PREVENTION OF COLON CANCERS AND POLYPS

Is it time to give aspirin yet?

Medical Grand Rounds
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There is much current interest in the potential cancer chemoprevention efficacy of aspirin (acetylsalicylic acid) and other non-steroidal antiinflammatory drugs (NSAIDS). Although NSAIDs have been useful for their analgesic, antipyretic, and antiinflammatory effects, more recent studies have suggested that NSAIDs, and especially aspirin, may have other uses, including prevention of cardiovascular disease and cancer. Aspirin, the rather unpretentious derivative from the bark of the willow tree, is now used as an antiplatelet drug for the secondary prevention of occlusive cardiovascular disease, including myocardial infarction, transient cerebral ischemia, and stroke.[1] Aspirin may also be useful in the primary prevention of myocardial infarction, and in the prevention of cataracts, migraines, and vascular dementia.[1]

Recent studies suggest that aspirin and the other NSAIDs may have a potential role in the prevention of colorectal cancer and perhaps also other digestive tract cancers. Extensive cell culture experiments and laboratory animal studies, as well as an increasing number of epidemiologic surveys and human studies, including a few clinical trials, have shown promising results.[2]

COLORECTAL CANCER

Colorectal cancer, along with cancer of the lung and breast, are the top three cancer killers in the United States. It has been estimated that in 1996, colorectal cancer will account for 134,000 new cases of cancer and 55,000 deaths.[3] The average American has a 6-7% life time probability of developing colorectal cancer and a 3% probability of dying from the disease. It is estimated that over 6 million Americans who are alive today will die of this disease. Although the frequency of new cases has shown a small gradual decline over the last four decades, especially in women, the case mortality rate has shown little change. [3-6]

It is now widely accepted that the adenoma (adenomatous polyp) is the primary premalignant precursor lesion for colorectal cancer. Several lines of evidence support this adenoma-cancer sequence. These lines of evidence come from epidemiologic surveys of geographic association of adenomas and cancers, similar anatomic distribution of adenomas and cancers, the chronologic time sequence between the appearance of adenomas and cancers, and more recently the demonstration of parallel genetic alterations in adenomas and cancers, and the correlation between progressive accumulation of genetic alterations and mutations and the progression from normal mucosa to adenoma and cancer. Perhaps the strongest clinical evidence is that patients who are maintained adenoma free by polypectomy are generally kept cancer free. This argument has been supported by cohort studies and intervention trials.[7,8]

With a long latency period (a decade or more) and the evolving understanding of the biology of the adenoma-cancer sequence, there is now increasing scientific and clinical interest in preventing colon cancer, by either the prevention of adenoma formation and recurrence, or by interference with neoplastic progression. Various interventions have been tried using evidence gathered from epidemiologic, animal, and human studies. The most commonly advocated strategies of chemoprevention (the use of drugs, foods, or food components in an attempt to prevent cancer) have included dietary alterations to decrease dietary fat and increase dietary fiber, the addition of vitamins such as vitamin A, C, and E, and micronutrients.[9,10] Much recent attention has also focused on the potential efficacy of NSAIDs.[11,12]

NSAIDS

The NSAIDs, non-steroidal antiinflammatory drugs, have been used for their analgesic, antiinflammatory, and antipyretic effect. Aspirin has been used for decades, and the other agents have been developed more recently. In addition to their clinical effect, the NSAIDs also share a common property as inhibitors of cyclooxygenase (COX, prostaglandin H synthase), one of the three key enzymes in arachidonic acid metabolism. Arachidonic acid may be converted by epoxygenase to produce epoxy-arachidonic acids. Lipoxygenases convert arachidonic acid eventually to hydroxy fatty acids, leukotrienes, and lipoxins. The cyclooxygenase pathway results in the formation of prostaglandins, thromboxanes, prostacyclin and malondialdehyde.[13]

The NSAIDs inhibit COX by binding to the protein. Aspirin not only binds, but covalently modifies the COX protein by acetylating a serine residue at position 529 on COX-1. It is believed that an analogous process occurs for COX-2 at a serine residue at position 516. The other NSAIDs bind COX, but not covalently , nor do they irreversibly modify the COX protein. Nevertheless, the binding appears to be extremely tight with an extremely slow dissociation rate. Indomethacin has one of the tightest binding constants and slowest dissociation rate.[14,15]

It has been recently found that mammalian cells contain two related but distinct cyclooxygenases. The two isozymes share about 75% homology at the mRNA level and 60% homology at the protein level, but the catalytic sites appear to be highly con- served.[16-18] The enzyme that was discovered first is termed COX-1 (prostaglandin H synthase 1, PGHS-1), and the one discovered more recently is known as COX-2 (PGHS-2).[14,15] It has been shown that COX-1 may be the constitutive enzyme responsible for maintaining gastrointestinal mycosal integrity, whereas COX-2 may be the inducible enzyme which modulates inflammatory response and tumorigenesis [14,15,19] Hence there has been a search for NSAIDs or analogs that preferentially inhibit COX-2 over COX-1, with the hope of finding an agent with potent anti-inflammatory (and perhaps cancer preventive) effects without inducing gastrointestinal mucosal injury.[20-22]

ANTI-TUMOR EFFECTS OF ASPIRIN AND OTHER POTENTIAL NSAIDS

Inhibition of carcinogen activation

The COX enzyme converts arachidonic acid to prostaglandin G2, a metastable cyclic endoperoxide, which is then reduced to prostaglandin H2, an alcohol. During the early peroxidase reaction, free radicals are produced which have the potential to damage cells. The peroxidase reaction also may metabolize other xenobiotics to reactive products which may be mutagenic or carcinogenic.[23] The COX enzyme has been shown to activate heterocyclic aromatic amines found in food to mutagenic reaction products [24]. Aspirin and indomethacin have also been shown to inhibit the peroxidation of colon carcinogens, and suppress the formation of colon cancers induced by these carcinogens.[23,25,26]

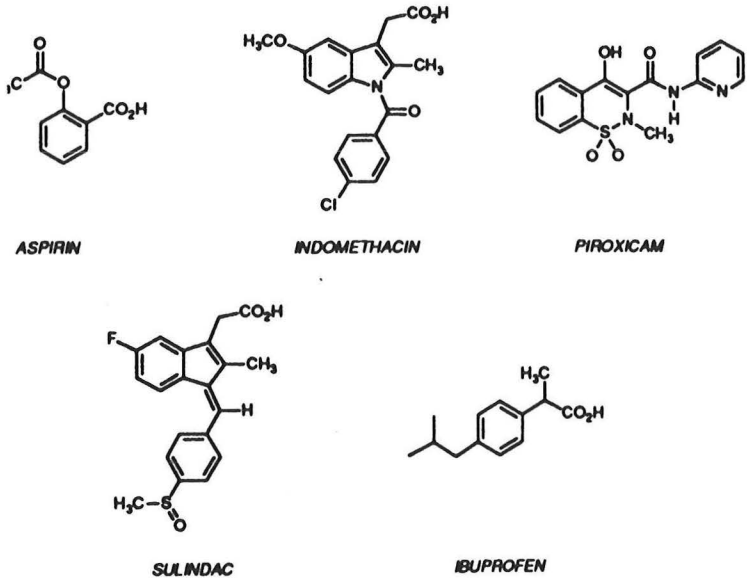

Figure 1. Structure of common NSAIDs, including aspirin.

