Chemoprevention of Gastrointestinal Cancer: The Reality and the Dream

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Despite substantial progress in screening, early diagnosis, and the development of noninvasive technology, gastrointestinal (GI) cancer remains a major cause of cancer-associated mortality. Chemoprevention is thought to be a realistic approach for reducing the global burden of GI cancer, and efforts have been made to search for chemopreventive agents that suppress acid reflux, GI inflammation and the eradication of Helicobacter pylori. Thus, proton pump inhibitors, statins, monoclonal antibodies targeting tumor necrosis factor-alpha, and nonsteroidal anti-inflammatory agents have been investigated for their potential to prevent GI cancer. Besides the development of these synthetic agents, a wide variety of the natural products present in a plant-based diet, which are commonly called phytoceuticals, have also sparked hope for the chemoprevention of GI cancer. To perform successful searches of chemopreventive agents for GI cancer, it is of the utmost importance to understand the factors contributing to GI carcinogenesis. Emerging evidence has highlighted the role of chronic inflammation in inducing genomic instability and telomere shortening and affecting polyamine metabolism and DNA repair, which may help in the search for new chemopreventive agents for GI cancer. (Gut Liver 2013;7:137-149)

Key Words: Chemoprevention; Gastrointestinal neoplasms; Phytoceuticals; Molecular target

INTRODUCTION

1. The general principle for chemoprevention of gastrointestinal (GI) cancers

1) General concept of chemoprevention

Since the incidence of new cancer cases as well as the rate of cancer mortality are increasing worldwide, the prevention of cancer is ranked as a prime importance to reduce the global burden of cancer. The perception of preventing cancer was first outset by Wattenberg in 1960s, after which a wide array of population-based as well as preclinical studies has been conducted to evaluate the cancer prevention potential of diverse classes of natural as well as synthetic compounds. In 1976, Sporn first coined the term “chemoprevention” that refers to the use of nontoxic chemical substances of either natural or synthetic origin to delay, retard or reverse the process of carcinogenesis. Over the last few decades, numerous preclinical and clinical studies demonstrated the success of the chemoprevention strategy in curbing the cancer incidence and mortality. Chemoprevention is the strategy to intervene multistage carcinogenesis process, which comprises of apparently three distinct phases: initiation, promotion, and progression. Tumor initiation is a rapid and irreversible process that involves damage of cellular DNA by various known and unknown carcinogens. Many carcinogens, either endogenous or exogenous, are inactive per se and are activated through biotransformation inside the body. Biotransformation is a process of eliminating relatively nonpolar carcinogenic substances by converting them into water soluble entities, hence called detoxification. Extensive metabolic activation of carcinogens and compromised detoxification leads to the accumulation of highly reactive carcinogens, which cause covalent modification of genomic DNA, thereby activating various oncogenes and inactivating tumor suppressor genes, which leads to the initiation of cell transformation. Therefore, chemopreventive agents that can either inhibit carcinogen activation or promote detoxification are generally termed as anti-initiating agents or blocking agents. Tumor promotion, a reversible process, is the clonal expansion of initiated or transformed cells to grow as a population of preneoplastic cells forming the benign tumor. Abnormal biochemical reactions encompassing inappropriate amplification and/or inactivation of cell signal-
ing pathways underlie tumor promotion stage that often spans over 10 years. Thus, the normalization of aberrant cell signaling pathways by chemopreventive agents can reverse or halt the journey of premalignant cells to become malignant. Tumor progression involves malignant conversion of preneoplastic cells with characteristic features of increased angiogenesis, invasion and metastasis.\textsuperscript{4,5} In summary, cancer can be prevented by intervening any of these three stages of carcinogenesis and chemopreventive agents that can interfere with tumor promotion or progression are known as suppressing agents. The aforementioned stage-specific prevention of cancer is a simplistic view of chemoprevention strategy. Conclusively, accumulating evidence of the success of chemopreventive agents in reducing the risk of various cancers suggests that chemoprevention is the first line of defense against carcinogenesis.\textsuperscript{6}

