NON-STEROIDAL ANTI-INFLAMMATORY DRUGS BUT NOT ASPIRIN ARE ASSOCIATED WITH A LOWER RISK OF POST-COLONOSCOPY COLORECTAL CANCER

SHORT TITLE: NSAID AND PCCRC

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Specific author contributions: Dr. Ka Shing Cheung was involved with study concept and design; analysis and interpretation of data; drafting of manuscript; and approval of the final version of the manuscript. Dr. Esther W Chan, Ms Lijia Chen and Dr Wai Kay Seto were involved with acquisition of data; critical revision of the manuscript for important intellectual content; and approval of the final version of the manuscript. Professors Ian CK Wong and Wai K Leung were involved with the study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.

Financial support: Health and Medical Research Fund, Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (Reference no: 16173001)

Conflicts of Interest:

EWC has received honorarium from Bayer, Bristol-Myers Squibb, Pfizer and Takeda, for work unrelated to this study. ICKW has received grant from Janssen, Pfizer, Bayer, Amgen and Novartis but not related with the present study. WKS received honorarium for attending advisory board meetings of AbbVie, Celltrion and Gilead; speaker fees from AbbVie, Astrazeneca, Eisai, Gilead and Ipsen; and research funding from Gilead. WKL has received speaker fee from Eisai, Ipsen and honorarium for attending advisory board for Janssen and Pfizer. There was none to declare for KSC and LC.

Word count: 3459

Word count of abstract: 249

Number of tables: 5; Number of figures: 2

Number of supplementary tables: 4; Number of supplementary figures: 0

ABSTRACT

Background: Although non-steroidal anti-inflammatory drugs (NSAIDs) reduces colorectal cancer (CRC) risk, its role in preventing post-colonoscopy CRC remains undetermined.

Aims: We aimed to investigate whether NSAIDs could reduce PCCRC risk after a negative baseline colonoscopy.

Methods: This is a retrospective cohort study based on a territory-wide healthcare database of Hong Kong. All patients (aged 40 or above) who underwent colonoscopies between 2005 and 2013. Exclusion criteria included CRC detected within six months of index colonoscopy, prior CRC, inflammatory bowel disease and prior colectomy. The primary outcome was post-colonoscopy CRC-3y diagnosed between 6 and 36 months after index colonoscopy. Sites of CRC were categorized as proximal (proximal to splenic flexure) and distal cancer. The adjusted hazards ratio (aHR) of post-colonoscopy CRC-3y with NSAID and aspirin use (defined as cumulative use for ≥90 days within five years before index colonoscopy) was derived by propensity score (PS) regression adjustment of 22 covariates (including patient's factors, concurrent medication use and endoscopy center's performance).

Results: Of 187,897 eligible patients, 21,757 (11.6%) were NSAID users. 854 (0.45%) developed post-colonoscopy CRC-3y (proximal cancer:147 [17.2%]). NSAIDs were associated with a lower post-colonoscopy CRC-3y risk (aHR:0.54, 95% CI:0.41–0.70), but not CRC that developed >3years (aHR:0.78, 95% CI 0.56-1.09). The aHR was 0.48 (95% CI:0.24–0.95) for proximal and 0.55 (95% CI:0.40–0.74) for distal cancer. A duration- and frequency-response relationship was observed (p-trend<0.001). For aspirin, the aHR was 1.01 (95% CI:0.80–1.28).

Conclusions: Non-aspirin NSAIDs were associated with lower post-colonoscopy CRC risk after a negative baseline colonoscopy.

Keywords: NSAID, colon cancer, rectal cancer, adenocarcinoma, interval cancer, post-colonoscopy colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and second leading cause of death worldwide.[1] Screening colonoscopy can reduce incidence[2-4] and mortality of CRC,[4-6] but CRC can still occur after initial colonoscopy in which no cancer was detected. These cancers are termed "post-colonoscopy CRC" by the recent World Endoscopy Organization (WEO) consensus.[7] In contrast to interval CRC which refers to cancer that develops shortly after screening/surveillance colonoscopy, post-colonoscopy CRC encompasses cancers that develops after any diagnostic colonoscopy and could account for up to 9% of all diagnosed CRCs,[8, 9] with a predilection for proximal colon.[10] The mechanisms for post-colonoscopy CRC development could be accounted by incomplete colonoscopy (due to technical difficulty or luminal obstruction), missed lesions at the index colonoscopy (around 50% of the cases),[8] incomplete resection of polyps, tumors arising from alternative pathway including the sessile serrated pathway with rapid growth,[11-13] and tumor seeding by biopsy forceps or needle injectors.[14]

