ORIGINAL ARTICLE

Primary prevention of colorectal cancer with low-dose aspirin in combination with endoscopy: a cost-effectiveness analysis

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ABSTRACT

Objective Low-dose aspirin reduces colorectal cancer (CRC) incidence and mortality. Recently, the aspirin effect has been shown to occur primarily in the proximal colon. Colonoscopy has been either less effective or ineffective in the proximal compared to the distal colon. The authors assessed the cost-effectiveness of adding low-dose aspirin to a simulated screening with colonoscopy or sigmoidoscopy.

Design A Markov model comparing the strategies of 10-year colonoscopy or sigmoidoscopy screening and the combination of either of the two with low-dose aspirin in 100 000 subjects aged 50 years until death was constructed. Proximal and distal CRC prevention rates with endoscopy or aspirin were extracted from the literature. Screening and aspirin prevention were simulated to stop at 80 years. The cost of aspirin and aspirin-related complications, as well as aspirin-related mortality, was included. Incremental cost-effectiveness ratios between the different strategies were calculated. Sensitivity and probabilistic analyses were also performed.

Results The addition of low-dose aspirin to colonoscopy and sigmoidoscopy screening increased the CRC death prevention rate from 68% and 39% to 81% and 69%, respectively. Lifetime aspirin-related mortality appeared to be 0.1%. Because of the substantial reduction in CRC care, the addition of aspirin to colonoscopy and sigmoidoscopy screening was cost-effective (incremental cost-effectiveness ratio: US$5413 per life-year saved) and cost saving (US$278 per person), respectively. When the proximal CRC prevention rate with colonoscopy was increased 56% to 73% from the baseline, the addition of aspirin was no longer cost-effective. The addition of aspirin to colonoscopy and sigmoidoscopy was a cost-effective strategy in 52% and 94% of the scenarios at probabilistic analysis.

Conclusions When assuming a suboptimal efficacy of endoscopy in preventing CRC, the addition of low-dose aspirin may be an effective and cost-effective strategy, mainly because of its high efficacy in preventing proximal CRC.

Significance of this study

What is already known on this subject?

- In population studies, colonoscopy screening has been shown to be either less effective or ineffective in preventing right-sided compared to left-sided cancer. Similarly, sigmoidoscopy screening was not associated with any proximal colorectal cancer (CRC) prevention
- In randomised studies, low-dose aspirin was shown to reduce CRC incidence and mortality by 38% and 52%, respectively
- The effect of low-dose aspirin appeared also to be site-specific, resulting in a high rate of proximal CRC prevention, while no distal CRC prevention was observed

What are the new findings?

- In a simulation model, the addition of low-dose aspirin to colonoscopy and sigmoidoscopy screening resulted in an additional 13% and 30% reduction in CRC mortality, respectively
- The substantial economic saving in CRC care compensated for the additional cost of low-dose aspirin and aspirin-related complications, with the addition of aspirin being cost-effective
- When assuming an increase in the colonoscopy-related proximal CRC prevention rate in the sensitivity analysis, the addition of aspirin did not become cost effective

How might it impact on clinical practice in the foreseeable future?

- In settings where colonoscopy is less effective or ineffective in preventing proximal colon cancer, the addition of low-dose aspirin may be an effective and cost-effective strategy, mainly because of its high efficacy in preventing proximal CRC

INTRODUCTION

Colorectal cancer (CRC) represents a major cause of morbidity and mortality in Western countries, also resulting in a substantial economic burden due to costs for surgery, chemotherapy and terminal care.[1 2]

In a 20-year follow-up of high-quality randomised trials on cardiovascular prevention including over 14 000 patients, ≥5-year treatment with low-dose aspirin (75–300 mg daily) was shown to reduce CRC incidence and mortality by 38% and 52%, respectively.[3] This result was consistent with previous randomised and observational studies showing the efficacy of high-dose aspirin in preventing CRC/adenoma incidence in patients at average or increased risk of CRC.[4–6] The effect of low-dose aspirin also appeared to be site-specific,

resulting in a high rate of proximal CRC prevention, while no distal CRC prevention was observed.[3] Compared to high-dose aspirin, which has also been effective in preventing CRC, low-dose aspirin may also be expected to reduce aspirin toxicity, including its potentially life-threatening side effects.[7]

CRC screening by means of endoscopy has been shown to prevent CRC incidence and mortality.[8–10] This has been related to the efficacy of polypectomy in preventing CRC incidence and the increase in 5-year CRC survival because of early diagnosis of already-developed CRC.[8–10] A high-quality randomised trial showed the efficacy of flexible sigmoidoscopy in reducing CRC incidence and mortality by 33% and 43%, respectively, in screening-attendant average-risk subjects.[11] A substantial difference between distal and proximal CRC protection by colonoscopy screening has also been shown. While confirming a substantial reduction in distal CRC incidence and mortality, population-based studies found a reduced, if any, prevention of proximal CRC.[12–14] This effect was operator dependent, and gastroenterologists achieved better protection in the proximal colon than did surgeons and primary care physicians performing colonoscopy.[15] In a German-based study, colonoscopy by gastroenterologists produced a 56% reduction in proximal cancer and an 84% reduction in distal cancer.[12] Thus, colonoscopy has been either less effective or ineffective in preventing right-sided compared to left-sided cancer, with the variation likely explained by operator performance.[12 15]

