

Users of Aspirin and Non-Steroidal Anti-Inflammatory Drugs Have Fewer and Smaller Dysplastic Polyps - Lessons from Colorectal Cancer Screening Program in Scotland

Taha AS^{1,2*}, McCloskey C¹, Craigen T¹, and Angerson WJ²

¹Department of Gastroenterology, University Hospital Crosshouse, Kilmarnock KA2 0BE, Scotland, UK

²Department of Medicine, Baylor College of Medicine, Houston, USA, the Chinese University of Hong Kong, UK

*Corresponding author:

Ali S Taha,
Department of Gastroenterology, University
Hospital Cross house, Kilmarnock KA2 0BE,
Scotland, UK, Tel: 44-1563827280;
Fax: 44-1563827973,
E-mail: ali.taha1@btinternet.com

Received: 10 Mar 2021

Accepted: 26 Mar 2021

Published: 01 Apr 2021

Copyright:

©2021 Taha AS, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Keywords:

Aspirin; Colorectal cancer; NSAIDs; Polyps; Screening

Abbreviations:

gFOB: Guaiac peroxidase fecal occult blood;
NSAIDs: Non-Steroidal anti-inflammatory drugs

Citation:

Taha AS. Users of Aspirin and Non-Steroidal Anti-Inflammatory Drugs Have Fewer and Smaller Dysplastic Polyps - Lessons from Colorectal Cancer Screening Program in Scotland. Japanese J Gastro Hepato. 2021; V6(7): 1-5

1. Abstract

1.1. Background & Aims: The potential influence of aspirin and NSAIDs in colorectal cancer screening programs is not clear. We aimed to assess the numbers and sizes of dysplastic polyps detected in colorectal cancer screening of subjects using low-dose aspirin, NSAIDs, and controls.

1.2. Methods: Screening kits were sent to 71026 Scottish citizens, aged 50-74 years, over the 12 calendar months of 2016: 38799 subjects filled in and returned the kits. Those with positive kits (n=849) were invited for colonoscopy. Their findings were classified according to their use of aspirin/ NSAIDs, or neither (controls). Only dysplastic or cancerous polyps were analysed.

1.3. Results: 535 subjects were colonoscoped including 165 on aspirin or NSAIDs, and 370 controls, with median (interquartile range) ages of 65 (58 – 71) and 63 (56 – 69) years, respectively, P=0.036. Polyps >10 mm or cancer were found in 16 (10%) of the aspirin/ NSAID group vs. 75 (20%) of controls, odds ratio adjusted for age and sex (95% confidence intervals), 0.39 (0.22 - 0.70), P=0.002. The median (IQR) size of dysplastic polyps including cancer in the aspirin/ NSAID group was 5 (3 – 10) vs. 9 (4 – 20) mm in controls, P=0.008.

1.4. Conclusions: In this colorectal cancer screening program, subjects taking low-dose aspirin or NSAIDs have smaller dysplastic polyps

and fewer big cancerous polyps than controls.

These results are relevant to the planning of the screening programs and provide further evidence for the potential use of aspirin or NSAIDs for colorectal cancer chemoprevention.

2. Introduction

Over the years, colorectal cancer continues to have significant health and financial consequences to the both the affected individuals and to society at large. It remains the third most common cancer after those of the lung and the breast [1]. Previous attempts at its prevention using dietary measures alone, as with high fibre diet, have not resulted in measurable or visible impact on its prevalence or outcomes [2]. Also, the concept of chemoprevention, using drug therapy, has been considered from time to time, but has not been formally recommended or implemented. The main drugs that have been considered in this area are aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) [3]. The use of these agents, while capable of causing mucosal damage throughout the gastrointestinal tract, [4-10] has also been associated with lower prevalence of colon cancer [3,10].

A more recent preventative strategy has been the increasing introduction of colorectal cancer screening programs in many parts of the world, using fecal occult blood test kits, flexible sigmoidoscopy, colonoscopy, or combinations of these interventions [11-18]. A key principle that underpins these programs, with both immediate and visible rewards, is the observation that nearly 90% of bowel cancers

are potentially curable when detected early, particularly at the polyp stage.¹, [10-18]. Given the invasive nature of these tests, their uptake by the general public remains less than ideal despite regular publicity campaigns.¹, [10-20]. This in turn has not diminished interest in chemoprevention by using low-dose aspirin or NSAIDs.

