NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

ASPIRIN

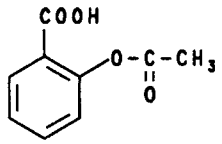
DRUG IDENTIFICATION

CAS Registry No.: 50-78-2

CAS Name (9CI): 2-(Acetyloxy)benzoic Acid

Synonyms: Acetylsalicylic Acid
ASA

Structure:



EXECUTIVE SUMMARY

Aspirin is the prototype non-steroidal antiinflammatory drug (NSAID). Like the other NSAIDs currently under consideration by the CB for development as chemopreventive agents (ibuprofen, piroxicam, and sulindac), aspirin derives its anti-inflammatory activity from inhibition of prostaglandin (PG) synthesis by inhibiting the cyclooxygenase activity of PGH_2 synthase [1,2]. Unlike the other NSAIDs, it is an irreversible inhibitor of the enzyme. It acetylates a serine residue at the substrate binding site of the enzyme, thereby preventing the attachment of arachidonic acid. This in turn inhibits the formation of PGs (*e.g.*, PGE_2, $PGF_{2\alpha}$) which may enhance carcinogenesis by proliferation induction, mutagenesis, formation of reactive oxygen species, and immune system suppression; the enzymes involved may also activate certain carcinogens by co-oxidation [reviewed in 3,4]. PGE_2 was higher in colon polyps and adenocarcinomas compared with normal-appearing mucosa from the same patients and mucosa from normal subjects [5]. Epidemiological studies provide evidence that aspirin use is associated with reduced risk for gastrointestinal (esophagus, stomach, colon, rectum) cancer [6–13] and mortality from these diseases [11,14,15]. Decreased risk for premalignant lesions in the colon has also been associated with aspirin use [6,16–18]. Further, aspirin has demonstrated chemopreventive activity in cancer models in the rat colon. Because of its chemopreventive activity in this tissue, colon is the primary site for development of aspirin as a cancer chemopreventive drug.

Besides its activity in rat colon, aspirin has also inhibited the development of carcinoma in hamster buccal pouch, and rat liver and bladder. The animal efficacy results are considered sufficient to support clinical development of aspirin. The CB is also sponsoring an additional animal efficacy study in rat colon exposed to the food mutagen PhIP [19].

A significant effort in the CB program is to identify and validate intermediate biomarkers of cancer. Aspirin has demonstrated activity against

one such putative biomarker, formation of foci of aberrant crypts in rat colon. It is also being evaluated for its ability to modulate other potential intermediate biomarkers in rat colon and bladder.

No preclinical toxicity or pharmacokinetics studies have been sponsored by the CB, and no further testing will be required for regulatory filings. In the clinic, the most significant side effect of chronic administration of NSAIDs, including aspirin, is gastrointestinal (GI) ulceration and bleeding attributed to lowered levels of PGs and thromboxane A_2 (TxA_2) in the gut. PGs promote protective mucin secretion and bicarbonate production, and TxA_2 is involved in platelet aggregation. Like PGs, TxA_2 is formed from arachidonic acid via the cyclooxygenase pathway. This side effect is a potential problem in development of aspirin for chronic administration as a chemopreventive agent. To address this, the CB is currently sponsoring a Phase I safety and pharmacokinetics study with the objective of defining the lowest effective dose of aspirin and evaluating the effects of low doses on drug effect and toxicity parameters.

Four NCI-funded Phase III clinical trials evaluating the potential of aspirin to prevent carcinogenesis in the colorectum and other sites are currently in progress (Table I). Of these, preliminary results from the aspirin component of the Physicians' Health Study demonstrated inhibition of cardiovascular events/mortality. Although no effect on colorectal cancer has been found so far, the optimal treatment duration may not have been attained. A Phase II study has been initiated to determine the effect of low doses of aspirin on a proliferation biomarker ($[^3H]$-thymidine labeling) in the colon of adenoma patients. A future Phase II trial of the combination of aspirin and calcium in the prevention of colon polyp formation is currently under consideration. These trials will be monitored and new Phase II/III trials will be initiated only as necessary to support FDA approval of aspirin as a chemopreventive drug.

