Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1071–1076, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00137-9

The Role of Nonsteroidal Anti-inflammatory Drugs in Colorectal Cancer Prevention

F.M. Giardiello, G.J.A. Offerhaus and R.N. DuBois

Colorectal cancer is the second leading cause of cancer death in the U.S.A. Recent research suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the prevention of colorectal neoplasia. This review summarises the results of research in animals and humans of these compounds in preventing tumours of the colorectum.

Key words: nonsteroidal anti-inflammatory drugs, NSAIDS, colorectal cancer, prevention, polyps, polyposis
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1071–1076, 1995

INTRODUCTION

COLORECTAL ADENOCARCINOMA is the most common cancer in North Americans and is the second leading cause of cancer death in the U.S.A. [1]. Almost 160 000 persons are diagnosed each year with colorectal cancer, and approximately 60 000 die annually from this tumour. Every North American has an approximately 6% lifetime risk of developing this neoplasm [1].

The preponderance of evidence implicates the colorectal adenomatous polyp as the precursor lesion for colorectal cancer. Adenomatous polyps are characterised histopathologically by cells with variable amounts of mucin and hyperchromatic elongated nuclei. The advancement of the adenoma to carcinoma is thought to result from an accumulation of molecular genetic alterations as described by Fearon and Vogelstein [2].

Despite advancements in medical practice and intensive research of various chemotherapeutic protocols, survival rates in patients with colorectal cancer have changed little in the past 20 years. Consequently, chemoprevention, a strategy to block the development of cancer, has emerged as a potential approach to decrease the incidence rates of colorectal cancer in both high risk groups and the general population.

NSAIDs AND ARACHIDONIC ACID METABOLISM

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a family of pharmacological compounds whose major mechanism of action is inhibition of cyclo-oxygenase, a key enzyme in the conversion of arachidonic acid to eicosanoids [3]. In addition to aspirin and nonacetylated salicylates, twelve additional NSAIDs, from a variety of chemical classes, are prescribed in the U.S.A. [4]. These agents exhibit anti-inflammatory, analgesic and antipyretic activity, and are indicated for the treatment of patients with acute and chronic rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gouty arthritis, bursitis and tendonitis.

Arachidonic acid is derived from the diet or through modification of linoleic acid. Arachidonic acid is metabolised though the cyclo-oxygenase pathway, the lipoxygenase pathway and/or cytochrome P450 enzymes. Primarily, NSAIDs interrupt the cyclo-oxygenase pathway by inhibiting the activity of the enzyme prostaglandin H synthase, also known as cyclo-oxygenase, and consequently, decrease the synthesis of prostaglandins and other eicosanoids generated by the action of cyclo-oxygenase. However, in general, doses of NSAIDs required to suppress inflammation may substantially exceed doses necessary to inhibit prostaglandin synthesis in plasma, suggesting that these drugs work through additional unidentified mechanisms [4].

There are two cyclo-oxygenase enzymes present in humans, cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) (also known as prostaglandin endoperoxide synthase, prostaglandin G/H synthase and prostaglandin H synthase). Recent data reveal that COX-2 has a different sensitivity to NSAID inhibition than COX-1 [5].

In addition to inhibition of prostaglandin synthesis, NSAIDs have a variety of other effects. These effects include inhibition of lipoxygenase enzymes, retardation of neutrophil function such as cell–cell aggregation, interference with activity of phospholipase C production and the unmasking of T-cell suppressor activity [4].

ANIMAL STUDIES

There have been 23 studies [6–28] reported investigating the effect of NSAIDs as chemopreventive agents for colorectal cancer in animals (Table 1). Experiments have been conducted in murine models using azoxymethane, dimethylhydrazine, methylnitrosurea or methylazoxymethanol as the chemical carcinogen inducing colorectal neoplasia. Indomethacin, piroxicam, sulindac and aspirin all have colorectal cancer chemopreventive effects.