No randomised trial compared the potential efficacy and costs of a primary CRC prevention with low-dose aspirin with those of an endoscopic screening, preventing definitive assumptions on the relative efficacy and interaction between the two strategies. Microsimulation models may partially compensate for the lack of clinical data, simulating the comparison and possible interaction among different preventive strategies based on the available, albeit incomplete, knowledge.[16]

The aim of this cost-effectiveness analysis was to assess the efficacy and costs of CRC primary prevention with low-dose aspirin in average-risk subjects, also assessing its potential interaction with an endoscopic screening, when assuming subsite-specific efficacies for the different strategies.

METHODS

The primary end points of this analysis address the following:

1. Is the addition of low-dose aspirin to colonoscopy screening cost-effective, when assuming a suboptimal colonoscopy-related proximal CRC protection?
2. Is the addition of low-dose aspirin to sigmoidoscopy screening cost-effective, when assuming no sigmoidoscopy-related proximal CRC protection?
3. What is the minimum level of colonoscopy-related proximal CRC protection at which aspirin addition is not cost-effective?

The secondary end points of this analysis address the following:

1. Is primary prevention with low-dose aspirin cost-effective as compared to no screening or endoscopic screening?
2. Is sigmoidoscopy or colonoscopy screening cost-effective when added to patients who have already taken aspirin for cardiovascular prevention?

To address these issues, we simulated primary prevention with low-dose aspirin and secondary prevention with either colonoscopy or sigmoidoscopy screening, as well as the possible interaction between the two, in a theoretical cohort of 100 000 male and female American citizens from 50 to 100 years of age generated by a Markov model (supplementary figure 1). Age-/size-/site-specific prevalences of non-advanced and advanced adenomas, as well as of hyperplastic polyps, were matched with estimates from autopsy and endoscopic data in order to compute the costs related with polypectomy and follow-up when an endoscopic screening was simulated (online appendices 1 and 2). In detail, endoscopic screening was simulated to be repeated every 10 years between 50 and 80 years of age, with postpolypectomy surveillance differing according to polyp size and histology.[8–10] Age- and site-related CRC incidence and mortality were integrally assumed from SEER (Surveillance, Epidemiology and End Results) database for the natural history cohort.[17] Overall and site-specific reduction of CRC incidence and mortality by primary prevention with aspirin and/or endoscopic screening were extracted from the available literature.[3 11 12] Natural attrition by the annual age-specific death rate of the US population was also simulated.[18]

Primary prevention was simulated as the daily administration of 75 mg of aspirin between 50 and 80 years of age (this dose was chosen since it is as effective as higher doses).[3] According to the recent pooling of randomised trials, CRC incidence and mortality were assumed to be reduced by 38% and 52%, respectively, by aspirin prevention.[3] This prevention appeared to be limited to a 65% and 76% reduction in incidence and mortality of proximal CRC and, to a lesser extent, to a 42% and 53% reduction for rectal cancer, respectively, while no protection for distal CRC was found.[3] This site-specific pattern was adopted in the reference case scenario. Because of the delayed effect of aspirin on CRC prevention, aspirin efficacy was simulated to begin only after 5 years of daily administration.[3 5 19] Aspirin efficacy has been shown to last for several years after treatment cessation.[3 5 19] Since we assumed a 10-year duration for the efficacy of endoscopic screening, we preferred to simulate the same duration for the post-treatment effect of aspirin prevention. The mechanism of action of aspirin on colorectal carcinogenesis is yet to be clarified. Consequently, we assumed independence between the (adenomatous) polyp and CRC compartments, so that any aspirin-related reduction of CRC incidence or mortality was not associated with a corresponding decrease in age- and size-specific polyp prevalences in the reference case scenario, while this possibility was explored in the sensitivity analysis. Since we integrally applied the estimates of CRC prevention shown by the pooling of cardiovascular trial to our simulated cohort of subjects undertaking CRC screening, we implicitly assumed the same compliance with aspirin treatment between the two conditions (ie, cardiovascular and CRC primary prevention). Previous studies on prevention of post-polypectomy adenomatous recurrence with aspirin showed indeed a very similar compliance with aspirin treatment to that achieved in the trials on cardiovascular prevention.[6 20]

