-alone arm, then the data contributed to the meta-analysis of all antioxidants versus placebo, and also to the meta-analyses of vitamin C versus placebo, vitamin E versus placebo, and combined vitamins C and E versus placebo. However, if the trial report only presented data on, for example, vitamin C (plus or minus other interventions) versus no vitamin C (plus or minus other interventions), and the 'other interventions' were of the same group (i.e. other antioxidants), then these data could not be used in the meta-analysis of all antioxidants versus placebo. These data were used in the meta-analysis of vitamin C versus placebo, as long as the study reported relative risks which were adjusted for the effects of the other antioxidants in the study; in this case, the data were meta-analysed using these adjusted relative risks directly (via the inverse variance method) rather than using event data.

Participant treatment and follow-up duration are stated to the nearest year within this report, for clarity. The way in which treatment and follow-up durations were measured was sometimes unclear in the study reports, but they generally referred to either the median value, or that which applied to the majority of patients.

With respect to the interpretation of clinical effectiveness evidence to inform the development of the health economic model, it was necessary to know the relative risks of both advanced adenomas and 'low-risk' adenomas (i.e. those that were not defined as advanced). 'Low-risk' adenoma rates were calculated by subtracting the rates of advanced adenomas from the rates of any adenomas, for studies which presented both outcomes (see Chapter 5).

Number of included studies

The search for RCTs of chemopreventive agents identified 3785 citations. Of these, 3518 were excluded at the title/abstract stage and 267 were obtained for examination of the full text. In total, 116 citations met the inclusion criteria. These citations related to 44 published RCTs as follows:

10 RCTs of aspirin, nine RCTs of non-aspirin NSAIDs, six RCTs of calcium and/or vitamin D, six RCTs of folic acid, and 19 RCTs of antioxidants (six RCTs covered more than one intervention type). In addition there were 12 systematic reviews as follows: three reviews of aspirin only, two reviews of NSAIDs only, two reviews of both aspirin and NSAIDs, two reviews of calcium, and three reviews of antioxidants. These existing reviews were screened to check for additional studies. The search also identified six ongoing RCTs: one ongoing RCT of aspirin plus calcium plus vitamin D, one ongoing RCT of NSAIDs (celecoxib), three ongoing RCTs of folic acid, and one ongoing RCT of antioxidants (selenium). The included studies are summarised in the flow diagram of studies (Figure 2) and in Table 4.

Results: aspirin

Aspirin: high-risk population (FAP or HNPCC)

Study and population characteristics

Two existing systematic reviews were identified which addressed the use of aspirin in high-risk groups; Asano and McLeod⁴⁸ and Wang *et al.*⁸² (Table 5). Through these, and the electronic searches, two controlled trials by Burn *et al.* were identified that compared aspirin with

a control group in the high-risk group: the Colorectal Adenoma/carcinoma Prevention Programme 1 (CAPP 1, Burn 2003;⁷¹ available only as a conference abstract) and CAPP 2 (Burn 2008).⁶⁷ These international multicentre studies randomised 206 and 1009 participants, respectively.

CAPP 1 recruited people with a genetic diagnosis of FAP;⁷¹ CAPP 2 recruited people with HNPCC, diagnosed either genetically or clinically.⁶⁷ The age profile of the CAPP 1 study was not reported; the mean age of subjects analysed in the CAPP 2 trial was 46 years (range 25–79 years).

Both studies compared aspirin (600 mg daily), with or without resistant starch (30 g daily), to resistant starch alone or placebo. Participants in CAPP 1 were analysed if they had received treatment for 1 year or longer; participants in CAPP 2 received the study drug for a mean of 27 months (range 1–67 months) and were followed up for a mean of 29 months (range 7–74 months).

Quality assessment

The method of allocation concealment was unclear in CAPP 1 and adequate in CAPP 2 (treatments were prepared by a central pharmacy) (see Appendix 2, Table 51). The generation of the randomisation sequence was not described for

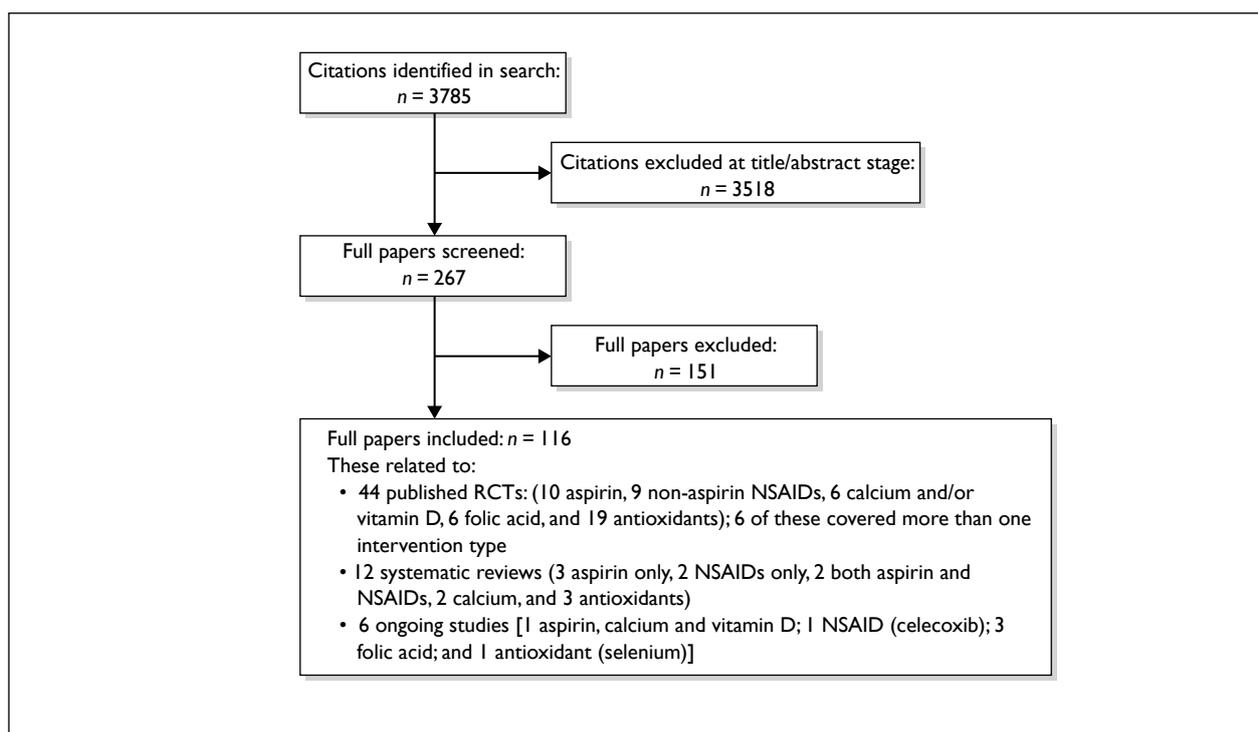


FIGURE 2 Flow diagram of study inclusion and exclusion.

TABLE 4 Summary of included studies

RCTs: high-risk population (FAP/HNPCC)	RCTs: intermediate-risk population (history of adenomas or CRC)	RCTs: low-risk population (no increased risk of CRC)	Systematic reviews (screened to identify additional studies)	Ongoing studies
Aspirin: 10 RCTs				
2 RCTs	4 RCTs	4 RCTs	5 reviews	1 ongoing study
Burn 2008 (CAPP2) ⁶⁷	Logan 2008 (ukCAP) ⁶⁰	Cook 2005 (Women's Health Study) ⁶⁸⁻⁷⁰	Asano 2004 (Cochrane) ⁴⁸	Aspirin, calcium, vitamin D
Burn 2003 (CAPPI) ^{71,72}	Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	Gann 1993 (Physicians' Health Study, PHS) ⁵	Dube 2007 ⁷⁶	
	Benamouzig 2003 (APACC) ⁶²	Farrell 1991 (UK-TIA) ^{21,77}	Cole 2009 ⁷⁸	
	Sandler 2003 ⁷⁹	Peto 1988 (British Doctors Aspirin Trial) ^{21,80}	Gao 2009 ⁸¹	
			Wang 2005 ⁸²	
Non-aspirin NSAIDs: 9 RCTs				
6 RCTs	3 RCTs	0 RCTs	4 reviews	1 ongoing study
Giardiello 2002 ⁸³	Arber 2006 (PreSAP) ^{63,84}		Asano 2004 (Cochrane) ⁴⁸	Celecoxib
Iwama 2006 ⁸⁵	Bertagnolli 2006 (APC) ^{64,84,86,87}		Rostrom 2007 ⁸⁸	
Steinbach 2000 ⁸⁹	Ladenheim 1995 ⁹⁰		Wang 2005 ⁸²	
Giardiello 1993 ⁹¹			Abir 2005 ⁹²	
Nugent 1993 ⁹³				
Labayle 1991 ⁹⁴				
Folic acid: 6 RCTs				
0 RCTs	3 RCTs	3 RCTs	0 reviews	3 ongoing studies
	Logan 2008 (ukCAP) ⁶⁰	Zhang 2008 Women's Antioxidant and Folic Acid Cardiovascular Study: WAFACS) ¹⁰⁵		Folic acid
	Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	Lonn 2006 (HOPE-TOO) ^{106,107}		Folic acid
	Jaszewski 2008 ¹⁰⁸	Zhu 2003 ^{109,110}		Folic acid

continued

TABLE 4 Summary of included studies (continued)

RCTs: high-risk population (FAP/HNPCC)	RCTs: intermediate-risk population (history of adenomas or CRC)	RCTs: low-risk population (no increased risk of CRC)	Systematic reviews (screened to identify additional studies)	Ongoing studies
Calcium and/or vitamin D: 6 RCTs				
1 RCT Thomas 1993 ⁹⁵	3 RCTs Bonithon-Kopp 2000 ⁹⁶	2 RCTs Lappe 2007 ⁹⁷	2 reviews Weingarten 2008 (Cochrane) ⁹⁸	1 ongoing study Aspirin, calcium, vitamin D
	Baron 1999 (Calcium Polyp Prevention Study) ^{99,100} Hofstad 1998 ^{103,104}	Wactawski-Wende 2006 (Women's Health Initiative) ¹⁰¹	Shaukat 2005 ¹⁰²	
Antioxidants (vitamins A, C, E, beta-carotene, selenium): 19 RCTs				
0 RCTs	7 RCTs Baron 2003/Greenberg 1994 (Antioxidant Polyp Prevention Study) ^{11,112} Bonelli 1998 ¹¹⁵	12 RCTs Gaziano 2009 (PHS II) ¹¹³ Lippman 2009 (SELECT) ¹¹⁶	3 reviews Bjelakovic 2008 (gastrointestinal cancers, Cochrane) ¹¹⁴ Bjelakovic 2008 (gastrointestinal cancers, alimentary pharmacology and therapeutics) ¹¹⁷ Bjelakovic 2006 (adenomas) ⁵¹	1 ongoing study Selenium
	Hofstad 1998 ^{103,104} Ponz de Leon 1997b ¹²¹	Lin 2009 (WACS) ¹¹⁸⁻¹²⁰ Lee 2005/Lee 1999 (Women's Health Study) ^{69,70,122,123} Lonn 2005 (HOPE-TOO) ^{107,125} Goodman 2004 (CARET) ^{114,127,128}		
	Roncucci 1993 ^{121,124} MacLennan 1995 (Australian Polyp Prevention Trial) ¹²⁶ McKeown-Eyssen 1988 ¹²⁹	Hercberg 2004 (SU.VI.MAX) ^{114,130-132} Zhu 2003 ^{105,110} Virtamo 2003/Malila 1999 (ATBC) ¹³³⁻¹³⁶ Duffield-Lillico 2002 (NPCT) ¹³⁷⁻¹³⁹ HPS 2002 ^{114,140,141} Hennekens 1996 (PHS) ¹⁴²		

TABLE 5 Aspirin: study characteristics (FAP/HNPCC patients)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Primary prevention (assessing adenoma incidence)					
Burn 2008 (CAPP2 Study) ⁶⁷	HNPCC carriers Age >25 eligible (mean 46, range 25–79)	Aspirin 600mg/day (n analysed=427; n randomised not reported) (some also received starch)	Placebo (n analysed = 510; n randomised not reported) (some also received starch)	2.5 years (approx.)	2.5 years (approx.)
Secondary prevention (assessing reduction in adenoma burden)					
Burn 2003 (CAPP1 Study) ^{71,72}	FAP and polyps	Aspirin 600mg/day ± resistant starch 30mg/day (n unknown; n = 133 analysed across both aspirin and placebo groups)	Placebo (n unknown; n = 133 analysed across both aspirin and placebo groups) (some also received starch)	At least 1 year	At least 1 year

CAPP 1, and was methodologically adequate in CAPP 2 (computer-generated sequence). Outcome assessors and participants were described as blinded in CAPP 1; investigators and participants were described as blinded in CAPP 2. Over 20% of randomised participants were excluded from the analyses in each trial (35.4% and 26.1%, respectively). In CAPP 1, at least some (it is not clear whether all) exclusions were made on the basis that they had not been followed up for 1 year at the time of analysis. In CAPP 2, the reasons for exclusions were not clear.

Outcome data

Effectiveness

Incidence of any adenoma and reduction in adenoma number and size

In the CAPP 1 study in FAP patients (133 analysed participants followed for at least 1 year), it was reported that aspirin did not result in a significant reduction in polyp number. The mean size of the largest polyps was reported as being significantly reduced in the aspirin-only group ($p = 0.01$; no other data reported so far). However, this study was designed to recruit 400 participants⁷² and so far data have been reported for only 133 participants.⁷¹

In the placebo-controlled CAPP 2 study in HNPCC carriers (746 analysed participants), aspirin use (with or without starch) did not result in a statistically significant reduction in the risk of developing new adenomas (RR 1.03, 95% CI 0.75 to 1.41, $p = 0.85$) (Table 6).⁶⁷

Incidence of advanced adenoma

The CAPP 1 study did not report data on advanced adenomas.⁷¹ In the CAPP 2 study (746 analysed participants), aspirin use (with or without starch) did not result in a statistically significant reduction

in the risk of developing new advanced adenomas (RR 0.70, 95% CI 0.44 to 1.12, $p = 0.14$).⁶⁷

Incidence of colorectal cancer

The CAPP 1 study did not report data on CRC.⁷¹ In the CAPP 2 study (746 analysed participants), aspirin use (with or without starch) did not result in a statistically significant reduction in the risk of developing CRC at approximately 2.5 years of follow-up (RR 0.87, 95% CI 0.39 to 1.96, $p = 0.74$).⁶⁷ However, after a mean of 4 years of follow-up (667 analysed participants having received aspirin or placebo for a mean of 2.4 years), the hazard ratio for time to first HNPCC cancer was 0.62 (95% CI 0.41 to 0.96, $p = 0.03$); no data were presented for CRC specifically, and the effect was significant for patients receiving at least 2 years of treatment but not for those receiving less than 2 years of treatment.¹⁴³

Compliance

The CAPP 1 study did not report compliance data.⁷¹ In CAPP 2, the mean proportion of unused aspirin tablets was 10%.⁶⁷

Adverse effects

The CAPP 1 study did not report data on treatment harms.⁷¹ The CAPP 2 study reported the number of participants with gastric ulcers or bleeds (aspirin 11; placebo 9), cerebrovascular events (aspirin 2, placebo 3) and cardiovascular events (aspirin 1, placebo 5).⁶⁷

Ongoing studies

No ongoing studies of aspirin in this population group were identified.

Excluded studies

The authors did not exclude any studies that closely matched the eligibility criteria.

TABLE 6 Aspirin: summary of results (FAP/HNPCC)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)
Burn 2008 (CAPP2 Study) ⁶⁷ in HNPCC carriers	Aspirin 600 mg/day vs placebo (some also received starch)	Placebo (some also received starch)	Adenoma	1	2.5 years (approx.)	61	350	67	396	1.03	0.75	1.41	N/C	0.01	-0.05	0.06	N/C
Burn 2008 (CAPP2 Study) ⁶⁷	As above	As above	Advanced adenoma	1	2.5 years (approx.)	26	350	42	396	0.7	0.44	1.12	N/C	-0.03	-0.07	0.01	N/C
Burn 2008 (CAPP2 Study) ⁶⁷	As above	As above	CRC	1	2.5 years (approx.)	10	350	13	396	0.87	0.39	1.96	N/C	0	-0.03	0.02	N/C

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

Aspirin: intermediate-risk population (history of adenomas or colorectal cancer)

Study and population characteristics

Four studies were identified which compared aspirin against a control group in the intermediate-risk population (Table 7).^{60–62,74,79} Two studies were USA-based: the Aspirin/Folate Polyp Prevention Study reported by Cole *et al.* and Baron *et al.*^{61,74} and the study reported by Sandler *et al.*⁷⁹ Two studies were European: the United Kingdom Colorectal Adenoma Prevention (ukCAP) study reported by Logan *et al.*⁶⁰ and the Association pour la Prévention par Aspirine du Cancer Colorectal (APACC) trial reported by Benamouzig *et al.*⁶² All four studies were multicentre RCTs, which each randomised between 272 and 1121 participants.

In three studies, people with a history of adenomas were eligible,^{60–62,74} whereas the Sandler study enrolled people with a history of CRC.⁷⁹ The included studies reported a median age between 57

and 65 years, a lower age limit of 21–30 years (one study had no lower limit) and an upper age limit of 75–80 years.

All studies compared aspirin (dose of 81–325 mg/day) to placebo. Two of the studies (Logan and Cole) also prescribed folic acid (dose of 0.5 or 1 mg/day) to 50% of the participants in both the aspirin and placebo arms within a 2 × 2 factorial design.^{60,61} The duration of treatment was 1 year in two studies (Benamouzig and Sandler) and 3 years in the other two studies (Logan and Cole). Participants were followed up for 3 years in three studies (Logan, Cole and Sandler). In the Benamouzig study, participants were treated for 1 year and followed up for 4 years,^{62,144} but only the 1-year data have been published and are included in this assessment, as in the Asano and McLeod Cochrane review.⁴⁸ A recent meta-analysis by Cole *et al.* obtained the unpublished 4-year data from the Benamouzig trial.⁷⁸ The 4-year data showed a lesser effect on adenoma recurrence than the 1-year data,

TABLE 7 Aspirin: study characteristics (history of adenomas or CRC)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Logan 2008 (ukCAP trial: United Kingdom Colorectal Adenoma Prevention) ⁶⁰	History of adenomas Age <75 eligible (mean 58, range 28–75)	Aspirin 300 mg/day only (n = 236) Aspirin 300 mg/day + folic acid 0.5 mg/day (n = 236)	Folic acid 0.5 mg/day only (n = 234) Placebo only (n = 233)	3 years	3 years
Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	History of adenomas Age 21–80 eligible (mean 57 or 58 in all groups, range not reported)	Aspirin 81 mg/day only (n = 169) Aspirin 325 mg/day only (n = 167) Aspirin 81 mg/day + folic acid 1 mg/day (n = 175) Aspirin 325 mg/day + folic acid 1 mg/day (n = 171) ^a	Folic acid 1 mg/day only (n = 170) Placebo only (n = 169)	3 years (approx.)	3 years (approx.)
Benamouzig 2003 (APACC Study) ⁶²	History of adenomas Age 18–75 eligible (mean 58, range not reported)	Aspirin 160 mg/day (n = 73) or 300 mg/day (n = 67)	Placebo (n = 132)	1 year	1 year
Sandler 2003 ⁷⁹	History of CRC Age 30–80 eligible (median age bracket 60–69, range not reported)	Aspirin 325 mg/day (n = 317)	Placebo (n = 318)	1 year	3 years (approx.)

a Analysis of aspirin ± folic acid versus placebo ± folic acid includes an additional 100 patients randomised to aspirin or placebo before folic acid component was added, giving the following numbers of patients per group: aspirin, 81 mg/day (n = 377); aspirin 325 mg/day (n = 372); no aspirin (n = 372).

which may relate to the fact that aspirin treatment was only given for 1 year.

In addition, the effect of aspirin on adenomas and CRC in the intermediate-risk population was analysed in a Cochrane systematic review by Asano and McLeod⁴⁸ and in a systematic review for the US Preventive Services Task Force by Dube *et al.*,⁷⁶ and the effect on adenoma recurrence in this population was meta-analysed by Cole *et al.*⁷⁸ and Gao *et al.*⁸¹

Quality assessment

Allocation concealment was considered adequate in all four studies (all were multicentre studies with treatment allocated via a central pharmacy), and all studies were randomised although the generation of the randomisation sequence was not described in two studies (see Appendix 2, Table 51). All studies reported adequate blinding. Randomised participants who did not have a follow-up colonoscopy to assess adenoma recurrence were excluded from the main analysis in all studies. In the study reported by Cole, fewer than 5% of randomised participants were excluded from the analysis,⁶¹ whereas in the other three studies, between 5 and 20% of randomised participants were excluded.^{60,62,79}

Outcome data

Effectiveness

Effectiveness results for aspirin in the intermediate-risk population (history of adenomas or CRC) are shown in Figure 3 and Table 8.

Recurrence of any adenoma

In the intermediate-risk population (history of adenomas or CRC), all four studies (2692 analysed participants) compared aspirin to no aspirin (50% of participants in the aspirin and placebo arms also received folic acid in the Logan and Cole studies); see Figure 3ai.^{60,61} A meta-analysis demonstrated a statistically significant 21% reduction in the relative risk of recurrence of an adenoma of any type (RR 0.79, 95% CI 0.68 to 0.92, $p = 0.002$), with a moderate level of statistical heterogeneity ($I^2 = 34\%$). There was a 7% reduction in the absolute risk [meta-analysed risk difference (RD) -0.07 , 95% CI -0.11 to -0.04 , $p < 0.0001$], with no statistical heterogeneity ($I^2 = 0\%$).

These four studies also provided data comparing aspirin to placebo alone ($n = 1662$, excluding those participants who also received folic acid; Figure 3aii). The relative risk for adenoma

recurrence remained similar and statistically significant at the 5% level (meta-analysed RR 0.80, 95% CI 0.65 to 0.98, $p = 0.03$) with a moderate level of statistical heterogeneity ($I^2 = 47\%$), and the absolute risk difference remained similar.

In addition, two of the studies (Logan and Cole; 916 participants in analysis) compared aspirin plus folic acid with placebo (Figure 3aiii).^{60,61} The differences in the relative and absolute risks of developing an adenoma of any type were not statistically significant at the 5% level (meta-analysed RR 0.90, 95% CI 0.75 to 1.08, $p = 0.27$; RD -0.04 , 95% CI -0.10 to 0.02 , $p = 0.23$), and there was no statistical heterogeneity between the studies ($I^2 = 0\%$).

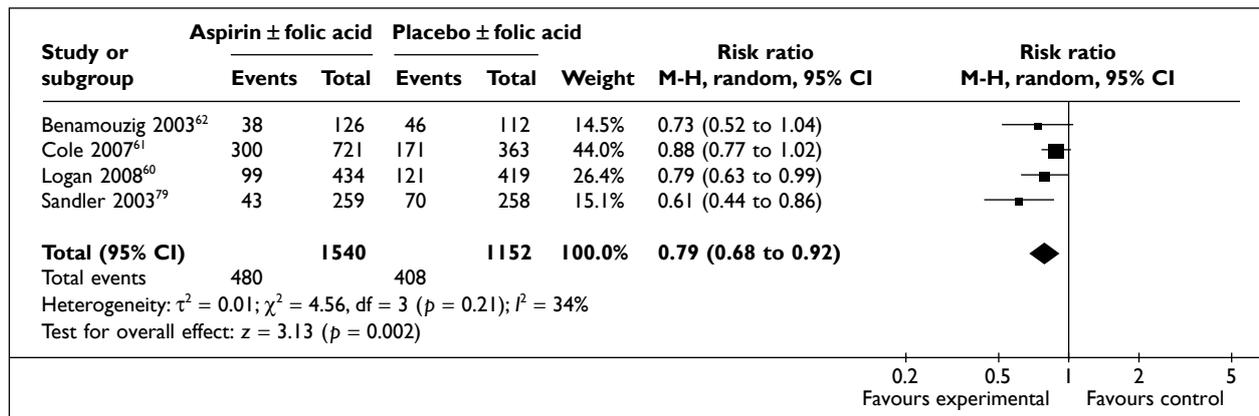
Incidence of advanced adenoma

Three of the studies (Logan, Cole and Benamouzig)⁶⁰⁻⁶² reported incidence rates for advanced adenomas (generally defined as ≥ 1 cm in diameter, villous or tubulovillous, having severe dysplasia, or CRC; see Figure 3bi). When analysing aspirin versus no aspirin ($n = 2175$, including some participants who also received folic acid), a meta-analysis demonstrated a statistically significant 34% reduction in the relative risk of advanced adenoma incidence (RR 0.66, 95% CI 0.51 to 0.84, $p = 0.0008$) and a 5% reduction in the absolute risk (RD -0.05 , 95% CI -0.07 to -0.02 , $p = 0.0008$), with no statistical heterogeneity between the studies ($I^2 = 0\%$ for both analyses).

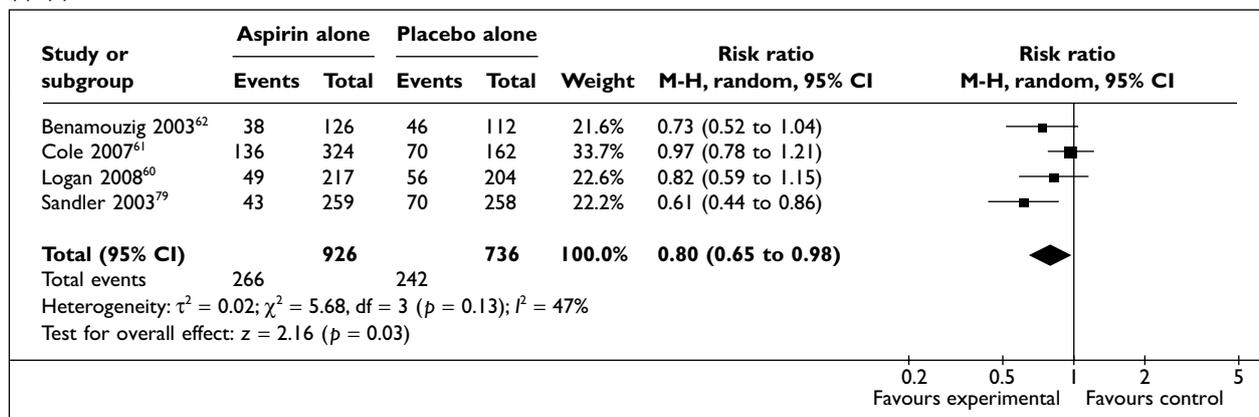
When comparing aspirin to placebo alone (three studies; $n = 1662$, excluding participants who also received folic acid, Figure 3bii), the risk of advanced adenoma incidence remained lower in the aspirin group but was no longer significant at the 5% level (meta-analysed RR 0.75, 95% CI 0.52 to 1.07, $p = 0.12$; RD -0.03 , 95% CI -0.06 to 0.01 , $p = 0.14$) with no heterogeneity ($I^2 = 0\%$ for both analyses).

In addition, two of the studies (Logan and Cole; 916 participants in analysis) compared aspirin plus folic acid versus placebo (Figure 3biii).^{60,61} The differences in the relative risk and absolute risk of developing an advanced adenoma were not statistically significant at the 5% level (meta-analysed RR 0.77, 95% CI 0.45 to 1.34, $p = 0.36$; RD -0.03 , 95% CI -0.09 to 0.04 , $p = 0.41$). The meta-analysis indicated moderate ($I^2 = 45\%$) and high ($I^2 = 58\%$) levels of statistical heterogeneity for the relative risk and absolute risk analyses, respectively.

(a) Recurrence of any adenoma (i)



(a) (ii)



(a) (iii)

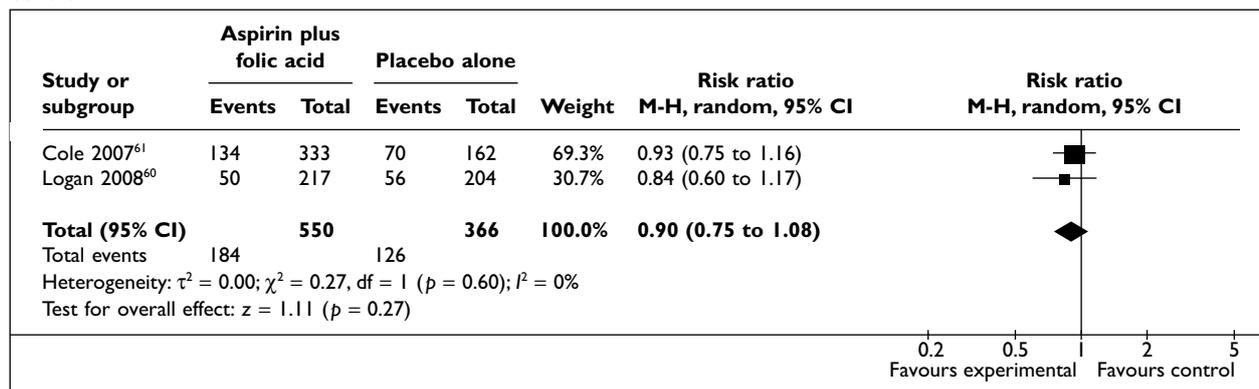


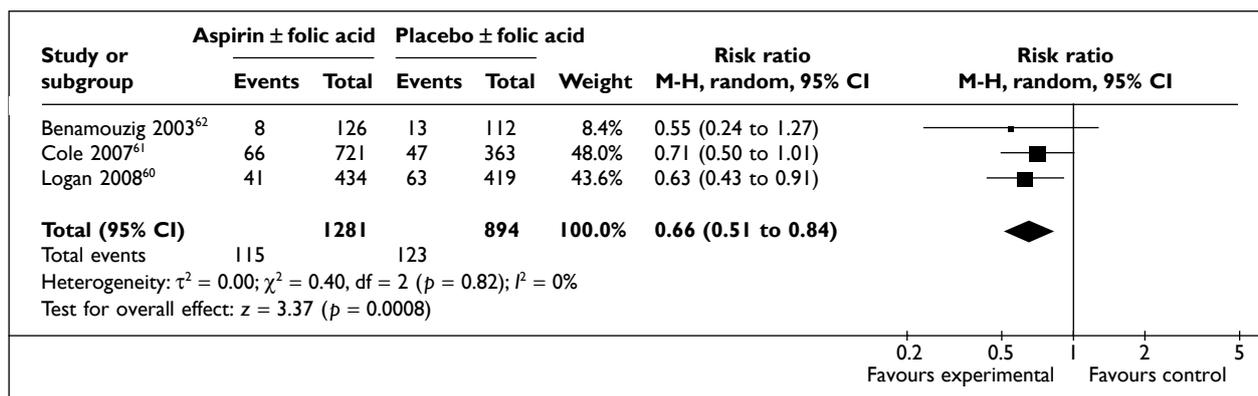
FIGURE 3 Aspirin: meta-analyses (history of adenomas or colorectal cancer). (a) Recurrence of any adenoma: (i) aspirin ± folic acid versus placebo ± folic acid, (ii) aspirin alone versus placebo alone, (iii) aspirin + folic acid versus placebo alone; (b) Incidence of advanced adenoma: (i) aspirin ± folic acid versus placebo ± folic acid, (ii) aspirin alone versus placebo alone, (iii) aspirin + folic acid versus placebo alone; (c) Incidence of colorectal cancer: aspirin ± folic acid versus placebo ± folic acid.

Incidence of colorectal cancer

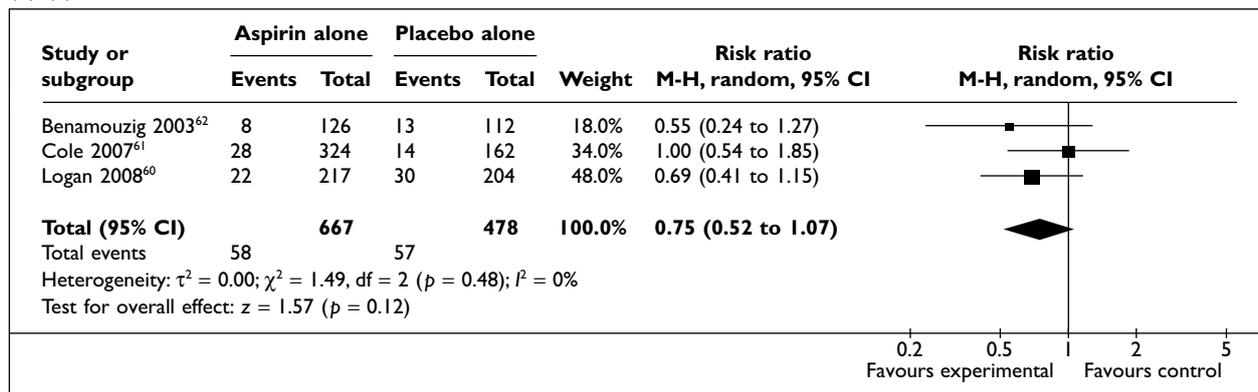
Two of the studies comparing aspirin to no aspirin also reported incidence of CRC (Logan and Cole; $n = 1937$, 50% of participants also received folic acid; Figure 3c).^{60,61} The differences in the

relative risk and the absolute risk of CRC were not significant at the 5% level (meta-analysed RR 0.84, 95% CI 0.15 to 4.74, $p = 0.84$; RD 0.00, 95% CI -0.02 to 0.01, $p = 0.82$) with moderate-to-high heterogeneity ($I^2 = 49\%$ and 72% , respectively).

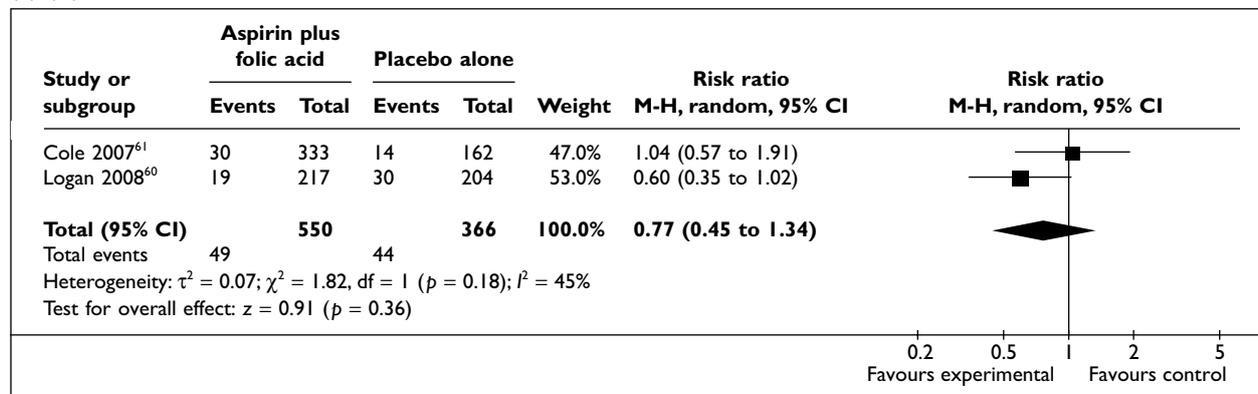
(b) Incidence of advanced adenoma (i)



(b) (ii)



(b) (iii)



(c) Incidence of colorectal cancer

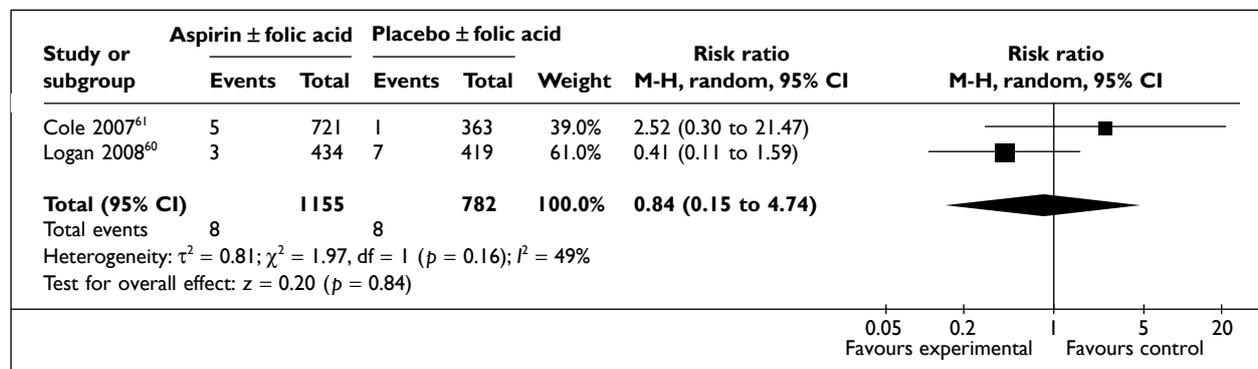


FIGURE 3 (continued) Aspirin: meta-analyses (history of adenomas or colorectal cancer). (a) Recurrence of any adenoma: (i) aspirin ± folic acid versus placebo ± folic acid, (ii) aspirin alone versus placebo alone, (iii) aspirin + folic acid versus placebo alone; (b) Incidence of advanced adenoma: (i) aspirin ± folic acid versus placebo ± folic acid, (ii) aspirin alone versus placebo alone, (iii) aspirin + folic acid versus placebo alone; (c) Incidence of colorectal cancer: aspirin ± folic acid versus placebo ± folic acid.

TABLE 8 Aspirin: summary of results (history of adenomas or colorectal cancer)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Recurrence of any adenoma																		
Baron, ^{61,73,74} Logan, ⁶⁰ Benamouzig, ⁶² Sandler ⁷⁹	Any aspirin (81–325 mg/day) (± folic acid 0.5–1 mg/day)	No aspirin (± folic acid)	Adenoma	4	1,3,3,3	480	1540	408	1152	0.79	0.68	0.92	34	-0.07	-0.11	-0.04	0	
Baron, ^{61,73,74} Logan, ⁶⁰ Benamouzig, ⁶² Sandler ⁷⁹	Aspirin alone (81–325 mg/day)	Placebo alone	Adenoma	4	1,3,3,3	266	926	242	736	0.80	0.65	0.98	47	-0.07	-0.11	-0.03	4	
Baron, ^{61,73,74} Logan, ⁶⁰	Aspirin (81–325 mg/day) + folic acid (0.5–1 mg/day)	Placebo alone	Adenoma	2	3,3	184	550	126	366	0.90	0.75	1.08	0	-0.04	-0.10	0.02	0	
Incidence of advanced adenoma																		
Baron, ^{61,73,74} Logan, ⁶⁰ Benamouzig ⁶²	Any aspirin (81–325 mg/day) (± folic acid 0.5–1 mg/day)	No aspirin (± folic acid)	Advanced adenoma	3	1,3,3	115	1281	123	894	0.66	0.51	0.84	0	-0.05	-0.07	-0.02	0	
Baron, ^{61,73,74} Logan, ⁶⁰ Benamouzig ⁶²	Aspirin alone (81–325 mg/day)	Placebo alone	Advanced adenoma	3	1,3,3	58	667	57	478	0.75	0.52	1.07	0	-0.03	-0.06	0.01	0	
Baron, ^{61,73,74} Logan, ⁶⁰	Aspirin (81–325 mg/day) + folic acid (0.5–1 mg/day)	Placebo alone	Advanced adenoma	2	3,3	49	550	44	366	0.77	0.45	1.34	45	-0.03	-0.09	0.04	58	
Incidence of colorectal cancer																		
Baron, ^{61,73,74} Logan ⁶⁰	Any aspirin (81–325 mg/day) (± folic acid 0.5–1 mg/day)	No aspirin (± Folic acid)	CRC	2	3,3	8	1155	8	782	0.84	0.15	4.74	49	0.00	-0.02	0.01	72	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

As these studies were primarily designed to assess adenoma recurrence, analysis of cancer incidence is limited by the relatively short follow-up time (3 years) and the low number of CRC cases ($n = 16$ cases across both studies) and these results should therefore be treated with caution.

Compliance

Three of the four studies (Cole, Benamouzig and Sandler)^{61,62,79} selected the most compliant participants during an aspirin run-in phase before randomisation, which may increase the observed compliance (and therefore effectiveness) relative to non-trial populations. Measures of compliance differed between studies, but in all three of the above studies, 87–90% of participants reported taking the majority of their study medications at the latest time point mentioned. In the Logan study (which did not report selecting for compliant participants),⁶⁰ 69–77% of participants in all study arms continued to take study medication (i.e. 23–31% discontinued medication), and during the time spent on medication, 76% reported taking the majority of their medications. Benamouzig reported no differences in compliance according to gender or to increased risk of CRC (e.g. because of family history, previous adenomas, adenoma number or size).⁶²

Adverse effects

In terms of the studies of aspirin for adenoma prevention, event numbers were not sufficiently large to allow for a meaningful analysis of adverse event rates.^{60,61,79} Dyspepsia or gastric upset rates were similar between the groups in the Logan study.⁶⁰ Included studies in the intermediate-risk population also reported data on bleeding events, gastrointestinal bleeding, peptic ulcers and cardiovascular adverse events, but event numbers were small.^{60,61,79}

Larger studies and reviews of the adverse effects of aspirin are discussed in the section that relates to aspirin use in the low-risk population.

Ongoing studies

An ongoing multicentre study is assessing aspirin, calcium and vitamin D (as a combination treatment) versus placebo for prevention of adenomas in participants with a history of adenomas, and aims to enrol 1000 participants, with a treatment duration of 3 years and follow-up at 3 and 5 years. The dose of aspirin is lower than that in many chemoprevention studies, at 75 mg/day (www.clinicaltrials.gov, NCT00486512).

Excluded studies

No additional studies of aspirin in the intermediate-risk population were excluded on final examination of the full text.

Aspirin: low-risk population (general population or no increased risk of colorectal cancer)

Study and population characteristics

Four studies were identified that compared aspirin with a control group in participants without increased risk for CRC (Table 9).^{21,68,75,77,80} All included studies were multicentre RCTs. Two were large US population-based studies: the Women's Health Study reported by Cook *et al.* ($n = 39,876$ female participants)⁶⁸ and the Physician's Health Study reported by Gann *et al.* ($n = 22,071$ male physicians).⁷⁵ The two remaining studies were smaller trials: the United Kingdom Transient Ischaemic Attack Aspirin trial (UK-TIA) reported by Farrell *et al.* [$n = 2435$ participants from the UK and Ireland with a history of transient ischaemic attack (TIA) or minor ischaemic stroke]⁷⁷ and the British Doctors' Aspirin Trial reported by Peto *et al.* ($n = 5139$ male physicians from the UK).⁸⁰ The included studies reported a mean age between 53 and 62 years, and three of the studies had a lower age limit of 40 or 45 years.

The two larger studies administered aspirin at a relatively low dose: 100 mg every other day for 10 years (Cook)⁶⁸ and 325 mg every other day for 5 years (Gann).⁷⁵ Both studies also administered antioxidants (beta-carotene and/or vitamin E) to 50% of the aspirin and placebo groups in a factorial design. These studies reported CRC outcomes after 10 years and 5 years of follow-up, respectively. Conversely, the two smaller studies gave aspirin at a higher dose of 300–500 mg/day for 1–7 years (Farrell)⁷⁷ and 300–1500 mg/day for 5–6 years (Peto).⁸⁰ These studies did not originally report CRC outcomes; however, data from the study participants were later reported by Flossmann and Rothwell²¹ in a long-term follow-up analysis over 23 years.

In addition, the effect of aspirin on adenomas and CRC in the low-risk population was analysed in a Cochrane systematic review by Asano and McLeod⁴⁸ and in a systematic review for the US Preventive Services Task Force by Dube *et al.*⁷⁶

TABLE 9 Aspirin: study characteristics (general population or low risk)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Cook 2005 (Women's Health Study) ⁶⁸⁻⁷⁰	General population (women only) Age 45+ eligible (mean 55, range not reported)	Aspirin 100 mg every other day, and/or vitamin E (600 IU every other day), and/or beta-carotene (50 mg every other day for 2 years, stopped early due to lack of effectiveness) Study groups with respect to aspirin and vitamin E were: – aspirin + vitamin E (n=9966); aspirin only (n=9968); vitamin E only (n=9971); placebo only (n=971)	Placebo (see groups on left)	10.1 years (aspirin and vitamin E) 2 years (beta-carotene)	10.1 years
Gann 1993 (Physicians' Health Study, PHS) ⁷⁵	General population (male physicians) Age 40–84 eligible (mean 53, range not reported)	Aspirin 325 mg every other day (n=11,037) (50% also received beta-carotene 50 mg every other day)	Placebo (n=11,034) (50% also received beta-carotene 50 mg every other day)	5 years (for aspirin)	5 years (for aspirin)
Farrell 1991 (UK-TIA Aspirin Trial) ^{21,77}	General population regarding CRC; history of TIA or minor ischaemic stroke Age >40 eligible (mean 60, range not reported)	Aspirin 300 or 1200 mg/day (not analysed separately) (n=1632)	Placebo (n=817)	1 to 7 years	23 years
Peto 1988 (British Doctors Aspirin Trial) ^{21,80}	General population (male physicians) Eligible age range not reported (mean age 62, range not reported)	Aspirin 300 or 500 mg/day (not analysed separately) (n=3429)	Open control (n=1710)	5 to 6 years	23 years

TIA, transient ischaemic attack.

Quality assessment

Allocation concealment was considered adequate in three studies (multicentre studies with treatment allocated via a central pharmacy)^{68,75,77} and was unclear in one study (Peto).⁸⁰ All studies were randomised; however, the generation of the randomisation sequence was not described in three studies^{68,77,80} (see Appendix 2, Table 51). Three studies reported adequate blinding^{68,75,77} while the Peto study was open-label with an untreated control group.⁸⁰ All four studies included all randomised participants in the analyses.

Outcome data

Effectiveness results for aspirin in the general population are shown in Figure 4 and Table 10.

Effectiveness

Incidence of any adenoma

Of all studies assessing the use of aspirin within the general population (no increased risk for CRC), only one study (Gann; n = 22,071) reported adenoma incidence.⁷⁵ The reduction in relative risk for adenoma incidence was not significant at the 5% level (RR 0.86, 95% CI 0.68 to 1.10, p = 0.24). No trend over time for adenoma incidence was noted over the 5 years. This outcome was measured as self-reported adenomas or cancer *in situ*, which contrasts with the studies in the intermediate-risk population in which adenomas were assessed via colonoscopy. The results should therefore be interpreted with caution.

Incidence of advanced adenoma

No studies of aspirin in the general population assessed advanced adenoma incidence.

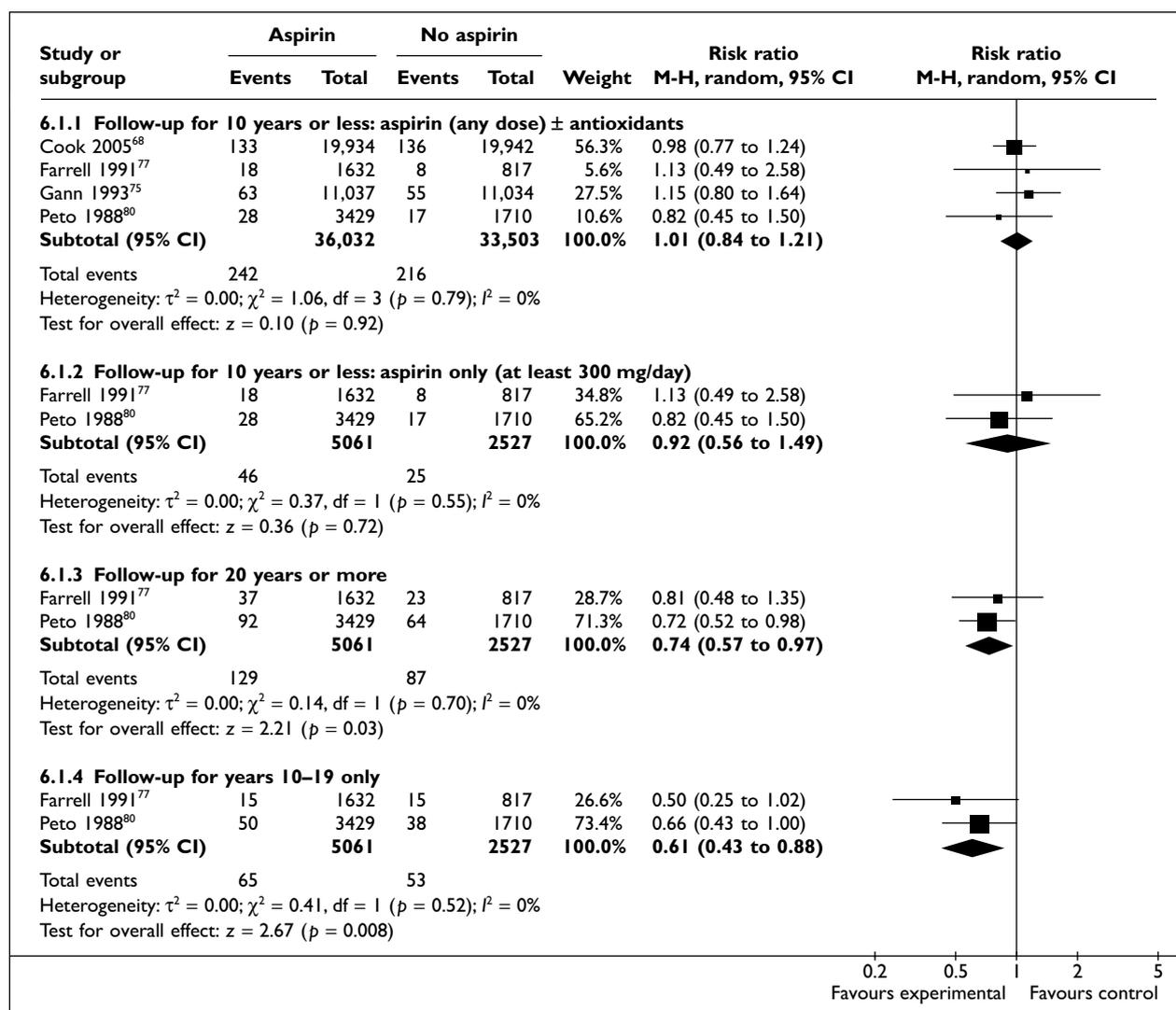


FIGURE 4 Aspirin: meta-analyses (general population or low-risk population). Incidence of colorectal cancer: aspirin alone (or ± antioxidants) versus placebo.

Incidence of colorectal cancer

Available data on the incidence of CRC is described here according to duration of follow-up. The two larger studies of lower-dose aspirin (Cook and Gann) reported CRC incidence after 10 and 5 years of follow-up respectively.^{68,75} The two smaller studies of higher-dose aspirin (Farrell and Peto)^{77,80} were analysed in the report by Flossmann and Rothwell²¹ for CRC incidence over the first 10-year period since start of treatment, the second 10-year period (i.e. years 10–19), and the entire 23-year follow-up period.

The meta-analysis of data from all four studies comparing aspirin to no aspirin in the general population ($n = 69,535$) indicated no effect of aspirin on CRC incidence over a follow-up period of 10 years or less (RR 1.01, 95% CI 0.84 to 1.21, $p = 0.92$; RD 0.00, 95% CI 0.00 to 0.00, $p = 0.82$).

The aspirin dose in these studies ranged from 100 mg every other day to 1200 mg/day. Data from the two smaller studies with a higher aspirin dose (Farrell and Peto; $n = 7588$; 300–1200 mg/day aspirin)^{77,80} was used to assess the effect of aspirin alone versus placebo, as the two larger studies also prescribed antioxidants to 50% of participants. The effect on CRC incidence over the first 10 years remained non-significant (RR 0.92, 95% CI 0.56 to 1.49, $p = 0.72$; RD 0.00, 95% CI –0.01 to 0.00, $p = 0.72$). There was no statistical heterogeneity in any of the above analyses ($I^2 = 0\%$).

However, when data from the two smaller studies (Farrell and Peto; $n = 7588$)^{77,80} with a higher aspirin dose (300–1200 mg/day) were analysed over a follow-up period of up to 23 years, there was a statistically significant 26% reduction in the relative risk of CRC incidence with aspirin versus placebo

TABLE 10 Aspirin: Summary of results (general population or low-risk population)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Incidence of colorectal cancer																		
Cook ⁶⁸⁻⁷⁰	Any aspirin (100 mg every other day to 1500 mg/day)	No aspirin (± vitamin E ± beta-carotene)	CRC, ≤ 10 years FU	4	5, 10, 10, 12	242	36,032	216	33,503	1.01	0.84	1.21	0	0.00	0.00	0.00	0	0
Gann, ⁷⁵																		
Farrell, ^{21,77}																		
Peto ^{21,80}																		
Farrell, ^{21,77}	Aspirin alone (300–1500 mg/day)	Placebo alone	CRC, 10 years FU	2	10, 10	46	5061	25	2527	0.92	0.56	1.49	0	0.00	-0.01	0.00	0	0
Peto ^{21,80}																		
Farrell, ^{21,77}	Aspirin alone (300–1500 mg/day)	Placebo alone	CRC, > 20 years FU	2	23, 23	129	5061	87	2527	0.74	0.57	0.97	0	-0.01	-0.02	0.00	0	0
Peto ^{21,80}																		
Farrell, ^{21,77}	Aspirin alone (300–1500 mg/day)	Placebo alone	CRC, 10–19 years FU	2	Years 10–19 only	65	5061	53	2527	0.61	0.43	0.88	0	0.00	0.00	0.00	0	0
Peto ^{21,80}																		

C, control; I, intervention; FU, follow-up; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

(RR 0.74, 95% CI 0.57 to 0.97, $p = 0.03$), and a 1% reduction in absolute risk (RD -0.01 , 95% CI -0.02 to 0.00 , $p = 0.04$). Interestingly, when this analysis was restricted to the second 10-year follow-up period only (i.e. years 10–19), there was an even greater 39% reduction in relative risk (RR = 0.61, 95% CI 0.43 to 0.88, $p = 0.008$). There was no statistical heterogeneity in these analyses ($I^2 = 0\%$).

Compliance

Two of the four studies (Cook and Gann) selected the most compliant participants during an aspirin or placebo run-in phase before randomisation,^{68,75} which may increase the observed compliance (and therefore effectiveness) relative to non-trial populations. Measures of compliance differed between studies, but in all four studies 70–88% of participants reported taking the majority of their study medications at the latest time point mentioned. In terms of changes in compliance over time, Cook reported that 76% of participants were compliant after 5 years, decreasing to 67% after 10 years.⁶⁸ The non-blinded study by Peto reported that 81% were compliant after 1 year but that a further 5% discontinued study aspirin during each of the next 5 years, mainly as a result of gastrointestinal symptoms.⁸⁰

Adverse effects

Adverse effect data from RCTs included in this review

Dyspepsia or gastric upset was similar between the groups in the two larger studies (Cook and Gann).^{68,75} The incidence of peptic ulcers was reported to be statistically significantly higher in the aspirin group than the control group in the studies by Cook (2.7% vs 2.1%; $p < 0.001$)⁶⁸ and Peto ($p < 0.05$),⁸⁰ and non-significantly higher in the study by Gann (1.5% vs 1.3%; $p = 0.08$).⁷⁵

Gastrointestinal bleeding was statistically significantly higher in the aspirin group in one large study (Cook; 4.6% vs 3.8%; $p < 0.001$),⁶⁸ and slightly higher in the aspirin group in the two smaller studies (one reported as not significant),^{77,80} whereas severe gastrointestinal bleeding was also reported to be statistically significantly higher in the aspirin group than ($p = 0.02$) within the study reported by Cook.⁶⁸ Gann reported bleeding events overall to be statistically significantly higher in the aspirin group ($p < 0.0001$).⁷⁵

No studies reported a significant between-group difference in overall incidence of stroke (Gann and Farrell)^{75,77} or in incidence of haemorrhagic

stroke (Cook and Gann).^{68,75} However, fatal strokes⁷⁷ and major/fatal haemorrhagic strokes^{75,77} were statistically significantly higher in the aspirin group in the studies by Farrell and Gann, although event numbers were small.

Systematic reviews of adverse effects (and benefits) of aspirin

There is a large existing literature regarding adverse effects (and benefits) associated with the use of aspirin. A previous systematic review of aspirin for chemoprevention of CRC prepared by Dube *et al.* for the US Preventive Services Task Force provides a summary of 12 good-quality systematic reviews assessing adverse effects and health benefits associated with aspirin use.⁷⁶ All-cause mortality and mortality due to cardiovascular events were not statistically significantly affected when aspirin was given as primary prevention, yet both outcomes were reported to be statistically significantly lower for aspirin use in the secondary prevention of cardiovascular disease. Myocardial infarction was significantly reduced in both settings. Stroke incidence was not statistically significantly affected in the primary prevention setting, while in the secondary prevention of cardiovascular disease, aspirin appeared to significantly reduce the risk of ischaemic stroke but to significantly increase the risk of haemorrhagic stroke.⁷⁶

In the review by Dube *et al.*, aspirin was consistently associated with statistically significant increases in the risk of gastrointestinal bleeding (RR 1.6–2.5 in systematic reviews of RCTs) and in the risk of adverse gastrointestinal symptoms such as nausea and dyspepsia. A dose effect has been suggested for aspirin-induced gastrointestinal toxicity. In one systematic review, the risk of gastrointestinal bleeding was 2.5% in patients taking more than 100 mg aspirin per day, and 1.1% in patients taking less than 100 mg/day. In another, the risk of gastrointestinal bleeding was higher in patients taking 1600 mg/day than in those taking 300 mg/day.⁷⁶

A recent meta-analysis of aspirin in the prevention of cardiovascular disease analysed six primary prevention trials ($n = 95,000$ individuals at low cardiovascular risk) and 16 secondary prevention trials ($n = 17,000$ individuals at high cardiovascular risk, i.e. history of myocardial infarction or stroke).¹⁴⁵ In the primary prevention trials, the relative risk of serious vascular events per person-year was reduced by 12% [incidence of 0.51% per year in the aspirin groups and 0.57% per year in

the control groups; RR 0.88 (95% CI 0.82 to 0.94); RD 0.07% per year]. This was largely the result of a reduction of approximately one-fifth in the relative risk of non-fatal myocardial infarction. There was no significant difference in the risk of stroke or deaths from vascular causes. However, the risk of internal bleeding increased by approximately one-third in the primary prevention trials. In the secondary prevention trials, the relative risk of serious vascular events per person-year was reduced by 19% (incidence of 6.7% vs 8.2% per year; RR 0.81, 95% CI 0.75 to 0.87, RD 1.49% per year). There were reductions of approximately one-fifth in the relative risk of coronary events and total stroke, but a non-significant increase in risk of haemorrhagic stroke. Therefore, it was concluded that the benefits of aspirin outweighed the risk of harm in secondary prevention of cardiovascular disease, but not necessarily in primary prevention.

Ongoing studies

No ongoing studies of aspirin in the low-risk population were identified.

Excluded studies

No additional studies of aspirin in the low-risk population were excluded on final examination of the full text.

Summary of results for aspirin

Four studies of aspirin (81–325 mg/day) in individuals with a history of adenomas (three studies) or history of CRC (one study) demonstrated a statistically significant 21% reduction in the relative risk of adenoma recurrence. Incidence of advanced adenomas also showed a significant 34% reduction when comparing aspirin versus no aspirin (this was no longer significant when comparing aspirin alone with placebo alone). Aspirin combined with folic acid produced a non-statistically-significant reduction in adenomas and advanced adenomas. Of the four studies of aspirin in the general population, two large studies giving a relatively low dose of aspirin (100–325 mg every other day) showed no effect on CRC over a follow-up period of 5–12 years. Two smaller studies in which a higher dose of aspirin was administered (300–1500 mg/day) showed no effect on CRC over the first 10 years of follow-up, but demonstrated a significant 26% reduction in CRC incidence over the full 23-year follow-up period, and an even greater reduction when analysing years 10–19 only. In addition, aspirin (600 mg/day) was assessed in FAP patients in one study and in

HNPCC patients in another study; both studies reported no statistically significant reduction in adenoma incidence. Aspirin is associated with an increased risk of upper gastrointestinal toxicity including nausea and dyspepsia, peptic ulcers and gastrointestinal bleeding, as demonstrated in the larger studies included here and in a review which collated systematic reviews of adverse effects of aspirin,⁷⁶ with higher aspirin doses being associated with greater risk of toxicity. Previous studies, particularly in individuals at higher risk of cardiovascular disease, have indicated that aspirin may reduce the risk of myocardial infarction and ischaemic stroke but increase the risk of haemorrhagic stroke.

Results: non-aspirin NSAIDs

Non-aspirin NSAIDs: high-risk population (FAP or HNPCC)

Study and population characteristics

Two previous systematic reviews addressed the use of NSAIDs in high-risk groups: Asano and McLeod⁴⁸ and Wang *et al.*⁸² Through these, and the electronic searches, 14 potentially relevant controlled trials were identified. Six controlled trials were included in the review (*Table 11*). Three were USA-based (Giardiello *et al.*, 1993;⁹¹ Giardiello *et al.*, 2002;⁸³ and Steinbach *et al.*, 2000),⁸⁹ one was based in the UK (Nugent *et al.*, 1993),⁹³ one in France (Labayle *et al.*, 1991)⁹⁴ and one in Japan (Iwama *et al.*, 2006).⁸⁵ Three were single centre;^{83,91,93} three were multicentre trials.^{85,89,94} Each trial randomised between 10 and 77 participants.

One study evaluated the use of NSAIDs for the primary prevention of polyps in people who had the FAP genotype (Giardiello 2002).⁸³ The remainder were secondary prevention studies in which at least some of the participants had undergone partial or total colectomy, and all currently had polyps. The mean age of subjects within the primary prevention study was 14.5 years (range 8–25).⁸³ In the secondary prevention studies, the mean age of subjects ranged from 23 years (Giardiello 1993)⁹¹ to 45 years (Nugent).⁹³ Only one study (Steinbach)⁸⁹ identified a statistically significant difference in the age profile of subjects between treatment arms ($p = 0.04$).

One secondary prevention trial (Steinbach)⁸⁹ compared celecoxib, in two doses (100 mg twice daily and 400 mg twice daily), with placebo. The

TABLE 11 Non-aspirin NSAIDs: study characteristics (FAP/HNPCC patients)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Primary prevention (assessing adenoma incidence)					
Giardiello 2002 ⁸³	FAP carriers but no current adenomas. Colorectal polyps assessed. Mean age 13–16 years (range 8–25)	Sulindac 150 or 300 mg/day (n=21)	Placebo (n=20)	4 years	4 years
Secondary prevention (assessing reduction in adenoma burden)					
Iwama 2006 ⁸⁵	FAP patients. Colorectal polyps assessed. Mean age 32–39 years	Tiracoxib 150 mg/day (n=21) or 200 mg/day (n=19)	Placebo (n=21)	6 months	6 months
Steinbach 2000 ⁸⁹	FAP patients. Not had entire colorectum removed, ≥5 adenomas of ≥2mm. Colorectal polyps assessed. Mean age 33–40 years	Celecoxib 200 mg/day (n=32) or 800 mg/day (n=30)	Placebo (n=15)	6 months	6 months
Giardiello 1993 ⁹¹	FAP patients, intact colon or subtotal colectomy with ileorectal anastomosis. Colorectal polyps assessed. Mean age 22–26 years	Sulindac 300 mg/day (n=11)	Placebo (n=11)	9 months	9 and 12 months
Nugent 1993 ⁹³	FAP patients, prior colectomy and ileorectal anastomosis. Rectal polyps assessed. Mean age 45 years (range 27–70)	Sulindac 400 mg/day (n=7)	Placebo (n=7)	6 months	6 months
Labayle 1991 ⁹⁴	FAP patients, prior colectomy and ileorectal anastomosis. Rectal polyps assessed. Mean age 37 years (range 24–52)	Sulindac 300 mg/day (n=10; crossover design)	Placebo (n=10; crossover design)	4 months (1 month washout)	4 months

primary prevention study (Giardiello 2002)⁸³ compared sulindac in two doses (75 mg or 150 mg twice daily) with placebo. Three placebo-controlled studies evaluated sulindac in the secondary prevention setting: Giardiello 1993 (150 mg twice daily);⁹¹ Labayle (100 mg three times daily);⁹⁴ and Nugent (200 mg twice daily).⁹³ The final secondary prevention study compared tiracoxib (150 mg/day or 200 mg/day) against placebo (Iwama).⁸⁵ Participants were followed up with endoscopy at 4 years in the primary prevention study and at between 4 months (Labayle)⁹⁴ and 12 months (Giardiello 1993)⁹¹ in the secondary prevention studies.

