REVIEW ARTICLE

Drugs 2002; 62 (6): 945-956
0012-6667/02/0006-0945/$30.00/0

NSAIDs and Gastrointestinal Cancer Prevention

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Contents

Abstract

Numerous studies report the relationship between aspirin and other nonsteroidal anti-inflammatories (NSAIDs) and cancer incidence, in particular for colorectal cancer. This paper systematically reviews the evidence of the effect of aspirin and other NSAIDs on the primary prevention of colorectal and other gastrointestinal cancers in the general population.

In 25 investigations of NSAIDs and colorectal cancer, 23 observational studies reported a relative risk reduction but estimates vary widely. Cohort studies generally indicate lesser reductions than case-control studies suggesting possible biases in the latter. Clear evidence of a dose relationship generally appears lacking but data do not indicate useful effects of aspirin in cardioprophylactic doses. Differences have otherwise not been detected between aspirin and other NSAIDs, nor between non-aspirin NSAIDs. There is some evidence that the risk of colorectal cancer reduces with increased duration of NSAID use. The lower incidence of oesophageal and gastric cancers results in smaller numbers of cases in the studies reporting these cancers, particularly in the cohort studies. The trend is for a risk reduction for oesophageal and gastric cancers in people taking NSAIDs, which is more likely to be statistically significant in the case-control studies. A very small number of observational studies have reported the relation-

ship between NSAIDs and the incidence of pancreatic, gallbladder and liver cancers. These show no consistent relationship.

In view of the inadequate information about optimal dose and duration of NSAIDs for colorectal cancer reduction, and the adverse effects of NSAIDs, we are not yet in a position to recommend NSAIDs for the primary prevention of colorectal cancer in the general population.

Aspirin has a long history of use in pain relief, as an anti-inflammatory agent and an anti-pyretic. More recently it has acquired a major role in the secondary prevention of cardiovascular and cerebrovascular disease and now evidence of its role in cancer prevention is increasing.

The main body of evidence for the chemopreventive effect of aspirin and other nonsteroidal anti-inflammatories (NSAIDs) relates to colorectal cancer. This is the third most common cause of cancer death in men and women in the world.[1] Since colorectal cancer is commonly diagnosed at an advanced stage, with a poor chance of cure, there is much interest in its early detection or prevention. In the majority of patients, colorectal carcinomas arise from adenomas, and there is now a considerable body of evidence that detecting and keeping the bowel free of adenomas greatly reduces the risk of colorectal cancer.[2] However, this approach will never offer full protection, particularly with the recent identification of flat adenomas which are inevitably more difficult to find at screening procedures.[3] Thus, the preventive approaches focussing on chemoprevention and lifestyle changes, in particular in relation to diet and social habits, deserve investigation.

Since the possible relationship between NSAIDs and a reduction in the incidence of colorectal cancer was first put forward, a large number of studies have investigated the chemoprotective effect of NSAIDs in isolated tissues, in animals, in patients with familial adenomatous polyposis (FAP) and in human epidemiological studies. More recently, the possibility of protection being conferred by NSAIDs against other cancers has been investigated.

This paper systematically reviews the evidence of the effect of aspirin and other NSAIDs on the primary prevention of colorectal and other gastrointestinal cancers in the general population. It updates a review by the International Agency for Research on Cancer (IARC),[4] and includes all gastrointestinal cancers, unlike other recent reviews which have focussed on colorectal cancer only.[5]

1. Methods

1.1 Inclusion and Exclusion Criteria

Studies were selected for inclusion if they met all of the following criteria: (i) used a randomised, prospective, controlled trial, cohort or case-control study design; (ii) involved either aspirin or non-aspirin NSAIDs; and (iii) had the incidence or mortality of a gastrointestinal cancer as an end point.

Study inclusion/exclusion decisions were made from publication abstracts. Where there was insufficient information in the abstract to make a decision the full study paper obtained.