Efficacy of the simulated screening with colonoscopy was adopted from a recent population-based case–control study, in which screening colonoscopy was shown to prevent 56% and 84% of proximal and distal (including the rectum) CRC, respectively.[12] Since proximal CRC protection is likely to be operator dependent, and no practical reduction of CRC incidence and mortality in the first 10 years following a negative colonoscopy was shown in other studies,[13 14] a progressive reduction of proximal CRC prevention by colonoscopy has been simulated in the sensitivity analysis. Efficacy of sigmoidoscopy screening has been integrally adopted from a recent randomised trial on flexible sigmoidoscopy.[11] In detail, we assumed a 50% reduction in distal CRC incidence, while the degree of reduction in distal CRC mortality was calibrated in order to match the 43% overall CRC mortality prevention reported from this study (ie, the study did not separately reported data on CRC mortality for

proximal and distal CRC).[11] When the addition of aspirin on endoscopic screening (or vice versa) was simulated, we applied the CRC prevention rates of aspirin over the residual CRC risk remaining in the population after assuming the initial efficacy of sigmoidoscopy or colonoscopy screening.

Complications were simulated for all the strategies. Endoscopy complications and related death rates were adopted from a recent US-based survey.[21] Upper gastrointestinal bleeding (UGB), haemorrhagic stroke and related mortality with low-dose aspirin were estimated from the literature, as detailed in online appendix 1.

Costs

Reimbursement data for direct costs of endoscopy and related complications, as well as for stage-specific CRC treatment, were based on Medicare data.[22 23] One-year wholesale cost for a daily administration of 75 mg (81 mg) aspirin was estimated to be US$3 at the Indiana University Medical Center pharmacy, Indianapolis, Indiana, USA. The cost of aspirin-related complications, namely, UGB and haemorrhagic stroke, was also included (see appendix 1). All costs were adjusted to 2010 US dollars using the Medical Consumer Price Index.[23]

Cost-effectiveness analysis

The clinical effectiveness of screening is measured in terms of life-years gained through prevention or downstaging of all the included diseases. In the natural history and screening models, the life-years lost by the age-dependent proportion of patients dying prematurely of CRC or aspirin-related complications are accumulated for each cycle during the entire expected lifetime. The number of life-years gained by screening corresponds to the difference in life-years lost from CRC between a Markov model with and one without screening. Future costs and future life-years saved were discounted using an annual rate of 3%. Strategies that were more costly and less effective were ruled out by simple dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out by weak dominance. The relative performance of the remaining strategies was measured using the incremental cost-effectiveness ratio (ICER), defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next least expensive strategy. An ICER of US$50 000 per life-year gained was used as willingness-to-pay threshold to differentiate an efficient procedure from an inefficient one.[24] Since the cost-effectiveness of the addition of aspirin over endoscopy is independent from the initial adherence to endoscopy screening, being equally applied to the two strategies, we assumed a 100% adherence to initial endoscopic screening in order to simplify the interpretation of the model outcomes. However, we simulated different rates of initial adherence in online appendix 3.

Sensitivity analysis

One- and two-way sensitivity analyses were performed for all the variables of the model, with the results being reported for those most relevant (see online appendix 4). To estimate the distribution of expected costs and efficacies of the screening strategies dependent on the uncertainty in the input parameters, we used Monte Carlo simulation to repeatedly sample from the distributions assigned to all the uncertain parameters shown in online appendix 1. In detail, β distributions were chosen for accuracy and adherence parameters, triangular distributions for costs and lognormal for the natural history transition rates. The model was simulated by using Excel spreadsheets (Microsoft Corp., Redmond, Washington, USA) and @risk 5.0 (Palisade Corp., Ithaca, New York, USA). All the input assumptions and corresponding ranges have been reported in online appendix 1.

RESULTS

Reference case scenario

As shown in table 1, in the no-screening simulation, 5903 CRC cases and 2482 CRC-related deaths occurred in the simulated cohort of 100 000 American subjects, resulting in the loss of 31 839 undiscounted life-years. Costs in the no-screening simulation were purely related with the expenditure for CRC care, with an estimate of US$2227 per person (table 1).

Endoscopic screening

Efficacy

Simulation of sigmoidoscopy and colonoscopy screening every 10 years (four rounds between 50 and 80 years of age) in the cohort of 100 000 subjects resulted in a 39% and 68% reduction in CRC mortality, respectively (table 1). The higher efficacy of colonoscopy screening was due to the 56% prevention rate for right-sided CRC (no effect of sigmoidoscopy on proximal CRC being assumed) and the higher left-sided CRC prevention rate simulated with colonoscopy. Sigmoidoscopy and colonoscopy efficacy resulted in 7945 and 13 922 discounted life-years gained, respectively, corresponding to 29 and 51 days per person (table 1).