Many subjects participating in colorectal cancer screening programs also use aspirin, NSAIDs, or anticoagulants. This has resulted in an increasing interest in the direct effect of aspirin, in particular, on the incidence of polyps in these programs and in the performance of the screening kits in users of these agents, with conflicting findings [21-26]. The influence of these drugs in colorectal cancer screening programs remains unsettled; we, therefore, aimed to assess the prevalence of dysplastic polyps or lesions detected in bowel cancer screening of patients who are using low-dose aspirin (75-mg/ day), NSAIDs, and in controls not using these drugs.

3. Methods

3.1. Design

This is an analysis of prospectively collected colonoscopic findings of subjects taking part in the colorectal cancer screening program, over the 12 calendar months of 2016, in Ayrshire and Arran County located in South West Scotland, UK.

3.2. Initial Screening of the Population with Faecal Occult Blood Tests

Guaiac peroxidase fecal occult blood (gFOB, Immunostics Inc., Eantontown, NJ 07724 USA) test kits were sent to all local residents, aged 50-74 years, over the 12 calendar months of 2016, as mentioned above. The analytical cut-off for the kit (hema-screen) was 0.6 mg hemoglobin/ g feces. This work was carried out before the introduction of faecal immunological testing for colon cancer screening in Scotland. It is part of the National Bowel Screening Program funded and approved by the Scottish Government and relevant regulatory and ethics agencies. Our analysis was also approved by the Information Governance Office, NHS Ayrshire & Arran, Scotland, UK.

Those with positive kits were interviewed, and invited for colonoscopy after obtaining their informed written consent.

3.3. Colonoscopy & Histology

The colonoscopies were carried out in two centers in our county. The majority were performed at our center, University Hospital Crosshouse, Kilmarnock, affiliated to University of Glasgow, where the colonoscopists standardized their main procedures, including withdrawal time, and their descriptions of the colonoscopic findings. Bowel preparation was performed in all patients, regardless of their drug intake, using two sachets of Moviprep (TM), Norgine, Harfield, Middlesex, UK. The ingredients include macrogol, sodium sulphate, sodium chloride, potassium chloride, ascorbic acid, and sodium ascorbate. Only the procedures performed at our center were included in this analysis.

The colonoscopic findings were grouped according to the use of low-dose aspirin, NSAIDs, or neither (controls).

Two histopathologists examined all removed and biopsied lesions [27]. Discrepancies in grading the dysplasia or cancer, level of local

invasion, or completeness of removal, etc., were resolved by a third histopathologist based at the Scottish Bowel Screening Headquarters, Dundee, UK.

Only dysplastic, i.e., adenomatous, or cancerous lesions, as shown by histological examination, were included in the analysis. When polyps were present, the size (maximal diameter, as measured by the histopathologist) of the largest polyp seen was estimated and recorded for each patient. The use of aspirin, NSAIDs and smoking, alcohol intake, and other demographic factors were ascertained by direct interviews with the subjects at a formally planned pre-operative assessment before attending for colonoscopy. The colonoscopists and histopathologists were not aware of patients' use of aspirin/ NSAIDs.

3.4. Statistical Analysis

Age and polyp size were compared between groups using the Mann-Whitney test. Binary demographic variables and the prevalence of cancer and polyps were compared using Fisher's exact test. Differences in prevalence between groups were expressed as odds ratios, which were calculated both for the raw data and adjusted for covariates using logistic regression. In the primary analysis, patients taking aspirin or NSAIDs were pooled and compared with controls taking neither type of medication. In secondary analyses, aspirin and NSAIDs were assessed as separate negative risk factors for cancer and polyps.

All authors affirm that they had access to the study data and reviewed and approved the final manuscript.

4. Results

4.1. Population

In the calendar months of 2016, gFOB test kits were sent to 71026 local residents, aged 50-74 years. A total of 38799 subjects filled in and returned the kits. Those with positive kits (n=849) were interviewed, their clinical background assessed, consented, and invited for colonoscopy: this was carried out at our center on 535 subjects, including 165 on aspirin/ NSAIDs [aspirin, n=112; NSAIDs, n=46; both, n=7], and 370 controls not taking either of these drugs. These agents were taken for a median of 5 years before colonoscopy for secondary cardiovascular prevention and anti-arthritis activity, respectively. Low-dose aspirin (75-mg/ day) and therapeutic doses of NSAIDs were reported to have been used by patients on daily basis. No formal tests of compliance with their use were carried out and the results were not stratified according to daily doses or types used. Colonoscopic withdrawal times were similar in users and non-users of aspirin/ NSAIDs, median of 11 minutes.

4.2. Demography

Subjects in the aspirin/ NSAID group were significantly older than controls, (Table 1). However, the two groups were comparable with respect to gender, smoking, and drinking habits.

