Very-low-dose aspirin and surveillance colonoscopy is cost-effective in secondary prevention of colorectal cancer in individuals with advanced adenomas: network meta-analysis and cost-effectiveness analysis

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Abstract

Background: Individuals with advanced colorectal adenomas (ACAs) are at high risk for colorectal cancer (CRC), and it is unclear which chemopreventive agent (CPA) is safe and cost-effective for secondary prevention. We aimed to determine, firstly, the most suitable CPA using network meta-analysis (NMA) and secondly, cost-effectiveness of CPA with or without surveillance colonoscopy (SC).

Methods: Systematic review and NMA of randomised controlled trials were performed, and the most suitable CPA was chosen based on efficacy and the most favourable risk–benefit profile. The economic benefits of CPA alone, 3 yearly SC alone, and a combination of CPA and SC were determined using the cost-effectiveness analysis (CEA) in the Malaysian health-care perspective. Outcomes were reported as incremental cost-effectiveness ratios (ICERs) in 2018 US Dollars ($) per quality-adjusted life-year (QALY), and life-years (LYs) gained.

Results: According to NMA, the risk–benefit profile favours the use of aspirin at very-low-dose (ASAVLD, ≤ 100 mg/day) for secondary prevention in individuals with previous ACAs. Celecoxib is the most effective CPA but the cardiovascular adverse events are of concern. According to CEA, the combination strategy (ASAVLD with 3-yearly SC) was cost-saving and dominates its competitors as the best buy option. The probability of being cost-effective for ASAVLD alone, 3-yearly SC alone, and combination strategy were 22%, 26%, and 53%, respectively. Extending the SC interval to five years in combination strategy was more cost-effective when compared to 3-yearly SC alone (ICER of $484/LY gain and $1875/QALY). However, extending to ten years in combination strategy was not cost-effective.

Conclusion: ASAVLD combined with 3-yearly SC in individuals with ACAs may be a cost-effective strategy for CRC prevention. An extension of SC intervals to five years can be considered in resource-limited countries.

Keywords: Colorectal cancer, Colorectal adenomas, Chemoprevention, Aspirin, Surveillance colonoscopy, Network meta-analysis, Cost-effectiveness analysis

Background

Colorectal cancer (CRC) is the third most commonly diagnosed malignant neoplasm and the second leading cause of cancer death worldwide [1]. Similarly, CRC is on
the rise in Malaysia, and from the most recent data from the national cancer registry indicate that CRC is now the second most common cancer and the commonest among males [2]. Colorectal adenoma is a known premalignant condition, but individuals with high risk of CRC are those with advanced colorectal adenomas (ACAs), typically defined as 1 cm or larger, and/or have villous component and/or high-grade dysplasia [3].

In high-risk individuals, it is attractive to have chemopreventive agents (CPAs) which are effective in protecting them from getting a recurrence of ACAs after initial polypectomy [4, 5]. In addition, the CPA should be ideally free from adverse events but also cost-effective considering its long-term use. There are several candidates, including aspirin and celecoxib but it is unknown if these agents fulfill all the requirements described above [6, 7]. The US Preventive Services Task Force (USPSTF) guideline supports the use of very-low-dose aspirin (ASA VLD, \( \leq 100 \) mg/day) for primary chemoprevention of CRC [8] but secondary chemoprevention in particular patients with a previous history of ACAs is unclear. That could be in part because of the absence of data informing the relative efficacy of aspirin at different doses (especially at a dose suggested by the USPSTF for the primary prevention [9]) on reducing the recurrence of ACAs. Previous systematic reviews and network meta-analyses (NMAs) also did not investigate this gap in the literature [4, 5]. Additional RCTs have since become available allowing re-examination of the existing evidence [10–12].

