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## Familial adenomatous polyposis and changes in the gut microbiota: New insights into colorectal cancer carcinogenesis

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### Abstract

Patients with familial adenomatous polyposis (FAP), an autosomal dominant hereditary colorectal cancer syndrome, have a lifetime risk of developing cancer of nearly 100%. Recent studies have pointed out that the gut microbiota could play a crucial role in the development of colorectal adenomas and the consequent progression to colorectal cancer. Some gut bacteria, such as *Fusobacterium nucleatum*, *Escherichia coli*, *Clostridium difficile*, *Peptostreptococcus*, and enterotoxigenic *Bacteroides fragilis*, could be implicated in colorectal carcinogenesis through different mechanisms, including the maintenance of a chronic inflammatory state, production of bioactive tumorigenic metabolites, and DNA damage. Studies using the adenomatous polyposis coli<sup>Min/+</sup> mouse model, which resembles FAP in most respects, have shown that specific changes in the intestinal microbial community could influence a multistep progression, the intestinal "adenoma-carcinoma sequence", which involves mucosal barrier injury, low-grade inflammation, activation of the Wnt pathway. Therefore, modulation of gut microbiota might represent a novel therapeutic target for patients with FAP. Administration of probiotics, prebiotics, antibiotics, and nonsteroidal anti-inflammatory drugs could potentially prevent the progression of the adenoma-carcinoma sequence in FAP. The aim of this review was to summarize the best available knowledge on the role of gut microbiota in colorectal carcinogenesis in patients with FAP.

**Key Words:** Familial adenomatous polyposis; Microbiota; Colorectal cancer; Polyps; Carcinogenesis; Bacteria

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**Core Tip:** A number of studies have demonstrated that gut microbiota dysbiosis could be a key factor in colorectal carcinogenesis. The adenomatous polyposis coli (*APC*)<sup>Min/+</sup> mouse model has been extensively used to study the underlying mechanisms of colorectal carcinogenesis in familial adenomatous polyposis. Interventions aimed at improving dysbiosis by administration of probiotics, prebiotics, or antibiotics could decrease colorectal cancer development in *APC* mutation carriers.

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## INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colorectal cancer (CRC) syndrome characterized by the development of numerous (*i.e.* tens to thousands) colorectal adenomas[1,2]. A mutation in the adenomatous polyposis coli (*APC*) gene, found on chromosome 5q21, is responsible for FAP[3]. The incidence of FAP is around 1/8300, and the onset is commonly in the second or third decade of life. The risk of CRC is nearly 100% by the time patients with FAP reach the age of 40-50 years[4,5]. Such patients have an increased risk of desmoid tumors and gastric, duodenal, biliary duct, and thyroid cancers[6]. Extraintestinal manifestations of FAP may include osteomas, dental abnormalities such as unerupted or supernumerary teeth, congenital absence of one or more teeth, odontomas, and dentigerous cysts; and congenital hypertrophy of the retinal pigment epithelium[7,8]. Prophylactic colectomy is generally performed by age 40 in patients with FAP, and is the gold standard treatment to reduce the risk of developing CRC[9]. Nonetheless, colectomy is associated with postoperative morbidity and does not reduce the risk of developing extraintestinal manifestations of FAP[10]. Endoscopic surveillance of patients with FAP and their family members has decreased the occurrence of CRC at the time of FAP diagnosis by 55% and has also increased overall survival[4,11].