Indomethacin has been the most actively investigated agent. In most studies, concomitant administration of the carcinogen and indomethacin resulted in a reduced number of animals with tumours, and a decreased number of tumours per animal

Correspondence to F.M. Giardiello, Blalock 935, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, Maryland 21287, U.S.A.
F.M. Giardiello is at the Departments of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland; R.N. DuBois is at Departments of Medicine and Cell Biology, Vanderbilt University Medical Center, Nashville, Tennessee, U.S.A.; and G.J.A. Offerhaus is at the Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands.

Table 1. *Effect of NSAIDs in animals*

Reference	No.	Year	Agent	Animal	Carcinogen	Results on colorectal tumours
Kudo	[6]	1980	Indomethacin	Rat	MAM	Dec. incidence, multiplicity
Pollard	[7]	1980	Indomethacin	Rat	DMH	Dec. incidence, multiplicity, size
Pollard	[8]	1981	Indomethacin	Rat	DMH	Dec. multiplicity
Narisawa	[9]	1981	Indomethacin	Rat	MNU	Inhibition of development
Narisawa	[10]	1982	Indomethacin	Rat	MNU	Inc. number of tumours after NSAID stopped
Narisawa	[11]	1983	Indomethacin	Rat	MNU	Inhibits promotion and initiation of antitumour activity
Sato	[12]	1983	Indomethacin	Mouse	—	—
Narisawa	[13]	1983	Indomethacin	Rat	AMMN	Dec. multiplicity
Pollard	[14]	1983	Indomethacin	Rat	DMH	Dec. incidence
Narisawa	[15]	1984	Indomethacin	Rat	MNU	PGE2 failed to re-establish anticarcinogenic activity of indomethacin
Metzger	[16]	1984	Meclofenamate/ indomethacin	Rat	DMH	Dec. incidence with separate agents
Pollard	[17]	1983	Piroxicam	Rat	MAM	Dec. incidence and multiplicity
Pollard	[18]	1984	Piroxicam	Rat	MNU	Dec. incidence and multiplicity
Nigro	[19]	1986	Piroxicam	Rat	AOM	Dec. multiplicity, DFMO additive
Reddy	[20]	1987	Piroxicam	Rat	AOM	Dose inhibitory response
Ross	[21]	1988	Piroxicam	Rat	—	Dec. tumour volume in transplantable model
Pollard	[22]	1989	Piroxicam	Rat	MAM	Dec. incidence and multiplicity
Reddy	[23]	1990	Piroxicam/DFMO	Rat	AOM	Both agents additive dec. in cancers, single agents not effective versus adenomas
Rao	[24]	1991	Piroxicam/DFMO	Rat	AOM	Dec. incidence and multiplicity
Moorghen	[25]	1988	Sulindac	Mouse	DMH	Dec. incidence and multiplicity
Moorghen	[26]	1990	Sulindac	Mouse	DMH	Dec. microadenomas
Skinner	[27]	1991	Sulindac	Rat	DMH	Dec. rate of development and growth, reversed with PGE1
Reddy	[28]	1993	Aspirin	Rat	AOM	Dec. incidence and multiplicity

AMMN, acetoxymethyl–methylnitrosamine; AOM, azoxymethane; DMH, dimethylhydrazine; MAM, methylazoxymethanol; MNU, methylnitrosurea; DFMO, D,L-α-difluoromethylornithine; Dec., decreased; Inc., increased.

compared with controls. The antitumoral effect of indomethacin appears to work at several stages of colorectal carcinogenesis. In a *N*-methyl-*N*-nitrourea model, Narisawa and associates [11] allowed the experimental group of rats to drink a water solution of indomethacin at various times during the initiation or promotion stages of carcinogenesis. At autopsy in week 31, the treatment reduced colon cancer development in the group of rats treated from week 1 (initiation stage) and for weeks 2–30 (early and late promotion stages) and for weeks 11–30 (late promotion stage) compared with untreated controls. However, removal of the treatment after inhibition of tumour growth in the promotion stage resulted in cancer development. Metzger and associates [16] noted that cancers in the indomethacin-treated group did not differ in size, number, location or spread from tumours in the control group, suggesting that this agent might influence the carcinogenic process itself, rather than the natural course of established disease. Moreover, the antitumoral effect of indomethacin appears to persist even when this agent is discontinued and prostaglandin PGE2 is added [15].

