Meeting Report

An International Evaluation of the Cancer-Preventive Potential of Nonsteroidal Anti-inflammatory Drugs[1]

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Abstract

The IARC convened a Working Group of experts in Lyon, France, on April 2–8, 1997 to evaluate the cancer-preventive activity of four nonsteroidal anti-inflammatory drugs (aspirin, sulindac, piroxicam, and indomethacin). Epidemiological observational studies of aspirin that differed in design, location, population, and motivating hypothesis have consistently shown that regular use lowers the risk for colorectal cancer by up to 50%; however, the one randomized trial did not show protection by aspirin. Definite evidence of chemopreventative activity normally requires data from appropriately designed randomized trials. The strength of the scientific evidence that aspirin prevents colorectal cancer in humans was thus considered to be *limited*. In animal models, there was *sufficient evidence* that aspirin prevented against cancer. Aspirin and aspirin-like drugs may have important adverse side effects, the most frequent of which are gastrointestinal disturbances ranging in severity from dyspepsia to peptic ulcer. Given the remaining uncertainties in the preventive effect and the risk of adverse side effects, detailed consideration of the total benefits and of toxicity will be required before widespread use of aspirin for the prevention of colorectal cancer can be recommended.

Sulindac shows promise in reducing the number and size of adenomatous polyps in patients with familial adenomatous polyposis. Further research is required, however, to determine whether and to what extent the risk for colorectal cancer in such patients is reduced. In people without familial adenomatous polyposis, there is *inadequate evidence* that sulindac has cancer-preventive activity.

Fewer data were available on piroxicam and indomethacin than on aspirin and sulindac. Although these drugs consistently prevent colorectal cancers in experimental animal models, the evidence that they prevent colorectal cancer in humans was considered to be *inadequate*.

The results of the meeting, including recommendations for future research, will be published as Volume 1 of the *IARC Handbooks of Cancer Prevention*.

Introduction

The history of aspirin can be traced to ancient Egypt, where an extract of willow bark was used to treat inflammation. Willow bark contains the glucoside of salicyl alcohol, which can be converted to the actual anti-inflammatory agent salicylic acid through stepwise hydrolysis and oxidation. The acetylation of sodium salicylate by the German company Bayer in 1897 led to mass production of acetylsalicylic acid in 1899. This compound was marketed for the treatment of fever and rheumatism under the trade name aspirin. Today, aspirin is a protected trade name of the Bayer Company in more than 70 countries.

The development of aspirin was a significant landmark in the history of medicine because it stimulated the development of a family of medicines that are collectively known as the NSAIDs.[3] NSAIDs, such as sulindac, indomethacin, and piroxicam, have established value in the alleviation of pain, inflammation, and fever, and they are commonly prescribed for the treatment of rheumatoid disorders, such as arthritis. It is believed that NSAIDs function pharmacologically primarily by reducing the synthesis of prostaglandins. At sites of inflammation, prostaglandins are produced in excessive amounts and exert pro-inflammatory effects. It is believed that NSAIDs reduce the production of prostaglandins by inhibiting the enzyme prostaglandin endoperoxide synthase, which exists in two isoforms, designated isoforms 1 and 2. This enzyme is commonly referred to as COX (COX-1 and COX-2) in the current literature.

Although NSAIDs are highly effective for the relief of inflammatory disease, their use is limited by adverse effects, particularly on the gastrointestinal tract and kidneys. All NSAIDs, including aspirin, cause a dose-dependent increase in the frequency of upper gastrointestinal tract toxicity, which can range in severity from dyspepsia to haemorrhage, ulceration, and perforation. The doses of NSAIDs used for the treatment of arthritis increase the risk for ulcer complications by 3–5-fold. These complications can lead to hospitalization and, rarely, death in elderly individuals who have additional risk factors, such as a prior history of ulcer disease.

