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GI ONCOLOGY (R BRESALIER, SECTION EDITOR)

Fiber, Fat, and Colorectal Cancer: New Insight into Modifiable Dietary Risk Factors

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Abstract

Purpose of Review To review recent data on the role and interactions of fiber and fat as dietary risk factors associated with colorectal cancer (CRC) risk in humans.

Recent Findings Fiber intake shows convincing and linear dose-response negative correlation with CRC risk. Dietary fiber stimulates butyrogenic activity of the gut microbiota, providing high amounts of butyrate that shows extensive anti-neoplastic effects. A high-fat diet promotes CRC risk through stimulated bile acid metabolism, facilitating bile acid conversion by the gut microbiota to tumor-promoting deoxycholic acid. Comprehensive interactions of these microbial metabolites are likely to underlie mechanisms driving diet-dependent CRC risk in different populations, but require further experimental investigation.

Summary Dietary fiber and fat shape the composition and metabolic function of the gut microbiota, resulting in altered amounts of butyrate and deoxycholic acid in the colon. Fiber supplementation and restriction of fat intake represent promising strategies to reduce CRC risk in healthy individuals.

Keywords Colorectal cancer risk · Fiber · Fat · Butyrate · Bile acids · Gut microbiota

Introduction

Colorectal cancer (CRC) was the third most common type of cancer worldwide in 2012 and accounted for about 1.4 million new cases [1]. CRC incidence is rising in many low- or middle-income countries that adopt a Western lifestyle, whereas rates decrease or remain at high level in countries already facing a high risk of CRC [2]. The majority of cases of sporadic CRC are attributed to environmental factors such as diet that promote detrimental genetic alterations in the colonic epithelium [3]. Dietary fiber shows a significant inverse correlation with CRC risk, whereas intake of fat and red meat is positively associated with CRC risk in humans [4]. Here, we focus on recent studies that investigated associations for fiber, fat, and CRC risk and critically review evidence on related multifaceted interactions of diet, the gut microbiota and host.

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Butyrate Links Dietary Fiber and the Gut Microbiota to CRC Risk

Dietary fiber is comprised of a heterogeneous group of complex carbohydrates that are indigestible for the host and fermented by gut bacteria in the colonic lumen to short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate. A recent meta-analysis covering 185 prospective trials and 58 clinical studies provided convincing evidence for an inverse correlation of fiber intake and CRC risk [5••]. Focusing on the observational studies in the meta-analysis, the highest fiber consumption was associated with a significant decrease in CRC incidence compared with lowest intake [5••]. Since a linear dose-response relationship for dietary fiber and CRC incidence was identified, the authors suggested the adult daily intake of fiber to be not less than 25–29 g and speculated that higher amounts would have greater protective effects [5••]. This was further supported by a recent

prospective study, where the highest intake of fiber was associated with a significantly reduced incidence of adenomas in distal colorectum [6]. Reynolds et al. confirmed a strong inverse association of whole grain intake and CRC risk and a similar trend was demonstrated for cereal fiber [5••, 6]. However, as stated by the authors, few data were available for other sources of fiber (e.g., fruit, vegetables), limiting the detailed analysis of specific dietary sources. The need for further studies to compare the impact of different types of fiber was highlighted by recent experimental evidence, showing that only some of the nine tested fiber types reduced severity of chemically induced colitis in wild-type mice [7].

A recent study by our group demonstrated that a switch from low-fiber, high-fat to high-fiber, low-fat diet resulted in significantly improved metabolic and microbial markers associated with CRC risk in healthy African American individuals that face the highest CRC risk in the contiguous US (CRC incidence: 65:100,000) [8••]. The high consumption of fiber led to increased levels of fecal SCFA, in particular butyrate, greater abundance of butyrogenic bacteria in feces, and improved mucosal markers of proliferation and inflammation in the colon of African Americans. In rural Africans, who consume a high-fiber, low-fat diet and have a remarkably low CRC risk (< 5:100,000), the switch to a Western diet, low in fiber and high in fat, resulted in significant decreases of fecal butyrate and butyrate-producing bacteria and increased CRC-associated markers in the colonic mucosa [8••]. Considering the genetic similarity of both ethnic populations and the isocaloric diet switches in their original environment, this study provided strong supportive evidence for dietary fiber protecting from high CRC risk (the role of dietary fat in that experimental setting is discussed further below). It also demonstrated that the retained butyrogenic capacity of the gut microbiota in individuals consuming a low-fiber diet can be targeted by supplying fiber as substrate. This conserved metabolic capacity provides an interesting target in terms of CRC prevention and indicates that the intake of fiber-rich foodstuffs may be well tolerated and highly butyrogenic in populations at high CRC risk.

