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WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Thrombocytosis as a prognostic marker in gastrointestinal cancers

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Abstract

Thrombocytosis is an adverse prognostic factor in many types of cancer. These include breast cancer, ovarian and other gynecologic cancers, renal cell carcinoma and lung cancers. In gastrointestinal cancers of various locations and histologic types, thrombocytosis has been reported in general to be associated with adverse clinical outcomes. Platelet count measurement is well standardized and available in every clinical laboratory, making its use as a prognostic marker practical. This paper will discuss the data on the prognostic value of thrombocytosis in gastrointestinal cancers as well as pathogenic aspects of the association that strengthen the case for its use in clinical prognostication.

Key words: Thrombocytosis; Platelets; Cancer; Gastrointestinal; Prognosis

Core tip: Thrombocytosis arises as a prognostic factor in various cancers, although it is not clear whether there is a pathogenic contribution or thrombocytosis merely reflects a pro-carcinogenic inflammatory milieu. This paper discusses the utility of thrombocytosis as a prognostic factor in gastrointestinal cancers.

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INTRODUCTION

Platelets play an important role in hemostasis and vascular integrity. They have a unique mechanism of derivation as fragments from the cytoplasm of bone marrow megakaryocytes in a process called thrombopoiesis[1]. The cytokine thrombopoietin stimulates platelet production through ligation of its cognate surface receptor c-Mpl. Other signals also contribute to thrombopoiesis including SDF1 (stem cell derived factor 1, also called CXCL12) ligating receptor CXCR4, integrins and PF4 (platelet factor 4). Support is lent to megakaryocytes by the bone marrow microenvironment in the form of both soluble factors and of direct cell-cell interactions with specialized resident stromal cells[2]. Platelets are derived from proplatelets which represent long protrusions of the mature magakaryocyte cytoplasm[3]. Abnormalities in platelet number, either increase (thrombocytosis) or decrease (thrombocytopenia) accompany diverse pathologic conditions and may aid in their diagnosis[4]. An elevated platelet count has various causes and is either primary due to essential thrombocytosis or other myeloproliferative disorders or secondary to malignancy, infection, chronic inflammation, trauma or surgery, iron deficiency and splenectomy. The common denominator of most of these secondary conditions is inflammation[5]. Inflammatory cytokines stimulate the process of platelet production by megakaryocytes in the bone marrow. Cancer is a pathology that is often associated with thrombocytosis. This relates to the cytokine milieu of several malignancies that stimulates thrombopoiesis. Possibly due to this fact of association with a particular cytokines setting, thrombocytosis has been found to be an adverse prognostic

factor in many common malignancies. Thrombocytosis appears to be a universal marker of adverse outcomes in cancer. Its association with worse oncologic outcomes has been reported in early and advanced breast cancer[6,7], ovarian cancer[8,9], genitourinary cancers[10,11] and several other types[12,13].

PATHOGENESIS OF THROMBOCYTOSIS IN CANCER

A recent publication has shed some light to the pathogenesis of thrombocytosis in cancer[8] and confirmed previous reports on the role of cytokines and in particular of IL-6[14]. In ovarian cancer patients, thrombocytosis was significantly correlated with plasma levels of IL-6[8]. In mouse models bearing human ovarian cancer, human IL-6 stimulates hepatocytes through the IL-6 receptor to trigger thrombopoietin production. Thus a proposed model stipulates that ovarian cancer tumor cells produce IL-6 which then stimulates hepatic thrombopoietin production. Thrombopoietin increases thrombopoiesis through stimulation of megakaryocyte progenitors in the bone marrow[8]. In other cancers IL-6 may also play a similar role in favoring thrombocytosis and increased serum levels or tumor positivity by immuno-histochemistry have been detected in a variety of types, such as renal, prostate and breast carcinomas[15-17]. In malignant mesothelioma levels of serum IL-6 correlate with thrombocytosis[18]. IL-6 is produced locally in the tumor environment because pleural effusion levels were much higher than in serum. Interestingly in that case IL-6 may not be derived directly by mesothelioma tumor cells but by attracted immune cells because it was found that patients with tuberculous effusions had even higher levels of IL-6[18]. Specifically in gastrointestinal carcinomas, IL-6 is reported to be higher in patients with gastric and colorectal carcinoma compared to controls[19,20]. Except for the indirect effect through platelets, IL-6 has a role directly in gut carcinogenesis and possibly to chemotherapy response[21,22]. Nevertheless, IL-6 levels do not always correlate with thrombocytosis and other factors produced in bowel inflammatory microenvironment must play a role in its induction[23]. Tumor infiltrating lymphocytes and macrophages are present in various degrees in cancer sites and their role in both promoting and suppressing the tumor development is described[24]. Conditions in tumor micro-environment, such as hypoxia, affect the function of infiltrating immune cells and shape the panel of cytokines produced by them, which in their turn influence tumor cells[25]. In view of this discussion, platelet effects must be considered as constituting only part of the inflammatory process in cancer micro-environment and results of platelets influences should be interpreted with this larger perspective in mind.

The mechanistic basis of platelets contribution to carcinogenesis is a subject of investigation[26]. Circulating tumor cells may use platelets as a protective shield from the attack of the immune system and as facilitators for attachment to endothelial cells at metastatic sites. Platelets have also roles in carcinogenesis directly related to their normal function in promotion of vascular integrity[27]. Newly formed tumor vasculature lack the normal architecture and robustness of local resident vasculature and platelets have been shown to be indispensable for preventing hemorrhage in tumor beds[28]. Both alpha and dense granules of platelets carry bioactive molecules and growth factors. These include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), transforming growth factor β (TGFβ), interleukin 1β (IL-1β), IL-8, CXC motif containing ligand 12 (CXCL12), sphingosine 1-phosphate (S1P) and lysophosphatidic acid[29,30]. Each of these molecules may actively facilitate metastatic progression. An example is platelet-derived TGFβ which promotes an EMT (epithelial to mesenchymal transition) program in cancer cells through transcription factors Smad and NF-κB signaling[31]. EMT constitutes a program endowing epithelial cells with a mesenchymal phenotype that promotes mobility and metastasis while protecting them from anoikis (Apoptosis due to lack of adhesion)[32]. Platelet-derived TGFβ may also contribute to tumor immune evasion[33]. There exist quantitative differences in platelet cargo of bioactive factors and platelets from patients with cancer have a higher VEGF level than platelets from individuals without cancer[34]. As a result platelet counts may more accurately account for VEGF concentrations in the tumor and metastases sites environment where they are activated. Interestingly IL-6 signaling through the STAT3 (signal transducer and activator of transcription 3) is able to induce VEGF receptor VEGFR2 in colorectal cancer cells[35] and thus to complete a pro-carcinogenic loop in cancer cells that includes IL-6, platelets and VEGF.

THROMBOCYTOSIS IN ESOPHAGEAL CANCER

In 293 patients with esophageal squamous cell carcinoma, thrombocytosis, defined as platelets more than 293 × 10^9/L, which was the mean plus one standard deviation of a healthy control group, was present in 21% of patients and was not correlated with patients age and gender[36]. In contrast, it was a significant independent prognostic factor for overall survival[36]. This association was statistically significant for patients with stage Ⅲ and Ⅳ but not for stage Ⅰ and Ⅱ disease. In multivariate analysis, thrombocytosis, together with higher T stage, tumor size and nodal involvement, predicted for worse survival.

In another study which included mainly patients with squamous carcinomas but also a minority (7%) with esophageal adenocarcinomas, thrombocytosis, defined this time as platelets more than 400 × 10^9/L, was present in 4% of patients and it was not associated with age, gender, location along the esophagus, degree of differentiation, lymphovascular or perineural invasion or node

involvement[37]. It was observed more often in patients with adenocarcinoma and correlated with tumor size. Although this report did not study thrombocytosis as it pertains to prognosis, either overall or progression free survival, it did confirm the finding of the previous study regarding its lack of association with other possible prognostic factors.