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to possess chemopreventive effect on CRC. A systematic review of clinical studies showed that NSAIDs reduced both adenoma and CRC development.[15] A recent population-based case-control study shows that non-aspirin NSAIDs were associated with a duration-dependent risk reduction of CRC with effect persisting up to one year after discontinuation.[16] Multiple mechanisms have been proposed. First, NSAIDs induce apoptosis in CRC cells by inhibiting prostaglandin (PG) synthesis and hence increase in the levels of precursor arachidonic acid, which is involved in mediating conversion of sphingomyelin to ceramide, a mediator of apoptosis.[17] Second, PGs are shown to

be associated with tumour angiogenesis, proliferation of tumour cells and immune surveillance inhibition.[18] Third, inhibition of cyclooxygenase-2 (COX-2) derived PG production inactivates epidermal growth factor receptor (EGFR) signalling.[19] Other non-COX-mediated mechanisms of NSAIDs in cancer prevention include inhibition of activating pathways of nuclear factor kappa B (NF-kappa B)[20] and insulin-related neoplastic pathways.[21] While NSAIDs inhibits both COX-1 and COX-2, aspirin is more selective for COX-1 inhibition,[22, 23] which may explain why NSAIDs appear to be more efficacious than aspirin in preventing advanced metachronous neoplasia in patients with previous colorectal neoplasia.[24] In addition, the chemopreventive effect of aspirin requires prolonged use (at least 5 years) in comparison to NSAIDs.[15, 25, 26]

While there is ample evidence that NSAIDs and aspirin reduce colorectal adenomas and cancer, studies that specifically focus on their chemopreventive role in post-colonoscopy CRC are lacking. NSAIDs/aspirin may not be effective or minimally effective in individuals who have already undergone colonoscopy in which no cancer was found and all polyps were removed. Moreover, as NSAIDs are associated with side effects like gastrointestinal bleeding (GIB), nephrotoxicity, and cardiovascular events, subgroups that will benefit from the chemopreventive effects of NSAIDs should be identified.

In this study, we aimed to determine the association between use of NSAIDs/aspirin and post-colonoscopy CRC development in a large cohort of patients who had undergone colonoscopy with no baseline CRC.

METHODS

Study design and data source

This was a retrospective cohort study with data retrieved from a territory-wide electronic healthcare database, the Clinical Data Analysis and Reporting System (CDARS), which is managed by the Hong Kong Hospital Authority. The Hong Kong Hospital Authority is the only statutory public healthcare provider offering 90% of all primary, secondary and tertiary care services of Hong Kong with a population of 7.3 million. The CDARS records all patient's demographics and clinical data including hospitalization, visits to outpatient clinics, investigation procedures and results, endoscopic and surgical procedures, as well as drug prescription and dispensing history. A number of territory-wide studies have been conducted by using the CDARS, with a high degree of coding accuracy (>90%) of the International Classification of Diseases, Ninth Revision (ICD-9) codings.[27-33]

Outcome definition and study subjects

Individuals aged at least 40 years and had undergone colonoscopy between 2005 and 2013 in all public hospitals in Hong Kong were identified. We excluded patients with prior CRC, inflammatory bowel disease, prior colectomy and detected CRC (defined as cancer found within 6 months of the index colonoscopy). The patient selection process is depicted in **Figure 1**. The primary outcome of interest was post-colonoscopy CRC between 6 and 36 months (post-colonoscopy CRC-3y), which is the definition of the World Endoscopy Organization (WEO) consensus on "post-colonoscopy CRC rate for an interval of 3 year".[7] This definition was also adopted by other previous studies.[34-39] In contrast, detected CRC was defined as CRC diagnosed within 6 months of index colonoscopy, presuming that CRC suspected at index

colonoscopy would be confirmed within 6 months.[34] The secondary outcomes of interest were (1) post-colonoscopy CRC-all (i.e. all post-colonoscopy CRC cases developing >6 months after index colonoscopy), and (2) post-colonoscopy CRC >3y (i.e. post-colonoscopy CRC cases developing >36 months after index colonoscopy) (**Figure 2**). Cancer site was subcategorized into proximal (from caecum to transverse colon [ICD-9 codes 153.4, 153.6, 153.0, 153.1]) and distal colon (from splenic flexure to rectum [ICD-9 codes 153.2, 153.3, 153.7, 154.0, 154.1]).

To investigate the primary outcome, we observed patients from 6 months after index colonoscopy (i.e. index date) and censored them at post-colonoscopy CRC-3y diagnosis, death or end of 36 months. For the secondary outcomes, we observed patients from 6 months after index colonoscopy and censored them at CRC diagnosis, death or end of study (31 December 2017).

Data validation

Due to anonymization of patient's identity in the electronic database, only data on the outcome of post-colonoscopy CRC-3y (n=137) from our own center, Queen Mary Hospital, could be retrieved for validation. The coding accuracy was 97.1%.

Study variables

The primary exposure of interest was NSAID use before index colonoscopy. Aspirin use was considered as a secondary exposure of interest. Covariates taken into analysis for post-colonoscopy CRC-3y risk included patient's factors and endoscopy centres' performance (annual endoscopy volume and polypectomy rate).[34, 36, 37, 40] Specifically, patient's factors included age at index colonoscopy, sex, history of colonic polyps,

polypectomy at index colonoscopy, smoking status, heavy alcohol consumption, comorbidities (cardiovascular, metabolic, neurological, renal and liver diseases) (**Table 1**) and concurrent usage of medications (aspirin,[41] cyclooxygenase [COX]-2 inhibitors[15] and statins[39, 42]). **eTable 1** provides details of ICD-9 codes of each disease. Smoking was identified by ICD-9 code of V15.82 and by proxy of chronic obstructive pulmonary disease (COPD). Heavy alcohol consumption was inferred from presence of alcohol-related disorders, including hepatic, gastrointestinal, neurological and psychiatric diseases.

