Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database

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Abstract

Objective To examine whether anti-inflammatory drug treatment protects against the commoner cancers in the United Kingdom.
Design Case-control study using the general practice research database.
Setting Practices throughout United Kingdom providing data to the database.
Subjects Patients who had a first diagnosis of five gastrointestinal (oesophagus, stomach, colon, rectum, and pancreas) cancers and four non-gastrointestinal (bladder, breast, lung, and prostate) cancers in 1993-5 for whom prescription data were available for the at least the previous 36 months. Each case was matched for age, sex, and general practice with three controls.
Main outcome measure Risk of cancer.
Results In 12 174 cancer cases and 34 934 controls overall risk of the nine cancers was not significantly reduced among those who had received at least seven prescriptions in the 13-36 months before cancer diagnosis (odds ratio 0.98, 95% confidence interval 0.89 to 1.07). Findings were nevertheless compatible with protective effects from anti-inflammatory drugs against cancers of the oesophagus (0.64, 0.41 to 0.98), stomach (0.51, 0.33 to 0.79), colon (0.76, 0.58 to 1.00), and rectum (0.75, 0.49 to 1.14) with dose related trends. The risk of pancreatic cancer (1.49, 1.02 to 2.18) and prostatic cancer (1.33, 1.07 to1.64) was increased among patients who had received at least seven prescriptions, but the trend was dose related for only pancreatic cancer.
Conclusions Anti-inflammatory drugs may protect against oesophageal and gastric cancer as well as colon and rectal cancer. The increased risks of pancreatic and prostatic cancer could be due to chance or to undetected biases and warrant further investigation.

Introduction

Epidemiological evidence has consistently shown that people who have taken aspirin or other non-steroidal anti-inflammatory drugs are at reduced risk of developing or dying from colon cancer.[1 2] The extent to which treatment protects against other cancers is unclear, although in epidemiological studies fewer fatal cases of gastric and oesophageal cancer than expected have been found[2] and the occurrence of experimentally induced bladder, breast, and colon cancer in animals has been reduced by giving non-steroidal anti-inflammatory drugs concurrently with carcinogens.[3–5]

The extent to which treatment might protect against different varieties of cancer in humans could be investigated by separate case-control or case-cohort studies, but this time consuming and labour intensive method can be avoided by examining information held on automated databases that record drug prescriptions and clinical outcomes. We used the general practice research database to examine information about previous prescription of aspirin and other non-steroidal anti-inflammatory drugs and occurrence of the common cancers in the United Kingdom.

Methods

The general practice research database is a national dataset managed for the Department of Health containing anonymised patient records on about four million UK residents. Contributing general practices, which are distributed throughout the United Kingdom, record standard data on demography, morbidity, and prescriptions and selected other information. The quality of data is regularly assessed.[6] With ethics committee approval we identified practices with at least four years of information meeting the required standard and abstracted data on all patients with a first diagnosis of five gastrointestinal cancers (oesophagus, stomach, pancreas, colon, and rectum) and four non-gastrointestinal cancers (bladder, breast, lung, and prostate) during 1993-5. Each case was then individually matched for age (within five years), sex, and general practice with three controls. Controls were patients without a diagnosis of the case's type of cancer at the time the case was diagnosed. We also obtained information on recorded current smoking habits.

Data on prescriptions for aspirin and other non-steroidal anti-inflammatory drugs (all drugs listed in *British National Formulary* subsection 10.1.1) were extracted for each case and control for the 13-36 months before cancer diagnosis (and equivalent data were extracted for controls). Information on smoking

habits was used to classify patients as ever smokers or never smokers. Conditional logistic regression was used to analyse associations between numbers of prescriptions and risk of cancer for all sites together and each separately. Odds ratios (adjusted for smoking habits and age) were calculated with 95% confidence intervals, and dose-response relations were tested for trend. In the primary analyses we examined overall cancer incidence in relation to drug use and compared risks of gastrointestinal and non-gastrointestinal cancers.