A positive result in one of the Phase III trials combined with the results of previous epidemiological studies may be sufficient to support FDA filing for off-label use of aspirin as a chemopreventive drug for colon cancer. Aspirin is widely available as an over-the-counter (OTC) drug in tablets of 80, 325, 500, and 650 mg [20]. Some formulations are buffered or enteric coated. There are no supply problems for aspirin; however, new placebo formulations may be required for some aspirin products (*e.g.*, enteric coated).

PRECLINICAL EFFICACY STUDIES

In studies sponsored by the CB, aspirin (at 200 and 400 mg/kg diet, or *ca.* 0.06 and 0.11 mmol/kg-bw/day) has demonstrated chemopreventive activity against AOM-induced carcinomas in rat colon [21]; in a published study, aspirin (at 250 mg/kg diet) given during promotion inhibited AOM-induced/cholic acid-promoted tumors in the same tissue [22]. In the CB testing program, the drug did not demonstrate chemopreventive efficacy against OH-BBN-induced transitional cell carcinoma in mouse urinary bladder (at 400 or 800 mg/kg diet or *ca.* 0.29 or 0.58 mmol/kg-bw/day) or MNU-induced rat mammary gland tumors (at 200, 400, 800, or 1600 mg/kg diet or *ca.* 0.06, 0.11, 0.22 or 0.44 mmol/kg-bw/day). However, studies in the literature indicate that aspirin was effective in inhibiting rat urinary bladder carcinogenesis initiated with OH-BBN [23] or with FANFT [24–26], alone or promoted with sodium saccharin. In limited studies, aspirin has also been shown to inhibit DMBA-induced carcinoma of hamster buccal pouch [27] and rat hepatocellular carcinoma induced by DEN/CCl_4/2-AAF/PB [28]. The results in animal efficacy studies are sufficient to support the clinical development of aspirin. In addition to the completed studies, the CB is sponsoring a further animal efficacy study against rat colon cancer initiated with PhIP.

A significant effort in the CB program is to identify and validate intermediate biomarkers of cancer and evaluate the potential of chemopreventive agents to modulate these markers. Such studies in animals contribute to the development of more efficient screens for identifying new chemopreventive agents, as well as identifying biomarkers to be used as surrogate endpoints in clinical trials. In a CB-funded study, aspirin (200, 400 mg/kg diet or *ca.* 0.06, 0.11 mmol/kg-bw) demonstrated activity against one such putative biomarker of colon cancer in AOM-treated rats—the formation of foci of aberrant crypts [29]. Published studies have demonstrated inhibition of DMH-induced aberrant crypt foci [30] and DEN/CCl_4/2-AAF/PB-induced hyperplastic nodules and GGT-positive altered foci in rat colon [28,31]. The CB is currently studying the effect of aspirin on other colon biomarkers, including GST-positive foci and other premalignant lesions, and oncogene (*myc*, *ras*, p53) expression. In the rat urinary bladder, a CB-funded study found decreased cells per GGT-positive focus, although the incidence of foci was not affected by aspirin [32].

PRECLINICAL SAFETY STUDIES

Safety There are abundant data available on the safety of aspirin [reviewed in 20,33]. FDA has determined that aspirin is safe and effective for OTC use. Aspirin has been available for non-prescription use worldwide for decades. No additional preclinical safety studies are anticipated.

ADME The pharmacokinetics of aspirin have been studied extensively [reviewed in 20,33]. No additional preclinical ADME studies are anticipated.

CLINICAL SAFETY: PHASE I STUDIES

A CB-sponsored Phase I chemoprevention study of aspirin in patients at high risk for colorectal cancer is near completion (Dr. D. Brenner, University of Michigan). The objectives of the study are to (1) determine the lowest effective daily dose of aspirin required to modulate rectal epithelial PGs and cyclooxygenase mRNA expression after 14 days; (2) describe and quantitate the toxicity of aspirin when administered daily for 14 days; and (3) correlate the plasma pharmacokinetics of aspirin and salicylic acid with inhibition of rectal epithelial drug effect measurements. Preliminary results from this study are discussed below in the appropriate sections, which also include summaries of safety and ADME information from the long history of clinical aspirin use [20,33].