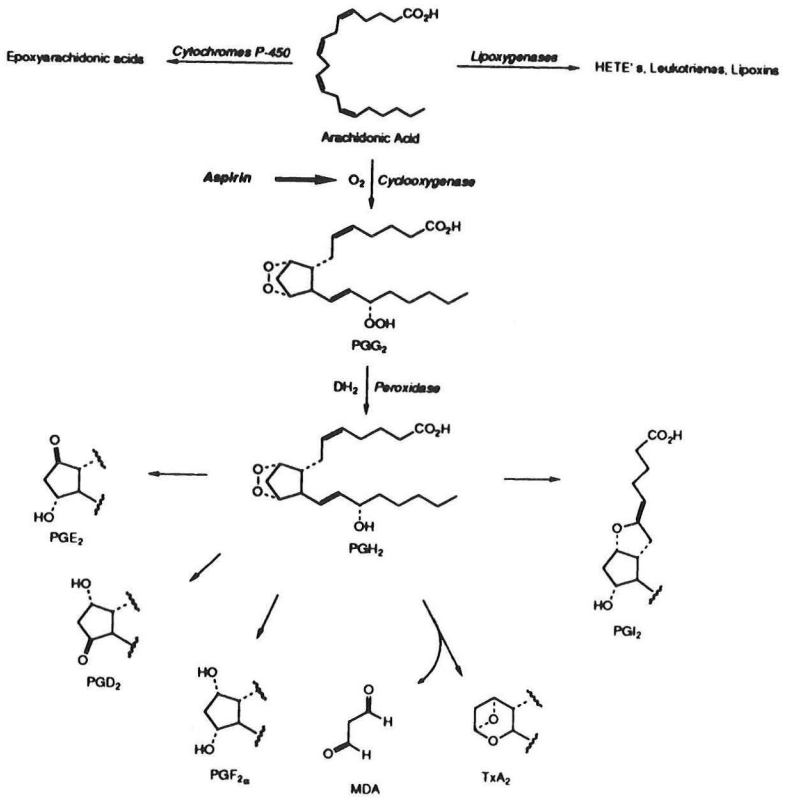

Figure 2. The cyclooxygenase pathway and prostaglandin synthesis.

Cellular anti-proliferative effect

The best understood cellular effect of NSAIDs is the inhibition of COX and hence suppression of prostaglandin synthesis. Prostaglandins have been shown to be elevated in colorectal cancers and important for cancer cell growth.[27,28] Several NSAIDs, primarily indomethacin, have been shown to inhibit DNA synthesis and cell growth of tumor cells in culture,[29-32] including murine colon adenocarcinoma [33], murine lung cancer[34], human stomach cancer[35], and human breast cancer cells.[36] In most studies, the effect of NSAIDs was cytostatic and not cytotoxic, cell viability was maintained and growth inhibition was reversible upon repletion of prostaglandins or removal of NSAIDs. This growth inhibition was subsequently shown to be a result of G_1-S phase arrest during cell cycle progression and suppression of DNA synthesis.[37,38] In addition, NSAIDs have also been shown to inhibit proliferation-associated enzymes such as phosphodiesterase, cyclic AMP protein kinase,[39] pyruvate kinase,[40] and ornithine decarboxylase.[41]

Immune surveillance

The prostaglandins appear to have an immune modulatory role.[42,43] PGE_2 has been shown to suppress T cell proliferation,[44] lymphokine production,[45] T cell mediated cytotoxicity,[44] antibody-dependent cellular cytotoxicity,[46] macrophage activation,[47] and NK cell mediated cytotoxicity.[48] NSAIDs, primarily indomethacin, has been shown to stimulate cellular immune function both in vitro and in vivo.[29,42,49,50] NSAIDs appear to be able to reverse the immune suppressive effect of high tissue levels of PGE_2.[42] In addition, NSAIDs have also been shown to enhance peripheral T cell proliferation in patients with colorectal cancer.[51]

Apoptosis (Programmed Cell Death)

Cell turnover in proliferative tissues such as colonic mucosa is tightly regulated by mechanisms which balance cell proliferation and cell death. Although much of the focus in cancer research has been on the proliferative aspect of carcinogenesis, a growing body of evidence suggests that apoptosis may be essential for the elimination of premalignant cells that might otherwise contribute to tumor formation. Apoptosis is a genetically determined program of autonomous cell death, distinct from necrosis, and appears critical for normal cell and tissue growth and development.[52,53] Among patients with familial adenomatous polyposis, colonic mucosa demonstrates diminished apoptotic activity when compared to colonic mucosa from normal controls.[53] Recently, both aspirin and sulindac have been shown to induce apoptosis normal and colon cancer cells in vitro. This has been shown to occur via mechanisms distinct from the inhibition of prostaglandin synthesis.[52,54-56]

A fundamental histologic feature of adenomatous polyps is colonic mucosal hyperproliferation. Until recently, reports in the literature attributed the anti-neoplastic activity of NSAIDs, such as aspirin and sulindac, on their ability to inhibit prostaglandin synthesis. This rationale was based on studies showing that prostaglandins are mitogenic and that high concentrations exist in certain tumors and cancer cell lines. However, several studies have now demonstrated that sulindac sulfone, an "inactive" metabolite of sulindac notable for its lack of cyclooxygenase inhibitory prostaglandin depleting activities, prevents tumor formation in animal models of chemical carcinogenesis.[52] These findings question the paradigm that the anti-neoplastic activity of sulindac and other NSAIDs is mediated by the inhibition of prostaglandin synthesis.

Evidence is now beginning to accumulate that the anti-neoplastic effect of NSAIDs is mediated at least in by the induction of apoptosis. Piazza *et al* studied the growth inhibitory effects of sulindac sulfide and sulfone on cultured colon cancer cells. Sulindac sulfide is the sulindac derivative that is known to be exclusively responsible for the anti-inflammatory activity of sulindac. This anti-inflammatory activity of sulindac sulfide and other NSAIDs is attributed to the inhibition of prostaglandin synthesis. The sulfone derivative of sulindac differs from sulfide only in that it lacks prostaglandin inhibitory activity. These investigators found that neither drugs inhibited the growth of cultured human colon cancer cell lines as well as normal epithelial cell lines. Neither drug inhibited cell proliferation (as measured by cell cycle progression or DNA synthesis) or induced cellular differentiation. However, both drugs strongly induce apoptosis in a time- and dose-dependent manner via a mechanism independent of their inhibitory effect of cell cycle progression.[52] The biochemical mechanism responsible for the apoptosis-inducing activity of sulindac sulfide and sulfone is not clear but does not appear to involve cyclooxygenase inhibition or cell cycle arrest.[52]

ANIMAL STUDIES

A large number of animal studies have shown that NSAIDs, suppress chemical carcinogen induced development of colon cancers in rodents. This is manifested by decreases in tumor incidence (percentage of animals with tumors) and multiplicity (tumors per animal), and therefore also total number of tumors in the entire experimental group.