Results

We identified 12 174 patients with a first diagnosis of the study cancers in 1993-5 who had prescription data available for the previous 36 months. Eighteen patients with multiple cancers were excluded from analyses of individual sites, with their controls. Table 1 shows, for each cancer site, the numbers of cases and matched controls by sex and the numbers who had ever received prescriptions for aspirin or other non-steroidal anti-inflammatory drugs.

Table 2 shows the odds ratios for gastrointestinal cancer associated with receipt of prescriptions for aspirin or other non-steroidal anti-inflammatory drugs in the periods studied. For oesophageal, gastric, colon, and rectal cancer the odds ratios tended to fall with increasing number of prescriptions issued. The trends occurred in both the 13-24 and 25-36 months before cancer diagnosis and were significant for oesophageal and gastric cancer in the combined period of 13-36 months ($P=0.03$ and $P=0.02$ respectively). For patients who had received at least seven prescriptions in the 13-36 months before diagnosis, odds ratios were consistently reduced for oesophageal (0.64, 95% confidence interval 0.41 to 0.98), gastric (0.51, 0.33 to 0.79), colon (0.76, 0.58 to 1.00), and rectal (0.75, 0.49 to 1.14) cancer, with matching, though not always significant, dose related trends.

By contrast, odds ratios were raised significantly in patients who had received at least seven prescriptions in the 13-36 months before diagnosis of pancreatic cancer (1.49, 1.02 to 2.18). Figures for prostatic cancer were also consistently raised, and the trend was highly significant ($P<0.0001$), although without a clear dose-response relation. Odds ratios for bladder and breast cancer were close to unity, and there was an insignificant trend towards a reduced risk for lung cancer. When all the nine cancers were considered together the odds ratio was close to unity (0.98, 0.89 to 1.07) in patients receiving at least seven prescriptions in the 13-36 months before cancer diagnosis. The odds ratios in table 2 were adjusted for age and smoking, although the estimates without adjusting were similar for all cancer sites.

Table 1 Number of cases and controls for each cancer site by sex and prescription of non-steroidal anti-inflammatory drug (NSAID) in 13-36 months before diagnosis of case

Cancer site	No of cases	No of controls	No prescribed NSAID in 13-36 months before diagnosis of case	
			Cases	Controls
Bladder:				
Male	764	2291	200	532
Female	277	831	100	239
Total	1041	3122	300	771
Breast:				
Male	21	63	8	14
Female	3084	9209	902	2684
Total	3105	9272	910	2698
Colon:				
Male	668	1997	181	512
Female	700	2092	197	638
Total	1368	4089	378	1150
Lung:				
Male	1653	4925	386	1204
Female	907	2718	271	808
Total	2560	7643	657	2012
Oesophagus:				
Male	348	1044	86	286
Female	202	606	50	165
Total	550	1650	136	451
Pancreas:				
Male	248	742	58	161
Female	265	793	88	235
Total	513	1535	146	396
Prostate:				
Male	1813	5354	570	1350
Rectum:				
Male	343	1028	79	255
Female	250	750	73	227
Total	593	1778	152	482
Stomach:				
Male	389	1165	92	302
Female	224	672	56	170
Total	613	1837	148	472
All sites:				
Male	6258	17 593	1660	4326
Female	5916	17 341	1739	5067
Total	12 174*	34 934†	3399	9393

*Eighteen cases (11 men, seven women) had multiple site cancer and were excluded from individual site categories. †Figure is less than total number of controls for each site individually as some patients were by chance selected as controls for more than one patient

Discussion

We found trends towards reduced incidence of colorectal cancers among people taking aspirin or other non-steroidal anti-inflammatory drugs, with the greatest reductions among those receiving more prescriptions. Our findings are similar to those of most previous case-cohort studies[1 2 7–9] but do not show the stronger protection found in some case-control studies. The trends towards protection existed whether drug prescription was examined in the 13-24 months or 25-36 months before cancer diagnosis.