THROMBOCYTOSIS IN GASTRIC CANCER

In a very large series of 1593 gastric adenocarcinoma patients, 6.4% had thrombocytosis (defined as platelets more than 400 × 10^9/L in this study)[38]. All patients had undergone gastrectomy with negative margins and extensive D2 lymph node dissection. Thrombocytosis was associated with higher T stage, node positivity and a worse survival. Despite that, in multivariate analysis, the prognostic value of thrombocytosis for long term survival was lost while T stage and node positivity remained statistically significant predictors of long term survival in these patients. Thrombocytosis was a strong predictor of overall recurrence and specifically of hematogenous metastasis but not of locoregional recurrence or peritoneal seeding[38]. These predictive values were retained even in multivariate analysis in this instance.

In another series of 369 gastric cancer patients, thrombocytosis was present in 11.4% and was associated with worse 1 year and 3 year survival[39]. The 1 year survival of patients with thrombocytosis was 72.9% while of those without thrombocytosis was 85.7%. The 3 year survival of patients with thrombocytosis was 23.4% while of those without thrombocytosis was 52.4%. Thrombocytosis was positively correlated with depth of tumor invasion and lymph node involvement[39].

In a smaller series of 98 patients operated for gastric carcinoma, pre-operative thrombocytosis was present in 21% and was associated with a statistically significant worse overall survival[40]. The 5 year survival of patients with thrombocytosis was 9.5% and of patients without thrombocytosis was 31.2% in this series. Interestingly the pro-angiogenic enzyme thymidine phosphorylase/platelet-derived endothelial cell growth factor expression was associated with thrombocytosis and both were independent predictors of survival in multivariate analysis[40]. Finally, a study of 181 gastric cancer patients investigated platelet number and serum VEGF level as prognostic factors and failed to correlate either with overall or progression-free survival. In contrast the ratio of VEGF to platelet number was significantly associated with progression-free survival in multivariate analysis[41]. This may relate to the pathophysiologic importance of activated platelet derived VEGF in promoting the neoplastic process.

THROMBOCYTOSIS IN PANCREATIC CANCER

Pre-operative thrombocytosis was investigated as a prognostic factor in 109 patients with pancreatic adenocarcinoma that were surgically resected[42]. It was found to be significantly associated with reduced overall survival. Significance was confirmed in a multivariate regression analysis. Disease-free survival was also worse with thrombocytosis in a series of patients with operable pancreatic cancer[43]. Mean progression-free survival was 4.9 and 46.5 mo for the thrombocytosis and normal platelet groups respectively. In this study prognosis was even better in the sub-group that retained a normal platelet count after the surgery.

In contrast to the above studies, a study that included pancreatic, duodenal and bile duct ampullary carcinomas found lower platelet counts to influence adversely overall and disease-free survival[44]. Lower pre-operative platelets counts were significantly associated with positive surgical margins, a fact that may at least partially explain the adverse prognostic association. Another explanation for this reverse association compared with the previously discussed studies is that this study used a lower cut-off to define high platelet counts at 300 × 10^9/L. The same cut-off of 300 × 10^9/L was used in another more extensive series of 205 patients exclusively with pancreatic adenocarcinoma that had negative results for an association of platelet counts with survival[45]. In both of these studies, results might have been blurred by inclusion of a significant number of patients with higher normal spectrum platelet number in the group of increased platelet counts.

THROMBOCYTOSIS IN HEPATOCELLULAR CARCINOMA

Platelets have a complex relationship with hepatic malignancies. On one hand, due to its association with cirrhosis hepatocellular carcinoma is often presenting with thromcytopenia which is also an adverse prognostic factor[46]. On the other hand, thrombopoietin, an important cytokine for thrombopoiesis, is produced by the liver and may lead to thrombocytosis if neoplastic cells mimic their normal counterparts and produce the cytokine[47] or alternatively if cancer cells stimulate normal liver to produce it[48]. An association of extreme thrombocytosis with both hepatocellular carcinoma and the childhood liver tumor, hepatoblastoma has been noted in the pediatric population[49]. Hepatoblastoma patients had significantly elevated levels of thrombopoietin compared to controls but only slightly elevated levels of IL-6 suggesting that thrombopoietin is down-stream to IL-6 in the pathway triggering thrombopoiesis[50]. Hepatocellular carcinoma patients with thrombocytosis have bigger tumors and a better liver function than patients with normal platelets[51]. A large study of 1154 patients disclosed a 2.7% incidence of thrombocytosis in hepatocellular carcinoma[52]. In addition, platelet count and thrombopoietin level correlated with effectiveness of treatment, decreasing after excision of the tumor and re-increasing upon recurrence. Thrombocytosis was significantly associated with younger age of the patients, higher tumor burden, development of portal

vein thrombosis by tumor involvement and a shorter mean survival time of less than 5 mo as opposed to over 12 mo in patients without thrombocytosis.

THROMBOCYTOSIS IN COLORECTAL CANCER

Thrombocytosis (more than 400×10^9/L) was evaluated as a prognostic factor in an extensive series of 1513 patients with localized colorectal cancer that had undergone surgery[53]. Patients with thrombocytosis had a significant worse overall survival than patients with normal platelets. Overall recurrence rate and distant metastatic recurrence but not loco-regional recurrence was worse in patients with thrombocytosis. These negative effects of thrombocytosis in overall survival and distant metastatic recurrence persisted over a 5 years period from surgery[53].

A retrospective series of 150 patients that underwent surgery for colorectal carcinoma disclosed that patients with pre-operative thrombocytosis had a 5-year survival of 13.3% while patients with normal count pre-operatively had a 5-year survival of 56.3%[54]. Thrombocytosis, together with lymph node positivity, increasing stage and presence of perineural invasion was statistically associated with worse survival. An association of thrombocytosis with survival or cancer specific survival in colorectal cancer was confirmed in two other larger series of 453 and 636 patients from Japan[55,56] and a smaller series of 180 patients from Europe[57]. The authors of one of these studies examined also thrombocytosis specifically in rectal cancer patients receiving chemo-radiotherapy[58]. They reported that patients with thrombocytosis before combined treatment had a lower rate of radiographic and pathologic response to treatment and a higher risk of local recurrence. In another study focusing in rectal cancer, patients with pre-operative thrombocytosis (more than 350×10^9/L) had a significantly worse survival than patients with lower counts[59].

Patients with node negative colorectal cancer represent a particular challenge for the medical oncologist because, although they have a risk for recurrence, they derive no clear benefit from chemotherapy as a whole group. Clinicopathologic characteristics such as T3 invasion, less complete lymph node dissection, high grade and clinical presentation with obstruction or perforation are used to assist in defining the need for adjuvant chemotherapy[60]. In node negative patients additional prognostic markers to guide therapeutic decisions would be particularly valuable. Thrombocytosis could be such a marker and it was found in an investigation of 198 patients with node negative disease to be associated with significantly worse survival than counterparts with normal pre-operative platelet counts[61]. In these node negative patients, thrombocytosis (platelet count more than 400×10^9/L) was independently associated in multivariate analysis, together with tumor depth (T stage), grade and lymphatic invasion, with both disease-free and overall survival.

In contrast to all the above investigations, a single study of 630 patients did not find a correlation of thrombocytosis with survival[62]. This study used a more stringent definition of thrombocytosis of platelet counts of more than 450×10^9/L and included patients of all stages. Inclusion of metastatic patients might have made the effect of platelet counts on outcome more difficult to discern. Despite this, the *P* value in the Cox multivariate model was just outside significance at 0.06[62].

