Genetic Syndromes as Potential Targets for Chemoprevention of Colorectal Neoplasia

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Abstract   Colorectal cancer is the second leading cause of cancer death in the United States (Landis et al. [1998] CA 48:6–29) and is the most common cancer in Israel (Muir et al. [1997] International Agency for Research on Cancer, Lyon, France). In the United States, it is estimated that 130,000 individuals will be diagnosed with colorectal cancer in 1999 and that 57,000 individuals will die from this disease. In Israel, approximately 2,000 individuals are diagnosed with colorectal cancer each year (Landis et al. [1998] CA 48:6–29). The incidence rate varies considerably in different population groups, viz. 21.1/100,000 among Jews born in Europe or North America, 19.3/100,000 in Jews born in Israel, 12.1/100,000 among Jews born in Africa or Asia (Muir et al. [1997] International Agency for Research on Cancer, Lyon, France). J. Cell. Biochem. Suppl. 34:19–22, 2000.   © 2000 Wiley-Liss, Inc.

Key words: chemoprevention; colorectal neoplasia; genetics

RISK FACTORS FOR COLORECTAL CANCER

As indicated in Table 1, risk factors include age, family history, dietary and life style factors, inherited predisposition, and chronic inflammatory bowel disease [Potter, 1996; Potter et al., 1993]. However, the majority of cases (80%) arise in individuals without a clearly recognizable risk factor.

The categories of familial risk that contribute to a higher incidence of colorectal cancer are as follows.

Rare Syndromes

While familial clustering of colon cancer is common [Fuchs, 1994], only a small fraction of familial cases arises from the well described cancer syndromes of familial adenomatous polyposis and hereditary non-polyposis colorectal cancer. Familial adenomatous polyposis accounts for about 0.5% of colon cancer cases while hereditary nonpolyposis colorectal cancer (HNPCC) has been estimated to account for between 3% and 5% [Burt, 1996]. (Fig. 1). The genetic defect in FAP is a mutation of the APC gene on the long arm of chromosome 5 (5q21–

22). It manifests itself in the formation of hundreds to thousands of adenomas in the colon and rectum of adolescents and young adults. Over a life time, cancer risk is about 100% and is related to the large numbers of adenomas present.

HNPCC Patients and Age

Patients with HNPCC also have a high risk of colorectal cancer which often presents at a young age and characteristically is right-sided in the colon. Adenomatous polyps are not abundant in the colon of these patients. HNPCC is caused by germline mutations in any of four genes (hMSH2, hMLH1, hPMS1, and hPMS2) which result in defective repair of mismatched DNA base pairs during replication. The phenomenon of microsatellite instability found in most patients with HNPCC and in 15% of sporadic cancers is identified by assays to detect abnormalities in short tandem repeat sequences (microsatellites). Rapid progression to carcinoma occurs from the adenomas in this condition [Reale, 1996]. Despite the presence of adenomas which are the phenotypic hallmarks of predisposition to colorectal malignancy, the rarity of these conditions, particularly in FAP, makes these conditions of great interest for chemoprevention research.

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TABLE I. Risk Factors for Colorectal Cancer

Average
  Age over 50 years
  —high fat, low fiber/vegetable intake
  —tobacco
  —excess alcohol, calories; obesity
Moderate
  —Personal history of colorectal adenomas
  —Family history of colorectal adenomas or
    colorectal cancer
High
  —Hereditary syndromes
  —Hereditary nonpolyposis colorectal cancer
    (Lynch Syndromes)
  —Familial adenomatous polyposis
  —Gardner's syndrome
  —Turcot's syndrome
  —Peutz-Jeghers syndrome
  —Familial juvenile polyposis
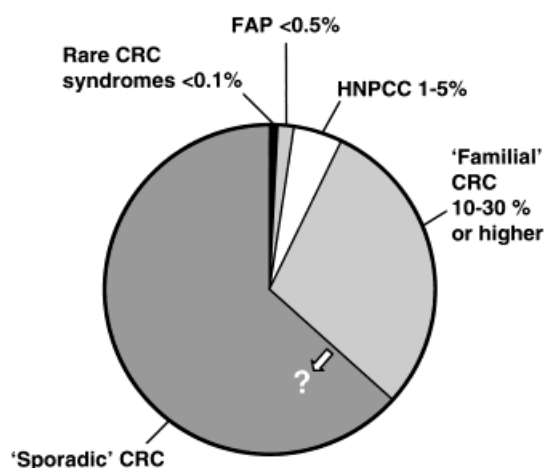 —Chronic inflammatory bowel disease

Fig. 1. Familial causes of colorectal cancer. The rare colorectal cancer (CRC) syndromes include the hamartomatous polyposis conditions and other extremely rare diseases. Familial adenomatous polyposis (FAP) accounts for about 0.5% of cases and hereditary nonpolyposis colorectal cancer (HNPCC) for 1-5%. Epidemiologic studies suggest that familial CRC outside the well-defined syndromes involves 10-30% of cases. Pedigree studies that include adenomatous polyps suggest that this proportion is much higher and that familial factors, probably inherited, may be present in the majority of colonic neoplasms.

Common Familial Clustering

Most familial cases do not fit into the well-characterized syndromes described in the previous two catagories. About 10% of persons in Western countries have a first-degree relative affected with colorectal cancer. Approximately 20% of individuals with large bowel cancer have an affected first-degree relative. A two- to three-fold increased risk is consistently observed in first degree relatives of persons with large bowel cancer [Winawer, 1996]. A similar cancer risk can be measured in first-degree relatives of persons with large bowel adenomas [Winawer, 1996]. An increased risk of adenomas is also observed in first degree relatives of those with colon cancer [Bazzoli, 1995]. The observed familial occurrence may arise from an inherited susceptibility that interacts with environmental factors, possibly dietary in nature. This type of inheritance appears to be a factor in 10–30% of colorectal cancer.