Studies beginning in the early 1980s, after some of the early work on in vitro cell culture studies described above were published, show that administration of indomethacin in their drinking water[57,58] or by intrarectal administration[59] decreased tumor incidence and multiplicity in rats given the carcinogen azoxymethane or one of its active metabolites. Subsequent studies found that the tumor suppressive effect lasted as long as 40 weeks and that the tumor suppressive effect was present even if indomethacin was administered several weeks after carcinogen administration.[60] These results suggested that the NSAIDs' tumor suppressive effect was not mediated entirely at the level of carcinogen activation, but might be a result of direct inhibition of tumor initiation and/or progression, or enhanced immune surveillance.

Yet other studies found that the tumor inhibitory effect of indomethacin persisted after the drug was stopped, and in fact persisted even if PGE_2 was administered.[61] It is suggested that NSAIDs have a direct and long lasting (perhaps even irreversible) direct inhibitory effect on tumor progression, propagation, or growth, at least in the rodent model. This direct antitumorigenesis effect was also suggested in other studies that showed a lower tumor incidence, but a similar number, distribution, size, location, and spread of tumors in those fewer tumor-bearing animals in the NSAID treated group.[62] However, other studies by some of these same investigators suggested that the antitumor effect of NSAIDs may be more pronounced at an earlier initiation phase than in later promotion phases, and that earlier studies may have missed the strong initiation effect because of lower carcinogen dose or other technical experimental differences. These studies suggested that the tumor inhibitory effect was partially to totally reversible after stopping indomethacin.[63,64]

TABLE 1

FEATURES OF SELECTED NSAIDS

Indomethacin - high potency cyclooxygenase inhibitor
(Indocin)

Sulindac - activation by colonic microflora
(Clinoril)

Piroxicam - long half-life, qd dosing
(Feldene)

Aspirin - most widely used, cardiovascular Rx
(Bufferin)

TABLE 2

NSAID ANIMAL STUDIES - INDOMETHACIN

Study	Design	Incidence	Multiplicity	
Pollard '80	In	↓	↓	
Kudo '80	In	↓	↓	(Intrarectal)
Pollard '81	In	↓	↓	
Narisawa '81	In/Pr	↓	↓	(In > Pr)
Pollard ' 83	Pr	↓	↓	(>40 wks)
Narisawa '83	In/Pr	↓	↓	(In > Pr)
Metzger '84	In	↓	-	
Narisawa '84	In/Pr	↓	↓	(PG ineffective)

TABLE 3

NSAID ANIMAL STUDIES - PIROXICAM

Study	Design	Incidence	Multiplicity	
Pollard '83	In	↓	↓	
Pollard '84	In	↓	↓	
Nigro '86	In/Pr	↓	↓	
Reddy '87	In/Pr	↓	↓	(Pr> 13 wks)
Reddy '90	In/Pr	↓	↓	
Rao '91	Prev.+	↓	↓	(40% MTD)
Reddy '92	Prev.+	↓	↓	(40% MTD)

More recent studies have utilized the NSAID piroxicam, partly because its long half-life (longer than 50 hrs) allows once daily dosing for animal studies. The results obtained with piroxicam were quite similar to those with other NSAIDs such as indomethacin and aspirin. Virtually all studies demonstrated a decrease in tumor incidence and multiplicity.[65-71] In addition, studies using sulindac also demonstrated tumor suppression.[72,73] Furthermore, some studies have used combinations of NSAIDs with other potential chemopreventive agents, and have shown antitumor efficacy with combinations with oltipraz,[74] interleukin-2,[75] and the ODC inhibitor, difluoromethylornithine.[67,69,70]

Other than colon cancers, animal carcinogenesis studies have also shown a tumor-inhibitory effect of NSAIDs on stomach cancer,[76] lung cancer,[76] breast cancer,[77,78] bladder cancer,[79,80] and fibrosarcoma.[81] As discussed in the next section, some epidemiologic surveys have suggested a protective effect of NSAIDs against stomach, lung,and breast cancer, along with colorectal cancer. Other than carcinogen-induced animal tumors, the NSAID piroxicam has been shown to decrease the frequency of naturally occurring tumors in dogs - transitional cell carcinomas, squamous cell carcinomas, and mammary adenocarcinomas.[82]

These animal tumor studies of NSAIDs take on added relevance when one considers that many human tumors, especially colorectal carcinomas, have been found to have elevated levels of tumor tissue prostaglandins.[29,83] The depletion of tissue prostaglandin levels by NSAIDs appear to be a plausible mechanism for the antitumor effects of NSAIDs. However, one study suggested that a single dose of indomethacin administered during adolescence (age 29 days) resulted in lower body weight, shorter survival, and increased numbers of tumors.[84] The tumors were testicular Leydig tumors, hepatocellular tumors, and intestinal and colonic adenocarcinomas. Nevertheless, the preponderance of scientific evidence suggests that NSAIDs have an anti-tumor and not a tumor promoting effect.

Other recent studies have focused on the potential chemopreventive effect of NSAIDs in colon tumorigenesis. These studies delayed the administration of NSAIDs for as long as 13 weeks after carcinogen administration, but at a time that was still several months before colon tumors would have eventually appeared.[68,85] These studies have shown colon tumor inhibitory and chemopreventive effects of several NSAIDs, including piroxicam, ibuprofen, ketoprofen [71] as well as aspirin.[25,85] The animal studies with aspirin represent one instance when animal studies follow the lead provided by epidemiologic surveys. For years aspirin was considered an innocuous and unpretentious compound by most investigators, and was seldom used in cell or animal studies. This has now changed with the tantalizing results found on epidemiologic surveys.