1.2 Search Strategy

A search strategy was developed which aimed to identify randomised, controlled trials (RCTs) and analytical epidemiological study designs. Specific keywords were developed on the basis of terminology and indexing terms identified from studies retrieved in the preliminary literature search e.g. anti-inflammatory agents, non-steroidal; aspirin; cancer and prevention. Separate searches were done for colorectal neoplasms, cancer and prevention; esophageal neoplasms, cancer and prevention; gastric neoplasms, cancer and prevention; liver neoplasms, cancer and prevention; pancreatic neoplasms, cancer and prevention. Searches of the following electronic databases were undertaken: Medline, Bids Embase, Cochrane Database of Sys-

tematic Reviews (CDSR), and the Cochrane Controlled Trials Register (CCTR). Date and language restrictions were not used. The reference lists of included studies were also used. Searches were undertaken to the end of September 2001.

1.3 Data Extraction

Data was extracted on: (i) the type and dose of NSAID; and (ii) the relative risk of cancer incidence or mortality in the comparative groups. Data extraction was undertaken by one of the reviewers (K. Jolly). A standard data extraction proforma was used to summarise each trial according to specific headings: population studied, period when the study was carried out, study design and size, drugs studied, frequency and period of their use, effect on cancer incidence or mortality rates, and general comments.

1.4 Data Synthesis

The results were not synthesised to produce a summary measure because of their heterogeneity.[6] A range of NSAIDs, taken at varying doses for widely differing time periods, has been examined using a range of study designs. The results of the papers are presented in tabular form to ease comparison of the findings.

2. Results

2.1 Colorectal Cancer

Twenty-six studies of NSAIDs and colorectal cancer prevention were identified: 11 cohort studies,[7-19] 14 case-control studies[20-33] and one RCT.[34,35] Nine of these studies assessed the effects of aspirin only, the rest looked at aspirin and other NSAIDs. In all studies except two, the outcome of interest was the incidence of colorectal cancer. One study only reported colon cancer incidence,[9-11] and one study reported colorectal cancer mortality rates.[12] The recorded period of use of the NSAIDs varied from within the previous 30 days[13] to 20 years.[15] Dosage varied from two tablets a week[14,15] to the heavy use associated with treatment for arthritis.[7,8]

Table I and table II show wide variations in estimated degrees of risk reduction with, in addition, one study suggesting raised risk.[9-11] In general, risk reductions appeared greater when derived from estimates in case-control investigations than in cohort studies. These findings might suggest that case-control data can suffer from bias, possibly in the later ascertainment of drug use in the participants questioned. The median risk reduction overall was one-third, but in five of the case-control studies (mainly hospital-based) the risk reduction was two-thirds.[22-24,28,31] The only cohort study to show an increased incidence of colon cancer in participants taking aspirin regularly, had an older age profile (median age 73 years) and only had information on aspirin use at entry to the study, with no information on duration of use. It is possible that non-users of aspirin at the start of the study became users at a later stage.[9-11]

The US Physicians Health Study is the only RCT to have compared regular aspirin use with a control group.[34] This was a double-blind, placebo-controlled trial of 22 071 male doctors to evaluate the effects of alternate daily doses of aspirin 325mg and β-carotene on cardiovascular disease and cancer. The trial was terminated after 5 years because of a significant reduction in the incidence of non-fatal myocardial infarction in the group receiving aspirin but not β-carotene. The relative risk of invasive colorectal cancer after the 5 years in those randomised to aspirin was 1.2 [95% confidence interval (CI), 0.8 to 1.7]. After 12 years of follow-up the relative risk of colorectal cancer in those originally randomised to aspirin was 1.1 (95% CI, 0.85 to 1.3).[35] Since many of the trial participants randomised to no aspirin started to take aspirin after the trial ended, the risk of colorectal cancer after 12 years has also been reported according to recent use of aspirin. Those taking aspirin in the later follow-up years had a relative risk of colorectal cancer of 0.88 (95% CI, 0.59 to 1.5).