However, this has to be critically tested in populations facing a high CRC risk, since a study by Wu et al. demonstrated that a higher intake of fermentable substrates did not lead to significantly increased levels of fecal SCFA in a small US study cohort [9]. The authors suggested that additional substrate availability may promote only minimally increased amounts of microbial metabolites due to a saturation effect that stems from a "restrictive" community structure of the gut microbiota prevalent in "Westernized populations" [9]. This is supported by a recent study, where the administration of a low-fiber diet to mice over several generations promoted a loss of taxa, that was not recoverable by reintroduction of fiber [10•]. Together, this may suggest the existence of a critical threshold for losses of butyrogenic bacteria or of "keystone species" involved in saccharolytic fermentation in populations pursuing a "Western lifestyle" [10•, 11].

A low-fiber diet also stimulated the activity and growth of mucus-degrading bacteria (e.g., *Akkermansia muciniphila*) in a simplified microbiota, resulting in a penetrable mucus barrier and aggravated colitis after infection of wild-type mice with a murine pathogen [12]. Similar defects in the colonic mucus layer were observed when conventional wild-type mice received a Western diet low in fiber, which was accompanied by attenuated butyrate levels in cecum and prevented by administration of inulin [13•]. A recent prospective cohort study identified an interesting inverse association of "prudent diet" consumption and CRC positive for *Fusobacterium nucleatum*, while there was no significant correlation with *F. nucleatum*-negative CRC or between Western diet and these parameters [14]. It was demonstrated that *Fusobacterium* is associated with colonic tumorigenesis [15, 16] and *F. nucleatum* showed increased abundance in feces when rural Africans switched to a low-fiber, high-fat diet [8••], but the underlying mechanistic link remains unclear. Together, these studies suggest the loss of dietary fiber to be a critical marker associated with CRC risk that modulates gut microbiota composition and metabolic activity, in particular butyrate synthesis.

Butyrate is the main source of energy for colonic epithelial cells (colonocytes), a major regulator of colonocyte proliferation, differentiation, and barrier integrity, and has potent tumorsuppressive effects in the colon [4]. In an elegant experimental study, Donohoe et al. associated gnotobiotic wild-type mice with a minimal microbiota with or without the butyrogenic bacterium *Butyvibrio fibrisolvens*, kept mice on a low- or high-fiber diet, and induced colonic tumorigenesis using azoxymethane (AOM) and dextran sodium sulfate (DSS) [17••]. Mice receiving a high-fiber diet and colonized with *B. fibrisolvens* showed significantly less colonic tumors after AOM/DSS treatment compared with mice on a high-fiber diet without *B. fibrisolvens*. The protective effect of butyrogenic *B. fibrisolvens* colonization was abolished when mice received a low-fiber diet [17••]. This was confirmed by a second experiment where wild-type *B. fibrisolvens* protected from colonic tumor formation in a fiber-dependent manner compared with an isogenic deletion mutant that produced less butyrate [17••]. Critically, an additional group of mice that received a diet supplemented with tributyrin, a stable derivative of butyrate that shows delayed absorption in the gut, had the lowest tumor levels in the colon after AOM/DSS treatment [17••]. Finally, the authors demonstrated that the anti-tumorigenic effect of butyrate could be attributed to its accumulation in tumor cells, where it acted as histone deacetylase inhibitor regulating cell proliferation and apoptosis [17••]. Further supporting a potential link between butyrate and DNA repair mechanisms, the administration of butyrylated starch inhibited the accumulation of the carcinogenic DNA

adduct O^6-methyl-2-deoxyguanosine (O^6MeG) caused by high intake of red meat in the colon of healthy human subjects [18]. Compared with high-red meat diet alone, the addition of butyrylated starch to the diet resulted in less enhanced rates of epithelial proliferation detected in rectal human biopsies [18]. Together, these studies demonstrate that fiber or butyrate, respectively, do not only preserve intestinal homeostasis, but also limit detrimental effects of other dietary factors associated with CRC risk.