We also found evidence of protection against oesophageal and gastric cancer. Four of the six previous studies were too small to give reliable information.[9–12] Thun et al found non-significant evidence of protection in 176 patients dying of oesophageal cancer and 308 dying of gastric cancer,[2] and Farrow et al, in a case-control study of over 500 cases each of oesophageal and gastric cancer, noted significant reductions in risk of oesophageal adenocarcinoma and squamous carcinoma (odds ratios 0.37 and 0.49 respectively) and of non-cardia gastric carcinoma (0.46) but not of cardia cancer.[13] Our findings support the case for protection and suggest that protection may be at least as good as for colorectal cancer. The results for gastric cancer could have been confounded by avoidance of anti-inflammatory drugs for patients infected with *H pylori* (a known risk factor for gastric cancer). However, this seems unlikely

Table 2 Numbers of cases and controls and adjusted odds ratios* for risk of cancer according to numbers of prescriptions of non-steroidal anti-inflammatory drugs received in 13-24 and 25-36 months before diagnosis and both periods combined

		Months 13-24					Months 25-36					Months 13-36				
		No of prescriptions				P for	No of prescriptions				P for	No of prescriptions				P for
Site	Total No	0	1	2-6	⩾7	trend	0	1	2-6	⩾7	trend	0	1	2-6	⩾7	trend
Oesophagus:																
No of cases (controls)	550 (1650)	451 (1314)	37 (111)	41 (142)	21 (83)	0.10	455 (1330)	45 (107)	28 (128)	22 (85)	0.07	414 (1199)	56 (150)	49 (164)	31 (137)	0.03
Odds ratio (95% CI)		1.00	0.90 (0.59 to 1.35)	0.82 (0.56 to 1.19)	0.72 (0.42 to 1.22)		1.00	1.23 (0.83 to 1.80)	0.65 (0.42 to 0.99)	0.72 (0.43 to 1.20)		1.00	1.04 (0.74 to 1.46)	0.82 (0.57 to 1.17)	0.64 (0.41 to 0.98)	
Stomach:																
No of cases (controls)	613 (1837)	508 (1491)	50 (129)	33 (122)	22 (95)	0.03	509 (1499)	46 (118)	42 (128)	16 (92)	0.02	465 (1365)	57 (159)	60 (156)	31 (157)	0.02
Odds ratio (95% CI)		1.00	1.08 (0.75 to 1.54)	0.72 (0.47 to 1.10)	0.61 (0.36 to 1.02)		1.00	1.14 (0.79 to 1.63)	0.80 (0.54 to 1.19)	0.49 (0.27 to 0.86)		1.00	1.07 (0.77 to 1.48)	1.02 (0.73 to 1.42)	0.51 (0.33 to 0.79)	
Pancreas:																
No of cases (controls)	513 (1535)	410 (1238)	38 (113)	37 (127)	28 (57)	0.34	406 (1276)	41 (97)	41 (114)	25 (48)	0.10	367 (1139)	46 (147)	50 (142)	50 (107)	0.08
Odds ratio (95% CI)		1.00	1.05 (0.70 to 1.56)	0.88 (0.59 to 1.32)	1.58 (0.96 to 2.59)		1.00	1.28 (0.85 to 1.92)	1.14 (0.76 to 1.70)	1.50 (0.87 to 2.56)		1.00	0.94 (0.64 to 1.36)	1.08 (0.75 to 1.54)	1.49 (1.02 to 2.18)	
Colon:																
No of cases (controls)	1368 (4089)	1116 (3255)	108 (322)	100 (340)	44 (172)	0.02	1101 (3309)	124 (280)	93 (335)	50 (165)	0.41	990 (2939)	157 (409)	138 (431)	83 (310)	0.09