Medication prescription and dispensing data were traced up to 5 years before index colonoscopy. All medication use including NSAIDs was defined as usage for ≥90 days as in our previous study.[39] The treatment duration of individual prescription between prescription start date and end date was calculated for a particular drug, and was then summed up as total treatment duration. Effects of individual NSAID (including diclofenac, naproxen, ibuprofen, mefenamic acid, indomethacin, sulindac, piroxicam, and ketoprofen) on post-colonoscopy CRC-3y were also analysed.

To study dose-response relationship, duration of NSAID use was categorized into three groups: (i) never use, (ii) ≤1 year and (iii) >1 year. Frequency of NSAID use was also categorized into three groups: (i) never use, (ii) <weekly use and (iii) ≥weekly use. The frequency of use was calculated by dividing the number of days of NSAID use by 5 years.

We further explored the association between the timing of NSAID uses before index colonoscopy and post-colonoscopy CRC. Current NSAID users were defined when

the last prescription ended ≤6 months before the index colonoscopy, while past users were defined when the last prescription ended >6 months before the index colonoscopy. NSAID non-users were defined when there was no recorded prescription both before and after index colonoscopy.

In addition, we determined the association of post-colonoscopy NSAID use (defined as ≥90-day use after index colonoscopy) on risks of post-colonoscopy CRC.

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median and interquartile range (IQR). Mann-Whitney U-test was used to compare continuous variables of two groups. Chi-square test or Fisher's exact test was applied for categorical variables. Propensity score (PS) regression adjustment was used as the primary analysis method to determine effect of NSAIDs on post-colonoscopy CRC-3y risk.[43, 44] PS represented the probability of NSAID use predicted by the 22 aforementioned covariates in a logistic regression model. Cox proportional hazards model with PS regression adjustment was used to calculate the adjusted hazard ratio (aHR) of post-colonoscopy CRC-3y with NSAID use.

Stratified analysis was performed according to cancer location (proximal or distal colon). Subgroup analysis was performed according to age, sex, history of diabetes mellitus and colonic polyps. To determine effect of NSAIDs on secondary outcomes, the aHR was derived by Cox proportional hazards model with PS regression adjustment.

PS matching was also performed to achieve balance in covariates between the two groups.[43-45] NSAID users were matched to NSAID non-users in a 1:2 ratio without replacement using a greedy distance-based matching algorithm with the logit of the PS within 0.1 standard deviation. Absolute standardized difference (ASD) allows an objective assessment of the matching result. It was defined as absolute difference in means or proportions divided by pooled standard deviation. Balance of covariates between two groups was achieved if an ASD was less than 0.20.[46] A two-sided p-value of <0.05 was used to define statistical significance.

RESULTS

Patient Characteristics and Risk of post-colonoscopy CRC-3y

Out of 234,827 patients who had undergone colonoscopy between 2005 and 2013, 187,897 (male: 91,961 [48.9%]) patients fulfilled the selection criteria (**Figure 1**), with a total duration of follow-up of 560,471 person-years. The median age at index colonoscopy was 60.6 years (IQR:52.3–71.9).

In total, there were 854 post-colonoscopy CRC-3y cases including 707 (82.8%) distal and 147 (17.2%) proximal cancers with an overall incidence rate of 15.2 per 10,000 person-years. The median age of diagnosis of post-colonoscopy CRC-3y was 75.9 years (IQR:65.5–83.8); and the median interval between index colonoscopy and post-colonoscopy CRC-3y was 1.2 years (IQR:0.8–1.9).

Association between NSAID use and post-colonoscopy CRC-3y

There were 21,757 NSAID users and the median duration of NSAID use was 0.7 years (IQR:0.4–1.6) within five years preceding index colonoscopy. Among them, 55 (0.25%) patients were diagnosed with post-colonoscopy CRC-3y with an incidence rate of 8.4 per 10,000 person-years. For NSAID non-users, the incidence rate of post-colonoscopy CRC-3y was 16.1 per 10,000 person-years.

On crude analysis, the HR of post-colonoscopy CRC-3y with NSAID use was 0.53 (95% CI:0.40 – 0.69). On PS regression adjustment, the aHR of post-colonoscopy CRC-3y with NSAID use was 0.54 (95% CI:0.41–0.70) (**Table 2**). Stratified analysis shows that NSAID use was associated with a lower post-colonoscopy CRC-3y risk in both proximal (aHR:0.48, 95% CI:0.24–0.95) and distal colon (aHR:0.55, 95% CI:

0.40–0.74). As for aspirin, the aHR of post-colonoscopy CRC-3y was 1.01 (95% CI:0.80–1.28;p=0.92).

Effects of individual NSAID on post-colonoscopy CRC-3y risk

Of the 21,757 NSAID users, 3,545 used more than one type of NSAIDs and were excluded in this analysis. **Table 3** shows the effects of individual NSAIDs on post-colonoscopy CRC-3y risk. Diclofenac (n=10,648) and naproxen (n=2,675) were the two NSAIDs found to be associated with a reduced post-colonoscopy CRC-3y risk (diclofenac, aHR: 0.48, 95% CI: 0.33–0.73; naproxen, aHR: 0.38, 95% CI: 0.16–0.92). There were no statistically significant association between post-colonoscopy CRC-3y and other NSAIDs (ibuprofen, mefenamic acid, indomethacin, sulindac, piroxicam and ketoprofen).