The chemopreventive properties of piroxicam, a drug from a new class of NSAIDs, the oxicams, sulindac and aspirin have similarly been evaluated. These agents also decrease the number of animals with tumours and multiplicity of tumours in animals in chemical carcinogen models of colorectal cancer. In two studies [19, 23], the effect of combined therapy with D, L-alpha-difluoromethylornithine, an ornithine decarboxylase inhibitor, and piroxicam had additive inhibitory effects on tumour formation. Reddy and associates [20] showed a dose–response relationship with increasing piroxicam treatment causing decreasing incidence of neoplasms. This effect was also noted when piroxicam was not given until 13 weeks after carcinogen administration, suggesting that piroxicam can induce the regression of already initiated neoplastic foci. Interestingly, Skinner and colleages [27], in contrast to Narisawa, reported that the administration of prostaglandin PGE1 reversed the inhibitory effects of sulindac on the rate of colon cancer development and growth in the rat.

Of particular interest is the study of Reddy and associates [28]. This report supports the epidemiological data which suggest that sustained use of aspirin may reduce human mortality from colorectal cancer. In F344 rats given azoxymethane to induce colorectal cancer, daily aspirin decreased the incidence and multiplicity of invasive colorectal carcinomas, as well as the size of adenocarcinomas.

In summary, a variety of reports generated in chemical carcinogen models, support the concept that NSAIDs are effective in chemoprotection against rodent colorectal cancer. These agents appear to work at the initiation and promotion stages of carcinogenesis with different strengths of effect. Preliminary data reveal that NSAIDs may have additive chemopreventive effects with other chemotherapeutic agents.

HUMAN STUDIES

Two lines of human evidence support NSAIDs as chemopreventives against colorectal neoplasia; administration of

Table 2. Effect of NSAIDs in humans in uncontrolled and controlled clinical trials

Reference	No.	Year	Agent	Study design	Results
Waddell	[29]	1983	Sulindac	Case series	Regression of adenomas in 4 pts with FAP
Gonzaga	[30]	1985	Sulindac	Case series	Regression of adenomas in 2 pts with FAP
Labayle	[31]	1986	Sulindac	Case series	Regression of adenomas in 2 pts with FAP
Waddell	[32]	1989	Sulindac	Case series	Regression of adenomas in 7 pts with FAP
Charneau	[33]	1990	Sulindac	Case series	Regression of adenomas in 7 pts with FAP
Rigau	[34]	1990	Sulindac	Case series	Regression of adenomas in 4 FAP pts and hyperplastic polyps in 2 pts
Hixson	[35]	1993	Sulindac/ Piroxicam	Case series	Regression of adenomas in 3/5 FAP and 1/2 solitary adenoma patients
Winde	[36]	1993	Sulindac	Case series	Regression of adenomas with rectal administration
Niv	[37]	1994	Sulindac	Case report	Rectal cancer in FAP pt while on sulindac
Muller	[38]	1994	Sulindac	Case series	Regression of adenomas in 10 FAP pts, 1 juvenile polyp pt, 1 HNPCC pt
Thorson	[39]	1994	Sulindac	Case report	Rectal cancer in FAP pt while on sulindac
Spagnesi	[40]	1994	Sulindac	Case series	Regression of adenomas in patients with FAP; no change in labelling index
Labayle	[41]	1991	Sulindac	Randomised-crossover	Regression of adenomas in all 9 FAP pts
Giardiello	[42]	1993	Sulindac	Randomised	Regression of adenoma size and number (22 pts)
Nugent	[43]	1993	Sulindac	Randomised	Regression of rectal not duodenal adenomas (24 pts)

FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer.

NSAIDs in uncontrolled and controlled trials (Table 2), and epidemiological, mainly case–control, studies (Table 3).

