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Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis

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Abstract

Background: Observational studies have consistently shown that aspirin and non-steroidal anti-inflammatory drug (NSAID) use is associated with a close to 50% reduced risk of colorectal cancer. Studies assessing the effects of NSAIDs on other cancers have shown conflicting results. Therefore, we conducted a meta-analysis to evaluate the relationship between NSAID use and cancer other than colorectal.

Methods: We performed a search in Medline (from 1966 to 2002) and identified a total of 47 articles (13 cohort and 34 case-control studies). Overall estimates of the relative risk (RR) were calculated for each cancer site using random effects models.

Results: Aspirin use was associated with a reduced risk of cancer of the esophagus and the stomach (RR, 0.51; 95%CI (0.38–0.69), and 0.73; 95%CI (0.63–0.84)). Use of NSAIDs was similarly associated with a lower risk of esophageal and gastric cancers (RR,0.65; 95% CI(0.46–0.92) and RR,0.54; 95%CI (0.39–0.75)). Among other cancers, only the results obtained for breast cancer were fairly consistent in showing a slight reduced risk among NSAID and aspirin users (RR, 0.77; 95%CI (0.66–0.88), and RR, 0.77; 95%CI (0.69–0.86) respectively)).

Conclusions: The results of this meta-analysis show that the potential chemopreventive role of NSAIDs in colorectal cancer might be extended to other gastrointestinal cancers such as esophagus and stomach. Further research is required to evaluate the role of NSAIDs at other cancers sites.

Background

People who have regularly taken aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) are at a reduced risk of developing or dying from colorectal cancer [1–3]. The association with other types of cancer remains unclear. Animal studies have shown a protective effect of these drugs in colon [4], esophagus [5], stomach [6,7], pancreas [8], breast [9,10], prostate [11], lung [12], and bladder cancer [13], suggesting a common mechanistic effect of NSAIDs in all these different cancers.

NSAIDs could reduce the risk of cancer through the inhibition of cyclooxygenase-2 (COX-2) [14], the enzyme that is responsible for the production of various

prostaglandins. Prostaglandins play a key role on the accelerated proliferation of tumor tissue. Furthermore there is mounting evidence that NSAIDs may have the ability to restore apoptosis and inhibit angiogenesis [15].

If this proposed protective mechanism of NSAIDs is valid, the preventive effect of NSAIDs could extend to other human cancers. To date, epidemiological studies in cancer other than colorectal are scarce and offer inconsistent results.

The primary aim of our analysis is the use of meta-analytical techniques to evaluate the effect of aspirin and non-aspirin NSAIDs (NA-NSAIDs) on cancer sites other than the colon and rectum. We present summary estimates for the effect of these drugs in cancer sites where at least two epidemiological studies could be found.

Methods

Our search included original articles indexed in Medline from January 1966 to December 2002. We searched for different common terms used to refer to non-steroidal anti-inflammatory drugs ("NSAIDs", "anti-inflammatory drugs") or specific drug names such as "aspirin". Similarly we used different terms referring to cancer ("neoplasm", "malignancies", and the prefix "carcino-"). Additionally we included references cited in original or review articles that were not included in our original list. We restricted our search to studies performed in humans and published in English or Spanish. We individually reviewed all the abstracts and obtained those articles that satisfied our inclusion criteria: cohort or case-control studies studying the association between NSAIDs and cancer other than colorectal, and reporting an estimate of association such as relative risk (RR) with confidence intervals or enough information to compute it. Forty-nine articles were considered to meet our inclusion criteria. After review by two of the authors, two of these articles were excluded. The reasons for exclusion were absence of a control group [16], invalid exposure and outcome ascertainment [17]. A total of forty-seven eligible studies were finally identified.

Two of the authors participated in the data extraction process using a standardized form. Data regarding study design, analyses and results were entered into a database. The fields extracted included study design, year of publication, country, matching used, percentage of response, exposure assessment, exposure definition, lag time between exposure and outcome, prevalence of exposure, outcome assessment, and RR with 95% confidence intervals (CI). We assumed that the odds ratio (OR) from case-control studies provided a valid estimate for the RR. The exposures of interest consisted of aspirin, and non-aspirin NSAIDs (NA-NSAIDs). In this study, the term NSAIDs refers to either aspirin and/or NA-NSAIDs. Some studies included paracetamol in the NSAID and/or NA-NSAID groups. Most studies reported a definition of regular use (n = 34) and whenever available the estimate for this exposure was the one extracted. When no clear definition of regular use was provided (n = 13), we extracted the most mechanistically meaningful estimate after reaching consensus between authors in all instances. A total of nine studies reporting estimates for multiple endpoints contributed to more than one cancer site. We explored all nine cancer sites for which two or more eligible studies were found. In the case of cancer of the esophagus we focused on adenocarcinoma when more than one histological type was studied.

