ORIGINAL PAPER

• Should Aspirin Be Used For Primary Prevention Of Colorectal Cancer In The General Population?

Should Aspirin Be Used For Primary Prevention Of Colorectal Cancer In The General Population?

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ABSTRACT

Objectives: The objective of this narrative review is to determine if aspirin is indicated for primary prevention of colorectal cancer in the general population.

Methods: A Pubmed search was conducted and 19 articles were included for this review.

Results and Discussion: In deciding if aspirin should be recommended for chemoprevention, we need to consider its efficacy, safety profile, patient compliance and cost-effectiveness.

Most of the observation studies suggested that aspirin had a protective effect against colorectal cancer. However, randomised control trials had not shown such benefit. For the general population, the harms of aspirin outweigh the potential benefits.

A long duration of 5-10 years of regular aspirin intake seemed to be required for significant protective effect. As such, compliance in the long term for an otherwise well patient is an issue.

While some cost-effectiveness analyses suggested that colonoscopic screening was more cost-effective than aspirin use, others suggested that a combination of low-dose aspirin with colonoscopy was cost-effective, especially for proximal colorectal cancer.

Conclusion: Based on the data from RCTs thus far, aspirin should not be recommended as a chemo-preventive agent against colorectal cancer for the general population.

Keywords:
Aspirin, Colorectal Cancer, Primary Prevention

SFP2016; 42(I): 61-65

INTRODUCTION

Colorectal cancer is the leading cancer among the local male population, and the second leading cancer among the female population.[1] There are well established guidelines with respect to screening for colorectal cancer (secondary prevention). However, the question still remains — Is there a role for primary prevention of colorectal cancer in the form of chemoprevention? If chemoprevention is found to be effective, it could be used as an adjunct to current screening recommendations. Uncovering an answer to this question is highly relevant to family physicians, as preventive health is one of the pillars of family medicine practice.

The idea that non-steroidal anti-inflammatory drugs (NSAIDs) could be used for chemoprevention of colorectal cancer started as early as 1981, when Narisawa, a Japanese surgeon, reported that chemical carcinogenesis in rats could be suppressed by Indomethacin.[2]

This was followed by the Melbourne Colorectal Cancer study in 1988, which showed a possible association of aspirin with lower incidence of colorectal cancer. This sparked off much interest and research into the role of aspirin as a suitable chemo-preventive agent for colorectal cancer.[3]

The objective of this narrative review is to determine if current literature available would shed light on whether aspirin is indicated for primary prevention of colorectal cancer in the general population.

The definitions for Population (P), Exposure (E) and Outcome (O) of this narrative review are as follows:

P—The "general population" refers to asymptomatic patients with no personal history of colorectal adenoma or carcinoma. It excludes those with familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC).
E—Aspirin. This excludes non-aspirin NSAIDs.
O—Primary prevention of colorectal cancer.

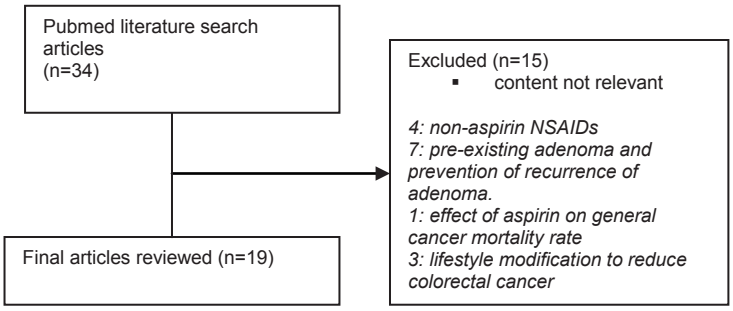
METHODS

A Pubmed search was conducted using keywords "aspirin", "colorectal cancer" and "primary prevention". Non-English articles were filtered out.

The articles underwent further selection by ensuring they fitted the Population (P), Exposure (E) and Outcome (O) mentioned earlier. A total of 19 articles were included for this narrative review.

Figure 1 is a flow chart to show the process of selecting articles.