Odds ratio (95% CI)		1.00	0.96 (0.76 to 1.22)	0.81 (0.63 to 1.04)	0.74 (0.52 to 1.05)		1.00	1.26 (1.00 to 1.59)	0.83 (0.65 to 1.07)	0.91 (0.64 to 1.27)		1.00	1.11 (0.90 to 1.36)	0.93 (0.75 to 1.15)	0.76 (0.58 to 1.00)	
Rectum:																
No of cases (controls)	593 (1778)	490 (1442)	50 (142)	35 (115)	18 (79)	0.17	488 (1442)	46 (140)	45 (129)	14 (67)	0.31	441 (1296)	70 (196)	51 (161)	31 (125)	0.18
Odds ratio (95% CI)		1.00	1.01 (0.71 to 1.44)	0.88 (0.59 to 1.32)	0.68 (0.40 to 1.16)		1.00	0.96 (0.67 to 1.39)	1.00 (0.69 to 1.44)	0.65 (0.36 to 1.18)		1.00	1.07 (0.79 to 1.46)	0.87 (0.61 to 1.23)	0.75 (0.49 to 1.14)	
Bladder:																
No of cases (controls)	1041 (3122)	827 (2561)	84 (218)	88 (221)	42 (122)	0.26	829 (2569)	80 (212)	90 (217)	42 (124)	0.28	741 (2351)	118 (270)	104 (292)	78 (209)	0.14
Odds ratio (95% CI)		1.00	1.21 (0.92 to 1.59)	1.20 (0.91 to 1.58)	1.01 (0.69 to 1.48)		1.00	1.10 (0.83 to 1.45)	1.24 (0.95 to 1.63)	0.99 (0.68 to 1.45)		1.00	1.38 (1.08 to 1.75)	1.09 (0.84 to 1.40)	1.14 (0.85 to 1.53)	
Breast:																
No of cases (controls)	3105 (9272)	2464 (7400)	269 (782)	240 (755)	132 (335)	0.48	2484 (7428)	271 (836)	229 (686)	121 (322)	0.56	2195 (6574)	376 (1120)	313 (979)	221 (599)	0.64
Odds ratio (95% CI)		1.00	1.03 (0.88 to 1.20)	0.95 (0.81 to 1.12)	1.17 (0.94 to 1.45)		1.00	0.96 (0.82 to 1.11)	1.01 (0.85 to 1.18)	1.12 (0.90 to 1.40)		1.00	0.99 (0.87 to 1.13)	0.96 (0.83 to 1.11)	1.10 (0.92 to 1.30)	
Lung:																
No of cases (controls)	2560 (7643)	2092 (6207)	181 (550)	187 (552)	100 (334)	0.16	2109 (6239)	187 (526)	168 (564)	96 (314)	0.10	1903 (5631)	235 (750)	250 (685)	172 (577)	0.17
Odds ratio (95% CI)		1.00	0.90 (0.74 to 1.09)	0.95 (0.79 to 1.15)	0.87 (0.68 to 1.11)		1.00	1.03 (0.86 to 1.25)	0.87 (0.71 to 1.05)	0.86 (0.67 to 1.11)		1.00	0.85 (0.72 to 1.01	1.05 (0.89 to 1.24)	0.84 (0.69 to 1.02)	
Prostate:																
No of cases (controls)	1813 (5354)	1386 (4400)	178 (366)	167 (368)	82 (220)	0.001	1422 (4420)	152 (352)	167 (376)	72 (206)	0.002	1243 (4004)	220 (485)	201 (492)	149 (373)	0.0001
Odds ratio (95% CI)		1.00	1.49 (1.22 to 1.82)	1.44 (1.17 to 1.76)	1.21 (0.92 to 1.60)		1.00	1.36 (1.10 to 1.67)	1.34 (1.09 to 1.64)	1.17 (0.87 to 1.55)		1.00	1.43 (1.19 to 1.71)	1.28 (1.06 to 1.54)	1.33 (1.07 to 1.64)	
All sites:																
No of cases (controls)	12 174 (34 934)	9760 (28 251)	996 (2642)	929 (2635)	489 (1406)	0.75	9820 (28 449)	992 (2594)	903 (2547)	459 (1344)	0.80	8775 (25 541)	1336 (3597)	1216 (3325)	847 (2471)	0.64
Odds ratio (95% CI)		1.00	1.08 (0.99 to 1.17)	1.00 (0.91 to 1.08)	1.00 (0.89 to 1.12)		1.00	1.09 (1.00 to 1.18)	1.00 (0.91 to 1.09)	0.98 (0.87 to 1.10)		1.00	1.06 (0.99 to 1.14)	1.04 (0.96 to 1.12)	0.98 (0.89 to 1.07)	

*Adjusted for age and smoking status.

because similar raised risks were found for oesophageal cancer and because adverse effects of these drugs have not been convincingly shown to be more common in people who are infected.