CHEMOPREVENTION IN LARGE BOWL CANCER

Cancer chemoprevention is defined as the use of specific chemical compounds to prevent, inhibit or reverse carcinogenesis [Kelloff, 1996]. Chemoprevention in large bowel cancer may be applied to suppress adenoma formation and may also extend to adjuvant therapy after colon cancer resection [Sinicrope, 1996]. The mechanisms of chemopreventive activity are summarized in Table 2.

TABLE II. Mechanisms of Chemopreventive Activity[a]

- Inhibit carcinogen uptake
- Inhibit formation and activation of carcinogen
- Deactivate or detoxify carcinogen
- Prevent carcinogen binding to DNA
- Increase level or fidelity of DNA repair
- Scavenge reactive electrophiles or oxygen radicals
- Inhibit arachidonic acid metabolism
- Modulate signal transduction
    Inhibit protein kinase C or tyrosine kinases
    Modulate hormonal or growth factor activity
    Inhibit oncogenes (tyrosine kinase, ras isoprenylation)
    Inhibit polyamine metabolism
- Induce terminal differentiation
- Restore immune response
- Increase intercellular communication
- Restore tumor suppressor function
- Induce programmed cell death (apoptosis)
- Correct methylation imbalances
- Inhibit basement membrane degradation
- Activate antimetastasis genes

[a]Reprinted with permission of Kelloff GJ, Boone CW, Sigman CC, Greenward P. Chemoprevention of Colorectal Cancer. In: Prevention and Early Detection of Colorectal Cancer, (eds) Young GP, Rozen P, Levin B, W.B. Saunders, London, England, 7:115–139, 1996.

INTERMEDIATE BIOMARKERS

Because of the length of time (5 to 15 years) for transformation of adenomas to cancer, a major thrust of chemoprevention drug development has been to identify surrogate endpoints for cancer incidence. Such intermediate biomarkers can then be used in phase II trials. Much attention has been focused on the adenoma as such a marker. Other intermediate end-points include markers of cellular proliferation and differentiation, and gene expression [Kelloff, 1996].

Patients with a history of adenomatous polyps including familial adenomatous polyposis, have been obvious candidates for chemoprevention studies since their risk of developing new adenomas is significant. Several chemoprevention trials with adenoma recurrence as a major endpoint have been conducted or are being conducted in patients with a history of sporadic adenoma. These trials include calcium carbonate, folic acid, difluoromethylornithine (DFMO), β-carotene, the combination of vitamin E and vitamin C, and aspirin. In patients with familial adenomatous polyposis, the administration of the NSAID, sulindac has been shown to produce a decrease and size in number of adenomas [Giardiello, 1993]. Sulindac sulfone, a metabolite of sulindac, may exert its effect not by inhibition of proliferation but by induction of apoptosis [Van Stolk, 1998].

CYCLOOXYGENASES AS TARGETS FOR CHEMOPREVENTION

A variety of cancers form more prostaglandins than the normal tissues from which they arise [Rigas, 1993]. The increased amounts of prostaglandins in tumors arise from enhanced synthesis which occurs as a result of cyclooxygenase-catalyzed metabolism of arachidonic acid. Prostaglandins are synthesized from arachidonic acid by two different isoforms of cyclooxygenases, viz. COX-1 and COX-2. COX-1 is a constitutive isoform whereas COX-2 is not detectable in normal tissues but is induced by cytokines, oncogenes, and growth factors [DuBois, 1994].

Epidemiological studies have shown that chronic intake of NSAIDs which interfere with prostaglandins synthesis, reduces the incidence of colorectal cancer [Thun, 1991], although this finding has not been confirmed in randomized trials [Sturner, 1998]. Almost all currently commercially available NSAIDs inhibit both COX-1 and COX-2 by competing with arachidonate for binding to the cyclooxygenase active site. Because of interference with COX-1, the use of NSAIDs has been limited by serious adverse effects such as nephrotoxicity and peptic ulcer disease.

Selective inhibitors of COX-2 have now been developed which block the synthesis of prostaglandins responsible for inflammation without limiting basal production of prostaglandins that are protective of the gastric mucosa and renal blood flow [Masferrer, 1994]. These are now under trial in populations with familial adenomatous polyposis and hereditary non-polyposis colorectal cancer and will soon be studied in individuals who have had prior sporadic adenomas.

COMBINATION THERAPY WITH CYCLO-OXYGENASE 2 INHIBITORS

COX-2 is induced by numerous agents that activate tyrosine kinase signaling such as EGF, Src and Ras. Naturally occurring inhibitors of tyrosine kinase also inhibit COX-2 expression [Blanco, 1995]. Retinoids block the formation of downstream targets of tyrosine kinases (Karin, 1995]. Specifically, all trans retinoic acid, 13-cis retinoic acid, and retinyl acetate suppress phorbol ester and EGF-mediated induction of COX-2 and prostaglandin production [Mestre, 1997; Subbaramaiah, 1997]. Retinoids of low toxicity may be suitable for combination with selective COX-2 inhibitors.

Recent data suggests that COX-2 overexpressing cells produce proangiogenic factors and stimulate both endothelial migration and endothelial tube formation [Tsujii, 1998]. This effect is inhibited by a selective COX-2 inhibitor and by aspirin. Treatment of endothelial cells with aspirin or a COX-1 antisense oligonucleotide inhibits COX-1 activity and suppresses endothelial tube formation. Future therapies may combine COX-1 inhibitors (with gastric cytoprotection) with selective COX-2 inhibitors.

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