EPIDEMIOLOGIC SURVEYS

In contrast to cell culture and animal studies, most epidemiologic surveys have focused on aspirin, because it is by far the one in longest use, and still the most widely and commonly used NSAID. Initial studies were done using case control methods. An Australian population-based case control study from Melbourne compared aspirin use in 715 incident cases of colorectal cancer with 727 controls. Aspirin use was determined by questioning whether each subject had used aspirin-containing medications on a regular basis. Use of aspirin was associated with a relative risk for colorectal cancer of 0.53. This protective effect persisted after controlling for potential confounding factors including diet, co-morbid illnesses, and hospitalization.[86]

In a subsequent case control study reported from the Northeast United States, a total of 1,326 incident cases of colorectal cancer was compared with 4,891 controls, of whom 1,011 had cancers at other sites and 3,880 were patients that were hospitalized for acute infections or trauma. Use of aspirin for at least 4 days a week during the previous year was associated with a relative risk for colorectal cancer of 0.5. Previous users who had discontinued aspirin use for a year or more showed no protective effect, suggesting that aspirin's protective effect might be reversible, and required continued usage to be manifest.[87] There appeared to be an age effect, with the protective effect being stronger in younger individuals. The median age of the cases was 63. For individuals under 60 years of age, the relative risk was 0.3; for those older than 60, it was 0.6.

At about the same time a cohort study was published which appeared to contradict the above studies. Cohort studies are generally accepted to provide stronger support for a hypothesis than do case control studies, due to a lower potential for bias in assessing exposure, selection bias, recall bias, as well as confounding variables. In a cohort study of 13,987 elderly (median age 73) residents of Leisure World, a southern California retirement community, those individuals who used aspirin at least once daily were found to have a relative risk for colon cancer of 1.3 and for rectal cancer of 1.0.[88] This was based on 181 incident cases of colorectal cancer found after a median follow-up of 7 years. The cohort has been followed continuously since 1981. When the results were re-analyzed to look at mortality instead of incidence, there was also no protective effect. In a subsequent follow-up report 3 years later on the same cohort, which then included 50 more cases of colorectal cancer (accounting for a total of 231 incident cases of colorectal cancer), there was again no protective effect, with a relative risk for colon cancer of 1.5 in men and 1.0 in women.[89] It is important to note that this study differs from most other epidemiologic surveys on aspirin and colorectal cancer in several aspects. First, this study found a substantial gender difference, which was not seen in any other epidemiologic survey. In addition, the subjects were quite elderly, with a median age of 73 at the time of analysis for the initial report. As shown in two other studies, the protective effect seems to be stronger for younger individuals, with greater protective effect for those under the age of 60-65 years. In addition, many of the subjects in this cohort study were quite health conscious, with most of the women being on calcium and estrogen. In fact, the cohort was designed to study osteoporosis, and its risk factors and protective factors, in the elderly.[90]

A subsequent cohort study was reported from the American Cancer Society in 1991 in the New England Journal of Medicine.[91] This raised great public awareness, especially coming at a time when aspirin was being shown to have significant protective effect in the secondary prevention of cardiovascular events. In this Cancer Prevention Study, a cohort of 662,424 adults had been surveyed about a variety of life style factors and medications in 1982 as part of a prospective study of cancer mortality. Aspirin use was ascertained as part of a large health and dietary habits questionnaire and recorded as usage on a monthly basis, dividing users into non-users, and those taking less than 1, 1-15, and more than 16 aspirins per month. A total of 1,111 deaths from colorectal cancer were recorded. There was a significant protective effect for aspirin users, with the relative risk for colon cancer in those who used aspirin more than 16 times per month of 0.6 for colon cancer, and 0.8 for rectal cancer. There was a protective effect at each level of use compared with non-users, and a dose-response effect was observed. No effect was found for acetaminophen, and the results persisted after correcting for potential confounding factors such as co-morbidity and diet.[92]

TABLE 4

ASPIRIN USE AND COLORECTAL CANCER

Study	Design	ASA	Site	RR
Melbourne	Case Cont	Any	C+R	0.5
N.E. US	Case Cont	4/wk x 1 yr	C+R	0.5
California	Cohort	Daily	C	1.3
			R	1.0
US (CPS)	Cohort	16/mo x 1 yr	C	0.6
			R	0.8
Buffalo	Case Cont	1-2/d	C	0.6
			R	0.3
US (NHANES)	Cohort	Past mo	C+R	0.9
		(Men <65 yrs)		0.4
US (HPFS)	Cohort	2/wk	C+R	0.7
US (PHS)	Trial	QOD	C+R	1.2
US (NHS)	Cohort	4/wk x 20 yr	C+R	0.6

TABLE 5

ASPIRIN USE AND COLORECTAL POLYPS

Study	Design	ASA Dose	Polyp	RR
Buffalo	Case Cont	1-2/d	All	0.4
Nottingham	Case Cont	Any	Adenoma	0.6
US (PPS)	Cohort	Any	Adenoma	0.5
US (HPFS)	Cohort	2/wk	Adenoma	0.8
US (PHS)	Trial	QOD	All	0.9

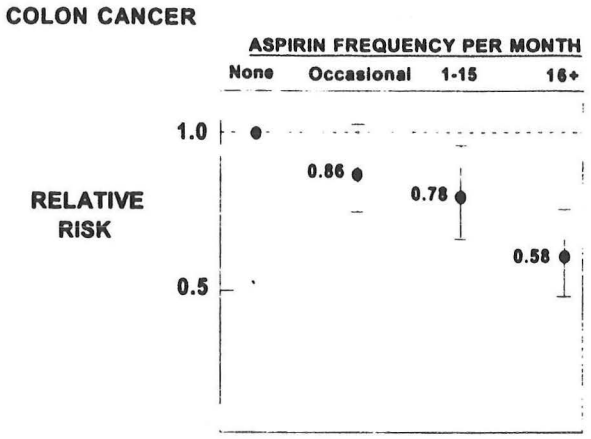

Figure 3. **Decreasing risk of colon cancer associated with increasing frequency of aspirin use.**

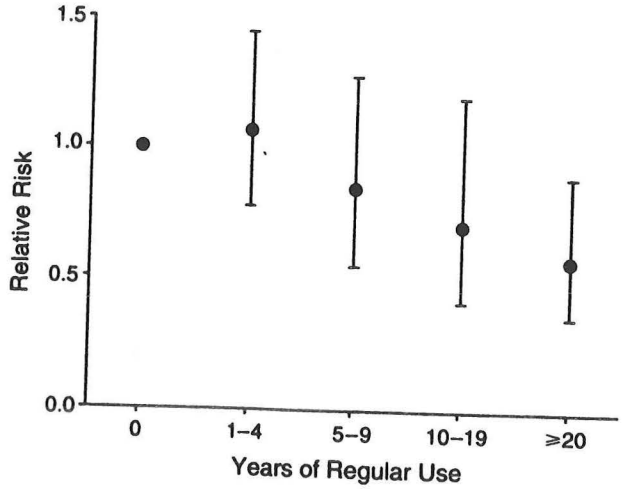

Figure 4. **Decreasing risk of colon cancer associated with increasing duration of regular aspirin use.**