Recent studies have shown that the gut microbiota could play an important role in the development of colorectal adenomas and the consequent progression to CRC[12]. Indeed, gut bacteria such as *Fusobacterium nucleatum*, *Escherichia coli*, *Clostridium difficile*, *Peptostreptococcus*, and enterotoxigenic *Bacteroides fragilis*, could be responsible for colorectal carcinogenesis through a number of mechanisms, including the maintenance of a chronic inflammatory state, production of bioactive tumorigenic metabolites, and DNA damage[13-15]. A number of studies investigated the interaction between gut microbiota and host genetics in patients with intestinal adenomatous polyps. A study by Liang *et al*[16] showed a close relationship between the presence of *APC* mutation and modification of the gut microbiota and serum metabolites. Low levels of *Faecalibacterium prausnitzii* and an abundance of *Fusobacterium mortiferum* had the potential to predict the development of CRC from adenomatous polyps. It has been also observed that mutation of the *APC* gene could modify colonic-microbial interactions before the development of polyposis in mouse models[17]. After *F. nucleatum* infection, *APC*<sup>Min/+</sup> mice, carrying an inactivated allele of the *APC* gene, had an increase of small intestinal and colonic adenoma formation and an acceleration of small intestinal adenocarcinoma development[18]. Thus, it has been hypothesized that interventions aimed at improving dysbiosis in *APC* mutation carriers, including administration of probiotics, prebiotics, or antibiotics, could decrease CRC development. The aim of this review was to summarize the best available knowledge on the role of gut microbiota on colorectal carcinogenesis in patients with FAP.

## GENETIC FEATURES

The classic colorectal carcinogenesis model described by Fearon and Vogelstein[19] includes development of most CRCs from a minimum of five or more genetic

alterations, while adenomas require fewer alterations. It has been hypothesized that inactivating mutations of the *APC* gene could represent the initial step of the “adenoma-carcinoma sequence” (Figure 1). The *APC* gene is a fundamental component of the  $\beta$ -catenin and Wnt signaling pathways, modulating cell differentiation, adhesion, migration, and apoptosis[20]. Somatic mutations of the *APC* gene occur in around 80% of sporadic CRCs, whereas germline *APC* mutations are responsible for FAP, making this a key target to study the environmental and genetic modifiers of CRC[16,17]. Loss of *APC* gene function has been shown to produce a survival advantage by mimicking hypoxic conditions and stimulate the accumulation of  $\beta$ -catenin and abnormal cell proliferation, associated with development of adenomatous polyposis[21-24].

### Mouse models of FAP

Laboratory mouse models have proven to be valuable in the study of CRC[25]. The Min (multiple intestinal neoplasia) is the first key CRC mouse model and is induced by treatment with ethylnitrosourea[26]. Adult *APC*<sup>Min/+</sup> mice develop multiple intestinal polyps and anemia and usually die at a young age because of intestinal blockage and bleeding from the larger polyps[27]. Other mouse models have also been reported, such as conditional *APC* mutant alleles[28]. The *APC*<sup>Min/+</sup> mouse model shares numerous phenotypic and genetic similarities with FAP. However, patients with FAP develop adenomas mainly in the colon, while adenomas in *APC*<sup>Min/+</sup> mice are mainly located in the small intestine and have benign characteristics. Also, desmoid tumors and epidermoid cysts are rarely seen in mouse models compared with patients with FAP[29]. Nonetheless, the *APC*<sup>Min/+</sup> mouse represents an outstanding experimental model for investigating genetic features and therapeutic responses of CRC in humans.