Among the family of NSAIDs, aspirin is the most widely used, since it is easily available and cheap, and it is valuable in a wide range of conditions. Low doses of aspirin (less than 100 mg daily) are increasingly used for the secondary prevention of cardiovascular disease. Mounting evidence has further suggested that NSAIDs might have another public health indication: colorectal cancer might be prevented by regular aspirin intake. This hypothesis was chosen as the subject for the inaugural meeting on chemoprevention evaluation held by the IARC in Lyon, France, on April 2–8, 1997. A working group of 25 scientists from 11 countries met to evaluate the evidence on four NSAIDs, namely aspirin, sulindac, piroxicam, and

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[3] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; FAP, familial adenomatous polyposis; COX, cyclooxygenase.

Table 1 Classification of strength of evidence for cancer-preventive activity

Cancer-preventive activity in humans	Cancer-preventive activity in experimental animals
Sufficient evidence of cancer-preventive activity. The Working Group considers that a causal relationship has been established between the use of the agent and prevention of human cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.	**Sufficient evidence of cancer-preventive activity.** The Working Group considers that a causal relationship has been established between the agent and a decreased incidence and/or multiplicity of neoplasms.
Limited evidence of cancer-preventive activity. The data suggest a reduced risk of human cancer with use of the agent but are limited for making a definitive evaluation either because chance, bias, or confounding could not be ruled out with reasonable confidence or because the data are restricted to intermediary biomarkers of uncertain validity in the putative pathway to cancer.	**Limited evidence of cancer-preventive activity.** The data suggest a preventive effect but are limited for making a definitive evaluation because, for example, the evidence for prevention is restricted to a single experiment, the agent decreases the incidence and/or multiplicity only of benign neoplasms or lesions of uncertain neoplastic potential, or there is conflicting evidence.
Inadequate evidence of cancer-preventive activity. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the cancer-preventive effect of the agent, or no data on prevention of cancer in humans are available.	**Inadequate evidence of cancer-preventive activity.** The studies cannot be interpreted as showing either the presence or absence of a preventive effect because of major qualitative and quantitative limitations (if there are unresolved questions regarding the adequacy of design, conduct, or interpretation of the study), or no data on prevention in experimental animals are available.
Evidence suggesting lack of cancer-preventive activity. Several adequate studies of use or exposure are mutually consistent in not showing a preventive effect. The evaluations are inevitably limited to the cancer sites, conditions, and levels of exposure and length of observation covered by the available studies.	**Evidence suggesting lack of cancer-preventive activity.** Adequate evidence involving conclusive studies in several models shows that within the limits of the tests used, the agent is not cancer preventive.

indomethacin. The list of participants is given in the Appendix. The IARC chemoprevention evaluation procedure has been described in detail previously (1). Definitions of the strength of evidence for cancer-preventive activity in humans and experimental animals are given in Table 1. The evaluations are inevitably limited to the cancer sites, conditions, levels of exposure, and length of observation covered by the available studies. For the overall evaluation, the body of evidence is considered as a whole, and summary statements are made that encompass the effects of the agents in humans on cancer-preventive activity and carcinogenicity and other beneficial and adverse effects, as appropriate. The overall evaluation is presented in the form of a narrative.

A summary of the key human and experimental data available to the Working Group at the time of the meeting is presented below.

Cancer Chemoprevention by NSAIDs: An Overview

The origins of this hypothesis can be traced to 1975, when Bennett and Del Tacca (2) observed that certain human cancers, including colorectal cancers, contain more prostaglandin E2 than surrounding normal mucosa. They hypothesized that tumors that overproduce prostaglandin E2 might promote their own growth and/or spread. Because NSAIDs reduce the synthesis of prostaglandins, this theory gave rise to a series of experimental studies in rodents to test whether NSAIDs would inhibit or prevent the growth of chemical-induced colorectal cancer. Most of the NSAIDs tested (aspirin, sulindac, piroxicam, and indomethacin) effectively inhibited colorectal tumours in rats and mice (3, 4). Whereas these early studies in rodents assessed the broad hypothesis that inhibition of prostaglandins might inhibit the occurrence or progression of colorectal carcinogenesis, subsequent studies have revealed the probable mechanistic complexity of these processes.