Three recent studies appear to confirm the protective effect of aspirin. In a case control study from the Roswell Park Memorial Institute in Buffalo, 490 incident cases of colon cancer and 340 incident cases of rectal cancer were compared to 1,138 controls that were healthy visitors to a cancer screening clinic and to another 524 controls who were hospitalized patients found not to have cancer. Aspirin use was recorded as the routine use over the previous one year of <1, 1-2, or >2 tablets per day. Aspirin users had a relative risk for colon cancer of 0.6 and for rectal cancer of 0.3. In this study, as in the Cancer Prevention Study, there was a protective effect at all three levels of use, compared with non-users, and a dose-response effect was observed.[93]

The data from another large cohort, the National Health and Nutrition Examination Survey I (NHANES) have recently been analyzed. This survey was conducted between 1971 and 1975, in which a sample of a civilian non-institutionalized U.S. population between the ages of 1 and 74 years were to be followed over time. The survey did attempt to over-sample for individuals considered to be at risk for malnutrition. A subpopulation of 12,668 subjects who were age 25-74 at the time of the initial survey was analyzed. At the time of the survey aspirin use over the previous 30 days was assessed by questionnaire. At the time of analysis subjects had been followed for a median of 12.4 years. After the initial 2 years of follow-up (when prevalent colorectal cancers that might have been present at the time of initial survey should have presented) a total of 1,257 new incident cases of colorectal cancer were found. In this study, the relative risk for colorectal cancer for aspirin users was 0.9. Subgroup analysis suggested that for men under the age of 65, the relative risk for colorectal cancer in aspirin users was 0.4.[94]

The most recently published case control study analyzed the association of aspirin and non-aspirin NSAIDs and risk of colorectal cancers and polyps in the Nurse's Health Study. An analysis of 93 patients with colorectal cancer and 113 with colorectal adenomas, matched with more than 500 controls, found that 2 years or more of regular NSAID use was associated with a significant risk reduction for colorectal cancers, with a relative risk of 0.6.[95]

The effect of aspirin on the incidence of colorectal cancer was also examined as a post facto analysis of the Physicians' Health Study.[96] This study randomized 22,071 U.S. male physicians to receive aspirin 325 mg every other day and beta carotene 50 mg every day using a 2 X 2 factorial design. Subjects received one of the following four treatments: i) aspirin and beta carotene, ii) aspirin and placebo, iii) beta carotene and placebo, or iv) both placebo. The primary hypotheses to be tested in the study were whether aspirin would reduce the risk of cardiovascular disease and whether beta carotene would reduce the risk of cancer. The trial was not designed to test the hypothesis that aspirin would reduce the risk of cancer, or more specifically colorectal cancer. In fact, the aspirin arm of the study was terminated after a mean follow-up of 5 years, when a statistically significant protective effect against cardiovascular disease was found.[97] Nevertheless, because the study was set up as a randomized clinical trial, it offered an opportunity to explore a potential effect of aspirin in an unbiased fashion. A total of 118 new incident cases of colorectal cancers were found between the time of study entry and study termination. Because of the small number of colorectal cancers which was primarily a result of the early stoppage of the aspirin arm, the study had inadequate power to determine if there was a protective effect of aspirin. The calculated relative risk was 1.2 but its accuracy was in doubt because of the inadequate power.[98] The power of the study was also influenced by the healthy outcome of the participants. At the start of the trial, the investigators had considered that volunteers for a prevention study might have only 80% of the general population's frequency of adverse cardiovascular and cancer events due to health-seeking behavior, and that physicians on a whole might have an additional 50% decrease in adverse

TABLE 6

ASPIRIN USE AND COLORECTAL CANCER

Study	vs. Dose	vs. Duration	vs. Age	Reversible
Melbourne				
N.E. US		+	+	+
California			(?)	
CPS	+	+		
Buffalo	+			
NHANES			+	
PHS		+		
HPFS	+			

TABLE 7

ASPIRIN USE AND OTHER CANCERS

RR	Esophagus	Stomach	Pancreas	Lung	Breast	Other
CPS	0.59*	0.53*	-	1.07	0.88	1.05
NHANES	-	0.93	0.67	0.68*	0.70*	0.88

** Statistically significant difference from RR 1.00*

TABLE 8

NSAIDS AND "SPORADIC" POLYPS

NSAID	n	Mos	CR/PR	
Sulindac 400 mg	5	6	0/1	(1 polyp disappeared)
Piroxicam 20 mg	2	6	0/1	(2 adverse events)

events. They thus hypothesized that the standard mortality ratio for these physician volunteers would be 0.4 (0.8 X 0.5). The eventual standard mortality ratio for their physician participants was 0.15, showing that those physicians that volunteered for the study and were enrolled after demonstrating initial compliance were indeed very healthy.

Colorectal polyps

Three of the above studies also analyzed data for a potential protective effect of aspirin on colorectal adenomatous polyps. The case control study from Buffalo also analyzed 212 incident cases of colorectal polyps (without any additional histologic classification). The relative risk for colorectal polyps in aspirin users was 0.4.[93] In a case control study in subjects participating in a randomized controlled clinical trial of fecal occult blood screening for colorectal cancer, a total of 147 new incident cases of colorectal adenomatous polyps who were found because of a positive fecal occult blood test were compared with 176 controls without colorectal adenomas who were also fecal occult blood positive and an additional 153 controls who had no colorectal adenomas and were negative for fecal occult blood. Aspirin use was determined by questioning whether any aspirin or aspirin containing drugs were taken on a regular basis for a period of 3 months or longer during the past 5 years. The relative risk for colorectal adenomas in aspirin users was .0.6 when compared to both control groups.[99] The protective effect was stronger when compared to the controls who were fecal occult blood negative than those who were fecal occult blood positive, thus suggesting that the protective effect of aspirin was probably not due to increased fecal occult blood loss or the resultant earlier serendipitous diagnosis of colorectal adenomas.

In a post facto cohort analysis of patients enrolled in a randomized controlled clinical trial of beta carotene, vitamin C and vitamin E, a total of 793 patients were asked for any ongoing use of aspirin at 6 months and 1 year after study entry. 593 did not report use of aspirin on either questionnaire and were recorded as non-users, 98 reported use on only 1 of the 2 questionnaires and were recorded as intermittent users, and 102 reported use on both questionnaires and were recorded as consistent users. For the consistent user, the relative risk for colorectal adenomas at 1 year after study entry was 0.52,[100] and the relative risk for the intermittent user was 0.95. Besides suggesting a dose response effect, the results also suggest that consistent use is required for a protective effect. The Physicians' Health Study was also analyzed for colorectal adenomatous polyps, and it was found that the relative risk for aspirin users for colorectal adenomas was 0.9.[98]

Other cancers

In two of the above trials, relative risks for mortality from other cancers were also examined. The results suggested that there may also be a protective effect of aspirin, in esophageal and stomach cancer in the Cancer Prevention Study[92], and perhaps also in lung and breast cancer in the NHANES study.[94]

In summary, the results from the above epidemiologic surveys that aspirin use had a protective effect against colorectal cancers are consistent, with the exception of the Southern California study in elderly subjects, and the Physicians Health Study with inadequate power. The strength of the association is quite good, with a relative risk of about 0.5 for the positive studies. A dose response effect was seen in several studies. There was also a suggestion that the protective effect was lost once aspirin use stopped. Lastly, there is biological plausibility from cell culture and animal studies for the observed effect. Based on these epidemiologic results, as well as the extensive and uniformly positive animal results, many small scale human intervention trials of NSAIDs have been performed, and several others are ongoing.