Clear relationships with dose were not detected, although the limited evidence on cardioprotective low-dose aspirin suggests that there might be negligible effects. Five studies have reported on the

Table I. Cohort studies of nonsteroidal anti-inflammatories (NSAIDs) and the risk of colorectal cancer in the general population. The first seven entries in this table have been reproduced from page 52 in the International Agency for Research on Cancer (IARC) Handbook of Cancer Prevention,[4] with the permission of International Agency for Research on Cancer

Reference	Population	Outcome	No. cases	Drug	Frequency	Results (RR)[a]	Comments
Isomaki et al.[7] (1978)	Rheumatoid arthritis; Finland; 34 618 women and 11 483 men; 1967-73	Colon cancer	33 women 11 men	Therapy for arthritis	Heavy use	0.84 (NS) 1.49 (NS)	
		Rectal cancer	20 women 7 men			0.58 (p<0.05) 0.64 (NS)	
Gridley et al.[8] (1993)	Rheumatoid arthritis; Sweden: 7933 women and 3750 men; 1965-84	Colon cancer Rectal cancer (incidence)	44 28	Therapy for arthritis	Heavy use	0.63 (0.5-0.9) 0.72 (0.5-1.1)	Risk for stomach cancer also reduced
Paganini-Hill et al.[9,10] (1989, 1991); Paganini-Hill[11] (1995)	US retirement community; 13 987 elderly men and women; 1981-87	Colon cancer (incidence)	181	Aspirin	Daily	1.5 (1.1-2.2)	Median age 73. No data on aspirin after baseline
Thun et al.[12] (1993)	American Cancer Society; 662 424 US adults; 1982-88	Colon cancer (fatal) Rectal cancer (fatal)	950 deaths 138 deaths	Aspirin	16x/m	0.58 (0.45-0.74) 0.66 (0.37-1.2)	Multivariate estimates. No data on aspirin after baseline. Decreased risk mostly confined to users of 10y
Schreinema-Chers & Everson[13] (1994)	12 688 US adults; 1971-87	Colorectal cancer (incidence)	169	Aspirin	Last 30d	0.74 (0.49-1.1)	RR reduced under age 65
Giovannucci et al.[14] (1994)	Harvard health professionals; 47 900 US men; 1986-91	Colorectal cancer (incidence)	251	Aspirin	2 tablets/wk	0.68 (0.52-0.92)	All cancers and metastatic or fatal cancers
Giovannucci et al.[15] (1995)	US Nurses Health Study; 89 446 women; 1984-92	Colorectal cancer (incidence)	297	Aspirin	2 tablets/wk for 20y	0.56 (0.36-0.9)	Risk decreased with duration but not with dose >2-4m
Kauppi et al.[16] (1996)	Patients hospitalised for rheumatoid arthritis; Finland; 9469; 1970-91	Colorectal cancer (incidence)	30	Therapy for arthritis	Heavy use	SIR 0.62 (0.42-0.88)	SIR for all malignancies 1.16 (1.07-1.26). Some overlap of cases with Isomaki et al.[7] (1978)
Cibere et al.[17] (1997)	862 patients with rheumatoid arthritis seen in Canadian hospital clinic 1966-74, follow-up till end 1994	Colorectal cancer (incidence)	10	Therapy for arthritis (97% taking NSAIDs)	No information given	SIR 0.52 (0.25-0.96)	Before 1988 cancers diagnosed only at death were excluded
Smalley et al.[18] (1999)	Medicaid programme, 104 217 aged 65+ years; Tennessee, USA; 1985-92	Colon cancer (incidence)	662	Non-aspirin NSAIDs	All doses, >12m cumulative use, with use within past year	0.61 (0.48-0.77)	For colon cancer risk decreased with duration of use.
		Rectal cancer (incidence)	146			0.81 (0.49-1.32)	All RRs for rectal cancer non-significant
Bucher et al.[19] (1999)	Autopsies; 618 analgesic abusers, 1236 controls; Switzerland; 1968-83	Colorectal cancer	16 (analgesic abusers) 68 (controls)	Aspirin, phenacetin, codeine and caffeine	Abusers *vs* 'normal use'	OR = 0.46 (0.27-0.79)	OR for all tumours: 0.4 (0.32-0.49)

a Results are expressed as relative risk (RR) unless stated otherwise with the 95% confidence interval.