### Bacterial genotoxicity

Interplay between the gut microbiota and genetic characteristics could be responsible for the genetic pattern of the adenoma-carcinoma sequence. It has been hypothesized that bacterial drivers could initiate the development of precancerous lesions and the subsequent accumulation of gene mutations[30,31]. Different gut bacteria, such as *E. coli*, *Enterococcus faecalis*, *Streptococcus gallolyticus* and *B. fragilis* have been shown to promote carcinogenesis through genotoxic effects[32]. Some *E. coli* strains, mainly B2 and D, strongly express virulence genes, such as those encoding toxins and effectors that could promote carcinogenesis (e.g., colibactin, cytotoxic necrotizing factors, cytolethal distending toxins, and cycle-inhibiting factor)[33,34]. Colibactin could be responsible for DNA alkylation on adenine residues, thus favoring double-strand breaks[35]. A recent study showed that expression of colibactin-producing polyketide synthase (*pks+*) in *E. coli* could be associated with the occurrence of a specific mutational signature in human gut organoids. The same mutational signature was detected in 5876 human cancer genomes in two independent study cohorts, especially in CRC[36]. Also, *pks+* *E. coli* could be responsible for aneuploidy and abnormal cellular division, an effect promoted by the mutagen colibactin[37]. Such effects of *pks+* *E. coli* were mainly observed in *APC*<sup>Min/+</sup> mice that lacked the autophagy gene *Atg16L1*, and consequently were not able to recruit the DNA repair protein RAD51, thus accumulating DNA double-strand breaks and developing tumors[38]. *Enterococcus faecalis* was shown to promote DNA damage by induction of inflammation and oxidative stress resulting from the release of reactive oxygen species and reactive nitrogen species[39]. Fragilysin (also known as BST), is a toxic virulence factor released by enterotoxigenic *B. fragilis* (ETBF) that can induce DNA damage *in vivo*[40]. Colonization by sulfidogenic bacteria, such as *F. nucleatum*, has been associated with genomic or chromosomal instability and CRC development associated with the genotoxic effects of hydrogen sulfide (H<sub>2</sub>S)[41,42]. A prior state of dysbiosis could enhance these specific bacterial genotoxic effects[31].

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## GUT MICROBIOTA AND CARCINOGENESIS

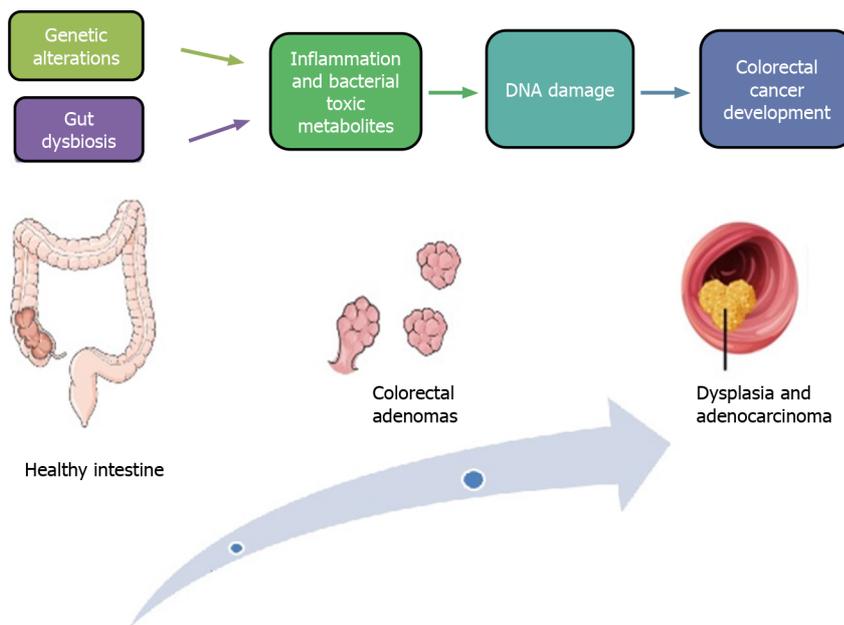
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There is extensive evidence of an association between infectious agents and development of tumors[43]. It has also been demonstrated that specific mucosa-associated bacterial species could play a pivotal role in the pathogenesis of CRC[44-46]. Indeed, bacterial toxins and effector proteins have been shown to damage host cell DNA, and therefore affect crucial host cell signaling pathways that regulate cell differentiation, apoptosis, proliferation, and immune signaling[47-57] (Table 1).

