Chemoprevention of GI Cancers with Dietary Agents: Are We There Yet?

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Despite exponential gains in our knowledge about its pathogenesis, gastrointestinal (GI) cancers continue to be one of the most devastating of the cancers prevalent in Western countries. More than 70 percent of GI cancers are sporadic, with no known family history. An increasing body of literature also indicates that specific dietary agents may help to reduce the risk of GI cancers, especially colorectal cancers (CRC). Cancers occur due to dysregulation (up-regulation) of multiple growth stimulatory signaling pathways; dietary agents block many of the up-regulated pathways, which contributes to their chemopreventative effects. Thus, a major change in dietary habits/life styles may help to reduce the risk for developing GI cancers, especially colorectal cancers (CRCs).

GI Cancers

Cancers of the gastrointestinal (GI) tract include cancers of the colon, rectum, anus, liver, gallbladder, pancreas and other digestive organs, with a total incidence of 263,060 cases and 136,180 deaths during 2006 in the U.S. (1) Among these, perhaps pancreatic cancer is the worst with 33,730 total annual cases and 32,300 deaths. Colorectal cancer, the third most common cancer diagnosed in the U.S., develops through a multistep process that involves transition from normal mucosa to adenomatous polyps (adenoma) and eventually to adenocarcinomas and invasive carcinoma. It is estimated that 5 percent to 10 percent of all cancers are due to inherited gene defects, while more than 70 percent are sporadic in nature with no known family history. Syndromes with a genetic pre-disposition for CRCs have been described, which include Lynch syndrome (or hereditary nonpolyposis colorectal cancer; HNPCC), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), Peutz-Jeghers syndrome, and juvenile polyposis syndrome. Hereditary diffuse gastric cancer and familial pancreatic cancers have also been noted. HNPCC is caused by mutation of MLH1 or MLH2 DNA repair genes, FAP by mutation of adenomatous polyposis coli (APC) gene, and MAP by mutation of MYH gene. Patients with genetic mutations exhibit increased risk for developing cancers. For instance, patients with HNPCC have an 80 percent life-time risk for developing colon cancer.

Molecular Targets

Extensive research suggests that most cancers (familial and sporadic) are a result of dysregulation of as many as 300 to 500 gene products. These include growth factors (e.g., EGF, VEGF IGF-1, progastrin), growth factor receptors (e.g., EGF receptors, IGF-1R), protein kinases (e.g., src), GTP binding proteins (e.g., Ras), inflammatory cytokines (e.g., TNF, IL-1, IL-6), inflammatory enzymes (e.g., COX2, 5-LOX, PLA2), pro-apoptotic proteins (e.g., TNF, Fas, TRAIL), anti-apoptotic proteins (e.g., bcl-2, bcl-xL, cFLIP, IAP-1, IAP-2, survivin), tumor suppressors (e.g., p53, Rb), and transcription factors (e.g., NF-κB, β catenin, AP-1, STAT3, HIF-1, PPAR-γ). Cell-signaling pathways, associated with these molecules, have been linked with GI cancers as well.

Perhaps one of the most important pathways in GI cancers is the pro-inflammatory pathway activated through NF-κB. This transcription factor is activated by many risk factors linked to GI cancers including grilled meat, fried foods, saturated fatty acids, chemical and physical stress, environmental pollutants, viruses (e.g., hepatitis A, B or C virus) and bacteria (*Helicobactor pylori*). (2) Furthermore, constitutively active NF-κB has been encountered in most GI cancers.