Non-gastrointestinal cancers

We found little evidence of protective effects of non-steroidal anti-inflammatory drugs on non-gastrointestinal cancers. Protection against breast cancer has been suggested by two studies (one of aspirin[9] and one of other non-steroidals[14]) but not by other studies that examined aspirin exclusively[2 15] or predominantly.[16] Our study is larger than these and found no evidence of protection despite the experimental finding that development of mammary tumours is inhibited by such drugs.[4] One study has suggested pro-

tection against lung cancer,[9] but this finding was not supported by two others[15 17] or by our study, which was larger than the other studies.

Our finding of a possible increased risk of pancreatic cancer needs interpreting cautiously. The difficulty in diagnosing pancreatic cancer could lead to non-specific prescription of analgesics. Although non-steroidal anti-inflammatory drugs are not usually prescribed for the long term relief of abdominal pain, they might be used for back pain. The relation we found is unlikely to be due to residual confounding by smoking since adjustment for smoking made little difference to the odds ratio estimates. The apparent dose-response relation, although not significant, supports the possibility of a causal relation.

The highly significant association between drug use and prostatic cancer in our data is unexplained, but it is noteworthy that it does not seem dose related. The finding runs counter to recent evidence that non-steroidal anti-inflammatory drugs may slow progression of prostatic cancer[18] and could, despite the level of significance, represent a chance finding or perhaps the treatment of undiagnosed bone pain.

We have failed to show that people taking anti-inflammatory drugs (most of whom have non-specific degenerative disease[19]) have reduced general risks of cancer. These findings agree with those of studies in people with rheumatoid arthritis,[2 10 11] which have found no convincing evidence of altered overall risk of cancer despite heavy use of anti-inflammatory drugs. The reasons why patients with gastrointestinal cancer may be relatively protected are unclear, but simple dose effects seem possible.

Validity of results

Our data may be criticised on the grounds that the drug prescription periods examined were relatively close to the time of diagnosis of cancer. However, trends towards protection were at least as evident for drug prescriptions 25-36 months before cancer diagnosis as in the 13-24 months beforehand. Secondly, examination of individual patient records indicated that the same patients were likely to receive prescriptions in the two periods. This agrees with other evidence suggesting that people taking anti-inflammatory drugs tend to do so long term. Furthermore, although it is plausible that such drugs might be prescribed to people with undiagnosed cancer, it is difficult to understand why they might be relatively underprescribed in patients with gut epithelial cancers.

We were unable to allow for the possible effects of alcohol consumption as a potential confounder and were limited in our ability to allow for smoking habits. However, it is difficult to see why, in oesophageal cancer in particular, such confounding would be likely to bring out, rather than diminish, any protective effects associated with use of anti-inflammatory drugs. Use of over the counter drugs is unlikely to be a significant confounder because people older than 60 years (the main age group for cancer) know that they can obtain any drugs needed free through general practice prescription. In addition, in the past we found little evidence of large scale over the counter purchases.[19] For all these reasons we consider that our evidence of protection against gut epithelial cancer outside the pancreas is well founded. Finally, although cancer diagnoses were not formally validated, the checks conducted by the general practice research database on diagnoses have been accepted as giving high reliability.[6]

What is already known on this topic

Treatment with aspirin and other non-steroidal anti-inflammatory drugs is associated with protection against colorectal cancer

Evidence of protection against other cancers is uncertain

What this study adds

In the 13 to 36 months before cancer diagnosis, treatment with non-steroidal anti-inflammatory drugs seemed to lower the risk of oesophageal, gastric, colon, and rectal cancer