CONCLUSION

Thrombocytosis occurs in a significant minority of patients with cancer and reflects the increase of thrombopoiesis-inducing cytokines in the tumor milieu. Thus it carries an adverse prognostic value both because of this reflection but also because platelets actively promote carcinogenesis and metastasis protecting tumor cells in their metastatic transit and providing bioactive molecules released upon activation in the tumor and metastatic sites. In the gastrointestinal tract, inflammation and infection play a significant role in carcinogenesis with several well-known associations such as inflammatory bowel disease and colorectal cancer, *Helicobacter pylori* infection and gastric cancer and viral hepatitis infection and hepatocellular carcinoma. In addition even in inflammation-independent cancers, cancer-associated molecular lesions may induce platelet-inducing cytokines. For example one of the most common colorectal cancer lesions, Smad4 mutations, lead to dysfunctional TGFβ signaling, resulting in its turn to increased IL-6 signaling[63]. Given these data, a combined treatment blocking IL-6 with the IL-6 monoclonal antibody inhibitor siltuximab or the IL-6R inhibitor tocilizumab together with an anti-platelet function inhibitor such as aspirin with or without inhibition of additional pathways activated by platelet granules cargo factors such as the CXCL12/CXCR4 or the VEGF/VEGFR axis could be a viable option for development in gastrointestinal cancer patients with thrombocytosis to improve their prognosis. Given its significance as a prognostic factor in gastrointestinal cancers and the ease and standardization of its measurement in the clinic, thrombocytosis should be considered as a factor in the stratification process of randomized trials in these cancers, as both a measure of the tumor inflammatory status but also an active propagator of the neoplastic process. Another emerging concept is that of thrombocytosis as a predictor of response to targeted treatments, for example of anti-VEGF therapies. A study in metastatic renal cell carcinoma has shown that patients with thrombocytosis had a higher risk to present a primary refractoriness to anti-VEGF treatments (OR = 1.7, $P = 0.0068$) than patients with normal platelets[64]. It remains to be seen if thrombocytosis could be a predictive factor for anti-VEGF therapies in gastrointestinal cancers and in particular colorectal cancer and hepatocellular carcinoma where the anti-VEGF monoclonal antibody bevacizumab and the small molecule inhibitor sorafenib are clinically used[65,66].

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MINIREVIEWS

Mechanisms linking dietary fiber, gut microbiota and colon cancer prevention

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Abstract

Many epidemiological and experimental studies have suggested that dietary fiber plays an important role in colon cancer prevention. These findings may relate to the ability of fiber to reduce the contact time of carcinogens within the intestinal lumen and to promote healthy gut microbiota, which modifies the host's metabolism in various ways. Elucidation of the mechanisms by which dietary fiber-dependent changes in gut microbiota enhance bile acid deconjugation, produce short chain fatty acids, and modulate inflammatory bioactive substances can lead to a better understanding of the beneficial role of dietary fiber. This article reviews the current knowledge concerning the mechanisms *via* which dietary fiber protects against colon cancer.

Key words: Dietary fiber; Gut microbiota; Colon cancer

Core tip: Dietary fiber modulates our health at nearly every level, and in every organ system, *via* complicated modes of action. This article reviews the mechanistic association of dietary fiber, gut microbiota and colon cancer prevention.

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INTRODUCTION

Colon cancer is one of the most common malignancies in the United States and accounts yearly for approximately 11% of all cancer deaths[1]. The incidence rates of colon cancer are higher in the Western world but are rapidly increasing in developing countries, and it is predicted that half of the Western population will develop at least one colorectal tumor by age of 70[1]. Although cancer treatments have made large strides in recent decades, prevention by diet and other healthy lifestyle factors and habits (*e.g.*, physical exercise) offers a more desirable alternative. Genetic variation and environmental exposures (*e.g.*, diet, physical activity), including diet, are the two main contributing factors influencing the occurrence of colon cancer[2]. Thus, colon cancer may be highly amenable to prevention through a dietary regimen, and dietary carbohydrates may play a critical role[3]. Carbohydrates can be separated into two basic groups based upon their digestibility in the gastrointestinal (GI) tract[4,5]. The first group is simple carbohydrates such as starch and simple sugars, which are easily hydrolyzed by enzymatic reactions and absorbed in the small intestine. The second group is composed of complex carbohydrates such as cellulose, lignin and pectin which are resistant to diges-

tion in the small intestine and undergo bacterial fermentation in the colon. These complex carbohydrates, referred to as dietary fibers, are found in plants[4,5]. Many studies suggest that there is an association between high dietary fiber intake and a low incidence of colon cancer, and that dietary fiber has anticancer properties[6-8]. Furthermore, the US Food and Drug Administration has approved health claims supporting the role of dietary fiber in cancer prevention[9].

It is known that the human GI tract represents the most abundant reservoir of microbes with over 100 trillion bacteria grouped in about 1000 species[10,11]. The bacterial gut populations can be shifted to a healthier composition by fermentable dietary fiber that provides substrates for bacterial fermentation[10,11]. Dietary fiber decreases the risk for type 2 diabetes mellitus, obesity, cardiovascular disease, colon cancer, and improves immunity by modulating the gut microbiota landscape[6]. Dietary fiber modulates our health at nearly every level, and in every organ system, *via* complicated modes of action, many of which remain to be determined[10,11]. In the present review, we focus on the mechanistic association of dietary fiber, gut microbiota and colon cancer prevention.

IMPACT OF DIETARY FIBER ON GUT MICROBIOTA

Dietary fiber constitutes a spectrum of non-digestible food ingredients including non-starch polysaccharides, oligosaccharides, lignin, and analogous polysaccharides with an associated health benefit[12,13]. Dietary fibers are not a static collection of undigestible plant materials that pass through the human GI tract without any function; instead, they bind potential nutrients, result in new metabolites, and modulate nutrient absorption/metabolism. Certain dietary fibers are fermentable, and in addition to their anaerobic degradation in the GI tract, there is also a concurrent anaerobic proteolytic fermentation[14]. Whereas the main fermentation products of fiber are thought to be beneficial (positive), the products of the proteolytic fermentation can be detrimental (negative), resulting in a ying-yang effect[14]. In healthy individuals, fermentation processes are primarily controlled by the amount and type of substrates accessible to bacteria in the colonic ecosystem[11]. The fate of fiber in the colon largely depends on the colonic microbiota and the physio-chemical characteristics of the fiber itself[15]. Fiber sources such as oat bran, pectin, and guar are highly fermented; whereas, cellulose and wheat bran may be poorly fermented[15,16]. On the other hand, the type of dietary fiber affects the microbial composition of the gut lumen. For example, inulin, a polymer of fructose monomers present in onions, garlic and asparagus[17], stimulates the growth of *Bifidobacteria*; whereas, it restricts the growth of potential pathogenic bacteria such as *E. coli, Salmonella,* and *Listeria*[17-19]. In experiments with a simulator of the human colon, dietary xylo-oligosaccharides decrease the major butyrate-producing bacteria *Faecalibacterium prausnitzii*, although total butyrate concentration is increased only in the distal vessel[20]. The same researchers reported that xylo-oligosaccharides also affect the levels of sulphate-reducing bacteria, *Bacteroides fragilis*, providing evidence that dietary carbohydrates modify the gut microbiota, and therefore, its ability to change the physiological properties of the colonic environment. In humans, diets high in nonstarch polysaccharides and/or resistant starch profoundly affect the types of fecal bacteria, including species related to *Ruminococcus bromii*, which can contribute to starch degradation and short chain fatty acid (SCFA) production[21].