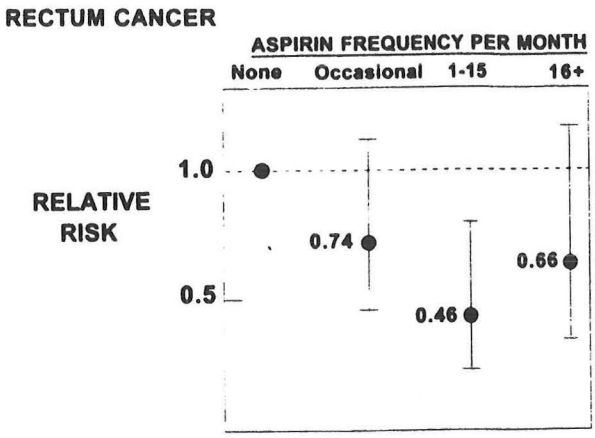

Figure 5. **Decreased risk of rectum cancer associated with increased frequency of aspirin use.**

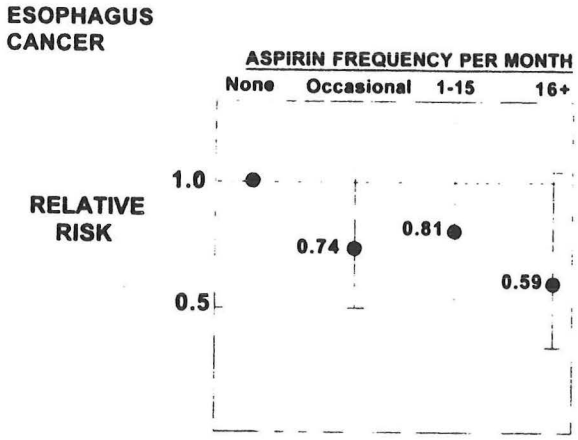

Figure 6. **Decreased risk of esophagus cancer associated with increased frequency of aspirin use.**

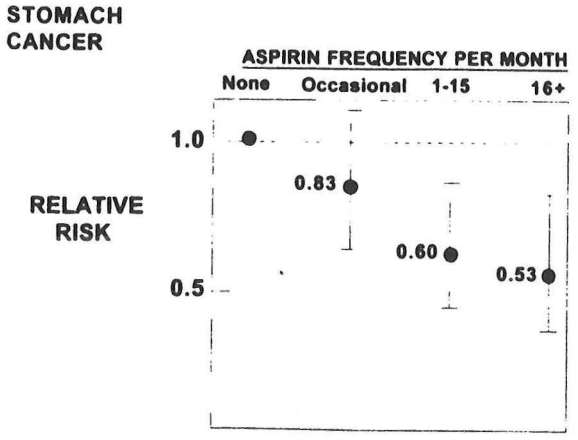

Figure 7. **Decreased frequency of stomach cancer associated with increased frequency of aspirin use.**

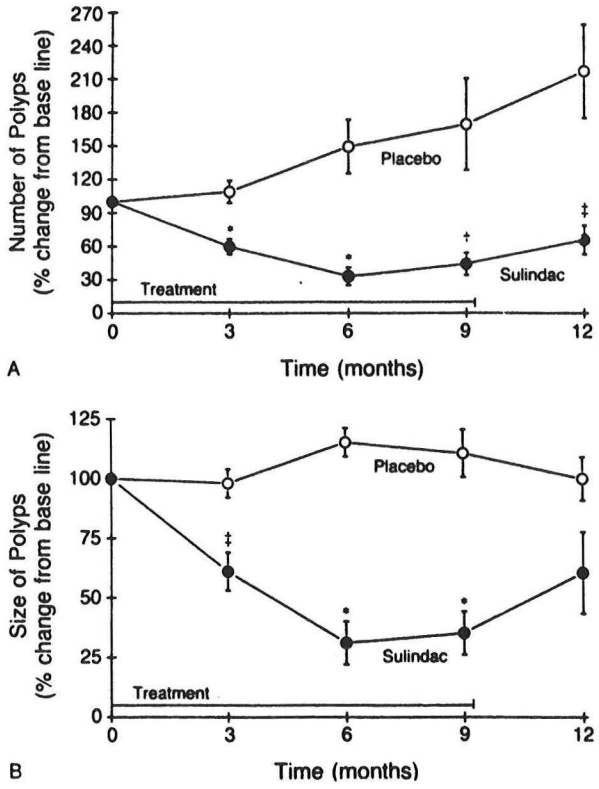

Figure 8. **Decrease in polyp number and size in patients with FAP given sulindac daily for 9 months, and regrowth of polyps after sulindac withdrawal.**

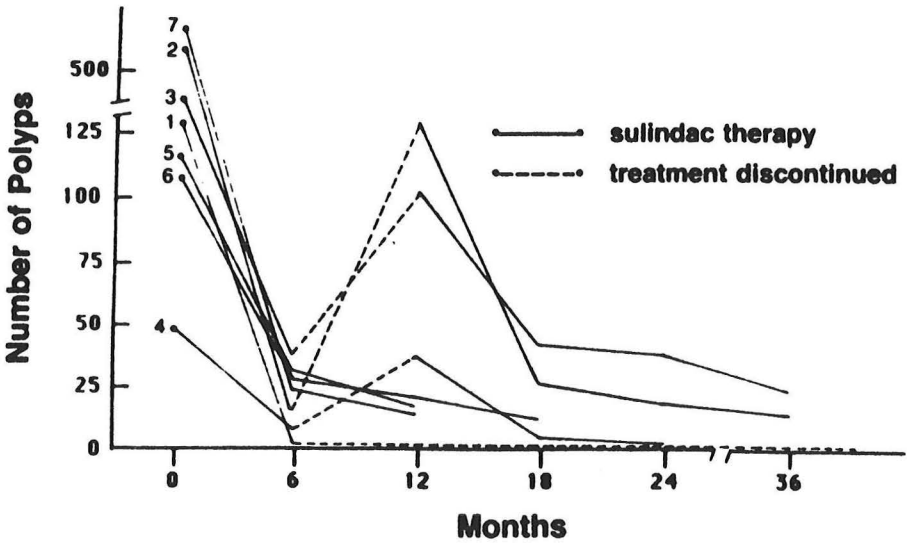

Figure 9. **Decrease in polyp number in patients with FAP given sulindac daily for 6 months, and regrowth of polyp after sulindac withdrawal.**