Dietary Fat Affects Gut Microbiota Composition and Alters Bile Acid Metabolism

Recent studies using different rodent models of intestinal tumorigenesis confirmed that a high-fat diet promotes intestinal tumor formation by several mechanisms: The administration of a Western diet containing high amounts of fat resulted in an increased penetrability of the inner mucus layer and overall slower mucus growth in the colon of wild-type mice compared with mice receiving a control diet [13•]. This correlated with an altered composition of the gut microbiota showing reduced abundance of potential fiber-fermenting bacteria and of the genus *Bifidobacterium*, lower α-diversity and lower levels of SCFA in mice fed the Western diet [13•]. Defects in mucus barrier were prevented when mice on the Western diet received a fecal transplantation from mice fed the control diet, suggesting the diet-driven changes of the colonic mucus barrier to be mediated by the gut microbiota. In a mouse model susceptible to intestinal tumorigenesis due to epithelial overexpression of oncogenic *K-ras*, the administration of a high-fat diet stimulated tumor formation in the small intestine compared with a control diet [19]. The gut microbiota showed an altered composition after a high-fat diet and its tumor-promoting activity was successfully transferred to susceptible mice on a control diet, but not to control mice, suggesting that genetic susceptibility of the host was required in this experimental setting [19]. Similar shifts in microbiota composition were observed when wild-type rats received additional cholic acid in their diet and oral supplementation with deoxycholic acid (DCA)-enhanced tumor progression in $Apc^{Min/+}$ mice [20, 21], indicating that bile acid metabolism may be involved in the tumor-promoting activity of the gut microbiota.

A high intake of fat stimulates hepatic synthesis of bile acids and their enhanced delivery to the colon, where complex biotransformation of bile acids is performed by the gut microbiota. Following de-conjugation of primary bile acids, the conversion by 7α-dehydroxylating bacteria during the colonic transit promotes high levels of secondary bile acids such as DCA, which demonstrated experimental tumor-promoting activity [22]. Healthy African Americans consuming a high-fat, low-fiber diet had greater amounts of bile acids and 7α-dehydroxylating bacteria in feces compared with healthy rural Africans that consumed a low-fat, high-fiber diet [8••]. Reciprocal diet switches promoted decreased levels of bile acids in feces of African American individuals, whereas rural Africans showed increased amounts of DCA and other bile acids, both correlating with mucosal markers of CRC risk [8••].

A growing body of evidence supports the hypothesis that the effect of fat on CRC risk may stem from its role in bile acid metabolism of the host and gut microbiota [22]. Wild-type mice fed a high-fat diet developed significantly more colonic tumors after 21 months compared with mice on a control diet, correlating with higher cell proliferation in colonic crypts, impaired bile acid transport, and altered activity of the farnesoid X receptor (FXR), a nuclear receptor that regulates bile acid synthesis [23]. Mice lacking FXR feature a dysregulated bile acid pool with high levels of hepatic DCA and high numbers of 7α-dehydroxylating bacteria in feces [24•]. The administration of a diet rich in fat augmented the dysregulation of bile acid metabolism and aggravated hepatic inflammation and tumor growth compared with FXR knock-out mice on control diet or wild-type controls [24•]. Finally, a recent meta-analysis confirmed a higher 7α-dehydroxylating capacity of the fecal microbiota in metagenomes from CRC patients [25]. Beyond its effect on bile acid metabolism, different dietary lipids may stimulate growth of different members of the gut microbiota. A diet rich in fish oil led to a different microbiota composition in mice compared with a lard-based diet, the latter being linked to inflammation in white adipose tissue [26]. Diets rich in saturated, but not poly-unsaturated fat, promoted the growth of *Bilophila wadsworthia*, a member of the gut microbiota associated with experimental colitis and CRC risk in humans [27–29]. In addition, recent studies suggested that fat affects the formation of carcinogenic DNA adducts [30] and triggers proliferation of intestinal stem and progenitor cells with tumor-initiating capacity [31], for example, highlighting the multifaceted effects of dietary fat in the context of CRC risk.

Lack of Fiber or Excess of Fat: Major Contributors to CRC Risk?

Recent experimental evidence supported the hypothesis that high-fat intake is associated with lower SCFA levels in the colon, in particular butyrate [8••, 13•, 19, 32, 33]. This coincided with a loss of butyrogenic bacteria after high-fat feeding or oral supplementation of bile acids, respectively [8••, 19, 20, 24, 33]. In addition, early dietary intervention studies in healthy individuals demonstrated that the addition of fiber to the normal diet, high in fat and low in fiber, led to significantly lower levels of secondary bile acids in feces [34, 35]. However, few studies investigated the relationship of tumor-promoting DCA and tumorsuppressive butyrate,

demonstrating an interesting antagonistic regulation of the reciprocal metabolite pools and related metabolic functions of the gut microbiota.