There are over 50 bacterial phyla described to date but the human gut microbiota is dominated by two of them, the *Bacteroidetes* and the *Firmicutes*; whereas, the phyla *Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria* are present in minor proportions[22,23]. The taxonomic composition of the "ideal" microbiota, if such exists, remains to be identified. Presently, individuals are categorized into "enterotypes" or clusters based upon the abundance of key genera in the gut microbiota[24]. Recent studies showed that gut microbial communities are clustered into three types: *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2) and *Ruminococcus* (enterotype 3), and these clusters seem unrelated to geographical origin, body mass index, age, or gender[25]. These findings suggest that there is not one ideal microbiota composition, but "a limited number of well balanced host-microbial symbiotic states"[25].

Much remains to be determined about what constitutes a healthy microbiota, but there are numerous diseases and conditions associated with a disturbed gut microbiota[26]. It has been generally accepted that the human gut contains approximately 500 to 1000 species[27], and the differential colonization suggests a relationship with disease susceptibility[28-30]. For example, the intestinal microbiota of children from Europe and rural Africa who are exposed to a modern Western diet and a rural diet respectively, exhibit significant differences in microbial composition. The major difference is that rural African children have microbiota enriched in *Bacteroidetes* and depleted in *Firmicutes* in comparison to European children[30].

Although amino acid fermenting bacteria and syntrophic species are present in the large intestine, the majority of colonic bacteria have predominantly saccharolytic metabolisms. Therefore, dietary fiber/carbohydrate availability is almost certainly the most important nutritional factor that determines the composition and metabolic activities of the gut microbiota, and many of the physiologic properties of the microbiota are attributed to the fermentation and production of SCFAs[31]. For example, lower dietary fiber intake and consistently lower SCFA production were observed in colon cancer risk subjects compared to healthy individuals, and these differences were accompanied by distinct profiles of

the fecal microbiota communities of the two groups[32]. In the same study, *Clostridium*, *Roseburia*, and *Eubacterium spp*. were significantly less prevalent in the colon cancer risk group than the healthy individuals group; whereas, *Enterococcus* and *Streptococcus spp*. were more prevalent in the colon cancer risk group[32]. Consistent with these observations, the low pH conditions resulting from fiber fermentation increase biosynthetic requirements for nitrogen-containing precursors, and subsequently inhibit toxin accretion in the colon[33]. Taken together, individual properties such as body mass index, age, or gender may not explain the three observed gut bacterial enterotypes[25], but data-driven marker genes/microbial markers can be identified for certain diseases and conditions[30-32].

SCFA PRODUCTION

Dietary fiber consumption can have significant health benefits, particularly in laxation, mineral absorption, potential anticancer properties, lipid metabolism and anti-inflammatory effects[34]. Many of these health benefits can be attributed to the fermentation of dietary fiber into SCFAs in the colon. These SCFAs are generated by the colonic microbiota, and an equation outlining overall carbohydrate fermentation in the colon has been described[35]:

$59\ C_6H_{12}O_6 + 38\ H_2O \rightarrow 60$ acetate $+ 22$ propionate $+ 18$ butyrate $+ 96\ CO_2 + 256\ H^+$.

The significance of carbohydrate breakdown by intestinal bacteria is broad. For example, the increased input of carbohydrates allows for increased bacterial cell mass, which supports laxative effects and shorter colonic transit times. The decreased transit times decrease protein breakdown and the accumulation of putrefactive substances, such as ammonia, phenols, amines and hydrogen sulfide in the colon.

The three major colonic SCFAs are acetate, propionate and butyrate, and the total concentration of SCFAs in colonic content may exceed 100 mmol/L [36]. The composition of diet and gut microbiota are the major factors in determining the molar proportion of SCFA species. In general, acetate makes up around 60%-75% of the total SFCA, and is generated by many of bacterial groups that inhabit the colon, with approximately one-third of the product coming from reductive acetogenesis[37]. The bacterial groups that form propionate and butyrate are specialized, and are of particular interest in terms of their health beneficial effects. The fact that a considerable number of bacterial species provide diverse molecular functions underscores the importance of a functional analysis to understand the composition of microbiota[25].

The data on the main propionate-producing bacteria in the human colon are still emerging, and several biochemical pathways for propionate formation are characterized[38,39]. The succinate route for propionate formation is generally employed by *Bacteroides* species, but the acrylate route from lactate is adopted by bacteria belonging to the clostridial cluster IX group. In addition, a third pathway is employed by the butyrate-producing bacterium *R. inulinivorans* with fucose as substrate[40].

Colonic bacteria that produce butyrate belong to the clostridial clusters I , III, IV, VI, XIVa, XV and XVI. Two particularly abundant groups that are estimated to consist 7%-24% of the total gut bacteria in healthy subjects are cluster IV bacteria related to *Faecalibacterium prausnitzii*, and cluster XIVa bacteria related to *Eubacterium rectal* and to *Roseburia spp*[41]. For example, reduced dietary intake of fiber by obese subject results in decreased concentrations of butyrate and butyrate-producing bacteria related to *Eubacterium rectal* and to *Roseburia spp*[42].

PHYSIOLOGICAL EFFECTS OF SCFA

Acetate (C2), propionate (C3) and butyrate (C4) are found in the human intestine at concentrations of approximately 13 mmol/L in the terminal ileum, approximately 130 mmol/L in caecum and approximately 80 mmol/L in the descending colon[36]. These SCFAs released in the intestinal lumen are readily absorbed and used as energy source by colonocytes (approximately 10% of basal energy requirements) and also by other tissues such as liver and muscle[43].

Acetate stimulates proliferation of normal crypt cell but reduces the frequency of spontaneous longitudinal muscle contractions in rat colonic smooth muscle[44]. Acetate enhances ileal motility, increases colonic blood flow, and plays a role in adipogenesis and host immune system through interacting with the G protein-coupled receptor (GPCR43, 41) in adipose tissue and immune cells[45,46]. In addition, it has been shown that acetate reduces lipopolysaccharide-stimulated tumor necrosis factor (TNF), interleukin (IL)-6 and nuclear factor (NF)-κB level while boosting peripheral blood antibody production in various different tissues[47].

Similar to acetate, propionate has been shown to exert a concentration-dependent effect on the frequency of spontaneous contractions in longitudinal muscle *via* enteric nerves in rat distal colon[44]. In both animal and human studies, it has been shown that propionate reduces food intake and increases satiety *via* augmentation of the satiety hormone leptin, and through activation of GPCR43, 41[48,49]. Also, propionate may be protective against carcinogenesis because it reduces human colon cancer cell growth and differentiation *via* hyperacetylation of histone proteins and stimulation of apoptosis[50,51]. In addition, propionate also inhibits the production of pro-inflammatory cytokines (*e.g.*, TNF-α, NF-κB) in multiple tissues[52,53].

Although acetate, propionate, and butyrate are all metabolized to some extent by the epithelium to provide energy, butyrate plays the most critical role in maintaining colonic health and moderating cell growth and differentiation[54]. More than 70% of oxygen consumption in isolated colonocytes is due to butyrate oxidation, and the uptake and utilization of butyrate by the colonic epithelium have been demonstrated in a study on the SCFA lev-

els in portal and arterial blood and in colonic contents[36]. Compared to acetate and propionate, butyrate exhibits strong anti-inflammatory properties, and this effect is likely mediated by inhibition of TNF-α production, NF-κB activation, and IL-8, -10, -12 expression in immune and colonic epithelial cells[55,56].

ANTI-INFLAMMATORY ACTION, SCFAS AND MICROBIOTA

Inflammation, a host defense mechanism, is an immediate response of the body to tissue injury caused by microbial infection and other noxious stimuli. However, inadequate resolution of inflammation and uncontrolled inflammatory reactions can evoke a state of chronic inflammation, which is a common etiologic factor for cancer[57].