4.3. Polyp Size

Dysplastic colonic polyps were significantly smaller in users of aspirin/ NSAIDs. Likewise, polyps including cancer, notionally assigned a size of >40 mm, were significantly smaller in users of these drugs than in controls, (Table 1).

Table 1: Demography and polyp size in users of aspirin or NSAIDs and in Controls

	Aspirin or NSAIDs (n=165)	Controls (n=370)	P value
Age (median, IQR)	65 (58 – 71)	63 (56 – 69)	0.036
Males	102 (62 %)	207 (56 %)	0.22
Smoking	27 (16%)	57 (15%)	0.80
Alcohol	88 (54%)	210 (57%)	0.51
Polyp size, mm, median (IQR):			
- All polyps	5 (2 – 10)	8 (3 – 15)	0.015
- Polyps including cancers	5 (3 – 10)	9 (4 – 20)	0.008

4.4. Prevalence of Polyps and Cancer

Subjects taking aspirin/ NSAIDs had significantly fewer dysplastic polyps measuring greater than 5 or 10 mm, with or without cancers, (Table 2). The greatest reduction was for the largest polyps. After adjusting for demographic factors, users of aspirin/ NSAIDs also had significantly fewer cancers.

4.5. Aspirin and NSAIDs as Separate Risk Factors

(Table 3) shows the effect of aspirin and NSAIDs as separate negative risk factors for polyps and cancer. Aspirin was associated with a

significant reduction in the odds of observing large polyps or cancer after adjustment for covariates, but its effect on the prevalence of polyps overall was non-significant. NSAIDs had a stronger negative association with polyps of all sizes, which was statistically significant with or without covariate adjustment despite there being relatively small numbers of NSAIDs-taking patients. Both aspirin and NSAIDs were associated with reductions in the odds for cancer alone comparable with those seen for large polyps, but these were not statistically significant, perhaps reflecting limited statistical power owing to the relatively small number of cancers.

Table 2: Prevalence of polyps and cancer

Colonoscopic results	Aspirin or NSAIDs n=165	Control n=370	OR (95% CI)	P value	OR (95% CI)	P value
			Unadjusted		Adjusted*	
Cancer alone	7 (4 %)	31 (8 %)	0.48 (0.21 - 1.12)	0.10	0.40 (0.16 – 0.98)	0.045
Polyps (any size)	67 (41 %)	168 (45 %)	0.82 (0.57 - 1.19)	0.35	0.75 (0.51 – 1.10)	0.14
Polyps or cancer	70 (42 %)	184 (50 %)	0.74 (0.51 - 1.08)	0.13	0.67 (0.45 – 0.98)	0.040
Polyps >5 mm	27 (16 %)	99 (27 %)	0.54 (0.33 - 0.86)	0.011	0.48 (0.30 - 0.79)	0.004
Polyps >5 mm or cancer	31 (19 %)	118 (32 %)	0.49 (0.32 - 0.77)	0.002	0.44 (0.28 - 0.70)	0.001
Polyps >10 mm	11 (7 %)	54 (15 %)	0.42 (0.21 - 0.82)	0.010	0.37 (0.18 – 0.74)	0.005
Polyps >10 mm or cancer	16 (10 %)	75 (20 %)	0.42 (0.24 - 0.75)	0.003	0.37 (0.20 - 0.67)	0.001

* Odds ratios (OR) adjusted by logistic regression for age, gender, smoking and alcohol

Table 3: Aspirin and NSAIDs as separate risk factors

Colonoscopic results	Agent	OR (95% CI) Unadjusted	P value	OR (95% CI) Adjusted*	P value
Cancer alone	Aspirin	0.51 (0.19 – 1.33)	0.22	0.46 (0.17 – 1.23)	0.12
	NSAIDs	0.49 (0.11 – 2.08)	0.57	0.25 (0.03 – 1.89)	0.18
Polyps (any size)	Aspirin	1.08 (0.72 – 1.62)	0.75	0.92 (0.60 – 1.41)	0.70
	NSAIDs	0.47 (0.25 – 0.88)	0.019	0.47 (0.24 – 0.90)	0.023
Polyps or Cancer	Aspirin	0.98 (0.65 – 1.47)	1.00	0.81 (0.53 – 1.24)	0.33
	NSAIDs	0.44 (0.24 – 0.82)	0.009	0.44 (0.23 – 0.84)	0.013
Polyps >5mm	Aspirin	0.68 (0.41 – 1.14)	0.18	0.59 (0.35 – 1.01)	0.055
	NSAIDs	0.38 (0.16 – 0.92)	0.026	0.32 (0.12 – 0.84)	0.021
Polyps >5mm or cancer	Aspirin	0.63 (0.38 – 1.02)	0.064	0.52 (0.32 – 0.87)	0.013
	NSAIDs	0.36 (0.16 – 0.83)	0.015	0.32 (0.13 – 0.78)	0.012
Polyps >10 mm	Aspirin	0.53 (0.25 – 1.10)	0.11	0.47 (0.22 – 1.00)	0.052
	NSAIDs	0.26 (0.06 – 1.10)	0.047	0.13 (0.02 – 0.96)	0.046
Polyps >10mm or cancer	Aspirin	0.53 (0.28 – 0.99)	0.052	0.45 (0.24 – 0.86)	0.015
	NSAIDs	0.27 (0.08 – 0.88)	0.020	0.18 (0.04 – 0.78)	0.021

