

# Chemoprevention of colorectal cancer

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## INTRODUCTION

Colorectal cancer is the third most common cause of cancer-related death in the Western countries, following lung and prostate cancer in men, and lung and breast cancer in women (1). Colorectal carcinogenesis is a multistep process characterized by the successive accumulation of cancer-associated mutations (2). In greater than 95% of cases, an adenomatous polyp is the predecessor of a colorectal cancer (3), making the presence of a colorectal adenoma the best known predictive biomarker for the development of these malignancies (Figure 1). The rate at which adenomatous polyps progress to cancer is estimated at about 2.5 polyps per 1,000 per year (4). Approximately 50% of men and 30% of women develop adenomatous polyps of the colon by age 50 (5, 6), and the lifetime incidence of colorectal cancer in Western populations is approximately 6% (1). Removal of adenomatous polyps (pre-malignant lesions) through colonoscopy with endoscopic polypectomy is an effective method of cancer pre-

vention (7), but it is invasive, costly, and not utilized on a population basis. Other strategies include prevention of the development of colorectal polyps and colorectal cancer through chemoprevention in the hope to reduce the need for colonoscopy in individuals with colorectal adenomas.

## PREDICTORS OF COLORECTAL CANCER RISK

The identification of a surrogate endpoint biomarker (SEB) is important to the development of cancer chemoprevention methods. The ideal SEB is the one that can be measured with minimal morbidity in pre-malignant tissue and that accurately predicts colorectal cancer risk. Molecular analysis of colorectal neoplasia indicates that pre-malignant changes occur in the gastrointestinal epithelium long before an adenoma develops (2). These genetic changes may be modulated through exogenous factors (examples: changes in diet, or use of chemopreventive drugs) (8, 9).

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## COLORECTAL CANCER PREVENTION

### Endoscopic Polypectomy

Endoscopic polypectomy is the only known effective method of primary prevention for colorectal carcinoma (10–14). In the National Polyp Study, 1,418 patients were followed-up for an average of 5.9 years after colonoscopic clearance of adenomas. These individuals had age- and sex-adjusted rates of colorectal cancer that were 76–90% lower than expected from comparison with reference groups who had not undergone surveillance (14).

### Chemoprevention of colorectal cancer:

#### Non-steroidal antiinflammatory drugs

Chemoprevention refers to the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the evolution into invasive cancer. Non-steroidal antiinflammatory drugs (NSAIDs) are one of the most promising classes of chemopreventive agents, as demonstrated by three well-established lines of evidence – *in vivo* models, human observational studies, and non-randomized human interventional research.

In several different animal models of colon cancer, NSAIDs (e.g. sulindac) inhibit tumour formation (15–17). Patients with familial adenomatous polyposis (FAP), who develop colorectal cancer as a result of a germline mutation in the APC gene, demonstrate regression of rectal adenomas with administration of sulindac (9, 18, 19). A series of observational studies (20–25) have investigated the relationship between aspirin/NSAIDs and sporadic colorectal neoplasia using case-control, nested case-control, and prospective study designs. All but one study suggest that NSAIDs are effective in preventing human colorectal adenoma incidence, carcinoma incidence, and/or cancer-associated mortality, regardless of age, gender, affected colorectal segment, or other underlying risk factors (e.g., diet, history of prior adenomas, socioeconomic status). The preventive effects of aspirin/NSAIDs may require extended periods of exposure, as most investigations reported

efficacy only within those using drugs for more than 8–10 years.

### Cyclooxygenase-2 and colorectal cancer

Cyclooxygenase is a key enzyme in the formation of prostaglandins. The enzyme is expressed in two forms, COX-1 and COX-2. Overexpression of COX-2 is observed in human and animal colon cancers (17, 26–28). Overexpression of COX-2 in rat intestinal epithelial cells is associated with resistance to apoptosis, an effect that is overcome by treatment with non-selective NSAIDs, such as sulindac (29). This relationship between COX-2 and apoptosis may also be valid *in vivo*, as sulindac induces apoptosis of intestinal epithelial cells of humans with FAP (30). In a murine model of FAP, abnormalities of both proliferation and apoptosis in the pre-neoplastic intestinal epithelium are normalized by administration of non-selective NSAIDs (31). It should be noted, however, that NSAIDs also inhibit carcinogenesis via COX-independent mechanisms. For example, sulindac sulfone, a metabolite of sulindac that does not inhibit COX-1 or COX-2, is chemopreventive in rat models of mammary and colon carcinogenesis (32, 33).