Quality assessment

Adequate concealment of the allocation sequence was described in only one study (Nugent);⁹³ in all other cases, the allocation method was unclear (see Appendix 2, Table 52). The method by which the allocation sequence was generated was unclear in all cases. Blinding was described as double blind (assumed to be participant and investigator) in all but one study, Nugent,⁹³ which described the use of placebo controls. The number of randomised participants excluded from the analysis was under

5% in three studies,^{83,89,91} between 5 and 20% in two studies,^{85,94} and unclear in the remainder.⁹³

Outcome data

Effectiveness

Incidence of any adenoma (primary prevention only)

In a single study with 41 participants, after 4 years of follow-up, the difference between sulindac and placebo in the primary prevention of adenomas was not statistically significant at the 5% level (RR 0.78, 95% CI 0.41 to 1.47, $p = 0.44$; Giardiello 2002)⁸³ (Table 12a).

Incidence of advanced adenoma (primary prevention only)

In the study evaluating sulindac for primary prevention, no participant had developed an advanced adenoma (defined as villous or tubulovillous adenomas) at the last follow-up (Giardiello 2002).⁸³

Percentage change in the number of colorectal polyps

Three studies reported percentage change in the number of colorectal polyps: one used the

TABLE 12a Non-aspirin NSAIDs: outcomes for studies in primary prevention of FAP

Study	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	<i>I</i> ² (%)	RD	LCI	UCI	<i>I</i> ² (%)
Giardiello 2002 ⁸³ (FAP carriers but no current adenomas)	Sulindac 150 mg/day or 300 mg/day	Placebo	Adenoma	1	4 years	9	21	11	20	0.78	0.41	1.47	N/C	-0.12	-0.43	0.18	N/C
Giardiello 2002 ⁸³	As above	As above	Advanced adenoma	1	4 years	0	21	0	20	N/C	N/C	N/C	N/C	N/C	N/C	N/C	N/C

C, control; I, intervention; *I*², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

TABLE 12b Non-aspirin NSAIDs: outcomes for studies in secondary prevention of FAP

Study	Intervention and control (brief summary)	I: Mean	I:SD	I: N	C: Mean	C:SD	C: N	Mean Difference	UCI	LCI
Percent change in number of colorectal polyps										
Iwama 2006 ⁸⁵	Tiracoxib 150mg/day vs placebo Treatment and follow-up 6 months	1.0	9.0	20	6.0	17.0	19	-5.00	-13.60	3.60
Iwama 2006 ⁸⁵	Tiracoxib 200mg/day vs placebo Treatment and follow-up 6 months	0.0	7.0	18	6.0	17.0	19	-6.00	-14.30	2.30
Steinbach 2000 ⁸⁹	Celecoxib 200 mg/day vs placebo Treatment and follow-up 6 months	-11.9	30.3	32	-4.5	16.4	15	-7.40	-20.78	5.98
Steinbach 2000 ⁸⁹	Celecoxib 800 mg/day vs placebo Treatment and follow-up 6 months	-28.0	24.0	30	-4.5	16.4	15	-23.50	-35.44	-11.56
Giardiello 1993 ⁹¹	Sulindac 300mg/day vs placebo Treatment 9 months, follow-up 12 months	-34.0	34.52	11	75.2	73.1	11	-109.20	-156.97	-61.43
Percentage change in colorectal polyp size										
Giardiello 1993 ⁹¹	Sulindac 300 mg/day vs placebo Treatment 9 months, follow-up 12 months	-39.0	56.38	11	-1.0	26.53	11	-38.00	-74.82	-1.18
Iwama 2006 ⁸⁵	Tiracoxib 150mg/day vs placebo Treatment and follow-up 6 months	3.0	15.0	20	4.0	18.0	19	-1.00	-11.43	9.43
Iwama 2006 ⁸⁵	Tiracoxib 200mg/day vs placebo Treatment and follow-up 6 months	4.0	16.0	18	4.0	18.0	19	0.00	-10.96	10.96
Percentage change in colorectal polyp burden										
Steinbach 2000 ⁸⁹	Celecoxib 200 mg/day vs placebo Treatment and follow-up 6 months	-14.6	31.7	32	-4.9	17.3	15	-9.70	-23.75	4.35
Steinbach 2000 ⁸⁹	Celecoxib 800 mg/day vs placebo Treatment and follow-up 6 months	-30.7	25.7	30	-4.9	17.3	15	-25.80	-38.50	-13.10

C, control; I, intervention; LCI, lower 95% confidence limit; UCI, upper 95% confidence limit.

circumference of the colorectum in the 20 cm from the anal verge (Giardiello 1993);⁹¹ one selected an area where five or more polyps existed in a limited area of the colon or rectum (Iwama);⁸⁵ the remaining study took a small area with a high density of polyps (Steinbach).⁸⁹ The percentage change in number of colorectal polyps compared with those receiving placebo was not statistically significant at the 5% level for the 100 mg twice daily dose of celecoxib (mean difference -7.40%, 95% CI -20.78 to 5.98, $p = 0.28$), but was statistically significant for those receiving the 400 mg twice daily dose of celecoxib (mean difference -23.50%, 95% CI -35.44 to -11.56, $p = 0.0001$; Steinbach).⁸⁹ The percentage change in number of colorectal polyps compared with those receiving placebo was statistically significant for those receiving the 150 mg twice daily dosage of sulindac (mean difference -109.20%, 95% CI -156.97 to -61.43, $p < 0.00001$; Giardiello 1993).⁹¹ The percentage change in number of colorectal polyps compared with those receiving placebo was not statistically significant for those receiving either the 150 mg/day (mean difference -5.00%, 95% CI -13.60 to 3.60, $p = 0.25$) or the 200 mg/day (mean difference -6.00%, 95% CI -14.30 to 2.30, $p = 0.16$) of tiracoxib (Iwama).⁸⁵

Percentage change in colorectal polyp size

Two studies reported the percentage change in colorectal polyp size: one reported measuring the diameters of the first five polyps counted by the endoscopist (Giardiello 1993);⁹¹ the other reported measuring using a standardised endoscopic ruler (Iwama).⁸⁵ The percentage change in the size of colorectal polyps compared with those receiving placebo was statistically significant at the 5% level in those receiving sulindac (mean difference -38.00%, 95% CI -74.82 to -1.18, $p = 0.04$; Giardiello 1993).⁹¹ The percentage change in the size of colorectal polyps compared with those receiving placebo was not statistically significant at the 5% level in those receiving either the 150 mg/day dose (mean difference -1.00% 95% CI -11.43 to 9.43, $p = 0.85$) or the 200 mg/day dose (mean difference 0.00% 95% CI -10.96 to 10.96, $p = 1.00$) of tiracoxib (Iwama).⁸⁵

Change in colorectal polyp burden

Two studies reported change in colorectal polyp burden: one used the sum of the polyp diameters in a small area with a high density of polyps (Steinbach);⁸⁹ the other used a categorical system (0; < 5; 5-10; 11-20; > 20 polyps) (Labayle).⁹⁴ The change in colorectal polyp burden compared with those receiving placebo was not statistically

significant at the 5% level for the 100 mg twice daily dose (mean difference -9.70, 95% CI -23.75 to 4.35%, $p = 0.18$), but was statistically significant for those receiving the 400 mg twice daily dose of celecoxib (mean difference -25.80, 95% CI -38.50 to -13.10, $p < 0.0001$) (Steinbach).⁸⁹ The other study reported that the polyp burden was reduced in all nine participants who received sulindac, compared with two out of nine participants who received placebo. The polyp burden increased in five patients and was unchanged in two patients receiving placebo.

Incidence of colorectal cancer

No studies reported incidence of CRC.

Compliance

In the primary prevention study (Giardiello 2002),⁸³ compliance was assessed by means of pill counts, review of participants' diaries, and telephone calls every other week. The mean compliance rate was 86.9%; all participants in the sulindac group took more than 76% of scheduled doses.

In one study of secondary prevention by sulindac (Giardiello 1993)⁹¹ compliance was assessed by pill counts and weekly telephone contact; the overall compliance rate was 85%. Another sulindac study reported that one participant was excluded for non-compliance (not defined); general compliance rates were not reported (Labayle).⁹⁴ The other sulindac study (Nugent)⁹³ did not report compliance rates. In the celecoxib study (Steinbach)⁸⁹ compliance was assessed by means of pill counts and review of patient-completed diaries. Two patients were withdrawn for non-compliance (not defined) and three further patients did not complete the study (reasons: suicide, acute allergic reaction and dyspepsia). In the tiracoxib study (Iwama),⁸⁵ compliance was monitored at each clinical visit by counting the numbers of tablets not taken and reviewing participant diary entries. At all times, more than 90% of the participants achieved 80% compliance.

Adverse effects

In the primary prevention study (Giardiello 2002),⁸³ one person was withdrawn as a result of what was described as 'mild' drug-induced leukopenia. The incidence of different categories of adverse event did not differ significantly between the sulindac group and the placebo group. The only category of adverse event to affect more than 5% of sulindac users was influenza-like illness

(29%), and all adverse events were described as minimal or mild.

In one sulindac study (Giardiello 1993),⁹¹ the authors noted that no adverse events were attributed to sulindac, and reported no adverse events. The other sulindac studies (Nugent and Labayle)^{93,94} did not report adverse events. The differences between adverse events experienced in the treatment and control arms were reportedly not significant in the celecoxib trial (no summary statistics were reported); common adverse events included diarrhoea and abdominal pain (Steinbach).⁸⁹ The tiracoxib study reported that symptoms of the common cold, diarrhoea, stomach-ache and decreased haemoglobin levels were more common in the research than the control arm (Iwama).⁸⁵

Excluded studies

One study was rejected because it was a dosage and administration study which did not have a non-NSAID comparator (Sheng *et al.* 2006).¹⁴⁶ Two studies were rejected because they evaluated an intervention (rofecoxib) which has been withdrawn from the market on safety grounds.^{147,148} Three studies were excluded because they did not report any patient-important outcomes.^{149–151} One study was excluded because it was a dose-finding and administration study without an alternative intervention or placebo control group.¹⁴⁶ One citation was identified through a published systematic review (Wang *et al.*);⁸² attempts to

retrieve a copy of this trial report were unsuccessful and we believe that the original citation may be inaccurate.¹⁵²

Non-aspirin NSAIDs: intermediate-risk population (history of adenomas)

Study and population characteristics

Three included studies compared NSAIDs other than aspirin versus placebo in the intermediate-risk population: the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) study reported by Arber *et al.*,⁶³ the Adenoma Prevention with Celecoxib (APC) trial reported by Bertagnolli *et al.*,⁶⁴ and the study by Ladenheim *et al.*⁹⁰ (Table 13). The Arber and Bertagnolli studies were multicentre studies, each randomising between 1561 and 2035 participants from several countries worldwide.^{63,64} The Ladenheim study enrolled 44 patients from three centres in the USA. [A study of rofecoxib¹⁵³ and a study of sulindac plus difluoromethylornithine (DFMO)¹⁵⁴ were excluded; see Excluded studies.]

The Arber and Bertagnolli trials enrolled participants with a history of adenomas, aged 30 years and over. The enrolled participants in the two trials had median ages of 59 and 61 years, a lower age range of 30–31 years, and an upper age range of 88–92 years.^{63,64} The Ladenheim study enrolled participants with colorectal polyps ≤ 1 cm in diameter; polyps were left *in situ* until

TABLE 13 Non-aspirin NSAIDs: study characteristics (history of adenomas)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Arber 2006 (PreSAP Study) ^{63,84}	History of adenomas Age ≥ 30 eligible (median 61, range 30–92)	Celecoxib 400 mg/day (n = 933) Study drug discontinued slightly early because of possible increase in cardiovascular disease risk	Placebo (n = 628)	2.5 years	1 and 3 years
Bertagnolli 2006 (APC trial) ^{64,84,86,87}	History of adenomas Age ≥ 30 eligible (median 59, range 31–88)	Celecoxib 400 mg/day (n = 685) or 800 mg/day (n = 671) Study drug discontinued slightly early due to possible increase in cardiovascular disease risk	Placebo (n = 679)	3 years	1 and 3 years
Ladenheim 1995 ⁹⁰	History of colorectal polyps ≤ 1 cm in diameter (left <i>in situ</i> until end of study) Age > 50 eligible (median 64, range not reported)	Sulindac 300 mg/day (n = 22)	Placebo (n = 22)	4 months	4 months

the end of the study because the aim was to assess polyp regression rather than recurrence; eligible participants were aged over 50 years with a mean age of 64 years.⁹⁰

The Arber and Bertagnolli studies both compared celecoxib to placebo (celecoxib dose 400 mg/day in Arber⁶³ and either 400 mg/day or 800 mg/day in Bertagnolli⁶⁴). The duration of treatment was 2.5 to 3 years. Participants were followed up using colonoscopy at 1 and 3 years in both studies, and the study authors used data from both time points to calculate the cumulative percentage of participants with adenoma recurrence. The Ladenheim study compared sulindac (300 mg/day) with placebo, with a treatment and follow-up duration of 4 months.⁹⁰

In addition, the effect of NSAIDs on adenomas and CRC in the intermediate-risk population was analysed in a Cochrane systematic review by Asano and McLeod,⁴⁸ a systematic review for the US Preventive Services Task Force by Rostom *et al.*⁸⁸ and a meta-analysis by Abir *et al.*⁹²

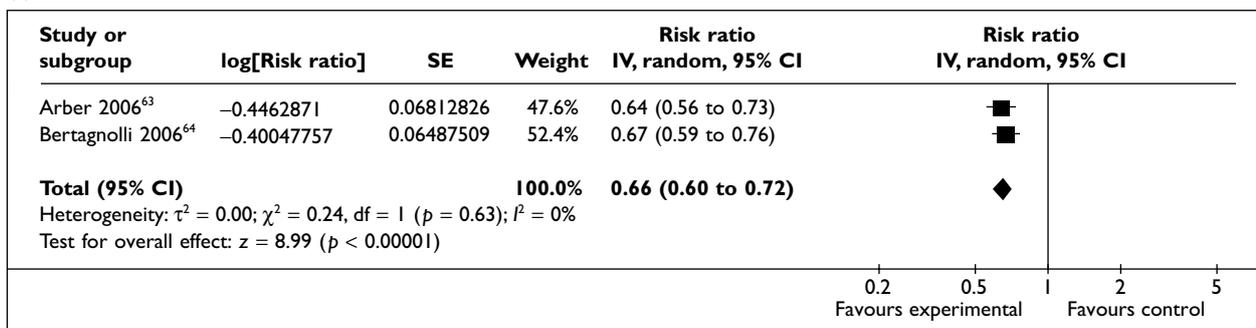
Quality assessment

Allocation concealment was considered adequate in the Arber and Bertagnolli studies^{63,64} (both were multicentre studies with treatment allocated via a central pharmacy) and was likely to be adequate in the Ladenheim study⁹⁰ (because the investigators were blinded). All three studies were randomised although the generation of the randomisation sequence was not described (Appendix 2, Table 52). All three studies reported adequate blinding. In the Arber and Bertagnolli studies, 10–11% of randomised participants who did not have a follow-up colonoscopy to assess adenoma recurrence were excluded from the main analysis.^{63,64} In the Ladenheim study, all participants were included in the analyses.⁹⁰

Outcome data

Effectiveness results for non-aspirin NSAIDs in the intermediate-risk population (history of adenomas) are shown in Figure 5 and Table 14. The Ladenheim study⁹⁰ did not report the recurrence of adenoma or CRC (only adenoma regression) and was therefore excluded from meta-analyses.

(a)



(b)

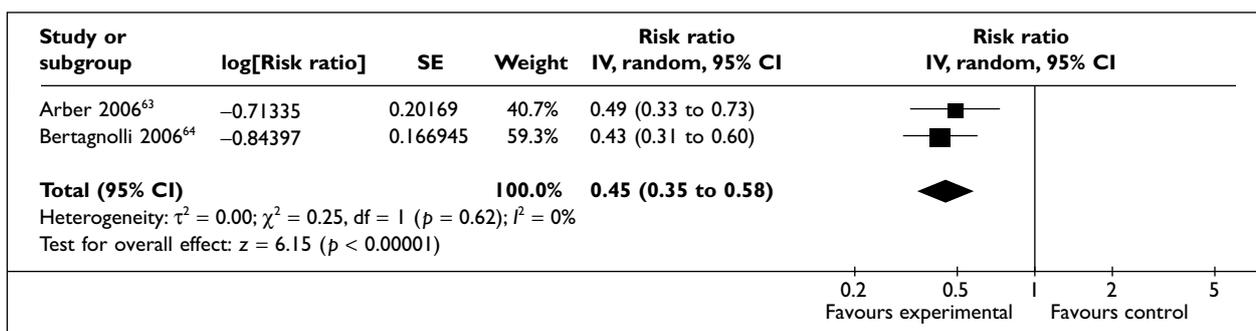


FIGURE 5 Non-aspirin NSAIDs: meta-analyses (history of adenomas). (a) Recurrence of any adenoma: celecoxib versus placebo; (b) Incidence of advanced adenoma: celecoxib versus placebo.

TABLE 14 Non-aspirin NSAIDs: summary of results (history of adenomas)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Recurrence of any adenoma																		
Arber, ^{63,84} Bertagnolli ^{64,84,86,87}	Celecoxib alone (400 mg/day)	Placebo alone	Adenoma	2	3	N/A	1453	N/A	1165	0.66	0.60	0.72	0	N/C	N/C	N/C	N/C	N/C
Incidence of advanced adenoma																		
Arber, ^{63,84} Bertagnolli ^{64,84,86,87}	Celecoxib alone (400 mg/day)	Placebo alone	Advanced adenoma	2	3	N/A	1453	N/A	1165	0.45	0.35	0.58	0	N/C	N/C	N/C	N/C	N/C
Incidence of colorectal cancer																		
Arber ^{63,84}	Celecoxib alone (400 mg/day)	Placebo alone	CRC	1	3	6	933	1	628	4.03	0.48	33.4	N/C	0.00	0.00	0.01	N/C	N/C

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk difference; UCI, upper 95% confidence limit.

Effectiveness

Recurrence of any adenoma

In the intermediate-risk population (history of adenomas or CRC), two studies (Arber and Bertagnolli; $n = 2618$ participants in analysis) compared celecoxib with placebo (Figure 5a).^{63,64} A meta-analysis demonstrated a statistically significant 34% reduction in the relative risk of recurrence of an adenoma of any type (RR 0.66, 95% CI 0.60 to 0.72, $p < 0.00001$), with no statistical heterogeneity ($I^2 = 0\%$). This was based on a meta-analysis of reported relative risks rather than on raw event data, because the study authors calculated the relative risk using data from both the 1-year and 3-year time points. Therefore, it was not possible to calculate an absolute risk difference.

Ladenheim⁹⁰ reported the effect of sulindac compared with placebo on the regression of colorectal polyps ≤ 1 cm in diameter which were left *in situ* over the 4-month study duration. The number of participants whose polyps disappeared or regressed significantly was five of 22 (23%) in the sulindac group and three of 22 (14%) in the placebo group (risk ratio 1.67, 95% CI 0.45 to 6.14).

Incidence of advanced adenoma

Two studies (Arber and Bertagnolli; $n = 2618$ participants) also reported incidence rates for advanced adenomas (generally defined as adenoma ≥ 1 cm in diameter, villous or tubulovillous adenoma, adenoma with severe dysplasia, or CRC; Figure 5b).^{63,64} A meta-analysis demonstrated a statistically significant 55% reduction in the relative risk of advanced adenoma incidence (RR 0.45, 95% CI 0.35 to 0.58, $p < 0.00001$), with no statistical heterogeneity ($I^2 = 0\%$).

Incidence of colorectal cancer

One study (Arber)⁶³ also reported incidence of CRC, with no significant difference in relative risk at the 5% level (RR 4.03, 95% CI 0.48 to 33.4). These data should be treated with caution because of the relatively short follow-up time in terms of detecting cancer (3 years) and the low number of CRC cases (six in the celecoxib arm and one in the placebo arm).

Compliance

Both studies selected the most compliant participants during a placebo run-in phase before randomisation, which may increase the compliance estimates relative to non-trial populations. In both studies, 68–79% of participants reported taking the majority of their study medications, with similar compliance between arms in each study.

Adverse effects

Adverse effect data from RCTs included in this review

In terms of the celecoxib studies included in this review, serious cardiovascular events were more frequent in the celecoxib groups than the placebo groups; this was significant in the Bertagnolli study⁶⁴ whereas there was a non-significant increase in the Arber study.⁶³ Both trials were stopped early because of this increased cardiovascular risk. Rates of gastrointestinal ulceration or haemorrhage were slightly, but not significantly, higher in the celecoxib groups in the Arber study,⁶³ but Bertagnolli reported no difference between the groups.⁶⁴ Renal or hypertensive disorders were significantly higher in the celecoxib group in the Arber study⁶³ and in one of the two celecoxib groups in the Bertagnolli study.⁶⁴ In the Ladenheim study of sulindac, four of 22 patients (18%) discontinued sulindac because of adverse events, three of which were thought to be related to sulindac (one anaemia, two moderate-to-severe heartburn) and one was thought to be unrelated (urosepsis); none of the 22 (0%) patients discontinued placebo.⁹⁰

Systematic reviews of adverse effects of NSAIDs

There is a large existing literature regarding adverse effects of NSAIDs. A previous systematic review of non-aspirin NSAIDs for chemoprevention of CRC prepared by Rostom *et al.* on behalf of the US Preventive Services Task Force provides a summary of systematic reviews assessing adverse effects associated with NSAID use.⁸⁸ These data are summarised below.

All-cause and cardiovascular-specific mortality were not shown to be statistically significantly affected in the majority of reviews. Three reviews demonstrated an increased risk of serious cardiovascular events associated with COX-2 inhibitors; this risk was greatest in patients at higher cardiovascular risk. Six reviews demonstrated statistically significant increases in risk of acute myocardial infarction with COX-2 inhibitors. Five reviews demonstrated no statistically significant increase in risk of stroke with COX-2 inhibitors. Two COX-2 inhibitors, rofecoxib and valdecoxib, were recently withdrawn from use because of concerns about their cardiovascular toxicity. The risks of hypertension and renal toxicity may also be increased with COX-2 inhibitors.⁸⁸

In terms of NSAIDs as a whole, the systematic reviews summarised by Rostom *et al.*⁸⁸ reported increased risk of peptic ulceration

and gastrointestinal haemorrhage with non-aspirin NSAID use. The increase in absolute risk of complicated peptic ulcers (perforation, obstruction or bleeding) was 0.48% across RCTs and 0.22% across cohort studies, with a higher risk in individuals who were older or had a history of peptic ulcers or cardiovascular disease. The risk for upper gastrointestinal toxicity as a result of NSAID use can be reduced through use of a gastroprotective agent such as misoprostol. Twelve systematic reviews assessed gastrointestinal adverse effects of COX-2 inhibitors specifically (as opposed to all NSAIDs). Several of these reviews demonstrated no statistically significant difference in gastrointestinal bleeding or ulceration with COX-2 inhibitors compared with placebo. One review demonstrated a statistically significant increase in risk of ulcers in patients receiving celecoxib at a dose of 400 mg/day, but not at a dose of 200 mg/day. A trial of rofecoxib reported an increase in risk of peptic ulceration.⁸⁸

Ongoing studies

An ongoing phase 3 RCT is assessing celecoxib versus placebo for prevention of adenoma incidence in participants with a history of resected stage 1 colon cancer (adenocarcinoma), and aims to enrol 1200 participants, with a treatment duration of 3 years; follow-up duration not specified (www.cancer.gov/clinicaltrials/NSABP-P-3; www.clinicaltrials.gov/NCT00087256).

Excluded studies

A study by Meyskens *et al.* assessed sulindac plus DFMO (or eflornithine) versus placebo in participants with a history of adenomas.¹⁵⁴ DFMO inhibits synthesis of polyamines which are involved in cell proliferation, inhibits colon carcinogenesis in animal models, and may act additively with sulindac. This study was excluded because the availability of oral DFMO is restricted (DFMO is available as a cream for hair removal).

A study by Baron *et al.* of rofecoxib versus placebo in participants with a history of adenomas¹⁵³ was excluded because its licence has been revoked and it has been withdrawn from the market.⁴⁷

Non-aspirin NSAIDs: low-risk population (general population or no increased risk of colorectal cancer)

No relevant published or ongoing studies were identified investigating NSAID use in populations without increased risk of CRC.

Summary of results for non-aspirin NSAIDs

In terms of non-aspirin NSAIDs, two studies of celecoxib (400 mg/day) in individuals with a history of adenomas demonstrated a statistically significant 34% reduction in the relative risk of adenoma recurrence and a statistically significant 55% reduction in the relative risk of advanced adenoma incidence. There were insufficient data to analyse the effect on CRC incidence. A small study of sulindac in patients with the FAP genotype showed a non-statistically significant reduction in adenoma incidence, whereas five studies of NSAIDs (sulindac, celecoxib or tiracoxib) in FAP patients with existing adenomas demonstrated reductions in polyp number and size, some statistically significant. The two celecoxib trials in individuals with a history of adenomas were stopped early because of an increased risk of serious cardiovascular events, which was statistically significant in one of the studies. A review that collated systematic reviews of adverse effects⁸⁸ also demonstrated increased risk of serious cardiovascular events with COX-2 inhibitors, the risk being greatest in patients with pre-existing cardiovascular risk factors. Two COX-2 inhibitors, rofecoxib and valdecoxib, were recently withdrawn from use because of concerns about their cardiovascular toxicity; a study of rofecoxib was therefore excluded from this review. COX-2 inhibitors may also increase the risks of hypertension and renal toxicity. NSAIDs can also cause upper gastrointestinal toxicity, although the risk is lower for COX-2 inhibitors than for some other types of NSAID.

Results: folic acid

Folic acid: high-risk population (FAP or HNPCC)

No studies were identified that investigated the use of folic acid as a chemopreventive agent within high-risk populations for CRC (i.e. FAP and HNPCC).

Folic acid: intermediate-risk population (history of adenomas)

Study and population characteristics

Three studies that compared folic acid with a control group were identified (*Table 15*). The study by Logan *et al.* was UK-based,⁶⁰ whereas the other two were USA-based. Two were multicentre studies randomising 945 participants (Logan)⁶⁰

and 1021 participants (Cole *et al.*).^{61,73,74} The third trial was a single-centre study that randomised 137 participants (Jaszewski *et al.*).¹⁰⁸

In all three study populations, subjects were eligible if they had a history of adenomas. The mean age reported ranged from 56 to 62 years across all study groups. Lower and upper age ranges were not reported in any of the trials.

Jaszewski conducted a comparison of folic acid versus placebo.¹⁰⁸ The other two trials conducted 2 × 2 or 3 × 2 factorial comparisons using aspirin as a co-intervention or comparator. Folic acid doses in the three studies were 0.5 mg/day (Logan),⁶⁰ 1 mg/day (Cole)⁶¹ and 5 mg/day (Jaszewski).¹⁰⁸ In the Jaszewski study,¹⁰⁸ folic acid at 5 mg/day was compared with placebo. The interventions in the Logan study were folic acid alone (0.5 mg/day) and folic acid plus aspirin (300 mg/day); controls were aspirin alone or placebo.⁶⁰ Interventions in the Cole study were folic acid alone (1 mg/day) and folic acid plus aspirin (85 mg/day or 325 mg/day); controls were aspirin alone or placebo.⁶¹ The duration of treatment in all three trials was 3 years. The follow-up of participants in all three trials was 3 years.

Quality assessment

Allocation concealment was adequate in two studies (Cole and Logan)^{60,61} and unclear in the third (Jaszewski)¹⁰⁸ (see Appendix 2, Table 53). In terms of randomisation, two studies used a

central, computer-generated randomisation sequence (Logan and Cole),^{60,61} stratified block randomisation was used in the third study (Jaszewski).¹⁰⁸ All three studies reported blinding of patients and carers; one study also reported blinding of analysts.⁶⁰ The methods of blinding were adequate in two studies, and unclear in the Jaszewski study. All studies experienced attrition. Attrition rates were 10% or less in two studies (Cole and Logan),^{60,61} and more than 20% in the Jaszewski study.¹⁰⁸ Intention-to-treat analyses were performed within all three studies. Power calculations were performed in two studies (Cole and Logan); however, the required sample size was not achieved for the designated outcome within the Logan study.⁶⁰ The Jaszewski study¹⁰⁸ did not involve a power calculation and, in this study, the numbers of patients in each arm were not reported consistently. All within-study groups appear to be comparable at baseline.

Outcome data

Effectiveness

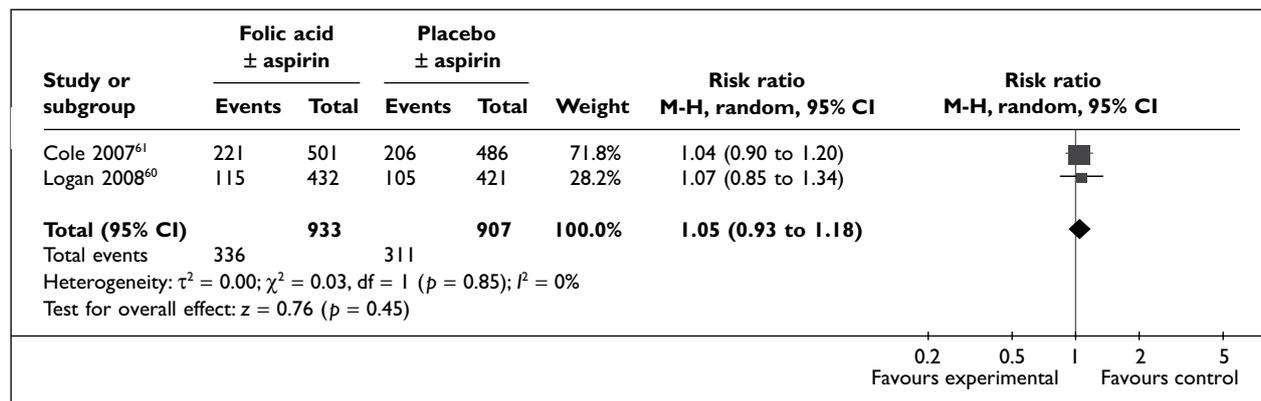
Effectiveness results for folic acid in the intermediate risk population (history of adenomas) are shown in Figure 6 and Table 16.

The Jaszewski study did not report event data (only mean numbers of adenomas) and was therefore excluded from meta-analysis.¹⁰⁸ The Cole study 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,

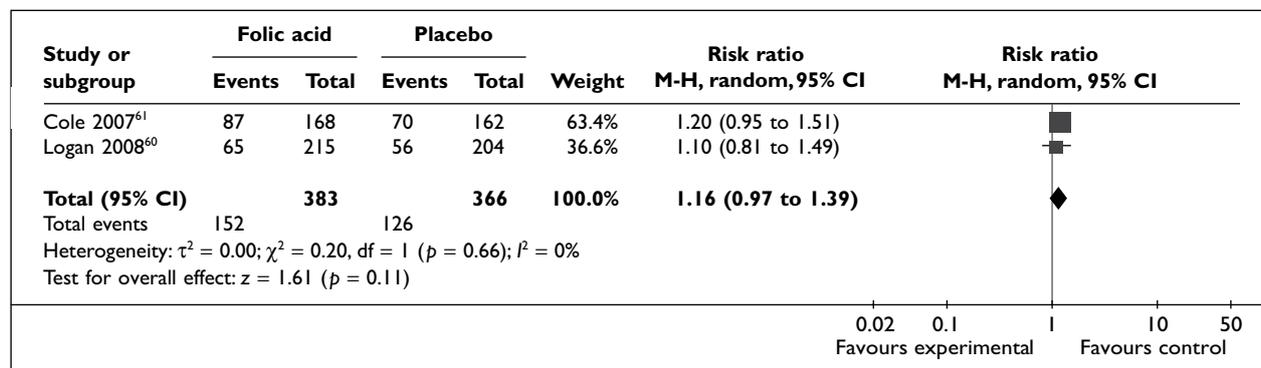
TABLE 15 Folic acid: study characteristics (history of adenomas)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Jaszewski 2008 ¹⁰⁸	History of adenomas, but not FAP or HNPCC Age 18–80 years eligible	Folic acid 5 mg/day (n=80)	Placebo 5 mg/day (n=97)	3 years	3 years
Logan 2008 (ukCAP trial: United Kingdom Colorectal Adenoma Prevention) ⁶⁰	History of adenomas, but not FAP or HNPCC Age < 75 years eligible (mean 58, range 28–75)	Folic acid 0.5 mg/day (n=234) Folic acid 0.5 mg/day + aspirin 300 mg/day (n=236)	Placebo only (n=233) Aspirin 300 mg/day (n=236)	3 years	3 years
Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	History of adenomas, but not FAP or HNPCC Age 21–80 years eligible (mean 57 or 58 in all groups)	Folic acid 1 mg/day only (n=170) Folic acid 1 mg/day + aspirin 81 mg/day (n=175) Folic acid 1 mg/day + aspirin 325 mg/day (n=171)	Placebo only (n=169) Aspirin 81 mg/day (n=169) Aspirin 325 mg/day (n=167)	3 years	3 years

(a) Recurrence of any adenoma (i)



(a) (ii)



(a) (iii)

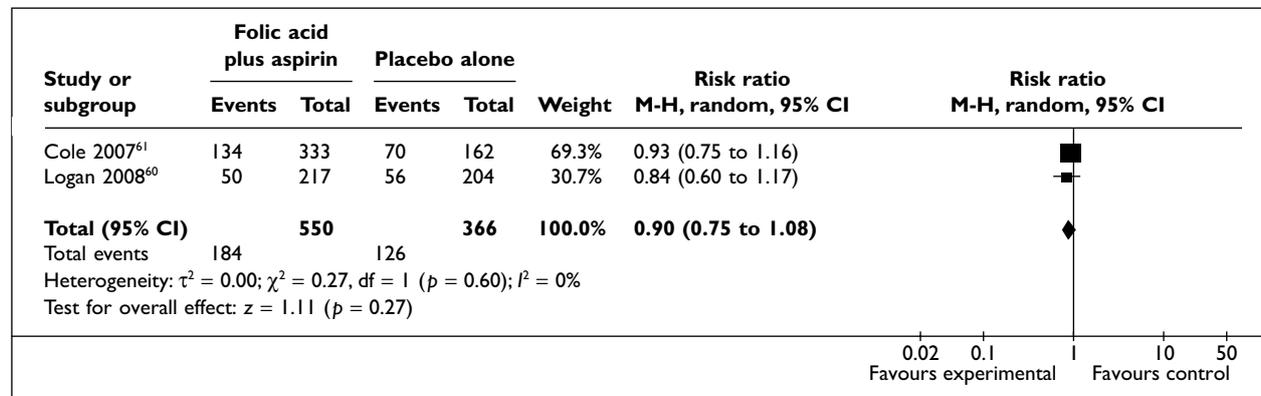


FIGURE 6 Folic acid: meta-analyses (history of adenomas). (a) Recurrence of any adenoma: (i) folic acid ± aspirin versus placebo ± aspirin, (ii) folic acid alone versus placebo alone, (iii) folic acid+ aspirin versus placebo alone; (b) Incidence of advanced adenoma: (i) folic acid ± aspirin versus placebo ± aspirin, (ii) folic acid alone versus placebo alone, (iii) folic acid+ aspirin versus placebo alone; (c) Incidence of colorectal cancer: folic acid ± aspirin versus placebo ± aspirin.

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.

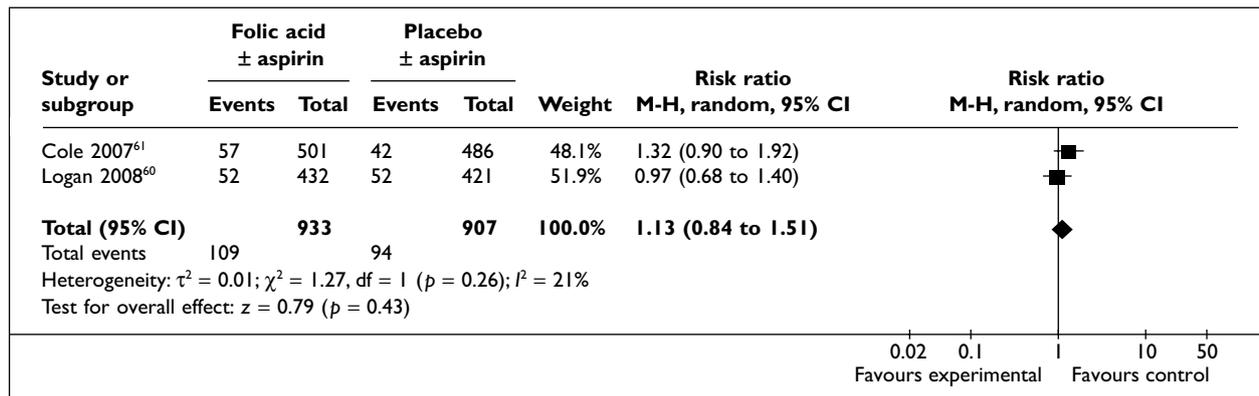
Recurrence of any adenoma

Two studies (Logan and Cole; 1840 participants in analysis) compared folic acid (with or without aspirin) versus no folic acid (Figure 6ai).^{60,61} The relative risk and absolute risk difference for

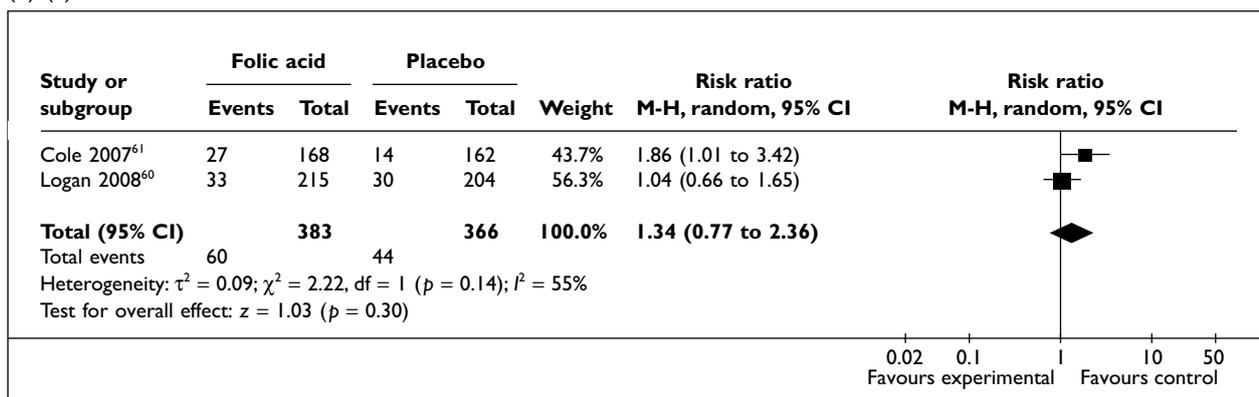
developing an adenoma of any type were not statistically significant at the 5% level (meta-analysed RR 1.05, 95% CI 0.93 to 1.18, $p = 0.45$; RD 0.02, 95% CI -0.03 to 0.06, $p = 0.43$), and there was no statistical heterogeneity ($I^2 = 0\%$).

Two studies (Logan and Cole; 749 participants in analysis) compared folic acid alone versus placebo (Figure 6aii).^{60,61} The relative risk and absolute risk difference for developing an adenoma of any type

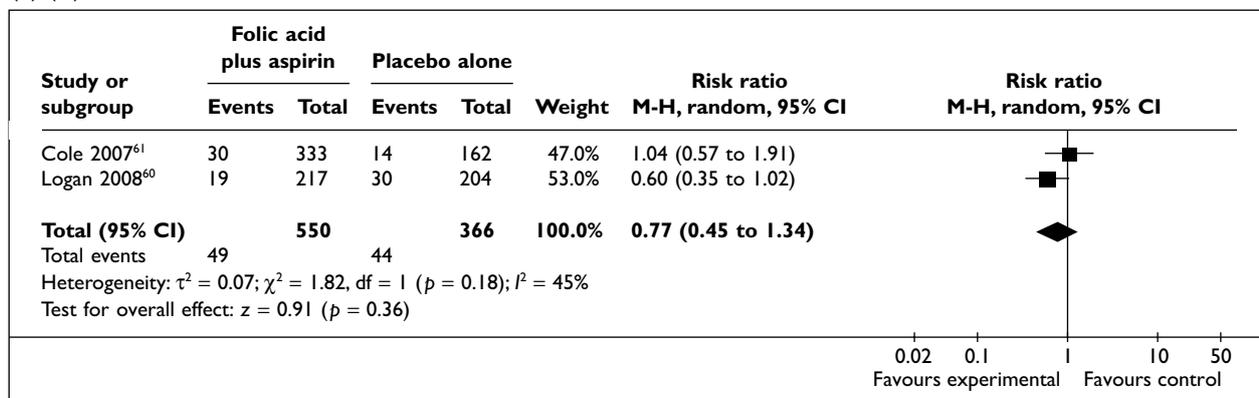
(b) Incidence of advanced adenoma (i)



(b) (ii)



(b) (iii)



(c) Incidence of colorectal cancer

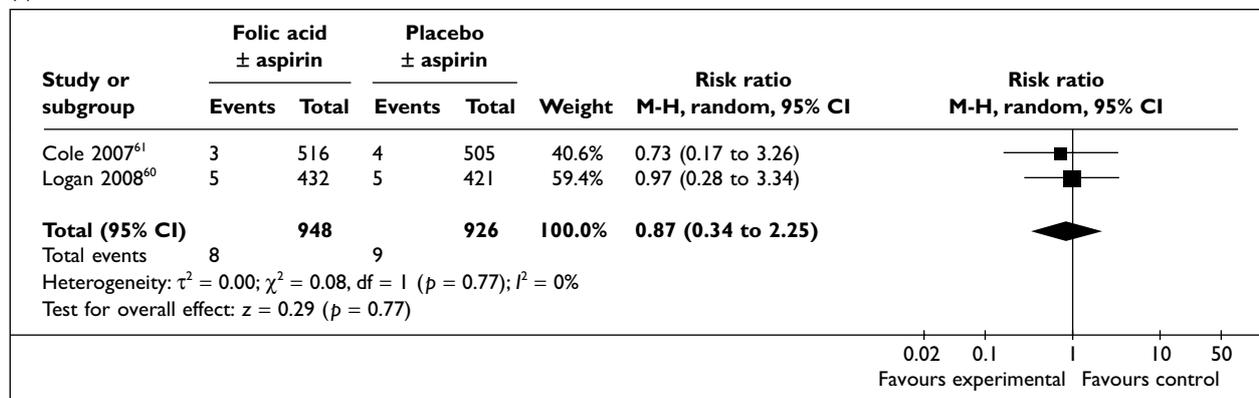


FIGURE 6 (continued) Folic acid: meta-analyses (history of adenomas). (a) Recurrence of any adenoma: (i) folic acid ± aspirin versus placebo ± aspirin, (ii) folic acid alone versus placebo alone, (iii) folic acid + aspirin versus placebo alone; (b) Incidence of advanced adenoma: (i) folic acid ± aspirin versus placebo ± aspirin, (ii) folic acid alone versus placebo alone, (iii) folic acid + aspirin versus placebo alone; (c) Incidence of colorectal cancer: folic acid ± aspirin versus placebo ± aspirin.

TABLE 16 Folic acid: summary of results (history of adenomas)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Recurrence of any adenoma																		
Cole, ^{61,73,74} Logan ⁶⁰	Any folic acid (0.5–1 mg/day) (± aspirin 81–325 mg/day)	No folic acid (± aspirin)	Adenoma (two high-quality studies)	2	3	336	933	311	907	1.05	0.93	1.18	0	0.02	-0.03	0.06	0	
Cole, ^{61,73,74} Logan ⁶⁰	Folic acid alone (0.5–1 mg/day)	Placebo alone	Adenoma (two high-quality studies)	2	3	152	383	126	366	1.16	0.97	1.39	0	0.05	-0.02	0.12	0	
Cole, ^{61,73,74} Logan ⁶⁰	Folic acid (0.5–1 mg/day) + aspirin (81–325 mg/day)	Placebo alone	Adenoma	2	3	184	550	126	366	0.90	0.75	1.08	0	-0.04	-0.10	0.02	0	
Incidence of advanced adenoma																		
Cole, ^{61,73,74} Logan ⁶⁰	Any folic acid (0.5–1 mg/day) (± aspirin 81–325 mg/day)	No folic acid (± aspirin)	Advanced adenoma	2	3	109	933	94	907	1.13	0.84	1.51	21	0.01	-0.02	0.04	8	
Cole, ^{61,73,74} Logan ⁶⁰	Folic acid alone (0.5–1 mg/day)	Placebo alone	Advanced adenoma	2	3	60	383	44	366	1.34	0.77	2.36	55	0.04	-0.03	0.11	46	
Cole, ^{61,73,74} Logan ⁶⁰	Folic acid (0.5–1 mg/day) + aspirin (81–325 mg/day)	Placebo alone	Advanced adenoma	2	3	49	550	44	366	0.77	0.45	1.34	45	-0.03	-0.09	0.04	58	
Incidence of colorectal cancer																		
Cole, ^{61,73,74} Logan ⁶⁰	Any folic acid (0.5–1 mg/day) (± aspirin 81–325 mg/day)	No folic acid (± aspirin)	CRC	2	3	8	948	9	926	0.87	0.34	2.25	0	0.00	-0.01	0.01	0	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

were not statistically significant at the 5% level, as demonstrated in a meta-analysis (RR 1.16, 95% CI 0.97 to 1.39, $p = 0.11$; RD 0.05, 95% CI -0.02 to 0.12, $p = 0.14$), and there was no statistical heterogeneity ($I^2 = 0\%$).

Two studies (Logan and Cole; 916 participants in analysis) compared folic acid plus aspirin versus placebo (Figure 6a_{iii}).^{60,61} The relative risk and absolute risk difference for developing an adenoma of any type were not statistically significant at the 5% level, as demonstrated in a meta-analysis (RR 0.90, 95% CI 0.75 to 1.08, $p = 0.27$; RD -0.04, 95% CI -0.10 to 0.02, $p = 0.23$), and there was no statistical heterogeneity ($I^2 = 0\%$).

A third, lower-quality, smaller study (Jaszewski; 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 to 0.84, $p = 0.025$).¹⁰⁸

Incidence of advanced adenoma

Two studies (Logan and Cole; 1840 participants in analysis) compared folic acid (with or without aspirin) versus no folic acid (Figure 6b_i).^{60,61} The relative and absolute risk difference between groups for developing an advanced adenoma were not statistically significant at the 5% level (meta-analysed RR 1.13, 95% CI 0.84 to 1.51, $p = 0.43$; RD 0.01, 95% CI -0.02 to 0.04, $p = 0.034$), and these suggested moderate and low levels of statistical heterogeneity ($I^2 = 21\%$ and 8%) respectively.

Two studies (Logan and Cole; 749 participants in analysis) compared folic acid alone versus placebo (Figure 6b_{ii}).^{60,61} The relative and absolute risk differences between groups for developing an advanced adenoma were not statistically significant at the 5% level (meta-analysed RR 1.34, 95% CI 0.77 to 2.36, $p = 0.30$; RD 0.04, 95% CI -0.03 to 0.11, $p = 0.24$). These were subject to high ($I^2 = 55\%$) and moderate ($I^2 = 46\%$) levels of statistical heterogeneity respectively.

Two studies (Logan and Cole; 916 participants included in the analysis) compared folic acid plus aspirin versus placebo (Figure 6b_{iii}).^{60,61} The relative and absolute risk differences between groups for developing an advanced adenoma were not statistically significant at the 5% level (meta-analysed RR 0.77, 95% CI 0.45 to 1.34, $p = 0.36$; RD -0.03, 95% CI -0.09 to 0.04, $p = 0.41$). These analyses suggested moderate ($I^2 = 45\%$) and

high ($I^2 = 58\%$) levels of statistical heterogeneity respectively.

Incidence of colorectal cancer

Two studies (Logan and Cole; 1874 participants included in the analysis) compared folic acid with or without aspirin versus controls without folic acid (Figure 6c).^{60,61} The differences in the relative and absolute risks of developing CRC were not statistically significant at the 5% level (meta-analysed RR 0.87, 95% CI 0.34 to 2.25, $p = 0.77$; RD 0.00, 95% CI -0.01 to 0.01, $p = 0.72$), and there was no statistical heterogeneity ($I^2 = 0\%$). These results should be interpreted with caution because of the relatively short follow-up duration and the low event rate (total of eight cases in the folic acid arms and nine cases in the control arms).

Compliance

Two studies (Logan and Cole) reported a compliance rate of between 87 and 90%.^{60,61} The Jaszewski study required at least 90% of pills to be taken, but results were not reported for the trial period.¹⁰⁸ Compliance was measured by periodic self-report in two studies^{60,61} and pill counting in two studies.^{60,108}

Adverse effects

Two studies (Logan and Cole) reported on serious adverse events.^{60,61} Neither study reported any significant differences between folate and non-folate groups in terms of death, bleeding, stroke, myocardial infarction, vascular events or dyspepsia. The Logan study reported no difference between groups for non-CRC but the Cole study did report a significant difference: incidence of non-CRC was higher in the folic acid (54/516) than the placebo group (32/505), $p = 0.02$. However, authors reported that this was a result of the high baseline rate of prostate cancer in the folic acid group (24/516 vs 9/505, $p = 0.01$).

Ongoing studies

Two ongoing studies are assessing folic acid for prevention of adenomas in participants with a history of adenomas (www.clinicaltrials.gov, NCT00512850 and NCT00002650). One aims to enrol 1000 participants and has a planned follow-up duration of 4 years (NCT00512850). Another small study (80 participants planned) aims to assess the effect of high-dose folic acid (dose not specified), with treatment and follow-up durations of 1 year (NCT00002650).

TABLE 17 Folic acid: study characteristics (general population or low-risk population)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Zhang 2008 (Women's Antioxidant and Folic Acid Cardiovascular Study: WAFACS) ¹⁰⁵	Women with or at high risk of cardiovascular disease Age >40 years (mean 63 years)	Folic acid 2.5 mg/day, vitamin B ₆ 50 mg/day, vitamin B ₁₂ 1 mg/day (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) ^{106,107}	History of vascular disease or diabetes or risk of atherosclerosis Age 55 years or older (mean 69 years)	Folic acid 2.5 mg/day, vitamin B ₆ 50 mg/day, vitamin B ₁₂ 1 mg/day (n=2758) Some participants also received antioxidants	Placebo (n=2764)	5 years	5 years
Zhu 2003 ^{109,110}	Patients with atrophic gastritis Age 28–77 years eligible (mean 55–57 years in all groups)	Folic acid 20 mg/day for 1 year then 20 mg twice weekly for 1 year; vitamin B ₁₂ 1 mg/month for 1 year then 1 mg every 3 months for 1 year (n=44)	Placebo (n=54) Beta-carotene (natural), 30 mg/day for 1 year then 30 mg twice/week for 1 year (n=61) Beta-carotene (synthetic), doses as above (n=57)	2 years	6 years

WACS, Women's Antioxidant Cardiovascular Study.

Excluded studies

No additional studies of folic acid in the intermediate risk population were excluded on final examination of the full text.

Folic acid: low-risk population (general population or no increased risk of colorectal cancer)

Study and population characteristics

Three studies were identified that compared a folic acid intervention with a control group (Table 17).

None of the studies were based in the UK; one study (Lonn *et al.*) was international including Canada, USA, Brazil, Slovakia and Western Europe;^{106,107} one study (Zhang *et al.*) was USA-based;¹⁰⁵ and one study (Zhu *et al.*) was based in China.^{109,110} All three were multicentre studies; the Zhu study randomised 216 patients,^{109,110} whereas the studies reported by Zhang¹⁰⁵ and Lonn^{106,107} were larger, randomising 5442 and 5522 participants, respectively.

Within all studies, the populations had no history of CRC or any risk greater than that of the general population. In the Lonn study, the population was composed of individuals with a history of vascular disease, diabetes or risk of atherosclerosis;¹⁰⁶ in the Zhang study, postmenopausal women aged 40 or over with a history of cardiovascular disease or at least three coronary risk factors;¹⁰⁵ and in the Zhu study, the population had atrophic gastritis.¹⁰⁹ The mean age reported in the three studies ranged from 55 to 69 years. The lower and upper age ranges were not reported.

All three trials included comparisons with placebo. In the two larger studies (Zhang and Lonn), folic acid (2.5 mg/day) plus vitamin B₆ (50 mg/day), and vitamin B₁₂ (1 mg/day) was compared with placebo.^{105,106} In the Zhu study, folic acid (20 mg/day) for 1 year, then 20 mg twice weekly for 1 year, were compared with placebo.¹⁰⁹ The duration of treatment ranged from 2 to 5 years. The follow-up of participants ranged from 5 to 7 years.

Quality assessment

Allocation concealment was considered adequate in one study (Lonn)^{106,107} and unclear in the other two studies (see Appendix 2, Table 53). In terms of randomisation, Lonn used a central, computer-generated randomisation sequence; the method of randomisation was unclear in the other two studies. Two studies reported blinding of patients, carers and investigators (Lonn and Zhang);¹⁰⁵⁻¹⁰⁷ however, blinding methods were only described in the Lonn study. Blinding was unclear in the study reported by Zhu.¹⁰⁹ In all three studies, fewer than 5% of the randomised participants were excluded from the analysis of participants with adenomas, and all three studies applied an intention-to-treat analysis. A power calculation was performed by Zhang and the required sample size was achieved for the designated outcome.¹⁰⁵ Lonn only performed a power calculation for the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction and stroke; no calculation was performed for secondary outcomes,

which included CRC.¹⁰⁷ Zhu did not perform a power calculation.¹⁰⁹

Outcome data

Effectiveness

Effectiveness results for folic acid in the general population (or populations with no increased risk for CRC) are shown in Figure 7 and Table 18.

Incidence of any adenoma

No studies of folic acid in the general population reported adenoma incidence.

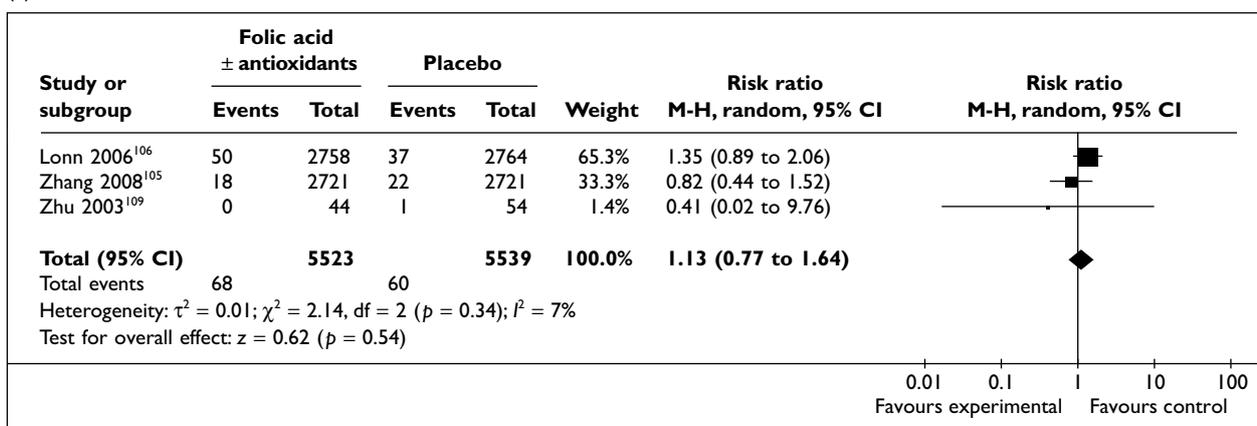
Incidence of advanced adenoma

No studies of folic acid in the general population reported advanced adenoma incidence.

Incidence of colorectal cancer

Three studies (11,062 participants in analysis) compared folic acid plus B vitamins (with or without antioxidants) versus placebo (\pm antioxidants; Figure 7a).^{105,106,109} A meta-analysis

(a)



(b)

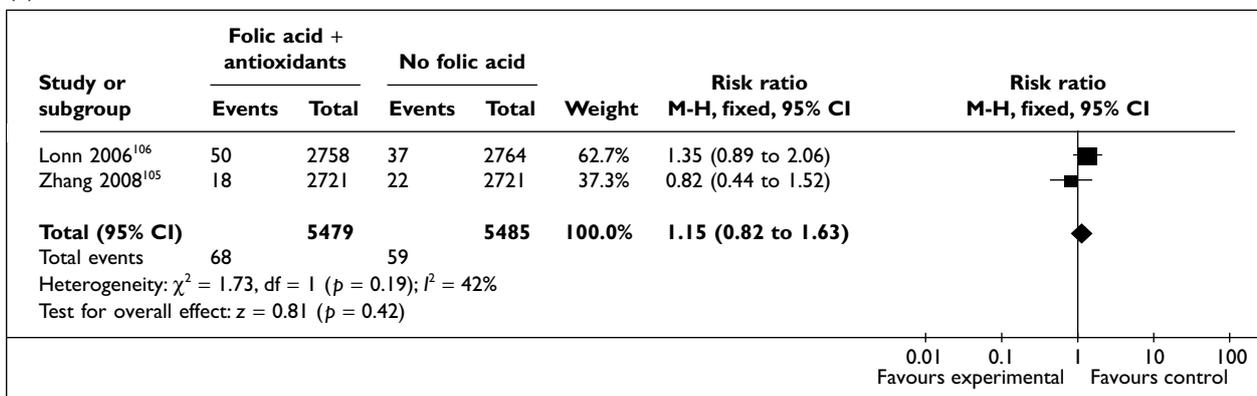


FIGURE 7 Folic acid: meta-analyses (general population or low-risk population). Incidence of colorectal cancer: (a) folic acid + vitamin B₁₂ \pm vitamin B₆ \pm antioxidants versus placebo \pm antioxidants: low risk, (b) folic acid + vitamin B₁₂ + vitamin B₆ + antioxidants versus placebo + antioxidants: low risk.

TABLE 18 Folic acid: summary of results (general population or low-risk population)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Incidence of colorectal cancer																		
Lonn, ^{106,107} Zhang, ¹⁰⁵ Zhu ^{109,110}	Any folic acid (2.5 mg/day to 20 mg/day) (+ B vitamins ± antioxidants)	No folic acid (± antioxidants)	CRC	3	5+6+7	68	5523	60	5539	1.13	0.77	1.64	7	0.00	0.00	0.01	36	
Lonn, ^{106,107} Zhang ⁰⁵	Folic acid (2.5 mg/day) + vitamin B ₆ + vitamin B ₁₂ + antioxidants	Placebo + antioxidants	CRC	2	5+7	68	5479	59	5485	1.15	0.82	1.63	42	0.00	0.00	0.01	63	
Zhu ^{109,110}	Folic acid alone (20 mg/day for 1 year then 20 mg twice weekly for next year)	Placebo alone	CRC	1	6	0	44	1	54	0.41	0.02	9.76	N/C	-0.02	-0.07	0.03	N/C	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

demonstrated that the relative and absolute risk differences between groups for developing CRC were not statistically significant at the 5% level (RR 1.13, 95% CI 0.77 to 1.64, $p = 0.54$; RD 0.00, 95% CI 0.00 to 0.01, $p = 0.76$). There were low ($I^2 = 7%$) and moderate ($I^2 = 36%$) levels of statistical heterogeneity, respectively.

Two studies (Zhang and Lonn; 10,964 participants in analysis) compared folic acid plus B vitamins plus antioxidants versus placebo (\pm antioxidants; *Figure 7b*).^{105,106} The relative and absolute risk differences between groups for developing CRC were not statistically significant at the 5% level, as demonstrated in a meta-analysis (RR 1.15, 95% CI 0.82 to 1.63, $p = 0.42$; RD 0.00, 95% CI 0.00 to 0.01, $p = 0.42$). The analyses of relative and absolute risk suggested moderate ($I^2 = 42%$) and high ($I^2 = 63%$) levels of statistical heterogeneity, respectively.

One study (Zhu; 98 participants in analysis) compared folic acid plus B vitamins versus placebo alone.¹⁰⁹ There was one case of CRC among 54 participants receiving placebo, and 0 cases among 44 participants receiving folic acid.

Compliance

Two studies (Lonn and Zhu) reported that at least 90% of pills were taken as required in the intervention groups over the treatment period.^{106,109} Compliance was measured by pill counting in two studies (Lonn and Zhu), by self-report in two studies (Lonn and Zhang) and serum concentration levels in one study (Zhu). In the Zhang study, compliance, defined as taking at least 66% of pills, was 83% over the study period by the intervention group.¹⁰⁵

Adverse effects

None of the studies reported any serious adverse events associated with the study treatments.

Ongoing studies

No ongoing studies of folic acid in the low-risk population were identified.

Excluded studies

No additional studies of folic acid in the low-risk population were excluded on final examination of the full text.

Summary of results for folic acid

Two studies of folic acid (0.5–1.0 mg/day) in individuals with a history of adenomas showed no statistically significant difference in the relative risk of adenoma recurrence or advanced adenoma incidence, with the event rates actually being slightly higher in the folic acid groups. Three studies of folic acid (2.5 mg/day in two studies and 20 mg/day in one study) in populations with no increased baseline risk of CRC demonstrated no statistically significant effect of folic acid on the relative risk of CRC, with the rates being slightly higher in individuals receiving folic acid. However, the duration of follow-up was 5–7 years, which may not be long enough to detect an effect on cancer incidence. No studies reported any difference in serious adverse event rates between the folic acid and placebo groups (except for one study reporting a higher incidence of cancers other than those of the colorectum in the folic acid group, which was thought to be the result of the higher baseline rate of prostate cancer in that group).

Results: calcium and/or vitamin D

Calcium and/or vitamin D: high-risk population (FAP or HNPCC)

Study and population characteristics

No previous systematic reviews of calcium or vitamin D in FAP or HNPCC patients were

TABLE 19 Calcium: study characteristics (FAP/HNPCC patients)

Study	Population and age	Intervention	Control	Treatment duration	Follow-up duration
Secondary prevention (assessing reduction in adenoma burden)					
Thomas 1993 ⁹⁵	FAP patients with previous colectomy and adenomas	Calcium carbonate 1500 mg/day ($n = \text{unclear}$)	Placebo ($n = \text{unclear}$)	6 months	6 months

identified. The electronic searches identified one eligible controlled trial comparing calcium with placebo (Thomas *et al.*; Table 19).⁹⁵ This single-centre study randomised 28 participants, recruiting people with FAP (median age 38 years; range 16 to 65) who had previously undergone total abdominal colectomy with ileorectal anastomosis who were under surveillance for rectal polyps. Subjects in the intervention arm were given calcium carbonate (1500 mg daily) for a 6-month period.

Quality assessment

The methods by which the allocation sequence was generated and concealed were unclear (see Appendix 2, Table 54). The trial was described as double blind. Three of the 28 randomised participants (11%) were excluded from the analysis of polyp counts for failing to take all of their tablets and it is unclear how many were randomised to or analysed from each arm.

Outcome data

Effectiveness

Any adenoma: number and size

The number of participants analysed in each arm was not reported in the study publication, hence it was not possible to calculate the difference between the mean change in the number of rectal polyps for participants receiving calcium and placebo. The authors reported that the effect on oral calcium on polyp number, progression and distribution was not statistically significant.

Advanced adenoma: number and size

The study reported by Thomas⁹⁵ did not report the effect of calcium carbonate on the number of advanced adenomas.

TABLE 20 Calcium: study characteristics (history of adenomas)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Bonithon-Kopp 2000 ⁹⁶	History of adenomas Age 35–75 years eligible (mean 59 years)	Calcium 2000 mg/day (n = 218)	Placebo (n = 221)	3 years	3 years
Baron 1999 (Calcium Polyp Prevention Study) ^{99,100}	History of adenomas Age ≤80 years eligible (mean 61 years)	Calcium 1200 mg/day (n = 464)	Placebo (n = 466)	4 years	4 years (analysed from end Y1 to end Y4)
Hofstad 1998 ^{103,104}	History of adenomas (polyps left <i>in situ</i>) Age 50–76 years eligible	Calcium 1600 mg/day + beta-carotene 15 mg/day + vitamin C 150 mg/day + vitamin E 75 mg/day + selenium 101 µg/day (n = 42)	Placebo (n = 51)	3 years	3 years

Incidence of colorectal cancer

The study reported by Thomas⁹⁵ did not report the effect of calcium carbonate on the number of CRCs.

Compliance

The authors did not define compliance. Three of 28 randomised participants were deemed to have been non-compliant.

Adverse effects

The authors stated that the tablets were well-tolerated in all subjects with no reported adverse side effects.

Ongoing studies

The study team are not aware of any ongoing studies of calcium in FAP or HNPCC patients.