Meanwhile, screening colonoscopy with resection of detectable adenomas followed by interval surveillance colonoscopy (SC) is typically regarded as the ideal preventive approach [13]. Unfortunately, SC has several limitations including cost, suboptimal adherence, limited access, possible complications and the risk of missing adenomas [14]. Hence, increasing attention is being given to chemoprevention as a substitute for routine SC, or alternatively a combination strategy using both approaches. It is unknown if chemoprevention may allow extension of surveillance intervals from the recommended 3-yearly to 5-yearly or 10-yearly, and such an approach may be cost-effective in countries with limited health-care resources.

Therefore, our objectives were first to identify the ‘ideal’ CPA for secondary prevention using NMA techniques, second to investigate the cost-effectiveness of that CPA alone, SC alone or combination strategy for prevention of new CRCs in a high-risk population with a previous history of ACAs, and third to determine if an extension of surveillance intervals to 5-yearly and 10-yearly is feasible in terms of cost-effectiveness. For the last 2 objectives, a health economic model was developed using data from our NMA as well as population and health-care settings of Malaysia, a developing nation with an estimated population of 30 million in the South-east Asia region.

### Methods

#### Systematic review and network meta-analysis

First, systematic review with network meta-analysis (NMA) was performed to identify a CPA with the most favourable risk–benefit profiles to be further examined in the proposed cost-effectiveness model. The NMA was registered with PROSPERO (CRD42015025849) [15] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement [16]. The primary efficacy outcome was the incidence of recurrent ACAs. Safety outcomes were the incidence of serious adverse events (SAEs) and cardiovascular (CV) events. Definitions of efficacy and safety outcomes are provided in Additional file 1: 1.1. Search strategy and study selection are described in Additional file 1: 1.2. Studies included were RCTs with a duration of treatment of at least one year. The intervention was any CPA including aspirin (high-dose or ASAHD > 325 mg/day, low-dose or ASALD 100–325 mg/day and very-low-dose or ASA VLD \( \leq 100 \) mg/day) [9], celecoxib, calcium and vitamin D, alone or in combination at different doses. Comparator intervention was another CPA or placebo. Inclusion criteria are provided in Additional file 1: 1.3. Data extraction and quality assessment are provided in Additional file 1: 1.4.

Details of statistical analysis are provided in Additional file 1: 1.5. The outcome measure was described using risk ratio (RR) and 95% confidence interval (CI). For direct comparisons between interventions, a standard pairwise meta-analysis was performed by using the random-effects model [17]. Trial sequential analyses (TSAs) were performed to assess the risk of random errors in pairwise meta-analyses [18] (Additional file 1: 1.5.1). Random effects NMA using consistency model was applied in comparison of all interventions using direct and indirect estimates [19] Inconsistency assumption was evaluated using a global inconsistency test by fitting design-by-treatment in the inconsistency model [20]. In order to rank intervention hierarchy, surface under the cumulative ranking (SUCRA) curves were derived [21] Publication bias was examined with comparison-adjusted funnel plot [22] To assess the robustness of primary outcome, multiple sensitivity analyses were performed (Additional file 1: 1.5). For statistical analysis and graph generation, Stata version 15.1 (StataCorp, College Station, TX, USA) was utilised. The risk–benefit integrated analysis was used to review the potential benefits and risks of CPAs (Additional file 1: 1.5.2). The quality of evidence from NMA was evaluated using the Grading of Recommendations,
of recurrence of 'low-risk' adenomas after index polypectomy was derived from the pooled estimates of the National Cancer Institute (NCI) pooling project [25].

The probabilities of subjects who were initially at pre-clinical stages and subsequently detected in clinical stages would depend if symptoms developed and also diagnostic accuracy of SC or other tests [29].

The sensitivity of diagnostic SC was obtained from a recent systematic review and meta-analysis of 25 studies [30]. The impact of SC on low- and high-risk adenomas was derived from per-patient miss rates (Additional file 1: 3.4) which were reasonably estimated based on meta-analyses of data from the Asian population (Additional file 1: Figs. 3.4.1-2). The probability of perforation (with or without polypectomy) and major bleeding due to colonoscopy was based upon the report of a systematic review undertaken for the USPSTF [31].