An agent used for prevention of colorectal adenomas in the general population must have very low toxicity. In addition to blocking the activity of COX-2, aspirin and other NSAIDs previously evaluated for colorectal cancer prevention also inhibit COX-1, the constitutively-expressed form of the enzyme. Unlike COX-2, which is induced in response to inflammation or mitogenic stimuli, COX-1 is constitutively present in tissues such as stomach, kidney, and platelets, where prostaglandins are necessary for normal physiologic function (34).

### Safety issues with aspirin/NSAIDs/COX-2 inhibitors

The benefit of chemoprevention should largely exceed the potential risks (adverse events under treatment) of therapy. Recently a series of articles has been published describing unexpected adverse cardiovascular effects of COX-2 inhibitors. These

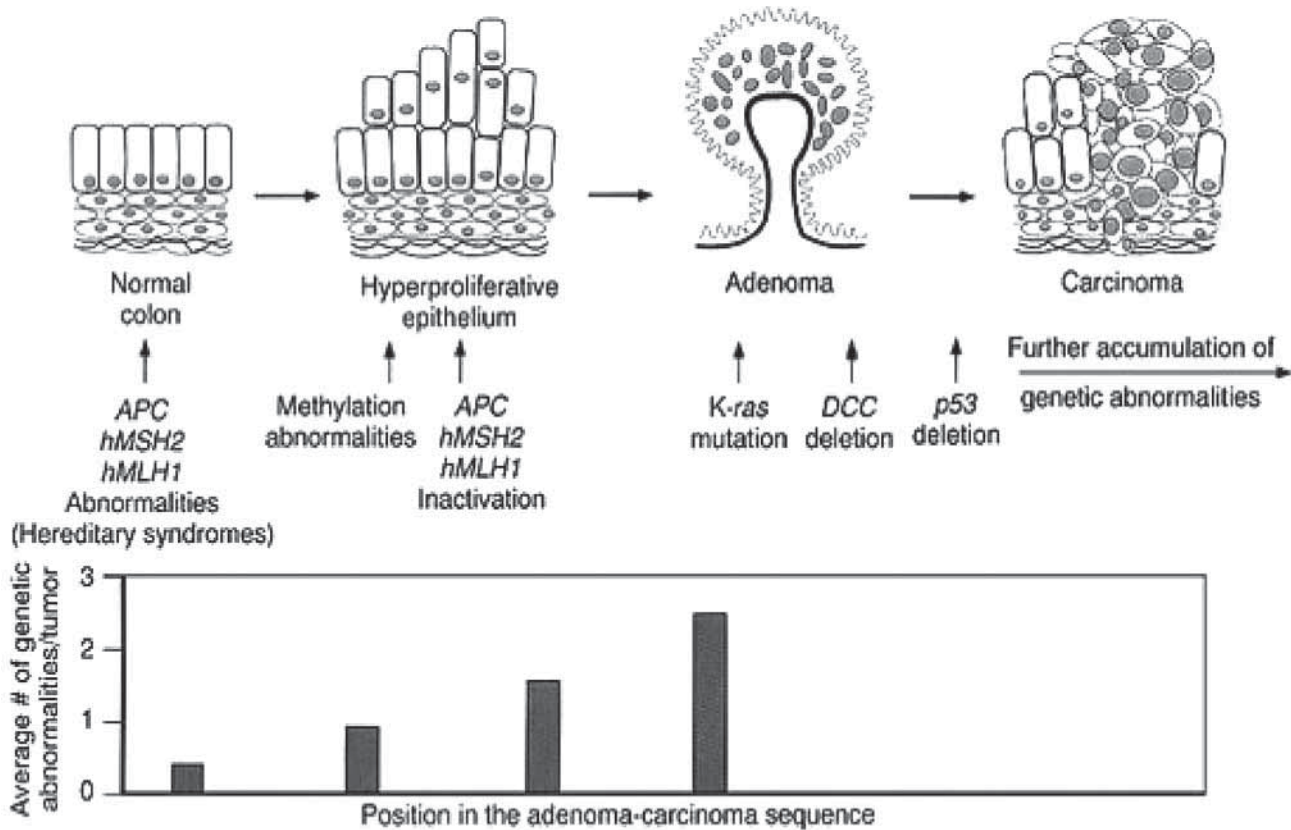


Figure 1. Adenoma-carcinoma sequence (according to Gottlieb, Spokane, USA).

cardiovascular toxicities raise important questions. Because we have a well-established option for the prevention of colorectal cancer (colonoscopy with endoscopic polypectomy), it is not justified to use these agents for the chemoprevention of sporadic colorectal cancer. Chemopreventive treatment should therefore not replace colonoscopic screening and surveillance. Patients who avoid colonoscopic examinations because of chemopreventive treatment may be increasing their colorectal cancer risk. Finally, the risk attached to treatment may outweigh the benefit to a few patients. The place of chemoprevention in colorectal cancer cannot be defined at the present time (35–39).

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