Figure 1: Process of article selection



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RESULTS

A. Hypothesised Mechanism of Action of Aspirin in Colorectal Cancer

Laboratory studies have found increased levels of enzymes cyclo-oxygenase (COX) 1 and 2 in chemically-induced colon cancers. It has been postulated that NSAIDs (including aspirin) work by inhibition of arachidonic acid (AA) metabolism via COX enzymes. This in turn modulates the synthesis of prostaglandins (PGs) that affect cell proliferation, cancer growth and immune responsiveness. Furthermore, NSAIDs may affect apoptosis through a mixture of prostaglandin-dependent and prostaglandin-independent pathways.[4]

B. Studies That Show Protective Effect of Aspirin in Reducing Incidence of Colorectal Cancer

Evidence from laboratory studies

One of the laboratory studies done that indicate a beneficial effect of aspirin includes the study done by Reddy et al, where aspirin was given to mice with chemically-induced colon cancer. Mice fed with aspirin had reduced incidence, multiplicity and size of colonic adenocarcinomas. It was also found that colonic mucosal and tumour PG E2 levels were reduced in mice given aspirin, supporting the hypothesis that aspirin reduces colonic cancer via the modulation of PG levels.[5]

Evidence from observational studies

The Melbourne colorectal cancer study in 1988 was one of the first studies that showed a possible protective effect of aspirin in reducing colorectal cancer incidence. It was a case-control study which showed a relative risk (RR) of 0.66 (95% CI, 0.47-0.92; p=0.001) for colorectal cancer in both genders.[3]

A population-based case-control study done in Massachusetts from 1992 to 1994 studied the effect of aspirin and non-aspirin NSAID on colorectal cancer. In this study, aspirin was the most commonly used NSAID. The RR estimate associated with regular use of aspirin was 0.7 (95% CI, 0.5-0.9). "Regular use" was defined as usage of at least four days a week, for at least three months. There was no statistically significant trend of relative risk in relation to duration or dose of aspirin found in this study.[6]

The Nurses' Health Study was a cohort study where the female participants who did not have a history of adenoma, cancer, inflammatory bowel disease or familial polyposis, were followed up from 1980 to 2000. This study found that the beneficial effect of aspirin in reducing colorectal cancer incidence is dose- and duration-dependent. The maximal benefit in reducing colorectal cancer incidence occurred at a high dose of aspirin (more than fourteen 325mg aspirin tablets per week). Furthermore, significant reduction in incidence was only observed after more than 10 years of use. Women who took the above-mentioned high dose of aspirin for longer than 10 years had a multivariate relative risk (RR) for colorectal carcinoma of 0.47 (95% CI, 0.31-0.71; p<0.001).[7] The number needed to treat was 42 (at dose of more than fourteen 325mg aspirin tablets per week).

The Cancer Prevention Study II Nutrition Cohort study was a large study of long-term daily use of adult-strength aspirin. This study showed that ≥ 325mg of aspirin per day for at least five years reduced incidence of colorectal cancer by almost 30% (RR 0.68, 95% CI 0.52-0.90). Use of aspirin for less than five years was not associated with a reduction in colorectal cancer incidence.[8]

Evidence from systematic reviews

The systematic review by the United States Preventive Service Task Force (USPSTF) involved the review of relevant randomised control trials (RCTs), case-control studies and cohort studies. This review aimed to shed some light on the effectiveness of aspirin, non-aspirin NSAID and COX-2 inhibitors in chemoprevention of colorectal cancer in average-risk individuals.

In the USPSTF review, "average-risk" participants were defined as those with no known risk factors for colorectal adenoma or carcinoma (other than age). Those with a personal or family history of colorectal adenoma, or a family history of sporadic colorectal cancer were included as well.

Exclusion criteria for this review were: Familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC) syndromes. Secondary prevention studies of patients with a personal history of colorectal cancer were also excluded.

The USPSTF review concluded that aspirin appeared to have an effect in reducing incidence of colorectal cancer, particularly if it was given in high doses for more than 10 years.

However, the data available on colorectal cancer incidence reduction was inconsistent. Observational studies tended to show a protective effect, while RCTs did not show any protective effect of aspirin.

For example, the pooled relative risk (RR) for cohort studies was 0.78 (95% CI 0.63-0.97). However, the two good-quality RCTs, namely the Physician Health Study[9] and Women's Health Study[10] (which will be discussed in further detail later in the topic review), did not show any protective effect of low-dose aspirin. One possible reason for this apparent discrepancy in findings between the observational studies and RCTs could be attributed to the lower dose of aspirin used in the two RCTs. Furthermore, observational studies may have other confounding factors which are not reduced or eliminated as compared to RCTs.