The addition of inulin or butyrate, respectively, restored the defective mucus barrier or impaired the intestinal tumor progression caused by high-fat feeding in different mouse models [13•, 19]. When cholic acid was supplemented to the diet of wild-type rats, lower levels of SCFA correlated with greater amounts of DCA in the cecal lumen [20]. Finally, mice showing an altered hepatic bile acid metabolism due to deletion of FXR had lower levels of butyrogenic bacteria and butyrate in the colon [24•]. The addition of butyrate to the diet of the mice lacking FXR reduced the grade of hepatic inflammation induced by high-fat feeding and led to lower numbers of 7α-dehydroxylating bacteria in feces [24•]. In this study, colonic levels of butyrate were negatively correlated with hepatic DCA, suggesting complex interdependences between both metabolites that are likely to affect other CRC-associated markers. It is tempting to speculate that the loss of butyrate and increase in DCA levels, initiated by diet-mediated changes of microbial metabolism, represent major early-stage events in the colonic lumen that precede epithelial dysfunction and transformation. Although the availability of butyrate seems to be a critical requirement to prevent intestinal tumorigenesis and inflammation caused by a high-fat diet [19, 24•], the specific sequence of events underlying the butyrate/DCA-mediated impact on CRC risk remains unclear. This targets unresolved questions: Are the relative loss of butyrate or the relative increase in DCA singular events coinciding or mutually conditioned by changes in host-gut microbiota co-metabolism in individuals at high CRC risk? Which of these two metabolites is the "main agent" mediating diet-related effects on CRC risk and how does this affect the evaluation of dietary intervention strategies to prevent CRC in high-risk populations?

The importance of these questions was supported by a series of in vitro experiments, which showed mostly opposing functions of DCA and butyrate on apoptosis and proliferation of epithelial cells. The incubation with DCA stimulated proliferation, inhibited apoptosis induced by butyrate, and promoted DNA damage in different human epithelial colon adenocarcinoma cell lines and colon biopsies, which was reduced in the presence of butyrate [36–38]. Both metabolites induced apoptosis in colon cancer cell lines, but while butyrate regulated cell cycle progression by increased expression of tumor suppressor p21, DCA stimulated the formation of intracellular reactive oxygen species, triggered DNA fragmentation, and led to phosphorylation of intracellular ERK1/2, known to promote tumor growth [39].

In an attempt to functionally characterize different metabolite profiles in relation to the corresponding fecal butyrate and DCA levels, we prepared fecal water extracts collected from feces of healthy individuals belonging to cohorts at high risk (HR) of CRC (urban Alaska Native people [40]) or low risk (LR) of CRC (rural African people from South Africa [8••]). Two human epithelial colon adenocarcinoma cell lines (Caco-2, HT-29) were incubated with fecal water extracts and the impact on cell growth assessed by colorimetric cell viability assay [41, 42]. The incubation with fecal water extracts derived from the HR population resulted in significantly