Leukocyte recruitment and SCFAs

Leukocytes are recruited and migrate from the bloodstream to the inflamed tissue through a multistep process that involves expression and activation of several proteins such as adhesion molecules and chemokines[58], and SCFAs modify this leukocyte recruitment[59,60]. Several lines of evidence show that SCFAs induce directional migration of neutrophils, which is dependent upon the activation of GPR43, a G protein-coupled receptor[59,61]. The function of SCFAs as agonists of GPR43 may result in activation of protein kinase B (PKB) and mitogen activated protein kinases in neutrophils. Furthermore, the receptors GPR41 and GPR109A, both of which are related to GPR43, are activated by SCFAs[62]. These results support a role for the SCFAs in the movement of neutrophils[61].

SCFAs also modulate the expression and secretion of cell adhesion molecules and chemokines that play a central role in leukocyte recruitment[52,60]. Cell adhesion molecules such as selectins, integrins, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 are critical for adhesion and transendothelial migration of leukocytes[63]. Recent studies have shown that SCFAs reduce the adherence of monocytes and lymphocytes to human umbilical vein endothelial cells, and this is associated with an attenuation of NF-κB and PPARγ activities and adhesion molecule expression (ICAM-1 and VCAM-1)[52,63]. In addition, butyrate reduces the constitutive and IFN-γ-induced expression of LFA-3 and ICAM-1; the LPS-stimulated production of CXCL-2, 3, and macrophage chemoattractant protein-1, IL-8 by neutrophils and macrophages[64,65]. Therefore, by modulating the amount or type of adhesion molecules and chemokines, SCFAs may alter the recruitment of leukocytes, and in part, reduce the chronic GI tract inflammatory response.

Proinflammatory mediators, SCFAs

A wide variety of cytokines and other proinflammatory mediators contribute to both extrinsic and intrinsic pathways of inflammation-associated carcinogenesis, and macrophages are the major source of inflammatory mediators[57]. Once activated, macrophages produce significant amounts of mediators such as TNF-α, Il-1β, IFN-γ and IL-6, chemokines, and nitric oxide (NO)[57,66]. SCFAs, mainly butyrate, reduce the LPS- and cytokine-stimulated production of pro-inflammatory mediators such as TNF-α, IL-6, IFN-γ and NO while increase the release of the anti-inflammatory cytokine IL-10[66,67]. The histone deacetylases (HDACs) and histone acetyltransferases control the degree of protein acetylation and gene expression, and the ability of butyrate to inhibit HDAC activity is the main mechanism *via* which the acid affects the expression of proinflammatory mediators[66-68]. In addition to increasing net histone acetylation and therefore, influencing gene expression, butyrate also augments the acetylation of nonhistone proteins such as NF-κB, MyoD, and p53[66].

Gastrointestinal barriers and microbiota

Gut microbiota contribute to the maintenance of an intact GI barrier, and the disruption of this barrier can cause an inflammatory process[10]. The primary or innate barrier is an interaction between the microbiota and the gut epithelial cell layer. This interaction is an active process, in which certain inflammatory mediators are produced. For example, the ligands of toll like receptors (TLRs) such as LPS and flagellin are microbially derived, and they activate respectively, TLR-4 and -5 to modulate distinct aspects of host metabolism and immune response[69]. The secondary physical barrier is formed by epithelial cell secretion of mucus, and this intestinal mucus layer is a critical physical barrier protecting the intestinal epithelium from the intestinal microbiota, including invasive microbes[70]. The mucus layer is composed by mucin proteins produced by Goblet cells[10], whereas, in the small intestine, the Paneth cells directly sense enteric bacteria through TLR activation, and release various antimicrobial peptides[71]. Therefore, mucus not only forms a physical barrier and provides a nutrition source for the microbiota, but it also contains protective mediators such as secreted antimicrobial peptides and Ig A[70,72]. Thus, the mucosal immune system and the homeostasis of gut microbiota are interdependent, and a balance between them maintains a stable intestinal environment.

EFFECT OF SCFAS ON CELL CYCLE, MIGRATION AND APOPTOSIS

Although SCFAs stimulate normal colonocyte proliferation at low concentrations (*e.g.*, 0.05 mmol/L-0.1 mmol/L butyrate), SCFAs also inhibit the growth of most human colon cancer cells by cell cycle arrest and apoptosis through a complex molecular regulation[73,74]. Several *in vitro* studies have demonstrated that butyrate inhibits HDACs, and allow histone hyperacetylation that leads to transcription of many genes including p21/Cip1, and cyclin D3[75]. The induction of the cyclin-dependent kinase

inhibitory protein p21/Cip1 accounts for cell arrest in the G_1 phase of the cell cycle[75]. In addition, we and others have also observed that at 0.5 or higher mmol/L concentration, butyrate inhibits the migration and invasion rate of cancer cells by increasing the expression of anti-metastasis genes (*e.g.*, metalloproteinases) and inhibiting the activation of pro-metastatic genes (*e.g.*, matrix metalloproteinases)[76,77].

There is also overwhelming evidence that dietary fiber counteracts the earliest stages of colonic carcinogenesis. For example, carbohydrates may protect colonocytes against the genotoxicity of a typical Western diet, which is characterized by increased levels of protein and fat intake. Thus, resistant starch decreases by 70% the DNA damage manifested by single-strand breaks in colonocytes of rats fed a Western diet[78]; significantly, when such DNA damage is not repaired, it may initiate colonic carcinogenesis. This interpretation is supported by experimental data that resistant starch protects rodents against tumors induced by the carcinogen azoxymethane[79,80]. The protective effect of resistant starch against such DNA alterations could be attributed to the increased production of SCFAs, and the decreased phenol and ammonia levels[78]. Among the SCFAs, butyrate has been demonstrated to have a significant physiological effect on neoplastic colonic cells[81]; however, acetate has also been implicated in protection against genotoxic agents[20] Interestingly, different carbohydrates affect differentially the extent of DNA damage; for example, dietary xylo-oligosaccharides but not inulin may alter the genotoxicity of the colonic environment. Utilizing a human colonic simulator inoculated with human feces and a soy protein isolate, the researchers have reported that xylo-oligosaccharides reduce genotoxicity of the liquid phase in the proximal vessel, but increase genotoxicity in the distal vessel[20].

It is evident that the DNA-protective effects of the carbohydrates are mediated by (1) their ability to sustain the existence of specific colonic microbiota; and (2) by the fermentation products resulting from the presence of the colonic bacterial species. In rats, a resistant starch-enriched diet increases the numbers of bifidobacteria and lactobacilli species; whereas, it decreases coliforms and results in higher levels of SCFAs[82]. However, the levels of the short-chain fatty acids are dependent not only upon the type and amount of dietary carbohydrates, but also by the present colonic bacterial species. Such two-way interactions explain the observations that rats fed resistant starch diet supplemented with the probiotic *Bifidobacterium lactis* exhibit a stronger apoptotic response to a genotoxic carcinogen in the colon than those fed the same diet without the probiotic supplement[82].

Evidence for a protective role of butyrate against colon cancer comes mostly from studies in carcinogen-induced rodent models of this malignancy. Thus, the effects of diets containing guar gum and oat bran (both highly fermentable, but associated with low butyrate levels in the distal colon) have been compared to these of a diet with wheat bran (resulting in high butyrate concentrations) in a rat dimethylhydrazine model of colon cancer[83]. The researchers reported the highest protection against colonic tumors in the group of rats fed the wheat bran diet. Similarly, rats fed diet with resistant starch exhibited a lesser burden of colonic adenocarcinomas after exposure to azoxymethane, and this protective effect seemed to be related to the production of butyrate in the colon[79]. It has been observed that in rats with tumors induced by azoxymethane and deoxycholic acid, dietary sodium gluconate increases butyrate levels and decreases the numbers of tumors in the colon[84]. Also, oral administration of the butyrate-producing bacteria *Butyrivibrio fibrisolvens* augmented butyrate levels, and reduced the formation of aberrant crypt foci, an early colonic lesion, in the colon and rectum of mice treated with dimethylhydrazine[85].