* Odds ratios (OR) adjusted by logistic regression for age, gender, smoking and alcohol

5. Discussion

In this colorectal cancer screening program, we have demonstrated that the use of low-dose aspirin or NSAIDs is associated with smaller colonic dysplastic polyps and fewer big cancerous polyps. This may renew interest in the use of these agents for colorectal cancer chemoprevention. It may also indicate that such group of subjects might require a different approach when it comes to screening them for colon cancer.

The strengths of this work include being population-based, in which seemingly normal and asymptomatic members of the public were invited to be screened and were studied by colonoscopy. It is also single center, where the colonoscopists had standardized their assessments, and their findings were backed up by histological examination. On the other hand, the main weakness, which is common to other similar screening programs, is the relatively low rate of uptake by the general public. [1, 12, 13, 19, 20] Also, while the screening process and the data collection were prospective, the analysis of use of aspirin or NSAIDs was observational in nature and did not involve randomization to their use.

We studied patients with positive screening kits, and, amongst these, we compared users with non-users of aspirin/ NSAIDs. This is because the colorectal cancer screening program allows performing colonoscopy only in positive subjects. It is impossible to try to estimate the ethical and logistical issues that might be encountered in trying to colonoscope another 37, 950 negative subjects in one year of screening in one region; and to do so is beyond the remit of our work.

It could be legitimately argued that aspirin/ NSAIDs, by causing varying degrees of blood loss from anywhere in the gastrointestinal tract including the colon, result in positive gFOB tests, the users of these drugs are then screened earlier than non-users, and they will, as a result have fewer and smaller polyps. Against this scenario are two points: firstly, the screening program invited all subjects aged 50-74 years to take part in the process and regardless of their drug use. Secondly, our aspirin/ NSAID users were in fact older than controls and still had fewer and smaller lesions. Therefore, the chemopreventive potential of these drugs remains a more plausible explanation for our results and this is supported by a recent population-based controlled study [23].

The mechanism behind the chemopreventive potential of aspirin/ NSAIDs is not clear, but it was previously suggested that aspirin reduces colorectal cancer incidence and increases survival in cancers over-expressing cyclo-oxygenase-2 enzyme [28, 29]. The length of time these agents have to be used, in order for them to confer their potential benefit, is also not clear. Our subjects used them for a median of 5 years: this is consistent with previous works that found a beneficial effect when used for 1-10 years [3]. This may also explain the failure of a recent study to demonstrate reduction in the number of polyps in response to using aspirin for only one year [21].

Low-dose aspirin and NSAIDs possess a number of criteria that are desirable to have in chemopreventive agents. These include being relatively cheap, easy to administer, and, more importantly, effective.

Therefore, their potential benefits have to be balanced against their known side effects particularly those on the gastrointestinal tract [4-10]. To tip this balance in favour of benefit, the drugs may be used in subjects at high risk of developing colorectal cancer such as those with strong family history of the condition and in patients with multiple polyps. Also, agents with milder or fewer side effects may be considered [30].

In conclusion, our results have two main clinical implications: one is related to the potential chemopreventive benefit of aspirin or NSAIDs against colorectal polyps and cancer and we accept that this is likely to continue to be debated. The second, and possibly the less contentious implication, is that users of aspirin or NSAIDs, and there are many of them, are likely to behave differently when they take part in colorectal screening programs. Perhaps they could be screened every 3 or more years instead of the current practice of biannual screening [19, 20].