**Table 1 Studies of colorectal cancer-associated bacteria in the APC<sup>Min/+</sup> mouse model**

Ref.	Bacterial strain	Mechanism of carcinogenesis
Kostic <i>et al</i> [18], 2013	<i>F. nucleatum</i>	Infiltration of CD11 <sup>+</sup> myeloid-derived immune cells
Tomkovich <i>et al</i> [49], 2017	<i>F. nucleatum</i> and <i>pks+</i> <i>E. coli</i>	Mediated by inflammation, with colibactin-producing <i>E. coli</i> but not with <i>F. nucleatum</i> (FadA <sup>+</sup> or Fap2 <sup>+</sup> )
Yang <i>et al</i> [50], 2017	<i>F. nucleatum</i>	Regulation of miR-21 <i>via</i> TLR4/MYD88/NF-κB pathway
Wu <i>et al</i> [51], 2018	<i>F. nucleatum</i>	TLR4/p-PAK1/p-β-catenin S675 pathway
Chen <i>et al</i> [52], 2018	<i>F. nucleatum</i>	Induction of M2 macrophage polarization <i>via</i> TLR4. Activation of the IL-6/p-STAT3/c-MYC signaling pathway
Rubinstein <i>et al</i> [53], 2019	<i>F. nucleatum</i>	FadA adhesin upregulates Annexin A1 expression through E-cadherin
Dejea <i>et al</i> [54], 2018	Mono- or co-colonization of ETBF and <i>pks+</i> <i>E. coli</i>	Upregulation of IL-17 and DNA damage
Chung <i>et al</i> [55], 2018	ETBF	Pathway involving activation of IL-17R, NF-κB, Stat3, and CXCL1
Goodwin <i>et al</i> [56], 2011	ETBF	Production of spermine oxidase, reactive oxygen species and DNA damage
He <i>et al</i> [57], 2019	<i>Campylobacter jejuni</i>	DNA damage due to cytolethal distending toxin
Li <i>et al</i> [15], 2019	Mixed strains from fecal samples of CRC patients after antibiotic cocktails	Wnt/β-catenin and cyclin D1 pathway

CRC: Colorectal cancer; *E. coli*: *Escherichia coli*; ETBF: Enterotoxigenic *Bacteroides fragilis*; *F. nucleatum*: *Fusobacterium nucleatum*; IL: Interleukin; NF-κB: Nuclear factor-kappa B; *pks*: Producing polyketide synthase; TLR: Toll-like receptor.



**Figure 1 Pathway of the development of colorectal adenomas and the consequent progression to colorectal cancer.**

**Dysbiosis and bacterial toxins**

Changes in the gut microbiota, can stimulate the c-Jun/JNK and STAT3 signaling pathways, thus promoting, in combination with anemia, tumor growth in APC<sup>Min/+</sup> mice[58]. A study carried out in APC<sup>Min/+</sup> mice by Son *et al*[17] reported that mutation of the APC gene modified colonic-microbial interactions prior to polyposis. Indeed, changes in the gut microbiota, characterized by an increased relative growth of *Bacteroidetes spp.* identified in association with intestinal tumors, has been shown to precede the development of microscopically evident intestinal tumors in 6-wk-old APC<sup>Min/+</sup> mice. A recent study by Dejea *et al*[54] detected colonic biofilms mainly composed of *E. coli* and *B. fragilis* in patients with FAP. Genes for colibactin (*clbB*) and *B. fragilis* toxin (*bft*) were highly expressed in the colonic mucosa of patients with FAP