NS = not significant; **OR** = odds ratio; **RR** = relative risk; **SIR** = standardised incidence ratio.

dose of NSAIDs and risk of colorectal cancer.[15,18,30,32,33] Two studies indicated no clear relationship between dose and colorectal cancer risk. One case-control study, which looked at NSAID use over a 3-year period, found an inverse association between numbers of prescriptions for NSAIDs and the odds ratio for colon cancer, but only for the period 13 to 24 months before the index date.[32] The US Nurses Health Study reported the lowest relative risk of colorectal cancer in women taking 4 to 6 tablets of aspirin weekly, but no linear trend with increasing dose was seen.[15] A population-based case-control study found a reduced risk for aspirin, only at dosages of at least 300 mg/day in current users, and a reduced risk in individuals taking 'high' doses of non-aspirin NSAIDs.[33]

The evidence for a relationship between increasing duration of NSAID use and reduced risk of colorectal cancer appears stronger. The US Nurses Health Study reported a significant linear trend of reducing relative risk of colorectal cancer over a 20 year period in women who took at least two tablets of aspirin each week.[15] A cohort study of US Medicaid patients also reported a decreasing risk of colon cancer over the 5 years of follow-up.[18] This relationship was not found in a retrospective case-control study in the US which relied on patient recall about duration of NSAID use.[30]

2.2 Oesophageal Cancer

Seven studies have explored the possible protective effects of NSAIDs against oesophageal cancer,[7,8,12,32,36-38] and an additional small cohort provided results for gastric and oesophageal cancers combined.[17] These reports are summarised in table III and table IV.

Significantly reduced risk of oesophageal cancer were found in users of aspirin in the National Health and Nutrition Examination Survey, with a relative risk of 0.1 (95% CI, 0.01 to 0.76),[36] and in two population-based case-control studies: Langman et al. reported an relative risk of 0.64 (95% CI, 0.41 to 0.98)[32] and Farrow et al. for adenocarcinoma 0.37 (95% CI, 0.19 to 0.73).[37] Similar, but nonsignificant, trends were detected in a small cohort study of oesophageal and gastric cancers combined,[17] of upper digestive tract cancers in a small cohort study of analgesic abusers who had died,[19] and for death from oesophageal cancer in a large study of 635 031 people by The American Cancer Society.[12] In addition, a small case-control study found a non-significant reduction in risk of oesophageal cancers in people reporting chronic analgesic use, but provided insufficient information as to the type, dosage or duration of use of analgesics.[41]

Oesophageal cancer may be either squamous or adenocarcinomatous. Only one study has reported data histologically, and found a significantly reduced risk of adenocarcinoma but not squamous cell carcinoma of the oesophagus.[37]

2.3 Gastric Cancer

Nine studies have examined the possibility that the chances of developing gastric cancer are reduced by taking NSAIDs,[7,8,12,13,32,37-40] with an additional study which considered gastric and oesophageal cancers together.[17]

Five case-control studies found a significant reduction in gastric cancer incidence in patients taking NSAIDs, with relative risks of 0.3[38] to 0.7[40] (table IV). Three of the four cohort studies found reductions in risk of gastric cancer incidence or mortality, but only one of these was significant.[8]

2.4 Pancreatic Cancer

A significant increase in the relative risk of pancreatic cancer in people who took NSAIDs was found in a population-based case-control study using the General Practice Research Database in the UK (relative risk 1.49, 95% CI 1.02 to 2.18).[32] This increase is not confirmed by a US hospital-based case-control study (relative risk 0.8, 95% CI 0.5 to 1.1).[38] A small cohort study of patients with rheumatoid arthritis, based on only 5 cases of pancreatic cancer, reported a standardised incidence ratio of 1.27 (95% CI, 0.41 to 2.96). These studies are summarised in tables III and IV.