We fit a DerSimonian and Laird random effects model [18] to obtain overall estimates for the effects of aspirin, NA-NSAIDs and NSAIDs in each specific cancer site using STATA software. This model is more robust than the fixed effects model and incorporates into the weighting scheme both the within-study and among-study variance. Heterogeneity was explored using Q test statistic [18] in sets where three or more studies were available. When the result from this test reached statistical significance we further assessed to what extent different study characteristics could explain the heterogeneity with meta-regression. We explored potential publication bias qualitatively and quantitatively using funnel plots and kendall's tau rank correlation tests [19].

Results

Studies characteristics

Among the 47 studies analyzed [20–66], 13 were cohort and 34 were case-control studies. Seventeen of the case-control studies were population based (either nested in a cohort or using methods like random digit dialing to ensure that controls are a sample of the underlying cohort that gave rise to the cases)[21,22,24,27,28,30,36,39,44,54,59–61,63–66] whereas the other seventeen were hospital based (using non-cancer hospital controls) [23,26,32–35,37,38,42,45,47–49,51,53,55,56,62]. Regarding exposure assessment, most studies (n = 22) used personal interview typically performed by trained personnel [22,24–26,28,30–34,38,41–43,45,47,51,56,60,63,65,66]. Thirteen studies used mailed questionnaires [21,23,27,29,39,40,46,50,52,54,56,58,64] and six used in-hospital questionnaires [35,37,48,49,53,55]. The rest used either automated databases (n = 4)[20,36,44,61] or medical records (n = 2) [59,62]. Exposure definition was very heterogeneous across the different studies and attempts to categorize it in a few groups for further analysis were unsuccessful. It ranged from more than 6 tablets per day to ever use of NSAIDs in the 30 days prior to start date. Prevalence of exposure among controls or cohort

Table 7: Lung

Author	Cases N	Controls$_a$/ Cohort$_b$	Source Population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Langman et al. [36]	2,560	7,643$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (7%) ⌖	0.84	0.69–1.02
Harris et al. [51]	489	978$_a$	Hospital based	>7 tablets per week during more than 2 years	Personal Interview	NSAIDs(26%)	0.32	0.23–0.44
Akhmedkhanov et al[54]	81	808$_a$	Population based‡	>2 tablets per week during at least 6 months. 1 year lag time	Mailed Questionnaire	Aspirin (19%)	0.66	0.34–1.28
Moysich et al. [55]	868	935$_a$	Hospital based	>1 tablet per week for at least 1 year	In hospital Questionnaire	Aspirin (18%)	0.57	0.41–0.78
Rosenberg[56]	1,110	4,906$_a$	Hospital based	>3 days/week for >3 months 1.5 years of lag time	Personal Interview	NSAIDs (6%)	1.0	0.7–1.4
Paganini-Hill et al. [40]	111	13,987$_b$	Cohort	Daily use of aspirin for an undefined time	Mailed Questionnaire	Aspirin (16%)	0.92§	0.54–1.55
Thun et al. [46]†	NR men	290,681$_b$	Cohort	More than 16 times per month for at least one year	Mailed Questionnaire	Aspirin (11%)	1.11	0.98–1.25
	NR women	344,350$_b$					1.07	0.88–1.30
Schreinemachers et al. [43]†	163	12,668$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (59%)	0.68	0.49–0.94

⌖ Prevalence of exposure among controls/cohort; †Respiratory (includes others); §Crude estimate calculated from data provided in the original manuscript; ‡Female population.

members ranged from 4 to 42 percent for NSAIDs (median, 8 percent), from 2 to 64 percent for aspirin (median, 16 percent), and from 3 to 46 percent for NA-NSAIDs (median, 12 percent).

Some studies incorporated the concept of lag time into their exposure definition (time period before the index date that was discounted for assessing the exposure status). This is mainly motivated by the belief that early symptoms of the disease (cancer in this case) in the subclinical phase (latent period) might induce or contra-indicate the use of NSAIDs (protopathic bias) [44,67]. Nine studies used a lag time of 1 year, one study used 1 year and a half, and two studies used 2 years.

All but ten case-control studies used matched designs (frequency matched (n = 12) or individually matched (n = 12)). Among the individually matched seven studies considered the matching in the analysis and five did not. All studies used newly diagnosed cancer as the primary endpoint except for studies by Thun et al and Suleiman et al that used fatal cancer as outcome.