The RRs of developing low- or high-risk adenomas or adverse effects related to the use of CPAs were derived from RCTs [32, 33] and meta-analyses [34–37] (Additional file 1: 3.6–7). The annual probability of mortality from any causes was estimated using repository data from the Global Health Observatory data (Additional file 1: Table 3.8.1). The probabilities of deaths for each stage of CRCs were calculated based on a meta-analysis of 5 studies in Malaysia (Additional file 1: Table 3.8.2). Probability of death following perforation was obtained from a large population-based cohort study [38]. Probability of death following major bleeding events, and the RRs of CV mortality on ASA/VLD was as previously reported in a systematic review [37].

The respective stage-specific utility scores for different stages of CRC were obtained from a study eliciting preferences for a hypothetical stage from individuals who had previously undergone polypectomy [39]. The utility of patients without CRC was obtained from a cross-sectional study of Malaysian adult population-based values for EQ-5D health states [40]. The impact on the quality of life from harms associated with colonoscopy and or use of the chosen CPA was also incorporated into the CEA model (Additional file 1: 3.9).

Cost estimates used within the CEA analysis have been derived from the amended Malaysia medical fee schedule 2013 [41], the consumer price guide database, data from the Ministry of Health of Malaysia [42], and other relevant literatures. Based on a standard operating procedure available from the Malaysia national guidelines, the total provider cost for initial treatment of CRC per year
Table 1  Summary of input parameters