UNCONTROLLED AND CONTROLLED TRIALS

Uncontrolled trials

In 1983, Waddell and Loughry first reported that sulindac caused regression of rectal adenomatous polyps in 4 patients with familial adenomatous polyposis (FAP) [29]. FAP is an autosomal dominantly inherited form of colorectal cancer in which teenage patients develop hundreds to thousands of adenomas throughout the colorectum. Inevitably, colorectal cancer occurs, usually by the fifth decade of life, if colectomy is not performed. Waddell used NSAIDs in an FAP patient attempting to regress a desmoid tumour; an extraintestinal manifestation which occurs in these individuals. Serendipitously, he noted striking polyp disappearance in one patient, and treated an additional 3, reporting a 70–100% polyp regression in these persons. All patients received clinically approved doses of sulindac (75–150 mg orally twice a day).

Following this initial account, similar observations of adenoma resolution with oral sulindac in over 35 FAP patients have been reported by several investigators [30–36, 38, 40]. Polyp regression occurred in patients having between several dozen to too numerous to count polyps, and in those with intact colons

Table 3. Effect of NSAIDs in humans in epidemiological studies

Reference	No.	Year	Agent	Study design	Results
Kune	[44]	1988	ASA-containing drugs	Case–control (715 cases)	Odds ratio for colorectal cancer 0.53 (95% CL, 0.4–0.7)
Rosenberg	[45]	1991	ASA	Case–control (1326 cases)	Odds ratio for colorectal cancer 0.5 (95% CL, 0.4–0.8)
Suh	[46]	1993	ASA	Case–control (830 cases)	Odds ratio for colorectal cancer 0.33, 0.44 (dose-dependent) (95% CL, 0.15–0.72; 0.18–1.18, respectively)
Logan	[47]	1993	ASA	Case–control (147 cases)	Odds ratio for colorectal adenomas 0.49 (95% CL, 0.3–0.8)
Muscat	[48]	1994	NSAID	Case–control (551 cases)	Odds ratio for colorectal cancer 0.64, 0.32 (men/women) (95% CL, 0.42–0.97; 0.18–0.57, respectively)
Paganini-Hill	[49]	1989	ASA	Cohort study (13 987 elders)	Relative risk for colorectal cancer 1.5 (95% CL, 1.1–2.2)
Thun	[50, 51]	1991	ASA	Cohort study (662 424 adults)	Relative risk for fatal colorectal cancer 0.60, 0.58 (men/women) (95% CL, 0.40–0.89; 0.37–0.90)
Giovannucci	[52]	1994	ASA	Cohort study (47 900 men)	Relative risk for colorectal cancer 0.68 (95% CL, 0.52–0.92)

ASA, aspirin; CL, confidence limits.

and in persons with ileorectal anastomosis. Winde and associates [36] utilised rectal administration of sulindac to achieve polyp disappearance. Interestingly, Spagnesi and colleagues [40] observed polyp regression, but labelling indexes of colorectal epithelial proliferation did not change. Of concern are several recent case reports of FAP patients maintained on sulindac who subsequently developed rectal cancer [37, 39].

The effect of NSAIDs on sporadic colorectal adenoma regression (adenomas in patients without a hereditary form of colorectal cancer) has been evaluated in one small uncontrolled pilot study lasting 6 months. Hixson and associates [35] used piroxicam in 2 individuals with solitary adenomas up to 10 mm in size; one polyp regressed partially.

Controlled trials

In 1991, Labayle and associates published a randomised, placebo-controlled, double-blinded, crossover study in 9 FAP patients with ileorectal anastomosis [41]. Patients received sulindac 300 mg/day, or placebo during two 4 month periods separated by a 1 month washout phase. With sulindac, a complete or almost complete regression of polyps was noted in all patients. With placebo, polyp numbers increased in 5 patients, remained unchanged in 2 patients and decreased in 2 patients. Differences in polyp numbers between sulindac and placebo groups were statistically significant ($P < 0.01$). In addition, the cellular proliferative index was evaluated by immunohistochemistry using the Ki67 monoclonal antibody in flat and polypoid mucosa of 6 patients. No difference in proliferative index was noted with sulindac.