Most studies were published after 1997 (n = 33). The rest were published in 1996 (n = 3), 1995 (n = 4), 1994 (n = 1), 1993 (n = 2), 1989 (n = 1), 1988 (n = 1), 1985 (n = 1) and 1980 (n = 1). The majority of the studies were conducted in North America (USA (n = 32) or Canada (n = 2)). Ten studies were conducted in Europe (U.K. (n = 4), Greece (n = 2), France (n = 1), Italy (n = 1), Russia (n = 1), and Sweden (n = 1)), one study in Australia and one study in New Zealand. Additionally, there was one multicentered international study.

Tables 1 through 9 show the exposure definition, exposure assessment, study type, and the estimates of association for each individual study according to the cancer site. Table 10 summarizes the results by type of drug and cancer site. The pooled RR estimates for esophagus and stomach showed a significant protective effect of NSAIDs in the range of a 40 percent reduction. Aspirin but not NA-NSAIDs appeared to be associated with a reduced pancreas cancer incidence around 30 percent (although this result was not significant). Breast cancer was the only other site where results were rather consistent in showing a protection ranging around a 20 percent reduction. Results obtained for other studied cancer sites, i.e. ovary, prostate, bladder, and lung were compatible with no effect or a possibly slight reduced risk. The result for kidney cancer is compatible with no effect or possibly a slight increased risk.

Studies assessing the effect of aspirin and other NSAIDs on cancer of the esophagus were consistent in finding a protective effect regardless of the study design or exposure assessment. Among the eight studies identified none yielded a point estimate larger than 0.85 independently of the exposure category (see table 1). All but one of the individual estimates of the effect of aspirin and other NSAIDs on the risk of developing gastric cancer were

Table 8: Bladder

Author	Cases N	Controls$_a$/ Cohort$_b$	Source Population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Castelao et al. [25]	1,514	1,514$_a$	Population based	>2 days/week for >1 month	Personal Interview	Aspirin (12%) ⌖ †	0.85	0.66–1.09
						NSAIDs (39%)	0.81	0.68–0.96
Langman et al. [36]	1,041	3,122$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (7%)	1.14	0.85–1.53
Rosenberg[56]	1,110	4,906$_a$	Hospital based	>3 days/week for >3 months 1.5 years of lag time	Personal Interview	NSAIDs (6%)	0.8	0.4–1.6
Paganini-Hill et al. [40]	93	13,987$_b$	Cohort	Daily use of aspirin for an undefined time	Mailed questionnaire	Aspirin (16%)	1.10§	0.65–1.85
Schreinemachers et al. [43]	35	12,668$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (59%)	1.06	0.54–2.09

⌖ Prevalence of exposure among controls/cohort; †Exclusive users of aspirin.

Table 9: Kidney

Author	Cases N	Controls$_a$/ Cohort$_b$	Source Population	Exposure definition	Exposure assessment	Drug	RR	95% CI
McLaughlin et al. [63]	495*	697$_a$	Population based	More than 14 times per month for >36 months	Personal Interview	Aspirin (8%) ⌖	0.5†	0.2–1.0
							1.8‡	0.7–4.1
McCredie et al. 1988[64]	360*	985$_a$	Population based	>0.1 kg lifetime use	Mailed questionnaire	Aspirin (18%)	1.2	0.7–1.9
McCredie et al.1995[65]	1,732*	2,309$_a$	Population based	>5 kg lifetime use	Personal Interview	Aspirin (5%)	1.2	0.9–1.7
Gago-Dominguez et al. [66]	1,201*	1,204$_a$	Population based	Two or more times a week for 1 month or longer	Personal Interview	Aspirin (27%)	1.5	1.2–1.8
Paganini-Hill et al. [40]	NR*	13,987$_b$	Cohort	Daily use of aspirin for an undefined time	Mailed Questionnaire	Aspirin (16%)	6.3	2.0–20.0
Schreinemachers et al. [43]	32	12,668$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (59%)	0.60	0.29–1.24

*Renal cell carcinoma only; ⌖ Prevalence of exposure among controls/cohort; †Male only; ‡Female only.

Table 10: Overall relative risks and 95% confidence interval according to cancer site and type of exposure

	N†	NSAIDs RR (95%CI)	N	Aspirin RR (95%CI)	N	NA-NSAIDs RR (95%CI)
Esophagus	4	0.65 (0.46–0.92)	4	0.51 (0.38–0.69)		
Stomach	3	0.54 (0.39–0.75)	5	0.73 (0.63–0.84)	2	0.91 (0.66–1.25)
Pancreas	2	1.09 (0.59–2.01)	3	0.69 (0.40–1.20)		
Breast	9	0.77* (0.66–0.88)	11	0.77 (0.69–0.86)	5	0.86 (0.73–1.00)
Ovary	6	0.74 (0.61–0.90)	6	0.91 (0.79–1.06)		
Prostate	4	0.64* (0.34–1.21)	7	0.92 (0.81 – 1.05)	2	0.84 (0.68–1.05)
Kidney			6	1.23* (0.86–1.75)		
Bladder	3	0.91 (0.71–1.18)	3	0.91 (0.73–1.13)		
Lung	3	0.65* (0.34–1.22)	5	0.84* (0.66–1.07)		

*$p < 0.05$ (Heterogeneity test); †Number of studies.