Duration- and frequency-response between NSAID use and post-colonoscopy CRC-3y

Table 4 shows that when compared with never user, a longer duration of NSAID use (>1 year) offers greater protection against post-colonoscopy CRC-3y (aHR:0.42, 95% CI:0.26–0.65) than shorter duration (≤1 year) of NSAID use (aHR:0.53, 95% CI:0.45–0.62;p-trend <0.001). Similar findings were observed for both proximal and distal cancers.

When compared with never user, more frequent NSAID use (≥weekly) also offers greater protection against post-colonoscopy CRC-3y (aHR:0.46, 95% CI:0.32–0.67) than infrequent (<weekly) NSAID use (aHR:0.53, 95% CI:0.45–0.61;p-trend<0.001). This finding was again observed for both proximal and distal cancer.

Subgroup analysis

Table 5 shows that protective effect of NSAIDs was limited to patients aged ≥60 years (aHR:0.48, 95% CI:0.35–0.66) and patients without diabetes mellitus (aHR:0.55, 95% CI:0.41–0.73). The aHR of post-colonoscopy CRC-3y with NSAIDs was lower in females (aHR:0.43, 95% CI:0.28–0.66) than in males (aHR:0.63, 95% CI:0.44–0.91). NSAIDs were also associated with a significantly lower post-colonoscopy CRC-3y risk in those without history of colonic polyps (aHR:0.46, 95% CI:0.32–0.67) but not in those with history of colonic polyps (aHR:0.67, 95% CI:0.45–1.01).

Association between NSAID use and secondary outcomes (post-colonoscopy CRC-all and post-colonoscopy CRC>3y)

We further looked into the effects of NSAIDs on post-colonoscopy CRC that developed in different time frames after index colonoscopy. There were a total of 1,290 post-colonoscopy CRC-all cases (i.e. all CRC cases diagnosed >6 months after index colonoscopy) including 436 (0.2%) PCCRC >3y (median:5.2 years; IQR:3.7–7.2). While NSAID use was associated with a lower risk of post-colonoscopy CRC-all (aHR:0.58, 95% CI:0.50–0.76; p<0.001), the benefit was not observed for post-colonoscopy CRC>3y (aHR:0.78, 95% CI:0.56–1.09; p=0.149).

Results from PS matching

Before PS matching, the majority of covariates were well balanced (ASD<0.2), except for sex (**eTable 2**). After PS matching, the cohort number was 64,806 including 21,650 NSAID users and 43,156 NSAID non-users, with good balance of all covariates (ASD<0.2). There were 246 (0.4%) post-colonoscopy CRC-3y cases in

this matched cohort and NSAID use was also associated with a lower post-colonoscopy CRC-3y risk (HR:0.57, 95% CI:0.42–0.77).

Effects of current or past NSAID use on post-colonoscopy CRC

The aHR of post-colonoscopy CRC-3y with current and past NSAID use was 0.55 (95% CI:0.43–0.71) and 0.58 (95% CI:0.49–0.69), respectively (**eTable 3**). The corresponding aHR of post-colonoscopy CRC-all with current and past NSAID use was 0.61 (95% CI:0.50–0.74) and 0.65 (95% CI:0.57–0.74), respectively. The aHR of post-colonoscopy CRC>3y with current and past NSAID use was 0.74 (95% CI:0.53–1.02) and 0.80 (95% CI:0.64–0.99), respectively.

Effects of NSAID use after index colonoscopy on post-colonoscopy CRC

The aHR of post-colonoscopy CRC-3y with post-colonoscopy NSAID use was 0.50 (95% CI:0.28–0.91), while the aHR of post-colonoscopy CRC-all and post-colonoscopy CRC>3y was 0.40 (95% CI:0.28–0.57) and 0.64(95% CI:0.40–1.01), respectively (**eTable 4**).

DISCUSSION

Although NSAIDs have been shown to be associated with a lower risk of CRC,[15] studies on the role of NSAIDs in post-colonoscopy CRC (which accounts for up to 9% of all diagnosed CRCs) are lacking.[8] To our knowledge, this is the first study involving more than 180,000 subjects to demonstrate the potential chemopreventive effects of NSAIDs on post-colonoscopy CRC. We showed that NSAIDs were associated with a 47% lower risk of post-colonoscopy CRC-3y and the benefits were observed for both proximal and distal cancers.

Although the magnitude of protection of NSAIDs against post-colonoscopy CRC-3y in our study was similar to that reported in studies on NSAIDs against all CRCs,[15] previous studies failed to stratify cancers into detected CRC and post-colonoscopy CRC. Results from this study would therefore shed new light onto the potential chemopreventive effects NSAIDs on CRC development according to the timing of NSAID uses and colonoscopy. Intuitively, NSAIDs appear to inhibit growth of pre-existing neoplastic lesions that are either missed or residual lesions left after polypectomy [18, 19, 47] as well as reducing the number and size of colonic adenomas.[48, 49] The effect of NSAIDs on post-colonoscopy CRC>3y however was non-significant on the main analysis. Further studies with even larger sample size may be needed to avoid possible underpower of the subgroup analysis in this study.

When individual NSAIDs were analyzed, diclofenac and naproxen were both associated with reduced post-colonoscopy CRC-3y risk. In contrast, a recent study showed all nearly all non-aspirin NSAIDs were associated with reduced CRC risk.[16] However, our results on individual NSAID analysis should also be interpreted with

caution due to the small number of events in patients using NSAIDs other than diclofenac and naproxen.