Table 1 Cost, effect and net benefit for all the included strategies for a cohort of 100 000 subjects invited for screening

	No screening	Aspirin	Sigmoidoscopy	Sigmoidoscopy and aspirin	Colonoscopy	Colonoscopy and aspirin
CRC cases (n)	5903	3858	4078	2487	1759	1105
CRC prevented (n)	—	2045	1824	3415	4014	4605
CRC prevention rate (%)	—	35	31	58	68	78
CRC deaths (n)	2482	1458	1503	779	803	477
CRC death prevention rate (%)	—	41	39	69	68	81
Life-years gained (n)	—	6232	7945	12 215	13 922	15 108
Gain in life expectancy per person (days)	—	23	29	45	51	55
Screening cost (US$ per person)	—	299	1293	1596	2486	2788
Care for CRC (US$ per person)	2227	1492	1524	944	619	381
Total (US$ per person)	2227	1791	2817	2540	3105	3169
ICER vs no screening (US$ per life-year gained)	—	Dominates (saving US$436 per person)*	7434	6511	6307	6237

*When a strategy was more effective and less costly than no screening (no screening being dominated), saving per person instead of the ICER was provided.
CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio.

Costs

Colonoscopy screening resulted in a substantial decrease in CRC treatment costs when compared with no screening (US$620 per person vs US$2227 per person at 3% discounting rate). This was offset by the cost of screening and follow-up testing (US$2486 per person at 3% discounting rate), resulting in an overall discounted cost per person of US$3105 (table 1). The reduced efficacy of sigmoidoscopy as compared to colonoscopy resulted in a smaller reduction of CRC cost (US$1524 per person). However, its reduced cost resulted in a lower cost of screening and follow-up (US$1293 per person), so that the overall cost of sigmoidoscopy (US$2817 per person) was slightly lower than that of colonoscopy (table 1).

Cost-effectiveness

When comparing endoscopic strategies with the no-screening scenario, sigmoidoscopy and colonoscopy screening appeared to be a cost-effective alternative with an ICER of US$7434 and US $6307 per life-year saved, respectively (table 1).

Addition of low-dose aspirin to endoscopic screening

Efficacy

The addition of low-dose aspirin between 50 and 80 years to sigmoidoscopy and colonoscopy strategies resulted in a 69% and 81% overall reduction in CRC mortality, respectively (table 1). The absolute differences of 30% and 13% with the corresponding values of the sigmoidoscopy and colonoscopy strategies without aspirin were due to the efficacy of aspirin in preventing 76% of proximal CRC mortality and—to a lesser extent—to a synergistic effect between the combined strategies on rectal cancer. The beneficial effect of aspirin was partially offset by the occurrence of 2110 and 513 major UGB and haemorrhagic stroke, respectively, corresponding to a lifetime risk of 2.1% and 0.5% for the entire cohort, resulting in 137 (0.1% as lifetime risk) deaths due to aspirin complications. Most of the aspirin-related deaths (105 of 137) were simulated to occur in subjects ≥65 years of age because of the higher risk of UGB assumed as compared to those younger than 65 years. Overall, the addition of aspirin primary prevention to sigmoidoscopy and colonoscopy screening resulted in 12 215 and 15 108 discounted life-years gained, respectively, corresponding to an absolute difference of 4270 and 1186 life-years saved with sigmoidoscopy and colonoscopy screening. Such a difference was due to the 5616 and 2533 life-years saved because of the increased CRC prevention as compared to sigmoidoscopy and colonoscopy strategies, compensated by the loss of 1346 life-years because of aspirin-related mortality (table 1).

Costs

The increased CRC prevention also reduced the cost for CRC treatment to US$944 per person and US$381 at 3% discounting rate, corresponding to a net saving of US$580 per person and US $238 as compared to sigmoidoscopy and colonoscopy (without aspirin) strategies. This was offset by the additional lifetime cost of aspirin (75 mg daily) corresponding to US$53 per person, as well as by the additional cost due to aspirin-related complications corresponding to US$249 per person (table 1).

Cost-effectiveness

Overall, the combination of aspirin and sigmoidoscopy screening was less costly and more effective than sigmoidoscopy screening only, so that the combined strategy was more cost-effective than sigmoidoscopy (ie, dominated), resulting in a net discounted saving of US$278 per person. The combined strategy was also cost-effective as compared to no screening, with an ICER of US$6511 per life-year saved (table 1), as well as when compared with an aspirin (without sigmoidoscopy) strategy (table 2).

Colonoscopy strategy (without aspirin) was more effective and cost-effective than the combined sigmoidoscopy and aspirin strategy (ICER: US$33 126). Moreover, the combination of aspirin and colonoscopy screening was more costly and more effective than colonoscopy screening only and was more cost-effective as well (ICER: US$5413, figure 1). The combined strategy was also cost-effective as compared to no screening, with an ICER of US$6237 per life-year saved (table 1), and to aspirin/sigmoidoscopy (ICER: US$21 765, table 2).

As shown in table 1, primary prevention with low-dose aspirin (ie, without colonoscopy) appeared to be cost saving as compared to no screening, with the saving in CRC treatment being larger than the expenditure in the drug and drug-related complications. The overall saving was US$436 per person.