Drug Effect Measurement The drug effect most commonly measured for NSAIDs is inhibition of PG synthesis—primarily as production of PGE_2 and $PGF_{2\alpha}$. The usual adult dose for analgesia or inflammatory conditions is 2.4–4.0 g daily in divided doses [33]. Preliminary results following lower doses in the Phase I trial show 86.5% and 93% inhibition of rectal epithelial PGE_2 and $PGF_{2\alpha}$ levels, respectively, at 2 hours after one 640 mg aspirin dose [34]. Most of the suppression was maintained at 24 hours post-administration (PGE_2, 79.7%; $PGF_{2\alpha}$, 89.2%), although plasma aspirin and salicylic acid were undetectable. No further changes in rectal PG levels were obtained after 14 daily 640 mg doses. Surprisingly, one 80 mg aspirin dose also appeared to produce substantial reductions in both PGs after 24 hours, with further decreases 24 hours after the 14th daily dose. Final data analysis on all dose levels should be completed by Fall 1994.

Safety Aspirin has been well-studied in humans and has a long history of clinical use [20,33]. The most common adverse effects occurring with therapeutic doses (625, 1000 mg daily) of aspirin are GI disturbances such as nausea, dyspepsia, and vomiting. Irritation of the gastric mucosa with erosion, ulceration, hematemesis and melena may occur; slight blood loss may occur in about 70% of patients with most aspirin preparations [20,35], whether buffered, soluble, or plain, and often this is not accompanied by dyspepsia. For example, in the Physicians' Health Study, 325 mg aspirin qod produced a significantly greater incidence of GI bleeding, hematemesis, melena, and epistaxis than placebo after 5 years [36,37]. Slight blood loss is not usually of clinical significance but may cause iron-deficiency anemia during long-term salicylate therapy. Gastric PGs protect the epithelium by increasing secretion of bicarbonate, protecting microvasculature and increasing blood flow, and enhancing repair [38]. In a small published study, gastric juice PGE_2 output was inhibited by 50% at daily aspirin doses as low as 30 mg [35]. However, it has been suggested that aspirin also has direct cytotoxic effects on the gastric mucosa due to increased production of oxygen radicals and leukotrienes [38,39].

Mild chronic salicylate intoxication, or salicylism, occurs at doses of >100 mg/kg-bw qd for 2 days or more [33]. The syndrome consists chiefly of headache, dizziness, ringing in ears, difficulty in hearing, dimness of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasionally diarrhea.

Some evidence of renal toxicity has been found in certain groups, but the risk appears to be small in the general population [40]. Since inhibition of prostaglandins in the kidney produces vasoconstriction, decreased glomerular filtration, hyperkalemia, and salt and water retention, the elderly and hospital patients may be at highest risk. In addition, an epidemiological study correlated an increase in the risk of kidney cancer with daily aspirin use in an elderly population [41]. In the CB-funded Phase I trial, no adverse effects unrelated to rectal biopsy procedures were observed at the high dose (640 mg qd dose level after 7 days). Toxicity results at the lower doses are expected by Fall 1994.

ADME Aspirin in solution is rapidly absorbed from the stomach and from the upper small intestine. About 50% of an oral dose is absorbed in about 30 minutes and peak plasma concentrations are reached in 40–120 minutes [20,42]. Higher-than-normal stomach pH or the presence of food slightly delays absorption.

Preliminary data from the Phase I trial show

comparable values for $t_{½}$ at the 40 and 640 mg doses. Without benefit of statistical analysis, t_{max} appeared to be smaller at the lowest dose, and C_{max} appeared to be dose-related. Final pharmacokinetic data analysis is expected by Fall 1994.