In 1993, we conducted a randomised, double-blinded, placebo-controlled study of 22 patients with FAP including 18 patients without prior colectomy [42]. Patients received oral sulindac 300 mg a day or placebo tablets for 9 months. A statistically significant decrease in mean polyp number and size occurred in patients treated with sulindac compared with placebo at 3, 6 and 9 months. In the sulindac group at termination of therapy (9 months), the polyp number had decreased to 44% of baseline levels, and polyp size to 35% ($P = 0.014$ and $P < 0.001$, respectively, compared with placebo group). No patient had complete resolution of polyps. Both the polyp number and size increased in sulindac-treated patients, but remained statistically significantly lower than baseline values after cessation of the drug. No drug side effects were noted.

Lastly, Nugent and associates [43] reported a randomised controlled trial of sulindac in 24 FAP patients with subtotal colectomy and ileorectal anastomosis. The effect of sulindac was evaluated by videotape assessment of adenoma number in the rectal remnant and the duodenum, and by analysis of mucosal cell proliferation by bromodeoxyuridine labelling index in these sites. Sulindac produced a statistically significant reduction in rectal polyp count and bromodeoxyuridine labelling index in the rectum and duodenum. The reduction in duodenal polyp count, however, was not statistically significant.

EPIDEMIOLOGICAL STUDIES

Retrospective (case–control) [44–48] and prospective (cohort) studies [49–51] of NSAIDs' chemopreventive effect against colorectal cancer have been published (Table 3).

Currently, five case–controlled studies have been reported. Results have been consistent [44–46, 48]; an approximately 50% decreased risk for colorectal cancer is noted in groups taking NSAIDs, primarily aspirin. Logan and associates [47] found similar risk reduction for colorectal adenomas in patients receiving aspirin. Several concerns have been raised about these studies including the appropriateness of specific control groups.

Three prospective studies have been published [49, 50, 52]. Thun and colleages [50] conducted a prospective colorectal cancer mortality study of over 660 000 American Cancer Society volunteers and family members who provided information on aspirin use. Death rates from colorectal cancer decreased with more frequent aspirin use. The relative risk for fatal colorectal cancer among persons using aspirin 16 times or more a month was 0.60 in men and 0.58 in women. Several criticisms of this study have been raised including the methodology employed, which excluded non-Caucasians. In addition, detection bias, in which aspirin use induces gastrointestinal bleeding, could have been operative. Such a bias would reduce the magnitude of any association between NSAID use and colorectal cancer. In a subsequent publication, Thun and associates evaluated aspirin use and the risk of any fatal cancer [51]. Death rates decreased with more frequent aspirin use for cancers of the oesophagus, stomach, colon and rectum, but not generally for other neoplasms. However, only in colon cancer were 95% confidence limits of the relative risk less than 1.

Giovannucci and associates conducted a prospective cohort study of 47 900 male health professions [52]. Regular aspirin users ($\geq$2 times per week) had a lower risk for total colorectal cancer (relative risk = 0.68). These results were controlled for numerous variables including age, history of polyp, previous endoscopy, parental history of colorectal cancer, smoking, body mass, intakes of red meat, vitamin E and alcohol. Also, the total number of adenomas discovered among aspirin users was lower with or without overt or occult faecal blood. Thus, earlier diagnosis and treatment of adenomas did not account for the inverse relationship between aspirin and cancer.

Lastly, Paganini-Hill and colleagues evaluated residents of a California retirement community [49]. In contrast, this investigation found an increased risk of colorectal cancer associated with daily aspirin with a relative risk of 1.5. Critics question whether the aspirin-exposed and non-exposed groups were mixed leading to spurious results. Also, in this elderly cohort, aspirin usage may have little effect on already established colorectal neoplasms.