Table II. Case-control studies of nonsteroidal anti-inflammatories (NSAIDs) and the risk of colorectal cancer in the general population. The first eight entries in this table have been reproduced from page 56 in the International Agency for Research on Cancer (IARC) Handbook of Cancer Prevention,[4] with the permission of International Agency for Research on Cancer

Reference	Population	Outcome	Study size	Drug	Frequency	Results (RR)[a]	Comments
Kune et al.[20] (1988)	Population-based; Melbourne, Australia; 1980-81	Colorectal cancer (incidence)	715 cases; 727 controls	Aspirin NSAIDs	Daily (?)	0.6 (0.44-0.82) 0.77 (0.6-1.01)	Adjusted for diet Unadjusted for aspirin use
Rosenberg et al.[21] (1991)	Hospital-based; 4 cities in eastern USA; 1977-88	Colorectal cancer (incidence)	1326 cases; 4891 controls	Mostly aspirin	4 d/wk for 3m	0.5 (0.4-0.8)	Trend with duration NS, risk increased after cessation
Suh et al.[22] (1993)	Hospital-based; Roswell Park, USA; 1982-91	Colorectal cancer (incidence)	830 cases; 1138 controls; 524 hospital controls	Aspirin	1/d in 4y before study	0.24 (0.12-0.5) 0.54 (0.26-1.1)	Men Women
Peleg et al.[23] (1994)	Hospital-based; Atlanta, USA; 1988-90	Colorectal cancer (incidence)	97 cases; 388 controls	Aspirin and non-aspirin	Used aspirin 624d in 4y before study; used NSAIDs >313d in 4y before study	0.08 (0.01-0.59)	Urban poor
Muscat et al.[24] (1994)	Hospital-based; American Health Foundation; 1989-92	Colorectal cancer (incidence)	511 cases; 500 controls	NSAIDs	3 x/wk for 1y	0.64 (0.42-0.97) 0.32 (0.18-0.57)	Men Women
Muller et al.[25] (1994)	Hospital-based; US veterans; 1988-92	Colorectal cancer (incidence)	12 304 cases; 49 216 controls	NSAIDs; Other anticoagulants	Not stated	RR range 0.52-0.91 RR range 1.2-1.3	For 6 diseases treated with NSAIDS For diseases treated with other anticoagulants
Reeves et al.[26] (1996)	Population-based; women in Wisconsin; 1991-92	Colorectal cancer (incidence)	184 cases; 293 controls	Aspirin and non-aspirin	1 tablet at least 2x/wk for 1y	0.65 (0.4-1.0)	Non-aspirin NSAIDS more strongly associated than aspirin
Bansal & Sonnenberg[27] (1996)	Hospital-based; US veterans; 1981-93	Colorectal cancer (incidence)	371 cases among 11 446 with and 52 243 without IBD	NSAIDs	Not stated	0.68 (0.65-72)	
Peleg et al.[28] (1996)	Hospital; Atlanta, Georgia, USA; 1987-92	Colorectal Adenocarcinoma (incidence)	93 cases; 186 controls	Aspirin, and non-aspirin NSAIDs	Consecutive years of regular NSAID use	0.34 (0.12-0.94) 0.13 (0.33-0.55) 0.12 (0.04-0.39)	1 year 3 years 5 years
La Vecchia et al.[29] (1997)	Hospital-based; Italy; 1992-96	Colorectal cancer (incidence)	1357 cases; 1891 controls	Aspirin	>4x/wk for >6m	0.7 (0.5-1.0) 0.9 (0.6-1.4) 0.6 (0.2-0.9)	Regular use Colon Rectal
Rosenberg et al.[30] (1998)	Population-based; Massachusetts, USA; 1992-94	Colorectal cancer (incidence)	1201 cases; 1201 controls	Aspirin and non-aspirin NSAIDs	>4x/wk for >3m	0.7 (0.5-0.8)	No trend with duration of use or with increasing dose

Table II contd.

2.5 Liver and Gallbladder Cancers

One hospital-based case-control study in the USA examined the effect of NSAIDs on liver and gallbladder cancer.[38] A non-significant reduction of gallbladder cancer was reported (relative risk 0.5, 95% CI 0.3 to 1.1), whilst no difference was found for liver cancer. The standardised incidence ratio of liver and gallbladder cancer combined was raised (standardised incidence ratio 1.93, 95% CI 0.62 to 4.5) in a small cohort study of patients with rheumatoid arthritis.[17] These studies are summarised in tables III and IV.

