Chemoprevention of colorectal cancer: systematic review and economic evaluation

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Executive summary

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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.

Publication

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NIHR Health Technology Assessment programme

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