TABLE 9

SULINDAC AND COLORECTAL ADENOMAS IN FAP

Study	n	Mg/day	Mos	F/U (mos)	CR/PR	Regrowth
Waddell '89	11	3-400	>6	12-85	6/5	All
Labayle '91	9	300	4	10	6/3	4/5
Rigau '91	5	400	6	4-36	0/5	4/5
Iwama '91	10	150	3	3	0/3	All
Winde '93	15	300	4	10	11/4	All
Tonelli '93	13	200	>6	28-64	0/8	All
Nugent '93	7	400	6	0	0/5	-
Giardiello '93	11	300	9	12	0/11	All
Spagnesi '94	20	200	2	0	0/20	-
Niv '94	1	450	28	28	1/0	CA
Lynch '95	1	300	15	15	1/0	CA

TABLE 10

SULINDAC AND COLORECTAL ADENOMAS IN FAP

Low Dose of 200 mg/d or lower

Post-colectomy	n = 32	0% disappear
		78% decrease
		78% response
No colectomy	n = 11	0% disappear
		55% decrease
		55% response

TABLE 11

SULINDAC AND COLORECTAL ADENOMAS IN FAP

High Dose of 300 mg/d or higher

Post-colectomy	n = 42	57% disappear
		38% decrease
		95% response
No colectomy	n = 17	0% disappear
		100% decrease
		100% response

HUMAN INTERVENTION TRIALS

Early uncontrolled reports suggested that the use of the NSAID sulindac was associated with regression of polyps in patients with familial adenomatous polyposis. Primarily in patients who have undergone total colectomy and ileo-rectal anastomosis, the number and size of polyps in the rectal stump appeared to decrease with sulindac administration.[101,102] Subsequently investigators reasoned that sulindac, which was a pro-drug that was activated by colonic microflora, might have its active metabolite sulindac sulfide concentrated in the colon and thus be highly effective in the colonic mucosa. What is unexplained is that sulindac's effect has been seen primarily in those patients with total colectomies. Nevertheless, sulindac has been the NSAID of choice in studies involving FAP patients, and other NSAIDs, including aspirin, have been virtually ignored. Several additional small trials have found a regression of polyps, although complete regression was not seen.[103-105] Two recent small controlled trials have been completed. In a double-blind crossover study completed in 9 FAP patients, 6 patients were found to have complete regression and the other 3 partial regression while on sulindac. After going off sulindac, 4 out of 5 patients had regrowth of polyps.[106] In another randomized placebo-controlled study, 11 FAP patients were randomized to receive sulindac 300 mg total daily dose for a total of 9 months and had follow-up for a total of 12 months. The number of polyps decreased by more than 50%, and the size of the polyps decreased by about one-third. However, complete regression was not observed in any patient.[107] One difference is that this study included 9 FAP patients who had not undergone colectomy and had a larger number of adenomas. Furthermore, this author and other investigators have found that rectal adenomas appear to be the most susceptible to regression, either spontaneously after initial colectomy and ileorectal anastomosis,[108] or with sulindac treatment.[107,109] A third randomized study found that 5 out of 7 FAP patients who had undergone colectomy and ileorectal anastomosis had significant but incomplete regression of polyps on sulindac.[110] A recent study found that rectal therapy with sulindac was also effective.[111]

Although most studies have suggested that duodenal adenomas in FAP patients were highly resistant to sulindac treatment and show little if any regression, one small randomized trial[110] and a single case report[112] suggested a small effect. The single case report in an FAP patient with multiple recurrent duodenal adenomas for more than a decade described complete regression of duodenal adenomas with continuous sulindac, 300 mg daily, for 3 years. The patient was reported to be free of duodenal polyps for 6 months with continued administration of sulindac.[112]

In one small trial of sporadic colon polyps, sulindac 400 mg daily or piroxicam 20 mg daily was found to have no significant effect on adenomatous polyps ranging 3-12 mm in size, and numbering 1 in most and up to 3 in any individual patient.[113] One 6 mm polyp disappeared and 3 other small polyps appeared to have decreased in size. All remaining polyps were found to be adenomas on removal. Most importantly, of the 4 patients on piroxicam, 2 were withdrawn due to a bleeding gastric ulcer in one and rash in the other.

Therefore to date, all reported studies of sulindac have shown significant partial or complete regression of colorectal and perhaps also duodenal adenomas in FAP patients. Complete regressions have generally been seen in colorectal adenomas in patients who have undergone total colectomy and ileorectal anastomosis. Those with an intact colon generally had only partial regression. Furthermore, virtually all patients had regrowth of adenomas after discontinuation of sulindac. Therefore, sulindac cannot be recommended as definitive medical treatment, although it might have an adjunctive role in an experimental protocol in patients who have undergone ileorectal anastomosis and still have a rectal remnant with recurrent adenomas.

TABLE 12

SULINDAC AND DUODENAL ADENOMAS IN FAP

Study	n	Mg/d	Mos	CR/PR
Nugent '93	11	400	6	0/5
Parker '93	1	300	>36	1/0

(Gradual decrease over 24-36 mos)
(Electrofulguration also done)

TABLE 13

SULINDAC ADVERSE EFFECTS IN FAP STUDIES (2-400 mg/d)

Dyspepsia	>5%
GI Bleed	>2%
Bleeding GU	>1%
Rash	>1%
Study Withdrawal	>4%

TABLE 14

NSAID ADVERSE EFFECTS

Intracranial hemorrhage	↑22%	(0.3%)
GI bleeding	↑ 6-10X	(3%)
Gastric mucosal injury	↑10-25X	(20%)
Constipation	↑ 3X	(6%)
Upper GI symptoms	↑20-60%	(35%)
Worsen chronic renal disease		
Worsen hypertension		

TABLE 15

NSAID TOXICITY IN SMALL BOWEL

Abdominal distress
Diarrhea
Increased mucosal permeability
Mucosal inflammation
Blood and protein loss
Ulceration
Perforation
Strictures

TABLE 16

NSAID TOXICITY IN COLON

Rectal bleeding
Ulceration
Perforation (diverticula)
Strictures
Non-specific colitis/proctitis
Necrotizing enterocolitis
Ulcerative colitis
Crohn disease

TABLE 17

RECTAL CANCER DURING SULINDAC TREATMENT

2 women, post-colectomy for FAP,
developed rectal cancer on sulindac

	Colectomy	Sulindac	Polyp-Free
55F	14 yrs	450 mg/d x 28 mos	18 mos
68F	37 yrs	300 mg/d x 15 mos	12 mos

TABLE 18

"A MOST PROMISING CANCER PREVENTION DRUG"