Aspirin is hydrolyzed to the major metabolite salicylic acid by gut epithelium and liver esterases [42]. The metabolite is distributed to all body tissues and fluids including fetal tissue, breast milk, and the central nervous system; however, highest concentrations are found in plasma, liver, renal cortex, heart, and lung [20]. Tissue salicylate concentrations are thought to produce the prolonged effects of aspirin [42–45]. The metabolite is a less potent cyclooxygenase inhibitor, but the plasma and tissue $t_{½}$s are prolonged—from 2–12 hrs depending on the dose [43]. More recent data suggest that salicylate is equipotent to aspirin in inhibition of cyclooxygenase gene transcription, which also contributes to the prolonged antiinflammatory effect [46]. Data from the Phase I trial (see **Drug Effect Measurement** above) confirm the inhibition of rectal PG synthesis for 24 hours following administration of a single dose of aspirin.

From 50 to 80% of the salicylic acid and its metabolites in plasma are loosely bound to proteins. Metabolism to salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acids (less than 1%) occurs primarily in the liver.

Almost all of a therapeutic dose of aspirin is excreted through the kidneys, either as salicylic acid or the above mentioned metabolic products. Renal clearance of salicylates is greatly augmented by an alkaline urine, as is produced by concurrent administration of sodium bicarbonate or potassium citrate. Toxic salicylate blood levels are usually >30 mg/dl.

CLINICAL EFFICACY: PHASE II/III STUDIES

Aspirin is being evaluated primarily as a colorectal cancer chemopreventive drug in four NCI-funded Phase III trials and one Phase II trial (grants). However, two of the Phase III trials (Physicians' Health Study, Women's Health Study) are investigating modulation of cancer incidence at multiple sites.

In 1982, Dr. C. Hennekens (Harvard Medical School) and colleagues began the Physicians' Health Study on β-carotene and low-dose aspirin in 22,071 healthy, male U.S. physicians aged 40–84 years [47–50]. The 2x2 factorial study was designed primarily to determine if 325 mg aspirin qod decreased cardiovascular disease/mortality and if 50 mg β-carotene qod reduced total cancer incidence [48–50]. The aspirin component was terminated in December 1987 after a treatment mean of 5 years due to a significant reduction in risk for myocardial infarction and the confounding practice of prescribing aspirin for those experiencing nonfatal vascular events [36]. In contrast, the aspirin dose and treatment duration did not significantly alter the risk for developing colorectal cancer or polyps [47]; however, it should be noted that this trial was not specifically designed to evaluate this endpoint.

The Women's Health Study, a Phase III trial (Dr. J.E. Buring, Brigham and Woman's Hospital) funded by the NCI and the National Heart, Lung and Blood Institute, is similar in design to the Physicians' Health Study. It is evaluating the effect of 50 mg β-carotene, 600 IU vitamin E, or 100 mg aspirin qod for four years on the incidence of epithelial cancers, especially lung, colon and breast, in female health professionals ≥45 years of age [51]. A second endpoint is alteration of risk for vascular events, such as nonfatal myocardial infarction, nonfatal stroke, and total cardiovascular mortality.

The NCI-supported cooperative group, Cancer and Leukemia Group B (Dr. R. Sandler, University of North Carolina), is investigating prevention of polyps and increase in disease-free survival in patients surgically treated for early stage colorectal cancer [51,52]. Phase III trial participants are being recruited to receive 325 mg aspirin or placebo qd (enteric coated) for four years.

In the fourth Phase III trial, the Polyp Prevention Group (Dr. J.A. Baron, Dartmouth College) is comparing 80 and 325 mg aspirin qd (with and without folate) with placebo in patients diagnosed with colon polyps [51,52]. Participants will be evaluated for polyp recurrence. A future Phase II trial is being considered using a combination of aspirin and calcium carbonate to inhibit polyp incidence.

A significant effort in the CB program is to identify and validate intermediate biomarkers of cancer as potential surrogate trial endpoints. An NCI-sponsored Phase II study (Dr. G. Luk, Dallas V.A. Medical Center) has been initiated to determine the effect of 80 and 325 mg aspirin qd for 3 months on a proliferation biomarker ($[^3H]$-thymidine labeling) in the colons of adenoma patients.

