decarboxylase, dopamine-β-hydroxylase and phenylethanolamine-N-methyltransferase were expressed in cultured colon cancer cells (HT-29 and SW1116). Inhibition of TH reduced adrenaline release concomitant with inhibition of cell proliferation of HT-29 cells. β_2-selective antagonist ICI 118, 551 not only inhibited the basal cell proliferation but also abolished the stimulatory action of adrenaline on cell growth. In the colon cancer xenograft model, HT-29 cells were implanted subcutaneously into the right flank of athymic nude mice. Mice were randomized to different treatment groups that received either tap water or nicotine in their drinking water. Tumor volume was measured. The concentrations of adrenaline and cotinine in plasma were determined by enzyme immunoassays. The expression of β-adrenoceptors was detected by reverse transcription-polymerase chain reaction. Results showed that nicotine treatment in drinking water did not affect the body weight and drinking solution consumption. However it promoted tumor growth when compared to the control group drinking tap water. Oral nicotine administration resulted in dose-dependent elevations of adrenaline and cotinine levels in plasma. Nicotine also increased β_1- and β_2-adrenoceptors expression in the tumors. β_2-selective antagonist blocked the stimulatory action of nicotine dose-dependently on tumor growth. In connection with this animal study, β-adrenoceptors and catecholamine-synthesizing enzymes were highly expressed in more than 80% of the surgical specimens in colon cancer patients. Taken together, our findings show that adrenaline contribute to colon cancer cell proliferation through the β_2-adrenoceptors-mediated pathway. Nicotine from cigarette smoke could modulate this biological process and promote cancer growth. These data suggest that tobacco-related carcinogenesis is probably mediated through β-adrenoceptors signaling pathway and this opens up a new avenue for colon cancer prevention and treatment especially in smokers.

Acknowledgements

This study was supported by the Hong Kong Research Grants Council, Hong Kong, China.

Chemoprevention of gastrointestinal cancer

JOHN A. BARON

Departments of Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA and Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA

Digestive tract cancers have been the subject of considerable research regarding chemopreventive interventions, arguably more than for any other organ system. Although there are essentially no promising leads for pancreatic cancer, there are indications that chemoprevention of other digestive tract malignancies might actually be possible.

The colorectum is the most studied digestive tract organ regarding chemoprevention [1]. Supplementation with relatively high doses of beta carotene, alpha tocopherol or ascorbic acid has not reduced risk of colorectal cancer or adenomas [1,2]. However, in a secondary analysis of a small skin cancer prevention trial, one "antioxidant," selenium, was apparently protective against colorectal cancer. Trials of cereal fiber supplements have showed no substantial effect on adenoma risk, and ursodeoxycholic acid seems at best to provide limited benefits. Emerging data regarding folate are also discouraging.

On the other hand, at least two interventions do appear to have chemopreventive efficacy in the colorectum. Clinical trials have shown that calcium supplementation reduces the risk of adenomas, and epidemiological data suggest that there is a similar effect for colorectal cancer itself. Extensive epidemiological and clinical trial data also support the efficacy of non-steroidal anti-inflammatory drugs.

For cancers of the upper luminal GI tract, observational studies suggest that NSAIDs have

Correspondence: John A. Baron, Departments of Medicine, and Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, USA. E-mail: John.A.Baron@Dartmouth.edu

ISSN 0284-186X print/ISSN 1651-226X online © 2007 Taylor & Francis
DOI: 10.1080/02841860701245884

promise, but the only clinical trial that has reported relevant data (for the esophagus) was negative [1]. H. Pylori eradication with antibiotics shows suggestions of benefit for carcinoma of the stomach, but the findings have not been consistent [1]. In one trial, supplementation with a combination of beta carotene, vitamin E, and selenium reduced risk of stomach cancer. Other agents, including nutrient mixtures and Asian traditional medicines have been tested in clinical trials focusing on the stomach or esophagus, but the findings have not been replicated [1].

Although definitive clinical trial data are still lacking, it seems likely that HBV vaccination will decrease liver cancer risk [1]. Interferon also may decrease cancer risk in patients with cirrhosis and hepatitis C [1]. Several other agents have been tested in trials, sometimes with positive results, but the findings remain isolated or have only been conducted in an adjuvant setting [1].

The interpretation of many of the chemoprevention trials is not straightforward. The vast majority of the studies have studied patients with a history of pre-invasive lesions, and the endpoints have typically been progression/regression or recurrence of the pre-invasive lesions, not cancer. This strategy focuses on the pre-invasive stages of carcinogenesis, and the results may not apply to cancer itself. For example, the small adenomas that comprise most of the endpoints in colorectal studies are themselves not particularly aggressive, and more prolonged intervention than is usually sustained in these trials might be required for a beneficial impact to emerge. Some of the trials used synthetic agents in high doses. Nonetheless, recent trials have helped establish that some agents can interfere with carcinogenesis in the large bowel, raising hopes for effective chemoprevention.

In summary, it is likely that chemoprevention of several gastrointestinal cancers will be possible. Further research will have to assess whether the interventions that reduce risk are cost effective.

References

[1] Grau MV, Rees JR, Baron JA. Chemoprevention in gastrointestinal cancers: Current status. Bas Clin Pharmacol Toxicol 2006;98:281–7.

[2] Bjelakovic G, Nagorni A, Nikolova D, Simonetti RG, Bjelakovic M, Gluud C. Meta-analysis: Antioxidant supplements for primary and secondary prevention of colorectal adenoma. Aliment Pharmacol Ther 2006;24:281–91.