MECHANISM OF CHEMOPREVENTION

The reason that NSAIDs are chemopreventive against colorectal neoplasia is unknown. NSAIDs inhibit the enzyme prostaglandin H synthetase or cyclo-oxygenase which catalyses the first step in the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Cyclo-oxygenase's role in carcinogenesis may be through activation of procarcinogens to electrophiles that bind DNA [53]. Several studies reveal that specific heterocyclic aromatic amines found in food are activated via cyclo-oxygenase to reaction products that are mutagenic. Indomethacin and aspirin treatment can block this activation and confer protection against colon and bladder cancer. Also, NSAIDs appear to inhibit other enzymes important in cancer initiation and promotion, including phosphodiesterase and cyclic adenosine monophosphate kinase [53].

Prostaglandins, the products of cyclo-oxygenase activity, affect cell proliferation and tumour growth through activation of second messengers in signal transduction pathways. In cell culture, prostaglandin E2 can stimulate tumour growth whereas indomethacin can suppress growth by retardation of the G1 to S phase cell cycle progression. Moreover, prostaglandin concen-

trations are increased in several cancers including both colorectal adenomas and adenocarcinomas [54].

NSAIDs influence the immune function. These compounds enhance a variety of immunological responses, possibly restoring antitumoral immunogenicity, probably through reduction of tissue prostaglandins. Prostaglandins can modulate the immune system via a variety of mechanisms [55].

CONCLUSION

Overall, the results of animal and human studies provide reasonable evidence that NSAIDs could be useful agents in chemoprevention of colorectal cancer. Intervention trials with NSAIDs in an attempt to reduce the risk of colorectal cancer in human populations at above average risk for cancer are feasible. Only with clinical trials can the risk benefit ratio of these chemopreventive agents be understood.