References:

1. Bowel screening in Scotland. www.nhsinform.scot/healthy-living/screening/bowel/bowel. 2021.
2. Fuchs CF, Giovannucci EL, Colditz GA. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med*. 1999; 340: 169-76.
3. Din FVN, Theodoratou E, Farrington SM. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. *Gut*. 2010; 59: 1670-9.
4. Strate LL. Nonsteroidal anti-inflammatory and antiplatelet drugs and the risk of GI bleeding: don't forget the colon. *Gastrointest Endosc*. 2014; 80: 1132-4.
5. Taha AS, McCloskey C, McSkimming P, McConnachie A. Misoprostol for the healing of small bowel ulcers in obscure bleeding related to aspirin and non-steroidal anti-inflammatory drugs (MASTERS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol* 2018; 3: 469-76.
6. Taha AS, McCloskey C, Craigen T, Simpson A, Angerson WJ. Small bowel and other GI lesions in obscure gastro-intestinal bleeding – low dose aspirin vs. NSAIDs. Screening Phase of the MASTERS Trial. *Gastroenterology*. 2017; 152: 475.
7. Taha AS, McCloskey C, Craigen A, Simpson A, Angerson WJ. Occult vs. overt upper gastrointestinal bleeding – inverse relationship and the use of mucosal damaging and protective drugs. *Aliment Pharmacol Ther*. 2015; 42: 375-82.
8. Taha AS. Editorial: lower gastrointestinal bleeding and low-dose aspirin. *Aliment Pharmacol Ther*. 2017; 46: 199.
9. Chen WC, Lin KH, Huang YT. Risk of lower gastrointestinal bleeding in low-dose aspirin users. *Aliment Pharmacol Ther*. 2017; 45: 1542-50.
10. Emilsson L, Holme O, Bretthauer M. Systematic review with meta-analysis: the comparative effectiveness of aspirin vs. Screening for colorectal cancer prevention. *Aliment Pharmacol Ther*. 2017; 45: 193-204.
11. Lowenfels AB. Fecal occult blood testing as a screening procedure for colorectal cancer. *Annals of Oncology*. 2002; 13: 40-43.

12. Kallenberg FGJ, Vleugels JLA, de Wijkerslooth TR. Adding family history to faecal immunochemical testing increases the detection of advanced neoplasia in a colorectal cancer screening programme. *Aliment Pharmacol Ther.* 2016; 44: 88–96.
13. Domingo BK, Grossman DC. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016; 315: 2564–75.
14. Pinsky PF. Flexible sigmoidoscopy screening: is once enough? *Lancet* 2017; 389: 1275-7.
15. Atkin WS, Wooldrage K, Parkin DM. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet.* 2017; 389: 1299–311.
16. Doubeni CA, Weinmann S, Adams K. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. *Ann Intern Med.* 2013; 158: 312–20.
17. Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M, et al. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology* 2014; 146: 709–17.
18. Nishihara R, Wu K, Lochhead P. Long-term colorectal-cancer incidence, and mortality after lower endoscopy. *N Engl J Med.* 2013; 369: 1095–105.
19. Scottish Bowel Screening Programme. Key Performance Indicators Report: November 2017 data submission. 2021.
20. Senore C, Basu P, Anttila A. Performance of colorectal cancer screening in the European Union member states: data from the second European screening report. *Gut* 2019; 68: 1232-44.
21. Hull MA, Sprange K, Hepburn T. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFood Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. *Lancet.* 2018; 392: 2583–94.
22. Dekker E, Kaminski MF. Take a pill for no more polyps: is it that simple? *Lancet* 2018; 392: 2519 – 21.
23. Miguel RA, Rodriguez LAG, Gil M. Population-based case-control study: chemoprotection of colorectal cancer with non-aspirin non-steroidal anti-inflammatory drugs and other drugs for pain control. *Aliment Pharmacol Ther* 2019; 50: 295-305.
24. Randel KR, Botteri E, Romstad KMK. Effects of oral anticoagulants and aspirin on performance of fecal immunochemical tests in colorectal cancer screening. *Gastroenterology* 2019; 156: 1642-9.
25. Spaander MCW, Kuipers EJ. Effects of oral anticoagulants and aspirin use on ability of fecal immunochemical tests to detect advanced neoplasia. *Gastroenterology* 2019; 156: 1553-5.
26. Nieuwenburg SAV, Vuik FER, Kruip MJHA. Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis. *Gut* 2019; 68: 866-72.
27. Schlemper RJ, Riddell RH, Kato Y. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut.* 2000; 47: 251–5.
28. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med.* 2007; 356: 2131-42.
29. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA.* 2009; 302: 649-58.
30. Chan FK, Lanas A, Scheiman J. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CON-DOR): a randomised trial. *Lancet.* 2010; 376: 173-9.