When simulating the addition of either sigmoidoscopy or colonoscopy screening to patients already undertaking a primary cardiovascular prevention with low-dose aspirin, such addition appeared to be cost-effective, with an ICER of US$12 509 and US$15 526 per life-year saved, respectively.

Sensitivity analysis

Efficacy

As shown in figure 2, when assuming an increase in the colonoscopy-related proximal CRC prevention from the baseline value of 56% to 73%, the addition of aspirin to a colonoscopy strategy was no longer cost-effective (ICER >US$50 000 per life-year saved).

The cost-effectiveness of colonoscopy (without aspirin) screening was also penalised by the assumption of a synergistic

Table 2 Cost-effectiveness of the different strategies for CRC screening in the simulated cohort of 100 000 American subjects

Strategy	Life-years saved	Cost (US$)	Δ Life-years saved	Δ Cost (US$)	ICER (US$ per life-year saved)
No screening	—	222 705 301	—	—	—
Aspirin	6232	179 120 901	6232	−43 584 400	Dominates (saving US$436 per person)*
Sigmoidoscopy	7945	281 768 855	—	—	—
Aspirin/sigmoidoscopy	12 215	253 964 689	5983	74 843 788	12 509†
Colonoscopy	13 922	310 511 159	—	—	—
Aspirin/colonoscopy	15 108	316 932 044	2893	62 967 355	21 765‡

Relative ICERs have been calculated only for non-dominated strategies. Costs and life-years have been discounted at 3% per year. ICERs of strategies ruled out by weak or strong dominance were not reported.
Δ life-years saved/costs indicate the incremental number of life-years gained/costs compared with the next-best non-dominated strategy.
*When a strategy was more effective and less costly than the less cost-effective strategy (ie, the latter being dominated), saving per person instead of the ICER was provided.
†It represents the ICER between aspirin/sigmoidoscopy and aspirin strategies, sigmoidoscopy alone being dominated by aspirin/sigmoidoscopy.
‡It represents the ICER between aspirin/colonoscopy and aspirin/sigmoidoscopy strategies, colonoscopy alone being less cost-effective (ie, weak dominance) than aspirin/colonoscopy.
CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio.

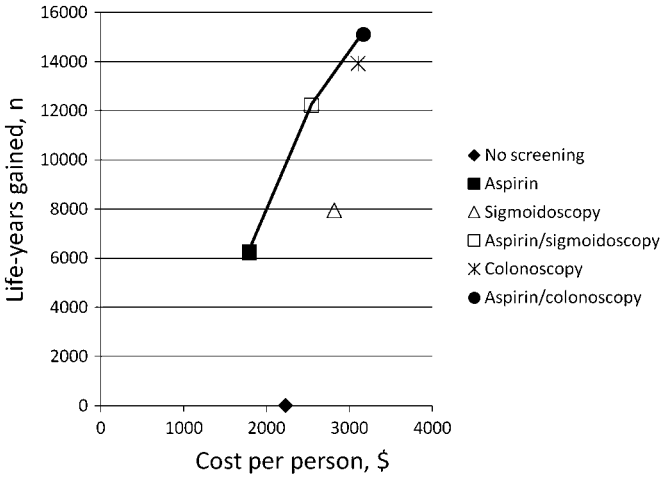

Figure 1 Cost-effectiveness among the different strategies, according to the reference case scenario. Non-dominated strategies are connected by a continuous line.

effect between colonoscopy and aspirin on rectal cancer. In the two-way sensitivity analysis, when assuming no aspirin-related rectal cancer prevention, a 64% colonoscopy-related prevention of proximal CRC was sufficient to increase the ICER of the combined strategy above US$50 000 per life-year saved (ie, the addition of aspirin being cost-ineffective). Alternatively, a decrease in the aspirin-related prevention of proximal CRC incidence and mortality to 42% was required for the combined aspirin/colonoscopy strategy to become not cost-effective.

The cost-effectiveness of the combined aspirin/sigmoidoscopy was robust to any plausible change in the efficacy of aspirin in preventing proximal CRC or any of the two in preventing distal CRC.

When assuming no proximal CRC prevention rate by colonoscopy, the addition of aspirin to a colonoscopy strategy became cost saving, with an earning of US$179 per person, as indicated in figure 2, according to which the ICER between the two strategies became negative (ie, the addition of aspirin being cost saving) for values of colonoscopy-related proximal CRC prevention rate lower than 50%. In this worst-case scenario for colonoscopy, the superiority of the combined aspirin/colonoscopy strategy was substantially more robust to changes in the aspirin-related complication rates, with a 4.5- and 2.6-fold increase in the aspirin-related UGB risk and stroke being required to increase the ICER between the two strategies above US $50 000 per life-year saved (figure 3A,B).