3. Discussion

The evidence for the protective effect of NSAIDs on the development of colorectal cancers is clear and consistent. We did not undertake a search for unpublished studies, so cannot rule out the possibility of some publication bias. Confounding cannot be ruled out in the descriptive epidemiological studies, in particular that NSAID use can cause gastrointestinal bleeding, which results in investigations that may reveal a tumour. This might explain the reduction in tumours diagnosed at an advanced stage, and thus reduced mortality, but does not explain the reduction in incidence of colorectal adenomas.[42,43] The other major confounding factor is the fact that people who take NSAIDs are more likely to be health conscious and may have a lower risk of colorectal cancer.

The results presented in this paper also make a case for the chemopreventive effect of NSAIDs on gastric and oesophageal cancers. The evidence for liver, gallbladder and pancreatic cancers is both limited and conflicting.

Current evidence does not clearly show how long treatment has to continue for protection to be demonstrable or be maximal, or what is the optimal dose. Case-control studies have suggested very high degrees of protection against colorectal cancer with recorded treatment periods of as little as one year,[28] however, the evidence may be flawed by unquantifiable biases in ascertainment of data.

Collett et al.[31] (1998)	Population-based; aged 35+; eligible to receive benefits; Canada; 1981-95	Colon cancer (incidence)	3844 cases; 15 373 controls	NSAIDs	>0.3 of max recommended daily dose in periods before diagnosis:		No significant reductions in interim time periods
					1-6m	0.68 (0.56-0.86)	
					11-15y	0.57 (0.36-0.89)	
		Rectal cancer (incidence)	1971 cases; 7882 controls		>0.3 of max recommended daily dose in periods before diagnosis:		
					1-6m	0.8 (0.59-1.08)	
					11-15y	0.26 (0.11-0.61)	
Langman et al.[32] (2000)	Population-based; UK; 1993-95	Colon cancer; (incidence)	1368 cases; 4089 controls	Aspirin, and non-aspirin NSAIDs	At least 7 prescriptions during 13-36m before diagnosis	0.76 (0.58-1.0)	
		Rectal cancer (incidence)	593 cases; 1778 controls			0.75 (0.49-1.14)	
Garcia Rodriguez & Huerta-Alvarez[33] (2001)	Population-based; UK; 1994-1997	Colorectal cancer	Colon: 1357 cases	Aspirin; non-aspirin NSAIDS	Current use for ≥6m	0.9 (0.7-1.5)	Nested case-control study from cohort derived from the GPRD. Risk reductions for aspirin only occurred with dose of 300 mg/day, not less
			Rectum: 645 cases			0.5 (0.4-0.7)	

a Results are expressed as relative risk (RR) unless stated otherwise with the 95% confidence interval

GPRD = general practice research database; **IBD** = inflammatory bowel disease; **RR** = relative risk.

Table III. Cohort studies of nonsteroidal anti-inflammatories (NSAIDs) and the risk of gastrointestinal cancers (other than colorectal cancer) in the general population. The first five entries in this table have been reproduced from table 6 (page 61) in the International Agency for Research on Cancer (IARC) Handbook of Cancer Prevention,[4] with the permission of International Agency for Research on Cancer