| Parameter | Base case | SE or range | Distribution | Source/references |
|-----------|-----------|-------------|--------------|-------------------|
| **Annual transition probabilities** | | | | |
| Normal to low-risk | 0.1976 | 0.0044 | Beta | Based on the National Cancer Institute pooling project [25] (S 3.1) |
| Low-risk state to high-risk | 0.0890 | 0.0028 | Beta | Meta-analysis of 4 data sets of population with high-risk adenomas at baseline (S 3.2) |
| High-risk to CRC1pre | ASR | NA | NA | Birth cohort analyses from German screening colonoscopy registry [26, 27] (S 3.3) |
| CRC1pre to CRC2pre | 0.2800 | 0.0357 | Beta | Estimated by calibration to the National Cancer Institute data statistics [28], 1973–1999 |
| CRC2pre to CRC3pre | 0.2800 | 0.0357 | Beta | | |
| CRC3pre to CRC pre | 0.6300 | 0.1405 | Beta | | |
| CRC1pre to CRC1cli (by symptoms) | 0.0700 | 0.0300 | Beta | Reported in an economic evaluation by Frazier AL et al. [29] |
| CRC2pre to CRC2cli (by symptoms) | 0.2500 | 0.0577 | Beta | | |
| CRC3 pre to CRC3cli (by symptoms) | 0.5500 | 0.0577 | Beta | | |
| CRC4pre to CRC4cli (by symptoms) | 0.8500 | 0.0763 | Beta | | |
| CRC1cli to dead | 0.0575 | 0.0087 | Beta | Based on meta-analyses of five studies reported survival data of CRC at different stages in Malaysia (S 3.8) |
| CRC2cli to dead | 0.0684 | 0.0099 | Beta | | |
| CRC3cli to dead | 0.0973 | 0.0132 | Beta | | |
| CRC4cli to dead | 0.1589 | 0.0666 | Beta | | |
| **Effectiveness: every 3-year colonoscopy** | | | | |
| Low-risk state to normal | 0.5800 | 0.0178 | Beta | Based on meta-analyses of per-patient miss rate (S 3.4.1–2) |
| High-risk state to normal or low-risk state | 0.9200 | 0.0204 | Beta | Available from a meta-analysis by Pickhardt PJ et al. [30] |
| CRC1pre to CRC1cli | 0.9470 | 0.013 | Beta | Available from an economic evaluation from the National Institute for Health Research (NIHR) (S 3.5) |
| CRC2pre to CRC2cli | 0.9470 | 0.013 | Beta | | |
| CRC3pre to CRC3cli | 0.9800 | 0.0950–0.9900 | Uniform | | |
| CRC4pre to CRC4cli | 0.9800 | 0.9600–1.0000 | Uniform | | |
| **Relative risk (RR) of benefits associated with ASA/AVLD** | | | | |
| Normal to low-risk | 0.86 | 0.0740 | Normal | Meta-analyses of two aspirin chemoprevention RCTs [39, 40] (S 3.6) |
| Low-risk to high-risk | 0.59 | 0.1352 | Normal | | |
| RR of CV mortality | 0.92 | 0.0536 | Normal | Reported in a recent network meta-analysis by Veettil et al. [37] |
| **Harms associated with interventions** | | | | |
| Intolerability due to initial side effects of ASA/AVLD | 0.052 | 0.025–0.200 | Uniform | Derived from an aspirin chemoprevention trial [39] |
| Major bleeding (any) due to ASA/AVLD per year | 0.0022 | 0.0005 | Beta | Available from a meta-analysis of nine primary CV disease prevention trials [34] (S 3.7.1) |
| Major GI bleeding due to ASA/AVLD | 0.0011 | 0.0003 | Beta | Available from the systematic review undertaken for the USPSTF [35, 36] and Veettil et al. [37] (S 3.7.2) |
| Ulcer due to ASA/AVLD | 0.0018 | 0.0002 | Beta | | |
| Dyspepsia due to ASA/AVLD | 0.1880 | 0.0800 | Beta | | |
| Perforation due to colonoscopy (with or without polypectomy) | 0.0004 | 0.00008 | Beta | Based on a systematic review undertaken for the USPSTF by Lin JS et al. [31] |
| Major bleeding due to colonoscopy | 0.0008 | 0.0002 | Beta | Available from a large population-based cohort study by Gatto NM et al. [38] |
| Mortality due to perforation | 0.0582 | 0.0100 | Beta | | |
| Mortality due to major bleeding events | 0.0600 | 0.0100–0.1600 | Uniform | Reported in a recent network meta-analysis by Veettil et al. [37] |
| **Utility values** | | | | |
| Non-CRC states | 0.8300 | 0.0500 | Beta | Based on a population based cross-sectional study using EQ-SD instrument [40] (S 3.9) |
| CRC I | 0.7400 | 0.0260 | Beta | Ness et al. [39] |
| CRC II | 0.7400 | 0.0260 | Beta | | |
| CRC III | 0.6700 | 0.0289 | Beta | | |
| CRC IV | 0.2500 | 0.0551 | Beta | |
was obtained from a cost analysis conducted at a tertiary hospital in the country [43]. The lifetime costs of CRC were reasonably estimated based on the follow-up policies advocated by the Malaysian clinical practice guideline on CRC (Additional file 1: Table 3.10.1). A detailed description of all cost estimates used within the analysis is provided in Additional file 1: 3.10.2. All costs were converted using the consumer price index (CPI) (https://www.dosm.gov.my/v1/) and reported in 2018 US Dollars ($).

**Sensitivity analyses**

One-way sensitivity analyses were performed to study the effects of altering parameters on the CEA findings. The 95% CI ranges were used whenever such data were available; but if absent, the ±15% range was applied. Results were shown using the tornado diagrams to identify parameters with the most significant impact on the model results. A probabilistic sensitivity analysis (PSA) was also conducted to simultaneously examine the effects of all parameter uncertainties using a Monte Carlo simulation performed using Microsoft Excel 2003 (Microsoft Corp, Redmond, WA) [44]. Results of the PSA were presented as cost-effectiveness acceptability curve.