In the reference case scenario, CRC screening with any strategy was simulated to end at 80 years of age. When anticipating such an end to 70 years, the addition of aspirin over colonoscopy remained cost-effective and cost saving when compared with colonoscopy (ICER: US$13 299) and flexible sigmoidoscopy, respectively.

The cost-effectiveness of the addition of aspirin was penalised by the assumption of no aspirin-related reduction of polyp prevalence. Indeed, any reduction of polyp prevalence would

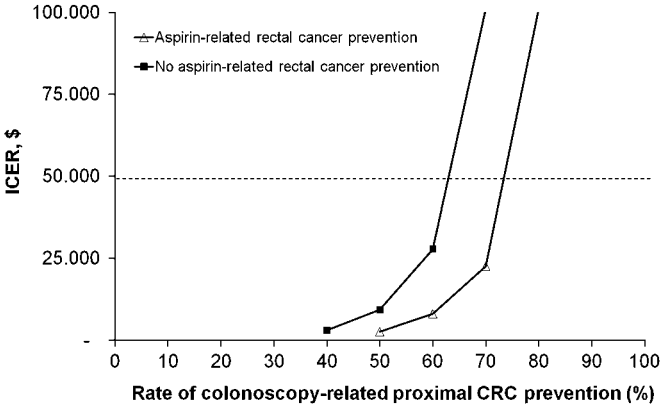

Figure 2 Sensitivity analysis. The cost-effectiveness of aspirin addition to colonoscopy screening according to proximal CRC prevention rate by colonoscopy. As shown in the figure, an increase in the proximal CRC prevention with colonoscopy was able to increase the ICER of the addition of aspirin versus colonoscopy (without aspirin) over US$50 000 per life-year gained, with the addition of aspirin being cost-ineffective in this scenario (see text). On the other hand, a decrease below 50% was required for the combined colonoscopy/aspirin strategy to become cost saving, including the possibility of no proximal (ie, 0%) CRC prevention rate by colonoscopy. The required rate of colonoscopy-related proximal CRC incidence and mortality prevention was substantially reduced when assuming no aspirin-related rectal cancer prevention (see text). Data above 64% for the latter scenario were not shown because they are negative (ie, colonoscopy without aspirin being more effective and less costly). CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio.

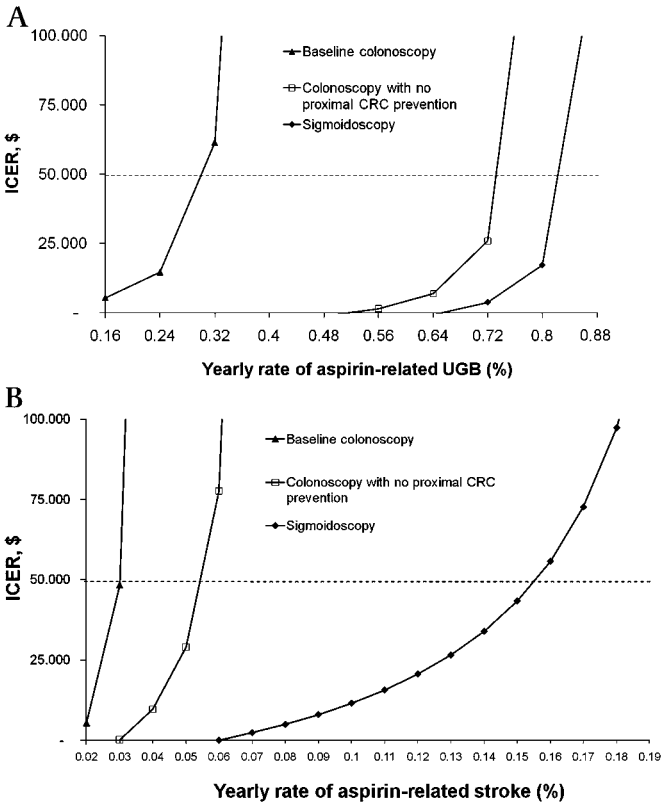

Figure 3 Sensitivity analysis. The cost-effectiveness of aspirin addition to colonoscopy and sigmoidoscopy screening was related with the simulated risk of aspirin-related UGB (A) and haemorrhagic stroke (B). As shown in the figure, a linear increase in UGB (represented as yearly risk in subjects over 65 years of age) and stroke complication risks affected the baseline cost-effectiveness of aspirin addition, rendering colonoscopy/sigmoidoscopy alone progressively more cost-effective (see text). Data below the x-axis are not shown because they are negative (ie, addition of aspirin cost saving). The addition of aspirin was substantially less sensitive to an increase in aspirin-related complications when no proximal CRC prevention by colonoscopy was assumed. CRC, colorectal cancer; UGB, upper gastrointestinal bleeding.

result in smaller cost of polypectomy and postpolypectomy surveillance. When assuming a 17% aspirin-related reduction of polyp prevalence, the addition of aspirin to colonoscopy became cost saving.