Table 1: Esophagus

Author	Cases n	Controls$_a$ /Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Coogan et al. [26]	207	5,833$_a$	Hospital based	>4 days/week for >3 months. Continuing use during 1 year of lag time	Personal Interview	NSAIDs (7%) ⊕	0.8	0.5–1.4
Farrow et al. [30]	277	687$_a$	Population based	>1 tablet/week during >6 months. 1 year lag time	Personal Interview	Aspirin (31%)	0.48†	0.32–0.70
	279					NA-NSAIDs (13%)	0.81†	0.51–1.30
Langman et al. [36]	550	1,650$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (8%)	0.64	0.41–0.98
Garidou et al. [32]	56	200$_a$	Hospital based	Chronic intake	Personal Interview	NSAIDs (14%)	0.52†	0.17–1.62
Suleiman et al. [59]	56	56$_a$	Population based	Ever use for >1 year	Medical records	NSAIDs (38%)	0.16	0.03–0.93
Cheng et al. [60]	74	74$_a$	Population based	Ever daily use for >1 month	Personal Interview	Aspirin (21%)	0.67	0.27–1.63
Funkhouser et al.[31]	15	13,179$_b$	Cohort	Use 30 days before baseline (ocasional)	Personal Interview	Aspirin (51%)	0.10	0.01–0.76
Thun et al. [46]	157	635,031$_b$	Cohort	More than 16 times per month for at least one year	Mailed questionnaire	Aspirin (11%)	0.59	0.34–1.03

⊕ Prevalence of exposure among controls/cohort; †Adenocarcinoma.

Table 2: Stomach

Author	Cases n	Controls$_a$ /Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Farrow et al. [30]	612	687$_a$	Population based	>1 tablet/week during >6 months. 1 year lag time	Personal Interview	Aspirin (31%) ⊕	0.76	0.60–0.97
	610					NA-NSAIDs (13%)	0.79	0.56–1.10
Akre et al. [22]	480	1,055$_a$	Population based	>30 tablets/month. 2 years lag time	Personal Interview	Aspirin (3%)	0.8	0.7–1.1
						NA-NSAIDs†	1.1	0.6–1.4
Zaridze et al. [48]	448	610$_a$	Hospital based	>2 days/week for >6 months	In-hospital Questionnaire	Aspirin (14%)	0.60	0.41–0.90
						NSAIDs (17%)	0.65	0.45–0.93
Langman et al. [36]	613	1,837$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (8%)	0.51	0.33–0.79
Coogan et al. [26]	250	5,883$_a$	Hospital based	>4 days/week for >3 months. Continuing use during 1 year of lag time	Personal Interview	NSAIDs (7%)	0.3	0.1–0.6
Thun et al. [46]	266	635,031$_b$	Cohort	More than 16 times per month for at least one year	Mailed Questionnaire	Aspirin (11%)	0.53	0.34–0.81
Schreinemachers et al. [43]	39	12,668$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (59%)	0.93	0.49–1.74

⊕ Prevalence of exposure among controls/cohort; †Exposure definition not provided.

smaller than one. Among the five studies evaluating the effect of aspirin on the risk of gastric cancer, all of them showed a protective effect. In three out of these five studies confidence intervals did not include the null.

We found a significant amount of heterogeneity for NSAIDs in two of the cancer sites, breast and prostate, for aspirin in renal cancer, and for aspirin and NSAIDs in lung cancer. Nine studies provided data on the association

Table 3: Pancreas

Author	Cases n	Cotrols$_a$/ Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Coogan et al. [26]	491	5,833$_a$	Hospital based	>4 days/week for >3 months. Continuing use during 1 year of lag time	Personal Interview	NSAIDs (7%) ⌖	0.8	0.5–1.1
Langman et al. [36]	513	1,535$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (7%)	1.49	1.02–2.18
Menezes et al. [49]	194	582$_a$	Hospital based	>1 tablet/week for at least 6 months	In-hospital Questionnaire	Aspirin (44%)	1.00	0.72–1.39
Schreinemachers et al. [43]	30	12,668$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Mailed Questionnaire	Aspirin (59%)	0.67	0.33–1.36
Anderson et al. [23]	80	28,283$_b$	Cohort	>6 times/week at baseline	Mailed Questionnaire	Aspirin (21%)	0.40	0.20–0.82
						NA-NSAIDs (NR)	1.28	0.68–2.43