**Results**

**The Choice of CPA based on NMA**

A flow diagram depicting the search and selection process is provided in Additional file 1: 1.2.1. From a total of 4673 citations from the search strategy, 14 RCTs [10–12, 32, 33, 45–53] comparing nine interventions (including placebo) were evaluated in the NMA. Figure 1 shows the available direct comparisons and network of RCTs for the efficacy outcome. Additional file 1: Tables 4.1.1-2 describe the characteristics of all included RCTs. A summary of risk of bias assessment is presented in Additional file 1: 4.2. Treatment effects estimated from pairwise meta-analyses are presented in Additional file 1: 4.3. Treatment effects estimated from NMA for efficacy and safety outcomes are presented in Fig. 2. Detailed descriptions of the results of NMA for efficacy and safety outcomes are provided in Additional file 1: 4.4-5, respectively.

![Figure 1: Network plot of chemopreventive agents tested in RCTs for recurrence of advanced colorectal adenomas. Connecting lines represent head-to-head (pairwise) comparisons, indicated by the connected nodes (size proportional to the number of studies). Line thickness is proportional to the number of studies comparing the two strategies. Abbreviations: ASALD, low-dose-aspirin; ASAVLD, very-low-dose-aspirin; Ca, calcium; Cele, celecoxib (400 mg and 800 mg daily), PLB, placebo; VD, vitamin D.](https://www.dosm.gov.my/v1/)

**Table 1 (continued)**

| Parameter | Base case | SE or range | Distribution | Source/references |
|-----------|-----------|-------------|--------------|-------------------|
| Colonoscopy (disutility) | 0.0025 | NA | NA | Reported in an economic evaluation by Saini SD et al. [57] (S 3.9) |
| Major GI bleeding/peptic ulcer due to ASAVLD (1 month) | 0.46 | NA | NA | Based on the analysis undertaken for the NICE osteoarthritis guidelines (S 3.9) |
| Dyspepsia (1 month) | 0.73 | NA | NA | Pharmacoeconomic guideline, Malaysia (https://www.pharmacy.gov.my/v2/en/documents/pharmacoeconomic-guideline-malaysia.html) |
| Base case assumptions | | | | |
| Annual discount rate for costs and outcomes | 0.03 | NA | NA | |
| Compliance to surveillance colonoscopy | 60% | 30–100% | NA | Taylor et al. [58] |

ASAVLD, aspirin very-low-dose; ASR, age-specific rate; cli, clinical; CRC, colorectal cancer; NA, not applicable; pre, pre-clinical; SE, standard error
Cost-effectiveness of ASAVLD, 3-yearly SC or combination strategy

With the choice of CPA now confirmed after NMA, a CEA model was then developed to assess the cost-effectiveness of using ASAVLD alone, 3-yearly SC alone, and the combination strategy of ASAVLD and 3-yearly SC. The base-case analysis of this model has demonstrated that, when compared to no screening, ASAVLD alone, 3-yearly SC, and combination strategy were less costly and more effective (in the order of decreasing costs and increasing effectiveness) (Table 2). Among all strategies, the combination strategy was the most cost-saving and the best buy option. For a base-case assumption of 60% compliance to colonoscopy, our model predicted a reduction in new cases of CRC by 14%, 23%, and 72% for ASAVLD alone, 3-yearly SC alone, and the combination strategy of ASAVLD and 3-yearly SC, respectively, compared to no surveillance (Additional file 1: 5.1).

Tornado diagrams illustrating the one-way sensitivity analysis results of the combination strategy compared to no screening are presented in Additional file 1: Figs. 5.1-2. All parameters had no impact on cost-saving for the combination strategy, except for utility in non-CRC states. The results of PSA based on 1000 Monte Carlo simulations are illustrated using the cost-effectiveness plane (Additional file 1: Fig. 5.3). The cost-effectiveness acceptability curves showed the superiority of the combination strategy over others for all the WTP values. Probabilities of being cost-effective for ASAVLD, 3-yearly-SC, and combination strategy were 22%, 26%,
and 53%, respectively, based on the Malaysian ceiling threshold of social WTP of $7024 per QALY gained.