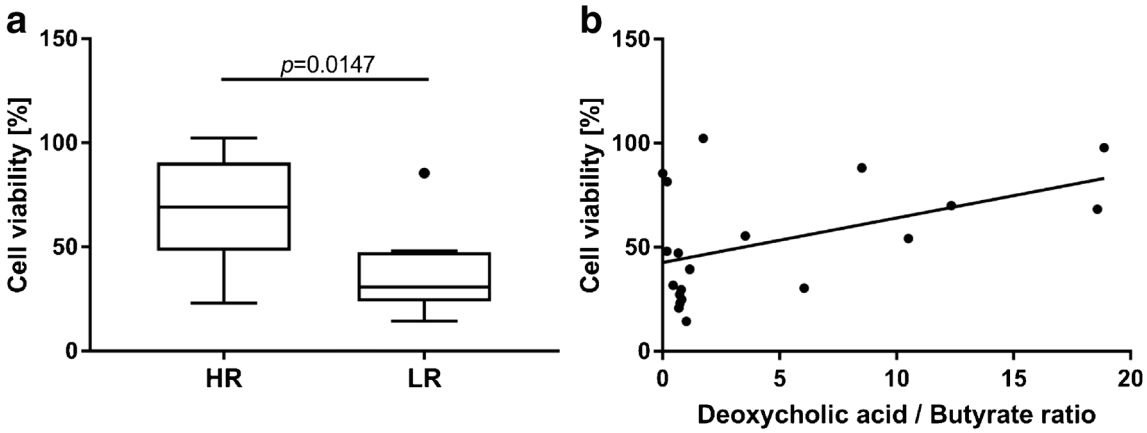

Fig. 1 Cell viability of human colon adenocarcinoma cells is differently affected by fecal water extracts from cohorts at different CRC risk. **a** Analysis of cell viability (calculated by relative comparison to untreated control) of Caco-2 or HT-29 human epithelial colon adenocarcinoma cells incubated with fecal water extracts by colorimetric cell viability assay (MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay; Invitrogen, Carlsbad, CA). Fecal water extracts were prepared from feces of healthy donors (n = 10/group; high-risk population (HR), low-risk population (LR)) as described before [41] and added to the cells for 48 h (10% final concentration). Graph shows combined percentaged change in cell proliferation for both cell lines (Caco-2, HT-29) using the same fecal water samples and similar conditions. Data are shown as box-and-whisker plot according to Tukey and statistical analysis performed by non-parametric Mann-Whitney U test. **b** Correlation analysis of detected cell viability and deoxycholic acid/butyrate ratio in corresponding fecal samples of healthy donors (HR and LR population, n = 10/group) (Pearson correlation coefficient r = 0.473; p = 0.035). Fecal deoxycholic acid and butyrate were quantified as described before [8•, 43].

higher cell viability of epithelial colon adenocarcinoma cells compared with the LR fecal water samples that restrained cell viability (Fig. 1a). The impact on cell viability showed a significant moderate correlation (Pearson's $r = 0.473$; $p = 0.0352$) with the DCA/butyrate ratio detected in the corresponding fecal samples (Fig. 1b) (DCA and butyrate were quantified as described before [8••, 43]). This suggests that fecal metabolite profiles with high DCA levels and low butyrate concentrations, both detected in high-risk populations of CRC [8••, 43], may be associated with lower inhibition of colon cancer cell proliferation in this assay setup. While it remains unclear, if butyrate or DCA, additional compounds or interactions of them, mediated the observed effects of fecal water on cell growth, this supports the idea that (1) individuals from populations at different CRC risk have functionally divergent colonic metabolite profiles, which (2) act differentially on the intestinal epithelium, and (3) this is related to DCA and butyrate as major microbiota-derived metabolites associated with CRC risk. Although the well-characterized setup and simple layout make this assay ideally suited for basic functional characterization of complex fecal metabolite extracts, the use of adenocarcinoma cell lines does not represent physiological conditions of the normal intestinal epithelium. Thus, it needs to be further investigated, if this functionally divergent effect of fecal water extracts from populations at different CRC risk can be confirmed in more physiological colonocytes or experimental models.

Conclusions

There is strong experimental evidence for fiber protecting from and fat promoting CRC risk. Both dietary factors have manifold effects on gut microbiota composition and metabolism, of which butyrogenesis and bile acid conversion are of critical importance in the context of CRC. The tumorsuppressive effects of butyrate are well characterized and warrant fiber supplementation as a promising conceptual approach to manipulate the microbial metabolism and reduce CRC risk also in high-risk populations. In addition, high-fat mediated changes in the bile acid pool and metabolism need to be restrained, in particular to reduce levels of tumor-promoting DCA in the colon. Together, this emphasizes the need for a balanced diet, a concept that has to be applied to other foodstuffs potentially involved in CRC risk, but not discussed in this review (e.g., red meat).

In the context of CRC risk, the sequence of diet- and microbiota-related events preceding early pre-neoplastic changes in the intestinal epithelium need to be further investigated. Given the lack of data regarding interactions of two major microbiota-derived metabolites associated with CRC risk, butyrate and DCA, controlled dietary intervention studies in populations of high CRC risk are warranted (e.g., by using fiber supplementation in high-risk cohorts). These need to be complemented by mechanistic studies to dissect interactions of the functional metabolic compartments (saccharolytic fermentation, SCFA production, bile acid metabolism), related substrates (fiber, fat), and microbial metabolites (butyrate, DCA) and to unravel their differential contribution to CRC risk.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent Fecal samples, used for preparation of water extracts, were taken during previous studies, where ethical and health research approval was obtained from all institutional review boards of all participating medical centers and health research entities. Informed consent was acquired before enrollment of study participants.

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