However, not all reports support a chemopreventive effect for butyrate[15]. Some epidemiological studies have also shown no relationship between fiber intake and colon cancer incidence, and no effect of SCFAs (*e.g.*, butyrate) on colonic tumorigenesis[86,87]. These observations were initially counter-intuitive given the reported anticancer-effects of dietary fiber/SCFAs. However, molecular analyses on the effect of SCFAs in colonic tumorigenesis may partly explain these seemingly controversial observations.

First, the constitutive activation of the canonical WNT signaling pathway is a common characteristic of colon cancer, and the beta-catenin- Tcf (BCT) transcriptional complexes are the downstream mediators of this pathway[88,89]. It has been proposed that WNT/beta-catenin activity exists as a gradient, within which absence of WNT signal results in terminal differentiation and apoptosis, relatively low levels of signaling lead to controlled self-renewal, moderate levels of signaling promote uncontrolled cell proliferation, and relatively high levels of WNT signaling lead to apoptosis[90]. Therefore, hyper-activation of WNT/beta-catenin signaling in butyrate-treated colon cancer cells is a required event to achieve high levels of apoptosis in these cells[91].

Second, studies on human colon cancer cell lines with different WNT/beta-catenin signaling mutations have identified two classes of cell lines: those which respond to butyrate treatment with (1) a high fold; and (2) a low fold induction of WNT/beta-catenin activity and apoptosis[91]. Thus, discrepancies in the literature as to the protective nature of fiber intake against colon cancer[5,15,92] may be due to the fact that only a subset of colonic lesions responds to butyrate with hyper-activation of WNT/beta-catenin signaling and enhanced apoptosis. Further, colonic lesions may become resistant to the effects of butyrate through exposure to suboptimal levels of this agent; for example, butyrate-resistant cells produced *in vitro* exhibit suppressed WNT/catenin hyperactivation and inhibited induction of apoptosis upon exposure to butyrate and other HDAC inhibitors[93]. This butyrate-resistant cell line may reflect the *in vivo* existence of human tumors that are

resistant or partially resistant to the effects of butyrate, and suggests that a high dietary fiber intake is required for an effective protective action against colon cancer. Differences in the responsiveness of colonic neoplastic cells to the effects of butyrate on WNT/catenin signaling may be mediated through the differential expression and activity of transcriptional coactivators that influence WNT/catenin activity, particularly CBP and p300[94,95]. For example, a butyrate-resistant cell line has been shown to be defective in p300 expression, which likely mediates effects of butyrate on WNT/catenin signaling and cell physiology[95].

Third, the composition of gut microbiota and diet (*e.g.*, fat) are factors that affect the SCFA productions and their action[15,96,97], and the effect of SCFAs on colon neoplastic cells might be modifiable by other dietary compounds and metabolites; thus, adding a particular type of oil (*e.g.*, fish oil *vs* corn oil) results in a variable reduction of colon tumors in rat azoxymethane model of carcinogenesis[98]. Finally, the effect of fiber and butyrate on colon carcinogenesis is likely dependent upon the timing of fiber and butyrate administration with respect to the stage of cancer development[15]. Several studies have shown that a high fiber intake specifically affects early tumor development in the colon; however, progression to advanced adenomas is unlikely to be influenced by fiber intake[7,86]. These data clearly support a multifaceted role of SCFA production/action, and more *in vivo* studies are warranted to further dissect the role of fiber intake in modulating colon cell cycle and apoptosis pathways.

FUNCTIONAL ROLE OF FIBER SOURCE PER SE

Although gut microbiota and fiber fermentation to SCFAs play a critical role in cancer prevention, the fiber source per se may have independent effects on colonic health. First, dietary fiber increases viscosity and fecal bulking (diluting potential carcinogens), and it therefore shortens the time for proteolytic fermentation (and production of harmful substances) and also decreases the contact between potential carcinogens and mucosal cells[4,99]. In addition, dietary fiber could bind/excrete potential luminal carcinogens (*e.g.*, secondary bile acids) and lower fecal pH in the colon[4,100,101]. Second, dietary fiber is not only a substrate for fermentation, but it is also a source of vitamins, minerals and slowly digestible energy; for example, bran fractions are rich in minerals, vitamin B6, thiamine, folate and vitamin E[102]. Third, dietary fiber is associated with phytochemicals such as phenolics, carotenoids, lignans, beta-glucan and inulin[102,103]. For example, arabinoxylan, a constituent of hemicelluloses, is an important source of phenolic compounds that may be released in the colon during fermentation of complexed fibers[4,102]. These bioactive substances may protect the GI tract from oxidative damage, although this possibility is controversial due to the anaerobic environment in the colon and the fact that the fiber-associated phytochemicals (*e.g.*, carotenoids) do not seem to be absorbed through the GI tract into the rest of the body, even though the colon is the primary site for fiber fermentation and the release of these chemicals[104]. However, since the concentrations of bioactive substances derived from dietary fiber sources can be much higher in the colonic lumen than in plasma and other tissue, these phytochemicals may delay the onset of colon cancer.

CONCLUSIONS AND PERSPECTIVES

A large amount of research has reported an inverse relationship between dietary fiber intake and colon cancer risk. The protective effect of fiber against colon cancer derives from a multi-layered system of mechanistic checks and balances, which may explain why not all studies report this beneficial effect. Although the anticancer mechanisms of dietary fiber are not fully understood, several modes of action have been proposed (Figure 1). First, dietary fiber resists digestion in the small intestine, and enters the colon where it is fermented to produce SCFAs that may enhance the healthy composition of gut microbiota. Second, SCFAs have anticancer properties which include the promotion of cancer cell cycle arrest, apoptosis, and the inhibition of chronic inflammatory process and cancer cell migration/invasion in the colon. Importantly, these molecular activities are effective only within a certain physiological concentration range of the SCFAs. Third, dietary fiber increases fecal bulking and viscosity, reduces the time for proteolytic fermentation that results in harmful substances, and shortens the contact between potential carcinogens and mucosal cells. In addition, dietary fiber can bind/excrete potential luminal carcinogens (*e.g.*, secondary bile acids), lower fecal pH in the colon, and thus provide a healthy intestinal environment.

Not all fibers have the same properties; therefore, the characteristics and components of dietary fibers (*e.g.*, arabinoxylan, β-glucan) may determine their modes of action against colon cancer cells. Future studies on the type of fiber and fiber components may provide a better understanding of how and why dietary fiber decreases the risk of colon cancer. Furthermore, evidence from many lines of research demonstrates that fiber consumption modifies the composition of gut microbiota, and a well balanced colonic microbiota influences the host at nearly every level including immunity and neoplastic development. Metagenomics is one of the newest approaches to determine gut microbiota composition, but it is still difficult to characterize the interactions between hosts and their microbiota. The combination of several "meta" analyses such as metagenomics, metabolomics, metatranscriptomics, and the shift of focus from a "who is there" to a "why are they there" will advance our understanding of the relationship between dietary fiber consumption, microbiota composition, and human health. Future studies are required to unravel the microbiota changes that correlate with the beneficial effects of fiber, although it is likely that such changes in the gut bacteria may be dose-,