Excluded studies

One study comparing the NSAID sulindac with calcium was excluded because the study was in the Chinese language and did not report any of our protocol-specified outcomes.¹⁵⁰

Calcium and/or vitamin D: intermediate-risk population (history of adenomas)

Study and population characteristics

Three studies compared calcium against a control group (Table 20). The study reported by Bonithon-Kopp *et al.* involved patients from 10 countries (nine in Europe, including the UK, plus Israel);⁹⁶ the study reported by Baron *et al.*

was USA-based;^{99,100} and the study reported by Hofstad *et al.* was based in Norway.^{103,104} All three were multicentre studies randomising between 116 participants (Hofstad)¹⁰³ and 930 participants (Baron).^{99,100}

In all three trial populations, people with a history of adenomas were eligible. The mean age in two studies ranged from 59 to 61 years. In the Hofstad study, the age range was 50 to 76 years.¹⁰³

Two studies (Baron and Bonithon-Kopp) employed comparisons of calcium against placebo^{96,99,100} but the Hofstad study administered a mixed intervention consisting of calcium (1600 mg/day) combined with beta-carotene (15 mg/day), vitamin C (150 mg/day), vitamin E (75 mg/day) and selenium (101 µg/day), compared with placebo.¹⁰³ The dose per day of calcium in all three studies ranged from 1200 mg (Baron)^{99,100} to 2000 mg (Bonithon-Kopp).⁹⁶ The duration of treatment and the follow-up of participants ranged from 3 to 4 years.

In addition, the effect of calcium on adenomas and CRC in the intermediate-risk population was analysed within a Cochrane systematic review by Weingarten *et al.*⁹⁸ and the effect on adenoma recurrence was meta-analysed by Shaukat *et al.*¹⁰²

Quality assessment

Allocation concealment was adequate in two studies (central allocation; Baron and Bonithon-Kopp)^{96,99,100} and unclear in the Hofstad study¹⁰³ (see Appendix 2, Table 54). In terms of randomisation, two studies used a computer-generated randomisation sequence; the method used in the Hofstad study was unclear. Two studies reported blinding of patients and analysts, with Bonithon-Kopp also blinding the study carers. Blinding was unclear in the Hofstad study. The methods of blinding were adequate in the Bonithon-Kopp study, and unclear in the other two studies. All studies experienced attrition. In all three studies, between 10 and 20% of randomised participants were excluded. Intention-to-treat analyses were performed in all three studies. Power calculations were performed in all three studies and in each case the required sample size was achieved.

Outcome data

Effectiveness

Effectiveness results for calcium in the intermediate-risk population (history of adenomas) are shown in Figure 8 and Table 21.

Recurrence of any adenoma

Two studies (Baron and Bonithon-Kopp; 1186 analysed participants) compared calcium alone with placebo (Figure 8a).^{96,99,100} A meta-analysis demonstrated an 18% relative reduction in the risk of developing an adenoma of any type for those taking calcium, and this was statistically significant at the 5% level (RR 0.82, 95% CI 0.69 to 0.98, $p = 0.03$). There was a 6% absolute reduction in the risk of developing an adenoma of any type (RD -0.06, 95% CI -0.11 to -0.01, $p = 0.03$) for those taking calcium. There was no statistical heterogeneity in either analysis ($I^2 = 0%$).

The third, smaller study (Hofstad; 93 participants in the analysis) reported that calcium plus antioxidants (vitamins C and E, beta-carotene and selenium) significantly reduced the risk of polyp recurrence compared with placebo. Event data were not reported but the odds ratio was reported as 0.31 (95% CI 0.11 to 0.84).¹⁰³

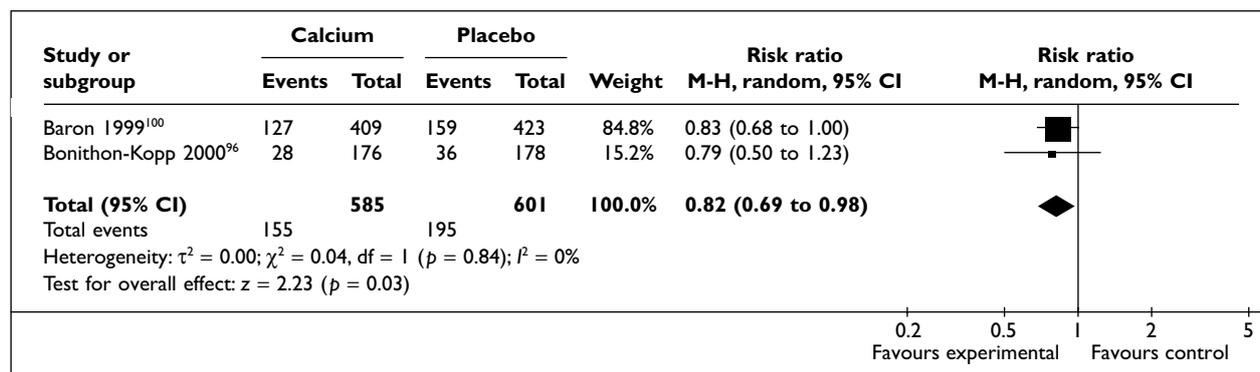
The study reported by Baron also presented follow-up data beyond the 4-year treatment period for participants with a subsequent colonoscopy; however, this was not controlled for post-trial calcium intake.¹⁵⁵ In the interval 0–5 years after the end of the trial (i.e. years 5–9 after the trial started), 347 patients had a further colonoscopy (37% of the 930 originally randomised) and the relative risk of adenoma was 0.63 (95% CI 0.46 to 0.87, $p = 0.005$). The calcium group therefore had a 37% relative reduction in the risk of an adenoma of any type, which was statistically significant at the 5% level. In the interval 6–10 years after the end of the trial (i.e. years 10–14 after the trial started), 424 patients had a further colonoscopy (46% of the 930 originally randomised) and the relative risk of adenoma was 1.09 (95% CI 0.85 to 1.39, $p = 0.511$), i.e. the reduction in risk was not shown to continue to this time point.

Incidence of advanced adenoma

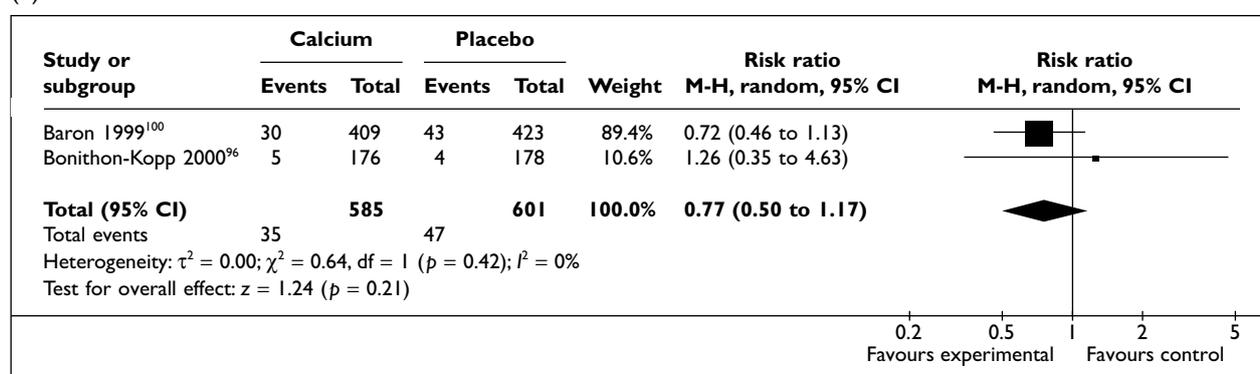
Two studies (Baron and Bonithon-Kopp; 1186 analysed participants) compared calcium alone with placebo (Figure 8b).^{96,99,100} The reductions in the relative and absolute risks of developing advanced adenoma were not statistically significant at the 5% level (meta-analysed RR 0.77, 95% CI 0.50 to 1.17, $p = 0.21$; RD -0.01, 95% CI -0.05 to 0.03, $p = 0.61$). The statistical heterogeneity was 0% for the relative risk and high (57%) for the risk difference.

The study reported by Baron also presented follow-up data beyond the 4-year treatment period

(a)



(b)



(c)

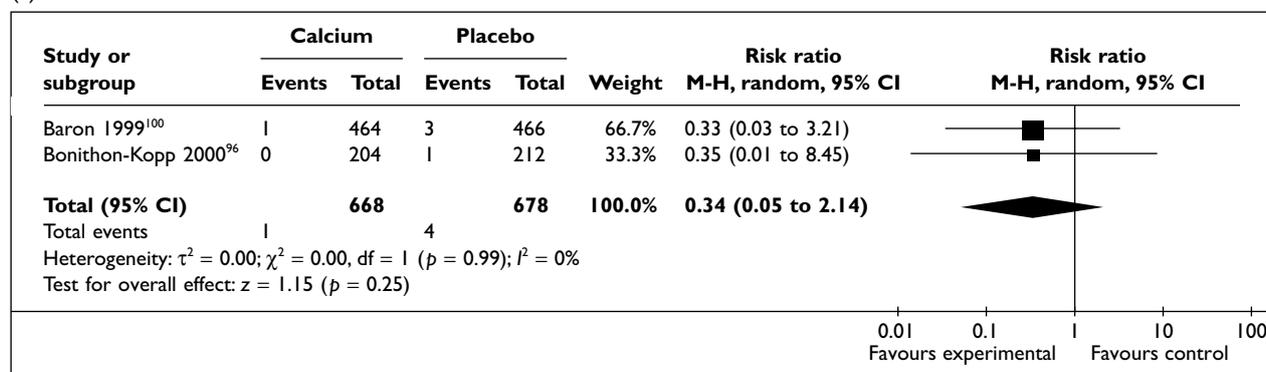


FIGURE 8 Calcium: meta-analyses (history of adenomas). (a) Recurrence of any adenoma: calcium alone versus placebo alone; (b) Incidence of advanced adenoma: calcium alone versus placebo alone; (c) Incidence of colorectal cancer: calcium alone versus placebo alone.

for participants with a subsequent colonoscopy; however, this was not controlled for post-trial calcium intake.¹⁵⁵ In the interval 0–5 years after the end of the trial (i.e. years 5–9 after the trial started), 347 patients had a further colonoscopy (37% of the 930 originally randomised) and the relative risk of advanced adenoma was 0.85 (95%CI 0.43 to 1.69, $p = 0.65$), which was not statistically significant at the 5% level. In the interval 6–10 years after the end of the trial (i.e. years

10–14 after the trial started), 424 patients had a further colonoscopy (46% of the 930 originally randomised) and the relative risk of advanced adenoma was 1.10 (95% CI 0.65 to 1.88, $p = 0.717$), which was not statistically significant at the 5% level.

Incidence of colorectal cancer

Two studies (Baron and Bonithon-Kopp; 1146 participants in analysis) compared calcium alone with placebo (Figure 8c).^{96,99,100} The reductions in

TABLE 21 Calcium: summary of results (history of adenomas)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Recurrence of any adenoma																		
Baron, ^{99,100} Bonithon-Kopp ⁹⁶	Calcium alone (1200–2000 mg/day)	Placebo alone	Adenoma	2	3	155	585	195	601	0.82	0.69	0.98	0	-0.06	-0.11	-0.01	0	
Incidence of advanced adenoma																		
Baron, ^{99,100} Bonithon-Kopp ⁹⁶	Calcium alone (1200–2000 mg/day)	Placebo alone	Advanced adenoma	2	3	35	585	47	601	0.77	0.50	1.17	0	-0.01	-0.05	0.03	57	
Incidence of colorectal cancer																		
Baron, ^{99,100} Bonithon-Kopp ⁹⁶	Calcium alone (1200–2000 mg/day)	Placebo alone	CRC	2	3	1	668	4	678	0.34	0.05	2.14	0	0.00	-0.01	0.00	0	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

the relative risk and absolute risk of developing CRC associated with calcium use were not statistically significant at the 5% level (meta-analysed RR 0.34, 95% CI 0.05 to 2.14, $p = 0.25$; RD 0.00, 95% CI -0.01 to 0.00, $p = 0.22$). There was no statistical heterogeneity in either analysis ($I^2 = 0\%$). These results should be interpreted with caution because of the relatively short follow-up duration and the low event rate (one of 668 in the calcium arms and four of 678 in the placebo arms).

Compliance

Compliance was measured by periodic self-report in two studies^{96,99,100} and by pill counting or renewal in two studies.^{96,103} Two studies reported that between 69 and 76% in the intervention group took 80% or more of pills.^{96,103} In the Bonithon-Kopp study, this was statistically significantly lower than the rate of compliance in the control group ($p = 0.04$).⁹⁶ The Baron study reported that at least 90% of pills were taken by between 79 and 85% of participants.^{99,100}

Adverse effects

The Bonithon-Kopp study reported a statistically significant difference between the calcium and placebo groups in terms of all side effects (26/176 vs 12/178, $p = 0.043$), yet there was no statistically significant difference in terms of the 'major side effects' of severe diarrhoea or abdominal pain (six of 176 vs three of 178, $p = 0.31$; p -value generated by reviewers).⁹⁶ The Hofstad study also reported the number of cases of diarrhoea and abdominal pain, but found no significant differences between groups (five versus seven and four versus four for intervention and control groups respectively).¹⁰³ The Baron study reported that 'medical symptoms

and complications were not associated with treatment assignment'.^{99,100}

Ongoing studies

An ongoing multicentre study is assessing aspirin, calcium and/or vitamin D (as a combination treatment) versus placebo for prevention of adenomas in participants with a history of adenomas, and aims to enrol 1000 participants, with a treatment duration of 3 years and follow-up at 3 and 5 years (www.clinicaltrials.gov, NCT00486512).

Excluded studies

No additional studies of calcium and/or vitamin D in the intermediate-risk population were excluded on final examination of the full papers.

Calcium and/or vitamin D: low-risk population (general population or no increased risk of colorectal cancer)

Study and population characteristics

Two studies were identified (Lappe and Wactawski-Wende *et al.*) which compared calcium or calcium plus vitamin D against a control group (Table 22).^{97,101} Both studies were USA-based. The number of centres involved was not reported, and the number of participants randomised was 1179 in the Lappe study⁹⁷ and 36,282 in the Wactawski-Wende study.¹⁰¹

The study population within both trials consisted of postmenopausal women. The mean age of women in the Wactawski-Wende study was 59 years,¹⁰¹ whereas the study reported by Lappe did not

TABLE 22 Calcium and/or vitamin D: study characteristics (general population or low-risk population)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Low risk population (general population or no increased risk of colorectal cancer)					
Lappe 2007 ⁹⁷	Post-menopausal women Age 55 years eligible	Calcium 1400–1500 mg/day (n=445) or Calcium 1400–1500 mg/day + vitamin D 1000–1100 IU/day (paper reports two different doses of vitamin D in abstract and text) (n=446)	Placebo (n=288)	4 years	4 years
Wactawski-Wende 2006 (Women's Health Initiative study) ¹⁰¹	Postmenopausal women Age 50–79 years eligible (mean 59 years)	Calcium 1000 mg/day + vitamin D 400 IU/day (n=18,176)	Placebo (n=18,106)	7 years	7 years

report a mean age but included women aged 55 years or over.⁹⁷

The trial reported by Wactawski-Wende employed a comparison of calcium plus vitamin D versus placebo,¹⁰¹ while the Lappe trial compared three groups: calcium alone, calcium plus vitamin D and placebo.⁹⁷ The dose per day of calcium ranged from 1000 mg¹⁰¹ to 1500 mg⁹⁷ and from 400 IU to 1000 IU dose per day of vitamin D₃. The control in each case was placebo. Both duration of treatment and follow-up of participants ranged from 4 to 7 years.

Quality assessment

Allocation concealment was adequate in the Wactawski-Wende study¹⁰¹ and unclear in the Lappe study⁹⁷ (see Appendix 2, Table 54). Both studies used a computer-generated, permuted-block algorithm randomisation sequence. The Wactawski-Wende study reported adequate blinding of patients and carers,¹⁰¹ but the methods of blinding were unclear in the Lappe study.⁹⁷ Both studies experienced attrition. In the Wactawski-Wende study, less than 5% of randomised participants were excluded,¹⁰¹ whereas in the Lappe study between 5 and 20% of randomised participants were excluded.⁹⁷ Intention-to-treat analyses were performed within both studies. A power calculation was performed in the Wactawski-Wende study and the required sample size was achieved¹⁰¹ but the Lappe study did not report a power calculation.⁹⁷

Outcome data

Effectiveness

Effectiveness results for calcium and/or vitamin D in the general population (or in populations with no increased risk for CRC) are shown in Figure 9 and Table 23.

Incidence of any adenoma

No studies of calcium in the general population assessed adenoma incidence.

Incidence of advanced adenoma

No studies of calcium in the general population assessed advanced adenoma incidence.

Incidence of colorectal cancer

Two studies (37,461 participants in analysis) compared calcium with or without vitamin D with placebo (Figure 9a).^{97,101} There was no statistically significant difference between groups in the relative risk of developing CRC (meta-analysed RR 0.62, 95% CI 0.11 to 3.40, $p = 0.58$); however, this analysis suggested a high level of statistical

heterogeneity ($I^2 = 58%$). There was no statistically significant difference between groups in the absolute risk of developing CRC (RD 0.00, 95% CI -0.01 to 0.00, $p = 0.80$), but there was a moderate level of statistical heterogeneity ($I^2 = 39%$).

One study (Lappe; 733 participants in analysis) compared calcium alone with placebo (Figure 9b).⁹⁷ The incidence of CRC was none of 445 in the calcium arm and two of 288 in the placebo arm.

Two studies (37,016 participants in analysis) compared calcium plus vitamin D with placebo (Figure 9c).^{97,101} The relative and absolute risk differences between groups for developing CRC were not statistically significant at the 5% level (meta-analysed RR 1.08, 95% CI 0.87 to 1.34, $p = 0.51$; RD 0.00, 95% CI 0.00 to 0.00, $p = 0.56$) and no statistical heterogeneity was evident ($I^2 = 0%$).

Data on CRC incidence in the studies of calcium should be interpreted with caution because of the relatively short follow-up durations in terms of detecting cancer outcomes (4 and 7 years in the two studies).

Compliance

The two studies reported a compliance rate (>80% of pills taken) in the intervention groups of ≥60% (Wactawski-Wende)¹⁰¹ or 74–86% (Lappe).⁹⁷ Compliance was measured by periodic weighing of pill bottles in both studies.

Adverse effects

Neither study reported any serious adverse events. There were no statistically significant differences between groups in terms of major symptoms or any major disease outcomes, including cardiovascular disease, any cancer or death.

Ongoing studies

No ongoing studies of calcium and/or vitamin D in the low-risk population were identified.

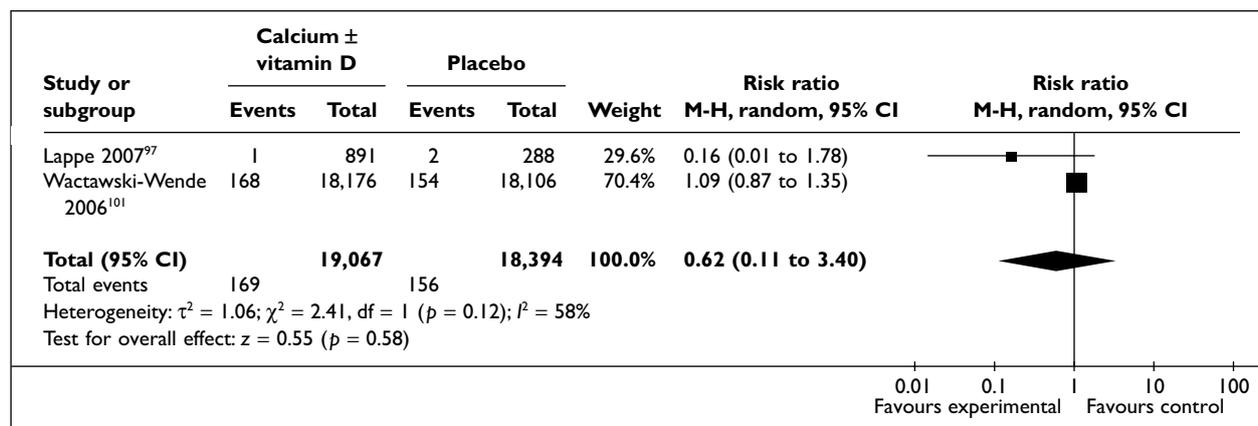
Excluded studies

No additional studies of calcium and/or vitamin D in the low-risk population were excluded on final examination of the full papers.

Summary of results for calcium and/or vitamin D

Two studies of calcium (1200–2000 mg/day) in individuals with a history of adenomas

(a)



(b)



(c)

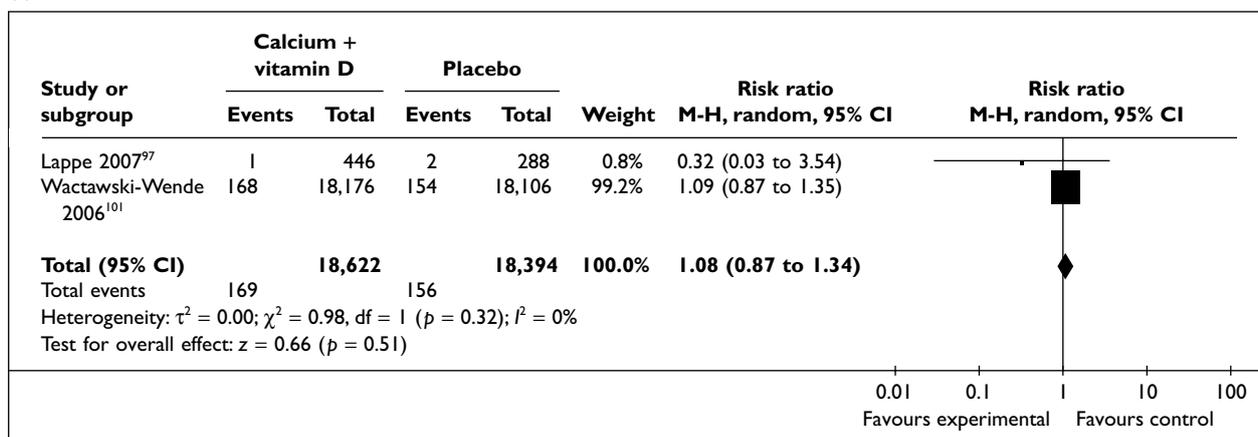


FIGURE 9 Calcium and/or vitamin D: meta-analyses (general population or low-risk group). Incidence of colorectal cancer: (a) calcium ± vitamin D versus placebo alone, (b) calcium alone versus placebo alone, (c) calcium + vitamin D versus placebo alone.

TABLE 23 Calcium: summary of results (general population or low-risk population)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Incidence of colorectal cancer																		
Lappe, ⁹⁷ Wactawski-Wende ¹⁰¹	Any calcium (1000–1500 mg/day) (± vitamin D 400–1100 IU/day)	Placebo alone	CRC	2	4+7	169	19,067	156	18,394	0.62	0.11	3.40	58	0.00	-0.01	0.00	39	
Lappe ⁹⁷	Calcium alone (1400–1500 mg/day)	Placebo alone	CRC	1	4	0	445	2	288	0.13	0.01	2.69	N/C	-0.01	-0.02	0.00	N/C	
Lappe, ⁹⁷ Wactawski-Wende ¹⁰¹	Calcium (1000–1500 mg/day) + vitamin D (400–1100 IU/day)	Placebo alone	CRC	2	4+7	169	18,622	156	18,394	1.08	0.87	1.34	0	0.00	0.00	0.00	0	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

demonstrated a statistically significant 18% reduction in the relative risk of adenoma recurrence. Two studies of calcium (1000–1500 mg/day) plus vitamin D (400–1100 IU/day) in populations with no increased baseline risk of CRC demonstrated no statistically significant effect on the relative risk of CRC. However, the duration of follow-up was 4 to 7 years, which may not be long enough to detect an effect on cancer incidence. One study assessed calcium in patients with adenomas due to FAP, and reported no significant reduction in polyp number or progression. No study reported any serious adverse events associated with calcium and/or vitamin D.

Results: antioxidants (includes selenium, beta-carotene and vitamins A, C and E)

Antioxidants: high-risk population (FAP or HNPCC)

No studies of antioxidant chemoprevention use within populations at high-risk for CRC (i.e. FAP and HNPCC) were identified.

Antioxidants: intermediate-risk population (history of adenomas or colorectal cancer)

Study and population characteristics

Seven studies were identified that compared antioxidants against a control group (Table 24).^{103,104,111,112,115,121,124,126,129} Three studies were based in Italy,^{115,121,124} one in Australia,¹²⁶ one in the USA,^{111,112} one in Canada¹²⁹ and one in Norway.^{103,104} All seven were multicentre studies randomising between 103 and 751 participants.

In all seven trials, subjects were eligible if they had a history of adenomas. The mean age in three studies ranged from 58 to 61 years.^{112,124,129} Three studies reported the age range of the population, 24–75 years (Bonelli *et al.*),¹¹⁵ 30–74 years (MacLennan *et al.*)¹²⁶ and 50–76 years (Hofstad *et al.*).^{103,104} Ponz de Leon *et al.* did not report the age of participants.¹²¹

Five of the seven studies employed comparisons of one or more antioxidants against placebo alone. This included the following antioxidant combinations: beta-carotene alone;¹¹² beta-carotene plus vitamin C plus vitamin E;¹¹² vitamin C plus vitamin E;^{112,129} vitamin A plus vitamin C plus vitamin E;^{121,124} selenium plus zinc plus vitamins A, C and E.¹¹⁵ MacLennan investigated the effects

of beta-carotene in conjunction with a low fat and/or bran diet.¹²⁶ The Hofstad study administered a mixed intervention consisting of calcium (1600 mg/day) combined with beta-carotene (15 mg/day), vitamin C (150 mg/day), vitamin E (75 mg/day) and selenium (101 µg/day) compared with placebo.¹⁰³

Six studies delivered daily doses of antioxidants. Ponz de Leon delivered doses of antioxidants every other day.¹²¹ The doses per day were as follows: beta-carotene ranged from 15 to 25 mg; vitamin C ranged from 150 to 1000 mg; vitamin E ranged from 30 to 400 mg; vitamin A was 30,000 IU in two studies^{121,124} and 2 mg in one study;¹¹⁵ and selenium ranged from 101 to 2000 µg. The control group within six studies was placebo. Some participants in the control group in the MacLennan study received a low fat and/or bran diet.¹²⁶ The duration of treatment ranged from 3 to 4 years. The follow-up of participants ranged from 1.5 to 5 years.

In addition, the effect of antioxidants on adenoma incidence was analysed in a systematic review by Bjelakovic *et al.* (2006),⁵¹ and the effect of antioxidants on any gastrointestinal cancer (including CRC) was analysed in a Cochrane systematic review by Bjelakovic *et al.* (2008).^{114,117}

Quality assessment

Allocation concealment was adequate (central pharmacy) in two studies (MacLennan and McKeown-Eyssen)^{126,129} and unclear in five studies (see Appendix 2, Table 55).^{112,115,121,124} Randomisation was adequately described in three studies,^{112,124,126} whereas four reports stated that the studies were randomised but did not describe the method of randomisation.^{103,115,121,129} Three studies reported adequate blinding of patients, caregivers and analysts.^{112,126,129} Roncucci *et al.* reported adequate blinding of patient and caregiver.¹²⁴ The methods of blinding were unclear in three studies (Ponz de Leon, Bonelli, Hofstad).^{103,115,121} Randomised patients who did not have a follow-up colonoscopy to assess adenoma recurrence were excluded from the main analysis in all studies. All studies experienced attrition. Between 10 and 26% of randomised participants were excluded from the analysis.

Outcome data

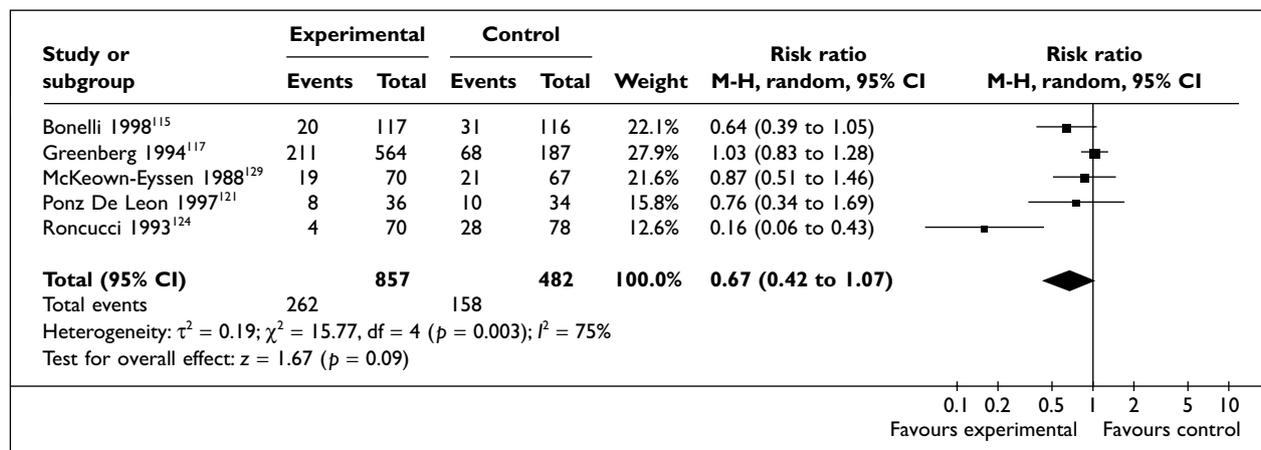
Effectiveness

Effectiveness results for antioxidants in the intermediate-risk population (history of adenomas) are presented in Figure 10 and Table 25.

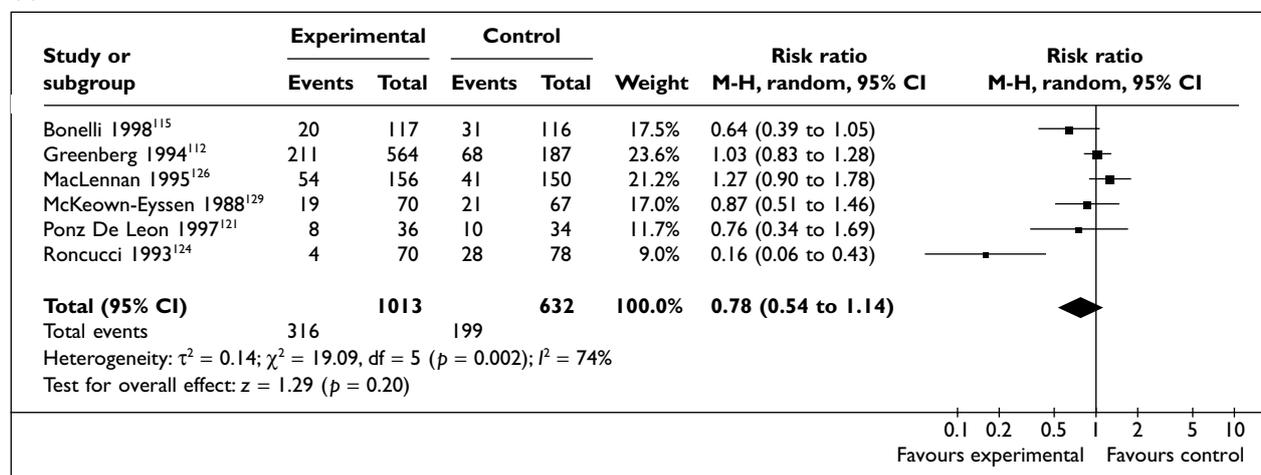
TABLE 24 Antioxidants (vitamins A, C, E, selenium and beta-carotene): study characteristics (history of adenomas)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Baron 2003/ Greenberg 1994 (Antioxidant Polyp Prevention Study) ^{11,112}	History of adenomas Age <80 eligible (mean 61, range not reported)	Beta-carotene 25 mg/day and/or vitamin C 1000 mg/day and/or vitamin E 400 mg/day 2 x 2 design. Study groups: beta-carotene (n = 217) vitamin C + vitamin E (n = 225) beta-carotene + vitamin C + vitamin E (n = 208) placebo only (n = 214)	Placebo (n = 214) (see left for study groups)	4 years	4 years
Bonelli 1998 ¹¹⁵	History of adenomas Age range 25–75 eligible (mean and range not reported)	Vitamin A 2 mg + vitamin C 180 mg + vitamin E 30 mg + selenium 200 µg + zinc 30 mg, all given daily (n = 147) placebo only (n = 157)	Placebo (n = 157)	5 years	5 years
Hofstad 1998 ^{103,104}	History of adenomas (polyps left <i>in situ</i>) Age 50–76 years eligible	Calcium 1600 mg/day + beta-carotene 15 mg/day + vitamin C 150 mg/day + vitamin E 75 mg/day + selenium 101 µg/day (n = 42)	Placebo (n = 51)	3 years	3 years
Ponz de Leon 1997b ¹²¹	History of adenomas Age not reported	Vitamin A 30,000 IU + vitamin C 1 g + vitamin E 70 mg, all given every other day (n = 36) or N-Acetylcysteine 600 mg/day (n = 33)	Placebo (n = 34)	Not reported – less than 2 years	Not reported – less than 2 years
Roncucci 1993 ^{121,124}	History of adenomas Eligible age not reported (mean age 59.2, range not reported)	Vitamin A 30,000 IU + vitamin C 1 g + vitamin E 70 mg, all given daily (n = 70) or Lactulose 20 g/day (n = 61)	Placebo (n = 78)	1.5 years (approx.)	1.5 years (approx.)
MacLennan 1995 (Australian Polyp Prevention Trial) ¹²⁶	History of adenomas Eligible age range 30–74 (mean age and range not reported)	Beta-carotene 20 mg/day and/or wheat bran 20 mg/day and/ or low-fat diet (reducing dietary fat to 25% of total calories) 2 x 2 x 2 design. Study groups (n = 411 randomised, allocation reported for n = 395 as follows): normal eating + placebo (n = 48) low-fat diet + placebo (n = 48) bran + placebo (n = 50) beta-carotene (n = 53) beta-carotene + low-fat diet (n = 51) low-fat diet + bran (n = 48) beta-carotene + bran (n = 47) beta-carotene + low-fat diet (n = 50)	Placebo (see left for study groups)	Low-fat diet and bran: 4 years Beta-carotene: approx. 2 years	4 years
McKeown-Eyssen 1988 ¹²⁹	History of adenomas Eligible age not reported (mean age 58, range not reported)	Vitamin C 400 mg/day + vitamin E 400 mg/day (n = 96)	Placebo (n = 89)	2 years	2 years

(a)



(b)



(c)

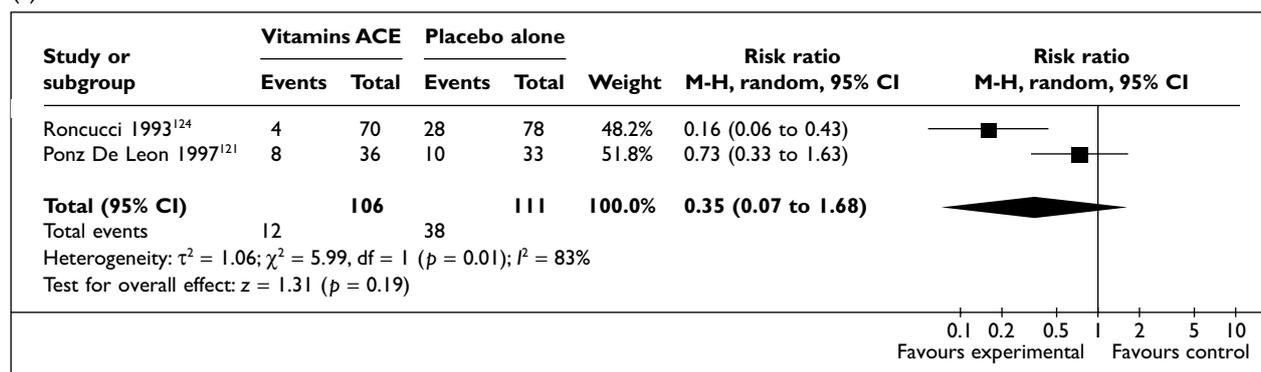


FIGURE 10 Antioxidants: meta-analyses (history of adenomas). Recurrence of any adenoma: (a) any antioxidants versus placebo alone; (b) any antioxidants (\pm low-fat diet \pm bran) versus no antioxidants; (c) vitamins A, C, E versus placebo alone; (d) vitamins C and E versus placebo alone.

(d)

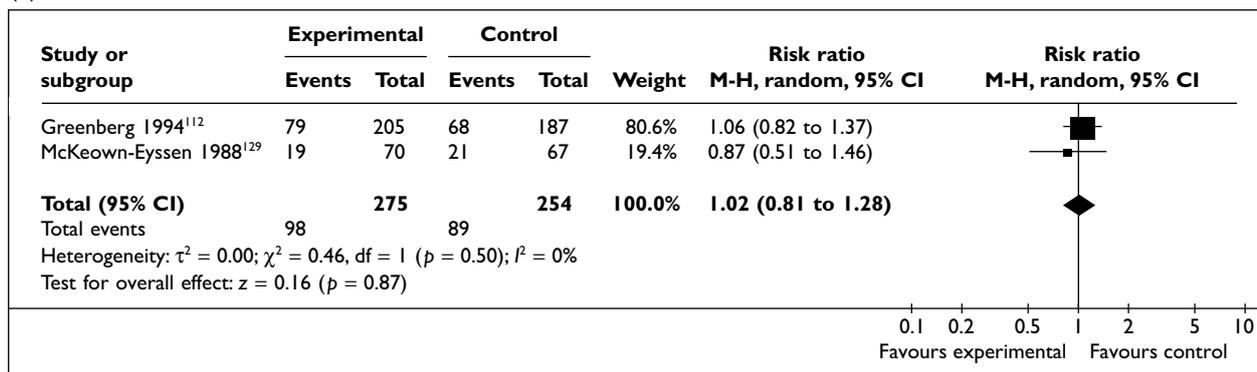


FIGURE 10 (continued) Antioxidants: meta-analyses (history of adenomas). Recurrence of any adenoma: (a) any antioxidants versus placebo alone; (b) any antioxidants (\pm low-fat diet \pm bran) versus no antioxidants; (c) vitamins A, C, E versus placebo alone; (d) vitamins C and E versus placebo alone.

Recurrence of any adenoma

Five studies (1339 participants in analysis) compared any antioxidant (alone or in any combination) with placebo (Figure 10a).^{112,115,121,124,129} A meta-analysis demonstrated that the differences in relative and absolute risks of developing at least one adenoma were not significant at the 5% level (RR 0.67, 95% CI 0.42 to 1.07, $p = 0.09$; RD -0.10, 95% CI -0.22 to 0.02, $p = 0.10$). There was a high level of statistical heterogeneity observed in both estimates ($I^2 = 75\%$ and $I^2 = 79\%$, respectively).

Six studies (1706 participants in analysis) compared any antioxidant (alone or in any combination) against no antioxidant (Figure 10b). This analysis included participants from MacLennan who had received 25 g/day wheat bran and/or a low-fat diet, in addition to placebo.¹²⁶ There was no statistically significant difference between groups in the relative risk of developing at least one adenoma (meta-analysed RR 0.78, 95% CI 0.54 to 1.14, $p = 0.20$). This analysis suggested a high level of statistical heterogeneity ($I^2 = 74\%$).

A number of discrete analyses were undertaken for different combinations of antioxidants (see Table 25 and Figure 10c-d). No statistically significant results were found for any of the five analyses; the interventions were neither effective nor harmful.

A seventh study (Hofstad; 93 participants in the analysis) reported that calcium plus antioxidants (vitamins C and E, beta-carotene and selenium) significantly reduced the risk of adenoma recurrence compared with placebo. Event data were not reported but the odds ratio was reported as 0.31 (95% CI 0.11-0.84).¹⁰³

Incidence of advanced adenoma

No studies of antioxidants in the intermediate-risk population reported incidence of advanced adenoma, as defined in studies of other interventions (i.e. adenoma ≥ 1 cm in diameter, villous or tubulovillous adenoma, adenoma with severe dysplasia or CRC). Three studies reported separate data on large adenomas or adenomas with other abnormalities (Roncucci, MacLennan, McKeown-Eyssen);^{124,126,129} however, these data are not presented here because of the lack of consistency in definitions of advanced adenoma.

Incidence of colorectal cancer

No studies of antioxidants in the intermediate-risk population reported CRC incidence.

Compliance

Three studies reported a compliance rate in the intervention group. McKeown-Eyssen gave a compliance range over the study period which was 89-100%, measured by urine concentrations of vitamin C.¹²⁹ Roncucci measured the compliance rate by periodic self-report as 85%.¹²⁴ Bonelli did not indicate how compliance was measured, but reported the overall value to be 63.7%.¹¹⁵ However, the compliance from Bonelli varied greatly between the two study centres from 40.5% to 96.1%.¹¹⁵ Greenberg did not provide compliance rates but indicated that five participants had stopped taking tablets because of their presumed toxicity.¹¹²

Adverse effects

Two studies reported minor adverse events. Roncucci reported that 1.4% of participants in the antioxidants intervention group experienced pruritus with no skin alteration and withdrew from the trial.¹²⁴ In the same trial, some participants were receiving lactulose and 4.9% had lactulose-

TABLE 25 Antioxidants: summary of results (history of adenomas)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)	
Recurrence of any adenoma																		
Bonelli, ¹¹⁵	Any antioxidant	No antioxidant	Adenoma	6	1.5, <2, 2, 4, 4, 5	316	1013	199	632	0.78	0.54	1.14	74	N/C	N/C	N/C	N/C	N/C
Greenberg, ^{111,112}	(± low-fat diet ± bran)	(± low-fat diet ± bran ± lactulose)																
MacLennan, ¹²⁶																		
McKeown-Eyssen, ¹²⁸	Ponz de Leon, ¹²¹																	
Roncucci ^{121,124}																		
Bonelli, ¹¹⁵	Any antioxidant	Placebo alone	Adenoma	5	1.5, <2, 2, 4, 5	262	857	158	482	0.67	0.42	1.07	75	-0.10	-0.22	0.02	79	
Greenberg, ^{111,112}																		
McKeown-Eyssen, ¹²⁸	Ponz de Leon, ¹²¹																	
Roncucci ^{121,124}																		
Roncucci, ^{121,124}	Vitamins A,C,E	Placebo alone	Adenoma	2	<2	12	106	38	111	0.35	0.07	1.68	83	-0.21	-0.42	0.01	70	
Ponz de Leon ¹²¹																		
Greenberg, ^{111,112}	Vitamins C,E	Placebo alone	Adenoma	2	2, 4	98	275	89	254	1.02	0.81	1.28	0	0.00	-0.08	0.08	0	
McKeown-Eyssen																		
Greenberg, ^{111,112}	Beta-carotene	Placebo alone	Adenoma	1	4	66	184	68	187	0.99	0.75	1.29	N/C	0.00	-0.10	0.09	N/C	
Greenberg, ^{111,112}	Vitamins C,E + beta-carotene	Placebo alone	Adenoma	1	4	66	175	68	187	1.04	0.79	1.36	N/C	0.01	-0.09	0.11	N/C	
Bonelli ¹¹⁵	Vitamins A,C,E + selenium + zinc	Placebo alone	Adenoma	1	5	20	117	31	116	0.64	0.39	1.05	N/C	-0.10	-0.20	0.01	N/C	

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

induced diarrhoea. Bonelli reported that 12.5% of participants in the intervention group and 2.9% of participants in the placebo group experienced minor adverse events but did not state what these were.¹¹⁵

Ongoing studies

An ongoing phase 3 RCT is assessing selenium versus placebo for prevention of adenoma recurrence in participants with a history of colorectal adenomatous polyps, and is aiming to enrol 2050 participants, with treatment and follow-up durations of 5 years, or up to 7.5 years in some participants (www.cancer.gov/clinicaltrials/UARIZ-00-0430-01).

Excluded studies

Hofstad¹⁰³ did not report event data (only mean numbers of adenomas) and this study was therefore excluded from meta-analysis. No further studies of antioxidants in the intermediate-risk population were excluded on final examination of the full papers.

Antioxidants: low-risk population (general population or no increased risk of colorectal cancer)

Study and population characteristics

Twelve studies comparing antioxidants with a control group were identified (Table 26).^{109,113,114,116,118,122,125,127,130,133,134,137,140,142} Six studies were based in the USA^{113,118,122,127,137,142} and two were international studies.^{116,125} The remainder were based in the UK,¹⁴⁰ France,¹³⁰ Finland^{133,134} and China.¹⁰⁹ All 12 trials were multicentre studies randomising between 216 and 39,876 participants.

Studies were undertaken in healthy populations [Physicians Health Study PHS II¹¹³, Selenium and Vitamin E Cancer Prevention Trial (SELECT),¹¹⁶ Women's Health Study,¹²² Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX),¹³⁰ PHS¹³⁰] and populations with histories of cardiovascular disease [Women's Antioxidant Cardiovascular Study (WACS),¹¹⁸ Heart Outcomes Prevention Evaluation – The Ongoing Outcomes (HOPE-TOO),¹²⁵ Heart Protection Study (HPS)¹⁴⁰], smoking or asbestos exposure [Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC study),^{133,134} The Beta-Carotene and Retinol Efficacy Trial (CARET)¹²⁷], skin cancer [Nutritional Prevention of Cancer Trial (NPCT)¹³⁷] and atrophic gastritis (Zhu *et al.*).¹⁰⁹

The mean age of subjects in 10 studies ranged from 48.95 to 66 years. The HPS reported the age range of the population as 40–80 years.¹⁴⁰ Lippman *et al.* reported the median age as 62–63 years in SELECT.¹¹⁶

Seven of the twelve studies employed comparisons of one or more antioxidants against placebo alone. This included the following antioxidant combinations: beta-carotene alone;^{109,133,134,142} vitamin E alone;^{116,133,134} selenium alone;^{116,137} beta-carotene plus vitamin C plus vitamin E;¹⁴⁰ vitamin A plus beta-carotene;¹²⁷ vitamin E plus beta-carotene;^{133,134} vitamin E plus selenium;¹¹⁶ and selenium, beta-carotene, vitamins C and E and zinc.¹³⁰ Two studies compared antioxidants in combination with another agent against placebo. In the HOPE-TOO study, Lonn *et al.* included ramipril with placebo.¹²⁵ Simvastatin was included with placebo in the HPS.¹⁴⁰ Gaziano *et al.*, Lin *et al.* and Lee *et al.* compared one or more antioxidant against placebo groups in which participants had received other antioxidants.^{113,118,122} In these cases, discrete event data were not available and analyses used relative risks that were adjusted to account for the effects of the antioxidant within the placebo group. These three studies were not included in the meta-analysis of any antioxidant versus placebo, but were included in the analyses of individual antioxidants.

Seven studies delivered daily doses of antioxidants.^{116,125,127,130,133,134,137,140} Gaziano and Lin delivered two antioxidants in combination, where one was delivered daily and the other on alternate days.^{113,118} Lee and Hennekens *et al.* delivered antioxidants every other day.^{122,142} Zhu delivered beta-carotene daily for 1 year and then twice a week for 1 year.¹⁰⁹ The doses per day/alternate day were as follows: beta-carotene ranged from 20 to 96 mg; vitamin C ranged from 120 to 500 mg; the dose of vitamin E ranged from 400–600 IU in five studies^{113,116,118,122,123,125} to 30–600 mg in three studies;^{130,133–136,140,141} selenium ranged from 100 to 200 µg. Goodman *et al.* delivered a vitamin A intervention and the dose per day was 25,000 IU.¹²⁷

The duration of treatment ranged from 2 to 12 years (Gaziano did not report duration of treatment).¹¹³ The follow-up of participants ranged from 5 to 12 years.

In addition, the effect of antioxidants on adenoma incidence was analysed in a systematic review by Bjelakovic *et al.* (2006),⁵¹ and the effect of antioxidants on any gastrointestinal cancer

TABLE 26 Antioxidants (vitamins A, C, E, selenium and beta-carotene): study characteristics (general population or low-risk population)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Gaziano 2009 (PHS II) ¹¹³	General population (male physicians) Age 50+ eligible (mean age 64, range not reported)	Vitamin E 400 IU every other day, and/or vitamin C 500 mg/day 2 × 2 × 2 design. Study groups: vitamin E (n = 3659) vitamin C (n = 3673) vitamin E + vitamin C (n = 3656) NB Patients were also randomised to beta-carotene, terminated early, no data reported	Placebo (no vitamin E or vitamin C) (n = 3653)	Not reported	8 years (approx.)
Lippman 2009 (SELECT) ¹¹⁶	General population (men only) Age 50+ eligible, (median 62–63 in all groups, range not reported)	Selenium 200 µg/day and/or vitamin E 400 IU/day 2 × 2 design. Study groups: selenium (n = 8910) vitamin E (n = 8904) selenium + vitamin E (n = 8863) placebo (n = 8856)	Placebo (see left for study groups)	5.5 years (approx)	5.5 years (approx.)
Lin 2009 (WACS) ^{118–120}	General population (women only, at high risk of cardiovascular disease) Age 40+ eligible (mean 60, range not reported)	2 × 2 × 2 study design. Total n = 8171 participants, randomised to eight study groups with the following interventions alone or in combination: vitamin C (500 mg/day), vitamin E (600 IU every other day) beta-carotene (50 mg every other day) placebo	Placebo (see left for study groups)	9 years	9 years
Lee 2005, Lee 1999 (Women's Health Study) ^{69,70,122,123}	General population (women only) Age 45+ eligible (mean 55, range not reported)	2 × 2 × 2 study design Vitamin E (600 IU every other day) and/or beta-carotene (50 mg every other day for 2 years, stopped early due to lack of effectiveness) and/or aspirin (100 mg every other day) Vitamin E (n = 19,937) vs no vitamin E (n = 19,939) Beta-carotene (n = 19,939) vs no beta-carotene (n = 19,937)	Placebo (see left for study groups)	10 years (aspirin and vitamin E) 2 years (beta-carotene)	10 years (aspirin and vitamin E) 4 years (beta-carotene)

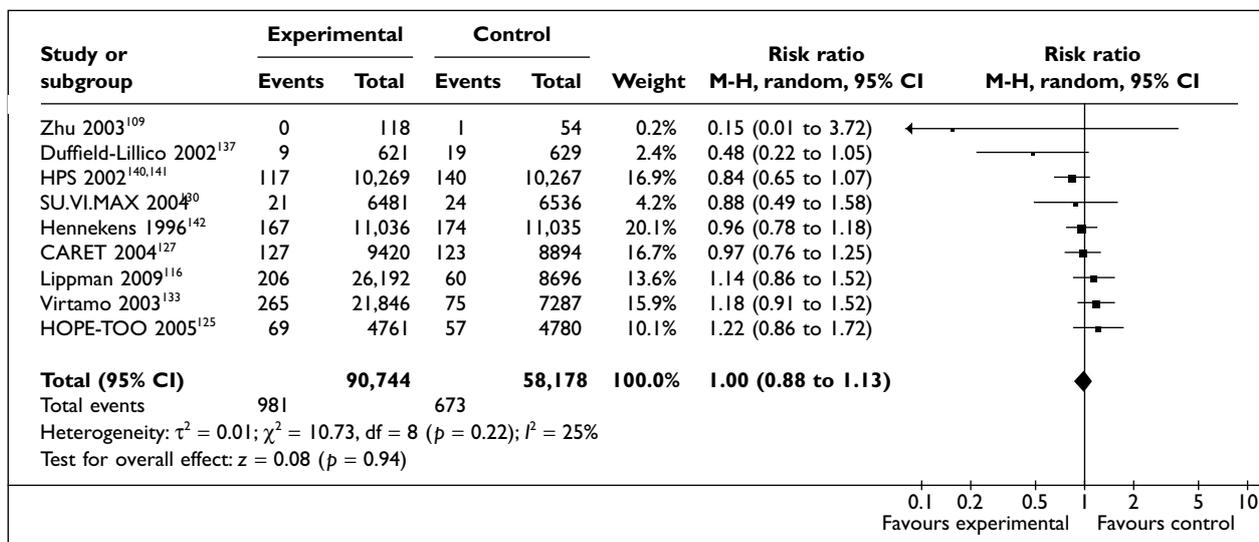
Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Lonn 2005 (HOPE-TOO Study) ^{107,125}	General population (male or female, history of cardiovascular disease or diabetes with one cardiovascular risk factor) Aged 55+ eligible (mean 66, range not reported)	Vitamin E 400 IU/day (n = 4761) Factorial trial; approximately 50% of participants in both vitamin E and placebo groups also received ramipril angiotensin-converting enzyme inhibitor, 10 mg/day	Placebo (n = 4780) (half received ramipril also)	6 years	7 years (approx.)
Goodman 2004 (CARET Study) ^{114,127,128}	General population (smokers, former smokers and workers exposed to asbestos at high risk of developing lung cancer) Age: mean 57 for asbestos cohort; mean 58 for smokers cohort	Vitamin A 25,000 IU and beta-carotene 30 mg/day (n = 9420)	Placebo (n = 8894)	7 years (approx.)	10 years (approx.)
Hercberg 2004 (SU.VI.MAX Study) ^{114,130-132}	General population (men and women) Age 35-60 years eligible (mean 48.95, range not reported)	Vitamin C 120 mg/day + vitamin E 30 mg/day + beta-carotene 96 mg/day + selenium 100 µg/day + zinc 20 mg/day (n = 6481)	Placebo (n = 6536)	7 years	7.5 years
Zhu 2003 ^{109,110}	Patients with atrophic gastritis Age 28-77 years eligible (mean 55-57 years in all groups)	Folic acid 20 mg/day for 1 year then 20 mg twice weekly for 1 year; vitamin B ₁₂ 1 mg/month for 1 year then 1 mg every 3 months for 1 year (n = 44)	Placebo (n = 54) Beta-carotene (natural), 30 mg/day for 1 year then 30 mg twice/week for 1 year (n = 61) Beta-carotene (synthetic), doses as above (n = 57)	2 years	6 years

continued

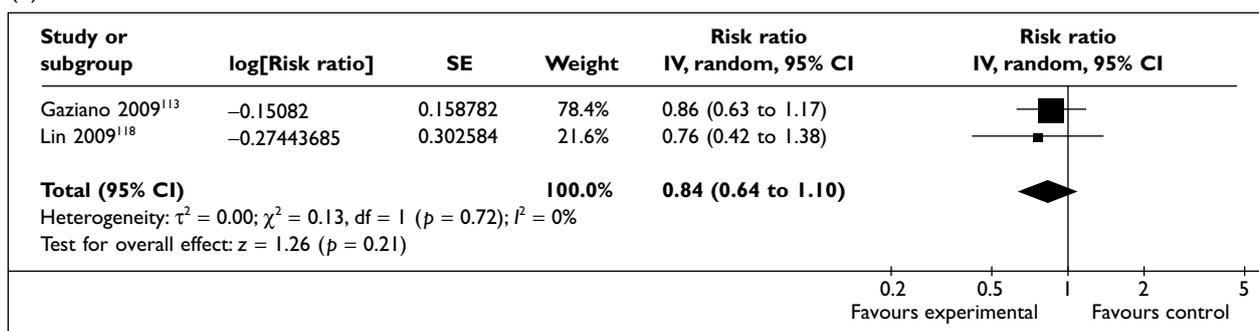
TABLE 26 Antioxidants (vitamins A, C, E, selenium and beta-carotene): study characteristics (general population or low-risk population) (continued)

Study	Population and age	Intervention (n randomised)	Control (n randomised)	Treatment duration	Follow-up duration
Virtamo 2003/ Malila 1999 (ATBC Study) ¹³³⁻¹³⁶	General population (male, smokers) Age range 50–69 (mean 57)	Vitamin E 50 mg/day and/or beta-carotene 20 mg/day 2 x 2 design: Study groups: vitamin E (n = 7286 for CRC analysis; n = 3890 for adenoma analysis) beta-carotene (n = 7282 for CRC analysis; n = 3883 for adenoma analysis) vitamin E + beta-carotene (n = 7278 for CRC analysis; n = 3878 for adenoma analysis)	Placebo (n = 7287 for CRC analysis; n = 3887 for adenoma analysis)	6 years (approx.)	12 years
Duffield-Lillico 2002 (NPCT) ¹³⁷⁻¹³⁹	General population (history of skin cancer) Age 18–80 eligible (mean 63, range not reported)	Selenium 200 µg/day (n = 653)	Placebo (n = 659)	4 years (approx.)	7–8 years
HPS Group 2002 (HPS) ^{114,140,141}	General population (males and females, history of coronary disease, other occlusive arterial disease, diabetes and non-fasting blood total cholesterol concentrations of at least 3.5 mmol/l) Age range 40–80 years (mean not reported)	Vitamin C 250 mg/day + vitamin E 600 mg/day + beta-carotene 20 mg/day (n = 10,269) Factorial trial; approximately 50% of participants in both intervention and placebo groups also received simvastatin, 40 mg/day	Placebo (n = 10,267) (half received simvastatin also)	5 years (approx.)	5 years
Hennekens 1996 (PHS) ¹⁴²	General population (male physicians) Age 40–84 (mean 53)	Beta-carotene: 50 mg on alternate days, (n = 11,036) (Aspirin 325 mg every other day, Aspirin component terminated early – after 5 years – and participants could then take open-label aspirin)	Placebo (no beta-carotene), n = 11,035 (half received aspirin also)	12 years for beta-carotene	12 years

(a)



(b)



(c)

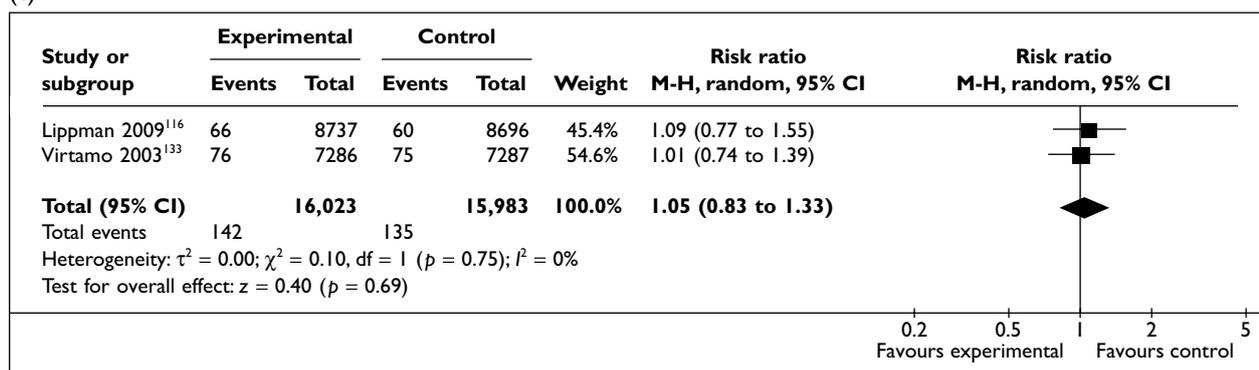
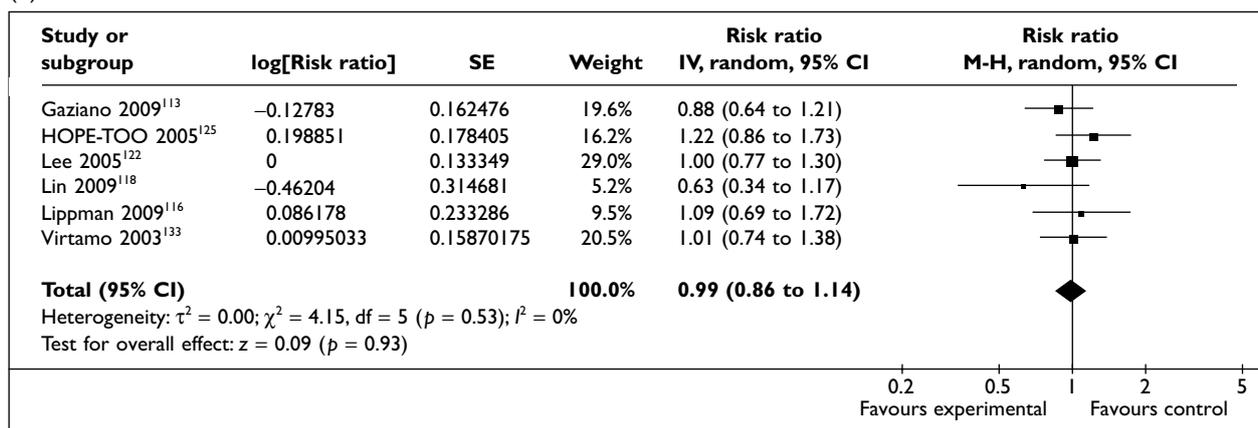
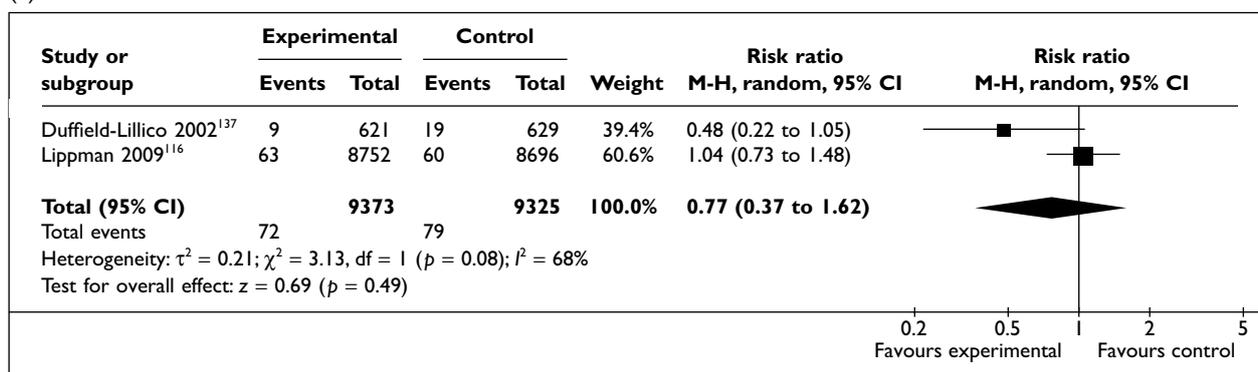


FIGURE 11 Antioxidants: meta-analyses (general population or low-risk population). Incidence of colorectal cancer: (a) any antioxidants (\pm aspirin, simvastatin, ramipril) versus no antioxidants; (b) vitamin C versus no vitamin C (adjusted for other antioxidants); (c) vitamin E alone versus placebo alone; (d) vitamin E versus no vitamin E (adjusted for other antioxidants); (e) selenium alone versus placebo alone; (f) beta-carotene (\pm aspirin) versus no beta-carotene: studies with event data; (g) beta-carotene (\pm aspirin and adjusted for other antioxidants) versus no beta-carotene: studies with or without event data.

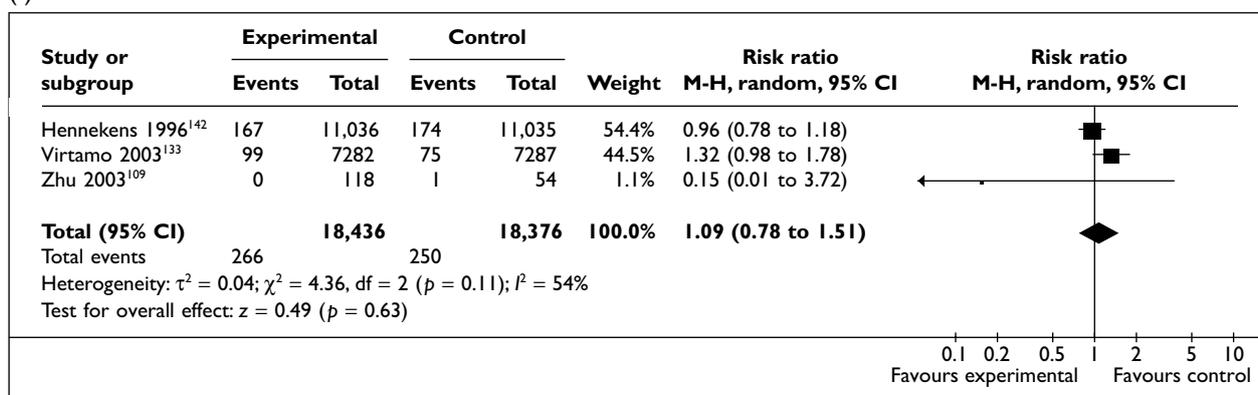
(d)



(e)



(f)



(g)

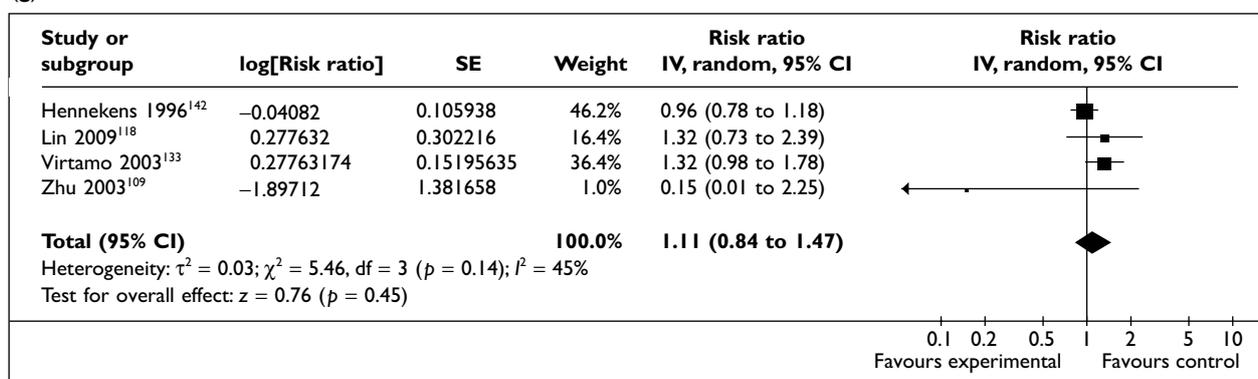


FIGURE 11 (continued) Antioxidants: meta-analyses (general population or low-risk population). Incidence of colorectal cancer: (a) any antioxidants (\pm aspirin, simvastatin, ramipril) versus no antioxidants; (b) vitamin C versus no vitamin C (adjusted for other antioxidants); (c) vitamin E alone versus placebo alone; (d) vitamin E versus no vitamin E (adjusted for other antioxidants); (e) selenium alone versus placebo alone; (f) beta-carotene (\pm aspirin) versus no beta-carotene: studies with event data; (g) beta-carotene (\pm aspirin and adjusted for other antioxidants) versus no beta-carotene: studies with or without event data.