PHARMACODYNAMICS

Five published epidemiological studies suggest that aspirin decreased relative risks for colon can-

cer or death from the disease by 49–60%; however, intake was primarily characterized as frequency within a certain time period rather than as dose [reviewed in 53–55]. Ongoing clinical trials are attempting to define an effective chemopreventive dose which concomitantly decreases the risk of toxicity.

Based on preclinical data, doses of aspirin below those used for inflammation or analgesia may not inhibit colon cancer. The lowest effective dose in the AOM-induced rat colon carcinogenesis model was 200 mg/kg diet (*ca.* 0.06 mmol/kg-bw/day), which is approximately one-half of the rat NOEL of 500 ppm (*ca.* 0.14 mmol/kg-bw/day). The human dose (325 mg qd, or *ca.* 0.026 mmol/kg-bw/day) in two of the Phase III clinical trials (see Table I) is already lower than the effective rat dose, and had no chemopreventive effect in the Physicians' Health Study after five years. However, 200 mg/kg diet was the lowest dose tested in the rat. Two Phase III trials are investigating doses of 100 and 80 mg qd (*ca.* 0.008 and 0.006 mmol/kg-bw/day, respectively) and 100 and 325 mg qod (*ca.* 0.004 and 0.013 mmol/kg-bw/day, respectively), which have less potential for gastric toxicity.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

PG synthesis, primarily of PGE_2 and $PGF_{2\alpha}$, is generally used and well-documented as a drug effect measurement for NSAIDs. General analytical methods for these measurements are well-documented; however, it is critical that procedures for PG measurements are standardized and validated for specific tissues studied in chemoprevention trials, such as colon mucosa.

Toxicology Issues

No further specific toxicology studies will be required for development of aspirin as a chemopreventive agent. However, gastric ulceration and bleeding, induced most probably by inhibition of PG and TxA_2 synthesis (via cyclooxygenase inhibition), is a significant side effect of long-term NSAID therapy. These potentially life-threatening effects are of added importance because they are often asymptomatic [39]. It will be important to develop information that delineates dosage regimens resulting in chemopreventive efficacy and minimal toxicity. Such a dose-titration study is part of a current Phase I trial (Table I, Dr. D. Brenner).

Two additional approaches are use of enteric coated aspirin formulations, or concurrent therapy with anti-ulcer drugs such as the PGE_1 analog misoprostol [38,39]. A recent randomized, placebo-controlled study in arthritis patients receiving long-term NSAID treatment found that misoprostol (0.2 mg qid for 12 wk) significantly lowered the frequency of both gastric and duodenal ulcers [55].

Pharmacodynamics Issues

ADME of aspirin suggests that the highest levels of exposure occur in the colon and bladder. The demonstrated chemopreventive efficacy of aspirin in these tissues suggests that regimens can be designed to minimize gastric ulceration and bleeding while maintaining chemopreventive efficacy.

Regulatory Issues

The actual mechanism for FDA approval of the use of aspirin for chemoprevention of colorectal cancer has not yet been resolved. It is highly probable that FDA would recognize the safety and effectiveness of aspirin for prevention of colorectal or other cancers by including such use in the authorized aspirin product labelling. A key issue is the type and number of Phase III studies required for any such FDA action.

Supply and Formulation Issues

Aspirin is approved for OTC use, and no relevant patent is active for this drug entity. No supply problems are anticipated; however, a new placebo formulation may be required for clinical trials of some aspirin products.

Intermediate Biomarker Issues

Regression of adenomatous polyps can be considered to be a histological intermediate biomarker for colon cancer. It is being used as an endpoint in at least one Phase III study of aspirin (Dr. J. Baron). If the results of this study are used to support regulatory filing for aspirin as a chemopreventive, it is important to insure that the adenomas considered have potential for progressing to frank cancers. It has been suggested that invasive stalk adenomas be evaluated in preference to other types for this purpose.