⌖ Prevalence of exposure among controls/cohort

Table 4: Breast

Author	Cases n	Controls$_a$/ Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Sharpe et al. [44]	5,882	23,517$_a$	Population based	>2 tablets/week during years 2 – 5 before index date	Automated Database	NSAIDs (4%) ⌖	0.76	0.63–0.92
Harris et al. [33]	744	767$_a$	Hospital based	>3 tablets/week during more than 5 years	Personal Interview	NSAIDs (16%)	0.6	0.4–0.8
Harris et al. [34]	511	1,534$_a$	Hospital based	>3 tablets/week for at least 1 year	Personal Interview	Aspirin (12%)	0.69	0.46–0.99
						NSAIDs (28%)	0.66	0.52–0.83
Coogan et al. [25]	6,558	2,925$_a$	Hospital based	>4 days/week for >3 months.	Personal Interview	Aspirin (N.R.)	0.7	0.5–0.8
				Continuing use during 1 year of lag time		NA-NSAIDs (N.R.)	0.8	0.6–1.1
						NSAIDs (7%)	0.7	0.6–0.8
Langman et al. [36]	3,105	9,772$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (6%)	1.10	0.92–1.30
Cotterchio et al. [27]	3,133	3,062$_a$	Population based	Daily use for more than two months. 1 year before start date excluded	Mailed Questionnaire	Aspirin (14%)	0.73	0.61–0.87
						NA-NSAIDs (11%)	0.79	0.66–0.96
						NSAIDs (26%)	0.76	0.66–0.88
Meier et al. [61]	3,706	14,155$_a$	Population based	≥30 prescriptions	Automated Database	NSAIDs (8%)	1.0	0.8–1.1
Rosenberg et al. [56]	4,485	4,906$_a$	Hospital based	>3 days/week for >3 months 1.5 years of lag timev	Personal Interview	NSAIDs (6%)	0.8	0.6–1.0
Neugut et al. [62]	252	176$_a$	Hospital based	Chronic aspirin use	Medical Records	Aspirin (9%)	0.80	0.35–1.80
Friedman et al. [20]	NR	143,574$_b$	Cohort	ever use	Medical Records	Aspirin‡ (2%)	0.20	0.05–0.80
						NA-NSAIDs» (3%)	0.50	0.28–0.88
Johnson et al. [58]	938	27,616$_b$	Cohort	>5 times per week	Mailed questionnaire	Aspirin (21%)	0.71	0.58–0.87

Table 4: Breast *(Continued)*

						NA-NSAID (13%)	1.01	0.83–1.25
Egan et al. [29]	2,414	89,528$_b$	Cohort	>2 tablets/week reported in 4 consecutive questionnaires	Mailed Questionnaire	Aspirin (15%)	1.01	0.80–1.27
						NA-NSAIDs (4%)	0.95	0.78–1.17†
Harris et al. [35]	393	32,505$_b$	Cohort	>4 tablest/week at start date	In-hospital Questionnaire	Aspirin (13%)	0.64	0.45–0.90
						NSAIDs (25%)	0.57	0.44–0.74
Paganini-Hill et al. [40]	214	8,881$_b$	Cohort	Daily use of aspirin for an undefined time	Mailed Questionnaire	Aspirin (15%)	1.05§	0.73–1.50
Thun et al. [46]	NR.	344,350$_b$	Cohort	More than 16 times per month for at least one year	Mailed Questionnaire	Aspirin (11%)	0.88	0.62–1.24
Schreinemachers et al. [43]	147	7,489$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (64%)	0.70	0.50–0.96

Prevalence of exposure among controls/cohort; §Crude estimate calculated from data provided in the original manuscript; † For NA – NSAIDs only the baseline questionnaire was considered; ‡ includes only Fiorinal (aspirin, phenacetin, caffeine and butalbital combination); » indomethacin only.