Reference	Population	Outcome	No. cases	Drug	Frequency	Results (RR)[a]	Comments
Isomaki et al.[7] (1978)	Rheumatoid arthritis; Finland; 34 618 women and 11 483 men; 1967-73	Oesophageal cancer	5	Therapy for arthritis	Heavy use	0.67 (NS)	
		Gastric cancer (incidence)	51			1.1 (NS)	
Gridley et al.[8] (1993)	Rheumatoid arthritis; Sweden; 8787 women and 3750 men; 1965-84	Oesophageal cancer	11	Therapy for arthritis	Heavy use	1.3 (0.7-2.4)	
		Gastric cancer (incidence)	39			0.63 (0.5-0.9)	
Thun et al.[12] (1993)	American Cancer Society; 635 031 US adults; 1982-88	Oesophageal cancer (fatal)	176 deaths	Aspirin	16 x/m	0.78 (0.42-1.4)	Multivariate estimates
		Gastric cancer (fatal)	308 deaths			0.49 (0.22-1.12)	
Schreinemachers & Everson[13] (1994)	12 688 US adults; 1971-87	Gastric cancer (incidence)	20	Aspirin	Last 30d	0.93 (0.49-1.7)	No data on aspirin after baseline; decreased risk mostly confined to users of 10 years
Funkhouser & Sharp[36] (1995)	12 688 US adults; 1971-87	Oesophageal cancer	15	Aspirin	Last 30d	0.1 (0.01-0.76)	Multivariate estimate, also for alcohol use and smoking
Cibere et al.[17] (1997)	862 patients with rheumatoid arthritis seen in Canadian hospital clinic 1966-74; follow-up till end 1994.	Liver/gallbladder cancer (incidence)	5	Therapy for arthritis (97% taking NSAIDs; 12% taking cytotoxic drugs)	No information given	SIR 1.93 (0.62-4.5)	Prior to 1988 cancers diagnosed only at death were excluded
		Stomach/oesophageal cancer (incidence)	5			SIR 1.27 (0.41-2.96)	
		Pancreatic cancer (incidence)	4			SIR 0.71 (0.19-1.84)	
Bucher et al.[19] (1999)	Autopsies; 618 analgesic abusers; 1236 controls; Switzerland; 1968-83	Upper digestive tract cancer	Analgesic abusers: 7; controls: 52	Aspirin, phenacetin, codeine and caffeine	Abusers *vs* 'normal use'	0.27 (0.13-0.57)	

a Results are expressed as relative risk (RR) unless stated otherwise with the 95% confidence interval.

NS = Not significant; **RR** = relative risk; **SIR** = standardised incidence ratio.

Table IV. Case-control studies of nonsteroidal anti-inflammatories (NSAIDs) and the risk of gastrointestinal cancers (other than colorectal cancer) in the general population

Reference	Population	Outcome	Study size	Drug	Frequency	Results (OR)[a]	Comments
Farrow et al.[37] (1998)	Population-based; USA; aged 30-79 years; cancers diagnosed 1993-95	Oesophageal Adenocarcinoma	293 cases	Aspirin or non-steroidal anti-inflammatory drugs	Initiated at least 1y before diagnosis, taken at least 1x/w for 6m	0.37 (0.19-0.73)	
		Oesophageal squamous cell carcinoma	221 cases			0.73 (0.43-1.22)	
		Gastric cardia Adenocarcinoma	261 cases			0.43 (0.21-0.89)	
		Other stomach Adenocarcinoma	368 cases			0.34 (0.2-0.59)	
			695 controls				
Zaridze et al.[39] (1999)	Hospital-based; Moscow, Russia	Gastric cancers (incidence)	448 cases; 610 controls	Aspirin or non-steroidal anti-inflammatory drugs	At least 2 d/wk for ≥6m	0.6 (0.41-0.9)	No risk reduction for cancer of the gastric cardia, only for non-cardia gastric cancer
Coogan et al.[38] (2000)	Hospital-based; USA	Pancreatic cancer	504 cases	Non-steroidal anti-inflammatory drugs	At least 4 d/wk for ≥3m initiated ≥1y before admission	0.8 (0.5-1.1)	Reference value = non-use
		Stomach cancer	254 cases			0.3 (0.1-0.6)	
		Oesophageal cancer	215 cases			0.8 (0.5-1.4)	
		Gallbladder cancer	121 cases			0.5 (0.3-1.1)	
		Liver cancer	57 cases			0.9 (0.3-2.9)	
			5952 controls				
Langman et al.[32] (2000)	Population-based, UK; 1993-95	Oesophageal cancer	550 cases; 1650 controls	Aspirin, and non-aspirin NSAIDs	At least 7 prescriptions during 13-36m before diagnosis	0.64 (0.41-0.98)	Significant trend with increasing doses for stomach and oesophageal cancers. Information also for lung, prostate and bladder cancer
		Stomach cancer	613 cases; 1837 controls			0.51 (0.33-0.79)	
		Pancreatic cancer (incidence)	513 cases; 1535 controls			1.49 (1.02-2.18)	
Akre et al.[40] (2001)	Population-based; Sweden; 1989-1995	Stomach cancer (incidence)	567 cases; 1165 controls	Aspirin	At least 1 tablet/m up until 2y before interview	0.7 (0.6-1.0)	Significant trend with increasing dose of aspirin

a Results are expressed as odds ratio (OR) unless stated otherwise with the 95% confidence interval.