(including CRC) was analysed in a Cochrane systematic review by Bjelakovic *et al.* (2008).^{114,117}

Quality assessment

Allocation concealment was unclear in two studies^{109,118} and adequate in the remaining ten studies (see Appendix 2, Table 55). All studies were randomised; however, the generation of the randomisation sequence was not described in the studies reported by Lin and Zhu.^{109,118} All studies reported adequate blinding in terms of patients and caregivers. Six trials stated that they were double-blind but did not state whether it was the caregiver or, outcome assessor or analyst who was blinded during the trial in addition to the patient (see Appendix 2, Table 55). Five studies included all patients that were randomised in the analyses (Lonn, Lee, Zhu, Virtamo, and Hennekens).^{109,122,125,133,142} The remaining seven studies excluded between 0.3% and 12% from their analyses.

Outcome data

Effectiveness

Effectiveness results for antioxidants in the general population (or populations with no increased risk for CRC) are shown in Figure 11 and Table 27.

Incidence of any adenoma

Malila *et al.* (15,538 participants in analysis) compared any antioxidant (alone or in any combination) with placebo.¹³⁴ There was no significant difference between groups in the relative risk of developing at least one adenoma (RR 1.47, 95% CI 0.97 to 2.23, $p = 0.07$). The absolute risk difference was 0.00 (95% CI: 0.00 to 0.01 $p = 0.04$).

Incidence of advanced adenoma

No studies of antioxidants in the low-risk population reported incidence of advanced adenoma.

Incidence of colorectal cancer

Nine studies (148,922 participants in analysis) compared any antioxidant (alone or in any combination) against no antioxidant (Figure 11a).^{109,116,122,127,130,133,134,137,140,142} A meta-analysis demonstrated no significant difference between groups in the relative or absolute risk of developing CRC (RR 1.00, 95% CI 0.88 to 1.13, $p = 0.94$; RD 0.00, 95% CI 0.00 to 0.00, $p = 0.94$). There was a low level of statistical heterogeneity ($I^2 = 25%$ and $I^2 = 24%$, respectively).

A number of discrete analyses were undertaken for different combinations of antioxidants (see Table 27

and Figure 11b–g). Of the 14 analyses undertaken, only two provided statistically significant results. In the ATBC study, Malila found a 74% relative increase in the risk of developing at least one adenoma in participants receiving vitamin E compared with placebo alone (RR 1.74, 95% CI 1.09 to 1.79, $p = 0.02$).¹³⁴ Malila found that there was a 63% relative increase in the risk of developing at least one adenoma in participants receiving vitamin E and beta-carotene compared with placebo alone (RR 1.63, 95% CI 1.01 to 2.63, $p = 0.04$).¹³⁴ However, given the small numbers of both participants and events, as well as the large number of separate analyses (uncorrected for repeated significance testing), these results should be treated with caution. The remaining 12 analyses showed no statistically significant difference between the intervention and placebo groups; the intervention was neither effective nor harmful (Table 27).

Compliance

All 12 studies reported a compliance rate for the intervention group. Seven studies provided average compliance rates over the whole trial period that ranged between 73 and 93%.^{109,118,122,127,133,134,137,140} Lin, Lee and Duffield-Lillico determined compliance by patient self-report alone.^{118,122,137} Goodman determined compliance by pill counting for 85% of participants and self-report for 15% of participants.¹²⁷ Zhu and Malila 1999/Virtamo 2003 used pill counting and random blood sampling^{109,133,134} whereas the HPS employed pill counting alone.¹⁴⁰

Herberg and Hennekens provided end of trial compliance rates that were 74% and 80% respectively.^{130,142} Five studies provided compliance rates at the start or during the trial and at the end of the trial.^{113,116,118,122,125} Initial compliance rates in these studies ranged between 76 and 94.2%. Final compliance rates ranged between 65 and 89.2%.

Adverse effects

Seven studies did not report adverse events. Gaziano reported a 74% increased risk in haemorrhagic strokes for the vitamin E intervention group when compared with the placebo group [hazard ratio (HR) 1.74, 95% CI 1.04 to 2.91].¹¹³ Lippmann reported a statistically significant increase in alopecia and grade 1–2 dermatitis in the selenium group.¹¹⁶ Lee reported a 6% increase in the risk of epistaxis in the vitamin E group compared with the placebo group (RR 1.06, 95% CI 1.01 to 1.11; $p = 0.02$).¹²² Zhu reported two false jaundices in the beta-carotene group

TABLE 27 Antioxidants: summary of results (general population or low-risk population)

Studies	Intervention (I)	Control (C)	Outcome	No. of studies	Follow-up (years)
Incidence of any adenoma					
Malila (Virtamo) ¹³³⁻¹³⁶	Any antioxidant (vitamin E and/or beta-carotene)	Placebo alone	Adenoma	1	6
Malila (Virtamo) ¹³³⁻¹³⁶	Vitamin E alone	Placebo alone	Adenoma	1	6
Malila (Virtamo) ¹³³⁻¹³⁶	Beta-carotene alone	Placebo alone	Adenoma	1	6
Malila (Virtamo) ¹³³⁻¹³⁶	Vitamin E + beta-carotene alone	Placebo alone	Adenoma	1	6
Incidence of colorectal cancer					
Zhu, ^{109,110} Duffield-Lillico, ¹³⁷⁻¹³⁹ HPS, ^{114,140,141} Hennekens, ¹⁴² SU.VI.MAX, ^{114,130-132} CARET, ^{114,127,128} Lippman, ¹¹⁶ Virtamo, ¹³³⁻¹³⁶ HOPE-TOO ^{107,125}	Any antioxidant (\pm aspirin, simvastatin, ramipril)	No antioxidant (\pm aspirin, simvastatin, ramipril)	CRC	9	5, 5, 5.5, 6, 7, 7-8, 10, 12, 12
Gaziano, ¹¹³ Lin ¹¹⁸⁻¹²⁰	Vitamin C (adjusted for other antioxidants; studies with no event data)	No vitamin C (adjusted for other antioxidants)	CRC	2	8, 9
Virtamo, ¹³³⁻¹³⁶ Lippman ¹¹⁶	Vitamin E alone (studies with event data)	Placebo alone	CRC	2	5.5, 12
Gaziano, ¹¹³ HOPE-TOO, ^{107,125} Lee, ^{69,70,122,123} Lin, ¹¹⁸⁻¹²⁰ Lippman, ¹¹⁶ Virtamo ¹³³⁻¹³⁶	Vitamin E (adjusted for other antioxidants; studies with or without event data)	No vitamin E (adjusted for other antioxidants)	CRC	6	5.5, 7, 8, 9, 10, 12
Duffield-Lillico, ¹³⁷⁻¹³⁹ Lippman ¹¹⁶	Selenium alone	Placebo alone	CRC	2	5.5, 7-8
Hennekens, ¹⁴² Virtamo, ¹³³⁻¹³⁶ Zhu ^{109,110}	Beta-carotene (\pm aspirin; studies with event data)	No beta-carotene (\pm aspirin)	CRC	3	6, 12, 12
Hennekens, ¹⁴² Virtamo, ¹³³⁻¹³⁶ Zhu, ^{109,110} Lin ¹¹⁸⁻¹²⁰	Beta-carotene (\pm aspirin, and adjusted for other antioxidants; studies with or without event data)	No beta-carotene (\pm aspirin, and adjusted for other antioxidants)	CRC	4	6, 9, 12, 12
Virtamo ¹³³⁻¹³⁶	Vitamin E + beta-carotene alone	Placebo alone	CRC	1	12
CARET ^{114,127,128}	Vitamin A + beta-carotene alone	Placebo alone	CRC	1	10
Lippman ¹¹⁶	Vitamin E + selenium alone	Placebo alone	CRC	1	5.5
HPS ^{114,140,141}	Vitamins C, E + beta-carotene (\pm simvastatin)	Placebo (\pm simvastatin)	CRC	1	5
SU.VI.MAX ^{114,130-132}	Vit CE + beta-carotene + selenium + zinc	Placebo alone	CRC	1	7.5

TABLE 27 Antioxidants: summary of results (general population or low-risk population) (continued)

Studies	I: n	I: N	C: n	C: N	RR	LCI	UCI	I ² (%)	RD	LCI	UCI	I ² (%)
Incidence of any adenoma												
Malila (Virtamo) ¹³³⁻¹³⁶	119	11,651	27	3887	1.47	0.97	2.23	N/C	0.00	0.00	0.01	N/C
Malila (Virtamo) ¹³³⁻¹³⁶	47	3890	27	3887	1.74	1.09	2.79	N/C	0.01	0.00	0.01	N/C
Malila (Virtamo) ¹³³⁻¹³⁶	28	3883	27	3887	1.04	0.61	1.76	N/C	0.00	0.00	0.00	N/C
Malila (Virtamo) ¹³³⁻¹³⁶	44	3878	27	3887	1.63	1.01	2.63	N/C	0.00	0.00	0.01	N/C
Incidence of colorectal cancer												
Zhu, ^{109,110} Duffield-Lillico, ¹³⁷⁻¹³⁹ HPS, ^{114,140,141} Hennekens, ¹⁴² SU.VI.MAX, ^{114,130-132} CARET, ^{114,127,128} Lippman, ¹¹⁶ Virtamo, ¹³³⁻¹³⁶ HOPE-TOO ^{107,125}	981	90,744	673	58,178	1.00	0.88	1.13	25	0.00	0.00	0.00	24
Gaziano, ¹¹³ Lin ¹¹⁸⁻¹²⁰	NR for some studies	0.84	0.64	1.10	0	N/C	N/C	N/C	N/C			
Virtamo, ¹³³⁻¹³⁶ Lippman ¹¹⁶	142	16,023	135	15,983	1.05	0.83	1.33	0	0.00	0.00	0.00	N/C
Gaziano, ¹¹³ HOPE-TOO, ^{107,125} Lee, ^{69,70,122,123} Lin, ¹¹⁸⁻¹²⁰ Lippman, ¹¹⁶ Virtamo ¹³³⁻¹³⁶	NR for some studies	0.99	0.86	1.14	0	N/C	N/C	N/C	N/C			
Duffield-Lillico, ¹³⁷⁻¹³⁹ Lippman ¹¹⁶	72	9373	79	9325	0.77	0.37	1.62	68	-0.01	-0.02	0.01	75
Hennekens, ¹⁴² Virtamo, ¹³³⁻¹³⁶ Zhu ^{109,110}	266	18,436	250	18,376	1.09	0.78	1.51	54	0.00	0.00	0.00	41
Hennekens, ¹⁴² Virtamo, ¹³³⁻¹³⁶ Zhu, ^{109,110} Lin ¹¹⁸⁻¹²⁰	NR for some studies	1.11	0.84	1.47	26	N/C	N/C	N/C	N/C			
Virtamo ¹³³⁻¹³⁶	90	7278	75	7287	1.20	0.89	1.63	N/C	0.00	0.00	0.01	N/C
CARET ^{114,127,128}	127	9420	123	8894	0.97	0.76	1.25	N/C	0.00	0.00	0.00	N/C
Lippman ¹¹⁶	77	8703	60	8696	1.28	0.92	1.79	N/C	0.00	0.00	0.00	N/C
HPS ^{114,140,141}	117	10,269	140	10,267	0.84	0.65	1.07	N/C	0.00	-0.01	0.00	N/C
SU.VI.MAX ^{114,130-132}	21	6481	24	6536	0.88	0.49	1.58	N/C	0.00	0.00	0.00	N/C

C, control; I, intervention; I², measure of heterogeneity; LCI, lower 95% confidence limit; N/C, not calculable; RD, absolute risk difference; RR, relative risk; UCI, upper 95% confidence limit.

of one study as a result of hypercarotenemia.¹⁰⁹ Hennekens reported a statistically significant increase in the minor side effects of yellowing of the skin and minor gastrointestinal problems such as belching, in the beta-carotene group.¹⁴²

Ongoing studies

No ongoing studies evaluating the use of antioxidants as chemoprevention in the low-risk population were identified.

Excluded studies

Reid *et al.*¹³⁸ presented data on the number of participants developing at least one adenoma after receiving 200 µg selenium or a placebo. This study was excluded because the participants were not certified as polyp-free at the beginning of the trial. The CRC incidence in the selenium and placebo groups in this study is included in our analyses using data from Duffield-Lillico.¹³⁷

Summary of results for antioxidants

There were six studies of antioxidants (including vitamins A, C and E, beta-carotene or selenium) in individuals with a history of adenomas. Doses and combinations varied between studies. Statistically significant differences in relative risk of adenoma recurrence were not demonstrated, either when all antioxidants were analysed together or when the separate combinations were assessed separately. There were 12 studies of antioxidants in populations with no increased risk of CRC, with follow-up durations between 5 and 12 years. Across the nine studies comparing antioxidants to no antioxidants, there was no statistically significant effect on incidence of CRC. In addition, one study assessing the effect of antioxidants on adenoma incidence in the low-risk population did not demonstrate a statistically significant effect. Of 14 discrete analyses for different combinations of antioxidants in the low-risk population, one study reported a statistically significant increase in relative risk of adenoma incidence in participants receiving vitamin E or vitamin E plus beta-carotene; however, this should be interpreted with caution because of the number of analyses undertaken. Reported side effects of antioxidants included pruritus (vitamins A, C, E), epistaxis (vitamin E), statistically significant increase in risk of haemorrhagic stroke (vitamin E), alopecia and dermatitis (selenium), yellowing of the skin and belching (beta-carotene). Other reviews have shown that antioxidants did not reduce gastrointestinal cancer incidence (beta-carotene and vitamin A

possibly increasing the risk),¹¹⁴ and that vitamin A, vitamin E and beta-carotene may increase overall mortality.¹⁵⁶

Discussion of clinical effectiveness evidence

Four studies of aspirin (81–325 mg/day) versus no aspirin in individuals with a history of adenomas (three studies) or history of CRC (one study) demonstrated a statistically significant 21% reduction in the relative risk of adenoma recurrence. There was also a significant 34% reduction in incidence of advanced adenomas when comparing aspirin with no aspirin (this was no longer significant when comparing aspirin alone vs placebo alone). Aspirin combined with folic acid produced a non-statistically-significant reduction in adenomas and advanced adenomas. Of the four studies of aspirin in the general population, two large studies giving a relatively low dose of aspirin (100–325 mg every other day) showed no effect on CRC over a follow-up period of 5–12 years. Two smaller studies giving a higher dose of aspirin (300–1500 mg/day) showed no effect on CRC over the first 10 years of follow-up, but demonstrated a significant 26% reduction in CRC incidence over the full 23-year follow-up period, and an even greater reduction when analysing years 10–19 only. Aspirin (600 mg/day) was assessed in a single study of HNPCC patients, which reported no statistically significant reduction in adenoma incidence or CRC incidence after 2.5 years of follow-up, but did report a significant reduction in time to first HNPCC cancer after 4 years of follow-up. Aspirin (600 mg/day) was also assessed in a single study of FAP patients; a preliminary report (so far under-recruited) showed no significant reduction in polyp number but a possible reduction in polyp size. Aspirin is associated with an increased risk of upper gastrointestinal toxicity including nausea and dyspepsia, peptic ulcers and gastrointestinal bleeding, as demonstrated in the larger studies included here and in a review which collated systematic reviews of adverse effects of aspirin,⁷⁶ with higher aspirin doses being associated with greater risk of toxicity. Previous studies, particularly in individuals at higher risk of cardiovascular disease, have indicated that aspirin may reduce the risk of myocardial infarction and ischaemic stroke but increase the risk of haemorrhagic stroke.

In terms of non-aspirin NSAIDs, two studies of celecoxib (400 mg/day) in individuals with a history of adenomas demonstrated a statistically

significant 34% reduction in the relative risk of adenoma recurrence and a statistically significant 55% reduction in the relative risk of advanced adenoma incidence. There were no studies assessing the effect of NSAIDs on CRC incidence in the general population. A small study of patients with the FAP genotype taking sulindac showed a non-statistically-significant reduction in adenoma incidence, while five studies of NSAIDs (sulindac, celecoxib or tiracoxib) in FAP patients with existing adenomas demonstrated reductions in polyp number and size, some statistically significant. The two celecoxib trials in individuals with a history of adenomas were stopped early because of an increased risk of serious cardiovascular events, which was statistically significant in one of the studies. A review that collated systematic reviews of adverse effects⁸⁸ also demonstrated increased risk of serious cardiovascular events with COX-2 inhibitors, the risk being greatest in patients with pre-existing cardiovascular risk factors. Two COX-2 inhibitors, rofecoxib and valdecoxib, were recently withdrawn from use as the result of concerns about their cardiovascular toxicity; a study of rofecoxib was therefore excluded from this review. COX-2 inhibitors may also increase the risks of hypertension and renal toxicity. NSAIDs can also cause upper gastrointestinal toxicity, although the risk is lower for COX-2 inhibitors than for some other types of NSAIDs.

Two studies of folic acid (0.5–1.0mg/day) in individuals with a history of adenomas showed no statistically significant effect on the relative risk of adenoma recurrence or advanced adenoma incidence. Three studies of folic acid (2.5 mg/day in two studies and 20mg/day in one study) in populations with no increased baseline risk of CRC demonstrated no statistically significant effect of folic acid on the relative risk of CRC, with the rates being slightly higher in individuals receiving folic acid. However, the duration of follow-up was 5 to 7 years, which may not be long enough to detect an effect on cancer incidence. No studies reported any difference in serious adverse event rates between the folic acid and placebo groups (except for one study reporting a higher incidence of non-CRC in the folic acid group, which was thought to be the result of the higher baseline rate of prostate cancer in that group).

Two studies of calcium (1200–2000 mg/day) in individuals with a history of adenomas demonstrated a statistically significant 18% reduction in the relative risk of adenoma recurrence. Two studies of calcium (1000–

1500mg/day) plus vitamin D (400–1100 IU/day) in populations with no increased baseline risk of CRC demonstrated no statistically significant effect on the relative risk of CRC. However, the duration of follow-up was 4 to 7 years, which may not be long enough to detect an effect on cancer incidence. One study assessed calcium in patients with adenomas due to FAP, and reported no significant reduction in polyp number or progression. No study reported any serious adverse events associated with calcium and/or vitamin D.

There were six studies of antioxidants (including vitamins A, C and E, beta-carotene or selenium) in individuals with a history of adenomas. Doses and combinations varied between studies. No statistically significant differences in relative risk of adenoma recurrence were demonstrated either when all antioxidants were analysed together or when the separate combinations were assessed separately. There were 12 studies of antioxidants in populations with no increased risk of CRC, with follow-up durations between 5 and 12 years. Across the nine studies comparing antioxidants to no antioxidants, there was no statistically significant effect on incidence of CRC. In addition, one study assessing the effect of antioxidants on adenoma incidence in the low-risk population did not demonstrate a statistically significant effect. Of 14 discrete analyses for different combinations of antioxidants in the low-risk population, one study reported a statistically significant increase in relative risk of adenoma incidence in participants receiving vitamin E or vitamin E plus beta-carotene; however, this should be interpreted with caution because of the number of analyses undertaken. Reported side effects of antioxidants included pruritus (vitamins A, C, E), epistaxis (vitamin E), statistically significant increase in risk of haemorrhagic stroke (vitamin E), alopecia and dermatitis (selenium), yellowing of the skin and belching (beta-carotene). Other reviews have shown that antioxidants did not reduce gastrointestinal cancer incidence (beta-carotene and vitamin A possibly increasing the risk),¹¹⁴ and that vitamin A, vitamin E and beta-carotene may increase overall mortality.¹⁵⁶ Observational studies have shown possible detrimental effects of antioxidant supplements on cardiovascular mortality, prostate cancer and lung cancer.¹¹⁴ As discussed by Bjelakovic *et al.*, beta-carotene may act as a cocarcinogen, and vitamin A may have pro-oxidant abilities. The action of antioxidants in reducing free radicals has been widely discussed in terms of potential benefits, but may also have undesired effects, because free radicals are required

in moderate concentrations for the removal of damaged cells from the body.¹¹⁴

In terms of study quality and internal validity, the main issue we identified for the studies in this review was the number of participants excluded from the main analyses. This was more of an issue for studies of adenoma recurrence because this outcome could only be assessed in participants who underwent a follow-up colonoscopy. Of the included studies assessing adenoma recurrence in people with a history of adenoma, two excluded less than 5% of randomised participants, 10 excluded between 5 and 20%, and four (all of which were studies of antioxidants) excluded more than 20%. In studies of CRC incidence in the low-risk population, the majority of studies analysed all (or nearly all) randomised participants, while five studies (mostly of antioxidants) excluded 5–20%. Of studies in people with FAP or HNPCC, three excluded less than 5% of randomised participants, three excluded 5–20%, four excluded more than 20%, and one was unclear. The majority of studies (though not all) described the generation of the randomisation sequence and method of allocation concealment. All studies were described as blinded except for one open-label study of aspirin, with most studies reporting details of blinding. Bjelakovic *et al.* undertook two reviews of antioxidants, first of trials assessing adenoma incidence, and second of trials assessing gastrointestinal cancer incidence.^{51,114} Interestingly, both reviews showed that studies with a high risk of bias demonstrated a statistically significant benefit of antioxidants, while studies with a low risk of bias showed a non-statistically-significant effect which actually favoured control. We have not undertaken separate analyses of antioxidants according to study quality because antioxidants were not shown overall to have a significant benefit. The majority of the other interventions included here were assessed in too few trials for separate analyses based on study quality to be feasible. However, we did undertake a sensitivity analysis for folic acid in people with a history of adenomas, omitting one trial of particularly low quality.

In terms of external validity (generalisability of trial populations to the wider population), the average age in all studies (other than those of FAP or HNPCC patients) was between 49 and 69 years. As screening has been introduced for individuals aged 60–69 years and is currently being extended to those aged up to 74, the age of included patients appears generalisable to people who may potentially use chemoprevention. Of the studies

in populations at no increased risk for CRC, some were conducted in the general population, and others in specific risk groups for other conditions. Three studies of antioxidants and/or folic acid and one study of aspirin involved participants with cardiovascular risk factors, one study of antioxidants and folic acid involved participants with atrophic gastritis, two studies of antioxidants involved smokers or people with asbestos exposure, and one study of antioxidants involved people with a history of skin cancer.

Compliance is an important issue for any intervention which is preventive rather than curative and which may potentially be recommended for use over an extended period of time. Although measures of compliance differed between studies, approximately 60–100% of patients across the different studies were reported as taking the majority of study medications at the latest time point reported, both in the intermediate-risk and low-risk populations. Five of eight studies of aspirin, and both studies of non-aspirin NSAIDs, selected the most compliant participants during an active or placebo run-in phase before randomisation, which may have increased estimates of compliance relative to non-trial populations.

The majority of studies in people with a history of adenoma only evaluated surrogate outcomes (adenoma and advanced adenoma incidence). Robust data on CRC incidence could not be obtained from these studies because of the relatively small number of participants and relatively short follow-up duration. The definition of advanced adenoma varied slightly between studies; most used a definition that included adenomas with a diameter ≥ 1 cm, villous or tubulovillous adenomas, and invasive cancer, whereas other studies reported separate data based on size or histological criteria. Although the existence of an adenoma–carcinoma sequence is widely described, the proportion of CRC that develop from pre-existing adenomas is not known, and a proportion of patients with colorectal adenomas will never develop invasive cancer.^{51,157}

It has been reported that the development of an adenoma into CRC may have a natural history of 10–15 years.¹⁵⁸ Therefore, it is unclear at present whether interventions given for a relatively short duration can interrupt this sequence, and also how long the follow-up duration needs to be to detect an effect on CRC incidence. For example, studies of aspirin showed no effect on CRC over

the first 10 years of follow-up but a significant effect over years 10–19 (although this analysis was partly confounded by differing doses and durations of treatment).²¹ Regarding the included trials of calcium, folic acid and arguably antioxidants, it was not clear whether the lack of reported effect on CRC incidence may be related to the lack of long-term follow-up.

There was some heterogeneity within our analyses, possibly as the result of differences in the duration of treatment and follow-up (particularly in the general population studies assessing CRC), sample sizes, doses and combinations of agents, and compliance rates. For example, there was relatively high heterogeneity between studies of antioxidants (which varied widely in terms of combinations and doses of agents); between general population studies of calcium (which varied in sample size, doses, duration of treatment and follow-up, and compliance rates); and between studies of folic acid (which varied in dose and sample size in the intermediate-risk population, and in age and gender of participants in the low-risk population). In terms of the studies assessing adenoma recurrence, there may also have been differences in colonoscopy methods and accuracy.

We chose to exclude observational data from this analysis because of the potential biases arising from lack of randomisation and blinding. Some of the interventions discussed in this assessment have shown effects in observational studies that have not been replicated in RCTs. Cohort studies indicated that regular use of aspirin is associated with a 22% relative risk reduction for CRC (RR 0.78, 95% CI 0.63 to 0.97); benefits were more evident when aspirin was used at higher doses and for periods longer than 10 years.⁷⁶ Cohort studies of non-aspirin NSAIDs also showed a reduction in relative risk for CRC of 39% (RR 0.61, 95% CI 0.48 to 0.77).⁸⁸ The Nurses' Health Study found that folic acid in green vegetables was associated with a modest reduction in risk of colon cancer, while folic acid supplementation had an even greater effect which increased over time. After 15 years, the incidence of colon cancer in those who regularly took folic acid was less than one-quarter of the incidence among those who did not (15 vs 68 new cases per 10,000 women aged 55 to 69 years). Other studies have also shown inverse associations between folate intake and colon cancer.¹⁵⁹ Low selenium intake (reflected in low serum selenium levels) has been shown to be associated with higher rates of colon cancer.¹⁶⁰

Other agents such as curcumin⁴⁵ and omega-3 fatty acids^{46,161} have also begun to be assessed for potential roles in chemoprevention, but were not included in this assessment because only preliminary data exist. Observational evidence has suggested that statins may reduce the risk of CRC.^{162,163} However, the randomised HPS study of simvastatin (with or without antioxidants) in adults with cardiovascular risk factors showed no effect on gastrointestinal cancer incidence (RR 1.02, 95% CI 0.85 to 1.23),¹⁴¹ and in a randomised trial of pravastatin in elderly patients with cardiovascular risk factors, the hazard ratio for gastrointestinal cancer incidence was 1.46 (95% CI 1.00 to 2.13, $p = 0.053$).¹⁶⁴ Therefore, the effect of statins on CRC is currently uncertain.¹⁶⁵

Some interventions (aspirin, NSAIDs and calcium) had a statistically significant effect in reducing adenoma recurrence in individuals with a history of adenoma. Further research would be useful to investigate the longer-term risk–benefit balance in this population; for example, whether there is a dose level that gives a significant benefit without unacceptable toxicity, what treatment durations are required, whether an effect on CRC can be demonstrated, and for how long the benefits are maintained after the intervention is stopped. In terms of the general population, it is important to consider the risk–benefit balance of chemopreventive strategies, and also to consider the relative benefit of chemoprevention when compared with, for example, action to increase compliance with screening programmes.⁴⁸ There is also a need for studies that include combinations of chemopreventive agents.

Conclusions for clinical effectiveness

Aspirin and celecoxib may reduce recurrence of adenomas and incidence of advanced adenomas in individuals with an increased risk of CRC due to a history of adenomas, and COX-2 inhibitors may decrease polyp number in patients with FAP. There is some evidence for aspirin reducing the incidence of CRC in the general population, although this effect was only observed in studies involving at least 300 mg/day aspirin with a follow-up duration greater than 10 years.²¹ There is an absence of long-term follow-up data for lower doses of aspirin or for other NSAIDs. Both aspirin and NSAIDs are associated with adverse effects, and so the risk–benefit ratio would have to be carefully considered

for each population before these agents could be recommended for chemoprevention. Calcium may also reduce adenoma recurrence in individuals with a history of adenomas; although studies of calcium and/or vitamin D in the general population did not demonstrate a significant effect on CRC, their follow-up durations were relatively short. Folic acid and antioxidants (vitamins A, C, E, beta-carotene and selenium) were not shown to reduce adenoma or CRC incidence, with some studies indicating an increase in these outcomes.

There are a number of uncertainties relating to the evidence of effectiveness. It is unclear whether the treatment durations and follow-up durations of existing studies are sufficient to detect any effect on CRC incidence. Therefore, the data on CRC are less robust than the data on the incidence of adenomas. In addition, careful consideration must be given to the balance between benefits and risks when considering any of these interventions as chemopreventive agents.

Chapter 4

Review of qualitative data on views and attitudes to the taking of agents that may be used for chemoprevention

Aims of review of qualitative data

The aim of the review of qualitative evidence was to explore adults' views regarding the taking of agents or supplements that may be used in the chemoprevention of CRC. The interventions in question are anti-inflammatory agents (NSAIDs, aspirin), vitamins, minerals, folate, selenium, calcium and dietary supplements generally.

Methods

A systematic search was performed to identify relevant studies. The inclusion and exclusion criteria were as follows.

Inclusion and exclusion criteria

Population/setting:

- adults only
- UK only (first search and screen); non-UK (second search and screen).

Interventions:

- anti-inflammatory agents (NSAIDs, aspirin), micronutrients (vitamins, minerals, folate, selenium, calcium) and dietary supplements generally.

Outcomes:

- attitudes, perceptions and beliefs surrounding the taking of such agents and supplements.

Study designs:

- qualitative: interviews, focus groups, open-ended questionnaires
- quantitative (satisfaction surveys).

Other:

- English language only
- dates: 2003 onwards.

Exclusion criteria:

- studies excluded if they do not fulfil the above criteria.

Identification and screening of studies

Two searches were performed by an information specialist (D Papaioannou) after the development and piloting of an appropriate search strategy. The first strategy sought studies that corresponded to the target population for the quantitative review, i.e. attitudes towards the stated agents reported in UK studies from the last 5 years. Consequently, the search used terms describing the agents of interest: NSAIDs, aspirin, vitamins, minerals, folate, selenium, calcium and dietary supplements generally, combined with a published, validated filter for identifying qualitative studies, together with the Medical Subject Headings (MeSH) term 'qualitative research',¹⁶⁶ and a pragmatically developed filter to identify UK studies (see Appendix 1 for the MEDLINE search strategy). The following databases were searched for published and unpublished material: MEDLINE, PREMEDLINE, CINAHL, EMBASE, AMED, ASSIA, IBSS, PsycINFO, Science Citation Index, and Social Science Citation Index. Searches for recently completed and unpublished research or grey literature were conducted using the Health Management Information Consortium (HMIC) and the King's Fund database. Searches were performed for citations from 2003 onwards, to increase relevance to current views and attitudes.

Three reviewers (C Carroll, A Booth, K Cooper) each screened a third of the citations for relevance

(based on the inclusion criteria) and any references identified for potential inclusion were discussed within the review team. Disagreements were either resolved by discussion or the full paper was retrieved to make a definitive judgment. Full papers of all relevant and potentially relevant citations were then screened using the same process.

This search (screen 1) produced only five papers that satisfied the initial UK-only inclusion criteria;¹⁶⁷⁻¹⁷¹ four of the studies focused on aspirin/NSAIDs¹⁶⁸⁻¹⁷¹ and one focused on folic acid;¹⁶⁷ none considered other agents or supplements, and no population used the agents for chemoprevention.

Given the apparent limitations of the sample, a decision was made to broaden the search beyond the original proposed scope of the review, to identify non-UK papers exploring people's views of taking any of these agents for the prevention or chemoprevention of CRC. This second search combined free text terms and related MeSH keywords for prevention and chemoprevention, with a filter for CRC, and the published, validated filter for identifying qualitative studies, with the addition of the MeSH term 'qualitative research', cited above (see Appendix 1 for an example search strategy). The following databases were searched for published and unpublished material from 2003 onwards: MEDLINE, PREMEDLINE, CINAHL, EMBASE, AMED, ASSIA, IBSS, PsycINFO, Science Citation Index, and Social Science Citation Index. Searches for recently completed and unpublished research or grey literature were conducted on HMIC and the King's Fund database.

The same process of study screening described above was followed for the results of this second search except for removal of the limitation to studies performed in the UK (screen 2). No non-UK studies were found to meet the revised inclusion criteria. The team therefore decided to revisit the original set of references from the first search (screen 3), but this time removed the UK-only limitation that had formerly been employed in screen 1. This resulted in the identification of 10 new non-UK studies that did satisfy the revised criteria (screen 3). The reference lists of all included studies were checked for additional, relevant studies, and some supplementary, unstructured, non-systematic searching testing various, different combinations of terms was performed by two members of the project team (A Booth, K Cooper). These supplementary

searches were not intended to be sensitive or comprehensive, but were undertaken as a means of identifying additional studies that may be relevant.

The overall aim of this iterative, pragmatic approach to searching was to identify a set of studies providing relevant information on views and attitudes towards the taking of chemopreventive agents.

Data extraction strategy

The resulting included studies were extracted using a form developed specifically for this review (see Appendix 3), and piloted on one included paper.

Critical appraisal strategy

The quality of included studies was assessed using a number of criteria derived from relevant critical appraisal checklists, principally for qualitative studies and surveys, the most dominant study designs.¹⁷²⁻¹⁷⁴ Using a small number of key quality assessment criteria, so-called prompts, that apply universally to qualitative studies, rather than appraising studies using large numbers of potentially irrelevant checklist questions, has been recommended as an approach for critical appraisal of qualitative studies.¹⁷⁵ It may not always be appropriate to exclude qualitative research studies simply on the basis of quality assessment of the study design^{175,176} so the aim of this assessment was to comment generally on the relative quality of the included studies, based on the following criteria common to the cited checklists for both types of studies described above: the reporting of their sampling strategies, and the reporting and conduct of methods of data collection and analysis. Satisfactory, good or very good studies provided details on all or most of these criteria, and the least good studies might only report on perhaps as few as one. The aim of this assessment was to explore quality as an explanation for any differences in the results of otherwise similar studies, and to consider its impact on the internal validity of the review. This is an accepted approach for quality assessment in the systematic review of qualitative data.¹⁷⁷

Evidence synthesis methods

Data for analysis consisted of either verbatim quotations from study participants or findings reported by authors that were clearly supported by study data. The latter included qualitative data from surveys, such as '75% of respondents said that

they were concerned about side effects of NSAIDs' or '27% of respondents reported that the views of family and friends affected their decision-making'.

Following discussions within the team regarding the competing merits of a grounded theory-type approach (starting with a completely blank sheet) and an augmentative approach (building on an existing model or framework) the decision was to go with the latter, a combination of framework analysis¹⁷⁸ and framework synthesis.¹⁷⁹⁻¹⁸¹ It was felt that a flexible framework-based approach does not militate against the identification or discovery of additional concepts. Indeed the existence of the best fit model could arguably be seen as privileging study-specific insights over the generic observations made within the pre-existing model. Nevertheless, the review team recognises that this approach represents a methodologically innovative middle ground on the continuum between grounded theory-type and framework-based syntheses and acknowledges the need for further evaluation.

Framework analysis involves the identification of *a priori* themes against which to map data from the studies identified for the review. However, in this case these predetermined themes were generated from a relevant pre-existing model in the literature, as is the case with framework synthesis. This model was identified in the following way. Key concepts (e.g. influence of family, health practitioners, media, considerations of cost etc.) were identified from the preliminary scoping literature searches and from an initial examination of articles for potential inclusion, before a definitive judgement. These concepts in combination were used to inform supplementary searches to try to identify existing models or frameworks within the general topic area of attitudes to vitamins and supplements. However, these supplementary searching processes failed to find a model or framework that was completely prespecified to the team's satisfaction. Nevertheless they did identify a framework that represented a 'best fit approach' and included the majority of the key concepts. This 'contingent' framework formed the categories under which the data extracted from the qualitative studies were summarised. This model was a conceptual model (not evidence-based, i.e. based on the author's views, not research) of young women's views and attitudes to the taking of micronutrients (including vitamins, minerals).¹⁸² This model provided an initial framework and pre-existing themes against which to map and code the data from studies identified for this review. A list of themes was derived from the conceptual model

and, if relevant, extracted data were coded against these pre-existing themes. New themes were created where data did not translate into any of the pre-existing themes. In this way, a relevant existing model acted as the basis for the synthesis and could be built-on, reduced or added to by these new data. Dixon-Woods *et al.*¹⁸³ suggest that such methods are most appropriate where concepts are relatively 'secure' and 'well specified'. Framework synthesis also usually excludes studies of lower quality, but this was not done in this case, and so differs from the published method.¹⁸¹

This method of synthesis therefore used current methodological developments within qualitative data synthesis for systematic review and the production of accompanying conceptual models and frameworks. It offered a means not only to reinforce, critique and develop an existing published model, conceived for a specific population, but also, by starting from the principle of *a priori* determined themes rather than the generation of theory grounded in data, produced a process of synthesis that was relatively rapid when compared with certain other more interpretative forms of synthesis (e.g. thematic analysis).¹⁸⁴

Two reviewers (C Carroll, K Cooper) each extracted data from half of the included studies using a form developed for this review. The reviewers assigned data to preset themes and, where relevant, created new themes that better captured or described the data. Each reviewer then checked and examined critically the extraction and assignment of data to themes performed by the other. A third reviewer (A Booth) independently examined the extracted data and, using a framework analysis approach, generated a new list of themes, independent from the published conceptual model. The team of reviewers then discussed the data and resulting list of themes, including themes recognised from the pre-existing model and any new themes generated by the study data. A consensus was reached on which preset themes were supported by the data; whether any of the new themes identified by all three reviewers mapped into any of the preset themes or into one another; and on the finalised list of new themes. These themes or concepts were then used to develop a new, revised conceptual model, drawing on the earlier model, to describe and explain people's views around the taking of aspirin, NSAIDs and micronutrients, such as vitamins, minerals, folic acid and other dietary supplements.

Results

The first search of electronic databases identified 1805 citations after the removal of duplicates. From the initial screen (screen 1), five studies were found from the UK that satisfied the inclusion criteria.¹⁶⁷⁻¹⁷¹ The second search for relevant non-UK studies identified 982 citations after the removal of duplicates. The screening of this database identified no relevant non-UK studies (screen 2). The third screen (screen 3) revisited the results of the first search, but using the revised inclusion criteria, i.e. the inclusion of non-UK studies, and identified 10 new papers, as noted above.¹⁸⁵⁻¹⁹⁴ Five further studies were identified by unstructured searching.¹⁹⁵⁻¹⁹⁹ In total, 20 studies were included. For details of the search and selection process, see the flow diagram of studies (Figure 12). No additional studies were found by reference tracking.

The characteristics of the included studies are described in Table 28. Nine studies were conducted in the USA;^{185,186,189,192,194-197,199} one of these was colocated in Puerto Rico;¹⁸⁵ five were conducted in the UK,¹⁶⁷⁻¹⁷¹ three in Australia,^{190,193,198} two in Canada^{187,188} and one in Germany.¹⁹¹ Thirteen studies evaluated adults' views concerning the taking of vitamins and minerals,^{169,185,187,189-193,195-199} five studies considered aspirin or NSAIDs,^{168-171,194} two folic acid^{167,185} and two dietary supplements generally.^{186,188} Only four studies explored the views of participants who had either a cancer diagnosis^{186,197,199} or a family history of cancer,¹⁹⁸ but 10 of the other included studies did focus specifically on either prevention alone¹⁶⁷ or the long-term management of chronic conditions, which included elements of prevention, including arthritis,^{170,194} heart disease,^{192,193} renal problems,¹⁸⁸ type 2 diabetes,¹⁹⁶ or a range of conditions.^{168,187,191} Most studies used interviews and/or focus groups to elicit people's opinions and views on the taking of the relevant agents;^{167,168,170,185-187,189,190,193-196} eight studies used structured surveys or questionnaires.^{169,171,188,191,192,197-199}

The 15 studies identified by the initial search came from six different databases: EMBASE,^{168,169,171,187} AMED,^{189,191,193,194} MEDLINE,^{190,192} MEDLINE In-Process & Other Non-Indexed Citations,^{167,170,185} CINAHL,¹⁸⁸ and the Science and Social Science Citation Index.¹⁸⁶ This is typical of findings regarding the distribution and degree of dispersal of social science and qualitative studies.^{200,201}

Nineteen of the 20 studies were of satisfactory or good reported quality, providing clarity and detail on the sampling of participants, and the collection and analysis of data. No studies failed to provide a clear description on one of more of these points. Some studies could have applied a more appropriate method than the one used (e.g. purposive rather than convenience sampling, interviews rather than surveys),^{169,171,188,190-192,194,195,197-199} although the study design was still transparent and otherwise robust in each case. Study quality cannot therefore be said to have been a moderator of the findings.

Synthesis

The following list of themes was derived from the conceptual model of factors determining use of micronutrients among women of reproductive age,¹⁸² and constituted the *a priori* themes against which data were extracted from included studies (Box 1).

The synthesis generated the accompanying model presented in Figure 13. This model describes the processes involved in an individual's decision about whether or not to take NSAIDs, aspirin, folic acid, vitamins, minerals, calcium or other dietary supplements. External factors, such as the influence of health professionals and family members, and internal factors, such as a person's own experience or health, all have an impact on an individual's perceived need for an agent or supplement, and their subsequent decision about whether or not to take it. These processes, described in the model Figure 13, correlate with versions of the Perceived need and Decision elements of the Huffman¹⁸² model of micronutrient use among women, and the Contemplation and Determination elements of Prochaska and Velicer's 1997 Stages of Change model regarding the development of health behaviours.²⁰²

A third, vital element in the decision-making process is the influence of the perceived risks or benefits associated with an agent or supplement, which appear as Benefits and Negative factors affecting use in the Huffman model.¹⁸² However, the model resulting from findings of this review highlights the even more complex nature of the influence of risk and benefit on decision-making and use. The perceived risks or benefits of an agent or supplement can either directly influence an individual's decision to use it, or may inform a

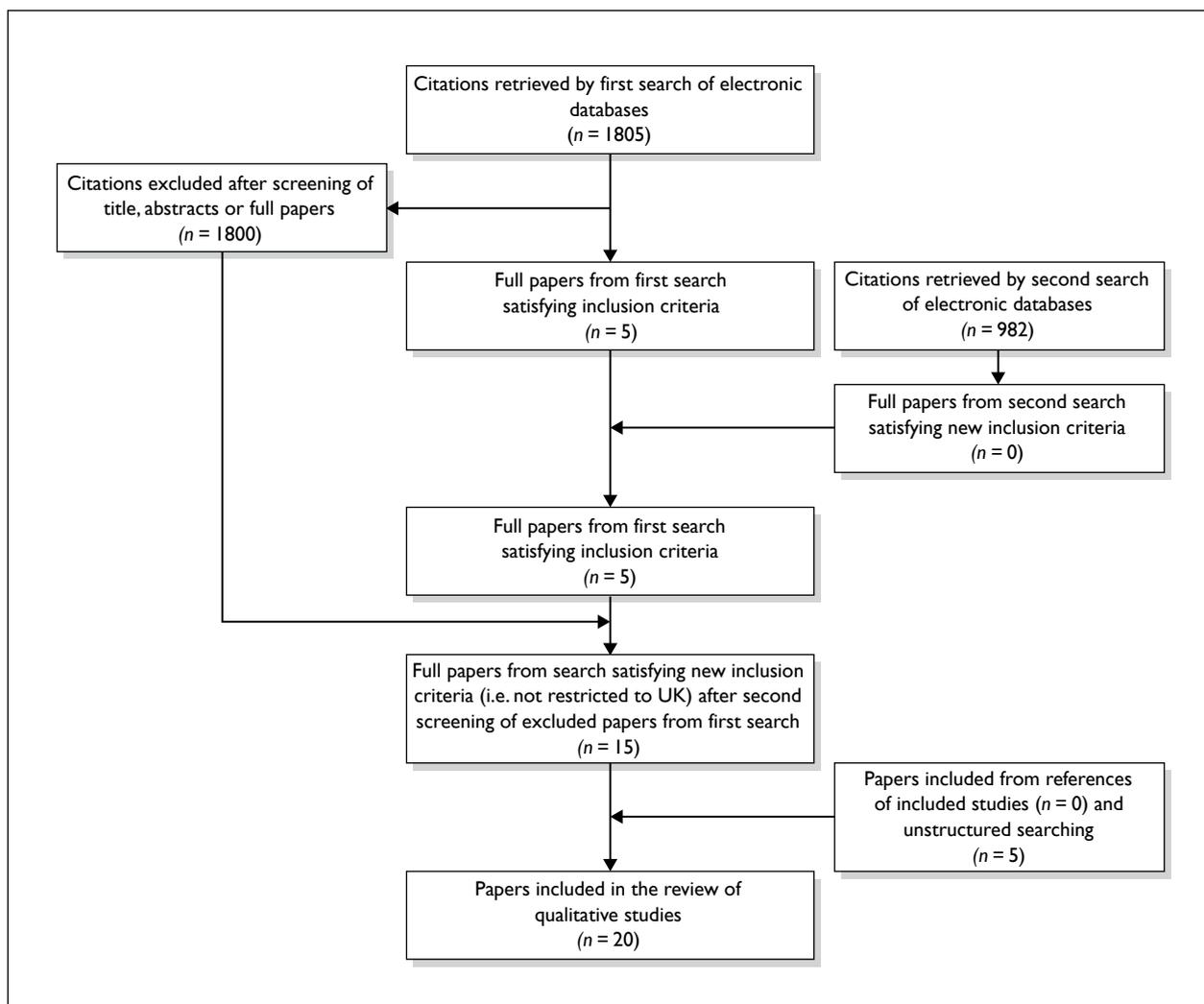


FIGURE 12 Flow diagram of study inclusion and exclusion.

personal assessment of the trade-off between these two elements, which in turn may also affect the decision-making process.

This process then results in the use or non-use of the agents in question, the so-called Action Stage of the Prochaska and Velicer's 1997 model.²⁰² Maintenance or continuity of use may be affected by three elements: the risks (side effects) and/or benefits experienced by taking the agents or supplements; the physical properties of the agents, which may facilitate or act as a barrier to continued use; and an individual's age or gender, which may predict the likelihood of their maintenance of a course of therapy.

All of the factors and processes described in this evidence-based model, determining the decision to take, and to continue to take, NSAIDs, aspirin, folic acid, vitamins, minerals, calcium or other dietary supplements, have emerged from qualitative literature published in the previous 5 or 6 years. The decision process runs from the first stages of perceived need, on the left, through decision-making itself, to final non-use or use, and maintenance of use on the right. The arrows representing Prochaska and Velicer's 1997 Stages of Change model, below our model, flow in the same direction, capturing the similar stages and processes of contemplation, determination and action. The details of this evidence are provided as follows.

TABLE 28 Characteristics and quality of studies reporting people's views and attitudes towards NSAIDs and supplements

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Carnes 2008 ⁷⁰ UK	To explore the rationale behind patients' decisions to choose topical or oral pain-relief medication	Older adults with knee pain (n = 30) Age 50–70+ years 18 men; 12 women Management and prevention of long-term chronic conditions	NSAIDs	Purposive samples from an RCT and related preference study on choice of topical or oral NSAIDs, to gain insight from a mixed sample in terms of choice of treatment, age, sex and GP	15 telephone interviews about medication preferences; 15 face-to-face interviews about adverse effects; using topic guide based on literature, brainstorming and exploratory, pilot interviews Framework analysis was applied to transcripts: triangulation was achieved by two authors validating and/or challenging thematic interpretation of transcripts by one author	Interviews are an appropriate method for eliciting people's views; topic guide for interviews was based on literature and piloting; purposive sampling was appropriate; triangulation of analysis A very good-quality qualitative study
French 2008 ⁷¹ UK	To explore beliefs about risks and necessity in taking mild analgesics	University students (n = 291) Age NR 104 men; 187 women Specific sample from the general population using relevant agents for short-term pain management	NSAIDs, aspirin	Convenience sample; response rate 87%	Validated survey: beliefs about medicines questionnaire (BMQ) Descriptive statistics and between groups tests	A survey (though validated) is not the most appropriate method for eliciting people's views; purposive sampling would have been more appropriate than convenience sampling; descriptive and group-based comparison statistics only, which are of limited value for 'views' as they can lack depth A satisfactory survey study
Tedstone 2008 ⁶⁷ UK	To explore consumers' knowledge in relation to folic acid and neural tube defects, and their views on various methods to increase folic acid intake	Young people, especially young mothers (n = NR) Age NR Gender NR Prevention	Folic acid	Quota sampling, especially from deprived communities to ensure sociodemographic and economic balance within and between groups	Five focus groups (12 people in each group) using a 'reconvened group approach' to facilitate reflection on issues; 24 face-to-face interviews; seven friendship groups (three to six people); interviews recorded and transcribed Content analysis of transcripts by one author, critically assessed by two others	Interviews and focus groups are appropriate methods for eliciting people's views; purposive sampling was appropriate but full details of sample were not given; type of analysis used was appropriate A good-quality qualitative study
Wazaify 2005 ⁶⁹ UK	To ascertain the general public's opinion and perceptions of over-the-counter medicines	People aged 16 or over (n = 1000) Age 16 years or over 417 men; 583 women General population using agents/supplements	Aspirin, NSAIDs, vitamins, minerals	Members of the public who appeared to be over 16 years of age were randomly approached and asked to participate	Semi-structured, pretested questionnaire with 34 questions (a mix of preformulated and free-text responses) – tool was administered using a structured interview technique Descriptive statistics and between groups tests	Questionnaires are not the best method for eliciting people's views; interviews would have been better; questionnaire was piloted; 'random' sampling; largely descriptive statistics only; good sample size A satisfactory survey study

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Townsend 2003 ⁶⁸ UK	To gauge participants' feelings about long-term use of drugs (including aspirin and NSAIDs) to manage chronic multiple morbidity	Adults with multiple chronic conditions (n = 23) Age 50 years (mean) 10 men; 13 women Management and prevention of long-term chronic conditions	NSAIDs	Purposive sampling of men and women resident in a large, socially varied (but mainly urban) area, who report high morbidity (four or more chronic conditions) 23 of 41 responded	Semi-structured interviews (no topic guide); interviews recorded and transcribed Analysis: constant comparative method conducted by several authors independently to identify major themes; themes agreed by discussion, one author did 'deeper' coding of subthemes	Interviews are an appropriate method for eliciting people's views, but no details were reported of topic guide for interviews; purposive sampling was appropriate; details of coding and analysis given A good-quality qualitative study
Huber 2004 ⁹¹ Germany	To evaluate use of and attitude towards complementary and alternative medicine (CAM) and conventional medicine	Various chronic conditions (n = 350) Mean age 55 years 65% men; 35% women Management and prevention of long-term condition	Vitamins, minerals, any CAM therapy	Purposive sampling of inpatients at a German university hospital (in cardiology, gastroenterology, oncology and psychosomatics departments); 80% response rate	Questionnaire survey based on literature and an existing questionnaire Descriptive statistics reported only. Questions on attitudes were answered on a 5-point scale and a rating of 4 or 5 was classified as agreement for the purpose of analysis	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only; good sample size A satisfactory survey study
Porter 2008 ⁹⁷ USA	To explore reasons for maintenance or discontinuation of CAM therapies	Men treated for prostate cancer 2 years earlier (n = 177) Mean age 66 years 177 men; 0 women Management and prevention of health condition	Vitamins, minerals, any CAM therapy or dietary supplement	Purposive sampling from participants in another study, from cancer centre and affiliated hospitals. Response rate 79%	Questionnaire survey based on literature and prior studies Descriptive statistics only	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only A satisfactory survey study
Lindsey 2007 ⁸⁵ USA, Puerto Rico	To explore beliefs and behaviours relating to vitamin use	General population from USA (n = 184) and Puerto Rico (n = 49) Age 18–34 years (USA); 15–50 years (Puerto Rico) 0 men; 233 women Prevention and well-being	Vitamins, minerals, folic acid, dietary supplements generally	US study: sampling via telephone, range of ages and postal codes Puerto Rico study: convenience sampling at supermarkets	US study: 24 focus groups of up to nine people in each. Puerto Rico study: five focus groups of 10–12 people each Transcripts coded by one of the focus group moderators and one other researcher, using themes derived from the research questions and topic guide and emerging from the data. Transcripts content-analysed using NVIVO and ATLAS. Each transcript coded by each coder independently, and inter-rater reliability was 0.91	Interviews are an appropriate method for eliciting people's views; sampling was appropriate; coding of interviews was performed by two analysts A good-quality qualitative study

continued

TABLE 28 Characteristics and quality of studies reporting people's views and attitudes towards NSAIDs and supplements (continued)

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Matthews 2007 ⁹⁹ USA	To assess CAM use and association between medical factors (cancer and other) or psychosocial factors and CAM use	Breast cancer survivors, mean of 5 years beyond active medical treatment (n = 115; 69% reported current use of CAM) Age 30–78 years (mean 56) 0 men; 115 women Management and prevention of health condition	Vitamins, minerals, any CAM therapy or dietary supplement	Purposive sampling during routine clinic visits	Questionnaire survey via structured telephone interview, partly based on validated measures and partly on a literature review and panel of experts Descriptive statistics only	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only. Questionnaire was partially validated A satisfactory survey study
Arcury 2005 ⁸⁹ USA	To explore health beliefs and behaviours surrounding CAM therapies	Community-dwelling older adults (n = 145) Age 70 years or over 57 men; 88 women 54 White, 48 African American; 43 Native American General population: not specifically prevention, management or long term	Vitamins, minerals	Purposive (approaching potential participants) and convenience (volunteer) sampling; and to achieve equal ethnic distribution	In-depth semi-structured interviews (between two and four per person, over 1 year); interviews recorded and transcribed Systematic text analysis: one author codes, one reviews and makes modifications; coded text then analysed by text analysis software: new codes	Interviews are an appropriate method for eliciting people's views, but no details were given on the topic guide for interviews or its piloting; combination of purposive and convenience sampling – the latter is less appropriate for this type of study; coding of interviews was only performed by one analyst – double-coding or validation would have been better A satisfactory qualitative study
Chagan 2005 ⁹² USA	To assess attitudes and beliefs regarding the safety and effectiveness of vitamin, mineral and herbal supplements in patients with cardiovascular diseases	Adult inpatients with cardiovascular diseases (n = 198; 94 supplement users and 104 non-users) Age 19–102 years (mean 60 years) 118 men; 80 women Management and prevention of long-term condition	Vitamins, minerals, dietary supplements generally	Purposive sampling via hospital physicians	Questionnaire survey administered via interview. Survey tool adapted from a previously published survey Descriptive statistics reported only. Attitudes and beliefs regarding the safety and effectiveness of supplement users and non-users were compared between supplement users and non-users via a chi-squared test for categorical data and Student's t-test for Likert-type scale questions	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only; good sample size A satisfactory survey study

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Reedy 2005 ⁶⁶ USA	To explore reasons for taking supplements; beliefs behind taking supplements	Older adults with (n = 10) and without (n = 12) a history of CRC Age 52–82 years (mean 65 years) 12 men; 10 women 15 White; 7 Black Management and prevention of long-term condition, and to improve health generally	Dietary supplements generally	Purposive sampling from a case-control health promotion study Response rate: 85%; 10 with a history of CRC; 12 controls	In-depth, semi-structured, open-ended telephone interview; interviews recorded and transcribed Coding by one reviewer to identify themes and compare groups	Interviews are an appropriate method for eliciting people's views, but no details were given on the topic guide for interviews or its piloting; purposive sampling was appropriate; coding of interviews was only performed by one analyst – double-coding or validation would have been better A good-quality qualitative study
Fraenkel 2004 ⁶⁴ USA	To examine the influence of medication characteristics (e.g. risks, benefits, costs, route of administration) on patients' treatment preferences for knee osteoarthritis	100 older patients with symptomatic knee osteoarthritis (n = 100) Mean age 70 years 21 men; 79 women Management of long-term condition	Aspirin, NSAIDs (and other treatments for osteoarthritis)	Purposive sampling: consecutive patients with knee osteoarthritis attending rheumatology practices	Interactive computer questionnaire administered during interviews. Descriptions of medication characteristics adapted from patient information sheets, and face and content validity assessed by experts and laypersons Conjoint analysis to derive patients' preferences for various medication characteristics (e.g. administration, risks, benefits, costs). The relative importance of different characteristics was expressed as a percentage of total importance	This study mainly aimed to assess the influence of different medication characteristics on treatment preferences, rather than a more general assessment about attitudes to medications. Therefore, this study used an interactive computer questionnaire rather than, for example, interviews. Purposive sampling appropriate A satisfactory survey study
Oldham 2004 ⁶⁵ USA	To explore attitudes towards taking dietary supplements	Older women with type 2 diabetes diagnosed for at least 1 year (n = 9) Age 65 years or over 0 men; 9 women Management and prevention of long-term chronic condition	Vitamins, calcium, dietary supplements generally	Purposive: nurse educators nominated participants who they knew met the selection criteria	Semi-structured interviews with open-ended questions led by an interview guide consisting of 10 pretested questions; interviews recorded and transcribed; respondent validation Data analysis guided by Moustakas's (1994) ⁷¹ method of analysing phenomenological data	Interviews are an appropriate method for eliciting people's views; interview guide had been piloted; very selective sampling; not appropriate; a limited form of respondent validation of interview text; no details on how many analysts performed coding A satisfactory qualitative study

continued

TABLE 28 Characteristics and quality of studies reporting people's views and attitudes towards NSAIDs and supplements (continued)

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Miller 2003 ⁹⁵ USA	To explore the decision-making criteria that women use in selecting dietary supplements	Women who consumed a dietary supplement at least four times per week ($n = 51$) Age 25–45 years 0 men; 51 women 43 White, 8 African American General population: not specifically prevention, management or long-term	Vitamins, calcium, dietary supplements generally	Convenience (volunteer) sampling; response rate 84% (nine did not fit criteria; one did not complete the interview)	In-store shopping interview based on a pretested verbal protocol; interviews recorded and transcribed Content analysis performed independently by two authors; then cluster analysis was performed to identify similarities and differences in the decision-making	Interviews are an appropriate method for eliciting people's views, but no details were given on the topic guide for interviews or its piloting; combination of purposive and convenience sampling – the latter is less appropriate for this type of study; coding of interviews was only performed by one analyst – double-coding or validation would have been better A satisfactory qualitative study
Legare 2007 ⁸⁷ Canada	To explore women's decision-making around the use of natural health products at menopause and to develop a decision aid	Menopausal or postmenopausal women ($n = 40$) Age 45–64 years 0 men; 40 women Also key informants (doctors, nurses, health-store owners) who may advise women on use of natural health products Management of a condition	Vitamins, minerals	For menopausal women: purposive sampling via bulletin boards, newspapers, etc. For key informants: purposive sampling within organisations	Six focus groups with menopausal or postmenopausal women, plus interviews with 15 key informants. Semi-structured topic guides based on standardised questions for conducting decision-making needs assessments. Recorded and transcribed Content analysis was guided by the Ottawa Decision Support Framework. Participants sent transcript with summary of identified themes and asked to verify accuracy	Interviews are an appropriate method for eliciting people's views; topic guide focused specifically on decision-making needs assessment; purposive sampling was appropriate; respondents validated the findings; A good-quality qualitative study
Spanner 2005 ⁸⁸ Canada	Attitudes and beliefs about, and use of, dietary supplements	Adults with chronic renal insufficiency ($n = 100$; 45 dietary supplement users, 55 non-users) Mean age 60 years (users) and 64 years (non-users) 68 men; 32 women Management and prevention of long-term condition	Dietary supplements generally	Purposive sampling at outpatient nephrology clinic	Questionnaire survey administered via interview Descriptive statistics reported only	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only; good sample size A satisfactory survey study

Study details	Research question or objective	Population (and their relevance to the issue of chemoprevention)	Agent of interest	Recruitment/sampling	Data collection and analysis	Comments
Cowan 2008 ⁹⁸ Australia	To assess beliefs, and reported and intended health behaviours, of unaffected men in response to information about their family history of prostate cancer	Men with a family history of prostate cancer ($n = 280$) Age 44% < 55 years, 32% 55–65 years, 24% 65+ years 280 men; 0 women Prevention of health condition	Vitamins, minerals, dietary supplements generally	Purposive/convenience sampling via advertisements for men with self-reported family history of prostate cancer, and from an existing study in which men were identified via relatives	Questionnaire survey including previously validated and new items, piloted Descriptive statistics only	Questionnaires are not the best method for eliciting people's views; interviews would have been better; descriptive statistics only. Questionnaire was piloted and partially validated A satisfactory survey study
Connor 2004 ⁹⁰ Australia	To explore attitudes to and reasons for use of alternative therapies (as part of a more general ethnographic study of health and illness)	General population ($n = 111$ for interviews, n not reported for focus groups) Age NR Gender NR General population: not specifically prevention or management	Vitamins, minerals, any CAM therapy	Convenience sampling via local sporting, church, school and social organisations and posters in post offices and shops	Semi-structured interviews ($n = 111$) and focus groups (n not reported); transcribed Data analysed by text analysis software; themes of interest further investigated by scrutinising transcripts and notes	Interviews are an appropriate method for eliciting people's views, but few details on the topic guide; convenience sampling less appropriate for this type of study A satisfactory qualitative study
George 2004 ⁹⁵ Australia	To investigate use of and beliefs about CAM	Patients with moderate-to-severe chronic obstructive pulmonary disease Survey: $n = 173$ (41% using CAM) Interviews: $n = 28$ (43% using CAM) Mean age 70 years 62% men; 38% women Management and prevention of long-term condition	Vitamins, minerals, any CAM therapy or dietary supplement	For survey of CAM use: data from patients in RCT For interviews: purposive sampling from an RCT and databases of respiratory patients	(1) Questionnaire survey to investigate frequency of use of medicines and CAM (2) In-depth interviews on beliefs about CAM. No information on development of interview topic guide. Interviews recorded and transcribed One researcher analysed transcripts for relevant content and themes using XT ANALYSIS software. Themes were verified by a second researcher and discussed among the research team	Interviews are an appropriate method for eliciting people's views, but few details on the topic guide; purposive sampling was appropriate; small sample size A satisfactory qualitative study

CAM, complementary and alternative medicine.