Rothwell et al published a systematic review involving a 20-year follow-up of five randomised trials of aspirin versus control in primary and secondary prevention of cardiovascular events, which sought to establish the effect of aspirin on incidence and mortality of colorectal cancer. Patients on aspirin had a reduced 20-year risk of colon cancer, with incidence hazard ratio (HR) of

0.76 (95% CI 0.60 to 0.96, p=0.02) and mortality HR of 0.65 (95% CI 0.48 to 0.88, p=0.005). However, this benefit was not seen in rectal cancer. This study also found that aspirin was effective in reducing incidence of proximal colon cancer (HR 0.45, 95% CI 0.28 to 0.74, p=0.001), but not distal colon cancer (HR 1.10, 95% CI 0.73 to 1.64). There was also no further increase in benefit at aspirin doses greater than 75mg per day.[11]

Flossmann et al aimed to assess the longer-term effect of aspirin on the incidence of colorectal cancer. Their paper involved the study of two large RCTs with reliable post-trial follow-up for more than 20 years (British Doctors Aspirin Trial and UK-TIA Aspirin trial), plus a systematic review of all relevant observational studies to find out if results were consistent with those of the two RCTs. In the two RCTs mentioned, aspirin reduced the incidence of colorectal cancer (pooled HR 0.74, 95% CI 0.56 to 0.97, p=0.02 overall). The HR was 0.63 (95% CI 0.47 to 0.85, p=0.002), if subjects were allocated aspirin for 5 years or more. However, this benefit was only seen after a latency of 10 years. Consistent benefit was only seen with use of ≥ 300 mg of aspirin a day, with diminished and inconsistent results for lower or less frequent doses. This study concluded that based on data from the two RCTs, the use of ≥ 300 mg of aspirin a day for about 5 years was beneficial in primary prevention of colorectal cancer, with a latency of about 10 years. This finding was consistent with that of observational studies.[12]

C. Studies That Show No Protective Effect of Aspirin

Evidence from observational studies

The Women's Health Initiative was a prospective cohort study of postmenopausal women who were followed up for a period of over six years. This study found that aspirin use did not significantly reduce the colorectal cancer incidence, with an HR of 0.96 (95% CI 0.8 to 1.2). This was regardless of aspirin dose or duration.[13]

Paganini-Hill et al published a prospective cohort study of elderly followed up for 6.5 years, which showed that those who took aspirin daily had an associated increased risk of colon cancer for both genders combined, with RR 1.5 (95% CI 1.1 to 2.2, p<0.05).[14]

Evidence from intervention studies

Both the Physician Health Study and Women's Health Study were RCTs that found low-dose aspirin did not reduce colorectal cancer incidence.

In the Physician Health Study, it was found that low-dose aspirin at 325mg taken every other day over a period of five years was associated with an RR of colorectal cancer of 1.[15] (95% CI 0.8-1.65).[9]

In the Women's Health Study, healthy women were given low-dose aspirin 100mg every other day and followed up for an average of 10.1 years. The results showed that low-dose aspirin did not reduce colorectal cancer incidence, with an RR of 0.97 (95% CI 0.77 to 1.24, p=0.83). However, a protective effect of higher doses of aspirin could not be ruled out.[10]

D. Adverse Effects of Aspirin

The USPSTF summarised the adverse effects of aspirin based on results of systematic reviews. When aspirin was given for secondary prevention of stroke, the risk of haemorrhagic stroke was dose-dependent, varying from 0.3% to 1.1% (100 mg/day: 0.3%, 95% CI 0.2% to 0.4%; 100-325 mg/day: 0.3%, 95% CI 0.2% to 0.3%; 325 mg/day: 1.1%, 95% CI 0.7% to 1.5%).

Furthermore, aspirin was associated with an increased risk of gastrointestinal bleeding, with RR ranging from 1.6 to 2.5 times that of study subjects not on aspirin (according to systematic review of RCTs). The risks of gastrointestinal bleeding or perforation were dose-dependent.[15]

Another meta-analysis of 24 RCTs looked at the incidence of gastrointestinal bleed associated with long-term aspirin (usage for minimum of one year). It found that gastrointestinal bleeds occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (pooled odds ratio 1.68; 95% CI 1.51 to 1.88, p<0.0001). The number needed to harm was 106 (82 to 140) based on an average of 28 months' therapy. There was also no evidence that reducing the aspirin dose or using modified release formulations would reduce the incidence of gastrointestinal bleed.16

E. Effect of Aspirin on Colorectal Cancer Mortality

The findings from the USPSTF systematic review (2007) were equivocal in terms of reduction in colorectal cancer mortality: with one cohort study showing benefit while the Women's Health Study (an RCT) did not show any positive effect.[15]

However, consideration has to be given to the systematic review in 2010 involving the 20-year follow-up of five randomised trials, which showed improved mortality outcomes, with a mortality HR of 0.65 (95% CI 0.48 to 0.88, p=0.005) for colon cancer.[11] This more recent systematic review included the pooled data derived from a larger pooled population and thus would be more reflective of the actual impact on mortality, as compared to the older USPSTF systematic review.