When assuming a suboptimal compliance with aspirin treatment, the relative ICERs of combined versus endoscopic strategies were unaffected, influencing the overall number of cancers prevented and the total costs in a linear fashion. However, the ICERs of the combined strategy versus the no-screening option tended to worsen. In detail, when assuming a 50% compliance with aspirin treatment, the ICER of the combined aspirin/colonoscopy strategy slightly increased from the baseline value of US$6237 per life-year saved to US$6270 per life-year saved.

Aspirin-related complications

The cost-effectiveness of the adjunction of aspirin to colonoscopy depended on the aspirin-related risk of UGB and haemorrhagic stroke. In detail, assuming a 2- and 1.7-fold increase in the aspirin-related UGB risk and stroke, corresponding to a lifetime risk of 4.2% and 1.4%, respectively, colonoscopy alone became more effective and cost-effective than the combination strategy (figure 3A,B). The corresponding values for sigmoidoscopy were a 5.3- and 8-fold increase in UGB and stroke risks, respectively. Alternatively, an increase in UGB- or stroke-related mortality from the baseline values of 5% and 6% to 11% and 23% resulted in the cost-ineffectiveness of the addition of aspirin to colonoscopy, with the corresponding values for sigmoidoscopy being 30% and 60%. The analysis was also sensitive to changes in cost assumptions. An increase in the per-year aspirin cost from the baseline US$3 to US$33 was able to increase the ICER of the combined strategy over US$50 000 per life-year saved, while even large variations of the per-year aspirin cost did not affect the cost-effectiveness of the combined sigmoidoscopy/aspirin strategy over sigmoidoscopy. Alternatively, a 7- and 5-fold increase in the costs of treatment of UGB and stroke resulted in the cost-ineffectiveness of the addition of aspirin to colonoscopy, with the corresponding values for sigmoidoscopy being a 32- and a 16-fold increase.

The cost-effectiveness of the addition of aspirin was not meaningfully affected by variations in the endoscopy cost, with endoscopy being equally represented in the two strategies.

Probabilistic sensitivity analysis

At Monte Carlo analysis, the addition of aspirin to colonoscopy and sigmoidoscopy screening was a cost-effective strategy in 52% and 94% of the possible scenarios. The corresponding 10–90 percentiles of the ICER were US$284 389 and US $328 856, and US$24 891 and US$69 381, respectively.

DISCUSSION

According to our simulation, the addition of low-dose aspirin to a colonoscopy screening was a cost-effective strategy, as well as cost saving when added to sigmoidoscopy. This result was explained by the synergistic effect between aspirin and endoscopy, when assuming no efficacy by sigmoidoscopy and a suboptimal efficacy by colonoscopy in preventing proximal CRC. Aspirin was indeed assumed to prevent 76% of proximal CRC-deaths potentially the proximal CRC potentially unprevented by endoscopic screening. It could be argued that the high efficacy of aspirin in preventing proximal CRC was shown in non-colonoscopic studies,[3] while in the present simulation, all the subjects were simulated to undertake a periodic colonoscopy screening. However, there is no apparent reason for which aspirin should be less effective in preventing proximal CRC following a negative or ineffective endoscopy rather than in patients never exposed to endoscopy. A second reason to explain the favourable cost-effectiveness of the combined strategy was the synergistic effect between aspirin and endoscopy in preventing rectal cancer mortality, when considering that the addition of aspirin was simulated to 'rescue' 53% of the deaths due to rectal cancer potentially unprevented by either sigmoidoscopy or colonoscopy. Although there is no definitive evidence on the synergistic effect between aspirin and endoscopy in preventing rectal cancer, aspirin has been shown to prevent postpolypectomy incidence of neoplasia,[6 20 25] providing plausibility to a potential synergistic effect on rectal cancer prevention. Third, the absolute cost of aspirin appeared to be low as compared to its efficacy. When considering an aspirin-related prevention of 38% and 52% for the overall CRC incidence and mortality, aspirin alone (ie, without colonoscopy) appeared to be the only cost-saving strategy as compared to a no-screening scenario.

We integrally applied the aspirin-related estimates of cost and efficacy shown in cardiovascular prevention trials to a simulated population undertaking CRC screening with endoscopy, implicitly assuming the same compliance with aspirin treatment in the two different clinical conditions. Indeed, previous trials on postpolypectomy prevention of adenomatous recurrence with aspirin showed a very high compliance with aspirin treatment (ie, >80%) that is in line with what was observed in the cardiovascular prevention trials from which our analysis was based.[6 20] Moreover, suboptimal compliance with aspirin treatment would not affect the relative ICERs between the combination of aspirin and endoscopy versus endoscopy alone, since it would proportionately decrease costs and efficacies, affecting only the relative ICER of combined strategies versus no screening, as shown in the sensitivity analysis.