Figure 1: Dietary Agents

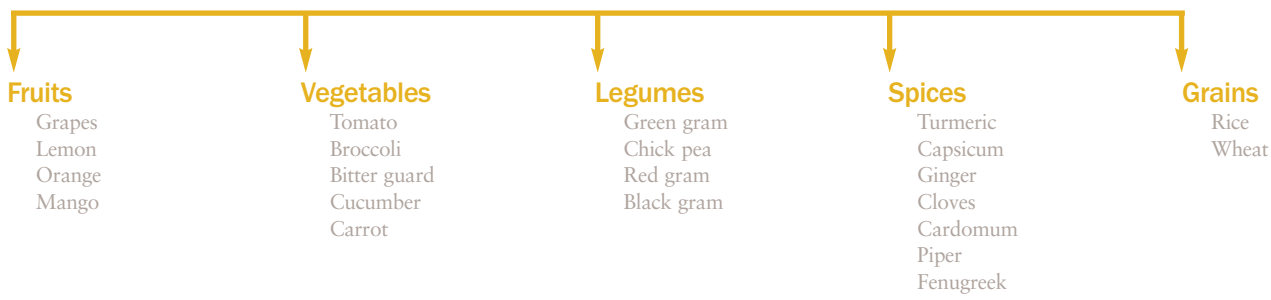
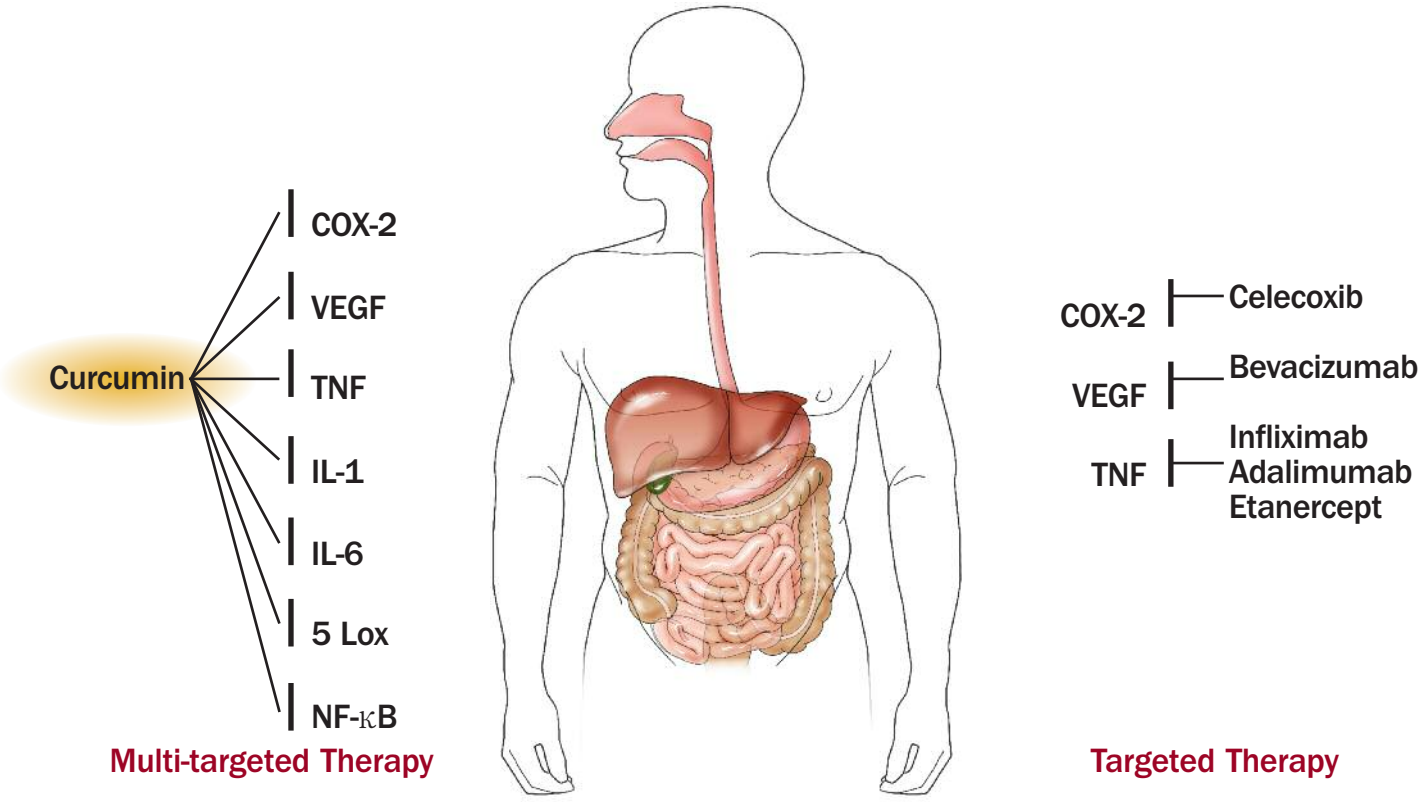


Figure 2: Curcumin For Multi-Targeted Chemoprevention Of GI Cancer



Once activated, NF-κB regulates the expression of gene products that mediate survival (e.g., the anti-apoptotic proteins bcl-2, bcl-xL, cFLIP, IAP-1, IAP-2, and survivin), proliferation (COX2, c-myc and cyclin D1), invasion (5-LOX, MMP-9, ICAM-1, ELAM-1 and VCAM-1) and neo-angiogenesis (e.g., VEGF, IL-8, TNF and IL-1. (3) Most currently employed approaches for the treatment of GI cancers involves targeted therapies, e.g., inhibitors of COX2, VEGF and EGFR. Such therapies are unlikely to prevent or ameliorate the disease when the GI cancers are result of dysregulation of multiple gene products. These treatments are expensive and have numerous side effects. (4-7) Thus, a multi-targeted approach is required for both prevention and treatment. Also, it is worth noting that the same molecular targets are used for preventative or treatment strategies. (8, 9)

Role of Dietary Agents

Most sporadic cancers, and GI cancers in particular, are considered preventable diseases. There are numerous reasons for this belief. First, GI cancers are more common in developed countries than in developing countries. For instance the incidence of colorectal cancer in India is less than a tenth that in the U.S. Second, grilled meat and fried foods, environmental pollutants, and certain viruses and bacteria have been linked to tumorogenesis of the GI tract in rodent models. Third, dietary components derived from fruits and vegetables have been shown to suppress carcinogenesis in animals. Fourth, epidemiological studies and limited clinical trials in humans suggest a role for fruits and vegetables in the prevention of GI cancers.