**Scenario analyses: extension of surveillance intervals in combination strategy**

Effects on ICER from an extension of SC intervals in combination strategy to 5-yearly and 10-yearly are presented in Table 3. With 5-yearly SC, the combination strategy was associated with ICER of $484/LY gain and $1875/QALY gain. This was considered cost-effective based on the Malaysian ceiling threshold of social WTP. With 10-yearly SC, the combination strategy became less cost-effective with respect to LYs saved and QALYs gained. A similar trend was seen with respect to new cases of CRC that could be prevented in the simulated cohort over a lifetime. The model of combination strategy with 5-yearly SC predicted a reduction in CRC incidence by 55% (vs. no screening) and 42% (vs. 3-yearly SC) (Additional file 1: Table 5.2).

**Discussion**

Based on systematic review and NMA, we are able to conclude that ASAVLD is probably the safest although not the most effective CPA for prevention of recurrence of ACAs among individuals with a previous history of colorectal adenomas. Celecoxib is the most effective CPA, but the CV adverse events are of great concern. Moreover, the protective effect of celecoxib does not persist after its withdrawal [7]. The risk–benefit profile favours the use of ASAVLD, especially for those with a history of ACAs. Therefore, taken together with the risk–benefit analysis, there is moderate-quality evidence to support the choice of ASAVLD and in our subsequent CEA but also its long-term clinical benefit in combination with SC.

From the CEA, combination strategy (ASAVLD with 3-yearly SC) was the more cost-effective and the best-buy option with significant gains in LYs and QALYs. Moreover, a 63% reduction in the occurrence of new CRC cases was observed with the combination strategy compared

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**Table 2** Base case results

| Strategies                        | Total costs (USD) | LYs | QALYs | Incremental costs (USD) | Incremental LYs | Incremental QALYs | ICER (USD/LY gained) | ICER (USD/QALY gained) |
|-----------------------------------|-------------------|-----|-------|-------------------------|----------------|-------------------|----------------------|------------------------|
| No screening                      | 5757              | 17.23 | 10.44 | -                       | -              | -                 | -                    | -                      |
| ASAVLD                            | 5472              | 17.69 | 10.60 | -285                    | 0.47           | 0.17              | Dominated*           | Dominated*             |
| Colonoscopy                       | 4296              | 18.03 | 10.81 | -1176                   | 0.34           | 0.21              | Dominated*           | Dominated*             |
| Colonoscopy and ASAVLD            | 3679              | 18.43 | 10.93 | -617                    | 0.40           | 0.12              | Cost-saving          | Cost-saving            |

ASAVLD, very low dose aspirin; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life years; USD, US dollar

* Dominated by combination of colonoscopy and ASAVLD

**Fig. 3** Cost-effectiveness acceptability curves of colorectal cancer preventive strategies. Abbreviations: ASAVLD: aspirin very-low-dose; COLO: colonoscopy; COLO_ASAVLD, combination strategy; USD, US dollar; WTP, willingness to pay
to 3-yearly SC alone. Furthermore, ASAVLD has a positive impact on the prevention of cardiovascular events, and this is added benefit besides CRC reduction at fewer adverse outcomes. For countries with limited healthcare resources including Malaysia, extending surveillance intervals to 5-yearly or 10-yearly may reduce health costs, however, in our scenario analysis, this was the case. For 5-yearly SC, while costlier, it could be the more cost-effective strategy in the Malaysian setting. However, we found 10-yearly SC was not cost-effective. Our findings may be applicable to countries with similar WTP thresholds as Malaysia [54].