The results of the present analysis do not confirm two previous simulations on the same issue, showing the cost-ineffectiveness of aspirin when added to colonoscopy screening in average-risk subjects.[26 27] This discrepancy appears to be mainly related to different input assumptions. When indeed we included the inputs from the previous two simulations in our model, the results were comparable (online appendix 2). The two previous models assumed a higher efficacy of colonoscopy in preventing CRC mortality, ranging from 75% to 85%. A second difference is represented by the cost assumptions. In detail, Suleiman *et al* assumed a yearly cost for aspirin (including aspirin-related complications) of US$172, which is more than 10-fold higher than our estimate.[27 28] The high aspirin cost was indirectly derived from relatively old series based on the use of non-steroidal anti-inflammatory drugs other than aspirin in patients with symptoms,[27 28] non-steroidal anti-inflammatory drugs being well known to be more toxic than low-dose aspirin.[7] Contrarily, our estimate is in line with the complications assessed in randomised trials on primary cardiovascular prevention with aspirin.[29 30] Of note, the two previous analyses, albeit not showing the cost-effectiveness of aspirin in the reference case scenario, did not exclude it in the sensitivity analysis.[26 27] In detail, when assuming a yearly aspirin cost of less than US$50 (as in our model) and an aspirin efficacy in preventing CRC of 50% (similar to our assumption), aspirin addition was cost-effective in the Suleiman *et al*[27] simulation. Similar results were shown in the Ladabaum *et al*[26] simulation, when considering adherence to colonoscopy as a reasonable proxy for colonoscopy efficacy.

The favourable cost-effectiveness of the addition of aspirin to sigmoidoscopy was robust to even large input changes in the

sensitivity analysis. On the other hand, there was uncertainty on the cost-effectiveness of the addition of aspirin to colonoscopy. Such uncertainty was related to both the efficacy of colonoscopy in preventing proximal CRC and the synergistic effect of aspirin on rectal cancer prevention. When assuming a ≥73% proximal CRC prevention rate by colonoscopy, the addition of aspirin became cost-ineffective. Since proximal CRC prevention rate has been shown to be operator dependent, we cannot exclude that such a high efficacy may be already achieved by expert endoscopists. Of note, when assuming no synergistic effect between aspirin and colonoscopy on rectal cancer prevention, a 64% proximal CRC prevention was enough to render the addition of colonoscopy not cost-effective, such a value being very similar to those shown in a setting of 'high-quality' endoscopy.[12 15] On the other hand, when assuming no proximal CRC prevention, as shown by previous Canadian studies, the cost-effectiveness profile of the addition of aspirin to colonoscopy became very similar to that of sigmoidoscopy, with the addition of aspirin being cost saving and robust to changes in the sensitivity analysis in this scenario. Thus, our result with regard to the added benefit of aspirin to colonoscopy may best apply to settings with proven low protection from proximal colonoscopy,[12–15 31] where colonoscopy is performed by under-trained physicians[32 33] or when colonoscopists are known to have low adenoma detection rates. As already stated above, it is currently unknown whether the addition of aspirin may further reduce the prevention of rectal cancer after a negative colonoscopy. Uncertainty on our estimates was also related with the risk of aspirin-related complications, namely, UGB and stroke.

There are limitations to the present analysis. Estimates on aspirin efficacy were derived from randomised studies on cardiovascular prevention, CRC incidence and death rates not representing primary end points.[3 4] Second, suboptimal colonoscopy efficacy in preventing right-sided CRC was extrapolated from a population study, with no randomised studies being available.[12–15] Third, we did not assume any aspirin-related reduction of polyp prevalence, potentially underestimating the cost-effectiveness of aspirin addition. In the sensitivity analysis, indeed, we showed that a 17% aspirin-related reduction of polyp prevalence would substantially improve the cost-effectiveness profile of aspirin addition. Fourth, we did not include any potential primary prevention of cardiovascular disease, which was outside the purposes of this analysis. However, when considering that we included all the potential aspirin-related complications both in terms of cost and in terms of loss of life-years, any further cardiovascular benefit would have further strengthened the cost-effectiveness of the aspirin addition. Fifth, we did not compare the endoscopic strategies with or without aspirin with non-endoscopic screening alternatives (ie, faecal occult blood tests), with the cost-effectiveness of the addition of aspirin over endoscopy being independent from the relative cost-effectiveness between endoscopic and non-endoscopic strategies. Finally, we did not assume a suboptimal adherence to endoscopic screening in the reference case scenario, since the cost-effectiveness of the addition of aspirin over endoscopy is independent from such adherence. However, we simulated the progressive decrease in absolute costs and efficacies with suboptimal adherence rates in online appendix 3.

In settings where the efficacy of colonoscopy is suboptimal for preventing proximal colon cancer, the addition of low-dose aspirin may be effective and cost-effective. Addition of aspirin loses cost-effectiveness when the efficacy of colonoscopy in preventing proximal colon cancer reaches 73%.

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