BOX 1 A priori themes for data extraction

Perceived need	1. Family factors affecting perceived need
Decision-making	2. Personal factors affecting perceived need
	3. Media representations of perceived need
	4. Spending capacity
	5. Media input into decision-making
Access	6. Physicians input into decision-making
	7. Family members input into decision-making
	8. Community input into decision-making
	9. Pharmacy input into decision-making
Use	10. Access: obtaining micronutrients
	11. Perceived benefits
	12. Perceived risks (negative factors)
	13. Habitual use
	14. Intermittent use

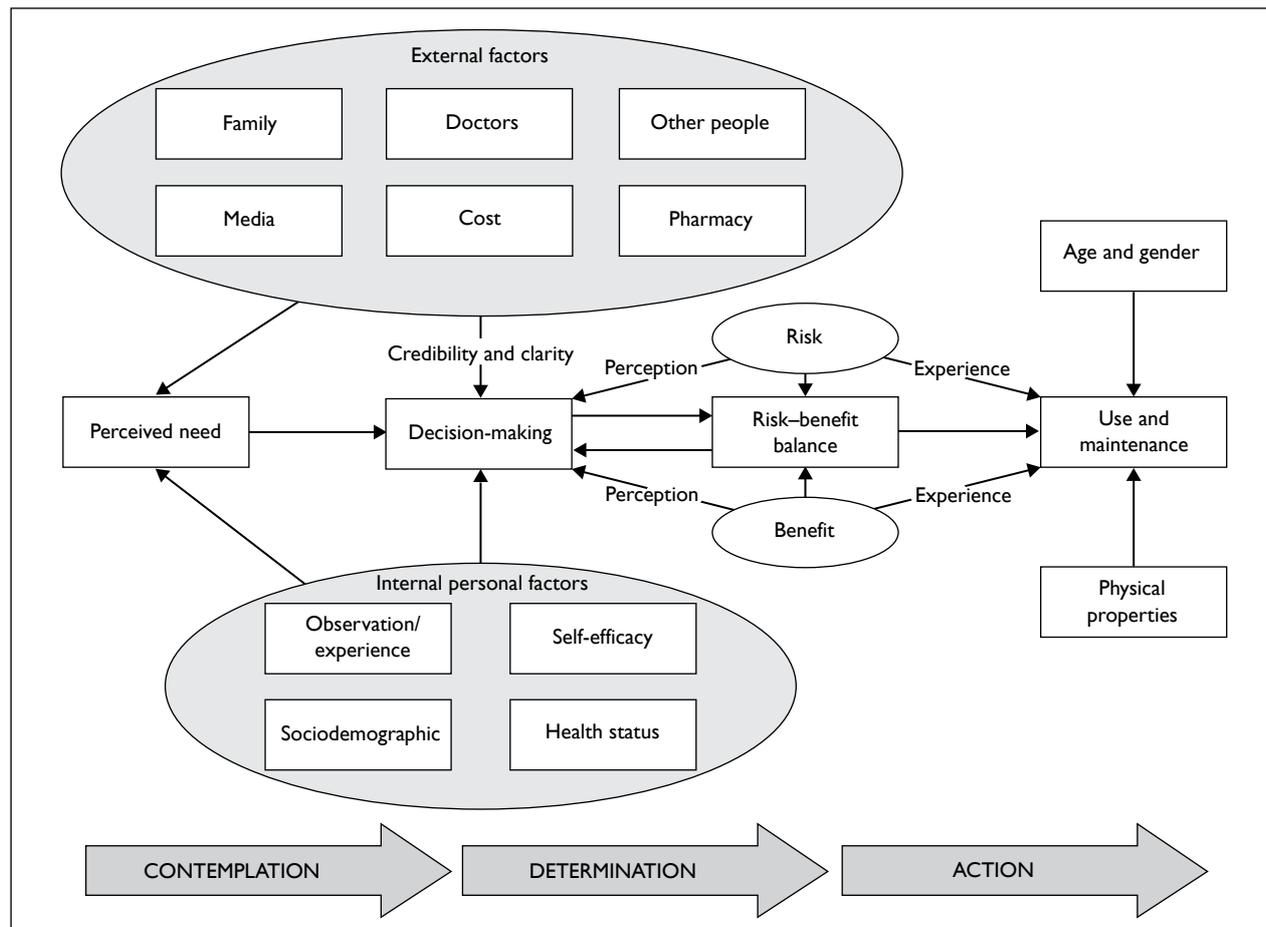


FIGURE 13 Conceptual model to describe views and experiences of adults concerning the taking of micronutrient supplements, aspirins and NSAIDs. Adapted from Huffman 2002¹⁸² and Prochaska and Velicer 1997.²⁰²

External factors affecting decision-making

Doctors and health professionals

Ten of the included studies reported people's views of, and attitudes towards, input by health professionals into the decision-making process when deciding whether or not to take NSAIDs, vitamins and minerals or dietary supplements generally.^{167-170,186-189,191,193} The extent to which these professional groups influenced people's decision-making appears to be determined by the type of agents or supplements involved. In three studies of NSAID use, people treated their doctors as the principal source of information on the taking of these agents,¹⁶⁹ or the most trustworthy source,¹⁷⁰ or the source of advice on dosage.¹⁶⁸ In contrast, only two of seven studies exploring people's views relating to the taking of vitamins, minerals, folic acid or complementary therapies, reported a similar perception of the authoritative nature of this professional group.^{188,189} The other five studies reported that people did not really want to talk to their doctors about supplement use,¹⁸⁶ or that they wanted to but found them to have closed minds to alternative therapies¹⁸⁷ or to be too busy to provide adequate or sufficiently long consultations on the use of these agents.^{187,191,193} Health professionals were also either seen as less trustworthy than other sources with reference to vitamins and minerals and other supplements^{167,186,191} or their advice was perceived to be less clear than required.¹⁸⁶

Family and friends

Eleven studies reported people's views on whether or not, and how, family members and friends influenced their decision to take NSAIDs, vitamins and minerals or dietary supplements.^{167-170,185-188,190,191,193} Family and friends played two principal roles, determined in large part by whether the agents concerned were antioxidants, such as vitamins, minerals and other supplements, or if they were drugs such as NSAIDs. On the one hand, family acted as a source of information and advice about agents. This was principally the case when the agents concerned were vitamins, minerals and other supplements.^{185-188,190,191,193} Different family members and friends were often reported to be the source of conflicting information, complicating the decision-making process.¹⁸⁷ However, when the agents were folic acid for pregnant women or NSAIDs, family members could also actively recommend the taking of them on the basis of their own personal experience, going beyond simply acting as a source of information or advice.^{167,169,170} The influence of family members on the decision-

making process could also be implicit: people reported taking NSAIDs because these drugs enabled them to live a normal life, socially and domestically, with their family (however, it should be noted that these studies related to NSAID use as treatment for an existing condition rather than as a preventive agent).^{168,170} In this sense, family members also influenced people's perceived need regarding the taking of agents, especially NSAIDs and folic acid: family members would recommend the taking of folic acid as something necessary and beneficial, and some people felt that they needed to take NSAIDs to function normally as part of their family.¹⁶⁷⁻¹⁷⁰

Alternative therapists

Participants in four studies reported how alternative therapists influenced their decision to take vitamins, minerals and other complementary and alternative (CAM) therapies, providing information and advice.^{187,188,190,191} Unlike doctors and health professionals, alternative therapists were believed to be willing to spend more time with people to discuss and offer advice on supplements.

Media

The influence of media on people's decisions whether or not to use a supplement or agent was reported in six studies, five of which concerned dietary supplements or alternative therapies,^{186,188,189,191,193} and only one of which considered NSAIDs.¹⁷⁰ Several different types of media were reported to be responsible for influencing people's decisions. The print media, including adverts, was mentioned by participants in three studies,^{186,189,193} while the internet,¹⁸⁸ television and radio¹⁹¹ were each mentioned by participants in a study, all in relation to decisions to use supplements or CAM therapies. Articles and promotional literature were identified as a credible source of information by older people who used NSAIDs for symptom management.¹⁷⁰

Cost

Five studies reported that the cost of the agents or supplements could affect people's decisions about whether or not to take them, and this applied regardless of whether the agent in question was an aspirin or NSAID,¹⁶⁹ folic acid,^{167,185} or vitamin and minerals.^{169,187,195} Three of the five studies focused on access to these agents by general populations,^{169,185,195} rather than groups with chronic conditions or cancer: cost may be a lesser factor for those with a greater motivation to take such agents or supplements.

Pharmacy

Two issues emerged from four studies concerning input from pharmacists. First, participants in two studies reported that recommendations and advice from pharmacists affected their use of over-the-counter medicines such as aspirin, and of vitamins and minerals.^{169,187} Second, participants in two studies reported wanting information on optimal dose from pharmacists; this was felt to be particularly unclear for vitamins and minerals,¹⁹⁵ but also applied to NSAIDs.¹⁷⁰

Summary

The impact on supplement use of the external factors described above was not straightforward, but rather could be moderated by the credibility and clarity of the information given and its source. The need for trustworthy sources of information, regardless of agent or supplement, was raised by participants in four studies.^{167,170,185,195} Doctors were perceived as either very credible sources of information,^{167,170} or as unhelpful,^{186,187,191,193} depending on whether the agent in question was an NSAID¹⁷⁰ or folic acid,¹⁶⁷ or a dietary supplement, such as vitamins or minerals.^{186,187,191,193} Participants reported wanting clarity in the advice that they were given, from whatever source, but also reported that such clarity was rarely forthcoming, whether from doctors,^{186,187} family¹⁸⁷ or the labels on supplements.¹⁹⁵

Internal factors affecting decision-making

Observation/experience

Previous positive experiences of taking either NSAIDs^{169,170} or vitamins and minerals^{169,193,196} have been found to be a factor affecting individuals' decisions about whether or not to take them. However, negative experiences of both types of agent were also found to adversely affect decisions concerning use, e.g. if a supplement was perceived to have 'not worked' previously,^{185,186} or if an individual's experience was that there was a perceived stigma to the taking of strong painkillers such as NSAIDs.¹⁶⁸

Health status

Participants in seven studies identified personal health status as a factor in their decision to take NSAIDs,^{170,171,194} vitamins, minerals, or other dietary supplements.^{185,186,196,199} The worse a person's state of health, the more likely they were to take supplements or drugs; either NSAIDs for pain relief^{171,194} or multiple supplements to manage

different conditions.^{186,196} Participants in three studies also reported that they decided to initiate the taking of dietary supplements as a result of a cancer diagnosis, increased risk of cancer, or the presence of other major conditions, such as heart disease.^{186,198,199} The presence of pre-existing conditions, which could be aggravated by an agent, were also found to affect decisions not to take an agent.¹⁷⁰ Health status was a personal factor that was also found to influence perceived need: in a study of vitamin use, young women reported that they did not think they needed such supplements when young, but anticipated that they would need them when older.¹⁸⁵ In a study of aspirin and NSAID users, those with chronic conditions were found to have stronger perceived need for the agent than those with only a temporary condition.¹⁷¹ It may be relevant that both studies reporting low perceived need involved young people who did not currently have any particular health problems or risks.

Sociodemographic factors

Four studies reported on the impact of factors such as age and gender on the decision to take NSAIDs or dietary supplements.^{168,185,194,199} Two studies found that young people, especially young women, were not particularly interested in taking dietary supplements, or in seeking information about them.^{168,185} However, a third study of young women with breast cancer found that this group were more likely to use dietary supplements and other CAM therapies than other groups.¹⁹⁹ These differences may be explained by the lack of such perceived need in the studies of younger people in the general population, or young women of reproductive age, compared with the strength of perceived need among young women with breast cancer. A study of NSAID users with a mean age of 70 years reported that attitudes did not differ between people based on gender or ethnicity.¹⁹⁴

Self-efficacy

A person's sense of control over their own health also influenced their decisions to take NSAIDs or other supplements. Older people around 50 years of age, or more, reported deciding to take NSAIDs because this enabled them to manage their pain,^{168,170} while participants in another study reported that the capacity to use 'natural therapies', such as vitamins or minerals, at their own discretion, also enabled the development of a sense of personal control.¹⁹⁰ In three studies, self-efficacy also extended to perceptions that supplements were not needed: good diet was perceived to

preclude the need for supplements.^{185,186,196} One such study also reported that participants felt that certain ailments, such as cancer, were beyond a person's control.¹⁸⁶ people felt that they were taking supplements with perceived benefits, but they still became ill, and therefore control had been lost.

The balance between benefit and risk in decision-making

Perceived risks of taking agents or supplements

Nine studies reported the views of participants on their perceptions of the risks surrounding the taking of either aspirin/NSAIDs^{169–171,194} or vitamins, minerals, folate or other dietary supplements.^{167,169,185,189–191} The perception of risk was determined in large part by the agent or supplement concerned: NSAIDs prompted more frequent expressions of anxiety about likely side effects^{169–171,194} than vitamins, minerals¹⁸⁵ or folate.¹⁶⁷ There was a perception that 'natural' supplements had fewer side effects than medicines or other pharmaceutical agents, such as aspirin or NSAIDs.^{190,191} More explicit concerns about the perceived risks of taking NSAIDs included addiction, toxicity, the perception that such oral agents might affect the whole body rather than treating the required site alone, and the lack of clarity surrounding the terminology and instructions on dosage accompanying NSAIDs.¹⁷⁰ Participants in the included studies therefore perceived greater risks from taking NSAIDs than from taking vitamins, minerals or other dietary supplements. However, a UK study also found that, despite different perceptions about the risks associated with short-term or long-term use, the decision to use NSAIDs remained largely unaffected.¹⁷¹ However, it should be borne in mind that the studies of NSAIDs included here related mainly to their use as treatment rather than prevention.

Perceived benefits of taking agents or supplements

Nine studies also reported the views of participants on the perceived benefits of taking either aspirin/NSAIDs^{168,170} or vitamins, minerals or other dietary supplements.^{185,186,188,190,192,193,196} Once again, the perception of benefit was determined for the most part by the agent or supplement concerned: the benefits of NSAIDs were viewed as limited: they were perceived to be beneficial for symptom control but were not seen to be a cure.^{168,170} By

contrast, dietary supplements were perceived to have a number of benefits, such as the prevention or treatment of various conditions,^{185,190,192,193} including cancer¹⁸⁶ and arthritis;¹⁹⁶ as a counter to the side effects of pharmaceutical agents;¹⁹³ the improvement of health generally;¹⁸⁸ and as an effective supplement to normal diet.^{185,193} Participants in the included studies therefore perceived greater benefits from taking vitamins, minerals or other dietary supplements than from taking NSAIDs.

The trade-off between benefits and risks

Participants in six studies commented on how their decision to use an agent or supplement was informed by an assessment of the perceived balance between the benefits and risks of taking the agent.^{167,168,170,191–193} In the case of three UK studies of NSAIDs^{168,170} and folic acid,¹⁶⁷ participants reported that, despite a reluctance to take the agents, the perceived risks were acceptable or tolerable when balanced against the benefits. By contrast, participants in three studies from the USA, Germany and Australia reported their belief that 'natural' supplements offered benefits and had fewer side effects than conventional medicines.^{191–193} In one study, a participant reported that they perceived natural supplements to be as effective as conventional medicine, while having fewer adverse effects.¹⁹¹ The trade-off was therefore perceived to be more difficult to achieve for NSAIDs: these agents were seen as effective, but caused unpleasant side effects. By comparison, the trade-off was simpler for dietary supplements: people felt that they could experience perceived benefits while being exposed to very little risk. All studies that reported participants' views on this risk–benefit balance focused on populations with, or at risk of, health problems, rather than general populations: this group arguably had more experience of relevant agents and their risks or side effects, and also greater motivation to use them, than the population generally.

Use and the maintenance of use

Experience of risks (side effects), benefits and the trade-off between the two

Participants in one comparatively good-quality study from the UK reported that their decision either to end their use of NSAIDs or to use them only intermittently was determined by side effects they had experienced, such as heartburn or stomach problems.¹⁷⁰ Participants in both

this study and another study also reported that they used aspirin or NSAIDs because their experience was that these agents worked, i.e. they were effective.^{168,170} The experiences of those who took vitamins or other dietary supplements were less clear-cut: they either continued taking a supplement because they felt it was working in some way, as they felt better,^{186,188} or they discontinued use because of medical advice,¹⁹⁷ unpleasant side effects,^{185,197} or because the supplement was apparently having no effect.^{185,197} This therefore resulted in an unfavourable risk–benefit balance.

By contrast, in one study of NSAID use, participants reported continued use because, despite experiencing side effects, they only felt able to function successfully when taking the agent:¹⁶⁸ the balance was in favour of the benefits. However, other participants, both in this study and in a second study of NSAID users,¹⁹⁴ reported modifying levels of use to control side effects, either by taking the agent only when required,¹⁶⁸ or by accepting a reduced treatment effect, rather than experiencing unacceptable side effects.¹⁹⁴ The balance was in favour of reducing the risk of adverse effects associated with the agent. Maintenance was therefore achieved, despite intermittent use, by accepting limited benefits in return for experiencing fewer side effects.

Physical properties of supplements

The physical properties of the interventions were not reported as an issue in any of the studies of NSAIDs or aspirin. However, two studies of dietary supplements identified concerns surrounding the size, smell and taste of the supplements, which acted as a barrier to their use.^{185,193} Similar issues were also raised concerning the concept of folate fortification of foodstuffs.¹⁶⁷

Sociodemographic factors

Few studies reported any effect of age, gender, ethnicity or income level on the maintenance of use of dietary supplements or NSAIDs. A UK study of over-the-counter medicines (including aspirin, NSAIDs, vitamins and minerals), found that men tended to increase the dose if they perceived that an intervention was not working, whereas women were more likely to discontinue use.¹⁶⁹ The same study found that older people and women were the groups most likely to use such medicines; a finding partly supported by a study of younger women, which found that this group led more ‘chaotic’ lives, preventing routine, habitual use of any agent

or supplement.¹⁸⁵ By contrast, a Canadian study of vitamin and mineral use found no differences between users and non-users in terms of age, gender or income.¹⁸⁸

Discussion

The internal validity of the review is determined in part by the quality of the included studies and the reliability of their findings. There is much debate around the validity and reliability of quality appraisals of qualitative studies and no consensus has been reached concerning whether such appraisals are possible or even meaningful.^{175,176} The brief appraisals performed for this review served to focus on how studies reported their sampling strategies and the methods they used for data collection and analysis; these were the most frequently reported and easily apprehended elements of study design to influence the results, and a reasonable route for the identification of the potential risk of bias in each study. No study was excluded from this review on the basis of the comprehensiveness or soundness of the reported processes, but the relative quality of studies could be discerned through such mechanisms. Nineteen of the 20 included studies were of similar, generally satisfactory or good quality, so, from this perspective, the review may be considered to be sound, and study quality is not an apparent explanation for any differences in the findings. Themes identified for this review emerged from studies employing different data collection methods, including the more obviously *qualitative study designs* of interviews and focus groups, and a smaller number of studies using quantitative methods to generate *qualitative data*, such as surveys. Triangulation of the findings across studies of different types and of differing quality demonstrated consistency in terms of the issues identified, which offers further validation of the findings.

The internal validity of a review may be compromised by poor execution of the methods employed, or the use of inappropriate methods. In this review, although two reviewers independently extracted half of the studies, the extracted data were always checked by a second reviewer, and although one reviewer performed the primary analysis, this was checked and critically examined by two other reviewers. The aim was to ensure the validity and reliability of the findings.

The external validity of the review is determined by the relevance of the findings to the intended population; in this case, UK adults at risk of CRC as a result of a family or personal history of the condition. Only one of the included studies considered this particular population,¹⁸⁶ but in this particular case the intervention was dietary supplements generally rather than any of the agents or supplements explicitly considered by this report. Three other studies did focus on participants with a family or personal history of prostate cancer,^{197,198} or breast cancer.¹⁹⁹ Eleven further studies elicited the views of adults with a mean age of 50 years or more.^{168,170,186,187,189,191–194,197,199} The Reedy study¹⁸⁶ also found that the views or attitudes to dietary supplements of people with cancer did not differ substantially from those who experienced other ‘life events’ or health problems, suggesting that non-cancer populations could provide relevant data. It is therefore relevant that nine studies explored the views of people without cancer but with chronic conditions requiring the taking of relevant agents over a long period.^{168,170,187,188,191–194,196} The authors believe that this provides a potentially valid insight into taking relevant chemopreventive agents long term. The majority of studies (15) were conducted outside the UK (only five UK studies were identified), raising issues surrounding the external validity of their findings to a UK population because of the potential cultural differences. However, as all studies were published within the last 5 years, they have a corresponding strength with regard to their applicability to contemporary populations. The findings of this review therefore possess some validity in terms of their applicability to the population of interest, but also have some distinct limitations.

There was very little potentially relevant research available, hence the initial revision of the searches and scope. The resulting synthesis and thematic framework is therefore the result of the limited amount of relevant, available research in this area. The model generated by the synthesis describes the processes involved in an individual’s decision about whether or not to take NSAIDs, folic acid, vitamins, minerals, calcium or other dietary supplements. Input from external factors, such as health professionals and family members, and internal factors, such as a person’s own experience or health status, both have an impact on an individual’s perceived need for an agent or supplement, and their subsequent decision about whether or not to take it. A further vital element

in this decision-making process is the influence of the perceived risks and benefits associated with an agent or supplement. These perceived risks and benefits can either directly influence an individual’s decision to take something, or may inform a personal assessment of the trade-off between risk and benefit, which in turn may also affect the decision-making process. It has been reported elsewhere that decision-making regarding agents for chemoprevention or symptom management may be affected both by health status, for example, a cancer diagnosis,^{203,204} and by people’s perceived need for an agent and the perceived risks that are associated with it.^{205–207} The model generated by this review, however, highlights the complexity of the influences at work in this decision-making process. Maintenance or continuity of use appears to be affected by three elements: the risks (side effects) and/or benefits experienced by taking the agents or supplements; the physical properties of the agents, which may facilitate or act as a barrier to continued use; and an individual’s age or gender, which may predict the likelihood of their maintenance of a course of therapy.

The review findings were not sensitive to differences in either study quality or design, but differences were apparent between studies according to whether the agent concerned was an NSAID or a dietary supplement (such as vitamins, minerals or dietary supplements generally). As far as NSAIDs were concerned, study participants reported having greater perceived need, principally because of symptom management; were more likely to seek and act on advice from health professionals; and were more likely to perceive risks associated with the agent, and to make an assessment of the balance between risk and benefit in both their decision to use the agent, and how they used it. They were also more likely to report modified use as a result of their experience of using the agent. The benefits and risks were usually quite specific, e.g. control of particular symptoms, or certain, explicit adverse events. NSAIDs were also deemed to offer symptom management, rather than preventive effects or a cure. Much of the data, therefore, revolve around the pharmaceutical nature of NSAIDs and their risks. The differences between NSAIDs and supplements may be explained in part by the presence of known side effects associated with NSAIDs,⁸⁸ and the comparative absence of such adverse effects associated with more ‘natural’ agents, such as antioxidants and vitamins or minerals. Previous research has also found that health professionals

are perceived to be an authoritative source of information on medicines, including NSAIDs,²⁰⁸ especially among older people.²⁰⁹

By contrast, users of vitamins, minerals, and other supplements reported that family and friends, rather than health professionals, were the single most influential source of information and advice, despite a willingness to discuss supplements with doctors; that the risks associated with these supplements were perceived to be comparatively limited, in return for some perceived benefit; and that the perceived effect of supplements could be both therapeutic and prophylactic. The risks and benefits associated with these supplements, in contrast to NSAIDs, were less exact, however: participants had a sense of ‘feeling better’, rather than reporting specific, symptom-based or condition-based outcomes. The perception that vitamins and minerals, along with CAM therapies, offer preventive benefits to individuals, and give them a sense of control over existing conditions, has been noted before both by people with cancer^{210,211} and by supplement users generally.²¹² The influence of family and friends on supplement use, despite seeking health professionals’ opinions, has also been reported by another review.²¹² As a consequence of people’s unwillingness to approach health professionals about supplements, it has been reported that many doctors do not know about the increased levels of vitamin and mineral intake by their patients with cancer.²¹³

The type of intervention was not the only variable to produce differences in the model. Some additional differences were also apparent between the reported findings of studies with general or young populations^{169,171,185,188,190,195} compared with those with older populations with chronic health conditions or cancer.^{168,170,186,187,189,191–194,196,197,199} Participants from the general population appeared to have more concerns about limited access to agents or supplements on the grounds of cost,^{169,185,195} a concern that was absent from the studies of potentially more motivated participants who had chronic or serious conditions, or were known to be at risk of them. This difference also appeared in relation to health status and sociodemographic factors that affected both the perceived need for, and use of, agents or supplements: young people without an existing condition perceived their need for such supplements to be limited,^{171,185} while older people who already were experiencing, or were at risk of,

health problems had greater perceived need and use. Populations with such health concerns were also far more likely to comment on the trade-off between risk and benefit than general populations with a more limited motivation and relatively less experience of agents that might carry a risk or side effects, such as NSAIDs.^{167,168,170,191–193}

Finally, the model can be viewed in terms of service delivery or intervention. Internal or personal factors that affect decision-making cannot be readily influenced by interventions seeking to improve the uptake of or compliance with the agents of interest. This is also the case for some of the external factors, such as the influence of family and friends. However, the cost of agents, and input from health professionals and the media, all affect people’s choices regarding the taking of these agents and can be influenced or shaped by policy or intervention decisions. The nature of this input may be determined by people’s concerns around perceptions of risk and benefit, which act as a moderating variable in progressing from decision-making to use: emphasis on perceived benefits, credible and clear information about risks, and the achievement of an optimal balance between benefit and risks, can affect decision-making and, consequently, the levels of use of an agent.

Conclusions

Both personal and external factors affect people’s decisions to use NSAIDs or supplements such as antioxidants, vitamins or minerals. People are more likely to use NSAIDs if there is a strong perceived need, principally determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also influence the process of decision-making and use: there are greater perceived risks or side effects associated with NSAIDs than dietary supplements, and individuals who are required to take NSAIDs tend to weigh up the balance of benefits against risks, and to modify their use of the agent accordingly. People have fewer concerns about using antioxidants or other supplements, but their perception of the benefits of these agents is less well defined. They would like more information and advice from health professionals, but their use of these supplements tends to be governed more by input from family, friends, alternative therapists and the media.

Chapter 5

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Methods

A systematic review of economic evaluations of chemoprevention for CRC was carried out as part of a separate project, which aimed to identify all economic evaluations of health-care interventions within the CRC health-care service.³³ The inclusion criterion for the economic evaluations of chemoprevention for CRC was broadly defined as economic evaluations describing any population given any form of chemoprevention. The search criteria are presented in Appendix 1. This review presents the current evidence base around economic evaluations of chemopreventive agents for CRC. The results of the review determine whether it is necessary to develop a health economic model for this evaluation.

Results

The electronic literature searches identified 4311 potentially relevant citations to economic analyses of bowel cancer technologies. Of these, only 11 citations appeared to relate to economic evaluation of agents used in the chemoprevention of CRC. A total of eight full papers were obtained for detailed inspection, of which six studies met the inclusion criteria.

Justification of excluded studies

Emmons *et al.*²¹⁴ was excluded from the review following full paper screening because the intervention considered within the evaluation was not specifically chemoprevention. This paper assessed the CRC risk reduction factor of interventions such as red meat consumption, fruit and vegetable intake, multivitamin intake, alcohol, smoking and physical inactivity; the majority of which did not meet our definition of chemoprevention. Ladabaum²¹⁵ was excluded because this was a secondary reporting of the work described by Ladabaum in two of the included studies.^{216,217} *Figure 14* shows the summary of the study selection and exclusion.

Included economic evaluations

The key characteristics of the studies identified for inclusion within the review are shown in *Table 29*. All of the economic evaluations included within the review were state transition models carried out in the USA and were restricted to the health economic evaluation of either aspirin or COX-2 inhibitors; other chemopreventive agents such as antioxidants were not included in any of the identified studies. Five of the six included economic evaluations compared chemoprevention with screening as well as with no prevention (see *Table 29*).^{216–220} These five studies used a health economic model with annual cycles and reported outcomes in terms of the incremental or marginal cost per life-year (LY) saved from a third-party payer (Medicare®) perspective. None of these five studies assessed the impact of treatment or the disease on HRQoL. The remaining evaluation included within the review, Hur *et al.*²²¹ assessed the costs, quality-adjusted life-years (QALYs), complication rates and mortality associated with aspirin chemoprevention and celecoxib chemoprevention from a societal perspective. This paper did not provide comparative results and considers competing chemoprevention options without reference to a 'no prevention' group. The population considered within all of the models was the US general population over the age of 50 years. None of the studies justified this choice of starting age. One of the included economic evaluations also considered people with first-degree relatives with a history of CRC within the model.²¹⁷ The time horizon, that is, the period over which costs and health outcomes differ between decision options, was inconsistent between the studies, ranging from 10 years to individuals' remaining lifetimes. Two of the economic evaluation studies did not incorporate a disease natural history component;^{219,221} where a natural history component was included, the definition of disease states and transitions between them were inconsistent.

The results of the studies which compared chemoprevention versus no prevention are extremely variable; at one end of the spectrum, chemoprevention was reported to dominate no prevention²¹⁶ whereas at the other,

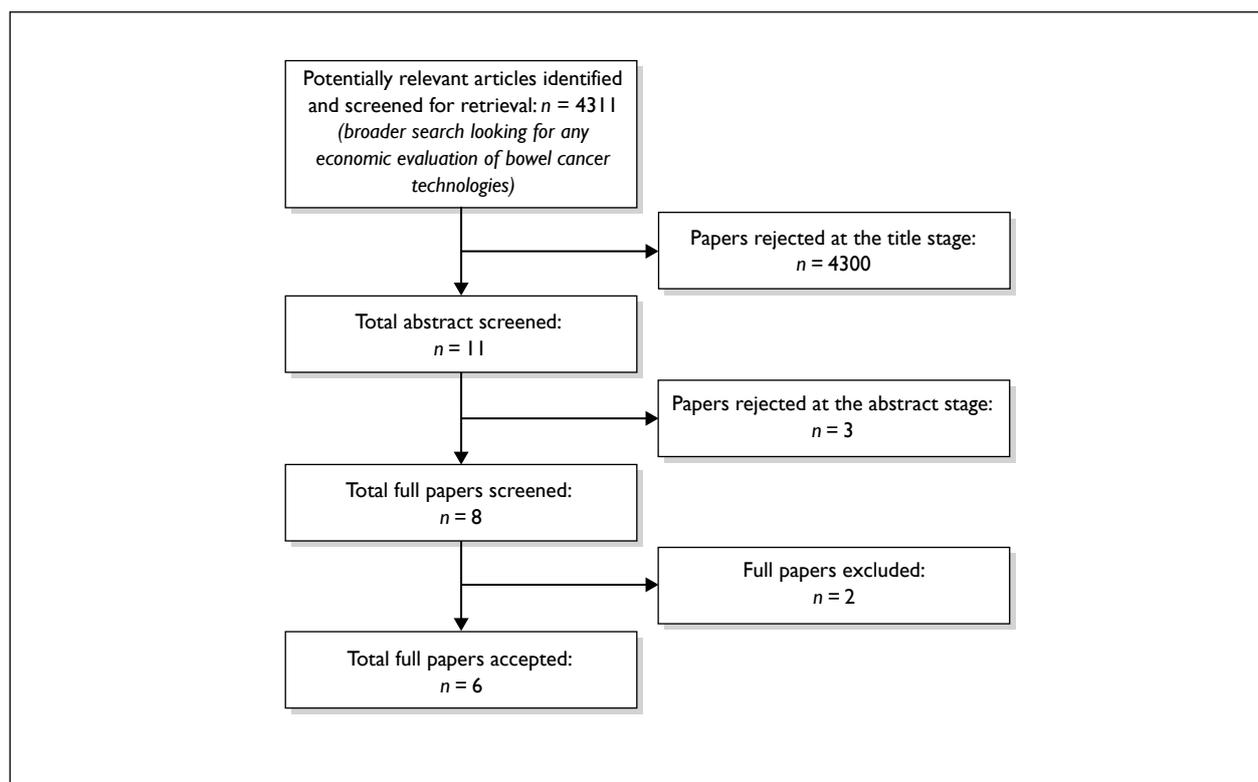


FIGURE 14 Summary of economic evaluation selection and exclusion.

chemoprevention was reported to have an estimated incremental cost per life-year gained (LYG) in excess of \$100,000 when compared with no prevention.²¹⁷ When chemoprevention is used alongside population screening, the cost per life year gained was estimated to be at least \$100,000 within all economic evaluations. A major limitation in the interpretation of the available evidence relating to the cost-effectiveness of chemoprevention concerns their US setting. Inherent differences between health-care systems and general population lifestyles in the US and the UK leads to problems of external validity and methodological problems in translating economic findings. In addition, the Medicare perspective is not representative of the standard NHS and Personal and Social Services perspective adopted in the UK.

Ladabaum *et al.*: Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer

Ladabaum *et al.*²¹⁶ present the methods and results of a cost-effectiveness analysis of aspirin chemoprevention (325 mg/day) versus CRC screening and versus no prevention within

the general US population. The analysis also compares a combination of screening and aspirin chemoprevention against screening alone and against no prevention. Screening using both colonoscopy every 10 years and flexible sigmoidoscopy every 5 years alongside annual FOBT is considered within the model. A state transition model was used to simulate a cohort of people aged 50 to 80 years using annual cycles. The choice of age group for the model population was not justified by the study authors. The analysis was undertaken from the perspective of a third-party payer (Medicare) and the outcome of the model is the cost per life-year saved (LYS). Health-related quality of life was not considered within the model.

The health states used within the model include normal (no polyps or cancer), polyp, cancer (localised, regional, distant) and death. Age-specific polyp incidence rates were taken from autopsy studies. CRC incidence was derived to match age-specific Surveillance, Epidemiology and End Results (SEER) data,²²² assuming that 90% of CRCs arise from pre-existing polyps (hence 10% of cancers are assumed to arise *de novo*) and that cancer progresses from localised to regional (2 years in each state) to disseminated cancer.

TABLE 29 Characteristics of studies included in the cost-effectiveness review

Author	Ladabaum ²¹⁶	Arguedas ²¹⁸	Suleiman ²¹⁹	Ladabaum ²¹⁷	Hur ²²¹	Dupont ²²⁰
Country and year of publication	USA, 2001	USA, 2001	USA, 2002	USA, 2003	USA, 2004	USA, 2007
Type of economic analysis	CEA	CEA	CEA	CEA	Costs and outcomes	CEA
Health economic perspective	Third-party payer (Medicare)	Third-party payer (Medicare)	Third-party payer (Medicare)	Third-party payer (Medicare)	Societal	Third-party payer (Medicare)
Health economic comparisons (listed interventions compared against chemoprevention)	No prevention Colonoscopy surveillance Combination of colonoscopy and chemoprevention	No prevention Colonoscopy surveillance	No prevention Colonoscopy surveillance Combination of colonoscopy and chemoprevention	No prevention Colonoscopy surveillance Combination of colonoscopy and chemoprevention	NA	No prevention Colonoscopy surveillance Combination of colonoscopy and chemoprevention
Type of chemoprevention	Aspirin (325 mg)	Celecoxib (200 mg twice daily)	Aspirin (325 mg)	COX-2 (400 mg twice daily)	Aspirin (325 mg) and celecoxib (400 mg twice daily)	Aspirin (325 mg)
Population characteristics	General US population (>50)	General US population who have had previous adenoma resection (>50)	General US population (>50)	General US population (>50) People with one first-degree relative (>50) People with two first-degree relatives (>50)	General US population (>50)	General US population (>50)
Time horizon	30 years	10 years	Lifetime	30 years	10 years	Lifetime
Health economic outcomes	Cost per LY saved	Cost per LY saved Cost per 'high-grade' adenoma prevented	Cost per LY saved	Cost per LY saved	Costs QALYs Complication rates Mortality	Cost per LY saved Cost per CRC prevented
Modelling approach	State transition model, annual cycles	State transition model, annual cycles	State transition model, annual cycles	State transition model, annual cycles	State transition model, annual cycles	State transition model, annual cycles
Effectiveness assumptions	Aspirin is estimated to reduce CRC by 30% (range 5–55%) (equal reductions in adenoma incidence and progression to cancer) based on 12 studies of aspirin use	COX-2 inhibitors are assumed to reduce incidence of adenomas by 50% (range 0–100%), based on assumption only	Relative risk of CRC is assumed to be 50% (range 25–75%) based on three studies	Reduction in CRC is estimated to be 30% (range 0–100%) based on two studies	NA	Relative risk of polyp incidence is assumed to be 0.85 based on three studies
CEA, cost-effectiveness analysis.						

Persons within the model may experience screening or aspirin-related complications, both of which are associated with a probability of death. During any model cycle, the authors report that individuals may die from CRC and CRC treatment or other causes. It is, however, unclear what is meant by CRC treatment in this context. The risk of death due to CRC was derived from the SEER Cancer Statistics Review²²² while other-cause mortality rates were derived from US life tables. The model incorporates the sensitivity and specificity of FOBT, flexible sigmoidoscopy and colonoscopy. Screening is assumed to be associated with a participation rate of 25%,²²³ whereas aspirin is assumed to be associated with perfect compliance. The reduction of CRC due to aspirin was assumed to be 30% (range 5–55%) through equal reductions in adenoma incidence and cancer progression rates, based on an analysis of 12 studies which assessed the impact of aspirin use on CRC incidence. It is unclear how the authors have used these 12 studies to derive the risk reduction parameter; the use of a meta-analysis is not mentioned within the paper.

Cost components include CRC care by stage (localised, regional, distant),²²⁴ aspirin and surveillance and treatment of complications.²²⁵ All costs are presented in 1998 US dollars. Both costs and life-years were discounted at a rate of 3%. One-way sensitivity analyses and a partial probabilistic sensitivity analyses (PSA) were undertaken. The authors did not consider uncertainty within all of the disease natural history parameters; however, the incidence of adenomas and the probability of CRC following adenoma development were varied within the PSA.

The results of the model suggest that aspirin chemoprevention dominates no aspirin or screening in 38% of the PSA iterations; however, if colonoscopy screening was available, the addition of chemoprevention would result in a cost per LYS of around \$150,000 in 1998 US dollars (approximately £120,000 in 2008 UK pounds). The model predicts that if flexible sigmoidoscopy and FOBT were currently used in practice, the addition of aspirin chemoprevention would be dominated. Conversely, if screening using flexible sigmoidoscopy/FOBT or colonoscopy was adopted in addition to chemoprevention, the cost per LYS was estimated to be \$26,000 or \$31,000, respectively in 1998 prices (approximately £21,000 and £25,000 in 2008 UK pounds). Similar results were presented for both the deterministic outcomes and the probabilistic outcomes; however, all of the probabilistic results were not presented within the

paper. The one-way sensitivity analysis suggested that the cost-effectiveness results are highly dependent on the effectiveness of aspirin, the rate of screening participation and the rate of aspirin-related complications. Results were improved if it was assumed that aspirin decreases cardiovascular death as well as CRC incidence.

The model presented by Ladabaum *et al.* has several limitations:

- Uniform distributions were used to describe the uncertainty in all model parameters. Ranges used to characterise uncertainty surrounding model parameters do not appear to be evidence-based.
- The model uses constant transition probabilities for simulating the disease natural history component rather than adjusting for age. With increasing age, polyp incidence will increase and more aspirin-related complications are likely to occur.
- Compliance associated with aspirin chemoprevention is assumed to be 100%, which is highly unlikely in practice.
- The analysis is presented from a Medicaid perspective; however, it is unlikely that Medicaid would fund chemoprevention within the general population.
- The characterisation of uncertainty surrounding the disease natural history model component is limited.
- No model validation was reported.

Arguedas *et al.*: Surveillance colonoscopy or chemoprevention with COX- 2 inhibitors in average-risk postpolypectomy patients: a decision analysis

Arguedas *et al.*²¹⁸ present a cost-effectiveness analysis of celecoxib (200 mg twice daily) against no prevention, surveillance colonoscopy every 3 years and surveillance colonoscopy every 5 years in 'average'-risk patients who have undergone prior adenoma resection (complete colonoscopy and polypectomy). The authors adopted a Markov framework, with the model following a cohort of people aged 50 for 10 years from the point of resection using an annual cycle length. No justification is provided concerning the choice of population age or the time horizon used within the analysis. The authors report the cost per LYS and a cost per 'high-grade' adenoma prevented from the perspective of a third-party payer (Medicare).

The health states included within the model were normal (no polyps or cancer), low-grade adenoma, high-grade adenoma, CRC and death. Constant probabilities rather than age-related probabilities were used to represent the development of polyps and CRC. The adenoma formation rate (incidence) and the incidence of CRC were estimated from the National Polyp Study (NPS).²²⁶ The model assumes that the incidence of polyps after the first colonoscopy is half the incidence after the index colonoscopy, as experts suggest that approximately 50% of the polyps found in the NPS represented polyps missed during the index colonoscopy.¹⁵⁸ The rates of progression from low-grade to high-grade polyps and CRC were estimated from Stryker *et al.*²⁰ The model optimistically assumes 100% compliance with both colonoscopy and celecoxib and that the sensitivity of colonoscopy is 100%; more conservative assumptions were tested within the sensitivity analysis. The authors assumed that celecoxib would reduce the incidence of adenomas by 50%. This value was varied from 0 to 100% within one-way and two-way sensitivity analyses. The annual incidence of ulcers due to aspirin was based on the CLASS study (Celecoxib Long-term Arthritis Safety Study)²²⁷ and the model assumes that there would be a discontinuation rate from aspirin of 1% following 6 months of chemoprevention. Health-related quality of life outcomes were not incorporated within the model and no information is reported in the paper around mortality rates due to any cause.

Endoscopy costs within the model were based on Medicare reimbursement rates and the cost of celecoxib was based on the *Drug Topics Red Book*.²²⁸ The overall cost of treating CRC was taken from a study by Brown *et al.*,²²⁹ which used SEER data to calculate average costs of treating CRC. All costs were valued at 1999 prices. All costs and health outcomes were discounted at a rate of 3%. One-way sensitivity analysis was carried out around the effectiveness of celecoxib. Two-way sensitivity analysis was carried out around the yearly cost of celecoxib and the effectiveness of the drug. Probabilistic sensitivity analysis was not presented within the paper.

The incremental cost-effectiveness ratio (ICER) for surveillance versus no prevention was estimated to be \$27,970 per LYS in 1999 US dollars (approximately £22,000 in 2008 UK pounds). The ICER for celecoxib chemoprevention versus surveillance was estimated to be \$1,715,199 per LYS (approximately £1,319,000 in 2008 UK pounds). The cost per LYS remains greater than

£1 million in 2008 UK pounds within the one-way sensitivity analysis around the effectiveness of celecoxib. The two-way sensitivity analysis suggests that if the annual drug cost was below \$150 (£115 in 2008 UK pounds) and with a risk reduction in the incidence of adenomas of greater than 50%, chemoprevention may become a reasonable option in comparison with colonoscopy surveillance.

The model presented by Arguedas *et al.* is subject to several limitations:

- The effectiveness of celecoxib is based on an assumption by the authors rather than clinical trial evidence (50% assumed risk reduction in adenoma incidence).
- The probability of adenoma formation (incidence) and CRC incidence is assumed to be constant and unrelated to age.
- The model assumes 100% compliance with both colonoscopy and celecoxib and that the sensitivity of colonoscopy is 100%.
- There is a limited analysis of uncertainty.
- There is no consideration of chemoprevention alongside endoscopic surveillance.
- HRQoL is not considered within the model.
- No model validation was presented.

Suleiman *et al.*: Chemoprevention of colorectal cancer by aspirin: a cost- effectiveness analysis

Suleiman *et al.*²¹⁹ assess the cost-effectiveness of aspirin chemoprevention (325 mg daily) and colonoscopy surveillance (once every 10 years; every 3 years in patients with polyps) versus no prevention, both individually and in combination. This model is based upon a previous model of CRC screening developed by Sonnenberg *et al.*²³⁰ A Markov process model was used to simulate the experience of a cohort of 100,000 people aged 50 years over a lifetime horizon using an annual cycle length. No justification is provided concerning this starting age. The model assesses the cost per LYS as a result of prevention within the general US population from a third-party payer perspective (Medicare). The states within the model are:

1. a state after a negative colonoscopy without polyps/disease-free on aspirin prophylaxis
2. a state after colonoscopy plus polypectomy
3. a state after developing CRC
4. death.

The natural history of CRC is not explicitly modelled.

The model used a 1% annual polyp incidence rate to calculate the number of polypectomies and repeat colonoscopies after polypectomy. This rate was not related to age or whether the person had had polyps in the past. The annual age-specific incidence of CRC was estimated using SEER data.²²² Death from other causes was also included within the model based on standard US life tables. Colonoscopy and aspirin chemoprevention were assumed to reduce the incidence of CRC but have no effect on reducing the incidence of polyps. This is contrary to the clinical evidence identified within the systematic review described within Chapter 3 (see Results: aspirin), which suggests that aspirin does have an impact upon polyp incidence. Importantly, the model does not include a disease natural history component. No relationship between adenomas and cancer is specified, for example, it is unclear which cancer incidence rates are applied to persons with a negative screen result, a group that includes both true-negative and false-negative test results. Overall, the methodology adopted within this model which 'tried to reduce the complex natural history of CRC to few essential states and avoid transition assumptions for which little or no published data existed',²³⁰ resulted in a model that appears to fail to capture the events relevant to an assessment of either CRC screening or chemoprevention. The relative risk of CRC incidence was assumed to be 75% using colonoscopy surveillance and 50% using aspirin chemoprevention. These estimates were based on a range of sources including the NPS²²⁶ and the assumed values were tested within a one-way sensitivity analysis. The source of the estimate of the effectiveness of the combination of aspirin and colonoscopy in reducing CRC incidence is unclear; this was assumed to be 87.5%, a much higher relative effectiveness than either method of prevention alone. The model includes a probability of perforation and bleeding due to colonoscopy and polypectomy; however, there the model does not include the possibility of death due to prevention.

The costs of aspirin, colonoscopy, polypectomy and associated adverse events were taken from Medicare Payments in 2000.²³⁰ The total cost of CRC was based on the uplifted costs from a study by Lee *et al.*²³¹ All costs were valued in 2000 US dollars. All costs and life-years were discounted at a rate of 3%. One-way sensitivity analyses were undertaken to explore the impact of the cost of

chemoprevention and the preventive effectiveness of both colonoscopy and daily aspirin on resulting cost-effectiveness estimates. No further analysis of uncertainty was undertaken.

The results of the model suggest that the cost per LYS associated with chemoprevention versus no prevention is \$47,249 in 2000 US dollars (approximately £35,000 in 2008 UK pounds). The use of aspirin chemoprevention and colonoscopy surveillance compared with colonoscopy surveillance alone results in a much higher estimated cost per LYS of \$227,607 (approximately £167,000 in 2008 UK pounds). The authors suggest that based upon the one-way sensitivity analysis the costs of chemoprevention would need to fall below \$70 per person per year (£51 in 2008 UK pounds) to become more cost-effective than colonoscopy.

The model presented by Suleiman *et al.* has several limitations:

- The disease natural history is not modelled.
- The model does not appear to account for costs and outcomes associated with cancer treatment if the cancer is curable.
- The model does not seem to account for mortality due to perforation.
- The model uses constant transition probabilities. With increasing age, polyp incidence will increase and more aspirin-related complications are likely to occur (although there is also some evidence to suggest that the effectiveness of aspirin may increase over time).
- It is not clear how compliance is dealt with in the model.
- No HRQoL has been accounted for within the model.
- The analysis is presented from a Medicaid perspective; however, it is unlikely that Medicaid would fund chemoprevention within the general population.
- There is a limited analysis of uncertainty.
- No model validation has been carried out.

Ladabaum *et al.*: Potential effect of cyclo-oxygenase-2-specific inhibitors on the prevention of colorectal cancer: a cost-effectiveness analysis²¹⁷

Ladabaum *et al.*²¹⁷ assess the potential cost-effectiveness of COX-2 inhibitors (400 mg twice daily) versus no prevention. This is assessed with

and without screening surveillance consisting of either colonoscopy or flexible sigmoidoscopy alongside FOBT. The same model previously developed by Ladabaum and described previously was used for this analysis.²¹⁶ The population considered within this analysis is people who:

- are at average risk of CRC
- have one first-degree relative who have previously been diagnosed with CRC
- have two first-degree relatives with/who have previously been diagnosed with CRC.

This model includes the effectiveness, costs and complications associated with COX-2 inhibitors rather than aspirin; however, all other model parameters and assumptions are as described within the 2001 paper.²¹⁶ The reduction in incidence of CRC as a result of COX-2 inhibitors is estimated to be 30% (range 0–100%) based on two studies assessing the use of COX-2 inhibitors on the reduction of CRC; one of which was in the FAP population.^{89,232}

The results of the model suggest that for a person at average risk of CRC, the cost per LYS will be \$233,300 in 1998 US dollars (approximately £187,000 in 2008 UK pounds). For people with one and two first-degree relatives with CRC the cost per LYS decreases to \$80,300 (£64,000 in 2008 UK pounds) and \$56,700 (£45,000 in 2008 UK pounds), respectively. If CRC screening is current standard practice the cost per LYS of chemoprevention in addition to CRC screening is estimated to be greater than \$195,000 (£156,000 in 2008 UK pounds) for all patient groups assessed. The one-way and two-way sensitivity analyses suggest that the key drivers of cost-effectiveness are the acquisition costs of COX-2 inhibitors and the effectiveness of COX-2 inhibitors; however, varying these parameters within plausible ranges is unlikely to affect the conclusions of the analysis.

Limitations of the model are as described in the 2001 paper described above.²¹⁶

Hur *et al.*: The cost-effectiveness of aspirin versus cyclo-oxygenase-2-selective inhibitors for colorectal carcinoma chemoprevention in healthy individuals

Hur *et al.*²²¹ estimate the costs and QALYs associated with celecoxib (400 mg twice daily) versus enteric-coated aspirin (325 mg/day) in

healthy men aged 50 years. Aspirin or COX-2 inhibitors are not compared against 'no prevention' within the analysis. The analysis was undertaken from a US societal perspective over a 10-year time horizon. The authors also report other outcomes in terms of mortality and complication rates. The differences in costs and QALYs are not combined to produce a cost-effectiveness ratio.

A Markov model of the complications associated with aspirin and celecoxib was produced alongside the cardioprotective benefit of aspirin using a monthly cycle length. The natural history of CRC was not incorporated into the model; instead the authors assumed that the potential cancer benefits would be equally effective for either therapy. There is, however, no evidence to suggest that this is the case. Health-related quality of life utility values were taken from a study by Fryback *et al.*²³³ Utility estimates were adjusted by age and gender using the 'Beaver Dam Health Outcomes Study',²³³ and adjusted to reflect recuperation from complications. The probability that an individual will experience complications (including ulcer, ulcer perforation, bleed, myocardial ischaemia) was taken from several literature sources including Sanmuganathan *et al.*,²³⁴ the PHS²³⁵ and Spiegel *et al.*²³⁶ The model also includes a probability of death due to these complications. Importantly, death due to other causes was not included within the model.

The costs of aspirin and celecoxib were based on the *Drug Topics Red Book*²²⁸ and the costs of treating most of the complications associated with aspirin or celecoxib were based on a study by Spiegel *et al.*²³⁶ Costs were valued in 2000 US dollars. All costs and outcomes were discounted at a rate of 3%. One-way sensitivity analyses were undertaken to examine the impact of starting age, length of follow-up, the cost of the drug and the discount rate on cost-effectiveness outcomes. Threshold analyses were also reported around several additional parameters including the relative excess myocardial infarction rate for aspirin compared with COX-2 inhibitors, the relative ulcer rate for aspirin compared with COX-2 inhibitors, the cost of celecoxib and the relative bleeding rate of aspirin compared with COX-2 inhibitors.

The results of the model suggest that aspirin is associated with an increase in QALYs (7.60 vs 7.57) and lower costs (\$181 vs \$23,403) than celecoxib, i.e. aspirin dominates celecoxib. The results were not sensitive to the start age, the length of follow up or the discount rate. The cost of celecoxib

affected the model results substantially; however, this is unlikely to alter the conclusions.

The model reported by Hur *et al.* is subject to several limitations:

- The report presents a cost-effectiveness analysis comparing aspirin and celecoxib; however, it is not known whether either chemopreventive agent would be cost-effective compared with a 'do nothing' alternative.
- The model assumes that the efficacies of aspirin and celecoxib are equivalent (no prevention of cancer is incorporated).
- The analysis is presented from a Medicaid perspective; however, it is unlikely that Medicaid would fund chemoprevention within the general population.
- There is a limited analysis of uncertainty.

Dupont *et al.*: Aspirin chemoprevention in patients with increased risk for colorectal cancer: a cost-effectiveness analysis²²⁰

Dupont *et al.*²²⁰ present a cost-effectiveness analysis of aspirin chemoprevention (325 mg daily) and colonoscopy surveillance (every 3 or 5 years depending on polyp risk) versus no prevention, individually and in combination. A cohort of individuals with prior adenoma resection (complete colonoscopy and polypectomy) without FAP or HNPCC are simulated from age 50 over a lifetime within a Markov model using annual cycles. No justification was provided within the paper concerning the starting age of the model cohort. Outcomes are presented in terms of the cost per LYS and the cost per case of CRC prevented. The analysis was carried out from the perspective of a third-party payer (Medicare).

The natural history of the disease was modelled using the health states normal (no polyps or cancer), low-grade adenoma, high-grade adenoma, carcinoma *in situ*, advanced CRC and death. The annual probability of developing polyps was obtained from the placebo group in the study by Baron *et al.*⁷⁴ and was not age-related. The relative risk of polyp incidence was assumed to be 0.85 based on three studies of aspirin use within this population.^{62,74,79} The initial colonoscopy was assumed to be 100% successful in removing all polyps, but a miss rate of 8% for subsequent colonoscopies was assumed.²³⁷ All colonoscopies were assumed to be complete and compliance with

aspirin and colonoscopy was assumed to be 100%; these assumptions are both highly optimistic. The probabilities of developing complications associated with aspirin or colonoscopy were drawn from a number of journal sources including the paper by Ladabaum *et al.* reviewed here.²¹⁶ The model assumes that death may occur as the result of a colectomy, aspirin or colonoscopy complication, CRC or other causes.

The cost of aspirin was based on the costs used in Suleiman *et al.*²¹⁹ and Ladabaum *et al.*,²¹⁶ both described above. The cost of colonoscopy and polypectomy, complications of colonoscopy and aspirin, initial side effects of aspirin and CRC resection were based on Medicare reimbursement rates. The cost of treating incurable CRC was based upon several sources including Arguedas *et al.*²¹⁸ and Ladabaum *et al.*²¹⁶ described above. A formal price year for model results was not reported; for the purposes of uplifting the costs, the authors assume that it is 2006 given that it was published in 2007. Costs and life-years were discounted at a rate of 3%.

Probabilistic sensitivity analysis and a one-way sensitivity analysis were undertaken. A scenario analysis where the length of time between colonoscopy surveillance was increased was also reported. No uncertainty was considered around the reduction in polyp incidence associated with aspirin. Results were presented incrementally. Aspirin is predicted to cost \$87,609 per LYS compared with no prevention (approximately £50,000 in 2008 UK pounds). The use of aspirin chemoprevention in addition to colonoscopy compared with colonoscopy alone is estimated to cost \$60,942 per LYS (approximately £35,000 in 2008 UK pounds). These results presented by Dupont *et al.* are less favourable than other studies in terms of the use of aspirin as a chemopreventive agent compared with no prevention strategy; however, they are more favourable than those from other studies when considering the use of aspirin in addition to colonoscopy surveillance.

The model presented by Dupont *et al.* is subject to several limitations:

- The model assumes that the initial colonoscopy is 100% successful in removing all polyps within the base case.
- The model assumes that the compliance rate is 100% for both surveillance and aspirin use.
- The model uses constant transition probabilities. With increasing age, polyp

incidence will increase and more aspirin-related complications are likely to occur (although there is also some evidence to suggest that the effectiveness of aspirin may increase over time).

- HRQoL is not considered within the model.
- The analysis is presented from a Medicaid perspective; however, it is unlikely that Medicaid would fund chemoprevention within the general population.
- The model does not consider any uncertainty around the reduction in polyp incidence as a result of aspirin use.
- No model validation has been carried out.

Current chemoprevention model limitations

This review identifies a number of key limitations employed within existing economic evaluations of CRC chemoprevention, outlined in *Box 2* below.

This review highlights the limited number of economic assessments that have been undertaken around chemopreventive agents. The only chemopreventive agents that have been modelled are aspirin and COX-2 inhibitors, and there are numerous limitations associated with these economic evaluations as described above. None of the economic evaluations undertaken to date are appropriate for use within this analysis; hence a novel health economic model has been developed.

Independent economic assessment

Methods

Modelling scope and methodology

Population

A health economic model was developed to assess the cost-effectiveness of chemoprevention for two populations with different levels of risk of developing CRC:

- the general population, referred to as low-risk population in previous sections
- men and women at an intermediate-risk of CRC due to previous polyps.

The use of chemoprevention for individuals at high-risk of CRC due to FAP or HNPCC was excluded from the economic analysis presented here. This exclusion is justified as (1) little is known about the underlying disease natural history for these patients and (2) there is limited evidence concerning the impact of reducing polyp incidence upon subsequent cancer incidence (see Chapter 1). Where studies are available, the impact of chemoprevention upon polyp incidence is poor; of the limited number of available studies, these are subject to sample sizes below 50 patients. From a clinical point of view, it is unlikely that a small reduction in the incidence of polyps will impact upon the incidence of CRC. As such, chemoprevention is unlikely to be effective at

BOX 2 Key limitations of existing health economic evaluations of chemoprevention

- Inadequate time horizons to capture all impacts on costs and outcomes
- Missing comparators
- Inconsistency in handling screening
- External validity of US models
- Adherence assumptions are generally not evidence-based
- Omission of mortality outcomes
- Failure to model disease natural history/inconsistent modelling of disease natural history/constant age-independent transition probabilities
- Limited/inadequate characterisation of uncertainty
- Exclusion of HRQoL impacts
- Inappropriate perspective of analysis

preventing CRC within this population, and hence treatment decisions would not change. On this premise, the impact of chemoprevention upon health outcomes is expected to be neutral while the impact upon costs is expected to be positive. Chemoprevention would therefore not be a cost-effective intervention for these patients.

Comparator and interventions assessed within the model

The model analysis includes costs and outcomes associated with FOBT screening for individuals aged 60–74 years as part of the underlying context of the disease service under evaluation. This programme has been rolled out across England and Wales for individuals aged 60–69 years and is currently being extended to those aged up to 74 years. The costs and health outcomes associated with each chemoprevention option in both the intermediate-risk and general populations are estimated in comparison to no chemoprevention (alongside screening). In this sense, chemoprevention is evaluated as an adjunct to the existing CRC screening programme. Decisions concerning the specific chemopreventive agents assessed within the model were based upon the systematic review and meta-analyses presented in Chapter 3. For the general population, only aspirin and no chemoprevention are considered within the economic analysis. For the intermediate-risk population, the economic analysis includes aspirin, celecoxib and calcium versus no chemoprevention.

Other potential chemopreventive agents including antioxidants, folic acid and other NSAIDs were excluded from the economic analysis either because

of the presence of evidence which suggests that they are ineffective or because of insufficient evidence to describe effectiveness. In particular, evidence surrounding the use of antioxidants for chemoprevention provided mixed conclusions around their effectiveness. The results of some of these trials are contradictory and the effectiveness of both individual antioxidants and combinations of antioxidants is unclear (see Chapter 3; Results: antioxidants). It was thought that assessing the cost-effectiveness of antioxidants as a group rather than individually would be unhelpful because they are each associated with different costs, effects and adverse events. Therefore, antioxidants were not included within the health economic analysis. *Table 30* shows which interventions were included within the health economic model and the reasons for exclusion.

Outcomes evaluated within the health economic analysis

The economic analysis includes the following outcomes:

- incremental cost per LYG
- incremental cost per QALY gained.

Health economic perspective

The model includes costs and outcomes from the perspective of the NHS and Personal and Social Services.

Time preference and discounting

In line with current recommendations from NICE, all costs and utilities were discounted at a rate of

TABLE 30 Interventions assessed within the model

Intervention	General population		History of adenomas (intermediate risk)	
	In model?	Justification	In model?	Justification
Aspirin	Yes	Trials indicated reduction in CRC with follow-up to 23 years	Yes	Trials indicated reduction in adenoma recurrence
Celecoxib	No	No trials identified	Yes	Trials indicated reduction in adenoma recurrence
Calcium	No	Event numbers within trials too small to suggest any effect, but follow-up only 4–7 years	Yes	Trials indicated reduction in adenoma recurrence
Folic acid	No	Trials indicated non-significant negative effect on CRC, but follow-up only 5–7 years	No	Trials indicated non-significant increase in adenoma recurrence
Antioxidants	No	Trials provided poor and unclear evidence for individual antioxidants, but follow-up only 5–12 years	No	Trials provided poor and unclear evidence for individual antioxidants

3.5% from the point at which the patients begin receiving chemoprevention.

Time horizon

The model evaluates the costs and outcomes associated with chemoprevention over a lifetime horizon.

Model structure

In 2003, Tappenden *et al.*²³⁸ developed a state transition model to assess the cost-effectiveness of alternative options for CRC screening. This model has been further developed to incorporate the expected costs and outcomes associated with chemoprevention. This model is comprised of three inter-related model components: a model of the natural history of CRC, a model of screening and surveillance interventions, and a mortality model.

Natural history submodel

The natural history of CRC was modelled as a series of transitions between the following mutually exclusive health states: normal epithelium, low-risk adenomas, high-risk adenomas, Dukes' A, Dukes' B, Dukes' C and Dukes' D as shown in *Figure 15*.

The model uses age-dependent transition matrices to estimate the number of individuals in each health state for each model cycle through a process

of iterative matrix multiplication. Transitions between model health states are calculated on a cohort-level basis using an annual cycle length and a lifetime horizon. Health states were defined according to the true underlying histological state of the individual. Health states describing the presence of neoplasia (adenomas and/or cancer) were defined in terms of the 'index' lesion; that is the adenoma with the greatest malignant potential or the most advanced tumour. Individuals with adenomas were defined as 'low-risk' or 'high-risk' to reflect current guidelines for endoscopic surveillance following adenoma removal.⁵⁹ Cancer stage was modelled according to the Turnbull modification of the Dukes' staging system.^{239,240}

Screening submodel structure

The potential impact of earlier detection and removal of screen-detected adenomatous polyps, the detection and treatment of CRC, and the ongoing surveillance of high-risk individuals in whom adenomas are detected are simulated processes within the model. Test characteristics associated with screening and colonoscopy are defined in terms of the probability of achieving a positive or negative test result given an individual's true underlying histological state (i.e. sensitivity and specificity). The impact of the screening test, follow-up colonoscopy and treatment of detected polyps and cancers is modelled by redistributing

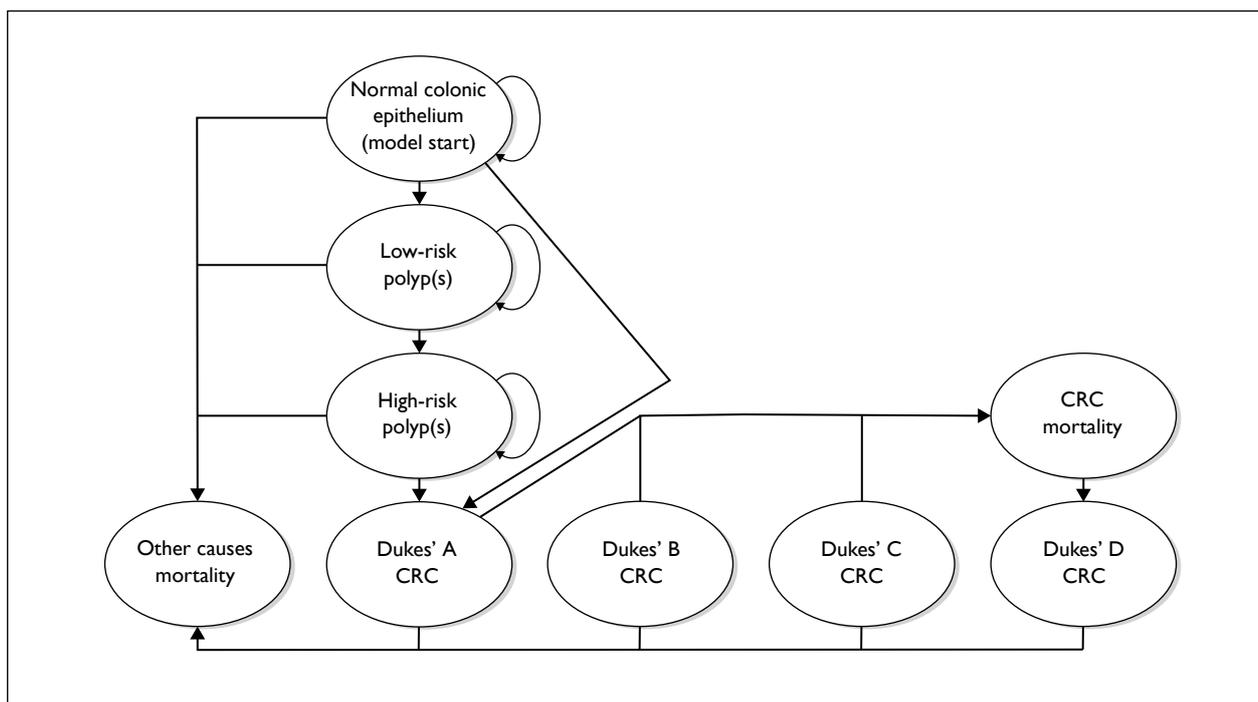


FIGURE 15 Model schematic of disease natural history.

the model cohort across the health states at the point of screening and surveillance. Individuals in whom adenomas are found are assumed to undergo polypectomy via snare diathermy and are subsequently assigned a higher risk of adenoma recurrence.²⁴¹ Individuals identified as having high-risk polyps are divided into two groups; higher-risk and intermediate-risk. This terminology is unrelated to the use of the terms high-risk (i.e. FAP/HNPCC) and intermediate-risk (i.e. history of adenomas) within the clinical review. Individuals identified as having low-risk polyps continue to be classified as low-risk within the model. Individuals who are identified as being at an intermediate risk of developing CRC following screening are assumed to be invited to attend a 3-yearly colonoscopic surveillance programme, whereas those at higher risk are assumed to enter into an annual colonoscopic surveillance programme. It is assumed that individuals with preclinical detectable CRC may present symptomatically during any model cycle; the probability of clinical presentation was estimated through model calibration; this probability is assumed to increase according to cancer stage. These parameters are shown in *Table 31*. Individuals in whom previously undetected CRC is identified are assumed to enter into a clinical management state. Individuals in whom neither adenomas nor cancer are detected are assumed to be reinvited to attend CRC screening during the next round in 2 years. Clinical management states are modelled according to Dukes' stage as prognosis, treatment options, HRQoL impacts and costs differ considerably between stages.