Table 5: Ovary

Author	Cases n	Controls$_a$/ Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Tzonou et al. [47]	189	200$_a$	Hospital based	>2 tablets/week	Personal Interview	NSAIDs (26%)	0.51	0.26–1.02
Cramer et al. [28]	563	523$_a$	Population based	>1 tablet/week for >6 months. 1 year lag time.	Personal Interview	Aspirin†(14%)	0.75	0.52–1.10
						NSAIDs‡ (7%)	0.91	0.53–1.54
Tavani et al. [45]	749	898$_a$	Hospital based	>1 tablet/week for >6 months. (current and/or former)	Personal Interview	Aspirin (6%)	0.93	0.53–1.62
Rosenberg[56]	448	4,906$_a$	Hospital based	>3 days/week for >3 months 1.5 years of lag time	Personal Interview	NSAIDs (6%)	0.8	0.5–1.3
Rosenberg et al. [42]	780	2,570$_a$	Hospital based	>4 days/week for at least 6 months.1 year lag time	Personal Interview	Aspirin (5%)	0.8	0.5–1.2
						NA-NSAIDs (3%)	0.5	0.3–1.0
						NSAIDs (8%)	0.7	0.5–1.0
Moysich et al. [37]	547	1,094$_a$	Hospital based	>1 day/week for 6 consecutive months	In-hospital Questionnaire	Aspirin (12%)	1.00	0.73–1.39
Akhmedkhanov et al. [21]	68	680$_a$	Population based	Ever use of >3 tablet/week for >6 months. 1 year lag time	Mailed Questionnaire	Aspirin (16%)	0.60	0.26–1.38
Meier et al. [61]	483	1,877$_a$	Population based	≥30 prescriptions. 1 year lag time	Automated Database	NSAIDs (5%)	1.1	0.6–1.8
Fairfield et al. [50]	333	76,821$_b$	Cohort	>1 tablet/week	Mailed	Aspirin (46%)	1.00	0.80–1.25
						NSAIDs (N.R.)	0.60	0.38–0.95

Prevalence of exposure among controls/cohort; †Over-the-counter only; ‡Prescription only.

between NSAID use and breast cancer incidence. The overall estimate for this effect was 0.77 (95% CI, 0.66–0.88) and significant between-study variation was found. Study design (hospital based case-control, population based case-control, or cohort study) and exposure assessment appeared to be the variables that explained heterogeneity to a greater extent in the meta-regression. The pooled estimate for hospital based case-control studies (n = 4) was 0.69 (95%CI,0.62–0.77) whereas the pooled estimate for population based case-control studies (n = 4)

Table 6: Prostate

Author	Cases n	Controls$_a$/ Cohort$_b$	Source population	Exposure definition	Exposure assessment	Drug	RR	95% CI
Nelson et al. [38]	417	420$_a$	Hospital based	>1 tablet/day in the year prior to admission	Personal Interview	NSAIDs (15%) ⊕	0.34	0.20–0.58
Langman et al. [36]	1,813	5,354$_a$	Population based	>7 prescriptions during months 13–36 before index date	Automated Database	NSAIDs (7%)	1.33	1.07–1.64
Norish et al. [39]	317	480$_a$	Population based	>1 tablet/week	Mailed Questionnaire	Aspirin (29%)	0.85	0.61–1.19
						NA-NSAIDs (7%)	0.87	0.49–1.55
						NSAIDs (36%)	0.88	0.64–1.20
Irani et al. [53]	639	659$_a$	Hospital based	Ever use	In-hospital Questionnaire	NA-NSAIDs (46%)	0.80	0.66–1.07
Neugut et al. [62]	319	189$_a$	Hospital based	Chronic aspirin use	Medical records	Aspirin (7%)	1.60	0.82–3.11
Roberts et al. [41]	91	1,362$_b$	Cohort	Daily use	Mailed Questionnaire	NSAIDs (42%)	0.37	0.22–0.62
Paganini-Hill et al. [40]	149	5,106$_b$	Cohort	Daily use of aspirin for an undefined time	Mailed Questionnaire	Aspirin (17%)	0.94§	0.61–1.44
Thun et al. [46]†	N.R.	290,681$_b$	Cohort	More than 16 times per month for at least one year	Mailed Questionnaire	Aspirin (11%)	0.82	0.56–1.19
Schreinemachers et al. [43]	123	5,179$_b$	Cohort	Ever use of aspirin in the 30 days prior to start date	Personal Interview	Aspirin (51%)	0.95	0.66–1.35
Leitzmann et al. [52]	2,479	47,882$_b$	Cohort	≥2 tablets per week reported in 4 consecutive questionnaires	Mailed Questionnaire	Aspirin (N.R.)	1.04	0.86–1.26
Habel et al. [57]	2,574	90,100$_b$	Cohort	>6 tablets almost ever day	In hospital Questionnaire	Aspirin (2.7%)	0.76	0.60–0.98

⊕ Prevalence of exposure among controls/cohort; §Crude estimate calculated from data provided in the original manuscript; †Genital (includes prostate and testis).

was 0.89 (95% CI, 0.74–1.08). There was only one cohort study (RR, 0.57;95%CI,0.44–1.73). Regarding exposure assessment, only two studies used mailed questionnaires to ascertain NSAID exposure. The combined estimate for these studies was 0.67 (95%CI, 0.51–0.89). For studies using personal interview as exposure assessment method (n = 4) the overall estimate was similar (RR,0.69; 95%CI,0.62–0.77). The other three studies used automated databases to elicit exposure and they found little or no effect (RR,0.95;95%CI,0.77–1.16). Once we adjusted for exposure assessment, study design did not explain additional heterogeneity. We found that the protective effect of NSAID use was slightly stronger among studies not using lag time (n = 3) (RR,0.69;95%CI,0.51–0.94) than among those using lag time (n = 5) (RR, 0.81; 95%CI,0.69–0.96). It is somewhat difficult to draw conclusions about possible sources of heterogeneity in the other two cases (prostate, kidney and lung) due to the limited number of studies.