Evidence from preclinical studies suggests that other types of intermediate biomarkers should be carefully chosen when assessing modulation of colon carcinogenesis by NSAIDs. For example, changes in proliferation biomarkers do not always correlate with decreases in colon tumor incidence or local PG synthesis. Oral aspirin treatment of either control or DMH-exposed rats decreased colon PGE_2 production by *ca.* 96% [56]. In contrast, the NSAID had no effect on mucosal proliferation (measured as [^{3}H]-thymidine incorporation) in the DMH-induced group even though colon adenocarcinoma incidence significantly decreased. Furthermore, aspirin enhanced colon proliferation in the absence of carcinogen. In a related example, indomethacin had no effect on colon PGE_2 synthesis at a dose which reportedly inhibited colon tumor formation [57]; administration of a stable PGE analog did not neutralize the chemopreventive efficacy of indomethacin [reviewed in 56]. Conversely, numerous reports have demonstrated that prostaglandins can inhibit proliferation of animal and human tumor cells *in vitro* and *in vivo* and rat colon mucosa *in vitro* [reviewed in 4]. Thus, the influence of NSAIDs on colon carcinogenesis is complex. The response may depend on the identity of the NSAID or carcinogen, or the dose employed. Differences in the cell populations sampled (*e.g.*, scraping of the entire mucosa) may also be a confounding factor; it has been suggested that host cells rather than tumor cells are the major sources of prostaglandins that contribute to colon carcinogenesis [4]. Finally, the carcinogenic mechanism related to cyclooxygenase activity in the colon may not be related to a direct effect of the PG endproducts. For example, generation of mutagens could be decreased by inhibition of PG synthase-related production of reactive species or co-oxidation of carcinogens. Other possible mechanisms include altered signal transduction or immune response, or induction of apoptosis. Thus, genetic or differentiation biomarkers should be investigated along with proliferation biomarkers as potential surrogate endpoints for clinical trials of aspirin as a colon chemopreventive agent.

A final issue is the standardization, validation, and quality control of intermediate biomarker assays, especially those related to proliferation. A recent conference illustrated the importance of strict criteria for countable crypt columns, a defined minimum number of crypts counted per rectal biopsy, sufficient rectal biopsies per individual to decrease site-to-site variability, and control of external factors such as diet [58–62].

Clinical Studies Issues

Colon carcinogenesis is considered to be the primary target for chemopreventive intervention by aspirin. There are currently four clinical efficacy trials of aspirin in progress. These studies are summarized in Table I and are directed primarily to inhibition of colorectal cancer. The progress of these studies will be monitored, but no further studies of aspirin as a single agent will be initiated unless they are judged to be important to insure regulatory approval. However, a trial investigating prevention of colon polyps with a combination of aspirin and calcium carbonate is under consideration for 1995. This strategy takes advantage of the chemopreventive effect of each agent, while potentially decreasing the necessary individual doses.

New commercial 5-aminosalicylic acid (5ASA) conjugates, such as ursodeoxycholic acid-5ASA, may be considered for future development in place of aspirin. These are being proposed as target-specific alternatives for colon cancer chemoprevention since the 5ASA moiety is released directly in the colon and the ursodeoxycholic acid moiety may alter the luminal equilibrium of bile acids to less toxic metabolites.

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Table I. Clinical Trials of Aspirin Sponsored/Funded by NCI, DCPC