1. American Cancer Society. Cancer facts and figures–1990. Atlanta (GA): American Cancer Society, 1990.
2. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990, **61**, 759.
3. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. *Nature* (New Biol) 1971, **231**, 232–235.
4. Brooks PM, Wood AJJ. Nonsteroidal antiinflammatory drugs—differences and similarities. *N Engl J Med* 1991, **324**, 1716.
5. Bishop PH, Awad JA, DuBois R. Inhibition of immediate early gene expression by sulindac sulfide in rat epithelial cells. *Gastroenterology* 1994, **106**, A372.
6. Kudo T, Narisawa T, Abo S. Antitumor activity of indomethacin on methylazoxymethanol-induced large bowel tumors in rats. *Gann* 1980, **71**, 260–264.
7. Pollard M, Luckert PH. Indomethacin treatment of rats with dimethylhydrazine-induced intestinal tumors. *Cancer Treat Rep* 1980, **64**, 1323–1327.
8. Pollard M, Luckert PH. Effect of indomethacin on intestinal tumors induced in rats by the acetate derivative of dimethylnitrosamine. *Science* 1981, **214**, 558–559.
9. Narisawa T, Sato M, Tani M, Kudo T, Takahashi T, Goto A. Inhibition of development of methylnitrosourea-induced rat colon tumors by indomethacin treatment. *Cancer Res* 1981, **41**, 1954–1957.
10. Narisawa T, Sato M, Sano M, Takahashi T. Inhibition of development of methylnitrosourea-induced rat colonic tumors by peroral administration of indomethacin. *Gann* 1982, **73**, 377–381.
11. Narisawa T, Sato M, Sano M, *et al.* Inhibition of initiation and promotion by *N*-methylnitrosurea-induced colon carcinogenesis in rats by non-steroidal anti-inflammatory agent indomethacin. *Carcinogenesis* 1983, **4**, 1225–1227.
12. Sato M, Narisawa T, Sano M, Takahashi T, Goto A. Growth inhibition of transplantable murine colon adenocarcinoma 38 by indomethacin. *J Cancer Res Clin Oncol* 1983, **106**, 21–26.
13. Narisawa T, Hermanek P, Hab M, Schmahl D. Reduction of acetoxymethyl–methylnitrosamine induced large bowel cancer by indomethacin. *Tohoku J Exp Med* 1984, **144**, 237–243.
14. Pollard M, Luckert PH. Prolonged antitumor effect of indomethacin in autochthonous intestinal tumors in rats. *J Natl Cancer Inst* 1983, **70**, 1103–1105.
15. Narisawa T, Hermanek P, Habs M, Schmahl D. Reduction of carcinogenicity of *N*-nitrosomethylurea by indomethacin and failure of resuming effect of prostaglandin E2 (PGE2) against indomethacin. *J Cancer Res Clin Oncol* 1984, **108**, 239–242.
16. Metzger U, Meier J, Uhlschmid G, *et al.* Influence of various prostaglandin synthesis inhibitors on DMH-induced rat colon cancer. *Dis Colon Rectum* 1984, **27**, 366–369.
17. Pollard M, Luckert PH, Schmidt MA. The suppressive effect of piroxicam on autochthonous intestinal tumors in the rat. *Cancer Lett* 1983, **21**, 57–61.
18. Pollard M, Luckert PH. Effect of piroxicam on primary intestinal tumors induced in rats by *N*-methylnitrosurea. *Cancer Lett* 1984, **25**, 117–121.
19. Nigro ND, Bull AW, Boyd ME. Inhibition of intestinal carcinogenesis in rats: effect of difluoromethylornithine with piroxicam or fish oil. *J Natl Cancer Inst* 1986, **77**, 1309–1313.
20. Reddy BS, Maruyama H, Kelloff G. Dose related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal antiinflammatory drug, during different stages of rat colon tumor development. *Cancer Res* 1987, **47**, 5340–5346.
21. Ross DS, Bitzer D, Roy T, Murphy JE. Piroxicam inhibits the growth of an adenocarcinoma isograft in Fischer rats. *J Surg Res* 1988, **45**, 249–253.
22. Pollard M, Luckert PH. Prevention and treatment of primary intestinal tumors in rats by piroxicam. *Cancer Res* 1989, **49**, 6471–6473.
23. Reddy BS, Nayini J, Tokumo K, Rigotty J, Zang E, Kelloff G. Chemoprevention of colon carcinogenesis by concurrent administration of piroxicam, a nonsteroidal antiinflammatory drug with DL-α-difluoromethylornithine, an ornithine decarboxylase inhibitor, in diet. *Cancer Res* 1990, **50**, 2562–2568.
24. Rao CV, Tokumo K, Rigotty J, Zang E, Kelloff G, Reddy BS. Chemoprevention of colon carcinogenesis by dietary administration of piroxicam, α-diflouromethylornithine, 16α-fluor-5-androsten-17-one, and ellagic acid individually and in combination. *Cancer Res* 1991, **51**, 4528–4534.
25. Moorghen M, Ince P, Finney KJ, Sunter JP, Appleton DR, Watson AJ. A protective effect of sulindac against chemically induced primary colonic tumors in mice. *J Path* 1988, **156**, 341–347.
26. Moorghen M, Ince P, Finney KJ, Sunter JP, Watson AJ, Appleton DR. The effect of sulindac on colonic tumour formation in dimethylhydrazine-treated mice. *Acta Histochem* Suppl. 1990, **39**, 195–199.
27. Skinner SA, Penny AG, O'Brien PE. Sulindac inhibits the rate of growth and development of colon tumors in the rat. *Gastroenterology* 1990, **100**, A403.
28. Reddy BS, Rao CV, Rivenson A, Kelloff G. Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F344 rats. *Carcinogenesis* 1993, **14**, 1493–1497.
29. Waddell WR, Loughry RW. Sulindac for polyposis of the colon. *J Surg Oncol* 1983, **24**, 83–87.
30. Gonzaga RAF, Lima FR, Carneiro S, Maciel J, Junior MA. Sulindac treatment for familial polyposis. *Lancet* 1985, **1**, 751.
31. Labayle D, Fischer D, Hagege JP. Efficacité du sulindac dans le traitement de la polypose rectocolique. *Gastroenterol Clin Biol* 1986, **10**, 436.
32. Waddell WR, Ganser GF, Cerise EJ, Loughry RW. Sulindac for polyposis of the colon. *Am J Surg* 1989, **157**, 175–179.
33. Charneau J, D'Aubigny N, Burtin P, Person B, Boyer J. Micropolypes rectaux apres colectomie totale pour polypose familiale: efficacité du sulindac. *Gastroenterol Clin Biol* 1990, **14**, 153–157.
34. Rigau J, Pique JM, Rubio E, Planas R, Tarrech JM, Bordas J. Effects of long-term sulindac therapy on colonic polyposis. *A Intern Med* 1991, **115**, 952–954.
35. Hixson LJ, Earnest DL, Fennerty MB, Sampliner RE. NSAID effect on sporadic colon polyps. *Am J Gastroenterol* 1993, **88**, 1652–1656.
36. Winde G, Gumbinger HG, Osswald H, Kemper F, Bunte H. The NSAID sulindac reverses rectal adenomas in colectomized patients with familial adenomatous polyposis: clinical results of a dose-finding study on rectal sulindac administration. *Int J Colorect Dis* 1993, **8**, 13–17.
37. Niv Y, Fraser GM. Adenocarcinoma in the rectal segment in familial polyposis coli is not prevented by sulindac therapy. *Gastroenterology* 1994, **107**, 854–857.
38. Muller A, Hurlimann R, Meyenberger C, Staub P, Kobler E, Ammann R. Sulindac in familial adenomatous polyposis coli preliminary findings of a prospective study. *Schweiz Med Wochenschr* 1994, **124**, 651–654.
39. Thorson AG, Lynch HT, Smyrk TC. Rectal cancer in FAP patient after sulindac. *Lancet* 1994, **343**, 180.
40. Spagnesi MT, Tonelli F, Dolara P, *et al.* Rectal proliferation and polyp occurrence in patients with familial adenomatous polyposis after sulindac treatment. *Gastroenterology* 1994, **106**, 362–366.
41. Labayle D, Fischer D, Vielh P, *et al.* Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991, **101**, 635–639.
42. Giardiello FM, Hamilton SR, Krush AJ, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993, **398**, 1313–1316.
43. Nugent KP, Farmer KCR, Spigelman AD, Williams DB, Phillips