Discussion

This meta-analysis attempts to evaluate the effectiveness of NSAIDs in reducing the risk of cancer other than colorectal as primary prevention. Based on a limited number of studies, the results show that NSAIDs overall and aspirin in particular are associated with a decreased risk of developing both esophageal cancer and gastric cancer with a magnitude of effect (40 % reduction) comparable to the one observed with colorectal cancer. A recently published meta-analysis addressing esophageal cancer found similar results [68]. The results for breast are consistent in showing a slight protection. Overall results for the effect of aspirin on pancreatic cancer show a non-significant risk reduction, while results from ovary, prostate, kidney, bladder and lung cancer are compatible with no effect of NSAIDs in preventing these cancers.

The association with NSAIDs has been extensively studied for colorectal cancer through observational methods and it is now pending confirmation on the results of experimental studies currently ongoing for secondary prevention [69]. If the observed association in colorectal cancer were true, one could expect a similar effect in other cancers of the gastrointestinal tract. The consistency observed in the results for esophageal and gastric cancer in our meta-analysis tends to support this hypothesis. Unfortu-

nately, very few studies assessed whether contraindication for use of aspirin and NA-NSAIDs could explain the observed protective effect. It is most likely true that patients with upper gastrointestinal symptoms or disease are likely to use less NSAIDs than the general population, and these conditions are positively correlated with the occurrence of both esophageal and gastric cancer.

Overall results for the effect of aspirin on pancreatic cancer show a non-significant risk reduction around 30%. While the two cohort studies show a strong protective effect (close to 50% reduction)[23,43] a recently published case-control study shows no effect [49].

The results for breast are consistent in showing a slight protection (around 20%). However, as we previously indicated, results from other sites (ovary, prostate, kidney, bladder and lung cancer) are compatible with no effect of NSAIDs in preventing these cancers. This seems to confirm the idea that NSAID primary prophylaxis for cancer, far from being the new panacea, has limited results and restricted to some cancers mainly in the gastrointestinal area[70,71] although evidence for other cancers is sparse and would require additional studies to have a more robust estimate of the true association.

Phenacetin-containing analgesics have been shown to increase renal cancer [72], and it is unclear whether this effect is common to NSAIDs. Our result on cancer of the kidney cannot exclude a slight increased risk associated with aspirin use. However caution must be taken when interpreting these results. Phenacetin was commonly used in combination with aspirin, so the studied effect of aspirin often combines the effect of aspirin and phenacetin given together [73]. The results for prostate cancer are not compatible with an increased risk of NSAIDs, which seems to support the hypothesis that the elevated risk observed in some studies might result from detection bias.

In table 10 the estimate for the overall effect of NSAIDs on gastric cancer is not the weighted average of the corresponding estimates of aspirin and NA-NSAIDs. This is due to the fact that none of the studies assessed simultaneously the three different types of drug exposure and therefore estimates for each type of NSAID arise from different studies with different characteristics.

Tests for heterogeneity found a significant amount of between-study variance in four of the combined estimates. One problem with these tests is that they are not sensitive enough when a small number of studies is being pooled. Consequently, caution must be taken when interpreting these results. However, the use of a random effects model takes into account to certain extent this additional source of variability and incorporates it in obtaining the pooled estimate. Our analysis found significant heterogeneity among the studies addressing the association between NSAIDs and breast cancer. Further analysis of this variation showed that among case-control studies, hospital based studies yielded a more optimistic result than population-based. Two key features that define the quality of a case-control study are the selection of controls and the way in which the exposure is ascertained. Controls in hospital-based studies rarely attain to be a true representative sample from the source population where cases have arisen. This is especially troublesome when the reason for admission could be related to the exposure, which represents the greatest limitation of this study design [74]. On the other hand, controls in population-based studies tend to give a more valid estimate of the exposure in the source population. The method used to elicit the exposure will also determine the quality of the data. Automated databases (AD) offer some advantages when long term drug exposure is to be ascertained. In contrast to personal interviews or self-administered questionnaires that rely heavily on the subject's ability to recall, AD provide detailed information on dates of use and type of drugs used. Furthermore this information is equally good for cases or controls irrespective of the event of interest since it was recorded prospectively (as opposed to methods based on subject's ability to recall which may depend on the case status). We found that the estimate for the subset of studies using AD was more conservative than the estimates for studies using personal interviews or mailed questionnaires. On the other hand, the downside of using ADs in assessing NSAID exposure is its inability to capture exposure to widely available over-the-counter NSAIDs. This could result in non-differential misclassification of exposure that would dilute the underlying effect, and represents an alternative explanation for the more conservative results obtained in the AD subset.