Our findings are unique as none of the previous studies specifically evaluated the effectiveness of aspirin at very-low-dose in high-risk individuals with a history of advanced adenomas. Other differences include the following: 1) previous analyses [55, 56] have involved individuals with a history of ‘any’ colorectal adenomas, i.e. including non-advanced adenomas with a lesser risk for CRC and hence, we observed a higher number of new CRC cases in our model compared to others (e.g., 6.4% vs. 5.5% [55]) 2) the duration of surveillance colonoscopy was up to 75 years [13] in our model rather than lifetime [55, 57] or intermittent [52] in others, and 3) our model opted for 60% compliance with SC, [58] as opposed to 80–100% in previous chemoprevention models [55, 56], which, in our opinion, is not realistic in the real-world practice. The National Polyp Study suggested that SC should prevent at least 75% of all CRCs [59], and in our model, we predicted a reduction of 23%–57% for new or early-stage CRCs and 81% for late-stage CRCs.

When formulating the aspirin chemoprevention policy with SC, it is important to take into account the way in which aspirin chemoprevention may be implemented. Aspirin chemoprevention is more feasible in terms of human resources and budgetary burdens. Weighing the benefits of ASAVLD against the potential harms is of particular relevance in the chemoprevention setting. The use of aspirin needs shared decision making with patients but also comprehensive understanding of patients’ values and preferences. However, there are other factors relevant to the implementation of this strategy, including the budget impact, feasibility, and ethical and social implications that need to be considered for decision making. At present time, our findings are likely more applicable for countries with established colonoscopy screening programs and regular post-polypectomy surveillance. However, individuals from countries without colonoscopy

### Table 3: Scenario analyses: Effect of extending colonoscopy surveillance intervals in the combination strategy

| Strategies                                      | Total costs (USD) | LYs    | QALYs  | Incremental costs (USD) | Incremental LYs | Incremental QALYs | ICER (USD/LY gained) | ICER (USD/QALY gained) |
|-------------------------------------------------|------------------|--------|--------|-------------------------|----------------|-------------------|---------------------|------------------------|
| **Aspirin combined with colonoscopy at up to 5-year intervals** |                  |        |        |                         |                |                   |                     |                        |
| No screening                                    | 5757             | 17.23  | 10.44  | -                       | -              | -                 | -                   | -                      |
| ASAVLD                                          | 5472             | 17.69  | 10.60  | -285                    | 0.47           | 0.17              | Dominateda          | Dominateda             |
| Surveillance colonoscopy (3 years)              | 4296             | 18.03  | 10.81  | -1176                   | 0.34           | 0.21              | Cost-saving         | Cost-saving            |
| ASAVLD + surveillance colonoscopy (5 years)     | 4446             | 18.34  | 10.89  | 150                     | 0.31           | 0.08              | 484 (Cost-effective) | 1875 (Cost-effective)  |
| **Aspirin combined with colonoscopy at up to 10-year intervals** |                  |        |        |                         |                |                   |                     |                        |
| No screening                                    | 5757             | 17.23  | 10.44  | -                       | -              | -                 | -                   | -                      |
| ASAVLD                                          | 5472             | 17.69  | 10.60  | -285                    | 0.47           | 0.17              | Dominateda          | Dominateda             |
| Surveillance colonoscopy (3 years)              | 4296             | 18.03  | 10.81  | -1176                   | 0.34           | 0.21              | Cost-saving         | Cost-saving            |
| ASAVLD + surveillance colonoscopy (10 years)    | 5878             | 18.11  | 10.78  | 1582                    | 0.08           | -0.03             | 19,775 (Not cost-effective) | Dominateda |
| **Aspirin combined with colonoscopy every 5-year versus every 3-year** |                  |        |        |                         |                |                   |                     |                        |
| ASAVLD + surveillance colonoscopy (5 years)     | 4446             | 18.34  | 10.89  | -                       | -              | -                 | -                   | -                      |
| ASAVLD + surveillance colonoscopy (3 years)     | 3679             | 18.43  | 10.93  | -767                    | 0.09           | 0.04              | Cost-saving         | Cost-saving            |

The Malaysian ceiling threshold of social willingness to pay (WTP) for interpretation of cost-effectiveness findings considered for the analysis was $7024 /QALY