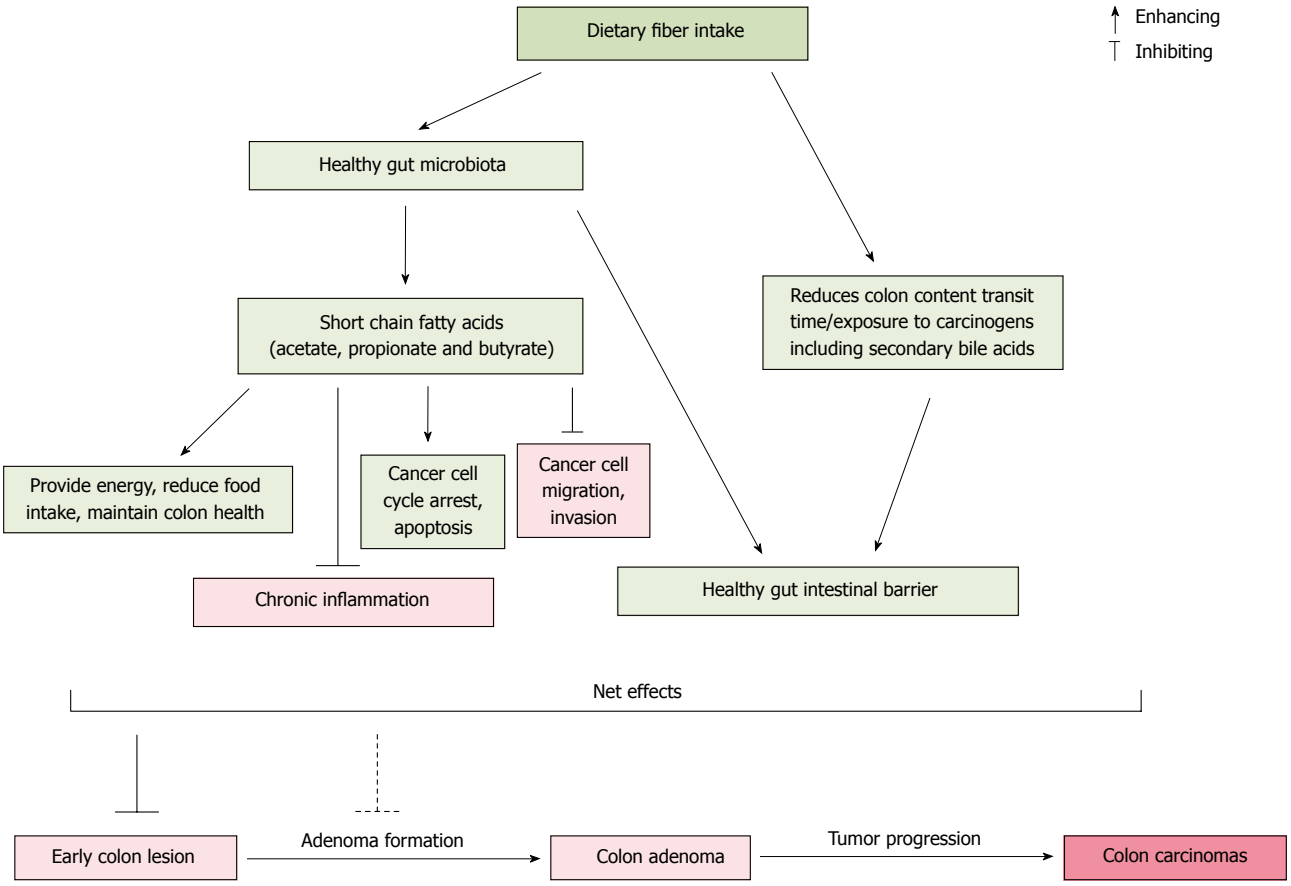

Figure 1 The proposed interaction of primary pathways related to dietary fiber consumption, gut microbiota and colon cancer risk.

time-, and strain-dependent. These efforts may lead to identification of microbiota signatures that are causal or correlative biomarkers for fiber consumption and colon cancer prevention.

If butyrate is indeed the key mediator for the protective effect of fiber against colon cancer, then the effects of diet and microbiota on the butyrate levels in the colon, and our ability to manipulate these levels *via* dietary supplements, will be important for designing effective colon cancer preventive strategies. The levels of fecal butyrate among individuals differ widely (3.5-32.6 mmol/kg), and these inter-individual differences have been explained in part by body-mass index and dietary intake of protein, fiber, and fat[105]; however, there are additional factors that remain to be determined.

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CASE REPORT

Extended cancer-free survival after palliative chemoradiation for metastatic esophageal cancer

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Abstract

We report on a patient who remained cancer-free for an extended time after palliative radiotherapy (RT) and chemotherapy (nedaplatin plus 5-fluorouracil) treatment for stage Ⅳ (cT3N3M1) esophageal squamous cell carcinoma. Although multiple lymph nodes outside the RT field recurred, the local primary tumor within the RT field did not recur, even 17 mo after palliative RT of 30 Gy in 10 fractions. In this case, acute toxicity, such as myelosuppression or esophagitis, was not enhanced by increasing the fraction dose from 1.8-2.0 Gy to 3.0 Gy. Because 30 Gy in 10 fractions can be completed within a shorter time and is less expensive than 50.4 Gy in 28 fractions, we think that 30 Gy without oblique beams is a more favorable RT method for patients.

Key words: Radiotherapy; Chemotherapy; Esophageal cancer; Esophageal stenosis; Metastatic esophageal cancer

Core tip: The palliative therapy method has not been confirmed for metastatic esophageal cancer. This case report represents a patient who was cancer-free for an extended period of time after palliative chemoradiation of 30 Gy in 10 fractions. We think that 30 Gy without oblique beams is a more favorable radiotherapy method for patients.

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INTRODUCTION

Esophageal cancer, which has the highest incidence and mortality worldwide, is one of the most common malignant tumors in Japan. Japan is recognized as having one of the highest incidence rates of esophageal squamous cell carcinoma in the world.

Due to a lack of obvious early symptoms, patients are often diagnosed at advanced stages, and more than half of patients present with metastases[1]. The recurrence and metastasis rates of esophageal cancer after treatment have tended to increase in recent years. In 2007, Grünberger *et al*[2] confirmed that palliative chemotherapy can prolong the survival of stage Ⅳ esophageal cancer patients, relieve their symptoms and improve their quality of life. Esophageal squamous cell carcinoma is the most common histology in Japan, and its constituent ratio is different from that in Europe and America.

Most patients with esophageal cancer present with dysphagia, and more than half of the patients have inoperable disease at the time of presentation[3,4]. The pri-