One possible explanation of RR heterogeneity is variation in background rate. This ought to be addressed by considering the background rates in study populations exhibiting heterogeneity. However, most of the population based case-control studies did not report incidence rates (or enough information to compute) and there were a limited number of cohort studies. Therefore we were unable to assess the influence of different background rates.

The limited number of studies involved in the estimates for the effects of aspirin on lung cancer and NSAIDs on prostate cancer prevents us from a conclusive analysis of the source of heterogeneity observed in these estimates.

Exposure definition in all the reviewed studies was quite heterogeneous. According to the proposed mechanism, chronic exposure to NSAIDs would be needed in order to

observe the hypothesized protective effect. However, we found that studies using relatively broad exposure definitions (such as "ever use of aspirin in the 30 days prior to start date") were able to detect associations similar to the ones observed in studies with more specific and "valid" exposure definitions. In general, the consistency in the results was surprisingly high considering the large amount of heterogeneity in exposure definition across studies. In our opinion, this is due to the fact that, in these populations, different exposure definitions are still highly correlated (i.e. subjects classified as exposed by "loose" exposure definitions have still a relatively high probability of being chronic users as compared to the ones called non users). This, somehow, justifies pooling these studies to obtain an overall estimate. However, this correlation between different exposure definitions will be different between aspirin and NA-NSAIDs. Since the relative prevalence of chronic use is greater among aspirin users (as a result of its predominant use for prevention of cardiovascular disease) than among NA-NSAID users, this grouping of exposure would result in a greater misclassification among NA-NSAID users than aspirin users. This might partly explain the closer to the null results obtained for NA-NSAIDs though the number of individual studies were too limited to analyze this with confidence. Overall prevalence of NSAID exposure among the controls/cohort was quite variable across studies. Based on a qualitative review, we could say that it was a function of both the nature of the study population and the looseness of the exposure definition applied. It is noteworthy that studies that reported abnormally low or high prevalence of exposure (inversely related to studies using AD) tended to find extreme results in both directions.

Protopathic bias could overestimate exposure among cases in those studies that do not include lag time in their exposure definition if early symptoms of cancer influenced the subsequent use of NSAIDs. Our analysis did not identify large differences between studies using and not using lag time although the latter generally yielded more conservative results. Also, since the primary endpoint in most of these studies was clinical diagnosis of cancer, and given that this endpoint can be associated with screening frequency, this potential bias deserves consideration. This is especially true for cancers such as breast or prostate where screening methods are widely available. Barry hypothesized that if NSAID use is a proxy for poorer general health, one would expect these people to get less screening and therefore to be less likely to be diagnosed with cancer [75], but the exact opposite argument can be made with equal force. At present, most chronic NSAID use comes from low dose aspirin indicated for cardioprotection, and people pursuing this prophylactic measure are likely to be more health-conscious and follow other preventive actions such as timely screening. This would associate NSAID exposure spuriously with a higher risk of cancer. Therefore, the net effect of this potential bias, if any, is difficult to predict.

Some authors have questioned the use of random effect models arguing that it might not always be more conservative than the fixed effects model [76]. The use of fixed effects models in our data resulted in very similar point estimates and full consistency regarding statistical significance (data not shown). We evaluated the potential for publication bias plotting the log RR from each study against its standard error as well as using kendall's tau test and found no substantial evidence of publication bias.

Conclusions

In summary, the results of this meta-analysis show that the potential chemopreventive role of NSAIDs in colorectal cancer might extend to other gastrointestinal cancers such as esophagus and stomach. There is evidence that supports a similar effect, though to a smaller extent, of NSAIDs in breast cancer whereas such potential in other cancers appears to be slim based on the reviewed literature. In general, the extent to which this potential benefit might be offset by the adverse effects of long-term use of these drugs is not clear especially in cancers with low incidence and clearly needs to be taken into account when evaluating the chemoprophylactic role of NSAIDs. The role of a new class of NSAIDs such as selective COX-2 inhibitors is yet to be assessed as well as the optimal dose and duration regimen for a hypothetical prevention therapy. Further research is required to solve all these open and important questions.

Competing interests

None declared.

Authors' contributions

LAGR had the original idea, and contributed to the analysis and the report. RLR contributed to the literature search and review. AGP contributed to the literature review, the analysis and the report. All authors read and approved the final manuscript.

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