Study No. Title (PI) Period of Performance IND No. (Sponsor)	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase I (Safety, ADME)					
NO1-CN-15336-01 Phase I and Pharmacokinetic Studies of Acetylsalicylic Acid (Dr. Dean E. Brenner, University of Michigan) 9/92– IND 41,243 (CB)	---	Normal, healthy subjects Part 1: 15 subjects Part 2: 15 subjects Part 3: 10 subjects/ dose	Oral Part 1: 640 mg qd for 14 days Part 2: Diurnal and gender effects (no drug) Part 3 (converging dose-seeking protocol): 40, 80, 160, and 320 mg qd for 14 days 8 months (Part 3)	Part 1: Pharmacokinetics; toxicity; drug effect measurements (rectal PGE_2 and $PGF_{2\alpha}$, cyclo-oxygenase mRNA) Part 2: Diurnal and gender variations in drug effect measurements (rectal PGE_2 and $PGF_{2\alpha}$, cyclooxygenase mRNA) Part 3: Minimum dose to modulate drug effect measurements (rectal and platelet PGE_2 and $PGF_{2\alpha}$ and cyclooxygenase mRNA); toxicity; pharmacokinetics	Part 1: Study near completion. Preliminary results show 86.5% and 93% inhibition of rectal epithelial PGE_2 and $PGF_{2\alpha}$ levels, respectively, at 2 hours after the first aspirin dose; suppression was maintained at 24 hours although plasma aspirin and salicylic acid were undetectable. One case of biopsy-related adverse reactions: lightheadedness, bloody stools (Grade 2), and abdominal cramps Part 2: Study completed; preliminary results on 8 subjects suggest no diurnal variation in PG production Part 3: Study will be completed by Fall 1994. Preliminary results show 60–70% inhibition of PGE_2 in 50% of subjects after a single 40 mg aspirin dose and in 60% of subjects after the same daily dose for 14 days Published report: [34]

Table I. Clinical Trials of Aspirin Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No. (Sponsor)	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers)					
UO1-CA-59349 Aspirin, Mucosal Prostaglandins, and Colon Proliferation (Dr. Gordon D. Luk, Dallas V.A. Medical Center) Investigator IND	Colon	Adenoma patients 160 patients	80, 325 mg qd for 3 months	Intermediate biomarker: Rectal mucosa proliferation ([^{3}H]-thymidine labeling) Drug effect measurement: PGs	Study in progress
Proposed Study Colon Polyp Prevention Study with Aspirin and Calcium 1995	Colon	Patients with previously resected colorectal polyps	Aspirin + calcium carbonate 3 years	Efficacy: New polyps and other intermediate biomarkers	Study not designed
Phase III (Efficacy, intermediate biomarkers)					
RO1-CA-59005 Aspirin Prevention of Large Bowel Polyps (Dr. John A. Baron, Dartmouth Medical College) 1992– Investigator IND	Colon	Patients with previous adenomatous polyp 700 patients	Oral 80, 325 mg qd (with and without folate) for 3 years	Efficacy: Polyp recurrence	Study in progress

Table I. Clinical Trials of Aspirin Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No. (Sponsor)	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase III (Efficacy, intermediate biomarkers) *(continued)*					
NCI-P93-0048 Phase III Randomized Chemoprevention Study of Aspirin in Patients with Colorectal Cancer (Dr. Robert S. Sandler, University of North Carolina School of Medicine) Investigator IND	Colon	Surgically treated Dukes' A or B1 colorectal cancer (Stage I, T1–2, NO, MO) 900 patients	Oral 325 mg qd for 4 years	Efficacy: Colon polyp incidence, polyp size, time to recurrence of cancer, disease-free survival, overall survival, toxicity/morbidity of treatment	Study in progress (accrual)
RO1-CA-47988 Randomized, Placebo-controlled Study of β-Carotene, Vitamin E and Aspirin for Chemoprevention of Cancer and Cardiovascular Disease in Women (Dr. Julie E. Buring, Brigham and Women's Hospital) Investigator IND	Epithelial cell origin (breast, lung, colon)	Female health professionals, age ≥45 years 41,600 women	100 mg qod for 4 years	Efficacy: Incidence of epithelial cancer, cardiovascular events and mortality	Study in progress
RO1-CA-40360 A Randomized Trial of Aspirin and β-Carotene in U.S. MDs (Dr. Charles H. Hennekens, Harvard Medical School) 12/81–11/96 Investigator IND	All	Healthy male physicians 22,071 physicians (5,515+/arm)	325 mg qod for 5 years 14 years	Efficacy: Epithelial cancer incidence, cardiovascular disease and mortality Toxicity	Aspirin randomization component ended 1987; however, each subject may continue if they so choose. Preliminary report indicates that aspirin had no effect on colon tumor incidence after up to 5 yrs of follow up, but prevented myocardial infarction. Published reports: [50]

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