ASAVLD, very low dose aspirin; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life years; USD, US dollar

* Dominated by surveillance colonoscopy (3-year)
screening programs but have been identified at increased risk due to advanced adenomas during any endoscopic examinations can still apply these findings, although the number of such individuals is expected to be minimal. Over the last ten years, an increase in screening rates in the general population has been observed in Malaysia [2]. This could further increase the burden of surveillance colonoscopy over time due to the scarcity of resources. Hence, the findings from this analysis have potential applications in the Malaysian setting and other lower-middle-income countries where resources are limited for the surveillance programs.

There are some limitations. First, CEA did not include the indirect costs of CRCs due to a lack of published data. Second, there is evidence for suboptimal efficacy of screening colonoscopy for proximal CRCs [60–62], which is currently the principal target of aspirin chemoprevention, but we did not consider the location of CRCs in our model. Third, the annual probabilities of input parameters (especially utility parameters, benefits, and harms associated with ASAVLD) were assumed to be constant over time but more likely is that with increasing age there would be a decrease in utility values and increase in risks of aspirin and colonoscopy-related morbidities. Fourth, the impact of ASAVLD on other cancers was not explored, and this could be a topic for future research. Fifth, for our base-case analysis, we assumed that the initial colonoscopy was 100% successful in removing all adenomas. Unfortunately, this is not the case in real life, especially for the right colon. Lastly, our results are best replicated in future using the RCT and prospective designs, however, such studies are likely expensive and take a long time to complete.

Conclusions
In conclusion, ASAVLD in combination with 3-yearly SC may be considered a cost-effective and safe strategy to prevent CRCs among high-risk individuals with a previous history of ACAs. For individuals already receiving ASAVLD, extension from 3-yearly to 5-yearly SC could be considered in the setting of limited resources.

Abbreviations
ACAs: Advanced colorectal adenomas; ASALD: Aspirin at low-dose; ASAVLD: Aspirin at very-low-dose (≤ 100 mg/day); CEA: Cost-effectiveness analysis; CPA: Chemopreventive agent; CPI: Consumer price index; CRC: Colorectal cancer; CV: Cardiovascular; GRADE: The Grading of Recommendations, Assessment, Development and Evaluation; ICER: Incremental cost-effectiveness ratio; LY: Life-years; LYG: Life-years gained; NCI: National Cancer Institute; NMA: Network meta-analysis; NSAIDs: Nonsteroidal anti-inflammatory drugs; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life-year; RCT: Randomized controlled trial; RR: Risk ratio; SAE: Serious adverse event; SC: Surveillance colonoscopy; SUCRA: Surface under the cumulative ranking; TSA: Trial sequential analysis; US: United States; USPSTF: US Preventive Services Task Force; WTP: Willingness to pay threshold/ cost-effectiveness threshold.

Supplementary Information
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Authors’ contributions
SKV and STK drafted the protocol. NC revised the protocol. SKV and LKG coordinated the identification of studies. SKV and SK conducted the data extraction. SKV and LKG independently assessed the risk of bias. SKV conducted the statistical analyses. SKV and PP developed the model and conducted economic analyses. NC, YYL, and STK validated the model. SKV, PP, SK, and LKG drafted this paper. STK, YYL, and NC revised the paper. All authors participated in the interpretation of analyses, reviewed and commented on the article, and approved the final version of the manuscript.

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Availability of data and materials
All data generated or analyzed during this study was taken from published RCTs, systematic reviews, and other relevant literatures and are included in this article (and its supplementary information files).

Declarations

Ethical approval and consent to participate
As this was a retrospective study based on primary research, and as all data entry, analysis and results output was anonymised, no informed consent, verbal or written was obtained. No ethical approval is required because this study includes no confidential personal data or interventions with the patients.

Consent for publication
The authors are responsible for the reported research, and have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted.

Competing interests
The authors have no competing interest to declare.

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