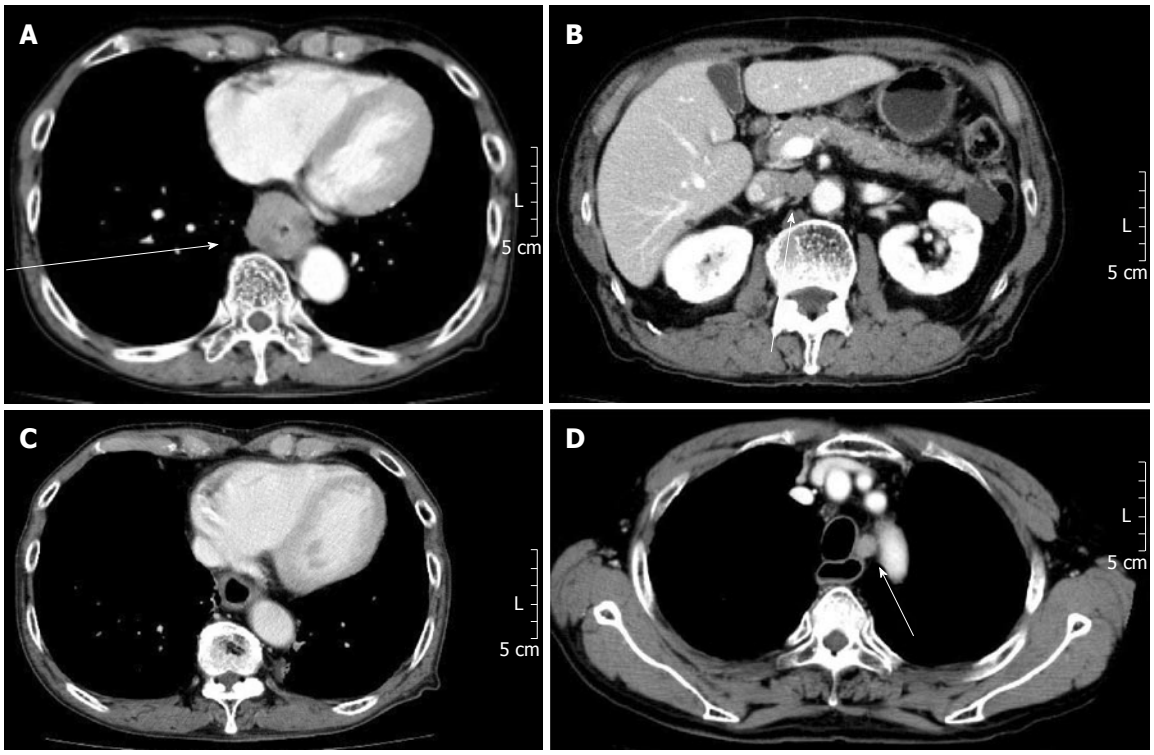

Figure 1 Computed tomography. A: Circumferential wall thickening and a 39 mm × 35 mm tumor on the lower thoracic esophagus; B: Swelling of the abdominal para-aortic lymph node; C: A remarkable shrinking of the mass in the lower esophagus; D: Swelling of the left para-tracheal lymph node.

mary aim of treatment in these patients is to relieve the dysphagia with minimal morbidity and mortality and thus improve their quality of life.

We present a case of extended cancer-free survival after palliative radiotherapy (RT) and chemotherapy in a stage IV esophageal squamous cell carcinoma patient.

CASE REPORT

A 76-year-old Japanese man was referred to our hospital after a few months of dysphagia due to esophageal stenosis. A chest X-ray did not show any characteristic malignancy. A gastrofiberscopy and computed tomography (CT) scan showed a circumferential wall thickening and a 39 mm × 35 mm tumor on the lower thoracic esophagus (Figure 1A). A biopsy on December 13, 2011, revealed squamous cell carcinoma. Laboratory findings, including staining for tumor markers, such as p53, and squamous cell carcinoma, were all within the normal ranges, except for the cytokeratin 19 fragments (CYFRA), which were elevated at 4.3 ng/mL (normal 0-2.0 ng/mL, IRMA method). A chest/abdominal CT scan with enhancement on December 5, 2011, revealed multiple lymph node metastases, including the left supraclavicular, tracheal bifurcation, gastric cardia, and abdominal para-aortic lymph nodes (Figure 1B) (cT3N3 M1, c-Stage IV).

It was decided that our patient should undergo chemoradiation therapy (CRT). The patient received 30 Gy in 10 fractions of 3 Gy on the original tumor location using a 2-field technique of external beam irradiation from December 21, 2011, to January 10, 2012. The patient also received nedaplatin chemotherapy at a dose of 80 mg/m^2 (day 1) plus 5-fluorouracil at 800 mg/m^2 per day (days 1-4) starting on December 26, 2011.

A plain chest/abdominal CT scan on January 23, 2012, after a single cycle of chemotherapy, revealed a remarkable shrinkage of the mass in the lower esophagus and in all lymph nodes (Figure 1C). An enhanced chest/abdominal/pelvic CT scan on April 17, 2012 (after 4 cycles), August 20, 2012 (after 7 cycles), and October 16, 2012, revealed that the tumors continued to shrink. After 6 cycles of chemotherapy, the CYFRA levels had decreased to normal by June 15, 2012. One additional cycle of chemotherapy was added on July 17, 2012. After CRT, the patient had regular follow-up appointments every 3-4 mo.

After 8 completely asymptomatic months following chemotherapy and 14 mo after palliative RT, the tumor was found to have recurred during a regular follow-up appointment. A chest and abdominal enhanced CT scan on March 12, 2013, revealed that the metastatic tumor had spread to multiple lymph nodes, including the retro-esophageal, left para-tracheal (Figure 1D), supraclavicular, and bilateral hilum lymph nodes, but local recurrence was not observed. According to a cervical/chest/abdominal enhanced CT scan that was performed on June 11, 2013 (17 mo after palliative RT), local disease remained controlled.

DISCUSSION

More than 50% of patients with esophageal cancer are not amenable to surgical excision at the time of diagno-

sis, because of either advanced disease or the presence of comorbid conditions. For such patients, palliation of the symptoms is the mainstay of treatment[4].

According to the Radiation Therapy Oncology Group 94-05 trial[5], the standard radiation dose for patients with clinical stage T1 to T4, N0/1, M0 esophageal carcinoma that are selected for a nonsurgical approach and concurrent treatment with 5-FU and cisplatin chemotherapy is 50.4 Gy. Additionally, at our institution, 50.4 Gy in 28 fractions is selected as a curative method. In this case, 30 Gy in 10 fractions was selected as a palliative irradiation dose. Although multiple lymph nodes outside the RT field recurred, the local primary tumor within the RT field did not recur, even 17 mo after RT. In this case, acute toxicity, such as myelosuppression or esophagitis, was not enhanced by increasing the fraction dose from 1.8-2.0 Gy to 3.0 Gy. Because 30 Gy in 10 fractions was completed within a shorter time and was less expensive than 50.4 Gy in 28 fractions, we think that 30 Gy without oblique beam is a more favorable RT method for patients. Because control of the primary lesion of esophageal cancer is directly connected to the inability of the patient to ingest and the subsequent QOL deterioration, a total radiation dose of as much as 30 Gy, not 25 or 20 Gy, was used with palliative intent in our institution.

According to Matsumoto *et al*[5], docetaxel and nedaplatin combination chemotherapy with and without radiation therapy is well tolerated (2-year overall survival was 11.1%) and useful as a second-line chemotherapy for patients with relapsed or metastatic esophageal cancer.

COMMENTS

Case characteristics

A 76-year-old male was referred to our hospital with a few month history of dysphagia due to esophageal stenosis.

Clinical diagnosis

A gastrofiberscopy and computed tomography scan showed a circumferential wall thickening and a 39 mm × 35 mm tumor on the lower thoracic esophagus.

Differential diagnosis

Esophageal leiomyoma, polyp, hemangioma, papilloma, lipoma, cyst.

Laboratory diagnosis

Laboratory findings, including tumor markers like p53 and squamous cell carcinoma, were all within normal values, except for cytokeratin 19 fragments, which was raised at 4.3 ng/mL (normal 0-2.0 ng/mL, IRMA method).

Imaging diagnosis

A chest/abdominal computed tomography scan revealed multiple lymph node metastases such as left supraclavicular, tracheal bifurcation, gastric cardia, and abdominal para-aortic lymph node (cT3N3M1, c-Stage Ⅳ).

Pathological diagnosis

A biopsy revealed a squamous cell carcinoma.

Treatment

The patient was treated with 30 Gy in 10 fractions of external beam irradiation and chemotherapy of nedaplatin plus 5-fluorouracil.

Related reports

According to Matsumoto H, docetaxel and nedaplatin combination chemotherapy with and without radiation therapy is well tolerated and useful (2-year overall survival was 11.1%) as second-line chemotherapy for patients with relapsed or metastatic esophageal cancer.

Experiences and lessons

The authors think that 30 Gy without oblique beams is a more favorable palliative radiotherapy method for patients with metastatic esophageal cancer.

Peer review

This article applies a rare case who survived long time after palliative chemoradiation.

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Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computa-

tional effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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