RKS. Randomized controlled clinical trial of sulindac on intestinal polyposis in FAP. *Br J Surg* 1993, **80**, 1618–1619.
44. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations and medications: case–control results from the Melbourne colorectal cancer study. *Cancer Res* 1988, **48**, 4399–4404.
45. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst* 1991, **83**, 355–358.
46. Suh O, Mettlin C, Petrelli NJ. Aspirin use, cancer and polyps of the large bowel. *Cancer* 1993, **72**, 1171–1177.
47. Logan RFA, Little J, Hawtin PG, Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case–control study of subjects participating in the Nottingham faecal occult blood screening programme. *Br Med J* 1993, **307**, 285–289.
48. Muscat J, Stellman S, Wynder E. Nonsteroidal antiinflammatory drugs and colorectal cancer. *Cancer* 1994, **74**, 1847–1854.
49. Paganini-Hill A, Chao A, Ross R, Henderson B. Aspirin use and chronic diseases: a cohort study of the elderly. *Br Med J* 1989, **299**, 1247–1250.
50. Thun M, Namboodiri M, Heath C. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991, **325**, 1593–1596.
51. Thun M, Namboodiri M, Calle E, Flanders W, Heath C. Aspirin use and risk of fatal cancer. *Cancer Res* 1993, **53**, 1322–1327.
52. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and risk for colorectal cancer and adenoma in male health professionals. *A Intern Med* 1994, **121**, 241–246.
53. Earnest DL, Hixson LJ, Alberts DS. Piroxicam and other cyclooxygenase inhibitors: potential for cancer chemoprevention. *J Cell Biochem*, Suppl. 1992, **161**, 156–166.
54. Earnest DL, Hixson LJ, Sim WW, Ahnen JD, Alberts DS. Piroxicam as an agent to inhibit colonic neoplasia. *Gastroenterology* 1989, **96**, A134.
55. Kelloff GJ, Malone WF, Boone CW, *et al.* Progress in applied chemoprevention research. *Semin Oncol* 1990, **17**, 438–455.