2) The basis for chemoprevention of GI cancers

GI cancers include cancers of the esophagus, stomach, intestine, colon, rectum, pancreas, and liver. Among these, the esophageal squamous cell carcinoma accounts for approximately one-sixth of all cancer-related mortality worldwide.\textsuperscript{7} Esophageal adenocarcinoma (EAC) has received considerable attention because of the dramatically increased incidence in the past 2 decades and the poor prognoses with a 5-year survival rate of 10% to 20%.\textsuperscript{8,9} In spite of relative decline in the incidence and mortality, gastric cancer is still the fourth most common cancer worldwide and ranks the third most common cause of cancer-related deaths.\textsuperscript{10} Likewise, hepatocellular carcinoma (HCC) remains as the fifth common cancers and a major cause of cancer-related deaths.\textsuperscript{11} Pancreatic cancer, the most lethal form of GI cancer, is the fourth leading cause of cancer mortality with an overall median 5-year survival rate of only 5%.\textsuperscript{12} Colorectal cancers are also increasing worldwide with an estimate of 1,200,000 new cases in the year 2011 and half of them are going to die from the disease.\textsuperscript{13,14} Based on the looming scenario of cancer mortality, chemoprevention appears to be the forefront in fighting against GI cancers. Majority of the GI cancers have etiologic link with dietary and life style factors, of which point is critical basis for prevention. For instance, the association between gastric cancer and high salt diet intake or \textit{Helicobacter pylori} infection, the positive corelation between HCC and aflatoxin-B1 contaminated food consumption or chronic hepatitis virus infection or excessive alcohol consumption, and the causal relationship between colon cancer and the intake of burnt meat are notable examples. Thus, GI cancers can be prevented by changing dietary habit and life style. Whereas the maintenance of proper hygiene, abstinence from alcohol and smoking, increasing physical activity and avoidance of high salt and burnt food intake are commonly advocated, the pharmacological intervention for chemoprevention of GI cancers have been sought for over last several decades. Since oxidative stress and chronic inflammation, in general, play a key role in carcinogenesis, antioxidants, and anti-inflammatory agents have been shown to prevent various GI cancers. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been extensively investigated for the chemoprevention of colorectal cancers.\textsuperscript{15,16}

MOLECULAR BASIS IMPLICATED IN THE PREVENTION OF GI CANCERS

1. Inflammation and oxidative stress

Despite having unique etiology, all forms of GI cancers share the common mechanisms of oxidative stress-induced damage of genomic DNA, modification of cellular proteins and lipids, altered cell signaling and persistent local tissue inflammation. Whereas oxidative stress incites local tissue inflammation, persistent inflammation leads to the generation of reactive oxygen species (ROS). Excessive ROS as well as reactive nitrogen species (RNS) perturbs cellular homeostasis by inducing genetic and epigenetic changes and amplifying and/or inactivating cell signaling network, thereby inducing premalignant transformation of cells. ROS and RNS generate other reactive species, such as malondialdehyde and 4-hydroxynonenal (4-HNE), which can cause DNA damage by forming DNA adducts,\textsuperscript{17} thereby initiating the tumor formation. For example, 4-HNE forms 1,\textsuperscript{N}′-ethenodeoxyadenosine (\textsuperscript{\textit{dA}}) and 3,\textsuperscript{N}′-ethenodeoxycytidine (\textsuperscript{\textit{dC}}) DNA adducts in inflamed human pancreas and colon, respectively.\textsuperscript{18} DNA damage caused by oxidative stress is a major contributor to colorectal cancer development in ulcerative colitis patients.\textsuperscript{19} Peroxynitrite, a powerful oxidant, causes DNA damage through the formation of 8-nitroguanine (8-NG).\textsuperscript{20,21} In addition, elevated expression of nitrative and oxidative DNA lesion products, 8-NG and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), and iNOS was detected in inflammation sites of HCC, gastric cancer and cholangiocarcinomas.\textsuperscript{22} The incidence of EAC in patients with Barrett’s esophagus with dysplasia is increased by 30- to 125-fold.\textsuperscript{23} Likewise, inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn’s disease) are associated with about 10-fold increase in the risk of colorectal cancer\textsuperscript{24} and the use of anti-inflammatory therapy reduces this risk.\textsuperscript{25} The fact that inflammation precedes tumor development has recently been reported in a mouse model of pancreatic cancer.\textsuperscript{25} According to this study, authors developed a method to tag pancreatic cancer cells in order to track the movement of these cells. It was found that tagged pancreatic cells acquired mesenchymal phenotype and appeared in circulation much before the development of pancreatic tumor, and these cells were seeded into liver. This phenomenon was aggravated in the presence of pancreatitis and was most abundant at the inflammatory foci.\textsuperscript{25} Mouse pancreatic ductal adenocarcinomas arising from pancreatic acinar cells, which are resistant to transformation by oncogene activation or tumor suppressor gene inactivation, have been reported to form pancreatic intraepithelial neoplasia when exposed to limited bouts of nonacute pancreatitis and harbor K-ras oncogene.\textsuperscript{26}