- Naturally occurring food component
- Abundant in fruits and vegetables
- No known adverse effects or toxicity
- Effective in cell and animal studies
- Low levels associated with increased cancer risk
- All epidemiologic surveys (>20) positive
- Promising ongoing clinical trials

ADVERSE EFFECTS

Although aspirin and other NSAIDs are widely used and widely prescribed, they are not totally free of side effects. NSAIDs have been shown to cause gastrointestinal lesions,[114,115] including colitis,[116] and to cause decrease in renal function[117] and worsening of blood pressure control. The most commonly encountered adverse effect is probably gastrointestinal (GI) bleed. In fact, even at the lower doses used in cardiovascular prophylaxis trials, upper GI bleeding developed in 3% of patients on 1200 mg total daily dose of aspirin and about 1.5% of those on 300 mg daily aspirin.[118-120]

An even more devastating potential adverse effect is that the administration of aspirin or other NSAIDs may lull the physician and patient into a false sense of security. It must be remembered that the most optimistic interpretation of available data only suggests a 50% reduction, not a complete elimination, in the frequency of colon cancers and polyps. Physicians and patients cannot become complacent and delay or forego clinically indicated screening and surveillance.

In fact, the possibility exists that the NSAIDs, specifically sulindac when given to patients with FAP, may only suppress the polypoid growth of adenomas without any inhibitory effect on the progression of adenomas to carcinomas. There has been two highly sobering reports describing two patients who developed rectal cancer while being polyp-free on sulindac.[121,122]

Furthermore, it is seldom justifiable to administer a treatment with definite adverse effects but only hopeful benefit, unless the benefit truly outweigh the risks. Although aspirin shows great promise as a cancer preventive agent, we need to heed its definite toxicities and still unproven clinical benefit. All suggestions of aspirin's efficacy have come from epidemiologic surveys, which are not designed to prove clinical efficacy. We only need to recall the recent fall from grace of another "most promising cancer prevention drug".

HOPE vs. FACT

Beta-carotene had all the makings of a superstar agent - all the goodness of fruits and vegetables in a once-a-day pill. There was strong support from positive epidemiologic surveys and population serum studies.[123-126] The evidence was considered so overwhelming by some that beta-carotene was one of the biggest sellers in health food stores.[127] When the results were published from two small trials showing no effect in preventing skin cancers [128] or colorectal adenomas [123] and the large Finnish Alpha-Tocopherol Beta-Carotene (ATBC) study in 14,000 heavy smokers suggesting an 18% increase in lung cancer and 8% increase in mortality [129,130], most people were skeptical of the negative or adverse effects. There was a persistent expectation that larger trials (or presumably better-run trials in the U.S.) and longer periods of follow-up would eventually confirm the foregone conclusion that beta carotene is effective in preventing cancer.[127]

Alas, as we now can look back with perfect 20/20 hindsight, beta-carotene is not the panacea. Two large US trials recently published highly negative results and these were widely publicized and have probably sealed the fate of beta-carotene as a non-contender in cancer prevention. The Physicians' Health Study showed no benefit from beta-carotene 50 mg every other day given to 11,000 physicians (out of a total study population of 22,000), 90% of whom were non-smokers, in preventing cancers or cardiovascular mortality.[131] The beta-Carotene and Retinol Efficacy Trial (CARET) was stopped 2 years early because 9,400 heavy smokers (out of a total of 18,000 subjects) who took 30 mg of beta carotene and 25,000 IU of retinol

TABLE 19

BETA-CAROTENE: FALL FROM GRACE

- Finnish ATBC Trial in 14,000 heavy smokers
  - 18% increase in lung cancer
  - 8% increase in mortality
- US CARET Trial in 9,400 smokers
  - 28% increase in lung cancer
  - 17% increase in mortality
  - 25% increase in cardiovascular mortality
- Physicians' Health Study in 11,000 physicians
  - no effect on lung cancer
  - no effect on mortality
  - no effect on cardiovascular mortality

TABLE 20

SULINDAC SULFONE
? THE NON-NSAID NSAID

- "Inactive" metabolite of sulindac
- Lacks cyclooxygenase inhibitory activity
- Induces apoptosis
- Strong cancer cell growth inhibitory effect

TABLE 21

PREVENTION OF COLORECTAL CANCER

	RR
No tobacco use (all cancers)	0.3
No tobacco use (adenomas)	0.4
Low-fat, high fiber diet	0.5
NSAID use	0.5
Exercise	0.8
Ideal body weight	0.8

TABLE 22

NSAIDS AND COLON CANCERS AND POLYPS

- Aspirin for cardiovascular prevention
- NSAIDS to prevent cancer NOT proven
- Optimal agent or dose unknown
- Chronic daily NSAIDS have substantial adverse effects
- NSAIDS cannot be recommended for cancer prevention
- Sulindac may be effective in SELECTED patients with FAP or recurrent adenomas with high grade dysplasia AFTER all surgical/endoscopic options exhausted
- Consider "healthy" life style changes

daily had a 28% increase in lung cancer, a 17% increase in total mortality and a 25% increase in cardiovascular mortality.[132]

The results are now so convincing that the U.S. National Cancer Institute has stopped all ongoing trials using beta carotene in patients with or at high risk for lung cancer. Other beta-carotene trials have been modified to inform patients of current findings and to offer them a choice of opting out of beta carotene. The Danish Health Ministry has taken the additional step of mandating warning labels for smokers to be placed on the packaging of all beta-carotene containing food supplements.[127]

CURRENT RECOMMENDATIONS FOR ASPIRIN

Although the epidemiologic studies on aspirin in cancer prevention appear convincing they do not provide definitive proof of effect. In the only available large clinical trial, the study had inadequate power, and no protective effect of aspirin 300 mg every other day was detected.[98] Even in that trial, 1.5% of patients were hospitalized for GI bleeding during the 5-year aspirin study period.

Therefore, until there is more definitive proof of efficacy, in the form of positive results from randomized, placebo-controlled clinical trials, an endorsement of aspirin for prevention of colorectal adenomatous polyps or colorectal cancer cannot be provided. It would seem more prudent to endorse another intervention that has shown a similar protective effect in epidemiologic studies, with a relative risk of also about 0.5. Dietary changes to a low fat and high fiber diet has not been shown to have any adverse clinical effects (although life style changes can be stressful), and can be endorsed with a bit more enthusiasm. Those dietary changes can also be beneficial for cardiovascular health. And of course tobacco use should be strongly discouraged.

> **"But such hypotheses cannot be presumed to be true simply because of hope or belief, no matter how fervently they are held. These studies demonstrate how hard it is to isolate a single component of a healthful diet as the beneficial element...We do not know how to replace a healthful diet and a healthful lifestyle with simple pills".**
>
> Richard Klausner, M.D.
> Director, National Cancer Institute
>
> *Press Conference, May 2, 1996*

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