Interestingly, aspirin was not found to be associated with a lower post-colonoscopy CRC-3y risk in this study. First, while COX-2 inhibition is believed to play an important role in the chemopreventive effect of NSAIDs,[22, 23] aspirin is more selective for COX-1 inhibition. Our finding is in line with a recent network meta-analysis which showed that NSAIDs are superior to low-dose and high-dose aspirin in preventing advanced metachronous neoplasia (advanced adenoma and CRC) in patients with previous colorectal neoplasia (odds ratio of 0.37 and 0.71 for NSAIDs and aspirin respectively).[24] Second, chemopreventive effect of aspirin depends on duration of use and latency period. Both post-hoc analysis of clinical trials and prospective studies have shown that chemopreventive effect of aspirin is evident only after more than 5 years of use with a latency period of at least 10 years.[25, 26] On the other hand, multiple observational studies have demonstrated a much shorter duration of NSAID use might be enough for the chemopreventive effect to exert.[15] Collectively, these data might hint that NSAIDs appear to be more potent than aspirin on CRC prevention, particularly over a relatively short period of time as in post-colonoscopy CRC prevention.

In this study, the beneficial effect of NSAIDs was found to be similar in both proximal and distal cancers. In contrast, the chemopreventive effect of statins on post-colonoscopy CRC-3y is limited to proximal cancer as demonstrated in our recent study.[39] The current subgroup analysis also shows that beneficial effect of NSAIDs was observed in both sex, but may be higher in females. However, it was only

significant among those aged 60 years or above, which may be explained by lower burden of both adenomatous[50] and serrated polyps[51] in younger patients, and hence a lower risk of missed colonic polyps or incomplete resection of lesions. The beneficial effect of NSAIDs was also limited to non-diabetic patients and those without history of colonic polyps. Hyperinsulinemia in diabetic patients, which promotes cancer growth, may override beneficial effect of NSAIDs. However, cautions should be undertaken in interpreting these results due to possible underpower from subgroup analysis, in particular those with history of colonic polyps in which borderline significance was noted. As NSAIDs are associated with gastrointestinal bleeding and cardiovascular diseases,[15] subgroup analysis provide insights into which subgroup of patients may benefit more from NSAID use. Further studies are warranted to determine whether there are subgroups in which a favorable risk-benefit profile exists. Concomitant use of proton pump inhibitors (PPIs) to reduce risk of upper GIB may also be considered to increase the benefit-risk ratio in at-risk groups, as a recent study showed that the chemopreventive effect of NSAIDs on CRC was not modified by PPIs.

There are several strengths of this study. First, the use of territory-wide healthcare database, which captured all diagnoses, drug prescription and dispensing history, would limit some of the biases common to traditional observational studies including selection and recall biases.[41] Importantly, “reverse causality” was minimized by defining NSAID exposure as baseline drug use prior to index colonoscopy. This is well illustrated by another study showing a possible “reverse causality” mainly occurred when NSAID use within 1-6 months before CRC diagnosis was considered.[47] Immortal time bias was negligible in this study as the primary analysis

focussed on NSAID use before index colonoscopy. Second, no previous studies specifically investigated the effect of NSAIDs in patients who had prior colonoscopy and negative for CRC.[15]

Certain limitations of this study exist. First, data on some of the risk factors for CRC like family history and lifestyle factors were unavailable in the electronic database. However, the prevalence of positive family history of CRC would unlikely to differ between the NSAID users and non-users as they shared similar baseline characteristics, in particular history of colonic polyps and polypectomy. Although true prevalence of smoking and alcoholism may be underestimated by diagnosis coding, cardiovascular risk factors and diseases were similar between NSAID users and non-users (**Table 1**). Second, drug compliance and over-the-counter NSAID use could not be ascertained, although this is likely a non-differential misclassification bias attenuating result to null. Third, some quality measures related to index colonoscopy such as individual endoscopist's adenoma detection rate, quality of bowel preparation, polyp characteristics (e.g. number, size, histology) were not available in the database. Instead, the center's colonoscopy volume and polypectomy rates, two surrogate markers of center's performances, were considered. It is also unlikely that these characteristics determined NSAID use. Fourth, the causes of post-colonoscopy CRC-3y could not be defined, which prevent further delineation of the exact chemopreventive mechanisms of NSAIDs. Fifth, as inherent to all observational studies, residual/unmeasured confounding is possible, although a large number of variables were included to minimize this risk. Sixth, as the majority of our patients are Chinese, generalizability should be corroborated by studies on different ethnic groups.

CONCLUSION

NSAID, but not aspirin, use before colonoscopy were associated with a 46% lower risk in post-colonoscopy CRC-3y risk. As NSAIDs are associated with potential adverse effects, further studies are warranted to identify the subgroup of patients who will benefit more from NSAIDs after considering the risk-benefit profile.