The study of the impact of NSAIDs on colon cancer in humans initially evolved independently of the experimental data. In 1988, Kune *et al.* (5) reported an observational study in which a negative association was found between the incidence of colon cancer and the use of aspirin. People who used aspirin had a 40% lower incidence of colorectal cancer than those who reported no aspirin use. A reduction of lesser magnitude was noted with the use of other NSAIDs. No reduction in risk was observed with the use of steroids, oral contraceptives, tranquilizers, or sedatives. The reductions in risk associated with aspirin use were of similar magnitude in men and women. In a later epidemiological study on NSAIDs and the risk for colorectal cancer, Rosenberg *et al.* (6) noted that existing experimental data on the pharmacology of aspirin supported a specific mechanism.

The potential cancer-preventive activity of aspirin has been addressed in several other epidemiological studies (7–9), including a large cohort study by epidemiologists at the American Cancer Society (10). This study reported a comparable reduction in mortality from colon cancer to that reported by Kune *et al.* (5) but also related its magnitude to the frequency of aspirin use. In several subsequent studies that have examined the association between intake of aspirin and a diminished risk for colon cancer (11, 12), the findings were generally consistent, with the exception of one study in an elderly population (13). In an illustrative study of the dose-duration relationship, Giovannucci *et al.* (11) followed the incidence of colorectal cancer among 89,446 female United States nurses between 1984 and 1992. Data on aspirin use were obtained by questionnaire in 1980, 1982, 1984, and 1986, and deaths and cases of colorectal cancer were ascertained over 8 years. The duration of aspirin use was correlated with a reduced risk for colorectal cancer: nurses who reported taking two or more aspirin tablets weekly for 20 years or more had a significantly lower risk than nonusers. Although the risk appeared to be decreasing after 5 years of regular use, the decrement did not become statistically significant until after a decade of sustained use.

Overall, 21 of 23 epidemiological studies have shown that regular use of aspirin lowers the risk for colorectal cancer by up to 50%. These observational studies cover more than 18,000 cases of colorectal cancer and differed in design, location, population, and motivating hypothesis. Despite this consistency, however, there are no clear data on the dose, duration, or frequency of use required for cancer-preventive activity.

Clinical use of the NSAID sulindac for the treatment of FAP was first reported by Waddell and Loughry (14) in 1983. Administration of sulindac to affected individuals induced polyp regression that was reversed by cessation of therapy. This

finding was confirmed in several subsequent studies (15–18). The efficacy of sulindac may be related to its unique pharmacokinetic properties, which lead to high concentrations of its active metabolite, sulindac sulfide, in the colonic lumen. In other reports, however, rectal cancers have occurred in FAP patients taking sulindac, in spite of a regression of polyps (19, 20).

Experimental Studies

Experimental models have provided a system for examining cancer-preventive effects and insights into the early stages of tumour growth. Several models of FAP exist in which mouse strains carry various mutations in the *Apc* gene. The first of these was the Min/+ mouse (21). The Min/+ mouse carries a fully penetrant dominant mutation at codon 850 of the murine *Apc* gene and develops adenomas throughout its intestinal tract, mostly in the small intestine, without carcinogen treatment. To that extent, the phenotypic expression of an *Apc* mutation in the Min/+ mouse is different from that in humans with FAP, who develop adenomas exclusively in the colon and duodenum. Nevertheless, this model has been used to demonstrate the cancer-preventive potential of sulindac and piroxicam (22–24). Another study indicates that mice carrying an *Apc* mutation cross-bred with animals with a disrupted *COX-2* enzyme system establishes that induction of *COX-2* is an early, rate-limiting step for adenoma formation (25).