No effect was found on bladder, breast, or lung cancer

Risk of pancreatic and prostatic cancer was increased, although this was not necessarily a causal relation

Mechanism of protection

Colon cancer has been intensively studied, and up regulation of the cyclo-oxygenase 2 (cox-2) gene has been consistently shown in 80% or more of cancers.[20 21] Up regulation of cox-2 expression has been shown in tumours of the oesophagus, stomach, and breast,[22–24] but evidence of protection against breast cancer is insecure. The assumption that cox-2 inhibition is the critical mechanism may not be justified, although gastrointestinal effects could reflect responses to high levels of direct drug exposure.

We conclude that although aspirin and other non-steroidal anti-inflammatory drugs may protect against gut epithelial cancers, there may be no overall benefit from use of non-selective cox-2 inhibitors in preventing cancer. Further investigation is warranted to confirm or refute that use of such drugs raises the risks of pancreatic and prostatic cancers.

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Tribulations of clinical trials

There's more inside the tablet

Several years ago I was invited to be the medical officer for a geological expedition to the Arctic. The attractions of the beauty and grandeur of the high Arctic in summer are somewhat diminished by swarms of mosquitoes, which are notable for their size and ferocity. Even the locals find the attentions of the cuculid hordes hard to bear, with the caribou preferring to rest on patches of snow, where the lower air temperature discourages the biters. There was at that time unfounded speculation that B vitamins acted as systemic insect repellants,[1 2] possibly because of the aroma of yeast excreted via the sweat. It therefore seemed a good idea to conduct a randomised clinical trial of the effect of daily vitamin B supplements on the number of mosquito bites. For convenience, I used a dark green multivitamin capsule, which we routinely gave to our patients with endstage renal failure.

I thought that the trial was perfect: using a safe intervention to prevent a distressing problem. However, my geologist colleagues were deeply suspicious from the start, perhaps because they were not keen on the idea of me counting their bites every day, or perhaps because randomisation had placed me in the control group. However, I persuaded them to participate and on the first night in mosquito country half the scientists took a vitamin capsule without ill effect. The following morning, however, I was woken by generalised uproar and howls of distress. The early risers had left their tents to relieve themselves, only to be shocked by the sight of fluorescent green urine.

The pea green urine was due partly to the colouring in the capsule. I thought this was interesting as, of course, I had not observed this colourful effect in the anuric dialysis patients, but my colleagues were convinced that they had barely escaped with their lives. Informed consent, such as it was, was immediately withdrawn. The trial collapsed and faith in the medical profession was restored only when one of the geologists fell several hundred feet down a snow field and I was able to help retrieve his bag of precious specimens (and render first aid).

Did I learn anything from this experience? Firstly, there is a great deal more inside a tablet or capsule than appears on the label. These colorants and other excipients may be biologically active.[3] Secondly, even the most straightforward clinical trial may encounter unexpected problems and therefore requires stringent safety monitoring. Thirdly, if my dialysis patients could not excrete the colorant from the capsules, what became of it? Did it contribute to the patients' sallow skin and funny smell, which we had assumed to be due to anaemia and uraemia, but which we never see nowadays. Finally, what about the mosquito bites? I learnt that some individuals suffer disproportionately, being bitten more often or reacting more violently than their equally unwashed companions. I also learnt that tobacco smoke was far more effective than any of the then available insect repellants, but I suppose I am not allowed to say that.

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1 Strauss WG, Maibach HI, Khan AA. Drugs and disease as mosquito repellants in man. *Am J Trop Med Hygiene* 1968;17:461-4.
2 Khan AA, Maibach HI, Strauss WG, Fenley WR. Vitamin B1 is not a systemic mosquito repellant in man. *Trans St Johns Hosp Dermatol Soc* 1969;55:99-102.
3 Acomb C, Hordon LD, Judd AT, Turney JH. Metabolic alkalosis induced by "Panadol soluble." *Lancet* 1985;ii:614.

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.