Although based on the same conceptualisation of the underlying disease process and clinical pathways, the decision node differs for the analysis of chemoprevention within the general population and the intermediate-risk groups. For the economic analysis of chemoprevention within the general population, the simulation begins with a cohort aged 30, at which point the prevalence of polyps and CRC is assumed to be zero. The model uses age-dependent transition matrices as described above to calculate the number of individuals in each health state for each annual cycle over a lifetime horizon. For the intermediate-risk population, the analysis begins immediately after the point of postpolypectomy.

Mortality submodel

The model includes three types of mortality: other-cause mortality, CRC-specific mortality and death

following endoscopic perforation. The probability of dying from other causes is modelled as an age-dependent probability, which is dependent on the age of the cohort during each model cycle, based on UK life tables.²⁴² Dukes' stage-specific mortality rates are represented using a mixed model, which divides the population into terminal and non-terminal cancer patients. This analysis is based upon 1-, 3- and 5-year survival data produced by the Northern and Yorkshire Cancer Registry and Information Service (see *Figure 16*).²⁴³ The probability of death due to endoscopic perforation was modelled according to the experience of existing screening studies.^{59,37}

Model parameters

The following sections outline the methods used to derive specific types of parameter values within the model.

Methods for calibrating the natural history model

Importantly, model parameters such as transition probabilities for preclinical disease and the probabilities of symptomatic presentation are largely unobservable through empirical study. These unknown parameters were estimated through a process of model calibration. This involved fitting intermediate model outputs to available data on CRC incidence and mortality,²⁴³ cancer and polyp detection rates at screening (NHS Cancer Screening Programme, personal communication) and colorectal autopsy evidence²⁴⁴ using a Metropolis–Hastings algorithm (an analytic Markov Chain Monte Carlo sampling approach). This algorithm allows the calculation of a set of possible permutations of transition probabilities used to represent the disease natural history. Rather than assuming that one particular combination of transition probabilities is 'correct' within a base case, the base model is probabilistic and includes several sets of possible permutations of natural history transition probabilities. In describing the disease natural history, there is structural uncertainty around whether there are a proportion of cancers which arise *de novo* (i.e. there may be some cancers that do not arise following polyp incidence). The calibration process allows a small proportion of cancers to arise *de novo*. As this proportion is unknown, a prior distribution was used assuming that a mean of 5% of cancers arise *de novo* (95% CI 1% to 13%) within the model calibration process. This resulted in an average of around 1–2% of cancers arising *de novo* within the model. The ranges around the parameters used to

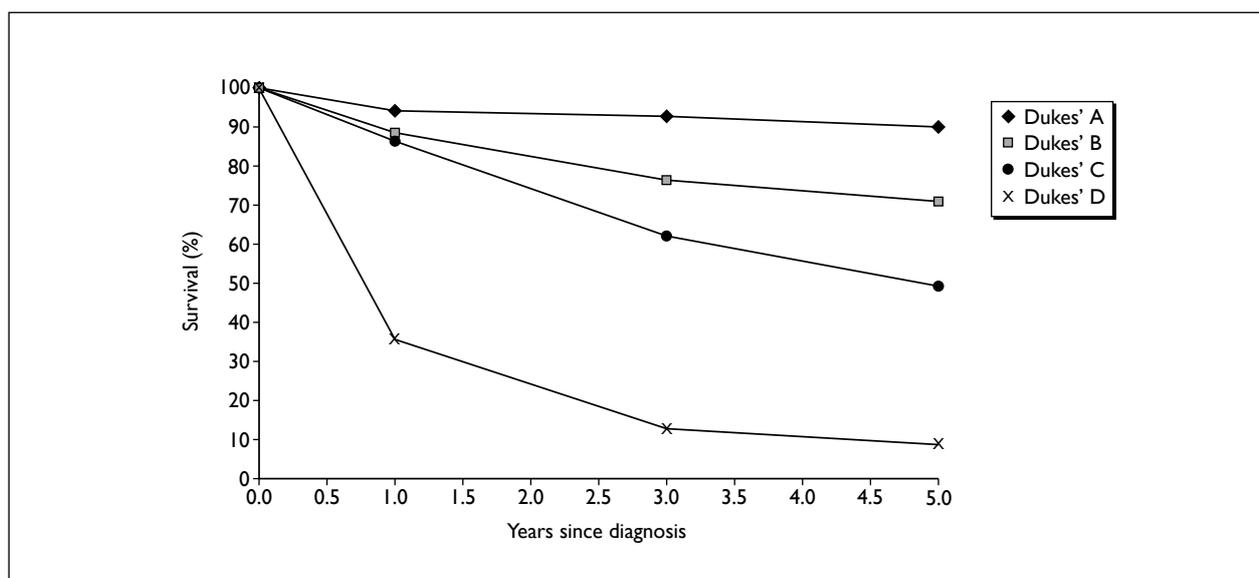


FIGURE 16 Survival estimates for CRC patients.²⁴³

simulate the disease natural history are shown in *Table 31*.

Methods for modelling the effectiveness of chemoprevention

The systematic review presented in Chapter 3 highlighted considerable evidence concerning the effectiveness of chemoprevention in the

general population and intermediate-risk groups. However, the evidence base leaves a number of relevant questions unanswered. In particular, key uncertainties concern the length of time required for chemoprevention to start to become effective in reducing adenomas, whether the effectiveness is constant over time or gradual, and the length of time over which chemoprevention is likely to

TABLE 31 Disease natural history parameters

Natural history model transition probability	Lower 95% CI	Upper 95% CI
Normal epithelium to low-risk polyp – age 30	0.001	0.003
Normal epithelium to low-risk polyp – age 40	0.000	0.002
Normal epithelium to low-risk polyp – age 50	0.004	0.006
Normal epithelium to low-risk polyp – age 60	0.003	0.010
Normal epithelium to low-risk polyp – age 70	0.008	0.014
Normal epithelium to low-risk polyp – age 80	0.000	0.009
Normal epithelium to low-risk polyp – age 90	0.000	0.024
Normal epithelium to low-risk polyp – age 100	0.000	0.026
Low-risk polyp to high-risk polyp	0.048	0.109
High-risk polyp to Dukes' A	0.037	0.086
Normal epithelium to Dukes' A	0.000	0.000
Dukes' A to Dukes' B	0.574	1.000
Dukes' B to Dukes' C	0.507	1.000
Dukes' C to Dukes' D	0.577	0.998
Dukes' A to Dukes' A clinical	0.058	0.102
Dukes' B to Dukes' B clinical	0.162	0.285
Dukes' C to Dukes' C clinical	0.404	0.550
Dukes' D to Dukes' D clinical	0.534	0.999

continue to be effective, the relationship between compliance and effectiveness, and whether additional benefits accrue when an individual has stopped taking the chemopreventive agent. Furthermore, none of the studies identified within the review attempted to establish an optimal treatment duration, and limited data are available surrounding optimal dosing regimens. Owing to these uncertainties, it is unclear how chemoprevention would be adopted in practice within England and Wales. Based on published literature and expert opinion, the model assumes the following within the base-case analysis.

- *The general population will begin chemoprevention at age 40 or 50 (both ages tested within analyses)* Polyp prevalence estimates suggest that polyps generally begin to appear when people are aged over 40 years.²⁴⁵
- *The intermediate-risk population will be offered chemoprevention following a polypectomy* Within the model several ages are tested; the polypectomy is assumed to be undertaken at ages 60, 64 or 70 and chemoprevention is assumed to begin a year later at ages 61, 65 or 71.
- *Chemoprevention will not be taken beyond age 80 years in either the intermediate-risk population or the general population* This is based on the assumption that chemoprevention will have an effect on reducing CRC up to 15 years post-treatment²¹ because of the time lag between adenoma incidence and CRC development. Hence chemoprevention is unlikely to be beneficial beyond age 80 years. This is varied from age 50 to age 80 within the analyses.

Assumptions around treatment dosing are based upon the included studies describing the effectiveness of chemoprevention. The following dosing was assumed within the model:

- aspirin: 300 mg/day
- celecoxib: 400 mg/day
- calcium: 1200 mg/day.

The following additional effectiveness assumptions have been made within the base-case model:

- *The effects of chemoprevention manifest at the point at which the individual begins taking the agent* A study by Baron *et al.* reported a positive effect of rofecoxib after 1 year of treatment.¹⁵³ Given the absence of evidence to the contrary, it is assumed that all chemopreventive agents begin to take effect within the first year of treatment.

It should be noted that the initial impacts of chemoprevention would be upon adenoma incidence rather than CRC incidence.

- *The relative risk of developing low-risk adenomas will be constant over the period during which the individual is taking chemoprevention* Only two studies identified within the review report results at more than one follow-up time (Arber and Bertagnolli)^{63,64}. These studies suggest that the relative risk of developing adenomas when given celecoxib is likely to be similar at 1 year and at 3 years. Therefore, the model assumes that this assumption can be applied to other chemopreventive agents and over longer periods of time such that the relative impact of chemoprevention upon the number of cancers is constant while chemoprevention is being taken.
- *The preventive effects for adenomas of all chemoprevention agents drop off at the point at which the patient stops taking the agent* Flossmann and Rothwell²¹ suggest that the impact of chemoprevention upon CRC incidence decreases around 15 years after treatment with chemoprevention has stopped; this is approximately consistent with the reported average time taken to progress from a polyp to CRC suggesting that the main impact of chemoprevention is likely to be on polyp incidence.

The impact of the above assumptions is tested within the model analysis to examine potentially optimal indications for chemoprevention (see Results). It should be noted that within the model it is assumed that chemoprevention will continue to be taken for 10 or 20 years; however, no trials have assessed treatment duration greater than 5 years; hence the effectiveness of taking chemoprevention over this longer time frame is not known.

Preventive effectiveness estimates were based only upon studies that compare chemoprevention with placebo; studies in which patients received other chemoprevention agents in both arms have not been included. It should be noted that there are heterogeneities between the studies used to estimate effectiveness of the chemopreventive agents such as age and treatment time. These are discussed in more detail in Chapter 3.

The clinical trials identified within the systematic review provide evidence for a wide range of chemopreventive agents. Outcomes reported within the clinical trials varied according to the population receiving chemoprevention. Within

the general population trials, the number of people developing CRC was reported but the number of people developing polyps was not, which is likely to be because of ethical concerns around undertaking colonoscopies on healthy individuals within the general population. Within the intermediate-risk population, the number of people with advanced adenomas and the number of people with any adenomas were commonly reported; however, the follow up and sample sizes were insufficient for CRC incidence to be reported. In the instances where CRC incidence was reported in the intermediate-risk group, too few events had occurred to suggest an effect. Many of the chemopreventive agents were shown to be ineffective in preventing adenomas within intermediate-risk populations, or in preventing CRC in the general population. Those chemopreventive agents that were reported to be ineffective were not included in the economic analysis because they are expected to be dominated. For the purposes of the model analysis, the chemopreventive agents were considered to be ineffective if they had a pooled relative risk of developing polyps/CRC of 1.0 or greater. In instances whereby the meta-analysis of available trial data resulted in a mean relative risk that was below 1.0, the chemopreventive agent has been included in the analysis.

The systematic review of clinical effectiveness suggests that aspirin chemoprevention is likely to be effective within the general population. Other NSAIDs have not been tested within the general population, and calcium and antioxidants currently have limited trial follow-up which may not be sufficient to demonstrate any effects of chemoprevention upon cancer incidence. The only chemopreventive agent assessed within the model for the general population is therefore aspirin. The chemopreventive agents assessed within the modelling framework for the intermediate-risk group are aspirin, celecoxib and calcium. The evidence around the use of antioxidants for chemoprevention provided variable results. The results of some of these trials are contradictory and the effectiveness of both individual antioxidants and combinations of antioxidants is unclear. Antioxidants were therefore not included within the main analysis.

Methods for modelling the effectiveness of chemoprevention

The current evidence suggests that chemoprevention, if effective, will have an effect upon the incidence of low-risk adenomas. Studies

also suggest that there may be some impact upon the incidence of high-risk adenomas, but there is currently no evidence to suggest whether this is as a result of the reduction in low-risk adenomas or if there is an additional direct impact upon high-risk adenomas. There is also currently limited evidence to suggest whether there would be a direct impact upon CRC. The model assumes that chemoprevention has a direct impact upon polyp incidence and hence an indirect impact upon the incidence of CRC. The model assumes that there would be no direct impact upon CRC incidence. The model also assumes that people would discontinue receiving chemoprevention if they were diagnosed with CRC.

General population

The relative risk for CRC incidence for patients receiving aspirin within the general population was based upon a meta-analysis of two studies^{77,80} for which the long-term CRC incidence data have been reported in Flossmann and Rothwell.²¹ The results of this meta-analysis are shown in *Table 32*.

As described previously, there is a probability of progressing through each stage of the disease based upon calibrated disease natural history parameters. Within the model, a relative risk can be applied to these transition probabilities based upon the estimated effect of chemoprevention upon each transition. Assuming that chemoprevention has an equivalent impact upon the incidence of low-risk polyps and the incidence of high-risk polyps, the calibrated disease natural history model was used to estimate these relative risks based on fitting the number of cancers within the model to match the number of cancers reported within the trials for both the control group and the aspirin chemoprevention group. Flossmann and Rothwell²¹ suggest that the chemopreventive effect upon CRC incidence is minimal for the first 10 years; however, from 10 to 19 years the relative risk for CRC incidence is estimated to be 0.61. This is consistent with the current model of disease natural history, which suggests that on average it takes more than 10 years to progress from normal epithelium to adenoma incidence to cancer incidence. The model therefore uses the relative risk from years 10–19 from Flossmann and Rothwell²¹ and matches the number of cancers for both the control group and the aspirin chemoprevention group at this time point. This means that the relative risk of CRC incidence will gradually decrease from 1 at initiation of chemoprevention (when there will be an effect upon adenoma incidence only) to 0.61 at 10–19 years. This process was undertaken

TABLE 32 Relative risk of incidence of CRC in general population

Chemopreventive agent	RR for incidence of CRC at 10–19 years	Source
Aspirin	0.61 (95% CI 0.43 to 0.88)	Two trials: Farrell, ⁷⁷ Peto ⁸⁰ Long-term follow-up data presented in: Flossmann ²¹

using the SOLVER add-on in EXCEL using a model where screening is not currently rolled out so as to correspond to the trials.

These figures were derived within a framework that does not include screening so it is not possible to calculate the relative risks of the transitions from postpolypectomy to low-risk or high-risk polyps. Within the intermediate-risk population model, the relative risk associated with the transition from postpolypectomy to low-risk polyps is assumed to be the same as the relative risk associated with the transition from low-risk polyps to high-risk polyps, whereas the relative risk associated with the transition from postpolypectomy to high-risk polyps is allowed to be different (see Intermediate-risk population). Therefore, within the general population model, it is assumed that the relative risk associated with the transition from postpolypectomy to low-risk polyps is equivalent to that derived for the relative risks associated with the transitions from normal epithelium to low-risk polyps and from low-risk polyps to high-risk polyps. Using this method, because the relative risk of the incidence of CRC was so low (0.61), the relative risk associated with these transitions was low (0.0419). Within the intermediate-risk model, the relative risk associated with the transition from postpolypectomy to high-risk polyps was consistently lower than the relative risk associated with the transition from postpolypectomy to low-risk polyps. Within the general population model, the relative risk associated with the transition from

postpolypectomy to high-risk polyps was therefore assumed to be zero. As such a small proportion of patients follow this pathway within the general population model, this assumption would not have a large impact upon the model results. These assumptions are shown in *Figure 17*.

For the probabilistic sensitivity analysis, a distribution was fitted to the relative risk shown in *Table 32* and a value was sampled from this distribution. This sampled value was then used within SOLVER to estimate the relative risks for the transition probabilities outlined in *Figure 17*. This process was repeated 1000 times to generate a distribution for these relative risks.

Intermediate-risk population

Within the clinical trials, the number of people with low-risk adenomas was not provided; however, the number of people with any adenoma and the number of people with high-risk adenomas was provided within the intermediate-risk group. The number of people with low-risk adenomas was therefore estimated as the difference between these two values. The following calculation was undertaken to calculate event rates of low-risk adenomas in each arm of the study:

$$\text{No. of low-risk adenomas} = [(\text{Cumulative rate of all adenomas} - \text{Cumulative rate of high-risk adenomas}) / 100] \times \text{Total number of patients in study arm}$$

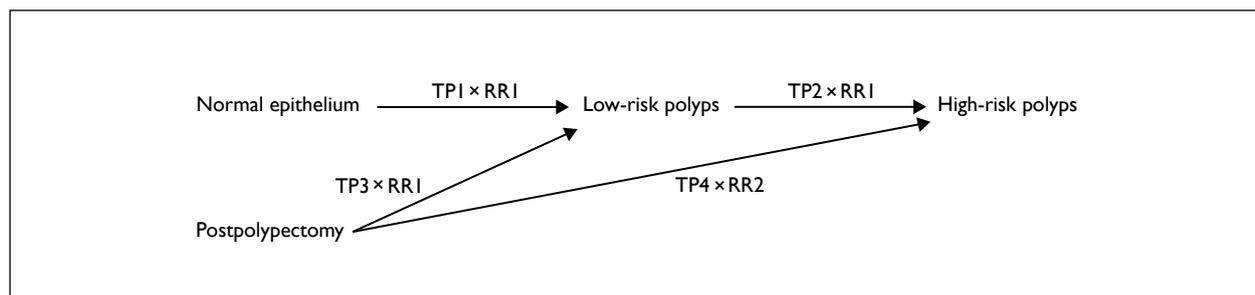


FIGURE 17 Relative risk (RR) assumptions for chemoprevention. TP, transition probability.

The result of this calculation was then used within the meta-analysis (see *Table 33*).

The relative risk of developing low-risk and high-risk adenomas for patients receiving aspirin was based upon a meta-analysis of three studies.^{60–62} Within both celecoxib studies identified by the review,^{63,64} the event numbers at the 3-year follow-up were biased by the intervention following the 1-year follow-up. The cumulative proportion of events therefore provided a more reasonable approximation for calculating the relative risks. Two calcium studies were identified within the review for the intermediate-risk population.^{96,99} Within Bonithon-Kopp,⁹⁶ high-risk adenomas were described as either > 1 cm or villous; the former of which was used to calculate incidence of low-risk adenomas. Within Baron,⁹⁹ the relative risk of developing high-risk adenomas was not reported; however, the authors were contacted and were able to provide these data for use within the analysis. Both of these calcium studies also provided CRC incidence; however, event numbers were close to zero because of the short follow-up of the trials. Therefore these studies could not be used for the purposes of validation. The relative risks of the incidence of low-risk and high-risk polyps in the intermediate-risk population are shown in *Table 33*.

For the intermediate-risk population, it was assumed that an equivalent relative risk can be applied to the transition probability from the postpolypectomy state to low-risk polyps and from low-risk polyps to high-risk polyps. A second relative risk was assumed to apply to the probability

of transiting from normal epithelium following a polypectomy to high-risk polyps (*Figure 17*). The calibrated disease natural history model was used to estimate these relative risks based on fitting the number of low-risk polyps and high-risk polyps within the model to match the number of low-risk polyps and high-risk polyps reported within the trials for both the control group and the chemoprevention group. This process was undertaken using the SOLVER add-on in EXCEL as in the general population model. The samples for the PSA values were generated in the same way as those for the general population model.

Chemoprevention compliance

It is likely that compliance estimates observed within the clinical trials represent overestimates of the expected compliance rates for chemoprevention in practice (see Chapter 4). In particular, some of the studies selected patients based on prior analysis that had suggested that they were likely to be compliant. However, as the effectiveness estimates and compliance estimates within the clinical trials cannot be separated, compliance within the model is based upon the compliance within the trials. This is assumed to capture discontinuation as the result of harms associated with the chemopreventive agents. Costs of chemoprevention were adjusted within the model according to compliance reported within the trials. If compliance in practice was reduced compared with the compliance experienced within the trials, the implications for the cost-effectiveness of the chemopreventive agents is likely to be minimal because both costs and effects have been

TABLE 33 Relative risk of incidence of low-risk and high-risk polyps in the intermediate-risk population

Chemopreventive agent	RR for incidence of low risk polyps (95% CI)	RR for incidence of high risk polyps (95% CI)	Source
Aspirin	0.93 (0.76 to 1.14)	0.75 (0.52 to 1.07)	Logan, ⁶⁰ Cole, ⁶¹ Benamouzig ⁶²
Celecoxib	0.77 (0.69 to 0.86)	0.45 (0.35 to 0.58)	Arber, ⁶³ Bertagnolli ⁶⁴
Calcium	0.84 (0.68 to 1.03)	0.77 (0.50 to 1.17)	Bonithon-Kopp, ⁹⁶ Baron ⁹⁹
95% CI in parentheses.			

TABLE 34 Compliance estimates

Population	Chemoprevention	Compliance	Source
General population	Aspirin	72.5%	Farrell, ⁷⁷ Peto ⁸⁰
Intermediate-risk population	Aspirin	90%	Logan, ⁶⁰ Cole, ⁶¹ Benamouzig ⁶²
	Celecoxib	75%	Arber, ⁶³ Bertagnolli ⁶⁴
	Calcium	80%	Bonithon-Kopp, ⁹⁶ Baron ⁹⁹

modelled under the same compliance assumptions. Compliance estimates based upon the trials for each of the chemopreventive agents are shown in *Table 34*.

Adverse events/positive or negative impacts associated with chemoprevention upon other diseases

Each of the chemopreventive agents assessed within the model are associated with harms to the individual and/or reductions in the incidence of other diseases. It is important to weigh these harms and benefits against the chemopreventive benefits. There is generally poor longitudinal evidence around the extent of the harms associated with aspirin, celecoxib and calcium chemoprevention; hence numerous simplifying assumptions have been made within this analysis.

The trials identified within the effectiveness review provide limited evidence around harms and other benefits associated with the chemopreventive agents because of the low prevalence of the harms/benefits within the population and hence the large number of patients required to demonstrate an effect. Therefore, reviews of aspirin, celecoxib and calcium harms were identified. The studies used to model harms within the model were a meta-review of 12 systematic reviews of the use of aspirin (Dube)⁷⁶, a review of eight systematic reviews of the use of COX-2 inhibitors (Rostom)⁸⁸ and a RCT of the impact of calcium upon vascular events in healthy older women (Bolland).²⁴⁶ The last of these may introduce some bias because the review focuses on women; however, this was the most appropriate evidence identified to represent harms associated with calcium. Relative risks for celecoxib are based upon a mixture of NSAIDs and doses and hence may be slightly overestimated.⁸⁸ A sensitivity analysis was undertaken to assess the impact of no harms associated with 400 mg celecoxib to assess whether this would have a substantial impact upon the model results.

Based on these three studies, key harms and benefits of chemoprevention included within the modelling were dyspepsia, serious gastrointestinal bleed/ulcer, stroke and myocardial infarction. The relative risk of experiencing each of these events for each chemoprevention agent is shown in *Table 35*. These relative risks are assumed to be constant over time while the person is taking the intervention. It is possible that the incidence of some such events may decrease over time, whereas the incidence of others may increase; however, there is very limited evidence to support these assertions.

There is limited evidence surrounding the duration and level of severity of harms associated with chemopreventive agents. There is also no evidence of the harms around the daily consumption of aspirin, celecoxib or calcium beyond 10 years. Evidence suggests that harms occurring as a result of chemoprevention are likely to be short-term and mild.²⁴⁷ For example, strokes occurring as a result of chemoprevention are likely to be mild and hence more likely to have only short-term impacts upon quality of life. The three studies used to model the harms and benefits for each chemopreventive agent suggest that there is no evidence of an impact upon other-cause mortality.^{76,88,246} Hence the model assumes that there will be no increase in deaths as a result of the use of chemoprevention. Each of the harms is assumed to occur for less than a year.

Only excess harms to those normally experienced within the population are included within the health economic model. The relative risk of experiencing each harm is applied to the baseline incidence within the general population to calculate the additional probability of experiencing each harm or benefit as a result of the chemopreventive agent. Incidence of each of the harms and benefits within the general population

TABLE 35 Relative risk of experiencing harms

Chemopreventive agent	Mean relative risk of experiencing harms			
	Dyspepsia	Serious gastrointestinal bleed/ulcer	Stroke	Myocardial infarction
Aspirin	1.7	2.3	1.4 ^a	0.74
Celecoxib	1.7	1.53	1	1.86
Calcium	1	1	1.42	2.12

a Haemorrhagic only.

was based upon the analysis undertaken for the NICE osteoarthritis guidelines. Incidence of myocardial infarction within this analysis appeared low compared with other sources of evidence, which suggested that the incidence is likely to be around 1%;^{246,248} hence this was used for myocardial infarction. The assumed incidence of harms within the general population is shown in *Table 36* and the resultant probabilities of excess harms as a result of chemoprevention are shown in *Table 37*. This analysis makes the simplifying assumptions that the excess harms are constant over time and are not age-dependent because of the very limited evidence of such impacts.

There is some evidence that chemoprevention impacts upon the incidence of other cancers (in particular oesophageal and gastric cancer), in addition to CRC. However, given the inconsistencies within this evidence in general, these effects are excluded from the economic analysis.

Health-related quality of life

A systematic review was undertaken to identify relevant HRQoL evidence. A search was undertaken for HRQoL associated with CRC by the School of Health and Related Research in 2005 for a HTA systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic CRC.²⁴⁹ This search was updated using the same search strategy from 2005 onwards. This search strategy is shown in Appendix 1. The original search identified a total of six studies that attempted to estimate utility scores for patients with CRC. The current search identified no new evidence. Details of the methods used within these studies are reported in *Table 38*.

These studies do not demonstrate a clear relationship between HRQoL and stage of cancer, treatment, phase of disease, or time since diagnosis. Only two studies have attempted to estimate health utility scores for patients according to stage of cancer (Ness and Ramsey).^{251,252} The study by Ness,²⁵¹ undertaken using hypothetical health status scenarios, suggests a substantial difference between early-stage and late-stage cancers (Stage I utility: 0.74; Stage IV utility: 0.24). The study by Ramsey,²⁵² which was undertaken using long-term survivors of bowel cancer, does not demonstrate this relationship between cancer stage and declining HRQoL (Stage I utility: 0.84; Stage IV utility: 0.84). The results of the MABEL study (Corrie²⁵⁵) lend further weight to this suggestion, as the sample of patients included in this study had metastatic bowel cancer and had failed on at least one prior line of chemotherapy and had a health utility of 0.73. However, the study by Ness *et al.* involved eliciting preferences for hypothetical health states from individuals who had previously undergone polypectomy, while the other studies involved eliciting preferences from patients currently experiencing the health state. As NICE recommend that utilities should be based upon public preferences,²⁵⁶ the study by Ness was used to estimate utilities associated with CRC.²⁵¹

Simplistic assumptions were made within the model because of the limited evidence concerning the relationship between utility, stage of cancer and time since diagnosis. Age-specific utility scores were assigned to patients without bowel cancer based upon the 1996 General Health Survey for England.²⁵⁷ The paper by Ness provided mean utilities for each Dukes stage and also a mean utility associated with non-CRC states. A relative

TABLE 36 Incidence of harms in general population

Dyspepsia	Serious gastrointestinal bleed/ulcer	Haemorrhagic stroke	All stroke	Myocardial infarction
26.85%	0.24%	0.06%	0.3%	1%

TABLE 37 Resultant additional probability of experiencing specific harms

Chemopreventive agent	Dyspepsia	Serious gastrointestinal bleed/ulcer	Stroke	Myocardial infarction
Aspirin	18.795%	0.312%	0.024% (haemorrhagic)	-0.260%
Celecoxib	18.795%	0.127%	0%	0.860%
Calcium	0%	0%	0.126% (all)	1.120%

TABLE 38 Summary of characteristics of utility studies for bowel cancer

Study	Study population	Method of preference elicitation and details of scenarios used
Ko ²⁵⁰	Colon cancer subgroup included 169 patients	The Health and Activities Limitation Index was mapped onto a utility scale. This does not appear to be preference-based but is a conversion of a numerical Likert rating scale
Ness ²⁵¹	90 individuals who had previously undergone removal of colorectal adenoma; 81 of these patients were included in the study	Seven health states describing various states of severity of colon and rectal cancer. Preferences elicited using standard gamble
Ramsey ²⁵²	173 subjects with CRC (various stages) sampled from US SEER database completed the survey	Preferences elicited using the Health Utilities Index Mark 3 (HUI3)
Petrou and Campbell ²⁵³	30 nurses experienced in oncology care	Utility scores for six chemotherapy-specific scenarios elicited using the standard gamble technique
MRC FOCUS trial ²⁵⁴	Subset of clinical trial population with metastatic bowel cancer	EQ-5D questionnaire
Merck MABEL trial ²⁵⁵	Clinical trial population with metastatic bowel cancer	EQ-5D questionnaire

EQ-5D, EuroQoL 5-dimension measure of health-related quality of life.

utility of patients with CRC versus the general population could therefore be derived from Ness according to Dukes stage. These relative risks were then multiplied by the age-specific utility scores for people without cancer to provide an age-specific utility score for people with each Dukes stage. Within the probabilistic sensitivity analysis, the relative risks were varied using the confidence intervals around the mean utility estimates from Ness.²⁵¹

The utility parameters used to model people with or without CRC within the model are shown in *Table 39*.

These utilities are adjusted for harms associated with chemoprevention including dyspepsia, serious gastrointestinal bleed/ulcer, stroke and myocardial infarction. The quality of life impacts of dyspepsia and serious gastrointestinal bleeds/ulcers are assumed to be incurred for 1 month within the model, whereas stroke and myocardial

infarction are assumed to last for 3 months (given that evidence suggests that these events are likely to be mild as a result of chemoprevention²⁴⁷). Relative utilities associated with each of the harms have been taken from the NICE osteoarthritis guidelines²⁴⁷ and are shown in *Table 40*. These relative utilities are multiplied by the age-related utilities to provide utility scores adjusted for these harms.

With the exception of those patients who experience harms due to chemoprevention, the model assumes that there are no substantial HRQoL implications associated with receiving daily chemoprevention.

Costs included in the economic analysis

The analysis was undertaken from a NHS perspective assuming that the NHS pays for chemoprevention. In practice, this would only be viable if the NHS were to provide chemoprevention

TABLE 39 Utilities within the model

Parameter	Mean	Source
Non-CRC utility	Age-dependent	Health Survey for England 1996 ²⁵⁷
Dukes' A utility relative risk	0.88	Ness ²⁵⁸
Dukes' B utility relative risk	0.70	
Dukes' C utility relative risk	0.70	
Dukes' D utility relative risk	0.30	

TABLE 40 Utilities associated with chemopreventive harms

	Dyspepsia	Serious gastrointestinal bleed/ulcer	Stroke	Myocardial infarction
Utilities	0.73	0.46	0.35	0.37
Duration	1 month	1 month	3 months	3 months

without prescription charges. Cost components within the model include:

- the cost of the chemoprevention agent
- costs associated with doctor's appointments to obtain chemoprevention (it is assumed that one doctor's appointment would be required per year for a prescription)
- the cost of CRC diagnosis (this includes the cost of flexible sigmoidoscopy, colonoscopy and barium enema and other diagnostic/staging modalities; it also includes the cost of perforation as a result of diagnostic tests)
- the cost of treating CRC (this is calculated according to Dukes' stage within an existing model developed by the authors²⁵⁹)
- costs associated with treating adverse events/harms (dyspepsia, serious gastrointestinal bleed/ulcer, stroke, myocardial infarction) associated with regular aspirin, celecoxib or calcium use.

The costs included within the model are presented in *Table 41*. All costs have been uplifted to 2007–8 prices where appropriate.

TABLE 41 Cost parameters included in the economic model

Parameter	Cost	Source
Annual cost of aspirin (300 mg/day)	£17.19	BNF 57, 2008 ⁵⁶
Annual cost of celecoxib (400 mg/day)	£524.38	BNF 57, 2008 ⁵⁶
Annual cost of calcium (3 tablets per day)	£34.53	BNF 57, 2008 ⁵⁶
Cost of doctor's appointment	£36	PSSRU, 2008 ²⁶⁰
Colonoscopy (with polypectomy)	£389	NHS reference costs 2005 (colonoscopy) ²⁶¹
Colonoscopy (without polypectomy)	£389	NHS reference costs 2005 (colonoscopy) ²⁶¹
FOBT (two tests)	£13	Tappenden ²³⁸
Treating bowel perforation	£2164	NHS reference costs 2006–7 (Major therapeutic open or endoscopic procedures 19 years and over with major colon cancer) ²⁶²
Cost of admittance for bleeding	£278	NHS reference costs 2006–7 (Very major procedure for gastrointestinal bleed) ²⁶²
Pathology cost for adenoma	£27	NHS reference costs 2006–7 (histopathology) ²⁶²
Pathology cost for CRC	£27	NHS reference costs 2006–7 (histopathology) ²⁶²
Treatment of Dukes' A (lifetime)	£11,917	Pilgrim ²⁵⁹
Treatment of Dukes' B (lifetime)	£16,397	Pilgrim ²⁵⁹
Treatment of Dukes' C (lifetime)	£22,487	Pilgrim ²⁵⁹
Treatment of Dukes' D (lifetime)	£24,593	Pilgrim ²⁵⁹
Dyspepsia	£40	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷
Serious gastrointestinal bleed/ulcer	£3052	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷
Stroke	£2419	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷
Myocardial infarction	£1532	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷

PSSRU, Personal Social Services Research Unit.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken whereby all model parameters were varied simultaneously within plausible ranges to produce distributions of expected costs and outcomes. Costs were represented using gamma distributions because these parameters may be skewed. Beta distributions were used to represent utilities and percentages. In a small number of cases, it was not possible to fit a beta distribution because the mean percentage was very close to one or zero; a uniform distribution was used to represent these parameters. Relative risks of experiencing harms associated with chemoprevention were represented using a normal or log normal distribution depending upon the confidence intervals presented within the systematic reviews. All parameter values are shown in *Table 42* with the distribution used to represent uncertainty. Disease natural history parameters are excluded from this table because the way in which they are calibrated means that they cannot be represented by mean values. Ranges around the disease natural history parameters are shown in *Table 31*.

Model results and sensitivity analyses

Costs and outcomes associated with chemoprevention were compared incrementally against each other and against no chemoprevention; it should be noted that the baseline option includes screening and so is not strictly a 'do nothing' comparator. Each chemopreventive agent was compared against the next most effective option. Strongly dominated and extendedly dominated options were excluded from the incremental cost-effectiveness estimates. Discounted and undiscounted cost-effectiveness results are presented for each scenario.

As noted earlier (see Model parameters), a key uncertainty surrounding the potential use of chemoprevention concerns the nature of the chemoprevention policy that would be adopted in practice. Cost-effectiveness is assessed within a range of age subgroups in terms of when people are assumed to begin and discontinue use of chemoprevention. Evidence suggests that, excluding people with a hereditary disease associated with CRC, polyps generally begin developing from age 40 onwards. It has therefore been suggested that giving people chemoprevention when they are in their fourth and fifth decades of life is likely to be the optimum treatment approach.²⁶⁷ Within the general population, the age ranges assessed are:

- begin chemoprevention at age 40 years, discontinue at age 50 years
- begin chemoprevention at age 40 years, discontinue at age 60 years
- begin chemoprevention at age 50 years, discontinue at age 60 years
- begin chemoprevention at age 50 years, discontinue at age 70 years.

For the intermediate-risk population, the age at which a person begins receiving chemoprevention would probably be dependent on the point at which they undergo polypectomy within the CRC screening programme. Many individuals will undergo polypectomy at age 60 following the first screening round. Within the model it is assumed that these individuals will begin chemoprevention within a year following polypectomy. However, some individuals may develop polyps during screening intervals or may not attend until later in the screening programme. Furthermore, some individuals may receive a polypectomy outside of the screening programme. Analyses were also undertaken whereby (1) individuals with adenomas undergo polypectomy at age 64 and begin chemoprevention at age 65 and (2) individuals with adenomas undergo polypectomy at age 70 and begin chemoprevention at age 71, to assess the impact of different chemoprevention starting ages on incremental cost-effectiveness. For the intermediate-risk population the age ranges assessed for receiving chemoprevention within the model are:

- begin chemoprevention at age 61 years, discontinue at age 70 years
- begin chemoprevention at age 61 years, discontinue at age 80 years
- begin chemoprevention at age 65 years, discontinue at age 80 years
- begin chemoprevention at age 71 years, discontinue at age 80 years.

The policy for each population that provided the most economically attractive option is presented as the base-case analysis and the remaining policies are presented as secondary scenarios.

The most substantial uncertainty surrounding the decision problem concerns the ratio of benefits to harms associated with specific chemopreventive agents. This was therefore assessed within a two-way sensitivity analysis using the most cost-effective policy above. The net benefit of each chemopreventive agent was compared against a

TABLE 42 Model parameters

Parameter	Mean	SE (unless otherwise stated)	Distribution	Source
Screening and diagnostic test parameters				
gFOBT – Sensitivity for polyps	11%	3.5%	Beta	Burch ²⁶³
gFOBT – Sensitivity for CRC	58%	8%	Beta	Weller ²⁶⁴
gFOBT – Specificity	97%	0.5%	Beta	Assumption
COL – Sensitivity for low-risk polyps	77%	2%	Beta	Calculated from Van Rijn ²⁶⁵
COL – Sensitivity for high-risk polyps	98%	Range 93–99%	Uniform	Calculated from Van Rijn ²⁶⁵
COL – Sensitivity for CRC	98%	Range 95–99%	Uniform	Bressler ²⁶⁶
COL – Specificity	97%	0.5%	Beta	Assumption
COL – Probability of perforation (without polypectomy)	0.08%	Range 0.17–0.30%	Uniform	Atkin ⁵⁹
COL – Probability of perforation (with polypectomy)	0.17%	Range 0.01–0.25%	Uniform	Atkin ⁵⁹
COL – Probability of death following perforation	5.82%	1%	Beta	Gatto ³⁷
Probability of bleeding following COL	0.439%	Range 0.07–0.45%	Uniform	Atkin ⁵⁹
Probability of inadequate bowel preparation (COL)	10%	2%	Beta	Assumption
Surveillance transition probabilities				
Proportion of HR polypectomy requiring annual surveillance	29%	NA	NA	Based on model calibration
LR polypectomy, transition probability to LR polyp	11%	NA	NA	
LR polypectomy, transition probability to IR polyp	2%	NA	NA	
LR polypectomy, transition probability to HR polyp	2%	NA	NA	
IR polypectomy, transition probability to LR polyp	15%	NA	NA	
IR polypectomy, transition probability to IR polyp	4%	NA	NA	
IR polypectomy, transition probability to HR polyp	4%	NA	NA	
HR polypectomy, transition probability to LR polyp	18%	NA	NA	
HR polypectomy, transition probability to IR polyp	6%	NA	NA	
HR polypectomy, transition probability to HR polyp	6%	NA	NA	
Effectiveness parameters (general population)				
Relative risk applied to transitions to polyp incidence – aspirin	0.0401	Range 0–0.7165	See Model parameters	Farrell, ⁷⁷ Peto, ⁸⁰ Flossmann ²¹

continued

TABLE 42 Model parameters (continued)

Parameter	Mean	SE (unless otherwise stated)	Distribution	Source
Effectiveness parameters (intermediate-risk population)				
Relative risk applied to transitions to LR/HR polyps from polypectomy – aspirin	0.83/0.54	Range 0.49/0.2 to 1.33/1.03	See Model parameters	Logan, ⁶⁰ Cole, ⁶¹ Benamouzig ⁶²
Relative risk applied to transitions to LR/HR polyps from polypectomy – celecoxib	0.51/0.07	Range 0.36/0 to 0.68/0.26	See Model parameters	Arber, ⁶³ Bertagnolli ⁶⁴
Relative risk applied to transitions to LR/HR polyps from polypectomy – calcium	0.66/0.64	Range 0.35/0.2 to 1.09/1.34	See Model parameters	Bonithon-Kopp, ⁹⁶ Baron ⁹⁹
Compliance parameters				
Probability that a person ever complies with a screening programme	75%	5%	Beta	Derived from Weller ²⁶⁴
Compliance with gFOBT	52%	3.5%	Beta	Weller ²⁶⁴
COL follow-up compliance	82.5%	NA	NA	Weller ²⁶⁴
Surveillance colonoscopy compliance	82.5%	NA	NA	Assumed to be same as above
Aspirin (general population)	72.5%	NA	NA	Farrell, ⁷⁷ Peto ⁸⁰
Aspirin (intermediate-risk population)	90%	NA	NA	Logan, ⁶⁰ Cole, ⁶¹ Benamouzig ⁶²
Celecoxib (intermediate-risk population)	75%	NA	NA	Arber, ⁶³ Bertagnolli ⁶⁴
Calcium (intermediate-risk population)	80%	NA	NA	Bonithon-Kopp, ⁹⁶ Baron ⁹⁹
Cost parameters				
Annual cost of aspirin (300mg/day)	£17.19	NA	NA	BNF 57, 2008 ⁵⁶
Annual cost of celecoxib (400mg/day)	£524.38	NA	NA	BNF 57, 2008 ⁵⁶
Annual cost of calcium (3 tablets per day)	£34.53	£3	Normal	BNF 57, 2008 ⁵⁶
Cost of doctor's appointment	£36	£4	Normal	PSSRU, 2008 ²⁶⁰
Colonoscopy (with polypectomy)	£389	£20	Gamma	NHS reference costs 2005 (colonoscopy) ²⁶¹
Colonoscopy (without polypectomy)	£389	£20	Gamma	NHS reference costs 2005 (colonoscopy) ²⁶¹
FOBT (two tests)	£13	NA	NA	Tappenden ²³⁸
Treating bowel perforation	£2164	£200	Gamma	NHS reference costs 2006–7 (Major therapeutic open or endoscopic procedures 19 years and over with major colon cancer) ²⁶²
Cost of admittance for bleeding	£278	£20	Gamma	NHS reference costs 2006–7 (Very major procedure for gastrointestinal bleed) ²⁶²
Pathology cost for adenoma	£27	£3	Gamma	NHS reference costs 2006–7 (Histopathology) ²⁶²
Pathology cost for CRC	£27	£3	Gamma	NHS reference costs 2006–7 (Histopathology) ²⁶²
Treatment of Dukes' A (lifetime)	£11,917	£1000	Gamma	Pilgrim ²⁵⁹
Treatment of Dukes' B (lifetime)	£16,397	£1000	Gamma	
Treatment of Dukes' C (lifetime)	£22,487	£1000	Gamma	
Treatment of Dukes' D (lifetime)	£24,593	£1000	Gamma	

TABLE 42 Model parameters (continued)

Parameter	Mean	SE (unless otherwise stated)	Distribution	Source
Treatment for dyspepsia	£40	£5	Gamma	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷
Treatment for serious gastrointestinal bleed/ulcer	£3052	£305	Gamma	
Treatment for stroke	£2419	£242	Gamma	
Treatment for myocardial infarction	£1532	£153	Gamma	
Utility estimates				
Non-CRC utility	Age-dependent			Health Survey for England 1996 ²⁵⁷
Dukes' A utility relative risk	0.88	0.05	Beta	Ness ²⁵⁸
Dukes' B utility relative risk	0.70	0.05	Beta	
Dukes' C utility relative risk	0.70	0.05	Beta	
Dukes' D utility relative risk	0.30	0.04	Beta	
Dyspepsia	0.73	NA	NA	Appendix 4 of NICE osteoarthritis guidelines (2008) ²⁴⁷
Serious gastrointestinal bleed/ulcer	0.46	NA	NA	
Stroke	0.35	NA	NA	
Myocardial infarction	0.37	NA	NA	
Relative risk of harms associated with aspirin				
Dyspepsia	1.70	0.1	Normal	Dube ⁷⁶
Serious gastrointestinal bleed/ulcer	2.30	0.4	Normal	
Haemorrhagic stroke	1.40	0.3	Normal	
Myocardial infarction	0.74	0.7	Normal	
Relative risk of harms associated with celecoxib				
Dyspepsia	1.70	0.5	Normal	Rostom ⁸⁸
Serious gastrointesinal bleed/ulcer	1.53	(0.47, 0.4, 0.89) ^a	Lognormal	
Myocardial infarction	1.86	(0.63, 0.19, 0.97) ^a	Lognormal	
Relative risk of harms associated with calcium				
Stroke	1.42	(0.37, 0.3, 0.94) ^a	Lognormal	Bolland ²⁴⁶
Myocardial infarction	2.12	(0.79, 0.4, 0.89) ^a	Lognormal	
COL, colonoscopy; gFOBT, guaiac faecal occult blood test; HR, high-risk; IR, intermediate-risk; LR, low-risk; NA, not available; PSSRU, Personal Social Services Research Unit.				
a Log normal parameters are logged mean, logged standard error, multiplier.				

screening-only option and the impact upon the model results of increasing harms while decreasing effectiveness was estimated over a range of values. For the model of the general population, within this analysis the impact of different assumptions around effectiveness is assessed by varying the relative risk of the incidence of CRC associated with aspirin from 0.6 to 0.95. The impact of different assumptions around harms are assessed by multiplying the excess probability of each harm

by some number, x , which would lead to aspirin having an incremental cost per QALY gained of around £20,000 for each effectiveness assumption. For example, currently the excess probabilities of dyspepsia, serious gastrointestinal bleed/ulcer and haemorrhagic stroke are 18.795%, 0.312% and 0.024%, respectively. If x were equal to 2, this would mean that these probabilities would become 37.59%, 0.624% and 0.048%, respectively. The impact of a range of values of x was therefore

assessed. The limitation of this approach is that it does not allow for the excess probability of one form of harm to increase more than the excess probability of another form; however, doing this would lead to an unmanageable set of possible permutations to assess. The excess probability of myocardial infarction was not varied within this analysis because aspirin decreases rather than increases the probability of a myocardial infarction.

For the model of the intermediate-risk population, a similar method was employed within the two-way sensitivity analysis. The impact of different assumptions concerning effectiveness was assessed by varying the relative risk of the incidence of low-risk polyps associated with each chemopreventive agent from 0.7 to 0.95. The relative risk of the incidence of high-risk polyps was then adjusted according to the relationship between the relative risk of the incidence of low-risk and high-risk polyps for the mean values. For example, the mean relative risk of the incidence of low-risk polyps was estimated to be 0.93 from the clinical trials of aspirin and the mean relative risk of the incidence of high-risk polyps was estimated to be 0.75. If the relative risk of the incidence of low-risk polyps was then varied such that it becomes 0.8, the relative risk of the incidence of high-risk polyps becomes $(0.75/0.93) \times 0.8 = 0.65$. Harms are then varied in the same way as in the general population model two-way sensitivity analysis. Results of the sensitivity analysis are presented in terms of the incremental cost per QALY gained.

This two-way sensitivity analysis was undertaken only for aspirin and calcium because celecoxib has such a high cost-effectiveness ratio within the base case. A one-way sensitivity analysis assuming that celecoxib is associated with no harms was tested as an extreme assumption to assess the impact of these harms upon the model results.

Results

This section presents the results of the economic analysis of chemoprevention. Unless otherwise stated, all model results are expected cost-effectiveness estimates derived from probabilistic sensitivity analyses.

General population model analysis

Base-case option

The model analysis suggests that the most cost-effective age-range policy would be to provide chemoprevention to all individuals within the general population from age 50 to 60 years. This

result is highly dependent upon the assumptions surrounding the natural history of the disease, particularly with regard to adenoma incidence by age. The results of this policy are shown in *Table 43*.

This analysis suggests that the use of aspirin chemoprevention in addition to screening within the general population is likely to result in a discounted cost per LYG of around £10,000 and a discounted cost per QALY gained of around £23,000 compared with screening alone. It should be noted that the cost per LYG estimate does not incorporate the negative health effects associated with harms due to chemoprevention. When costs and health outcomes are not discounted, aspirin chemoprevention is expected to cost around £5000 per QALY gained when compared with screening alone. This is because the costs of daily aspirin are incurred from age 50, but the benefits of chemoprevention do not manifest until a number of years into the future. Discounting therefore has a substantial impact upon the model results. *Figure 18* presents cost-effectiveness acceptability curves (CEACs) associated with this policy.

Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that screening plus aspirin chemoprevention results in more net benefit than screening alone is expected to be around 0.80. *Figure 18* suggests that if society is willing to pay up to £30,000 per QALY gained, there remains a 20% probability that screening alone results in a larger net benefit than screening plus aspirin chemoprevention. Even if society was willing to pay £100,000 per QALY gained, there remains a small probability (< 5%) that screening alone would be more economically attractive. This highlights the substantial uncertainties within the model.

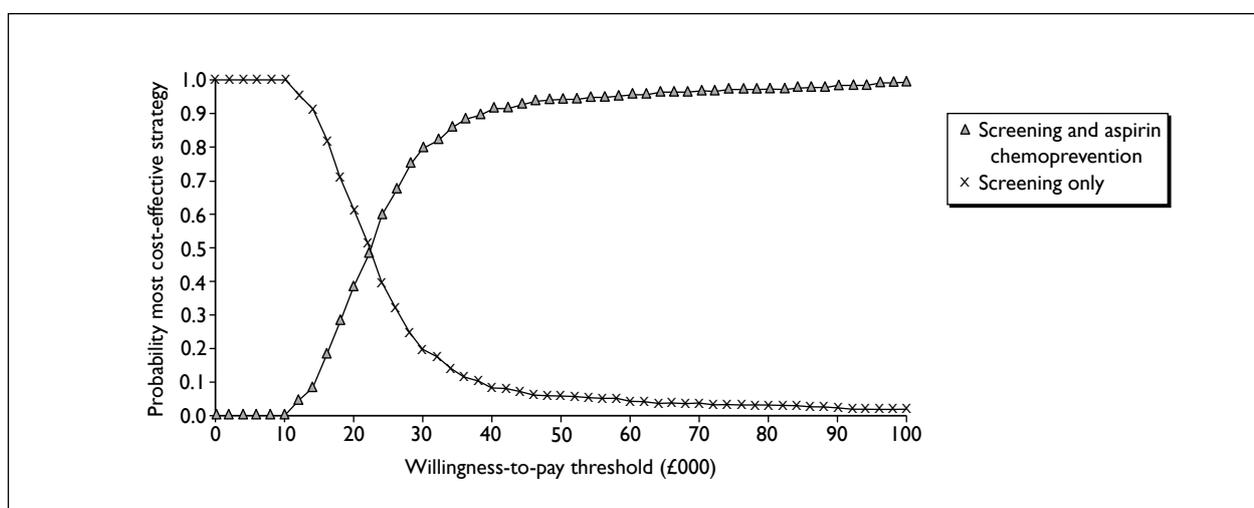
Other age-related policies within the general population

As described previously, a range of other age-related policies for receiving chemoprevention were assessed within the health economic model. Cost-effectiveness estimates for the use of chemoprevention between 50 and 70 years are shown in *Table 44*.

Extending the upper age for chemoprevention from 60 to 70 years reduces the cost-effectiveness of aspirin chemoprevention plus screening to an estimated £35,000 per QALY gained compared with screening alone. It is possible that harms associated with aspirin may increase beyond age

TABLE 43 Results of chemoprevention given to general population age 50–60 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£997	16.87	13.74	–	–
Screening plus aspirin	£1367	16.91	13.76	£10,169	£22,800
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£1807	26.36	21.08	–	–
Screening plus aspirin	£2134	26.45	21.14	£3799	£5164

**FIGURE 18** CEAC for chemoprevention given to general population age 50–60 years (discounted QALYs).**TABLE 44** Results of chemoprevention given to general population age 50–70 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£997	16.87	13.74	–	–
Screening plus aspirin	£1524	16.92	13.76	£10,654	£34,888
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£1807	26.36	21.08	–	–
Screening plus aspirin	£2319	26.49	21.16	£4137	£6452

60. This impact is not captured within the model because of the limited evidence base; however, its inclusion would further increase the ICER for this age range. *Figure 19* presents the CEAC for this policy.

Figure 19 again highlights the extent of the uncertainties within the model. If society is willing to pay £100,000 per QALY gained there remains an 8% probability that screening alone would remain the more economically attractive option.

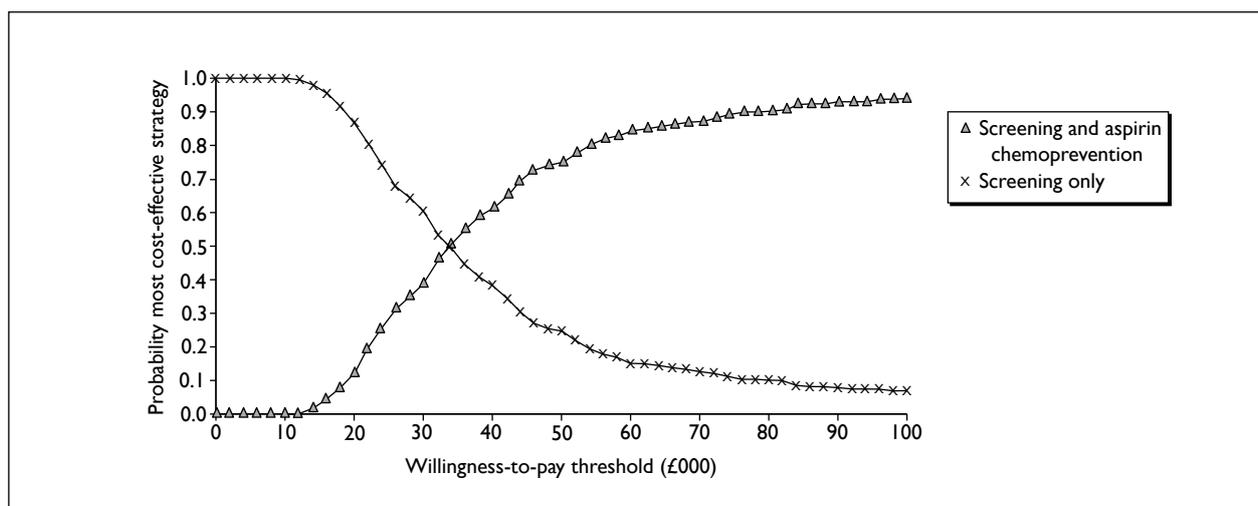


FIGURE 19 CEAC for chemoprevention given to general population age 50–70 years (discounted QALYs).

TABLE 45 Results of chemoprevention given to general population age 40–50 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£715	20.07	16.94	–	–
Screening plus aspirin	£1169	20.10	16.95	£16,986	£123,935
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£1786	35.37	29.10	–	–
Screening plus aspirin	£2241	35.44	29.15	£6006	£9326

Table 45 shows the impact of reducing the age of providing chemoprevention to people within the general population aged 40–50 years.

The incremental cost per QALY gained associated with offering chemoprevention to the general population from age 40 to age 50 in addition to screening is estimated to be around £124,000 compared with screening alone. This ICER is particularly high because of the small expected gains in effectiveness. Again, the cost per LYG appears favourable in comparison to the incremental cost per QALY gained by the exclusion of negative health effects due to harms associated with chemoprevention. It should be noted that both health benefits and costs are small so very small differences in effectiveness have a substantial impact upon the ICER. Within this analysis, discounting has an even greater impact upon the model results because of the cohort being younger

when they begin chemoprevention. Figure 20 shows the CEAC for this policy.

Figure 20 suggests that for willingness-to-pay thresholds below £100,000 per QALY gained, screening alone is expected to produce the greatest level of net benefit.

Table 46 presents the results of an analysis assessing the cost-effectiveness of providing aspirin chemoprevention to the general population from age 40 to 60.

The use of aspirin chemoprevention in addition to screening for individuals aged 40–60 is expected to result in an incremental cost per QALY gained of around £95,000. Figure 21 presents the CEAC for this policy and indicates that for willingness-to-pay thresholds below around £90,000 per QALY gained, screening alone is expected to produce the greatest level of net benefit.

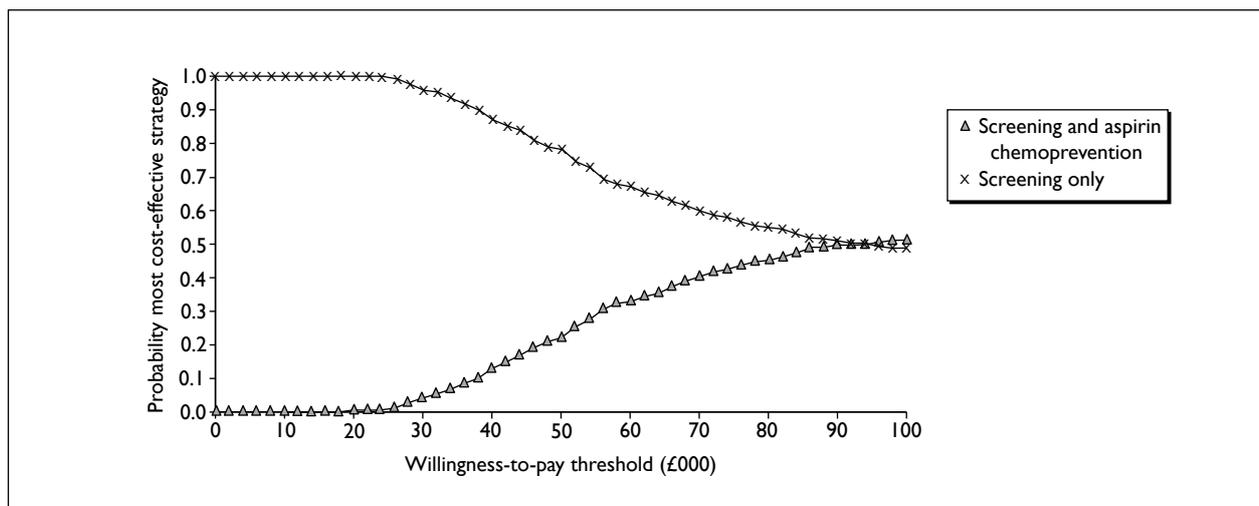


FIGURE 20 CEAC for chemoprevention given to general population age 40–50 years (discounted QALYs).

TABLE 46 Results of chemoprevention given to general population age 40–60 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£715	20.07	16.94	–	–
Screening plus aspirin	£1441	20.12	16.95	£15,423	£95,397
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£1786	35.37	29.10	–	–
Screening plus aspirin	£2590	35.51	29.20	£5552	£8683

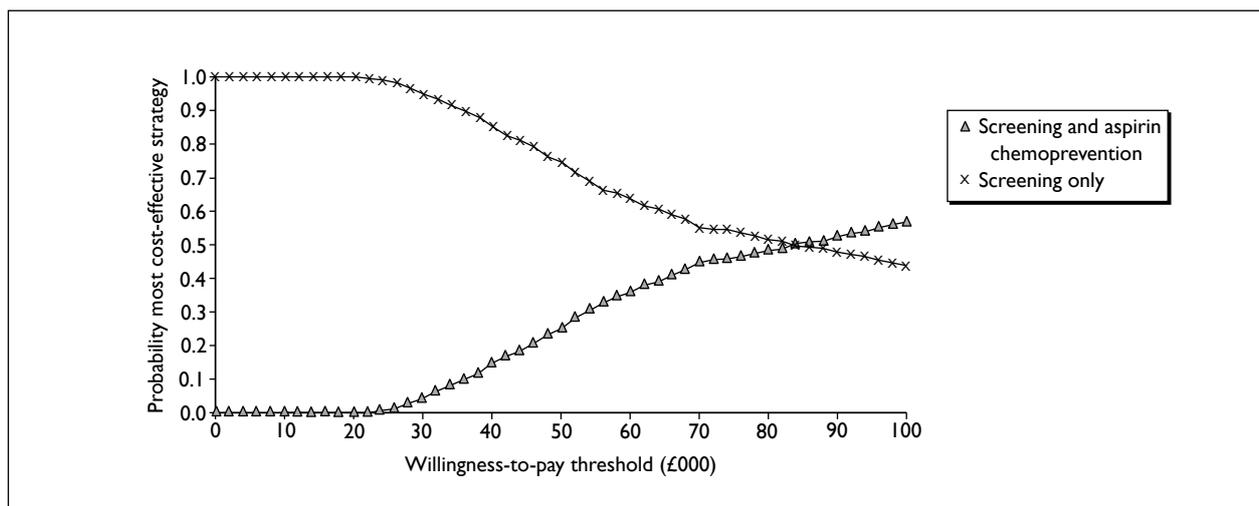


FIGURE 21 CEAC for chemoprevention given to general population age 40–60 years (discounted QALYs).

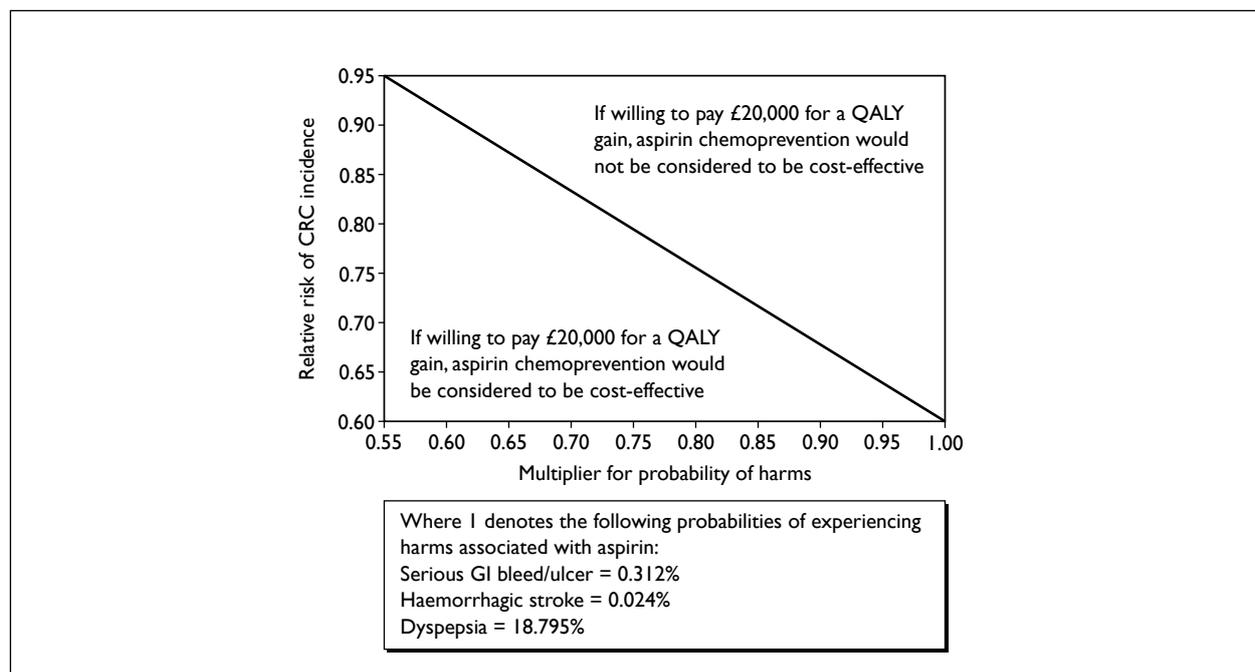


FIGURE 22 Two-way sensitivity analysis of the relative risk of CRC incidence and the probability of harms associated with aspirin chemoprevention compared with screening only.

Two-way sensitivity analysis of benefits to harms

As a result of the uncertainties associated with both benefits and harms of aspirin chemoprevention, two-way sensitivity analysis was undertaken to assess the impact of these model inputs upon cost-effectiveness outcomes within the model for people aged 50–60. These results are presented in *Figure 22*.

Figure 22 indicates that if the relative risk of CRC incidence is greater than 0.6, then aspirin would need to cause fewer harms than currently assumed within the model for aspirin chemoprevention to be considered to be cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained. For example, if the relative risk of cancer incidence is estimated to be 0.85, then the harms associated with aspirin shown at the base of *Figure 22* would need to be approximately one-third of those assumed within the model for aspirin chemoprevention to be considered to be economically attractive at a willingness-to-pay threshold of £20,000 per QALY gained (i.e. excess harms as a result of aspirin would need to be less than 0.104% for serious gastrointestinal bleed/ulcer, 0.008% for haemorrhagic stroke and 6.265% for dyspepsia).