A prospective mortality study (cohort study) showed that mortality rates from colon cancer decreased with more frequent use of aspirin for both genders. The RR of fatal colon cancer, among those who used aspirin ≥ 16 times per month for at least one year, was 0.60 in men (95% CI 0.40 to 0.89, p 0.0004) and 0.58 in women (95% CI 0.37 to 0.90, p value 0.0022).[17]

F. Cost-effectiveness of Aspirin in Chemoprevention of Colorectal Cancer

Two cost-effectiveness analyses done showed that compliance to colonoscopic screening was superior to aspirin use, as a

cost-effective strategy to prevent colorectal cancer. The studies recommended that aspirin chemoprevention not be a substitute for colonoscopic screening.[18, 19]

On the other hand, Pence et al suggested that the combination of low-dose aspirin with colonoscopy was a cost-effective strategy for colorectal cancer prevention in the general population.20 Hassan et al suggested that the combination of low-dose aspirin and colonoscopy might be a cost-effective strategy, especially in proximal colorectal cancer where the efficacy of colonoscopy might be reduced.[21]

DISCUSSION

This narrative review aims to find out if aspirin is indicated for primary prevention of colorectal cancer in the general population. In deciding if aspirin should be recommended for chemoprevention, we need to consider its efficacy and safety profile, as well as patient compliance and cost-effectiveness.

EFFICACY AND SAFETY PROFILE

From the above findings, there have been some inconsistent data with respect to the efficacy of aspirin in preventing colorectal cancer. Most of the observation studies generally indicated that aspirin did have a protective effect against colorectal cancer. However, a couple of RCTs (i.e. Physician Health Study and Women's Health Study) had not shown the same protective benefit of aspirin. The current general recommendations lean towards the stand that, for the general population, the harms (i.e. gastrointestinal bleed and haemorrhagic stroke) of aspirin appear to outweigh the potential benefits (i.e. reduction of colorectal cancer incidence).

COMPLIANCE ISSUE

Compliance might be a real issue as patients who are otherwise well, might not have much impetus to be compliant with aspirin daily. Furthermore, studies had varying recommendations on the minimal duration of aspirin required in order to achieve significant protective effects, which could range from 5 years to 10 years. A rather long duration of regular aspirin intake seemed to be required for significant protective effect. As such, compliance in the long term is an issue.

COST- EFFECTIVENESS

Two cost-effectiveness analyses showed that compliance to colonoscopic screening was a more cost-effective strategy as compared to aspirin use, in the prevention of colorectal cancer. On the other hand, two other studies suggested that the combination of low-dose aspirin with colonoscopic screening might be a cost-effective strategy, especially for proximal colorectal cancer.

LIMITATIONS

There were some limitations in this narrative review:

1. Pubmed was the journal database that was used in the article search. Ideally, the other databases such Cochrane and EMBASE could be used as well.
2. Ideally non-English articles could be included in the review and translated.

There are some limitations to current knowledge

Firstly, there's still ambiguity with regards to aspirin dose, duration, age at which to begin treatment and length of protection after cessation. The various studies conducted thus far had varying doses and durations, adding to the difficulty in determining the standard dose and duration that should be recommended.

Some of the meta-analysis studies involved studies which had cardiovascular events as main outcomes, rather than colorectal cancer. The analysis of associated incidence of colorectal cancer was retrospective.

The other limitation of the current available studies is that they were not conducted in an Asian population. As such, it is uncertain how much of the conclusions could be applied to our local population.

RECOMMENDATIONS FOR FUTURE RESEARCH

Ideally, RCTs could be carried out in the local population, with the main endpoint studied being colorectal cancer incidence. Hopefully, this would yield more information regarding optimal dose, duration, age at which to begin treatment and length of protection after cessation.

CONCLUSION

More research still needs to be conducted to provide family physicians more concrete evidence on the suitability of aspirin as a chemo-preventive agent of colorectal cancer in the general population.

Based on the data from RCTs thus far, aspirin should not be recommended as a chemo-preventive agent against colorectal cancer for the general population.

DECLARATION OF CONFLICTS OF INTEREST

The author(s) declare(s) that he/she/they has/have no conflict of interest in relation to this article.

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