FIGURE LEGEND

Figure 1: Patient selection flow diagram

CRC, colorectal cancer; CLN, colonoscopy

Figure 2: Study time frame

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; CRC, colorectal cancer; CLN, colonoscopy

Detected CRC: CRC diagnosed within 6 months after index colonoscopy

post-colonoscopy CRC-3y: CRC diagnosed between 6 to 36 months after index colonoscopy

post-colonoscopy CRC-all: CRC diagnosed >6 months after index colonoscopy

post-colonoscopy CRC>3y: CRC diagnosed >36 months after index colonoscopy

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Table 1. Characteristics of NSAID and NSAID non-users

	NSAID users (n=21,757)	NSAID non-users (n=166,140)
Age at index colonoscopy (years)*	61.2 (53.9 – 71.7)	60.5 (52.1 – 71.9)
Male sex (n, %)	8503 (39.1%)	83458 (50.2%)
History of colonic polyps (n, %)	4345 (20.0%)	34721 (20.9%)
Polypectomy at index colonoscopy (n, %)	3203 (14.7%)	25521 (15.4%)
Smoking (n, %)	391 (1.8%)	3483 (2.1%)
Alcohol (n, %)	118 (0.5%)	947 (0.6%)
DM (n, %)	2388 (11.0%)	15547 (9.4%)
Hypertension (n, %)	4302 (19.8%)	24680 (14.9%)
Dyslipidemia (n, %)	1462 (6.7%)	8095 (4.9%)
AF (n, %)	567 (2.6%)	5106 (3.1%)
IHD (n, %)	1770 (8.1%)	11496 (6.9%)
CHF (n, %)	777 (3.6%)	5525 (3.3%)
Stroke (n, %)	878 (4.0%)	6760 (4.1%)
CRF (n, %)	357 (1.6%)	3567 (2.1%)
Cirrhosis (n, %)	96 (0.4%)	1154 (0.7%)
Dementia (n, %)	124 (0.6%)	1134 (0.7%)
Parkinsonism (n, %)	94 (0.4%)	685 (0.4%)
Aspirin (n, %)	3866 (17.8%)	24703 (14.9%)
COX-2 inhibitors (n,%)	237 (1.1%)	141 (0.1%)
Statins (n,%)	3786 (17.4%)	21661 (13.0%)
Annual center endoscopy volume*	2942 (2054 – 3397)	2892 (2045 – 3363)
Annual center polypectomy rate*	25.0% (21.8% - 28.6%)	24.7% (21.7% - 28.4%)

* Continuous variables were expressed as median (years) with interquartile range

Drug use was defined as at least 90-day use

DM, diabetes mellitus; AF, atrial fibrillation; IHD, ischemic heart disease; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2

Table 2. Association between NSAID use and risk of post-colonoscopy CRC-3y for the whole cohort and according to cancer sites (proximal and distal cancer)

	Crude analysis		PS adjustment	
	(n=187,897, post-colonoscopy CRC-3y=854)		(n=187,897, post-colonoscopy CRC-3y=854)	
All post-colonoscopy CRC-3y	**HR**	**95% CI**	**AHR***	**95% CI**
NSAID non-use	Ref	-	Ref	-
NSAID use (at least 90 days)	0.53	0.40 – 0.69	0.54	0.41 – 0.70
	(n=187,190, post-colonoscopy CRC-3y=147)		(n=187,190, post-colonoscopy CRC-3y=147)	
Proximal Cancer	**HR**	**95% CI**	**AHR***	**95% CI**
NSAID non-use	Ref	-	Ref	-
NSAID use (at least 90 days)	0.50	0.25 – 0.98	0.48	0.24 – 0.95
	(n=187,750, post-colonoscopy CRC-3y=707)		(n=187,750, post-colonoscopy CRC -3y=707)	
Distal Cancer	**HR**	**95% CI**	**AHR***	**95% CI**
NSAID non-use	Ref	-	Ref	-
NSAID use (at least 90 days)	0.53	0.39– 0.72	0.55	0.40– 0.74

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval; PS, propensity score

Table 3. Association between individual NSAID and risk of post-colonoscopy CRC-3y

NSAIDs	Number of cohort and post-colonoscopy CRC-3y	AHR*	95% CI
Diclofenac (n=10,648)	n=178,320, PCCRC-3y=822	0.48	0.33 – 0.73
Naproxen (n=2,675)	n=173,347, PCCRC-3y=803	0.38	0.16 – 0.92
Ibuprofen (n=1,322)	n=168,994, PCCRC-3y=802	0.60	0.23 – 1.59
Indomethacin (n=761)	n=168,322, PCCRC-3y=803	1.24	0.51 – 2.99
Mefenamic acid (n=716)	n=168,388, PCCRC-3y=799	1.27	1.77 – 9.06
Sulindac (n=145)	N=167,817, PCCRC-3y=799	1.37	0.19 – 9.75
Piroxicam (n=387)	N=168,059, PCCRC-3y=802	1.87	0.70 – 5.01
Ketoprofen (n=26)	N=167,698, PCCRC-3y=798	0.33	n.a.