What is there in fruits and vegetables that prevents cancer and what are the mechanisms which mediate the beneficial effects, are major issues in cancer prevention. (2) The foods and the active agents that have been so far linked with prevention of GI cancers include resveratrol from grapes, peanuts and berries; catechins from tea; genistein from soybean; caffeic acid from mustard seeds, olive oil from olives; curcumin from turmeric; quercetin from onions; ellagic acid from pomegranate; diallyl disulfide from garlic; sulforaphane from broccoli; lycopene from tomato; and indole-3-carbinol from cruciferous vegetables (Fig. 1). Extensive studies have provided proof of concept that these agents may have protective effects against GI cancers and that they mediate their effects by targeting multiple molecular targets.

Curcumin gives curry powder (turmeric) its yellow color, and is the dietary agent about which we know most with respect to GI cancers (Table 1). Its active ingredient has been identified as diferuloylmethane. Curcumin has been shown to protect animals from a wide variety of carcinogens that cause GI cancers (Table 1A). The protective effects of curcumin have also been reported in patients with Crohn's disease, ulcerative colitis, FAP, irritable bowel disease (IBS) and tropical pancreatitis (Table 1B). For instance, in one clinical trial of five FAP patients there was an ~60% decrease in polyp number and 50% decrease in polyp size from baseline after treatment with curcumin. (10) A similar

study involving 77 patients treated with celecoxib showed only 28% and 30% reduction in polyp number and burden, respectively. (11) Additionally, in countries such as India where curcumin is consumed several times daily, the incidence of GI cancers is very low.

The mechanisms mediating the inhibitory effects of curcumin have been extensively investigated (Fig. 2). (12) Our group showed that curcumin down-regulates the activation of NF-κB (13), thus leading to down-regulation of anti-apoptotic, cell proliferative, invasive and angiogenic gene products. (14) Besides NF-κB, curcumin also suppresses the activation of STAT3 (15), HIF-1 (16) and PPAR-γ. (17) Curcumin down-regulates the activity and expression of both COX2 and 5-LOX (18), down-regulates the expression of TNF, IL-1 and IL-6; and inhibits EGF receptor signaling. (19) In spite of interfering with all these targets, curcumin has been found to be pharmacologically safe at very high doses, with no dose-limiting toxicity. (20)

Overall from this brief perspective, it is clear that dietary agents have great potential for both prevention and treatment of GI cancers. These agents may provide safe, inexpensive and effective solutions to the problem. Thus an "old-age" disease, such as GI cancers also responds to an "age-old" cure. ❖

Table 1: Preclinical and clinical evidence that curcumin exhibits chemo-preventive effects against GI cancers

A. Preclinical

Cancer	Carcinogen	Animal
Aberrant crypt foci (ACF)*	Azoxymethane	Rat
Colon cancer	Azoxymethane	Mice
Colon cancer	DMH	Mice
Colon cancer	Azoxymethane	Rat
Colon cancer	Azoxymethane	Rat
Colon cancer	PhIP	Apc (min) mice
Colon cancer	Azoxymethane	Rat
Colon cancer	Azoxymethane	Rat
Colon cancer	1,2-dimethylhydrazine	Rat
Colitis	TNBS	Mice
Colitis	DNB	Mice
Colitis	TNBS	Mice
Ulcerative colitis	DNCB	Rat
Duodenal tumor	MNNG	Mice
Esophageal cancer	NMBA	Rat
FAD*	Azoxymethane	Mice
FAP*	—	Min/+ mice
Forestomach neoplasia	B[a]P	Mice
Forestomach cancer	B[a]P	Mice
Forestomach neoplasia	B[a]P	Mice
Stomach cancer	MNNG	Rat

B. Clinical

Disease	Patients	End point modulation
Crohn's disease	5	Improved symptoms
FAP	5	Decrease in the number of polyps (60.4%) Decrease in the size of polyps (50.9%)
IBS	207	Reduced symptoms
Ulcerative colitis	89	Low recurrence; improved symptoms
Tropical pancreatitis	20	Reduction in the erythrocyte MDA levels Increased in erythrocyte GSH levels
CRC	12	Decreased MIG DNA adducts
CRC	15	Decreased leukocyte COX-2 activity
CRC	15	Lowered GST
CRC	15	Lowered inducible serum PGE2 levels
Liver metastases of CRC	12	Low bioavailability

Note: FAP: familial adenomatous polyposis; ACF: Aberrant crypt foci; FAD: focal areas of dysplasia; B[a]P: benzo[a]pyrene; PhIP: 2-amino-1-methylimi-dazo[4,5-b]pyridine; DMH:Dimethylhydrazine; TNBS: Trinitrobenzene sulphonic acid; DNB: Dinitrobenzene sulfonic acid; DNCB: 2,4-dinitrochlorob-enzene; MNNG: N-Methyl-N'-nitro-N-nitrosoguanidine; NMBA: N-nitrosom ethylbenzylamine; IBS: Irritable bowel syndrome; CRC: Colorectal cancer (for references, please ref. 19).

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