Intermediate-risk model analysis

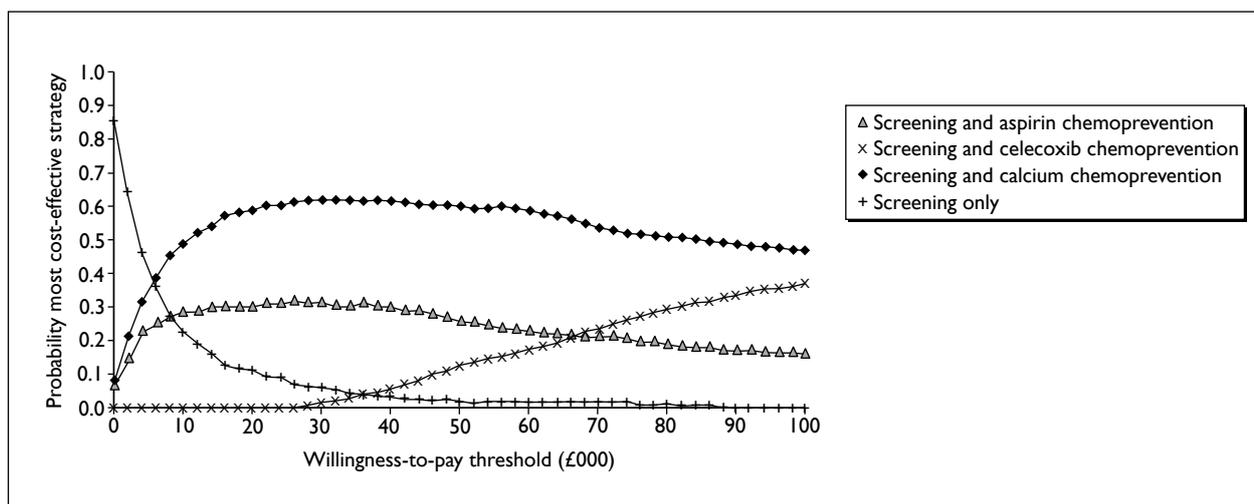
Base-case option

The model analysis suggests that the most economically viable age-range policy would be to provide chemoprevention to individuals following polypectomy aged 61–70 years. Clearly, this finding is dependent upon the age at which a polypectomy is undertaken. Therefore three different starting ages for chemoprevention are assessed. As with the general population analysis, these results are highly dependent upon the assumptions around the disease natural history, particularly with regard to polyp incidence following polypectomy. The results of this policy are shown in *Table 47*.

This model analysis suggests that calcium chemoprevention is expected to have a discounted cost per QALY gained of around £8000 compared with screening only. Although aspirin chemoprevention in addition to screening is expected to be associated with an ICER of £21,185 compared with screening alone (not reported within *Table 47*), under the current assumptions of benefits to harms of aspirin and calcium, aspirin is expected to be extendedly dominated by calcium. In other words, calcium is expected to be more effective and to have a lower ICER than aspirin.

TABLE 47 Results of chemoprevention given to intermediate-risk population age 61–70 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£2865	12.55	9.72	–	–
Screening plus aspirin	£3121	12.57	9.73	Extendedly dominated (by calcium)	
Screening plus calcium	£3159	12.58	9.75	£8046	£8383
Screening plus celecoxib	£5604	12.61	9.77	£60,805	£55,696
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£4146	17.16	13.10	–	–
Screening plus aspirin	£4387	17.20	13.14	Extendedly dominated (by calcium)	
Screening plus calcium	£4418	17.22	13.17	£4121	£4117
Screening plus celecoxib	£7137	17.28	13.22	£37,106	£34,300

**FIGURE 23** CEAC for chemoprevention given age 61–70 years (discounted QALYs).

However, this comparison is subject to considerable uncertainty because of the paucity of evidence around the long-term effectiveness and harms of both aspirin and calcium. This uncertainty is highlighted within the CEAC for this policy (see *Figure 23*). The probabilistic analysis suggests that society would need to be willing to pay around £56,000 per QALY gained for celecoxib chemoprevention to be considered to be cost-effective compared with calcium. *Figure 23* shows the CEAC for this policy.

Figure 23 suggests that for thresholds between £10,000 and £100,000 per QALY gained, the probability that calcium chemoprevention produces the greatest level of net benefit is between 50%

and 60%. Similarly, there is an estimated 20–30% probability that aspirin chemoprevention would be the most economically attractive option over these willingness-to-pay thresholds. The majority of this uncertainty concerns the balance of benefits and harms associated with each of the chemopreventive agents. For thresholds greater than £30,000 per QALY gained, there is an increasing probability that celecoxib chemoprevention produces the greatest amount of net benefit. However, as celecoxib chemoprevention is substantially more expensive than aspirin and calcium chemoprevention, the probability that it would be considered to be the most cost-effective option at a willingness-to-pay threshold below £30,000 is zero.

TABLE 48 Results of chemoprevention given to intermediate-risk population age 61–80 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£2865	12.55	9.72	–	–
Screening plus aspirin	£3251	12.58	9.73	Extendedly dominated (by calcium)	
Screening plus calcium	£3332	12.59	9.76	£9845	£10,870
Screening plus celecoxib	£7087	12.64	9.79	£69,002	£64,456
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£4146	17.16	13.10		
Screening plus aspirin	£4547	17.23	13.14	Extendedly dominated (by calcium)	
Screening plus calcium	£4638	17.25	13.19	£5397	£5636
Screening plus celecoxib	£9333	17.33	13.26	£44,124	£41,416

Other age-related policies

Results are presented for a policy of giving chemoprevention from age 61 to 80 years in *Table 48*.

Table 48 suggests that extending the use of chemoprevention to age 80 leads to similar results to those of the base-case policy, but with slightly higher expected ICERs. Again, aspirin chemoprevention is expected to be extendedly dominated by calcium chemoprevention under the current assumptions of the ratio of benefits to harms; however, it should be noted that because of the uncertainties around both long-term effectiveness and long-term harms associated with both aspirin and calcium chemoprevention, the results of this comparison should be treated with caution. As shown by the CEAC in *Figure 24* it is

possible that aspirin would result in the highest net benefit rather than calcium at willingness-to-pay thresholds above around £10,000. The incremental cost per QALY gained associated with calcium chemoprevention compared with screening alone is estimated to be around £11,000, whereas the estimated incremental cost per QALY gained associated with celecoxib chemoprevention versus calcium is around £64,000. *Figure 24* shows the CEAC associated with this policy.

Figure 24 provides similar estimates of uncertainty around each of the chemopreventive agents as for the previous analysis. Again, there is an estimated 50–60% probability that above a willingness-to-pay threshold of around £10,000, calcium chemoprevention is expected to produce the greatest level of net benefit. However, there is

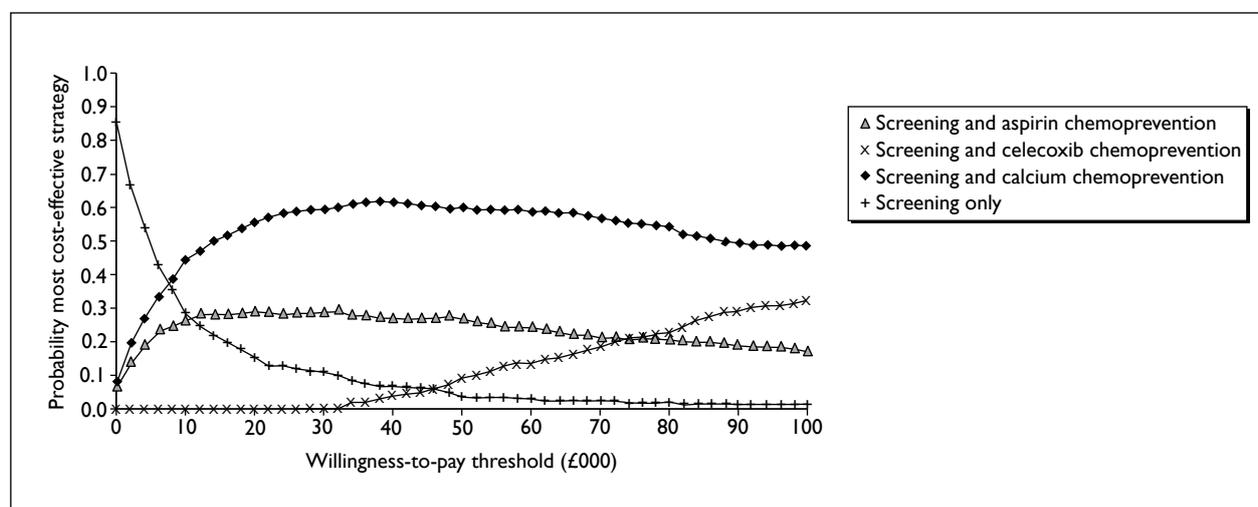


FIGURE 24 CEAC for chemoprevention given to intermediate-risk population age 61–80 (discounted QALYs).

TABLE 49 Results of chemoprevention given to intermediate risk population age 65–80 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£2340	10.98	8.37	–	–
Screening plus aspirin	£2689	11.01	8.37	Extendedly dominated (by calcium)	
Screening plus calcium	£2750	11.02	8.39	£13,262	£15,657
Screening plus celecoxib	£5938	11.04	8.41	£92,103	£87,298
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£3226	14.38	10.83		
Screening plus aspirin	£3582	14.43	10.85	Extendedly dominated (by calcium)	
Screening plus calcium	£3641	14.44	10.89	£7414	£8042
Screening plus celecoxib	£7444	14.49	10.92	£59,826	£56,456

also an estimated 20–30% probability that aspirin chemoprevention would have the highest net benefit.

Results are presented for a policy of giving chemoprevention from age 65 to 80 in *Table 49* because people may undergo polypectomy at a later age.

Providing chemoprevention to individuals following polypectomy from age 65 to age 80 leads to similar results as the previous analyses, again with slightly higher ICERs. The incremental cost per QALY gained associated with calcium chemoprevention in addition to screening compared with screening only is estimated to be around £8000, whereas the incremental cost per QALY gained associated

with celecoxib chemoprevention compared with calcium chemoprevention is estimated to be around £56,000. Aspirin is again extendedly dominated by calcium, although again this result should be treated with caution because of the uncertainties around the long-term effectiveness and harms associated with aspirin and calcium. These results suggest that the cost-effectiveness of chemoprevention is driven by the age at which chemoprevention begins. Therefore, the age at which polypectomy is undertaken affects the cost-effectiveness of subsequent chemoprevention. *Figure 25* shows the CEAC for this policy.

Figure 25 suggests that as the starting age for chemoprevention increases following a polypectomy, the probability that calcium chemoprevention results in a higher net

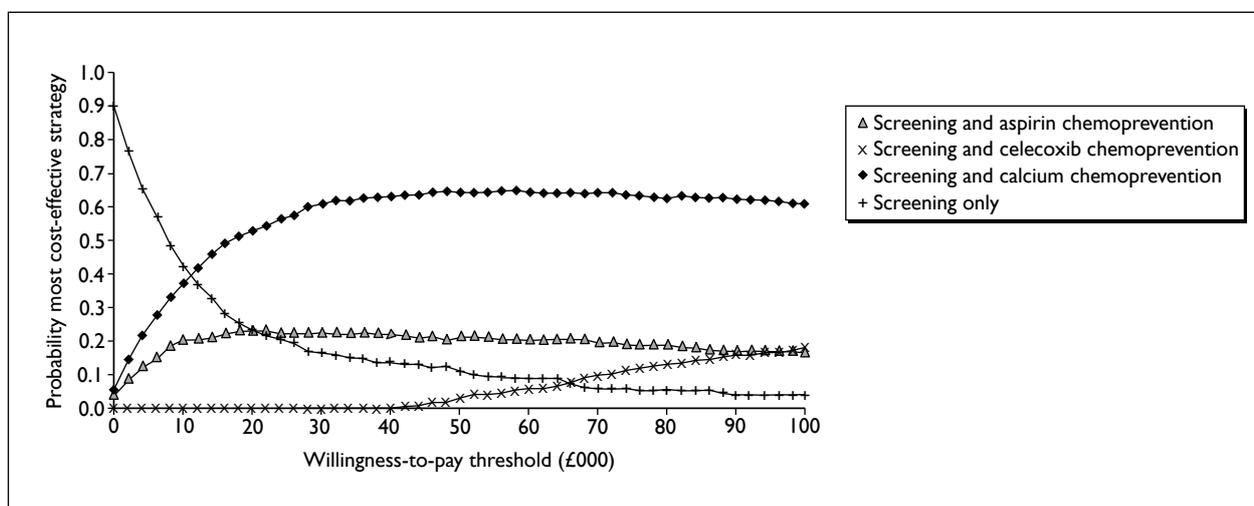
**FIGURE 25** CEAC for chemoprevention given to intermediate-risk population age 65–80 years (discounted QALYs).

TABLE 50 Results of chemoprevention given to intermediate-risk population age 71–80 years

	Total costs	Total LYGs	Total QALYs	Cost per LYG	Cost per QALY gained
Incremental cost-effectiveness estimates (discounted)					
Screening only	£1548	8.61	6.38	–	–
Screening plus aspirin	£1814	8.62	6.37	Dominated (by screening only)	
Screening plus calcium	£1851	8.62	6.39	£21,829	£30,201
Screening plus celecoxib	£4056	8.64	6.39	£147,357	£144,778
Incremental cost-effectiveness estimates (undiscounted)					
Screening only	£1996	10.60	7.79	–	–
Screening plus aspirin	£2261	10.62	7.80	Extendedly dominated (by calcium)	
Screening plus calcium	£2289	10.63	7.81	£12,681	£15,002
Screening plus celecoxib	£4731	10.65	7.82	£97,543	£93,540

benefit compared with aspirin or celecoxib chemoprevention increases.

The cost-effectiveness results for intermediate-risk individuals who begin taking chemoprevention from age 71 to age 80 are presented within *Table 50*.

The results presented in *Table 50* suggest that increasing the starting age for chemoprevention to 71 increases the ICERs further compared with a starting age of 65. For this age group, aspirin chemoprevention in addition to screening is estimated to result in lower QALYs and greater costs than screening alone. This is because the estimated harms outweigh the estimated reduction in CRC incidence. The incremental cost per QALY gained associated with calcium chemoprevention

in addition to screening is estimated to be around £30,000 compared with screening only, whereas the incremental cost per QALY gained associated with celecoxib chemoprevention is estimated to increase to around £145,000 compared with calcium chemoprevention. *Figure 26* shows the CEAC associated with this policy.

Figure 26 suggests that increasing the starting age for chemoprevention to 71 years results in a lower probability that either aspirin or celecoxib will have a higher net benefit than calcium chemoprevention or screening only. The model suggests that for people receiving chemoprevention over the age of 70, the option to provide no chemoprevention is more likely to be considered to be economically attractive compared with aspirin chemoprevention or celecoxib chemoprevention at willingness-to-

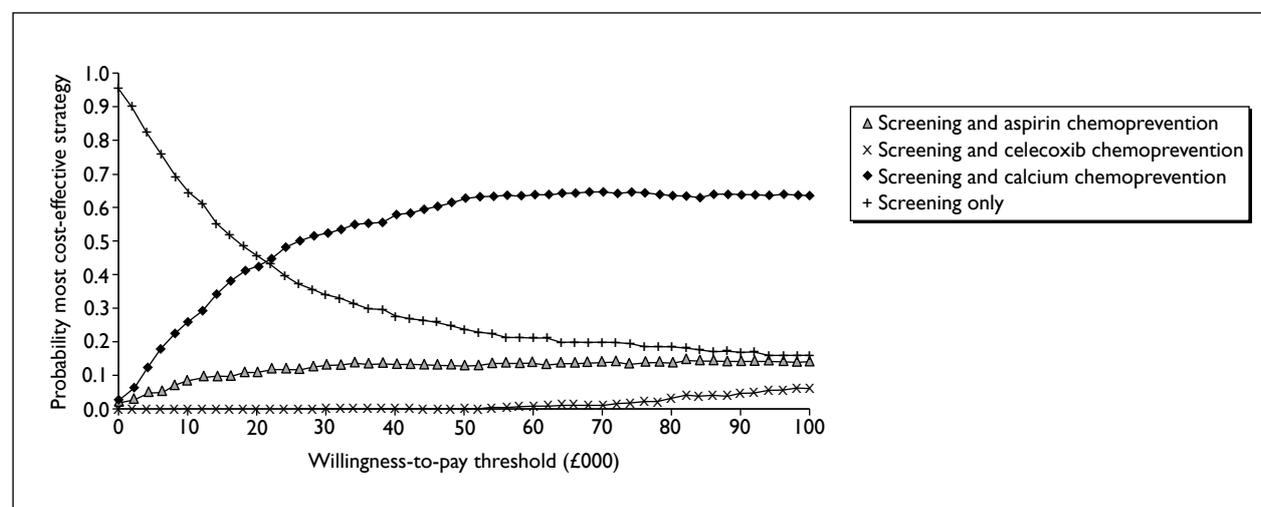


FIGURE 26 CEAC for chemoprevention given to intermediate-risk population age 71–80 years (discounted QALYs).

pay thresholds below £100,000 per QALY gained. For a threshold of £30,000 per QALY gained, the model suggests that the probability that calcium chemoprevention produces the greatest level of net benefit is around 60%.

Two-way sensitivity analysis of benefits to harms

Owing to the uncertainties associated with both benefits and harms of the chemopreventive agents, two-way sensitivity analyses were undertaken to assess the impact of these model inputs upon cost-effectiveness. This analysis provides only an indication as to the potential impact of increases or decreases in harms or benefits because a number of simplifying assumptions have been required; (1) that the ratio between the relative risk of high-risk polyps and low-risk polyps remains the same as in the base-case analysis; (2) that all probabilities of experiencing harms are increased or decreased by the same proportion; (3) that the harms continue to remain constant over time; and (4) that there are no other harms or benefits associated with the chemopreventive agents. Celecoxib chemoprevention is not included within this analysis because of the high cost-effectiveness ratio associated with the chemopreventive agent. Calcium and aspirin chemoprevention in addition to screening are both assessed compared with screening only. Although aspirin was extendedly

dominated by calcium chemoprevention within the base-case analysis, it is important to assess aspirin within this two-way sensitivity analysis because of the uncertainties associated with both the long-term benefits and harms of aspirin and calcium, as shown by the CEACs within the above analyses. Results for the two-way sensitivity analysis of aspirin are presented in *Figure 27*.

This analysis suggests that compared with screening alone (not considering calcium chemoprevention), aspirin would be considered to be cost-effective at a willingness-to-pay threshold of £20,000 if it is associated with a relative risk of low-risk polyp incidence of 0.9 and a relative risk of high-risk polyp incidence of 0.73 with the current model estimates of harms. If the effectiveness of aspirin improves compared with those estimated within the trials such that it is associated with a relative risk of low-risk polyp incidence of 0.7 and a relative risk of high-risk polyp incidence of 0.56, then aspirin chemoprevention is predicted to remain cost-effective compared with screening only using a willingness-to-pay threshold of £20,000 per QALY gained if the probability of excess harms associated with aspirin more than trebles.

The results of the two-way sensitivity analysis for calcium chemoprevention compared with screening only are presented in *Figure 28*.

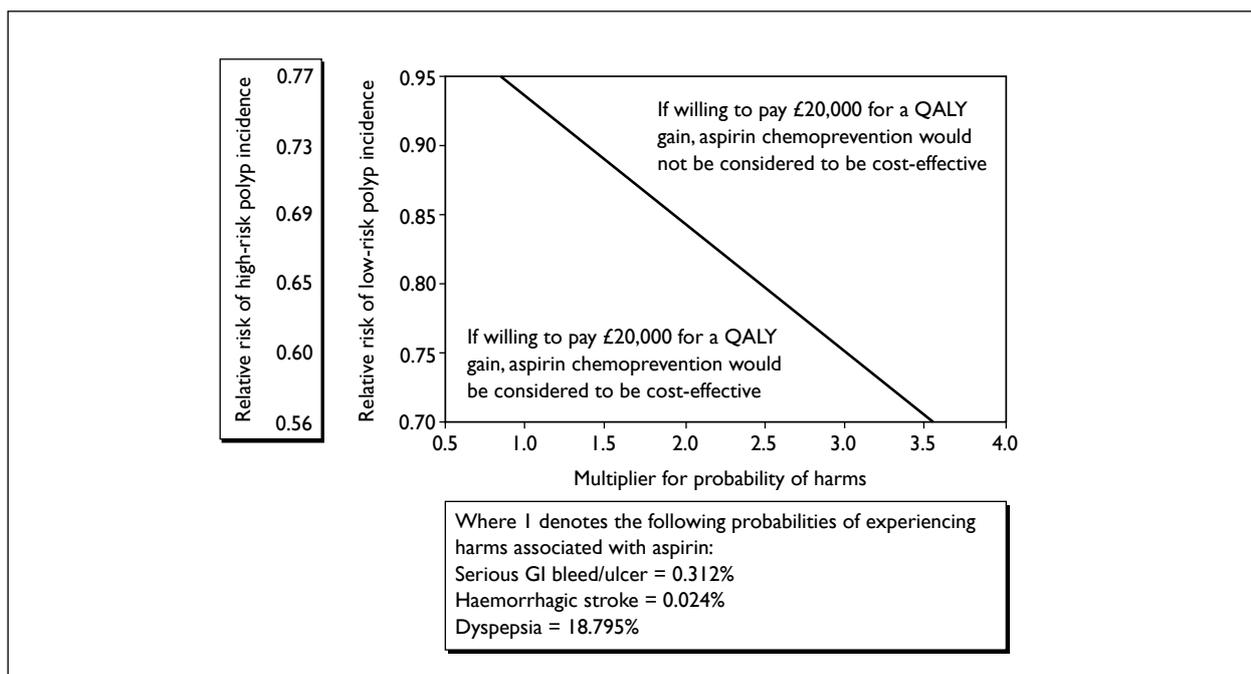


FIGURE 27 Two-way sensitivity analysis of the relative risk of polyp incidence and the probability of harms associated with aspirin chemoprevention compared with screening only within the intermediate-risk population.

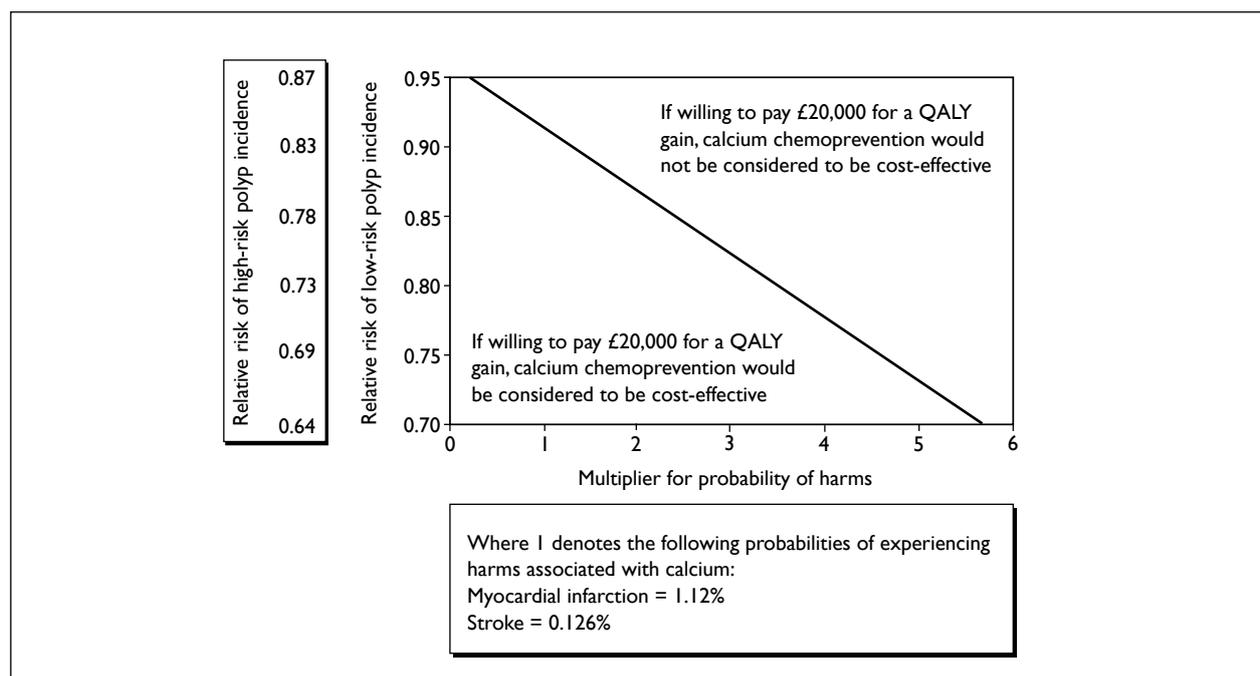


FIGURE 28 Two-way sensitivity analysis of the relative risk of polyp incidence and the probability of harms associated with calcium chemoprevention compared with screening only within the intermediate-risk population.

Figure 28 suggests that if the relative risk of polyp incidence is as predicted by the clinical trials, calcium chemoprevention is likely to be considered to be cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained if the harms were up to around 2.5 times those estimated within the base-case analysis. If calcium chemoprevention were less effective than predicted by the trials, with a relative risk of 0.92 or greater, then the harms would need to be less than or equal to those assumed within the model for calcium chemoprevention to produce an incremental cost per QALY gained below £20,000.

The one-way sensitivity analysis assessing the impact of assuming that celecoxib is associated with no harms suggests that the discounted cost per QALY gained associated with celecoxib chemoprevention compared with calcium chemoprevention decreases from £55,696 in the base case to £51,586 based upon this assumption. This indicates that the cost-effectiveness of celecoxib is driven by its comparatively high acquisition cost rather than its associated harms.

Value-of-information analysis

A global value-of-information analysis was undertaken to assess the value of eliminating current uncertainties through the collection of further information. This represents a maximum ceiling on future investment in research. The

results of this analysis suggest that, for the general population model, the per-patient expected value of perfect information (EVPI) is around £293. Assuming a population of 688,000 patients aged 50 years and a decision lifetime of 10 years, the global population-level EVPI is estimated to be in excess of £2 billion. This finding is perhaps unsurprising given the potential size of the beneficiary population. For the intermediate-risk groups, the patient-level EVPI is estimated to be £37. Assuming a constant population of 5582 patients a year (based on intermediate model outputs), and a decision lifetime of 10 years, the global population-level EVPI is estimated to be around £206,500.

Ideally, one would examine the contribution of uncertainty in individual or groups of model parameters towards the overall EVPI using partial EVPI analysis. However, in this instance partial value-of-information analysis has not been undertaken. This is justified on two grounds. First, the comparison of the mean ICER with the intersection of the CEACs (the median ICER) suggests some degree of non-linearity which indicates that the simpler one-level EVPI algorithm is inappropriate. However, the model itself is computationally expensive such that the use of the correct two-level EVPI algorithm²⁶⁸ would be prohibitive. Second, and perhaps more importantly, value-of-information analysis is a

means of examining the importance of current uncertainties in model parameters; it cannot deal with issues surrounding structural uncertainties that cannot be easily (or usefully) parameterised within the model. In particular, the true value of further information should encapsulate all feasible policy options concerning when chemoprevention should begin and end, structural assumptions surrounding the disease natural history, the interpretation of the effectiveness evidence (i.e. the mechanism of action), the external validity of the clinical evidence base, and the potential impacts of wider chemoprevention harms and benefits across other disease areas that are not captured within the model because of limitations in the evidence. Consequently, without the prior resolution of some of these issues, it is unlikely that a comprehensive value-of-information analysis would produce meaningful results.

Discussion

Summary of key results

The use of aspirin chemoprevention plus screening within the general population aged 50–60 years is expected to result in an incremental cost per QALY gained of around £23,000 compared with screening alone. All other age policies assessed for the general population resulted in an ICER that was greater than £30,000 per QALY gained. Currently, the relative risk associated with CRC incidence estimated by the clinical trials appears to be high in comparison to the estimated impact of aspirin within the intermediate-risk population. If the relative risk of CRC incidence decreased, the harms associated with aspirin chemoprevention would also need to be lower than those estimated within the model for aspirin chemoprevention to be considered to be economically attractive within the general population.

Within the intermediate-risk population, the use of chemoprevention is more likely to have a cost-effectiveness profile that is acceptable to NHS policy-makers. Based upon current evidence, calcium chemoprevention within this population is expected to have an incremental cost per QALY gained of between £8000 and £30,000 depending upon the starting and stopping age of chemoprevention. As the starting age for chemoprevention following polypectomy is increased, so too is its ICER. If an individual undergoes polypectomy at age 60, the model suggests that it is more cost-effective to provide chemoprevention until age 70 rather than until age 80.

Under current assumptions around the benefits and harms of aspirin and calcium, aspirin chemoprevention is extendedly dominated. However, this analysis is highly uncertain. The model predicts that there is a 20–30% probability that aspirin (rather than calcium) will result in the highest net benefit. Therefore, if the benefits of aspirin are expected to be greater than those estimated within the trials (or if the benefits of calcium are expected to be lower than those estimated within the trials), or if the harms associated with aspirin are overestimated within the model (or the harms associated with calcium are underestimated), then aspirin chemoprevention may be more cost-effective than calcium chemoprevention. Celecoxib chemoprevention within the intermediate-risk population is unlikely to be considered to be economically attractive.

Generalisability of results

The effectiveness evidence used to inform model parameters has been drawn from studies undertaken in different countries; only two of which are UK-based. There may be some dietary differences between countries that would influence disease incidence. Chemoprevention compliance may also vary between countries, and between trial and non-trial populations. It was not possible to capture the behavioural aspects of chemopreventive use identified within the qualitative review within the health economic model, and no data were identified that allowed a quantification of the relationship between compliance and outcome. It may be that within the general population people would self-select so that those who are likely to benefit more from chemoprevention are more likely to take chemoprevention. If this were the case, chemoprevention may be more effective than predicted within the studies.

Strengths and limitations of analysis

The clinical trials identified by the effectiveness review are heterogeneous, particularly in terms of dosage, treatment duration, follow-up duration, baseline characteristics of individuals and geographical location. These differences undoubtedly increase the uncertainty in the model results.

There is a marked disparity between the available evidence from clinical trials and the data requirements for the health economic model. Clinical trials provide either the relative risk of the incidence of adenomas (within the intermediate-risk population) or the relative

risk of the incidence of CRC (within the general population). However, the clinical trials do not provide evidence concerning the point at which chemoprevention begins to take effect relative to the start of treatment, the nature of this effect (whether this is gradual or constant), or if and when chemoprevention will stop being effective. Instead, the available trial evidence data provide only a single observation that, to assess the implications of chemoprevention over time, requires considerable extrapolation assumptions. Considering the effectiveness of chemoprevention as a mathematical function, there is very limited evidence to suggest where the line starts, where it stops or the shape it should take. The paper by Flossmann and Rothwell²¹ implicitly suggests that chemoprevention is effective for the duration that it is being taken; hence this has been assumed within the health economic model. The relative risk associated with the incidence of polyps/cancers predicted by the clinical trials is assumed to be constant because of the lack of data to the contrary. This implies that chemoprevention offers no cumulative protection. These assumptions are likely to have an important impact upon the cost-effectiveness results, particularly around the age at which to start and stop taking chemoprevention. Future clinical trials should focus on addressing questions concerning the optimal treatment duration, frequency, start age, end age and dose of chemoprevention.

Of further note is the limited evidence concerning whether chemoprevention has a direct impact upon CRC. The model assumes that if individuals develop CRC, they will discontinue chemoprevention, because the results would be biased if no impact upon CRC was assumed but costs continued to be incurred. Therefore, if chemoprevention also had a direct impact upon CRC, estimates of both effectiveness and costs would increase, meaning that this assumption is unlikely to have a substantial impact upon the model results.

The analysis of the harms associated with chemoprevention is limited. The model assumes that the excess harms associated with chemoprevention would be constant over time and by age. There is evidence to suggest that harms associated with chemoprevention may increase with age; however, this effect was not incorporated into the model because of data limitations. Second, minor adverse events such as diarrhoea were not included in the analysis because they were assumed

to have a minimal impact on both costs and health outcomes. Third, the analysis assesses the impact of chemoprevention upon CRC only; however, chemoprevention may also impact on the incidence of other cancers such as prostate or stomach cancers. Some studies suggest a positive impact of chemoprevention on other cancers whereas others suggest a negative impact. The impact of chemoprevention on the incidence of other cancers was outside the specified model boundary; the implicit assumption is that chemoprevention has no effect on other cancers.

The analysis of benefits to harms provides a comparison of aspirin and calcium against no chemoprevention, allowing for the fact that the base-case estimates of benefits and harms within the model are highly uncertain. As this is a threshold analysis, whereby one of the parameters assessed relates to a set of parameters around harms, the relationship between the harms has to remain constant (i.e. it is not feasible to make different assumptions around the relationship between those harms). Therefore this sensitivity analysis provides an indication of the relationship between benefits and harms, but it is unable to provide the results of all possible permutations of harms and benefits associated with the chemopreventive agents.

The evidence around the effectiveness of antioxidants is limited, for this reason we envisaged undertaking a threshold analysis to assess the necessary effectiveness of antioxidants to be considered cost-effective over various particular willingness-to-pay thresholds. However, as the long-term harms associated with antioxidants are also unclear, this did not prove feasible. The two-way analysis of calcium and aspirin may be used as an indicator of cost-effectiveness, although clearly the cost of antioxidants will vary alongside the harms associated with each of the agents. Further research is therefore indicated to assess both the long-term benefits and harms of antioxidants for chemoprevention.

Within England and Wales, NICE recommends that aspirin is taken for the prevention of occlusive vascular events in people who have had an ischaemic stroke or a transient ischaemic attack, for the prevention of cerebral embolic stroke, for people with unstable angina or who have had a mild heart attack and for people with non-ST-segment-elevation acute coronary syndrome who have a moderate-to-high risk of a major heart

attack or death. In people with type 2 diabetes, aspirin is recommended for people who have obvious signs of or a history of cardiovascular disease and for people with a more than 15% risk of heart problems in the next 10 years. There is a small probability of people experiencing heart attacks and strokes before age 30; hence they are likely to already receive aspirin. There are also people within the general population who regularly take calcium tablets for other conditions. This analysis excludes those people already taking chemopreventive agents.

Finally, an analysis considering the results of the model if the individual pays for chemoprevention was considered. However, the model analysis suggests that the cost savings associated with cancers avoided were always greater than the costs associated with treating harms. Therefore, from an NHS perspective where the individual pays, if chemoprevention is effective at preventing the incidence of polyps, then it will result in net cost savings. Hence, if the individual were to pay for chemoprevention, the question would no longer be whether it is cost-effective, but whether the benefits of chemoprevention outweigh the harms.

Chapter 6

Assessment of factors relevant to the NHS and other parties

Balance of benefits and harms for chemoprevention

It is important to consider the balance between benefits and harms of the various interventions in the different population subgroups. This balance may also differ according to the individual because of factors such as age and other comorbidities. Information on potential harms associated with aspirin, NSAIDs and other agents has been incorporated into the review and economic model as far as possible, but this information is limited and is subject to ongoing research. Changes in the estimates of effectiveness and harms for an intervention may substantially affect estimates of its cost-effectiveness.

In addition to potential harms, chemoprevention may also have positive effects on other conditions, including other cancers and cardiovascular disease. The effects of chemoprevention are not limited to a single condition so it may be relevant to consider current recommendations regarding chemoprevention for other conditions in addition to CRC. It may also be relevant to consider the balance between recommendations for specific supplements and more general healthy-eating campaigns. It is also important to consider the potential effect of the different chemopreventive agents when administered in combination. Ongoing studies are assessing combinations of interventions.

Compliance

Compliance is an important consideration when considering interventions used in a preventive setting. Approximately 60–100% of patients were compliant with the majority of medications in the studies included in this review, although some studies selected the most compliant participants during a run-in phase that may have increased estimates of compliance relative to the general

population. Analysis of qualitative data suggests that compliance may be improved if health professionals explain fully and clearly to patients the risks and benefits associated with the relevant agent.

Implementation of chemoprevention policy

When interpreting the cost-effectiveness results, it is important to take into account the way in which chemoprevention may be implemented in the UK. The economic assessment necessarily makes a range of assumptions about how chemoprevention might be used within the NHS, relating to which individuals are likely to take a chemopreventive agent, when they might be recommended to start and stop taking the agent, and how it will be paid for (which is a consideration because aspirin and many vitamin and mineral supplements can be purchased over the counter). These assumptions may have a substantial resource impact for any interventions recommended for use at a general population level.

If chemoprevention was recommended within the NHS and the NHS paid for the agents, because of their low costs, they would have to be provided in the same way as contraceptives are currently provided within the UK, where no prescription cost is required. The exception to this may be celecoxib. Although the cost of chemoprevention per person is low, if it was provided by the NHS, the budget impact to the NHS would be substantial because of the number of people requiring chemoprevention (particularly in the general population, but also in the intermediate-risk population) and because of the number of years over which it is required. Moreover, the cost savings associated with CRC treatment would not be observed for a number of years (which is expected to be greater than 10 years) after the substantial costs associated with the provision of chemoprevention had been incurred.

Chapter 7

Discussion

Statement of principal findings

Assessment of clinical effectiveness

Aspirin (81–325 mg/day) and celecoxib (400 mg/day) have been shown to reduce the recurrence of adenomas and incidence of advanced adenomas in individuals with an increased risk of CRC because of a history of adenomas. COX-2 inhibitors may decrease polyp number in patients with FAP. Preliminary results of a single study of aspirin in FAP patients did not demonstrate a significant benefit but preliminary results of a study of aspirin in HNPCC patients suggested a possible effect. There is some evidence for aspirin reducing the incidence of CRC in the general population, although this effect was only observed in studies of at least 300 mg/day aspirin with a follow-up duration greater than 10 years.²¹ There is an absence of long-term follow-up data for lower doses of aspirin or for other NSAIDs. Aspirin is associated with adverse effects including nausea and dyspepsia, peptic ulcers, gastrointestinal bleeding, and a possible increased risk of haemorrhagic stroke, but may reduce the risk of myocardial infarction and ischaemic stroke. COX-2 inhibitors are associated with increased risk of serious cardiovascular events as well as hypertension and renal toxicity. Two studies of calcium (1200–2000 mg/day) demonstrated reduction in risk of adenoma recurrence in individuals with a history of adenomas, while studies of calcium and vitamin D in the general population did not demonstrate a significant effect on CRC, although follow-up durations were relatively short (4–7 years). Folic acid was not shown to reduce adenoma recurrence in individuals with a history of adenomas; nor was it shown to reduce CRC in the general population, although the duration of follow-up was 5–7 years only. Antioxidants (vitamins A, C, E, beta-carotene and selenium) were not shown to reduce adenoma recurrence in individuals with a history of adenomas. In the general population, antioxidants were not shown to reduce the incidence of adenomas or CRC in studies with follow-up between 5 and 12 years. One study showed an

increase in adenoma incidence with vitamin E or vitamin E plus beta-carotene; however, this finding should be interpreted with caution because of the number of analyses undertaken.

It has been reported that the development of an adenoma into CRC may have a natural history of 10–15 years.¹⁵⁸ Therefore, it is unclear how long the treatment and follow-up durations must be to detect any effect on CRC incidence. For example, studies of aspirin only showed a significant effect on CRC after more than 10 years of follow-up (although this analysis was partly confounded by differing doses and durations of treatment). Regarding the included trials of calcium, folic acid and arguably antioxidants, it was not clear whether the lack of reported effect on CRC incidence may be related to the lack of long-term follow-up. Therefore, effects on adenoma incidence were potentially more robust than effects on CRC incidence.

There are a number of ongoing studies addressing chemoprevention of CRC. An ongoing multicentre study is assessing aspirin, calcium and vitamin D (as a combination treatment) versus placebo for prevention of adenomas in participants with a history of adenomas, and aims to enrol 1000 participants, with a treatment duration of 3 years and follow-up at 3 and 5 years. The dose of aspirin is lower than that in many chemoprevention studies, at 75 mg/day (www.clinicaltrials.gov, NCT00486512). An ongoing phase 3 RCT is assessing celecoxib versus placebo for prevention of adenoma recurrence in participants with a history of resected stage 1 colon cancer, and aims to enrol 1200 participants, with a treatment duration of 3 years; follow-up duration not specified (NCT00087256). A further ongoing study aims to enrol 1000 participants with a history of adenomas and is assessing folic acid for prevention of adenomas, with a follow-up duration of 4 years (NCT00512850). Another small study (80 participants planned) aims to assess the effect of high-dose folic acid (dose not specified) for prevention of adenomas in participants with a history of adenomas, with treatment and follow-up durations of 1 year

(NCT00002650). An ongoing phase 3 RCT is assessing selenium versus placebo for prevention of adenoma recurrence in participants with a history of colorectal adenomatous polyps, and is aiming to enrol 2050 participants, with treatment and follow-up durations of 5 years, or up to 7.5 years in some participants (www.cancer.gov/clinicaltrials/UARIZ-00-0430-01). These studies would add to the volume of data on individual agents, as well as assessing combination therapy in the study of aspirin, calcium and vitamin D. Study durations and sample sizes are likely to be sufficient to assess the short-term effects on adenoma recurrence, but not to assess effects on CRC incidence. All ongoing studies identified were in patients with a history of adenomas (or CRC), and none were in the general population.

Economic analysis

The economic analysis assessed the cost-effectiveness of chemoprevention for two populations with different levels of risk of developing CRC:

- the general population
- men and women at an intermediate risk of CRC due to previous polyps.

General population results

The model analysis suggests that the most cost-effective age-range policy would be to provide chemoprevention to all individuals within the general population from age 50 to age 60 years. This analysis suggests that the use of aspirin chemoprevention in addition to screening within the general population is likely to result in a discounted cost per LYG of around £10,000 and a discounted cost per QALY gained of around £23,000 compared with screening alone. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that screening plus aspirin chemoprevention results in more net benefit than screening alone is expected to be around 0.8. All other age policies assessed for the general population resulted in an ICER that was greater than £30,000 per QALY gained. This analysis is, however, subject to considerable uncertainty because of the paucity of evidence, particularly around the long-term effectiveness and long-term adverse events associated with aspirin chemoprevention. Although there was no evidence of other chemopreventive agents being effective, and hence potentially cost-effective within the general population, this may be because of the relatively short-term follow-up of the trials.

Intermediate-risk group results

The model analysis suggests that the most economically viable age-range policy would be to provide chemoprevention to individuals following polypectomy aged 61–70 years. This model analysis suggests that calcium chemoprevention is expected to have a discounted cost per QALY gained of around £8000 compared with screening only. Although aspirin chemoprevention in addition to screening is expected to be more effective and less costly than screening alone, under the current assumptions of benefits to harms of aspirin and calcium, aspirin is expected to be extendedly dominated by calcium. Between thresholds of £10,000 and £100,000 per QALY gained, the probability that calcium chemoprevention produces the greatest level of net benefit is between 50 and 60%. Similarly, there is an estimated 20–30% probability that aspirin chemoprevention would be the most economically attractive option over these willingness-to-pay thresholds. There are no trials directly comparing aspirin and calcium, and because the quality of the trials of each agent are variable, the trial populations vary and the follow-up is relatively short, it is not possible to ascertain which of aspirin or calcium would be either more effective or cost-effective within this intermediate-risk population. The model also suggests that the incremental cost-effectiveness of chemoprevention following polypectomy increases (becomes less favourable) as the chemoprevention start age increases. The results should be interpreted with caution because of uncertainty in the parameters.

Attitudes to chemoprevention agents

Twenty studies were identified reporting on individuals' views, attitudes and experiences relating to taking the various agents that may be used for chemoprevention. Both personal and external factors affect people's decisions to use NSAIDs or supplements such as antioxidants, vitamins or minerals. People are more likely to use NSAIDs if there is a strong perceived need, principally determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also influence the process of decision-making and use: there are greater perceived risks or side effects associated with NSAIDs than dietary supplements, and individuals who are required to take NSAIDs tend to weigh up the balance of benefits against risks, and to modify their use of the agent accordingly. People have fewer concerns about using antioxidants or other supplements,

but their perception of the benefits of these agents is less well defined. They would like more information and advice from health professionals, but their use of these supplements tends to be governed more by input from family, friends, alternative therapists and the media.

Strengths and limitations of the assessment

Included trials were generally of reasonable quality. Some studies excluded a number of participants from the analysis; the number of excluded individuals was higher in studies of adenoma recurrence because this outcome could only be assessed in participants who underwent a follow-up colonoscopy. We did not undertake separate analyses according to study quality because of the wide scope of this review, and also because antioxidants were not shown overall to have a significant benefit, and the other interventions included here were assessed in too few trials for an analysis based on study quality to be feasible. However, Bjelakovic *et al.* undertook two reviews of antioxidants, first of trials assessing adenoma incidence and second of trials assessing gastrointestinal cancer incidence,^{51,114} and both reviews showed that studies with a high risk of bias demonstrated a statistically significant benefit of antioxidants, whereas studies with a low risk of bias showed a non-statistically significant effect which actually favoured control. The average age in all studies was between 49 and 69 years. Since screening for CRC has been introduced for individuals aged 60–69 years and is currently being extended to those aged up to 74 years, the age of included patients appears generalisable to people who may potentially use chemoprevention. Some studies in populations at no increased risk for CRC recruited participants from specific risk groups for other conditions. Compliance with study medications was reported as approximately 60–100% of patients across the different studies; however, some studies preselected for the most compliant and tolerant patients; therefore, compliance with these interventions may be lower in a real-world context. It was not possible to capture the behavioural aspects of chemopreventive use identified within the qualitative review within the health economic model, and no data were identified that allowed a quantification of the relationship between compliance and outcome. It may be that within the general population people would self-select so that those who are likely to benefit more from chemoprevention are more likely

to take chemoprevention. For many of the included interventions, trials assessing CRC incidence had limited follow-up duration, which may not have allowed detection of an effect on cancer incidence because it has been estimated that the development of an adenoma into CRC may have a natural history of 10–15 years.¹⁵⁸

This review aimed to provide a consistent overview of the effects of different interventions on the prevention of adenomas and CRC. Results are presented separately for populations at low, intermediate or high risk of CRC, believing this to be most clinically meaningful. It also aimed to take into account factors such as duration of treatment and follow-up. The authors were also careful to disaggregate interventions and comparators as far as possible. The authors chose to exclude observational data from this analysis because of the potential biases arising from lack of randomisation and blinding. Relevant observational studies of aspirin and NSAIDs are summarised in other reviews.^{76,88}

There are two key limitations associated with the evidence base that impinge on the credibility of the model results. There is a marked disparity between the available evidence from clinical trials and the data requirements for the health economic model. Clinical trials provide either the relative risk of the incidence of adenomas (within the intermediate-risk population) or the relative risk of the incidence of CRC (within the general population). However, the clinical trials do not provide evidence concerning the point at which chemoprevention begins to take effect relative to the start of treatment, the nature of this effect (whether this is gradual or constant), or if and when chemoprevention will stop being effective. Instead, the available trial evidence data provide only a single observation that to assess the implications of chemoprevention over time requires considerable extrapolation assumptions. Considering the effectiveness of chemoprevention as a mathematical function, there is very limited evidence to suggest where the line starts, where it stops or the shape it should take. The relative risk associated with the incidence of polyps/cancers predicted by the clinical trials is assumed to be constant because of a lack of data to the contrary. This implies that chemoprevention offers no cumulative protection. These assumptions are likely to have an important impact upon the cost-effectiveness results, particularly around the age at which to start and stop taking chemoprevention. Future clinical trials should focus on addressing

questions concerning the optimal treatment duration, frequency, start age, end age and dose of chemoprevention.

The analysis of harms resulting from the use of chemoprevention is limited. The economic analysis assumes that the excess harms associated with chemoprevention are constant over time and independent of age. The analysis assesses the impact of chemoprevention upon CRC only; however, chemoprevention may also impact on the incidence of other cancers such as prostate or stomach cancers. In this sense, there are questions concerning the boundary assumed around the model. This in turn points towards a methodological requirement for developing a methodological framework for modelling public-health interventions.

Uncertainties

Given the uncertainties in the evidence base (see Strengths and limitations of the assessment)

and ambiguities concerning the potential implementation of potential chemoprevention policy, the results of the health economic analysis should be interpreted with caution. Future clinical trials should focus on addressing questions concerning the optimal treatment duration, frequency, start age, end age and dose of chemoprevention. Longer-term clinical evidence is required in terms of both benefits and harms associated with chemoprevention.

Other relevant factors

The model analysis suggests that the cost savings associated with cancers avoided were always greater than the costs associated with treating harms. Therefore, from an NHS perspective, if chemoprevention is effective at preventing the incidence of polyps, then it will result in net cost savings. Hence, if the individual were to pay for chemoprevention, the question would no longer be whether it is cost-effective, but whether the benefits outweigh the harms.

Chapter 8

Conclusions

Implications for service provision

There are a number of uncertainties relating to the evidence of effectiveness. It is unclear whether the treatment durations and follow-up durations of existing studies are sufficient to detect any effect on CRC incidence. Therefore, the data on CRC are less robust than the data on incidence of adenomas. In addition, careful consideration must be given to the balance between benefits and risks when considering any of these interventions as chemopreventive agents. Given the uncertainties in the evidence base and ambiguities concerning the potential implementation of potential chemoprevention policy, the results of the health economic analysis should be interpreted with caution.

Aspirin and celecoxib may reduce the recurrence of adenomas and incidence of advanced adenomas in individuals with an increased risk of CRC due to a history of adenomas, and COX-2 inhibitors may decrease polyp number in patients with FAP. There is some evidence for aspirin reducing the incidence of CRC in the general population, although this effect was only observed in studies of at least 300 mg/day aspirin with a follow-up duration greater than 10 years.²¹ There is an absence of long-term follow-up data for lower doses of aspirin or for other NSAIDs. Both aspirin and NSAIDs are associated with adverse effects, and so the risk-benefit ratio would need to be carefully considered for each population before these agents could be recommended for chemoprevention. Calcium may also reduce adenoma recurrence in individuals with a history of adenomas: studies of calcium and vitamin D in the general population did not demonstrate a significant effect on CRC, although follow-up durations were relatively short. Folic acid and antioxidants (vitamins A, C, E, beta-carotene and selenium) were not shown to reduce adenoma or CRC incidence, with some studies indicating an increase in these outcomes.

The economic analysis presented here suggests that either calcium or aspirin chemoprevention

may have the potential to represent a cost-effective intervention when targeted at the intermediate-risk populations following polypectomy, given levels of cost-effectiveness currently considered acceptable by NHS policy-makers. Within the general population, the most favourable cost-effectiveness ratio for aspirin chemoprevention is between £20,000 and £30,000 per QALY gained for individuals aged 50–60 years. These findings should be interpreted with due caution given the uncertainties in the current evidence base.

Suggested research priorities

Further research would be useful to investigate the longer-term risk-benefit balance for those potentially effective chemopreventive agents; for example, whether there is a dose level that gives a significant benefit without unacceptable toxicity, what treatment durations are required, whether an effect on CRC can be demonstrated, and for how long the benefits are maintained after the intervention is stopped. Larger studies that follow up participants over long time periods (e.g. 20 years) and assess CRC incidence as an outcome would be valuable. Also, studies in which participants take these interventions for longer durations (e.g. 10 years or more) would be valuable to assess the risk-benefit balance associated with long-term chemoprevention. Within the general population, even for studies with relatively short treatment duration, long-term follow-up is essential if the primary outcome is CRC incidence. Of the interventions targeting the general population assessed here, it is likely that only aspirin has so far been assessed in trials with a sufficient follow-up duration to assess the effect on CRC incidence.

It would be informative to test combinations of chemopreventive agents for which effectiveness has been demonstrated individually (for example, aspirin and calcium within the intermediate-risk population). It will also be important to test newer chemopreventive agents that have not yet been assessed in RCTs (for example, preliminary reports

have suggested possible chemopreventive effects of curcumin and omega-3 fatty acids). It may also be clinically useful to undertake trials in higher-risk patients for whom endoscopic surveillance is not sufficiently effective; for example, patients with ulcerative colitis. Finally, it would be useful to

consider the relative benefit of chemoprevention when compared with, for example, action to increase compliance with screening programmes.²⁶⁹ Very few of these suggested research priorities will be addressed by current ongoing trials.



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Contribution of authors

Paul Tappenden acted as principal investigator for this assessment. Andrew Booth, Christopher Carroll, Katy Cooper and Daniel Hind designed the review; Christopher Carroll, Katy Cooper and Daniel Hind coordinated the review; Andrew Booth, Christopher Carroll, Katy Cooper and Diana Papaioannou designed search strategies; Diana Papaioannou undertook searches; Christopher Carroll, Katy Cooper, Daniel Hind and Diana Papaioannou screened search results;

Christopher Carroll, Katy Cooper, Daniel Hind, Chin Maguire and Diana Papaioannou extracted data from papers; Andrew Booth, Christopher Carroll, Katy Cooper, Daniel Hind and Diana Papaioannou assessed the quality of identified papers, undertook analysis of and interpreted the data; wrote the clinical review, and wrote the review; Richard Logan provided a clinical and policy perspective; Hazel Squires (née Pilgrim) and Paul Tappenden undertook the health economic review and modelling analysis; Andrew Booth, Richard Logan, Hazel Squires and Paul Tappenden provided general advice on the review; and Hazel Squires and Paul Tappenden undertook the economic analysis.



References

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide*, Version 1.0. IARC CancerBase No. 5. Lyon: International Agency for Research on Cancer Press; 2001.
2. Office for National Statistics. *MB1 No. 37: Registrations of cancer diagnosed in 2006, England*; 2008. <http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=8843>.
3. Welsh Cancer Intelligence and Surveillance Unit. *Cancer incidence in Wales 2003–2007*; 2009. www.wcis.wales.nhs.uk.
4. Willett W. The search for the causes of breast and colon cancer. *Nature* 1999;**338**:389–94.
5. Reddy B, Engle A, Katsifis S, Simi B, Bartram HP, Perrino P, *et al.* Biochemical epidemiology of colon cancer: effect of types of dietary fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. *Cancer Res* 1989;**49**:4629–35.
6. Potter JD. Reconciling the epidemiology, physiology, and molecular biology of colon cancer. *J Am Med Assoc* 1992;**268**:1573–7.
7. Centre for Reviews and Dissemination (CRD) UoY. The management of colorectal cancers. *Effective Health Care* 2004;**8**:1–12.
8. National Institute for Health and Clinical Excellence (NICE). *Guidance on cancer services: improving outcomes in colorectal cancers (manual update)*. London: NICE; 2004.
9. Mason P. Colorectal cancer – the disease and its management. *Hosp Pharm* 2004;**11**:175–7.
10. Hill MJ, Morson BC, Bussey HJ. Aetiology of adenoma–carcinoma sequence in large bowel. *Lancet* 1992;**i(8058)**:245–7.
11. Ramssoekh D, van Leerdam ME, Wagner A, Kuipers EJ. Review article: detection and management of hereditary non-polyposis colorectal cancer (Lynch syndrome). *Aliment Pharmacol Ther* 2007;**26**(Suppl. 2):101–11.
12. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;**48**:526–35.
13. Bishop DT, Hall NR. The genetics of colorectal cancer. *Eur J Cancer* 1994;**30A**:1946–56.
14. Aaltonen LA, Salovaara R, Kristo P, Canzian F, Hemminki A, Peltomaki P, *et al.* Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* 1998;**338**:1481–7.
15. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. *Gut* 1992;**33**:783–6.
16. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991;**34**:424–5.
17. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;**36**:2251–70.
18. Hoff G, Vatn MH. Colonic adenoma: natural history. *Dig Dis* 1991;**9**:61–9.
19. Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* 2002;**51**(Suppl. 5):V6–V9.
20. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology* 1987;**93**:1009–13.
21. Flossmann E, Rothwell PM, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007;**369**:1603–13.
22. South West Cancer Intelligence Service. *Data held on file: audit study of patients with colorectal cancer undertaken in the Wessex region 1991–1995*. Bristol: South West Cancer Intelligence Service; 2005.
23. Cancer Research UK. *Large bowel (colorectal) cancer factsheet*; October 2008. <http://info.cancerresearchuk.org/cancerstats/types/bowel/?a=5441>.
24. Van Cutsem EJ, Kataja VV. ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of colon cancer. *Ann Oncol* 2005;**16**(Suppl. 1):i16–i17.

25. Trueman P, Chilcott J, Tappenden P, Lowson K, Pilgrim H, Bending M. *Bowel cancer services: costs and benefits. Report to the Department of Health*. York: York Health Economics Consortium/Sheffield: School of Health and Related Research (University of Sheffield); 2007.
26. Association of Coloproctology of Great Britain and Ireland. *Guidelines for the management of colorectal cancer*, 3rd edn. London: Association of Coloproctology of Great Britain and Ireland; 2007.
27. Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess* 2007;**11**(12).
28. Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(41).
29. Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(32).
30. Hind D, Tappenden P, Tumor I, Eggington S, Sutcliffe P, Ryan A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(15).
31. Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2006;**10**(45).
32. Phillips RKS. *Colorectal surgery*, 3 edn. London: Elsevier Saunders; 2005.
33. Tappenden P, Chilcott JB, Brennan A, Pilgrim H. Systematic review of economic evidence for the detection, diagnosis, treatment and follow-up of colorectal cancer in the UK. *Int J Technol Assess Health Care* 2009;**25**:470–8.
34. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemocult. *BMJ* 1998;**317**:559–65.
35. National Health Service (NHS) UK. *NHS Bowel Cancer Screening Programme website*; 2009. www.cancerscreening.nhs.uk/bowel/.
36. Cancer Research UK. *Bowel cancer screening and prevention website*; 2009. <http://info.cancerresearchuk.org/cancerstats/types/bowel/screeningandprevention/>.
37. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. *J Natl Cancer Inst* 2003;**95**:230–6.
38. National Institute for Health and Clinical Excellence (NICE). *Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer*. Technology Appraisal Guidance No. 61. London: NICE; 2003.
39. National Institute for Health and Clinical Excellence (NICE). *Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer*. Technology Appraisal Guidance No. 93. London: NICE; 2005.
40. National Institute for Health and Clinical Excellence (NICE). *Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer*. Technology Appraisal Guidance No. 118. London: NICE; 2007.
41. National Institute for Health and Clinical Excellence (NICE). *Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer*. Technology Appraisal Guidance No. 100. London: NICE; 2006.
42. National Institute for Health and Clinical Excellence (NICE). *Laparoscopic surgery for colorectal cancer*. Technology Appraisal Guidance No. 105. London: NICE; 2006.
43. Lynch PM. Chemoprevention with special reference to inherited colorectal cancer. *Familial Cancer* 2008;**7**:59–64.
44. Airey C, Becher H, Erens B, Fuller E. *National surveys of NHS patients: cancer – national overview 1999/2000*. London: Department of Health; 2002.
45. Villegas I, Sanchez-Fidalgo S, arcon de la LC. New mechanisms and therapeutic potential of curcumin for colorectal cancer. *Mol Nutr Food Res* 2008;**52**:1040–61.
46. Dupertuis YMM. Colon cancer therapy: new perspectives of nutritional manipulations using polyunsaturated fatty acids. *Curr Opin Clin Nutr Metabol Care* 2007;**10**:427–32.
47. European Medicines Agency (EMA). Press release: *EMA statement following withdrawal of Vioxx (rofecoxib)*; 2004. <http://www.emea.europa.eu/pdfs/human/press/pr/9794904en.pdf>. London: EMA.

48. Asano TK, McLeod RS. *Non steroidal anti-inflammatory drugs (NSAID) and Aspirin for preventing colorectal adenomas and carcinomas*. *Cochrane Database Syst Rev* 2004; Issue 2, Art. No. CD004079.
49. Dannenberg AJ, Zakim D. Chemoprevention of colorectal cancer through inhibition of cyclooxygenase-2. *Semin Oncol* 1999;**26**:499–504.
50. Gupta RA, Dubois RN. Translational studies on Cox-2 inhibitors in the prevention and treatment of colon cancer. *Ann N Y Acad Sci* 2000;**910**:196–204.
51. Bjelakovic G, Nagorni A, Nikolova D, Simonetti RG, Bjelakovic M, Gluud C. Meta-analysis: antioxidant supplements for primary and secondary prevention of colorectal adenoma. *Aliment Pharmacol Therapeut* 2006;**24**:281–91.
52. Maxwell SR. Antioxidant vitamin supplements: update of their potential benefits and possible risks. *Drug Saf* 1999;**21**:253–66.
53. Diplock AT. Antioxidants and disease prevention. *Mol Aspects Med* 1994;**15**:293–376.
54. Sporn MB, Suh N. Chemoprevention of cancer. *Carcinogenesis* 2000;**21**:525–30.
55. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: Molecular mechanisms. *Nat Rev Cancer* 2003;**3**:601–14.
56. *British National Formulary (BNF)*; 2009. www.bnf.org.
57. European Medicines Agency (EMA). *European public assessment report (EPAR): Onsenal: EPAR summary for the public*; 2009. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/onsenal/370303en1.pdf>. London: EMA.
58. Lynch PM. Prevention of colorectal cancer in high-risk populations: the increasing role for endoscopy and chemoprevention in FAP and HNPCC. *Digestion* 2007;**76**:68–76.
59. Atkin WS, Saunders B. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* 2002;**51**(Suppl. 5):v6–v9.
60. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology* 2008;**134**:29–38.
61. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, *et al.* Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *J Am Med Assoc* 2007;**297**:2351–9.
62. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, *et al.* Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* 2003;**125**:328–36.
63. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006;**355**:885–95.
64. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006;**355**:873–84.
65. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;**354**:1896–900.
66. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9.
67. Burn J, Bishop DT, Mecklin JP, Macrae F, Möslein G, Olschwang S, *et al.* Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *N Engl J Med* 2008;**359**:2567–78.
68. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, *et al.* Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *J Am Med Assoc* 2005;**294**:47–55.
69. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, *et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;**352**:1293–304.
70. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. *J Womens Health Genet Based Med* 2000;**9**:19–27.
71. Burn J, Chapman PD, Bishop DT, Dixon R, Turner F, Coaker J, *et al.* Results of the CAPP1 Study: aspirin and resistant starch are beneficial in familial adenomatous polyposis. *Am J Hum Genet* 2003;**73**:abstract-202.
72. Mathers JC, Mickleburgh I, Chapman PC, Bishop DT, Burn J. Can resistant starch and/or aspirin prevent the development of colonic neoplasia? The Concerted Action Polyp Prevention (CAPP) 1 Study. *Proceedings of the 7th International Vahouny Fibre Symposium*, Royal College of

- Physicians, Edinburgh, 27–30 May 2002. *Proc Nutr Soc* 2003;**62**:51–7.
73. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, *et al.* A randomized trial of folic acid to prevent colorectal adenomas. *Proceedings of the American Association for Cancer Research Annual Meeting* 2005;**46**.
74. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, *et al.* A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;**348**:891–9.
75. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst* 1993;**85**:1220–4.
76. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, *et al.* The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. [summary for patients in *Ann Intern Med* 2007;**146**:135; PMID:17339615]. *Ann Intern Med* 2007;**146**:365–75.
77. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;**54**:1044–54.
78. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, *et al.* Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Natl Cancer Inst* 2009;**101**:256–66.
79. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, *et al.* A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. [erratum appears in *N Engl J Med* 2003;**348**:1939]. *N Engl J Med* 2003;**348**:883–90.
80. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, *et al.* Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988;**296**:313–16.
81. Gao F, Liao C, Liu L, Tan A, Cao Y, Mo Z. The effect of aspirin in the recurrence of colorectal adenomas: a meta-analysis of randomized controlled trials. *Colorectal Dis* 2008;**11**:893–901.
82. Wang Y-P, Pan T, Yang J-L, Wang Q, Gan T. Nonsteroidal anti-inflammatory drugs for prevention of colorectal neoplasms: a systematic review. *Chinese J Evidence-Based Med* 2005;**5**:438–43.
83. Giardiello FM, Yang VW, Hylind LM, Krush AJ, Petersen GM, Trimbath JD, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002;**346**:1054–9.
84. Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, *et al.* Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006;**114**:1028–35.
85. Iwama T, Akasu T, Utsunomiya J, Muto T. Does a selective cyclooxygenase-2 inhibitor (tiracoxib) induce clinically sufficient suppression of adenomas in patients with familial adenomatous polyposis? A randomized double-blind placebo-controlled clinical trial. *Int J Clin Oncol* 2006;**11**:133–9.
86. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**:1071–80.
87. Brophy JM, Solomon SD, Wittes J, McMurray J, Psaty BM, Furberg CD. Cardiovascular risk associated with celecoxib. *N Engl J Med* 2005;**352**:2648–50.
88. Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, *et al.* Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. [summary for patients in *Ann Intern Med* 2007;**146**:135; PMID:17339615]. *Ann Intern Med* 2007;**146**:376–89.
89. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, *et al.* The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;**342**:1946–52.
90. Ladenheim J, Garcia G, Titzer D, Herzenberg H, Lavori P, Edson R, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995;**108**:1083–7.
91. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993;**328**:1313–16.
92. Abir F, Alva S, Kaminski DL, Longo WE. The role of arachidonic acid regulatory enzymes in colorectal disease. *Dis Colon Rectum* 2005;**48**:1471–83.
93. Nugent KP, Farmer KCR, Spigelman AD, Williams CB, Phillips RKS. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg* 1993;**80**:1618–19.