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval

Table 4. Duration- and frequency response between NSAID use and post-colonoscopy CRC -3y risk for the whole cohort and according to cancer sites

Duration	AHR*	95% CI	P_{trend}
All post-colonoscopy CRC-3y (n=187,897, PCCRC-3y=854)			
Never use	Ref	-	
≤ 1 year NSAID use	0.53	0.45 – 0.62	**<0.001**
> 1 year NSAID use	0.42	0.26 – 0.65	
Proximal Cancer (n=187,190, PCCRC-3y=147)			
Never use	Ref	-	
≤ 1 year NSAID use	0.51	0.35 – 0.74	**<0.001**
> 1 year NSAID use	0.33	0.10 – 1.04	
Distal Cancer (n=187,750, post-colonoscopy CRC-3y=707)			
Never use	Ref	-	
≤ 1 year NSAID use	0.53	0.45 – 0.63	**<0.001**
> 1 year NSAID use	0.43	0.26 – 0.70	
Frequency	**AHR***	**95% CI**	**P_{trend}**
All PCCRC-3y (n=187,897, post-colonoscopy CRC-3y=854)			
Never use	Ref	-	
< weekly NSAID use	0.53	0.45 – 0.61	**<0.001**
≥ weekly NSAID use	0.46	0.32 – 0.67	
Proximal Cancer (n=187,190, post-colonoscopy CRC-3y=147)			
Never use	Ref	-	
< weekly NSAID use	0.50	0.35 – 0.73	**<0.001**
≥ weekly NSAID use	0.43	0.17 – 1.05	
Distal Cancer (n=187,750, post-colonoscopy CRC-3y=707)			
Never use	Ref	-	
< weekly NSAID use	0.53	0.45 – 0.63	
≥ weekly NSAID use	0.47	0.31 – 0.71	**<0.001**

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval

Table 5. Subgroup analysis of the association between NSAID use and post-colonoscopy CRC-3y risk

	aHR*	95% CI
Age		
≥ 60 (n=97,162, PCCRC-3y=694)	0.48	0.35 – 0.66
< 60 (n=90,735, PCCRC-3y=160)	0.83	0.49 – 1.48
Sex		
Male (n=91,961, PCCRC-3y=513)	0.63	0.44 – 0.91
Female (n=95,936, PCCRC-3y=341)	0.43	0.28 – 0.66
Diabetes mellitus		
Yes (n=17,935, PCCRC-3y=89)	0.45	0.18 – 1.11
No (n=169,962, PCCRC-3y=765)	0.55	0.41 – 0.73
History of colonic polyps and/or polypectomy		
Yes (n=45,698, PCCRC-3y=326)	0.67	0.45 – 1.01
No (n=142,199, PCCRC-3y=528)	0.46	0.32 – 0.67

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval

1 STROBE Statement—Checklist of items that should be included in reports of ***cohort***
2 ***studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest

		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

eTable 1. ICD-9 codes for covariates

Covariates	
Lifestyle factors	
Smoking*	491, 492, 496, V15.82
Alcohol*	291, 303, 305.0, 571.0, 571.1, 571.2, 571.3, 980.8, 980.9
Cardiovascular and metabolic risk factors	
Obesity	278.0, 278.1
Diabetes mellitus	249, 250
Hypertension	401-405
Dyslipidemia	272.0-272.4
Cardiovascular diseases	
Ischemic heart disease	410-413, 414.0, 414.8, 414.9, 429.7
Atrial fibrillation	427.3
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Stroke	430-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 437.0, 437.1
Renal and liver diseases	
Chronic renal failure	585
Cirrhosis	571.2, 571.5, 571.6, 572.2-572.4, 573.5
Neurological diseases	
Parkinsonism	332
Dementia	290, 291.2, 292.82, 294.1-294.2
Gastrointestinal diseases	
Inflammatory bowel disease	555, 556
Colectomy	45.8, 45.81, 45.82, 45.83, V45.89
* Smoking was identified by the ICD-9 code of V15.82 and by the proxy of chronic obstructive pulmonary disease. Heavy alcohol consumption was inferred from the presence of alcohol-related disorders, including hepatic, gastrointestinal, neurological and psychiatric diseases.	

eTable 2. Baseline characteristics of study cohort before and after propensity score matching

		Before PS Matching			After PS Matching *		
	All (n=187,897)	**NSAID (n=21,757)**	**Non-NSAID (n=166,140)**	**ASD[#]**	**NSAID (n=21,650)**	**Non-NSAID (n=43,156)**	**ASD[#]**
Age at index colonoscopy (years)*	62.1 +/- 12.3	62.8 +/- 11.5	62.0 +/- 12.4	0.063	62.8 +/- 11.5	62.8 +/- 12.5	<0.001
Male sex (n, %)	91961 (48.9%)	8503 (39.1%)	83458 (50.2%)	0.229	8473 (39.1%)	16872 (39.1%)	0.002
History of colonic polyps (n, %)	39066 (20.8%)	4345 (20.0%)	34721 (20.9%)	0.023	4324 (20.0%)	8598 (19.9%)	0.001
Polypectomy at index colonoscopy (n, %)	28724 (15.3%)	3203 (14.7%)	25521 (15.4%)	<0.001	3184 (14.7%)	6599 (15.3%)	<0.001
Smoking (n, %)	3874 (2.1%)	391 (1.8%)	3483 (2.1%)	0.023	390 (1.8%)	714 (1.7%)	0.011
Alcohol (n, %)	1065 (0.6%)	118 (0.5%)	947 (0.6%)	0.004	117 (0.5%)	249 (0.6%)	0.005
Obesity(n, %)	774 (0.4%)	182 (0.8%)	592 (0.4%)	0.053	178 (0.8%)	301 (0.7%)	0.011
DM (n, %)	17935 (9.5%)	2388 (11.0%)	15547 (9.4%)	0.052	2375 (11.0%)	4705 (10.9%)	0.002
Hypertension (n, %)	28982 (15.4%)	4302 (19.8%)	24680 (14.9%)	0.124	4274 (19.7%)	8484 (19.7%)	0.001
Dyslipidemia (n, %)	9557 (5.1%)	1462 (6.7%)	8095 (4.9%)	0.074	1452 (6.7%)	2786 (6.5%)	0.010
AF (n, %)	5673 (3.0%)	567 (2.6%)	5106 (3.1%)	0.029	562 (2.6%)	1143 (2.6%)	0.003
IHD (n, %)	13266 (7.1%)	1770 (8.1%)	11496 (6.9%)	0.045	1761 (8.1%)	3473 (8.0%)	0.003
CHF (n, %)	6302 (3.4%)	777 (3.6%)	5525 (3.3%)	0.013	774 (3.6%)	1574 (3.6%)	0.004
Stroke (n, %)	7638 (4.1%)	878 (4.0%)	6760 (4.1%)	0.002	876 (4.0%)	1756 (4.1%)	0.001
CRF (n, %)	3924 (2.1%)	357 (1.6%)	3567 (2.1%)	0.040	357 (1.6%)	759 (1.8%)	0.009
Cirrhosis (n, %)	1250 (0.7%)	96 (0.4%)	1154 (0.7%)	0.038	93 (0.4%)	213 (0.5%)	0.009
Dementia (n, %)	1258 (0.7%)	124 (0.6%)	1134 (0.7%)	0.015	124 (0.6%)	246 (0.6%)	<0.001