OR = odds ratio.

NSAIDs for which evidence is available are conventional nonselective antagonists of cyclooxygenase (COX)-1 and COX-2 enzymes. It is, as yet, unclear whether selective COX-2 inhibitors are as effective as nonselective conventional NSAIDs. Clinical polyp suppression trials now underway seem likely to provide the required data because COX-2 is also upregulated in polyps, albeit to a lesser extent than in carcinomata.

The mechanism of action of NSAIDS on tumours is not fully established. A number of different mechanisms have been put forward. Almost 90% of colorectal cancers over-express COX-2, which is involved in prostaglandin synthesis and is inhibited by NSAIDs. Both prostaglandins and COX-2 have been shown to be raised in the tumours of patients with FAP.[44] Rodent experiments have shown that sulindac, a NSAID which inhibits both COX-1 and COX-2, reduces the number of experimentally induced colon tumours.[45] It is also known that COX-2 knockout in Min mice which are prone to develop multiple adenomatous polyps, the tendency to polyp formation is suppressed.[46-48] One of the mechanisms by which NSAIDs inhibit colon carcinogenesis is to induce apoptosis (programmed cell death). This has been shown to occur in colon cancer cells that both do and do not express COX enzymes or produce prostaglandins.[49-51]

It is likely, although not well demonstrated, that reductions in the chances of developing oesophageal and gastric cancer are reduced by NSAID treatment for the same reasons that colorectal cancer risks are reduced. Research in both oesophageal and pancreatic cancers have also identified tumour cell lines that express COX-2.[52,53] It has been proposed that increased expression of COX-2 in patients with Barrett's oesophagus is central to their predisposition to both oesophageal and colon cancers.[54] *In vivo* research using oesophageal cancer cell lines has demonstrated that NSAIDs can induce apoptosis in cell lines which express COX-2.[52,55] Whether oesophageal adeno- and squamous carcinomata behave the same way is unclear. However, reductions of risk of oesophageal cancer overall, irrespective of histological type, appear to be equivalent to risk reduction rates for colorectal cancer. This argues, perhaps, that treatment might have the same effects on squamous and adenocarcinomata of the oesophagus. No data are available which separate the histological types of gastric cancer. Apoptosis induced by aspirin has also been reported in oesophageal cancer, which provides a biologically plausible mechanism supporting the epidemiological studies.[52]

4. Conclusion

While there is consistent evidence that NSAIDs reduce the risk of some gastrointestinal cancers we are not yet in a position to recommend their use for cancer prevention in the general population. There is not yet adequate information on effective doses or the optimal duration of use. NSAIDs occasionally have severe adverse effects, including gastrointestinal bleeding and haemorrhagic strokes. In the absence of RCTs that evaluate both the benefits and risks of NSAIDs in cancer prevention, no population programmes of NSAIDs should be established.

While selective COX-2 inhibitors are likely to have better adverse effect profiles than non-selective NSAIDs, there is still insufficient evidence of their effectiveness in the chemoprevention of gastrointestinal cancers.

Even in patients with FAP, although NSAIDs have led to regression in numbers and size of polyps in placebo-controlled trials, this effect only lasts while the NSAIDs are taken.[56,57] It may well be that the importance of the findings of the chemopreventive effect of NSAIDs will lie not in their use as a preventive measure but in the understanding of the mechanism of their action, which opens up the possibility of targeted agents for treatment or prevention.

Acknowledgements

Professor Langman has acted as a consultant for Merck Sharp and Dohme. Any payment received goes to the University of Birmingham.

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