94. Labayle D, Fischer D, Vielh P, Drouhin F, Pariente A, Bories C, *et al.* Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991;**101**:635–9.
95. Thomas MG, Thomson JP, Williamson RC, Thomas MG, Thomson JP, Williamson RC. Oral calcium inhibits rectal epithelial proliferation in familial adenomatous polyposis. *Br J Surg* 1993;**80**:499–501.
96. Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J, Bonithon-Kopp C, *et al.* Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* 2000;**356**:1300–6.
97. Lappe JMT. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;**85**:1586–91.
98. Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. [update of *Cochrane Database Syst Rev* 2005; Issue 3, Art No. CD003548; PMID:16034903]. *Cochrane Database Syst Rev* 2008; Issue 1, Art No. CD003548.
99. Baron J, Beach M, Mandel J, van Stolk R, Haile R, Sandler R, *et al.* Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999;**340**:101–7.
100. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, *et al.* Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. *Ann N Y Acad Sci* 1999;**889**:138–45.
101. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, *et al.* Calcium plus vitamin D supplementation and the risk of colorectal cancer. [erratum appears in *N Engl J Med* 2006;**354**:1102]. *N Engl J Med* 2006;**354**:684–96.
102. Shaikat A, Scouras N, Schunemann HJ. Role of supplemental calcium in the recurrence of colorectal adenomas: a metaanalysis of randomized controlled trials. *Am J Gastroenterol* 2005;**100**:390–4.
103. Hofstad B, Almendingen K, Vatn M, Andersen SN, Owen RW, Larsen S, *et al.* Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. *Digestion* 1998;**59**:148–56.
104. Hofstad B, Vatn M, Hoff G, Larsen S, Osnes M, Hofstad B, *et al.* Growth of colorectal polyps: design of a prospective, randomized, placebo-controlled intervention study in patients with colorectal polyps. [erratum appears in *Eur J Cancer Prev* 1993;**2**:189]. *Eur J Cancer Prev* 1992;**1**:415–22.
105. Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE. Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. *J Am Med Assoc* 2008;**300**:2012–21.
106. Lonn E, Yusuf S, Arnold M, Sheridan P, Pogue J, Micks M, *et al.*, for the HOPE-2 investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;**354**:1567–77.
107. Lonn E, Yusuf S, Arnold M, Sheridan P, Pogue J, Micks M, *et al.*, for the HOPE-Z investigators. Rationale, design and baseline characteristics of a large, simple, randomised trial of combined folic acid and vitamin B6 and B12, in high-risk patients: the Heart Outcomes Prevention Evaluation (HOPE)-2 trial. *Can J Cardiol* 2006;**22**:47–53.
108. Jaszewski R, Misra S, Tobi M, Ullah N, Naumoff JA, Kucuk O, *et al.* Folic acid supplementation inhibits recurrence of colorectal adenomas: a randomized chemoprevention trial. *World J Gastroenterol* 2008;**14**:4492–8.
109. Zhu S, Mason J, Shi Y, Hu Y, Li R, Wahg M, *et al.* The effect of folic acid on the development of stomach and other gastrointestinal cancers. *Chin Med J* 2003;**116**:15–19.
110. Zhu S, Mason J, Shi Y, Hu Y, Li R, Wang M, *et al.* The interventional effect of folic acid on the development of gastric and other gastrointestinal cancers – clinical trial and follow-up for seven years. *Chin J Gastroenterol* 2002;**7**:73–8.
111. Baron JA, Cole BF, Mott L, Haile R, Grau M, Church TR, *et al.* Neoplastic and antineoplastic effects of beta-carotene on colorectal adenoma recurrence: results of a randomized trial. *J Natl Cancer Inst* 2003;**95**:717–22.
112. Greenberg ER, Baron JA, Tosteson TD, Freeman DH, Jr, Beck GJ, Bond JH, *et al.* A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *Polyp Prevention Study Group N Engl J Med* 1994;**331**:141–7.
113. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, *et al.* Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *J Am Med Assoc* 2009;**301**:52–62.
114. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. *Cochrane Database Syst Rev* 2008; Issue 4, Art No. CD004183.
115. Palmieri Y, editor. *Reduction of the incidence of metachronous adenomas of the large bowel by means of antioxidants*. Brussels: Se-Te Press; 1998.

116. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Am Med Assoc* 2009;**301**:39–51.
117. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Systematic review: primary and secondary prevention of gastrointestinal cancers with antioxidant supplements. *Aliment Pharmacol Ther* 2008;**28**:689–703.
118. Lin J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van DM, *et al.* Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. *J Natl Cancer Inst* 2009;**101**:14–23.
119. Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, *et al.* A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Arch Intern Med* 2007;**167**:1610–18.
120. Manson JE, Gaziano JM, Spelsberg A, Ridker PM, Cook NR, Buring JE, *et al.* A secondary prevention trial of antioxidant vitamins and cardiovascular disease in women. Rationale, design, and methods. The WACS Research Group. *Ann Epidemiol* 1995;**5**:261–9.
121. Ponz de Leon M, Roncucci L. Chemoprevention of colorectal tumors: role of lactulose and of other agents. *Scand J Gastroenterol Suppl* 1997;**222**:72–5.
122. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, *et al.* Vitamin E in the primary prevention of cardiovascular disease and cancer. The women's health study: a randomized controlled trial. *J Am Med Assoc* 2005;**294**:56–65.
123. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 1999;**91**:2102–6.
124. Roncucci L, Di DP, Carati L, Ferrari A, Perini M, Bertoni G, *et al.* Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Colorectal Cancer Study Group of the University of Modena and the Health Care District 16. *Dis Colon Rectum* 1993;**36**:227–34.
125. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, *et al.* Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *J Am Med Assoc* 2005;**293**:1338–47.
126. MacLennan R, Macrae F, Bain C, Battistutta D, Chapuis P, Gratten H, *et al.* Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas. *J Natl Cancer Inst* 1995;**87**:1760–6.
127. Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL, Jr, Omenn GS, *et al.* The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst* 2004;**96**:1743–50.
128. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, *et al.* Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst* 1996;**88**:1550–9.
129. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. *Cancer Res* 1988;**48**:4701–5.
130. Herberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, *et al.* The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004;**164**:2335–42.
131. Herberg S, Czernichow S, Galan P. Antioxidant vitamins and minerals in prevention of cancers: lessons from the SU.VI.MAX study. *Br J Nutr* 2006;**96**(Suppl. 1):S28–S30.
132. Herberg S, Preziosi P, Briancon S, Galan P, Triol I, Malvy D, *et al.* A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study – design, methods, and participant characteristics. *Supplementation en Vitamines et Mineraux Antioxydants. Control Clin Trials* 1998;**19**:336–51.
133. Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, *et al.* Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. *J Am Med Assoc* 2003;**290**:476–85.
134. Malila N, Virtamo J, Virtanen M, Albanes D, Tangrea JA, Huttunen JK. The effect of alpha-tocopherol and beta-carotene supplementation on colorectal adenomas in middle-aged male smokers. *Cancer Epidemiol Biomarkers Prev* 1999;**8**:489–93.
135. Albanes D, Malila N, Taylor PR, Huttunen JK, Virtamo J, Edwards BK, *et al.* Effects of supplemental alpha-tocopherol and beta-carotene on colorectal cancer: results from

- a controlled trial (Finland). *Cancer Causes Control* 2000;**11**:197–205.
136. Albanes D, Heinonen OP, Huttunen JK, Taylor PR, Virtamo J, Edwards BK, *et al.* Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr* 1995;**62**(Suppl. 6):1427S–1430S.
137. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF, Jr, Slate EH, Fischbach LA, *et al.* Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:630–9.
138. Reid ME, Duffield-Lillico AJ, Sunga A, Fakih M, Alberts DS, Marshall JR, *et al.* Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial. *Int J Cancer* 2006;**118**:1777–81.
139. Clark LC, Combs GF, Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, *et al.* Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *J Am Med Assoc* 1996;**276**:1957–63.
140. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:23–33.
141. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
142. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, *et al.* Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;**334**:1145–9.
143. Burn J, Mathers JC, Gerdes AM, Bisgaard ML, Evans G, Eccles D, *et al.* Cancer occurrence during follow-up of the CAPP2 Study – Aspirin use for up to four years significantly reduces Lynch syndrome cancers for up to 10 years. *InSiGHT Conference*; 2009. <http://www.capp2.com/newsZone/readnews.php?NewsID=45>.
144. Benamouzig R, Deyra J, Martin A, Bejou B, Raynaud JJ, Girard B, *et al.* Daily soluble aspirin and prevention of colorectal adenoma recurrence four years results of the APACC trial. *Gastroenterology* 2006;**130**:A101.
145. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60.
146. Sheng JQ, Li SR, Yang XY, Zhang YH, Su H, Yu DL, *et al.* [Clinical management of adenomatous polyposis in patients with hereditary non-polyposis colorectal cancer and familial adenomatous polyposis] [in Chinese]. *Chung-Hua i Hsueh Tsa Chih [Chin Med J]* 2006;**86**:526–9.
147. Higuchi T, Iwama T, Yoshinaga K, Toyooka M, Taketo MM, Sugihara K, *et al.* A randomized, double-blind, placebo-controlled trial of the effects of rofecoxib, a selective cyclooxygenase-2 inhibitor, on rectal polyps in familial adenomatous polyposis patients. *Clin Cancer Res* 2003;**9**:4756–60.
148. Wood NJ, Quinton NA, Burdall S, Sheridan E, Duffy SR. Exploring the potential chemopreventative effect of aspirin and rofecoxib on hereditary nonpolyposis colorectal cancer-like endometrial cancer cells in vitro through mechanisms involving apoptosis, the cell cycle, and mismatch repair gene expression. *Int J Gynecol Cancer* 2007;**17**:447–54.
149. De Vries E, Cats A, van der Meer R, Mulder N, Hardonk M, Kleibeuker J. Randomized, double-blind, placebo-controlled study with calcium in heredity nonpolyposis colorectal cancer (HNPPC). *Proc Am Assoc Cancer Res Annual Meeting* 1994;**35**:622.
150. Seow-Choen F, Vijayan V, Keng V, Seow-Choen F, Vijayan V, Keng V. Prospective randomized study of sulindac versus calcium and calciferol for upper gastrointestinal polyps in familial adenomatous polyposis. *Br J Surg* 1996;**83**:1763–6.
151. Sinicrope FA, Half E, Morris JS, Lynch PM, Morrow JD, Levin B, *et al.* Cell proliferation and apoptotic indices predict adenoma regression in a placebo-controlled trial of celecoxib in familial adenomatous polyposis patients. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:920–7.
152. Chen HP, Han SX, Zeng LM, Xu G, Yang H. Sulindac for treatment of colorectal adenomas. *Chin J Dig* 2001;**21**:340–1.
153. Baron JA, Sandler RS, Bresalier RS, Quan H, Riddell R, Lanos A, *et al.* A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. *Gastroenterology* 2006;**131**:1674–82.
154. Meyskens FL, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, *et al.* Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a

- randomized placebo-controlled, double-blind trial. *Cancer Prev Res Philad PA* 2008;**1**:9–11.
155. Grau MV, Baron JA, Sandler RS, Wallace K, Haile RW, Church TR, *et al.* Prolonged effect of calcium supplementation on risk of colorectal adenomas in a randomized trial. *J Natl Cancer Inst* 2007;**99**:129–36.
156. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2008; Issue 2, Art No. CD007176.
157. Jass JR. Limitations of the adenoma-carcinoma sequence in colorectum. *Clin Cancer Res* 2004;**10**:5969–70.
158. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;**329**:1977–81.
159. Giovannucci E, Stampfer MJ, Colditz GA, Hunter DJ, Fuchs C, Rosner BA, *et al.* Multivitamin use, folate, and colon cancer in women in the nurses' health study. *Ann Intern Med* 1998;**129**:517–24.
160. Virtamo J, Valkeila E, Alfthan G, Punsar S, Huttunen JK, Karvonen MJ. Serum selenium and risk of cancer. A prospective follow-up of nine years. *Cancer* 1987;**60**:145–8.
161. West NJ, Clark SK, Belluzzi A, Hutchinson JM, Hull MA, Leicester RJ, *et al.* Chemopreventive effect of eicosapentaenoic acid (EPA) free fatty acid in familial adenomatous polyposis (FAP): results of a randomised, placebo-controlled trial. *Gut* 2009;**58**(Suppl. 2):A1 Abstract OP004.
162. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, *et al.* Statins and the risk of colorectal cancer. *N Engl J Med* 2005;**352**:2184–92.
163. Hachem C, Morgan R, Johnson M, Kuebel M, El-Serag H. Statins and the risk of colorectal carcinoma: a nested case-control study in veterans with diabetes. *Am J Gastroenterol* 2009;**104**:1241–8.
164. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;**360**:1623–30.
165. Goldstein MR, Mascitelli L, Pezzetta F. Statins and colorectal cancer: the jury is still out. *Am J Gastroenterol* 2009;**104**:2858–9.
166. Wilczynski N, Marks S, Haynes RB. Search strategies for identifying qualitative studies in CINAHL. *Qual Health Res* 2007;**17**:705–10.
167. Tedstone A, Browne M, Harrop L, Vernon C, Page V, Swindells J, *et al.* Fortification of selected foodstuffs with folic acid in the UK: consumer research carried out to inform policy recommendations. *J Public Health* 2008;**30**:23–9.
168. Townsend A, Hunt K, Wyke S. Managing multiple morbidity in mid-life: a qualitative study of attitudes to drug use. *BMJ* 2003;**327**:837–40.
169. Wazaify M, Shields E, Hughes CM, McElnay JC. Societal perspectives on over-the-counter (OTC) medicines. *Family Practice* 2005;**22**:170–6.
170. Carnes D, Anwer Y, Underwood M, Harding G, Parsons S, *et al.* and the TOIB study team. Influences on older people's decision making regarding choice of topical or oral NSAIDs for knee pain: qualitative study. *BMJ* 2008;**336**:142–5.
171. French DP, James DH. Reasons for the use of mild analgesics among English students. *Pharm World Sci* 2008;**30**:79–85.
172. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;**19**:349–57.
173. Atkins C, Sampson J. Critical appraisal guidelines for single case study research. *Proceedings of ECIS 2002, the Xth European Conference on Information Systems*, Gdansk, 6–8 June. 2002.
174. Boynton P. Hands-on guide to questionnaire research: selecting, designing, and developing your questionnaire. *BMJ* 2004;**328**:1312.
175. Dixon-Woods M, Shaw R, Agarwal S, Smith J. The problem of appraising qualitative research. *Qual Saf Health Care* 2004;**13**:223–5.
176. Dixon-Woods M. Appraising qualitative research for inclusion in systematic reviews: a quantitative and qualitative comparison of three methods. *J Health Services Res Policy* 2007;**12**:42–7.
177. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: NHS Centre for Reviews and Dissemination; 2009.
178. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: A Bryman and RG Burgess, editors. *Analysing qualitative data*. London: Routledge; 1994.

179. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. (01/09). ESRC National Centre for Research Methods Working Paper Series; 2009.
180. Oliver S, Rees R, Clarke-Jones L, Milne R, Oakley A, Gabbay J, *et al.* A multidimensional conceptual framework for analysing public involvement in health services research. *Health Expect* 2008;**11**:72–84.
181. Brunton G, Oliver S, Oliver K, Lorenc T. *A synthesis of research addressing children's, young people's and parents' views of walking and cycling for transport.* London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London; 2006.
182. Huffman S. *Can marketing of multiple vitamin/mineral supplements reach the poor?* The Vitaldia Project, Bolivia. 2002.
183. Dixon-Woods M, Bonas S, Booth A, Jones DR, Miller T, Sutton AJ, *et al.* How can systematic reviews incorporate qualitative research? A critical perspective. *Qual Res* 2006;**6**:27–44.
184. Miles M, Huberman A. *Qualitative data analysis: a sourcebook of new methods.* Newbury Park, CA: Sage; 1984.
185. Lindsey LL, Hamner HC, Prue CE, Flores AL, Valencia D, Correa-Sierra E, *et al.* Understanding optimal nutrition among women of childbearing age in the United States and Puerto Rico: employing formative research to lay the foundation for national birth defects prevention campaigns. *J Health Commun* 2007;**12**:733–757.
186. Reedy J, Haines PS, Steckler A, Campbell MK. Qualitative comparison of dietary choices and dietary supplement use among older adults with and without a history of colorectal cancer. *J Nutr Educ Behav* 2005;**37**:252–8.
187. Legare F, Stacey D, Dodin S, O'Connor A, Richer M, Griffiths F, *et al.* Women's decision making about the use of natural health products at menopause: a needs assessment and patient decision aid. *J Altern Complement Med* 2007;**13**:741–9.
188. Spanner ED, Duncan AM. Prevalence of dietary supplement use in adult with chronic renal insufficiency. *J Renal Nutr* 2005;**15**:204–10.
189. Arcury TA, Bell RA, Vitolins MZ, Quandt SA. Rural older adults' beliefs and behavior related to complementary and alternative medicine use. *Complement Health Pract Rev* 2005;**10**:33–44.
190. Connor LH. Relief, risk and renewal: mixed therapy regimens in an Australian suburb. *Social Sci Med* 2004;**59**:1695–705.
191. Huber R, Koch D, Beiser I, Zschocke I, Luedtke R. Experience and attitudes towards CAM – a survey of internal and psychosomatic patients in a German university hospital. *Altern Ther Health Med* 2004;**10**:32–6.
192. Chagan L, Bernstein D, Cheng JW, Kirschenbaum HL, Rozenfeld V, Caliendo GC, *et al.* Use of biological based therapy in patients with cardiovascular diseases in a university-hospital in New York City. *BMC Complement Altern Med* 2005;**5**:4.
193. George J, Ioannides-Demos LL, Santamaria NM, Kong D, Stewart K. Use of complementary and alternative medicines by patients with chronic obstructive pulmonary disease. *Med J Aust* 2004;**181**:248–51.
194. Fraenkel L, Bogardus ST Jr, Concato J, Wittink DR. Treatment options in knee osteoarthritis: the patient's perspective. *Arch Intern Med* 2004;**164**:1299–304.
195. Miller CK, Russell T, Kissling G. Decision-making patterns for dietary supplement purchases among women aged 25 to 45 years. *J Am Dietet Assoc* 2003;**103**:1523–6.
196. Oldham L, Kendall P, Cobb B, Banning J, Slater M. Perceptions of dietary supplements among older women with diabetes. *The Diabetes Educator* 2004;**30**:658–64.
197. Porter M, Kolva E, Ahl R, Diefenbach MA. Changing patterns of CAM use among prostate cancer patients two years after diagnosis: reasons for maintenance or discontinuation. *Complement Ther Med* 2008;**16**:318–24.
198. Cowan R, Meiser B, Giles GG, Lindeman GJ, Gaff CL. The beliefs, and reported and intended behaviors of unaffected men in response to their family history of prostate cancer. *Genet Med* 2008;**10**:430–8.
199. Matthews AK, Sellergren SA, Huo D, List M, Fleming G. Complementary and alternative medicine use among breast cancer survivors. *J Altern Complement Med* 2007;**13**:555–62.
200. Papaioannou D, Carroll C, Booth A, Sutton A, Wong R. Literature searching for social science systematic reviews: consideration of a range of search techniques. *Health Information and Libraries Journal* 2010; in press.

201. Grayson L, Gomersall A. *A difficult business: finding the evidence for social science reviews*. Working paper 19. 2003. London: ESRC UK Centre for Evidence Based Policy and Practice.
202. Prochaska J, Velicer W. The transtheoretical model of health behavior change. *Am J Health Prom* 1997;**12**:38–48.
203. Demark-Wahnefried W, Peterson B, McBride C, Lipkus I, Clipp E. Current health behaviors and readiness to pursue life-style changes among men and women diagnosed with early stage prostate and breast carcinomas. *Cancer* 2000;**88**:674–84.
204. Strecher VJ, Rosenstock IM. The health belief model. In: Rimer BK, editor. *Health Behavior and Health Education*. San Francisco, CA: Jossey-Bass; 1997. pp. 41–59.
205. Floyd DL, Prentice-Dunn S, Rogers RW. A meta-analysis of research on protection motivation theory. *J Appl Soc Psychol* 2000;**30**:407–29.
206. Milne S, Sheeran P, Orbell S. Prediction and intervention in health-related behavior: a meta-analytic review of protection motivation theory. *J Appl Soc Psychol* 2000;**30**:106–43.
207. Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychol Health* 2002;**17**:17–32.
208. Fraenkel L, Wittink DR, Concato J, Fried T. Informed choice and the widespread use of anti-inflammatory drugs. *Arthritis Rheum* 2004;**51**:210–14.
209. Herve C, Mullet E, Sorum PC. Age and medication acceptance. *Exp Aging Res* 2004;**30**:253–73.
210. Nahleh Z, Tabbara I. Complementary and alternative medicine in breast cancer patients. *Pall Support Care* 2003;**1**:267–73.
211. Verhoef MJ, Balneaves LG, Boon HS, Vroegindewey A. Reasons for and characteristics associated with complementary and alternative medicine use among adult cancer patients: a systematic review. *Integr Cancer Ther* 2005;**4**:274–86.
212. Neuhouser ML, Patterson RE, Levy L. Motivations for using vitamin and mineral supplements. *J Am Dietet Assoc* 1999;**99**:851–4.
213. Velicer CMU. Vitamin and mineral supplement use among US adults after cancer diagnosis: A systematic review. *J Clin Oncol* 2008;**26**:665–73.
214. Emmons KM, McBride CM, Puleo E, Pollak KI, Clipp E, Kuntz K, et al. Project PREVENT: a randomized trial to reduce multiple behavioral risk factors for colon cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1453–9.
215. Ladabaum U. Potential cost-effectiveness of colorectal cancer chemoprevention with nonsteroidal anti-inflammatory drugs. *Expert Rev Pharmacoecon Outcomes Res* 2003;**3**:757–71.
216. Ladabaum U, Chopra CL, Huang G, Scheiman JM, Chernew ME, Fendrick AM. Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med* 2001;**135**:769–81.
217. Ladabaum U, Scheiman JA, Fendrick AM. Potential effect of cyclooxygenase-2-specific inhibitors on the prevention of colorectal cancer: a cost-effectiveness analysis. *Am J Med* 2003;**114**:546–54.
218. Arguedas MR, Heudebert GR, Wilcox CM. Surveillance colonoscopy or chemoprevention with COX-2 inhibitors in average-risk post-polypectomy patients: a decision analysis. *Aliment Pharmacol Therapeut* 2001;**15**:631–8.
219. Suleiman S, Rex DK, Sonnenberg A. Chemoprevention of colorectal cancer by aspirin: a cost-effectiveness analysis. *Gastroenterology* 2002;**122**:78–84.
220. Dupont AW, Arguedas MR, Wilcox CM. Aspirin chemoprevention in patients with increased risk for colorectal cancer: a cost-effectiveness analysis. *Aliment Pharmacol Therapeut* 2007;**26**:431–41.
221. Hur C, Simon LS, Gazelle GS. The cost-effectiveness of aspirin versus cyclooxygenase-2-selective inhibitors for colorectal carcinoma chemoprevention in healthy individuals. *Cancer* 2004;**101**:189–97.
222. Ries L, Kosary C, Hankey B, Miller B, Arras A. *SEER Cancer Statistics Review, 1973–1994*. NIH Pub. no. 97–2789. 1997. Bethesda, MD: National Cancer Institute.
223. Screening for colorectal cancer – United States, 1997. *MMWR Morb Mortal Wkly Rep* 1999;**48**:116–121.
224. Wagner JL, Herdman RC, Wadhwa S. Cost effectiveness of colorectal cancer screening in the elderly. *Ann Intern Med* 1991;**115**:807–17.
225. The DRG Handbook: *Comparative Clinical and Finalncial Standards*. Baltimore, MD: HCIA; 1997.

226. Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, *et al.* Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med* 1993;**328**:901–6.
227. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *J Am Med Assoc* 2000;**284**:1247–55.
228. Medical Economics. *Drug Topics Red Book*. Montvale, NJ: Medical Economics Company; 2000.
229. Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. *Med Care* 1999;**37**:1249–59.
230. Sonnenberg A, Delco F, Inadomi JM. The cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med* 2000;**133**:573–84.
231. Lee J, Vigil H, Leung J. The hospital costs for diagnosis and treatment of colorectal cancer. *Gastrointest Endosc* 1999;**49**:AB145.
232. Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. *N Engl J Med* 2000;**342**:1960–8.
233. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, *et al.* The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making* 1993;**13**:89–102.
234. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001;**85**:265–71.
235. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;**321**:129–35.
236. Spiegel BM, Targownik L, Dulai GS, Gralnek IM. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Ann Intern Med* 2003;**138**:795–806.
237. Bensen S, Mott LA, Dain B, Rothstein R, Baron J. The colonoscopic miss rate and true one-year recurrence of colorectal neoplastic polyps. Polyp Prevention Study Group. *Am J Gastroenterol* 1999;**94**:194–9.
238. Tappenden P, Chilcott J, Eggington S, Sakai H, Karnon J, Patnick J. Option appraisal of population-based colorectal cancer screening programmes in England. *Gut* 2007;**56**:677–84.
239. Turnbull RB, Kyle K, Watson FR. Cancer of the colon: the influence of the no touch isolation technique on survival rates. *Ann Surg* 1967;**166**:420–7.
240. Dukes CE. The classification of cancer of the rectum. *J Pathol Bacteriol* 1932;**35**:332.
241. Winawer SJ, Zauber AG, O'Brien MJ. Randomised comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N Engl J Med* 1993;**328**:901–6.
242. Government Actuary's Department. *Interim Life Tables 2005–07*. London: GAD; 2008.
243. UKACR. *Cancer Registry population denominators. 2009*. Experimental Statistics provided by Office for National Statistics Crown Copyright 2007.
244. Pendergrass CJ, Edelstein DL, Hyland LM, Phillips BT, Iacobuzio-Donohue C, Romans K, *et al.* Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. *Clin Gastroenterol* 2008;**6**:1011–15.
245. Imperiale TF, Wagner DR, Lin CY, Larkin MD, Rogge JD, Ransohoff DF. Results of screening colonoscopy among persons 40 to 49 years of age. *N Engl J Med* 2002;**346**:1781.
246. Bolland M. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008; Published online 15 Jan 2008.
247. National Collaborating Centre for Chronic Conditions. *Osteoarthritis: National clinical guideline for care and management in adults*. London: Royal College of Physicians; 2008.
248. British Heart Foundation. *Incidence of myocardial infarction*. 2009. URL:www.heartstats.org/.
249. Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess* 2007;**11**(12).
250. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer and lung cancer: A nationwide population-based assessment. *J Surg Res* 2003;**114**:1–5.

251. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. *J Gastroenterol* 1999;**94**:1650–7.
252. Ramsey SD, Andersen MR, Etzioni R, Moinpour CM, Peacock S, Potosky A, *et al.* Quality of life in survivors of colorectal cancer. *Cancer* 2000;**88**:1294–303.
253. Petrou S, Campbell N. Stabilisation in colorectal cancer. *Int J Pall Nurs* 1997;**3**:275–80.
254. Maughan MT, Ledermann TS, Topham JA, James C, Gwyther R, Smith SJ, *et al.* Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;**370**:143–52.
255. Corrie P. *The MABEL study. An open, uncontrolled, multicentre, phase II study of Erbitux. (cetuximab) in combination with irinotecan in patients with metastatic colorectal carcinoma expressing the epidermal growth factor receptor and having progressed on a defined irinotecan-based regimen as most recent treatment.* 2005. National Research Register.
256. NICE. *Guide to the methods of technology appraisal.* London: NICE; 2008.
257. Department of Health. *Health Survey for England, 1996.* Series HS no.6. London: DoH; 1998.
258. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. *Am J Gastroenterol* 1999;**94**:1650–7.
259. Pilgrim H, Tappenden P, Chilcott J, Bending M, Trueman P, Shorthouse A, *et al.* The costs and benefits of bowel cancer service developments using discrete event simulation. *J Operat Res Soc*; Advance Online Publication 22 Oct 2008.
260. Curtis L. *Unit Costs of Health and Social Care 2008.* Canterbury: PSSRU; 2008.
261. Department of Health. *NHS Reference Costs 2005.* London: DoH; 2006.
262. Department of Health. *NHS Reference Costs 2006–07.* London: DoH; 2008.
263. Burch JA, Soares-Weiser K, St John DJ, Duffy S, Smith S, Kleijnen J, *et al.* Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. *J Med Screen* 2007;**14**:132–7.
264. Weller D, Moss S, Butler P, Campbell C, Coleman D, Melia J, *et al.* *English Pilot of Bowel Cancer Screening: an evaluation of the second round.* 2006. Final Report to the Department of Health.
265. Van Rijn JC, Reisma JB, Stoker J. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol* 2006;**101**:343–50.
266. Bressler B, Paszat L, Chen D, Rothwell D, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007;**132**:96–102.
267. Cuzick J, Otto F, Baron J, Brown P, Burn B, Greenwald P, *et al.* Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet* 2009;**10**:501–7.
268. Brennan A, Kharroubi S, O'Hagen A, Chilcott J. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. *Med Decision Making* 2007;**27**:448.
269. Asano TK, McLeod RS. Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review. *Dis Colon Rectum* 2004;**47**:665–73.
270. Velicer WF, Prochaska JO, Fava JL, Norman GJ, Redding CA. *Transtheoretical model of change*; 2009. <http://www.uri.edu/research/cprc/TTM/detailedoverview.htm>.
271. Moustakas C. *Phenomenological research methods.* Thousand Oaks, CA: Sage; 1994.

Appendix I

Literature search strategies

Search strategy for RCTs (MEDLINE)

The following search strategy was used to identify RCTs of relevant interventions.

Terms for colorectal cancer or adenomas

1. exp Colorectal Neoplasms/
2. exp Rectal Neoplasms/
3. Colonic Polyps/
4. exp Intestinal Polyps/
5. exp Adenomatous Polyps/
6. or/1-5
7. exp Colon/
8. exp Rectum/
9. (colorect\$or colon\$or rectum\$or rectal\$or rectosigmoid\$or adenomatous).tw.
10. 7 or 8 or 9
11. (neoplas\$or cancer\$or carcinoma\$or adenocarcinoma\$or malignan\$or tumor\$or tumour\$or polyp\$or adenoma\$.tw.
12. exp Adenoma/
13. 11 or 12
14. 10 and 13
15. 6 or 14

Terms for antioxidants

16. exp Antioxidants/
17. anti-oxidant\$.tw.
18. antioxidant\$.tw.
19. selenium.tw.
20. Selenium/
21. exp Vitamin A/
22. retinol.tw. (8796)
23. exp Carotenoids/
24. carotene\$.tw.
25. carotenoid\$.tw.
26. beta-carotene.tw.
27. exp Ascorbic Acid/
28. vitamin c.tw.
29. ascorbic acid.tw.
30. exp Vitamin E/
31. exp Tocopherols/
32. Tocotrienols/
33. alpha-tocopherol\$.tw.
34. tocopherol\$.tw.
35. tocotrienol\$.tw.

Terms for vitamin D

36. exp Cholecalciferol/
37. vitamin d.tw.
38. exp Ergocalciferols/
39. Cholecalciferol\$.tw.
40. Ergocalciferol\$.tw.

Terms for NSAIDs and aspirin

41. exp Anti-Inflammatory Agents, Non-Steroidal/
42. exp cyclooxygenase inhibitors/or exp cyclooxygenase 2 inhibitors/
43. Non-steroidal anti-inflammatory\$.tw.
44. Nonsteroidal anti-inflammatory\$.tw.
45. Non-steroidal antiinflammatory\$.tw.
46. Nonsteroidal antiinflammatory\$.tw.
47. NSAID\$.tw.
48. Cyclo-oxygenase inhibitor\$.tw.
49. Cyclooxygenase inhibitor\$.tw.
50. Cyclooxygenase 1 inhibitor\$.tw.
51. Cyclooxygenase 2 inhibitor\$.tw.
52. COX-2 inhibitor\$.tw.
53. COX-2 selective inhibitor\$.tw.
54. COX-1 inhibitor\$.tw.
55. Coxib\$.tw.
56. Aminopyrine.af.
57. Amodiaquine.af.
58. Ampyrone.af.
59. Antipyrine.af.
60. Apazone.af.
61. Aspirin.af.
62. Aspirin/
63. Acetylsalicylic acid.tw.
64. Bromelains.af.
65. BW-755C.af.
66. Celecoxib.af.
67. osenal.af.
68. Clofazimine.af.
69. Clonixin.af.
70. Curcumin.af.
71. Dapsone.af.
72. Diclofenac.af.
73. Diflunisal.af.
74. Dipyrone.af.
75. Epirizole.af.
76. Etodolac.af.
77. Etoricoxib.af.

78. Fenoprofen.af.
 79. Flurbiprofen.af.
 80. Glycyrrhizic Acid.af.
 81. Ibuprofen.af.
 82. Indomethacin.af.
 83. Indoprofen.af.
 84. Ketoprofen.af.
 85. Ketorolac.af.
 86. Lumiracoxib.af.
 87. Meclofenamic Acid.af.
 88. Mefenamic Acid.af.
 89. Mesalamine.af.
 90. Naproxen.af.
 91. Niflumic Acid.af.
 92. Nordihydroguaiaretic Acid.af.
 93. Oxyphenbutazone.af.
 94. Parecoxib.af.
 95. Pentosan Sulfuric Polyester.af.
 96. Phenylbutazone.af.
 97. Piroxicam.af.
 98. Prenazone.af.
 99. Salicylate\$.af.
 100. Sulfasalazine.af.
 101. Sulindac.af.
 102. sulindac/
 103. clinoril.af.
 104. Suprofen.af.
 105. Tolmetin.af.
 106. Valdecoxib.af.
 107. Meloxicam.af.
 108. Nabumetone.af.
 109. Choline magnesium trisalicylate.af.
 110. Rofecoxib.af.
 111. Amoxiciprin.af.
 112. Benorylate.af.
 113. Benorilate.af.
 114. Choline magnesium salicylate.af.
 115. Ethenzamide.af.
 116. Faislamine.af.
 117. Methyl salicylate.af.
 118. Magnesium salicylate.af.
 119. Salicylamide.af.
 120. Aceclofenac.af.
 121. Acemetacin.af.
 122. Alclofenac.af.
 123. Bromfenac.af.
 124. Oxametacin.af.
 125. Proglumetacin.af.
 126. Dexibuprofen.af.
 127. Dexketoprofen.af.
 128. Fenbufen.af.
 129. Flunoxaprofen.af.
 130. Ibuproxam.af.
 131. Loxoprofen.af.
 132. Oxaprozin.af.
 133. Pirprofen.af.

134. Tiaprofenic acid.af.
 135. Flufenamic acid.af.
 136. Tolfenamic acid.af.
 137. Azapropazone.af.
 138. Clofezone.af.
 139. Kebuzone.af.
 140. Metamizole.af.
 141. Mofebutazone.af.
 142. Phenazone.af.
 143. Sulfinpyrazone.af.
 144. Droxicam.af.
 145. Lornoxicam.af.
 146. Tenoxicam.af.
 147. Licofelone.af.
 148. or/16–147
 149. 15 and 148

Terms for RCTs

150. randomized controlled trial.pt.
 151. controlled clinical trial.pt.
 152. randomized controlled trials/
 153. random allocation/
 154. double blind method/
 155. single blind method/
 156. clinical trial.pt.
 157. exp Clinical Trial/
 158. (clin\$adj25 trial\$.ti,ab.
 159. ((singl\$or doubl\$or trebl\$or tripl\$) adj25
 (blind\$or mask\$)).ti,ab.
 160. placebos/
 161. placebos.ti,ab.
 162. random\$.tw.
 163. research design/
 164. or/150–163
 165. 149 and 164

Date restriction

166. limit 165 to yr='2003 – 2008'

Search strategy for RCTs of calcium (MEDLINE, no date restriction)

Terms for colorectal cancer or adenomas

1. 1 exp Colorectal Neoplasms/
2. exp Rectal Neoplasms/
3. Colonic Polyps/
4. exp Intestinal Polyps/
5. exp Adenomatous Polyps/
6. or/1–5
7. exp Colon/
8. exp Rectum/
9. (colorect\$or colon\$or rectum\$or rectal\$or
 rectosigmoid\$or adenomatous).tw.
10. 7 or 8 or 9

11. (neoplas\$or cancer\$or carcinoma\$or adenocarcinoma\$or malignan\$or tumor\$or tumour\$or polyp\$or adenoma\$).tw.
12. exp Adenoma/
13. 11 or 12
14. 10 and 13
15. 6 or 14

Terms for calcium

16. Calcium/
17. calcium.tw.

Terms for RCTs

18. 16 or 17
19. 15 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized controlled trials/
23. random allocation/
24. double blind method/
25. single blind method/
26. clinical trial.pt.
27. exp Clinical Trial/
28. (clin\$adj25 trial\$).ti,ab.
29. ((singl\$or doubl\$or trebl\$or tripl\$) adj25 (blind\$or mask\$)).ti,ab.
30. placebos/
31. placebos.ti,ab.
32. random\$.tw.
33. research design/
34. or/20–33
35. 19 and 34

Search strategy for cost-effectiveness studies

1. exp Colorectal Neoplasms/
2. neoplasms/
3. carcinoma/
4. adenocarcinoma/
5. or/2–4
6. colonic diseases/
7. rectal diseases/
8. exp Colon/
9. exp Rectum/
10. or/6–9
11. 5 and 10
12. (carcinoma adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
13. (neoplasia adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
14. (neoplasm\$adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
15. (adenocarcinoma adj3 (colorectal or colon\$or intestin\$or bowel)).tw.

16. (cancer\$adj3 (colorectal or colon\$or intestin\$or bowel)).tw.
17. (tumor\$adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
18. (tumour\$adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
19. (malignan\$adj3 (colorectal or colon\$or rect\$or intestin\$or bowel)).tw.
20. or/12–19
21. 1 or 11 or 20
22. Economics/
23. 'costs and cost analysis'/
24. Cost allocation/
25. Cost-benefit analysis/
26. Cost control/
27. cost savings/
28. Cost of illness/
29. Cost sharing/
30. 'deductibles and coinsurance'/
31. Health care costs/
32. Direct service costs/
33. Drug costs/
34. Employer health costs/
35. Hospital costs/
36. Health expenditures/
37. Capital expenditures/
38. Value of life/
39. exp economics, hospital/
40. exp economics, medical/
41. economics, nursing/
42. economics, pharmaceutical/
43. exp 'fees and charges'/
44. exp budgets/
45. (low adj cost\$).mp.
46. (high adj cost).mp.
47. (health?care adj cost\$).mp.
48. (fiscal or funding or financial or finance).tw.
49. (cost adj estimate\$).mp.
50. (cost adj variable).mp.
51. (unit adj cost\$).mp.
52. (economic\$or pharmacoeconomic\$or price\$or pricing).tw.
53. or/22–52
54. 21 and 53

Search strategy for quality of life studies (MEDLINE)

1. health related quality of life.tw.
2. hrql.tw.
3. hrqol.tw.
4. hql.tw.
5. sf 36.tw.
6. sf thirtysix.tw.
7. sf thirty six.tw.
8. short form 36.tw.

9. short form thirty six.tw.
10. short form thirtysix.tw.
11. shortform 36.tw.
12. shortform thirty six.tw.
13. shortform thirty six.tw.
14. sf36.tw.
15. medical outcomes survey.tw.
16. mos.tw.
17. euroqol.tw.
18. eq 5d.tw.
19. eq5d.tw.
20. qaly\$.tw.
21. quality adjusted life years/
22. quality adjusted life year\$.tw.
23. hye\$.tw.
24. health\$year\$equivalent\$.tw.
25. psychological general well being index.tw.
26. psychological general wellbeing index.tw.
27. pgwb\$.tw.
28. health utilit\$.tw.
29. hui.tw.
30. quality of wellbeing\$.tw.
31. quality of well being.tw.
32. qwb\$.tw.
33. rosser.tw.
34. trade off\$.tw.
35. standard gamble.tw.
36. tto.tw.
37. 'Quality of Life'/
38. 'Outcome Assessment (Health Care)'/
39. (preference\$or utilit\$.tw. and (58 or 59)
40. ((preference\$or utilit\$) and quality of life).tw.
41. (preference\$adj2 (elicit\$or patient\$or population\$or measure\$or based or cost\$)).tw.
42. (utilit\$adj2 (elicit\$or patient\$or population\$or measure\$or based or cost\$)).tw.
43. or/22–57,60–63

Search strategy for qualitative studies (MEDLINE)

Qualitative search I

Two searches were undertaken relating to qualitative studies. Initially, the following search strategy was used to identify qualitative studies relating to the relevant interventions in a UK population.

Terms for interventions

1. vitamin\$.tw.
2. mineral\$.tw.
3. folate\$.tw.
4. selenium.tw.
5. calcium.tw.
6. exp Dietary Supplements/

7. dietary supplement\$.tw.
8. non-steroidal\$.tw.
9. non steroidal\$.tw.
10. nonsteroidal\$.tw.
11. NSAID\$.tw.
12. antiinflammator\$.tw.
13. anti-inflammator\$.tw.
14. anti inflammator\$.tw.
15. aspirin\$.tw.
16. or/1–15

Terms for qualitative studies

17. interview\$.tw.
18. experience\$.tw.
19. qualitative\$.tw.
20. qualitative research/
21. or/17–20

Terms for UK population

22. exp Great Britain/
23. (England or Scotland or Wales or Ireland or UK or United Kingdom).in.
24. (England or Scotland).cp.
25. (Britain or England or Scotland or Wales or Ireland or UK or United Kingdom).tw.
26. (London or Birmingham or Leeds or Glasgow or Sheffield or Bradford or Liverpool or Edinburgh or Manchester or Bristol).in.
27. (Kirklees or Fife or Wirral or North Lanarkshire or Wakefield or Cardiff or Dudley or Wigan or East Riding or South Lanarkshire or Coventry or Belfast or Leicester or Sunderland or Sandwell or Doncaster or Stockport or Sefton or Nottingham or Newcastle upon Tyne or Kingston upon Hull or Bolton or Walsall or Plymouth or Rotherham or Stoke on Trent).in.
28. (London or Birmingham or Leeds or Glasgow or Sheffield or Bradford or Liverpool or Edinburgh or Manchester or Bristol).tw.
29. (Kirklees or Fife or Wirral or North Lanarkshire or Wakefield or Cardiff or Dudley or Wigan or East Riding or South Lanarkshire or Coventry or Belfast or Leicester or Sunderland or Sandwell or Doncaster or Stockport or Sefton or Nottingham or Newcastle upon Tyne or Kingston upon Hull or Bolton or Walsall or Plymouth or Rotherham or Stoke on Trent).tw.
30. or/22–29
31. 16 and 21 and 30

Limit to year 2003 onwards

32. limit 31 to yr='2003 – 2008'
33. (review or editorial or comment).pt.
34. 32 not 33

Qualitative search 2

Secondly, the following search was undertaken to identify qualitative studies relating to chemoprevention and colorectal cancer.

Terms for colorectal cancer

1. exp Colorectal Neoplasms/
2. exp Rectal Neoplasms/
3. Colonic Polyps/
4. exp Intestinal Polyps/
5. exp Adenomatous Polyps/
6. or/1-5
7. exp Colon/
8. exp Rectum/
9. (colorect\$or colon\$or rectum\$or rectal\$or rectosigmoid\$or adenomatous).tw.
10. 7 or 8 or 9
11. (neoplas\$or cancer\$or carcinoma\$or adenocarcinoma\$or malignan\$or tumor\$or tumour\$or polyp\$or adenoma\$.tw.
12. exp Adenoma/

13. 11 or 12
14. 10 and 13
15. 6 or 14

Terms for chemoprevention

16. Chemoprevention/
17. chemoprevent\$.tw.
18. prevent\$.tw.
19. exp Anticarcinogenic Agents/
20. or/16-19

Terms for qualitative studies

21. interview\$.tw.
22. experience\$.tw.
23. qualitative\$.tw.
24. qualitative research/
25. or/21-24
26. 25 and 20 and 15

Limit to year 2003 onwards

27. limit 26 to yr='2003 - 2009'

Appendix 2

Study quality for effectiveness studies

TABLE 51 Aspirin: study quality

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
High-risk population (FAP/HNPCC)						
<i>Primary prevention (assessing adenoma incidence)</i>						
Burn 2008 (CAPP2 Study) ⁸⁷	191 of 937 (20%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst not stated	Y	None reported
<i>Secondary prevention (assessing reduction in adenoma burden)</i>						
Burn 2003 (CAPPI Study) ^{1,72}	73 of 206 (35%) excluded from analysis as not followed up for 1 year	Y (method not stated)	Unclear	Participants Y; caregivers not stated; analyst not stated	Unclear	50% participants (in both groups) also received resistant starch (30 mg/day)
Intermediate-risk population (history of adenomas or colorectal cancer)						
Logan 2008 (ukCAP trial: United Kingdom Colorectal Adenoma Prevention) ⁶⁰	92 of 945 (10%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	50% patients (in both groups) also received folic acid 0.5 mg/day, but no evidence of interaction
Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	37 of 1121 (3%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y (except slightly fewer patients in 81 mg/day aspirin group had adenoma \geq 1 cm at baseline: 81 mg/day group 29%, 325 mg/day group 34%, placebo group 33%)	50% patients (in both groups) also received folic acid 1 mg/day
Benamouzig 2003 (APACC Study) ⁶²	34 of 272 (13%) excluded from analysis as no follow-up colonoscopy	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y (except advanced adenomas at baseline: 79% in aspirin group and 68% in placebo group, $p = 0.04$)	None reported
Sandler 2003 ⁷⁹	118 of 635 (19%) excluded from analysis as no follow-up colonoscopy	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	None reported

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
Low-risk population (general population or no increased risk of colorectal cancer)						
Cook 2005 (Women's Health Study) ⁶⁸⁻⁷⁰	0 of 39,876 (0%) excluded from analysis (colonoscopy not required for follow-up)	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst not stated	Y	50% patients (in both groups) received vitamin E for 10 years and 50% received beta-carotene for 2 years. No significant difference in aspirin effect in participants who were or were not receiving vitamin E or beta-carotene
Gann 1993 (Physicians' Health Study, PHS) ⁷⁵	0 of 22,071 (0%) excluded from analysis (colonoscopy not required for follow-up)	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	Half of patients (in both groups) received beta-carotene. No results presented for effect of aspirin according to whether receiving beta-carotene
Farrell 1991 (UK-TIA Aspirin Trial) ^{71,77}	0 of 2435 (0%) excluded from analysis (colonoscopy not required for follow-up)	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	None reported
Peto 1988 (British Doctors Aspirin Trial) ^{71,80}	0 of 5139 (0%) excluded from analysis (colonoscopy not required for follow-up)	Y (method not stated)	Unclear (method not stated)	Participants No (open-label); caregivers No; analyst Y for long-term follow-up	Y	None reported
Y, yes.						

TABLE 52 Non-aspirin NSAIDs: study quality

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/other factors that may influence outcome
High-risk population (FAP/HNPCC)						
<i>Primary prevention (assessing adenoma incidence)</i>						
Giardiello 2002 ⁸³	None	Y (method not stated)	Unclear	Described as double	Unclear (no statistical tests; mean age of placebo arm 26 years vs 21 years in treatment arm)	None
<i>Secondary prevention (assessing reduction in adenoma burden)</i>						
Giardiello 1993 ⁹¹	None	Y (method not stated)	Unclear	Described as double	Y	None
Labayle 1991 ⁹⁴	None	Y (method not stated)	Unclear	Described as double	Y	None
Iwama 2006 ⁸⁵	1 of 61 (2%)	Y (method not stated)	Unclear	Described as double	Y	None
Nugent 1993 ⁹³	Unclear	Y (method not stated)	Adequate (sealed cards)	Patients blind, unclear for others	Y	None
Steinbach 2000 ⁸⁹	None	Y (method not stated)	Unclear	Described as double	Statistically significant difference in the age profile ($p=0.04$). Mean (Standard Deviation) ages: Placebo 39.9 (± 11.3); 100mg celecoxib 38.6 (± 10.0); 400mg celecoxib 33.1 (± 10.0)	None

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/other factors that may influence outcome
Intermediate-risk population (history of adenomas)						
Arber 2006 (PreSAP Study) ^{63,84}	164 of 1561 (11%) excluded from analysis as no follow-up colonoscopy at year 1 or year 3	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers unclear; analyst Y	Y (slightly more subjects with history of cardiovascular events in celecoxib group: 13.7% vs 11.1%)	Patients instructed to abstain from long-term NSAID use (> 21 days per year) but permitted to take cardioprotective doses of aspirin (≤ 162.5 mg/day or ≤ 325 mg every other day). Adenoma recurrence in patients taking or not taking aspirin similar to that in all patients
Bertagnolli 2006 (APC trial) ^{64,84,86,87}	213 of 2035 (10%) excluded from analysis as no follow-up colonoscopy at year 1 or year 3	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers unclear; analyst Y	Y	Patients instructed to abstain from long-term NSAID use (> 21 days per year) but permitted to take cardioprotective doses of aspirin (≤ 162.5 mg/day or ≤ 325 mg every other day). Adenoma recurrence in patients taking or not taking aspirin similar to that in all patients
Ladenheim 1995 ⁹⁰	0 of 44 (0%) excluded from analysis	Y (method not stated)	Y (investigators blinded)	Participants Y; caregivers Y; analyst Y	Y except sulindac group slightly older (66.5 years vs 62.2 years, $p = 0.06$) and mean number of polyps at baseline slightly but significantly higher in sulindac group [sulindac 2.0 (± 1.5), placebo 1.3 (± 0.9), $p < 0.005$]	36% in sulindac group and 18% in placebo group were taking 80 mg or 325 mg aspirin tablets routinely for cardiac reasons at baseline; this aspirin was discontinued for duration of study
Low-risk population (general population or no increased risk of colorectal cancer)						
No relevant studies						
Y, yes.						

TABLE 53 Folic acid: study quality

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/other factors that may influence outcome
High-risk population (FAP/HNPCC)						
No relevant studies						
Intermediate-risk population (history of adenomas)						
Jaszewski 2008 ⁰⁸	43 of 137 (31%) excluded from analysis as no follow-up colonoscopy	Y (block stratification)	Y (sealed envelopes)	Participants Y; caregivers unclear; analyst unclear	Y	Patients instructed to abstain from long-term NSAID use (>21 days per year) but could take cardioprotective doses of aspirin (≤ 162.5 mg/day or ≤ 325 mg every other day). Adenoma recurrence in patients taking or not taking aspirin similar to all patients
Logan 2008 (ukCAP trial: United Kingdom Colorectal Adenoma Prevention) ⁶⁰	92 of 945 (10%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	50% of patients (in both arms) received aspirin 300 mg/day – no significant effect on adenoma recurrence or evidence of interaction
Cole 2007/Baron 2003 (Aspirin/Folate Polyp Prevention Study) ^{61,73,74}	34 of 1021 (3%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst unclear	Y	Some patients (in both arms) also received aspirin
Low-risk population (general population or no increased risk of colorectal cancer)						
Zhang 2008 (Women's Antioxidant and Folic Acid Cardiovascular Study: WAFACS) ⁰⁵	0 of 5442 (0%) excluded from analysis	Y (method unclear)	Y (central pharmacy)	Participants Y; caregivers unclear; analyst Y	Y	Some patients also receiving vitamin C, vitamin E and/or beta-carotene
Lonn 2006 (HOPE-TOO study) ^{106,107}	0 of 5522 (0%) excluded from analysis	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y (except lower folate levels in populations from countries without folate fortification policies)	Not reported
Zhu 2003 ^{109,110}	0 of 216 (0%) excluded from analysis	Y (method not stated)	Unclear (method not stated)	Participants unclear; caregivers unclear; analyst unclear	Y	None reported
N/A, not available; Y, yes.						

TABLE 54 Calcium and/or vitamin D: study quality

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
High-risk population (FAPI/HNPCC)						
<i>Secondary prevention (assessing reduction in adenoma burden)</i>						
Thomas 1993 ⁹⁵	3 of 28 (10.7%) were excluded from the analysis because of non-compliance	Y (method not stated)	Unclear	Stated to be double blind. Assumed to be: Participants Y; caregivers: Y; analyst Y	Unclear	Unclear
Intermediate-risk population (history of adenomas)						
Bonithon-Kopp 2000 ⁹⁶	62 of 416 (15%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers: Y; analyst Y	Y	None reported
Baron 1999 (Calcium Polyp Prevention Study) ^{99,100}	98 of 930 (11%) excluded from analysis as no follow-up colonoscopy	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers: unclear; analyst Y	Y	None reported
Hofstad 1998 ^{103,104}	23 of 116 (20%) excluded from analysis	Y (method not stated)	Unclear	Participants: unclear; caregivers: unclear; analyst: unclear	Y	Calcium and various antioxidants given to all patients in one study arm
Low-risk population (general population or no increased risk of colorectal cancer)						
Lappe 2007 ⁹⁷	92 of 1179 (8%) excluded from analysis (colonoscopy not required for follow-up)	Y (computer-generated)	Unclear	Participants: Y; caregivers: unclear; analyst: unclear	Not reported	None reported
Wactawski-Wende 2006 (Women's Health Initiative study) ¹⁰¹	0 of 36,282 (0%) excluded from analysis (colonoscopy not required for follow-up)	Y (computer-generated)	Y (central pharmacy)	Participants: Y; caregivers: Y; analyst: unclear	Y	None reported
Y, yes.						

TABLE 55 Antioxidants: study quality

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
High-risk population (FAP/HNPCC)						
No relevant studies						
Intermediate-risk population (history of adenomas)						
Baron 2003/Greenberg 1994 (Antioxidant Polyp Prevention Study) ^{11,12}	113 of 864 (13%) excluded from 4-year analysis as no follow-up colonoscopy at 4 years	Y (patients assigned to groups with blocking according to study centre only)	Unclear (method not stated)	Participants Y; caregivers Y; analyst Y	Y	None reported
Bonelli 1998 ¹⁵	71 of 304 (23%) excluded from analysis as no follow-up colonoscopy	Y (method not stated)	Unclear (method not stated)	Participants not stated; caregivers not stated; analyst not stated	Unclear as participants' characteristics not reported	None reported
Hofstad 1998 ^{103,104}	23 of 116 (20%) excluded from analysis	Y (method not stated)	Unclear (method not stated)	Participants not stated; caregivers not stated; analyst not stated	Y	Calcium
Ponz de Leon 1997 ¹²¹	37 of 140 (26%) not evaluated yet but only preliminary analysis reported	Y (method not stated)	Unclear (method not stated)	Participants not stated; caregivers not stated; analyst not stated	Unclear as participants' characteristics not reported.	None reported
Roncucci 1993 ^{121,124}	21 of 209 (10%) had no follow-up colonoscopy and 59 of 209 (28%) (including the 21 above) had no follow-up beyond 1 year, but these patients WERE included in the analysis; presumably assumed no polyps for these patients	Y (patients recruited and randomised by balanced blocks)	Unclear (method not stated)	Participants Y; caregivers Y; analyst not stated	Y	None reported

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
MacLennan 1995 (Australian Polyp Prevention Trial) ¹²⁶	105 of 411 (26%) excluded from 4-year analysis as no follow-up colonoscopy at 4 years	Y (balanced block randomisation)	Y (central pharmacy)	Participants Y (to beta-carotene, N to low fat or bran); caregivers Y; analyst Y	Y	Some patients also received low-fat diet and/or bran supplement
McKeown-Eyssen 1988 ¹²⁹	48 of 185 (26%) excluded from analysis as no follow-up colonoscopy	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers Y; analyst Y	Y	None reported
Low-risk population (general population or no increased risk of colorectal cancer)						
Gaziano 2009 (Physicians Health Study II: PHS II) ¹³	121 of 14,641 (1%) not analysed for colorectal cancer as had this cancer at baseline	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers not stated; analyst not stated	Y	Hazard ratios were adjusted for other interventions (vitamin C, vitamin E and beta-carotene)
Lippman 2009 (SELECT: Selenium and vitamin E cancer prevention trial) ¹¹⁶	645 of 35,533 (2%) excluded from primary analysis as ineligible, insufficient data or lost to follow-up	Y (block scheme)	Y (central pharmacy)	Participants Y; caregivers not stated; analyst not stated	Y	None reported
Lin 2009 (Women's Antioxidant Cardiovascular Study: WACS) ¹¹⁸⁻¹²⁰	544 of 8171 (7%) excluded from analysis due to history of cancer before enrolment	Y (method not stated)	Y (central pharmacy)	Participants Y; caregivers not stated; analyst not stated	Y	None reported
Lee 2005, Lee 1999 (Women's Health Study) ^{69,70,122,123}	0 of 39,876 (0%) excluded from analysis	Y (randomised in blocks of 16 within 5-year age strata to the two groups)	Y (central pharmacy)	Participants Y; caregivers not stated; analyst not stated	Y	None reported
Lonn 2005 (HOPE-TOO Study) ^{107,125}	0 of 9541 (0%) excluded from analysis	Y (computer-generated, fixed block size stratified by centre)	Y (central telephone randomisation)	Participants Y; caregivers Y; analyst Y	Y	Approximately 50% participants in both vitamin E and placebo groups also received ramipril angiotensin-converting enzyme inhibitor, 10 mg/day

continued

TABLE 55 Antioxidants: study quality (continued)

Study	Number (%) of randomised participants excluded from main analyses	Randomisation	Allocation concealment	Blinding (participants; caregivers; analyst)	Baseline comparability between groups	Cointerventions/ other factors that may influence outcome
Goodman 2004 (CARET Study) ^{114,127,128}	1174 of 18,314 (6.4%) excluded from analysis as 1092 had died and 82 were lost to follow-up	Y (permuted block design with random block size chosen uniformly among 8, 10, 12, 14 and 16)	Y (according to Cochrane review) ¹¹⁴	Participants Y; caregivers Y; analyst Y	Y	None reported
Herberg 2004 (SU.VI.MAX Study) ^{114,130-132}	1567 of 13,017 lost to follow-up (12%)	Y (computer generated, block sequence generation stratified by sex and age group)	Y (capsule boxes were labelled with patient's number)	Participants Y; caregivers Y; analyst Y	Y	None reported
Zhu 2003 ^{109,110}	0 of 216 (0%) excluded from analysis	Y (method not stated)	Unclear (method not stated)	Participants not stated; caregivers not stated; analyst not stated	Y	None reported
Virtamo 2003/Mailla 1999 (ATBC Study: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) ³³⁻¹³⁶	0 of 15,538 (0%) excluded from adenoma analysis; 0 of 29,133 (0%) excluded from CRC analysis	Y (block randomisation, blocks of eight within each study area)	Unclear (method not stated)	Participants Y; caregivers not stated; analyst not stated	Y	None reported
Duffield-Lillico 2002 (NPCT: Nutritional Prevention of Cancer Trial) ¹³⁷⁻¹³⁹	62 of 1312 (5%) excluded from analyses as no valid baseline selenium values	Y (blocked on time and stratified by clinic)	Y (central pharmacy)	Participants Y; caregivers Y; analyst not stated	Y	None reported
HPS Group 2002 (Heart Protection Study: HPS) ^{114,140,141}	67 of 20,536 (0.3%) excluded from analysis. Participants without information to end of the scheduled treatment period for mortality and morbidity were excluded from analysis	Y (computer-generated)	Y (central telephone randomisation system)	Participants Y; caregivers Y; analyst Y	Y	Approximately 50% participants in both intervention and placebo groups also received simvastatin, 40 mg/day
Hennekens 1996 (Physicians Health Study: PHS) ¹⁴²	0 of 22,071 (0%) excluded from analysis	Y (computer-generated)	Y (central pharmacy)	Participants Y; caregivers not stated; analyst Y	Baseline characteristics are not reported in sufficient detail	None reported

Y, yes.

Appendix 3

Data extraction form for qualitative studies

Data extracted by:	Date:	Ref ID:
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Full paper screen

Question		If Yes	If No
1	Is the study 2003 onwards	Continue	Exclude
2	Does the intervention being evaluated include one or more of the following: aspirin, NSAIDs, vitamins, minerals, calcium, folic acid, dietary supplements generally	Continue	Exclude
3	Does the study report, as an outcome, people's attitudes, perceptions or beliefs concerning the taking of one or more of the agents listed above	Continue	Exclude
		Include	

Note: any population group may be included.

Data extraction

Study details	Location/country
Participants	Research question/objectives Population Age (mean/range) Mean Range Gender Male (n) Female (n) Not specified (n) Ethnicity Recruitment/sampling (e.g. inclusion criteria, response rate, test of any differences between those who participated and those who did not)
Intervention	Agents/nutrients
Outcomes	What is being evaluated?
Data collection	Method (e.g. survey, focus group, interviews) Validation and recording (e.g. is survey tool validated; are interviews transcribed and is respondent validation used?)
Analysis	Method [e.g. descriptive statistics (%) reported only; analysis of transcripts employing a stated method]
Results	Themes from conceptual framework Data (must be verbatim quotes or authors' statements clearly based on data) <ol style="list-style-type: none"> 1. Family factors affecting perceived need 2. Personal factors affecting perceived need 3. Media representations of perceived need 4. Spending capacity 5. Media input into decision-making

	<ol style="list-style-type: none"> 6. Physicians' input into decision-making 7. Family members' input into decision-making 8. Community input into decision-making 9. Pharmacy input into decision-making 10. Access: obtaining micronutrients 11. Perceived benefits 12. Perceived risks (negative factors) 13. Habitual use 14. Intermittent use 	
	New themes (i.e. data from studies that are not relevant to any of the preset themes)	Data
	<ol style="list-style-type: none"> 1. New theme 2. New theme 3. New theme 4. New theme 	
Comments	Limitations, reviewer comments etc.	
References	Possible new includes Background papers	

Appendix 4

Model

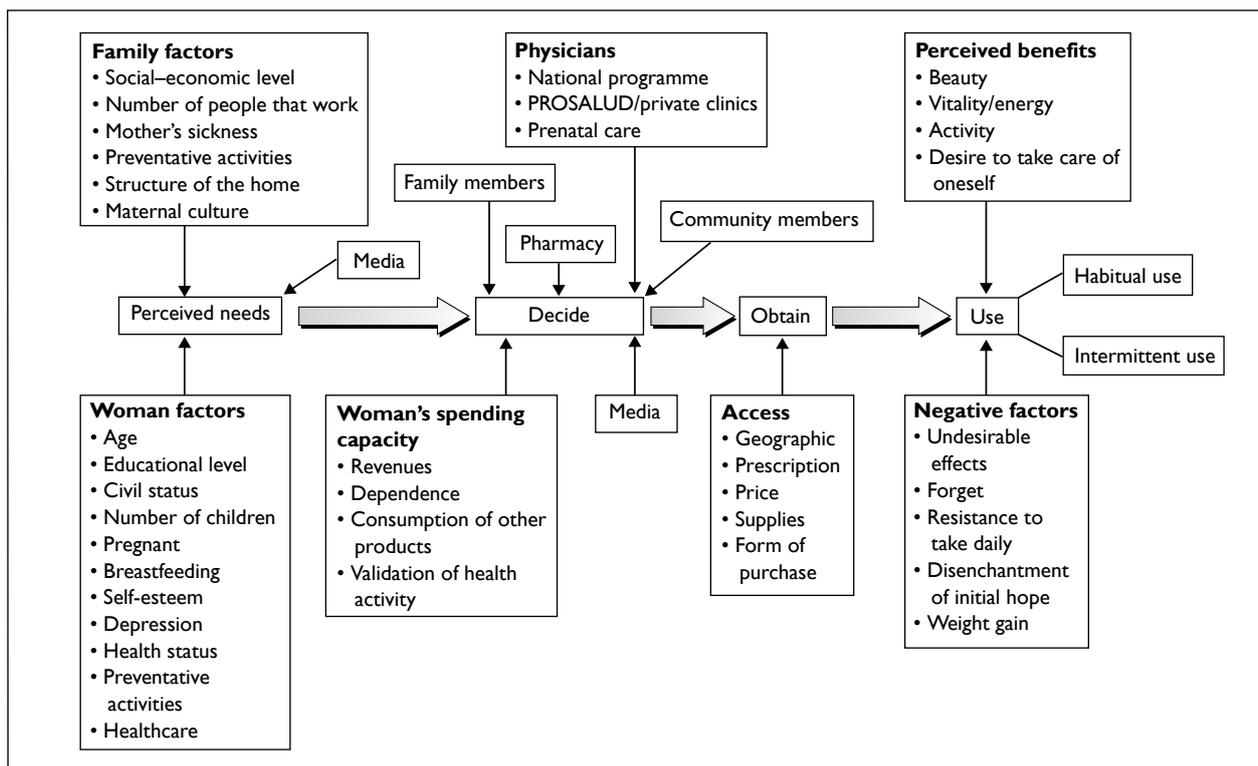


FIGURE 29 Conceptual model by Huffman,¹⁸² reproduced with permission from S Huffman.

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