Parkinsonism (n, %)	779 (0.4%)	94 (0.4%)	685 (0.4%)	0.003	94 (0.4%)	180 (0.4%)	0.002
Aspirin (n, %)	28569 (15.2%)	3866 (17.8%)	24703 (14.9%)	0.076	3845 (17.8%)	7584 (17.6%)	0.005
COX-2 inhibitors (n, %)	378 (0.2%)	237 (1.1%)	141 (0.1%)	0.097	134 (0.6%)	137 (0.3%)	<0.001
Statins (n,%)	25447 (13.5%)	3786 (17.4%)	21661 (13.0%)	0.115	3754 (17.3%)	7505 (17.5%)	0.002
Center endoscopy volume	2683 +/- 953	2735 +/- 975	2676 +/- 950	0.060	2739 +/- 949	2726 +/- 928	0.002
Center polypectomy rate	24.9% +/- 4.5%	25.1% +/- 4.5%	24.9% +/- 4.5%	<0.001	25.0 +/- 4.5%	25.1 +/- 4.4%	0.004

Continuous variables were expressed as mean (years) +/- 1 standard deviation
Categorical variables were expressed as number (%)
Drug use was defined as use for more than 90 days, and expressed as number (%)
Abbreviations: PS, propensity score; ASD, absolute standardised difference; DM, diabetes mellitus; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; n.a., not available
*). Non-NSAID users were matched to statin users on PS within a caliper width of 0.1. All variables were included in the model for PS estimation
[#] Variables with an ASD > 0.20 is considered to be imbalanced

eTable 3. Effects of current NSAID use, past NSAID use and NSAID-non use on risk of post-colonoscopy CRC

	Number of cohort and post-colonoscopy CRC	Adjusted HR*	95% CI
Post-colonoscopy CRC-3y			
NSAID non-use	n=107,229 post-colonoscopy CRC-3y=620	Ref	-
Current NSAID use	n=24,604 post-colonoscopy CRC-3y=67	0.55	0.43 – 0.71
Past NSAID use	n=56,064 post-colonoscopy CRC-3y=167	0.58	0.49 – 0.69
Post-colonoscopy CRC-all			
NSAID non-use	n=107,229 post-colonoscopy CRC-all=909	Ref	-
Current NSAID use	n=24,604 post-colonoscopy CRC-all=109	0.61	0.50 – 0.74
Past NSAID use	n=56,064 post-colonoscopy CRC-all=272	0.65	0.57 – 0.74
Post-colonoscopy CRC>3y			
NSAID non-use	n=107,229 post-colonoscopy CRC-all=289	Ref	-
Current NSAID use	n=24,604 post-colonoscopy CRC-all=42	0.74	0.53 – 1.02
Past NSAID use	n=56,064 post-colonoscopy CRC-all=105	0.80	0.64 – 0.99

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval

eTable 4. Association between post-colonoscopy NSAID use and risk of post-colonoscopy CRC

	Number of cohort and post-colonoscopy CRC	**Adjusted HR***	**95% CI**
Post-colonoscopy CRC-3y			
NSAID non-use	n=181,738 post-colonoscopy CRC-3y=843	Ref	-
NSAID use	n=6,159 post-colonoscopy CRC-3y=11	0.50	0.28 – 0.91
Post-colonoscopy CRC-all			
NSAID non-use	n=174,127 post-colonoscopy CRC-all=1260	Ref	-
NSAID use	n=13,770 post-colonoscopy CRC-all=30	0.40	0.28 – 0.58
Post-colonoscopy CRC>3y			
NSAID non-use	n=173,284 post-colonoscopy CRC-all=417	Ref	-
NSAID use	n=13,759 post-colonoscopy CRC-all=19	0.64	0.40 – 1.01

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; 95% CI, 95% confidence interval