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Donald S. Coffey, Program Chairperson
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An Integrated View of the Cancer Cell

SYMPOSIA
The Cell Cycle and Tumor Suppressor Genes
DNA Damage and Repair
Natural Products in Chemoprevention
Ribozymes and Antisense Oligonucleotides and the Alteration of Gene Expression
Genetic Susceptibility to Cancer
Environmental Carcinogens and Their Impact
Cell Surface Glycosylation
Apoptosis
The Biology of Radiation Oncology
Biomarkers of Carcinogenesis
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Gene Therapy in Cancer Clinical Trials
Telomeres and Telomerases
Extracellular Matrix, Gene Expression, and Cell Signalling
Signal Transduction
Angiogenesis
Genes, Development, and Cancer
Growth Factors, Their Receptors, and Differentiation
New Strategies and Targets for Chemotherapy
Genetic Approaches to Invasion and Metastasis
Immunotherapy: Tumor Vaccines
Dietary Intervention in Hormonal Carcinogenesis
The Role of Stromal-Epithelial Interactions in Growth and Neoplasia
Cancer Prevention and Intermediate Biomarkers
Translational Research in Breast Cancer
DNA Methylation

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General, In Situ, and Quantitative PCR (including Differential Display)
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Is Mammography Before Age 50 Beneficial?
What Are the Limits and Benefits of the PSA Assay?
Breast Cancer Prevention: What Will We Advise Women with BRCA1?
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The possibility that aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs) might inhibit certain cancers first arose in the late 1970s when higher concentrations of several prostaglandins, particularly PGE₂, were observed in human tumors of the colon, lung, and breast than were observed in surrounding normal tissue (Cancer Res., 52: 5575–5589, 1992). A series of experiments in rodents, beginning in 1980, showed conclusively that several NSAIDs, including indomethacin, sulindac, piroxicam, and aspirin, consistently inhibited chemically induced colon cancer in the rat. These studies generally involved high doses of NSAIDs other than aspirin. Recent experimental work by B. S. Reddy et al. has added impressive corroborative data on the inhibitory effects of aspirin itself on azoxymethane-induced colon cancer in F344 rats (Carcinogenesis, 14: 1493–1497, 1993). The model of chemically induced colon cancer in rats resembles human colon cancer except for a lower propensity to metastasize. Subsequent work of others in humans and animals has also pointed to beneficial effects of NSAIDs, but epidemiological evidence has been accumulating only recently.

The first epidemiological study suggesting that aspirin use might reduce the risk of colorectal cancer came in 1988 in a retrospective, exploratory analysis from Melbourne, Australia (Cancer Res., 48: 4399–4404, 1988). The study found a 40% lower risk of incident colon cancer among persons who regularly used aspirin (frequency unspecified) compared to those who used no aspirin. The researchers did not link this finding to previous experimental work on NSAIDs nor to case reports regarding sulindac and the inhibition of polyps in familial adenomatous polyposis, and their findings received little attention. In 1989, a prospective study of approximately 14,000 elderly Californians found a small increase, rather than a decrease, in risk among daily aspirin users compared to persons who used no aspirin (RR = 1.5; 95% CI = 1.1–2.2) (Br. Med. J., 299: 1247–1250, 1989). The relative risk of ischemic heart disease was also increased among daily aspirin users.

Not until 1991 did the aspirin hypothesis motivate further epidemiological studies of colorectal cancer. Lynn Rosenberg and colleagues at Boston University observed a lower risk of colorectal cancer among regular aspirin users in the Boston Collaborative Drug Study, an ongoing hospital-based case-control study (J. Natl. Cancer Inst., 83: 355–358, 1991). These authors cited the earlier experimental studies. In their massive Cancer Prevention Study II (CPS-II), epidemiologists Michael J. Thun, Mohan M. Namboodiri, and Clark W. Heath, Jr., with the American Cancer Society, observed a 40% lower risk of fatal colon cancer among persons who used aspirin 16 or more times per month compared to those who used no aspirin (N. Engl. J. Med., 325: 1593–1596, 1991). The CPS-II findings were noteworthy because of the size (over 650,000 adult Americans) and prospective design of the study, and because risk decreased with both the frequency and duration of aspirin use. Subsequent research in CPS-II showed a similar pattern of reduced risk for fatal cancer of the esophagus, stomach, and rectum, but not for other cancer sites (Cancer Res., 53: 1322–1327, 1993). Data relating frequency of aspirin use to risk of colon cancer in men and women enrolled in CPS-II are shown in the chart on the cover. Like other epidemiological studies, CPS-II had only crude information on aspirin use and could not entirely exclude the possibility that pain or bleeding from colon cancer could cause undiagnosed patients to avoid aspirin use, or that bleeding induced by aspirin might cause patients to be diagnosed and treated successfully early in their disease without affecting incidence.

Eight other epidemiological studies have now provided additional data on the aspirin-colon cancer hypothesis. In only one study was aspirin use randomized (J. Natl. Cancer Inst., 85: 1220–1224, 1993); the U.S. Physicians’ Health Study, designed to investigate the primary prevention of cardiovascular disease, found a slight increase in relative risk for invasive colorectal cancer (RR = 1.15, 95% CI = 0.80–1.65) and a slight decrease for in situ cancer or polyps (RR = 0.86, 95% CI = 0.68–1.10) among men randomized according to the use of one adult aspirin every other day compared to use of a placebo. During the five-year follow-up, subjects were not routinely evaluated using sigmoidoscopy or other diagnostic procedures; thus, aspirin-induced bleeding could have caused greater recognition of cancer in aspirin treated subjects, introducing detection bias. In contrast, two other trials that did not randomize aspirin use but evaluated all subjects systematically for the presence of polyps found reduced risk of adenomatous polyps among those who reported aspirin use (J. Natl. Cancer Inst., 85: 912–916, 1993; Br. Med. J., 307: 285–289, 1993). A recently published study of approximately 48,000 male health professionals (Ann. Intern. Med., 121: 241–246, 1994) found reduced risk of both colorectal cancers and adenomatous polyps, and a strong dose-response relationship.

In all, nine of eleven published epidemiological studies show some reduction in risk of either colorectal polyps or colorectal cancer in aspirin users. Two suggest some increase in risk. None of the observational studies is totally conclusive in the absence of experimental data on the efficacy of aspirin in preventing sporadic colorectal cancer in the general population. Clinical trials are needed to assess the efficacy, potential toxicity, optimal drug, and appropriate dose of NSAIDs in the prevention of colorectal polyps or cancer, and further experimental studies are needed to clarify mechanism. The American Cancer Society sponsored a workshop (March, 1994) to bring together researchers from the basic sciences, epidemiology, clinical medicine, and clinical trials to address such issues as the design of such trials in this intriguing area of research.

Dr. Heath, left, has been Vice-President for Epidemiology and Statistics of the American Cancer Society since 1988. He has an M.D. from Johns Hopkins University and is Professor of Community Health at Emory University, Atlanta, GA. He is highly active on many panels and in organizations dealing with public health and has published over 100 articles and book chapters.

Dr. Thun, right, is a graduate of the University of Pennsylvania. He is Director of Analytical Epidemiology and Statistics of the American Cancer Society. He is also active in many advisory capacities and is author or co-author of over 60 articles, book chapters, and proceedings.

We are indebted to Drs. Heath and Thun for information and photographs for this cover feature.

Sidney Weinhouse