The hypothesis that the *COX-2* gene is important in colorectal carcinogenesis is supported by studies in animals and humans. Analysis of colon cancer tissue from carcinogen-treated rats, colon polyps and adenocarcinomas from humans and intestinal polyps from Min/+ mice consistently shows that the expression of *COX-2* is elevated (26–28). Unlike *COX-1*, which is expressed uniformly at low levels in normal intestinal tissue, *COX-2* mRNA and protein increase selectively in neoplasia (29). Neither the mechanism by which *COX-2* is induced nor how NSAIDs might inhibit this process is currently known. These findings suggest, however, that *COX-2* expression is selectively increased during carcinogenesis and that its inhibition may account for the ability of NSAIDs to inhibit cancer development or induce polyp regression. Several recent reports support this hypothesis. Reddy *et al.* (30) found that the selective *COX-2* inhibitor SC-58635 can inhibit the development of aberrant crypt foci in rats treated with the carcinogen azoxymethane. The total number of foci and the number of crypts per focus were reduced, and the extent of inhibition by SC-58635 was comparable to that of sulindac, although higher doses of the former were required. This model may be particularly relevant for the chemoprevention of sporadic colorectal cancer because aberrant crypt foci are recognized as early preneoplastic lesions in the colonic mucosa of patients with colon cancer (31). Similar results have been reported by Takahashi *et al.* (32) with the structurally distinct *COX-2* inhibitor nimesulide. The cancer-preventive potential of SC-58635 and nimesulide may be related to restoration of normal apoptotic mechanisms because overexpression of *COX-2* in rat intestinal epithelial cells induces a G_1 delay and renders them resistant to the induction of apoptosis by sodium butyrate (33, 34).

Although inhibition of *COX* genes appears to be an important component of the action of NSAIDs, COX-independent mechanisms may also be significant. NSAIDs may induce apoptosis in colon cancer cells, including some lines that do not express *COX* or synthesize prostaglandins (35, 36).

Evaluations of Cancer-preventive Activity

The Working Group reviewed published articles on the selected NSAIDs and made critical summaries on cancer-preventive activity, other beneficial effects, and adverse effects. The cancer-preventive activity of the four NSAID was then evaluated according to the guidelines given in the "Introduction." The Working Group noted particularly that because chemopreventive agents may be administered to healthy (asymptomatic) populations to prevent a relatively rare event, their benefits should substantially outweigh any potential harm. This consideration was addressed in the overall evaluation of each NSAID.

Aspirin. Epidemiological studies in humans provide *limited evidence* for the cancer-preventive activity of aspirin, based on observational studies (both cohort and case-control), that show a moderately reduced risk for colorectal cancer in people using aspirin regularly and an indication of greater reduction in risk with prolonged use. In experimental animal models, there is *sufficient evidence* for the prevention of colon cancer by aspirin. Although aspirin is toxic, especially at high doses, other beneficial effects for humans have been demonstrated at relatively low doses, especially in the secondary prevention of cardiovascular disease. These findings indicate the need for more detailed research on cancer prevention, including randomized controlled trials with different regimens of aspirin, in an endeavor to determine whether aspirin can be of greater benefit in reducing cancer in human populations than its possible offsetting toxicity. Detailed consideration of the total benefits of the prevention of cancer and other diseases in contrast to toxicity will be required before use of aspirin for the prevention of cancer in asymptomatic humans can be recommended.

Sulindac. Randomized controlled trials in humans provide *limited evidence* that sulindac prevents colorectal cancer by suppressing adenomatous polyps in patients with FAP. There is *inadequate evidence* that sulindac has cancer-preventive activity in people without FAP. Experimental animal models provide *sufficient evidence* that sulindac prevents cancers of the colon, mammary gland, lung, and urinary bladder. These findings indicate the need for further evaluation of the cancer-preventive activity of sulindac against colorectal cancer in persons at high risk for the disease but are not applicable to the general population. The adverse effects of sulindac in humans comprise dose-dependent upper gastrointestinal bleeding and ulceration and hepatic and renal toxicity. If sulindac were to be used as a chemopreventive agent in large populations, the evidence of benefit would have to be clear and the benefits themselves significant.

Piroxicam. Epidemiological studies in humans provide inadequate evidence for the cancer-preventive activity of piroxicam. In experimental animal models, there is *sufficient evidence* that piroxicam prevents cancers at several sites. Owing to the toxicity of piroxicam, however, it is likely that it will have only limited applicability as a cancer-preventive agent in humans.

Indomethacin. Epidemiological studies provide *inadequate evidence* for the cancer-preventive activity of indomethacin, although some case reports suggest that the agent prevents the progression of adenomatous polyposis in patients with FAP. In experimental animal models, there is *sufficient evidence* for the cancer-preventive activity of indomethacin.

The adverse effects of indomethacin include dose-dependent upper gastrointestinal bleeding and ulceration and hepatic and renal toxicity. It seems unlikely that further research on the possible cancer-preventive activity of the agent in humans would lead to recommendations for its use for this purpose in human populations.

Additional Research Needed

Although there was a consensus by members of the Working Group that aspirin and, in more specific circumstances, sulindac show promise as chemopreventive agents against colorectal cancer, further research is needed. Knowledge about aspirin has significant gaps that should be addressed in further epidemiological studies, clinical trials, and studies of animal models. The protocols of studies in animal models should be standardized and biomarkers of surrogate end-points validated to obtain firm evidence about the relative potency of aspirin and other NSAIDs. Such studies should involve doses of aspirin that reflect those used in humans.

Evidence is lacking contrasting the possible beneficial effects of individual nonaspirin NSAIDs in humans. Second, there is a relative lack of information about the possible benefits of aspirin and nonaspirin NSAIDs against cancers outside the colon and rectum. Such evidence may be obtainable within existing databases on drug usage and clinical outcomes, such as the Medicaid in the United States and the General Practitioner Research Database in the United Kingdom.

Issues similar to those in animal studies arise in clinical trials with regard to the use of surrogate end points and biomarkers; questions should be answered about specificity, sensitivity, and positive predictive value. Adenomatous polyps may be perceived as biomarkers for the probable development of colon cancer, but confidence in this perception will increase as the relationship between these lesions and the later stages of colon cancer is more fully understood. The Working Group was aware that trials of aspirin use are in progress, mitigating against specific recommendations for future trial design.

Research to define the relative importance of the two metabolites of sulindac, sulindac sulfide, and sulindac sulfone, in the prevention of carcinogenesis in humans is a high priority. Better understanding of the chemopreventive action of sulindac in humans would require long-term studies of patients with FAP or large epidemiological studies in the general population.

Concluding Remarks

There is *inadequate evidence* that indomethacin and piroxicam have cancer-preventive activity in humans; however, aspirin and, in more specific circumstances, sulindac show promise against colorectal cancer. Further research on these agents is warranted in order to determine the optimal dose, duration, and frequency of use. The balance between cancer-preventive activity, other beneficial effects, and toxicity is a primary consideration for studies in humans.

Selective COX-2 inhibitors were not discussed at the meeting because such agents are still being developed for clinical use. Data from experimental animal models indicate, however, that selective COX-2 inhibitors have great potential in colorectal cancer prevention. Because these agents are likely to be less toxic than aspirin and sulindac, they hold promise as cancer-preventive agents in humans.

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Appendix 1

The meeting participants were H. O. Adami (University Hospital, Uppsala, Sweden), V. A. Alexandrov (Petrov Institute of Oncology, St. Petersburg, Russian Federation), J. A. Baron (Dartmouth Medical School, Hanover, NH), R. Benamouzig, (Hôpital Avicenne, Bobigny, France), J. Burn (University of Newcastle upon Tyne, United Kingdom), A. Castonguay (Laval University, Quebec City, Quebec, Canada), R. N. DuBois (Vanderbilt University Medical Center, Nashville, TN), D. L. Earnest (University of Arizona, Tucson, AZ), P. Greenwald (National Cancer Institute, Bethesda, MD), M. Griffin (Vanderbilt University, Nashville, TN), E. T. Hawk (National Cancer Institute), Y. Konishi (Nara Medical University, Nara, Japan), M. Langman (Queen Elizabeth Medical Centre, Birmingham, United Kingdom), J. Little (University of Aberdeen, Aberdeen, United Kingdom), M. Marselos (University of Ioannina, Ioannina, Greece), A. B. Miller, Chairman of the meeting (National Cancer Institute), B. S. Reddy (American Health Foundation, Valhalla, NY), B. W. Stewart, Vice-Chairman of the meeting (Sydney Children's Hospital, Randwick, Australia), M. J. Thun, (American Cancer Society, Atlanta, GA), M. D. Waters (United States Environmental Protection Agency, Research Triangle Park, NC), and G. Winde (University of Münster, Münster, Germany).

The meeting observer was Dr. G. Latta (Bayer Company, Germany).

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