compared with healthy subjects. Co-colonization with *E. coli* and ETBF led to an increase in interleukin-17 (IL-17) and DNA damage in colonic epithelium of tumor-prone mice, compared with mice with either bacterial strain alone. As ETBF and *pks+* *E. coli* frequently colonize young children, it has been suggested that constant co-colonization in the colon mucosa from a young age could play a role in the pathogenesis of FAP[54]. The *B. fragilis* toxin (BFT) can bind to intestinal epithelial-cell receptors, promoting cell proliferation through cleavage of the tumor suppressor protein E-cadherin[55]. It has been shown that BFT can provoke acute and chronic colitis in C57BL/6 mice, and colon tumors in an *APC<sup>Min/+</sup>* mouse model[59-61]. Infections with enterotoxigenic strains of *B. fragilis*, compared with non-toxigenic strains, were more frequently observed in patients with CRCs. Enterotoxigenic strains were detected in only 10%-20% of healthy controls, but enterotoxigenic *B. fragilis* was found in stool samples from 40% of CRC patients[62]. A study by Tomkovich *et al*[49] carried out in germ-free, specific-pathogen-free, and gnotobiotic *APC<sup>Min/+</sup>;IL10<sup>-/-</sup>* mice reported that colon carcinogenesis was associated with an inflammatory state. CRC did not develop in germ-free *APC<sup>Min/+</sup>;IL-10<sup>-/-</sup>*, and *pks+* mice. *E. coli* promoted carcinogenesis in the *APC<sup>Min/+</sup>;IL-10<sup>-/-</sup>* model in a colibactin-dependent way. An interesting study by Li *et al*[15] investigated the role of gut microbiota on adenoma progression in *APC<sup>Min/+</sup>* mice. Transplants of gut microbiota from CRC patients into *APC<sup>Min/+</sup>* mice enhanced the progression of adenoma, damaged the intestinal barrier, promoted chronic low-grade inflammation, and stimulated the Wnt signaling pathway. These results suggest that microbial targeted therapy could represent a novel FAP therapy.

### Inflammation

Commensal and pathogenic bacteria were found to promote CRC development after colonizing normal colonic mucosa and promoting sustained local inflammation, and by releasing genotoxic compounds against colonic epithelial cells to induce their tumorigenic transformation[63]. Conversely, a balanced population of microbiota prevented development of CRC by producing bacterial metabolites that reduced inflammation[64]. Chronic inflammation is associated with the development of various tumors, including CRC. Inflammation of the colonic mucosa may enhance carcinogenic mutagenesis, thus favoring CRC initiation[65]. Also, a chronic inflammatory state is characterized by loss of IL-10-secreting regulatory T cells (Tregs) and stimulation of Th17 cells producing IL-17A, which supports IL-17A-dependent tumor growth, and promotes colonic carcinogenesis in the *APC<sup>Min/+</sup>* mouse model, which resembles FAP in most respects[66]. An association between *F. nucleatum* infection and increased expression of the nuclear factor-kappa beta (NF- $\kappa$ B) pro-inflammatory profile in mouse intestinal cancers has been observed, consistent with the development of human CRC[18]. FadA, a *Fusobacterium*-specific adhesion molecule, can facilitate *F. nucleatum* adherence to host cells[67], and *F. nucleatum* colonization was found to recruit tumor-infiltrating myeloid cells and stimulate the Wnt/ $\beta$ -catenin pathway, leading to NF- $\kappa$ B activation and cancer cell proliferation[68]. Chronic inflammation in *APC<sup>Min/+</sup>;IL-10<sup>-/-</sup>* mice was shown to modify the gut microbiota composition and selectively favor the growth of *Enterobacteriaceae*. Chronic inflammation also supported the selection of pathogenic strains of *E. coli* and was essential for the cancer-promoting effects of those bacteria[69]. Colonization of *APC<sup>Min/+</sup>* mice with ETBF led to the activation of a pro-tumorigenic multistep inflammatory cascade involving IL-17R, NF- $\kappa$ B, and Stat3 signaling in colonic epithelial cells. Indeed, BFT could stimulate a protumorigenic signal in colon mucosal epithelial cells that led to a Th17 response that in turn activated NF $\kappa$ B and myeloid cell-dependent carcinogenesis in the distal colon [55]. Grivennikov *et al*[70] reported that the loss of intestinal barrier function in *APC<sup>Min/+</sup>* mice induced by CRC-initiating genetic alterations led to adenoma invasion by microbial metabolites that stimulated inflammation and, in turn, cancer growth. It is noteworthy that even colonization of commensal bacteria can promote CRC. Indeed, infection of germ-free *APC<sup>Min/+</sup>;IL-10<sup>-/-</sup>* mice with commensals of specific-pathogen free mice enhanced the tumor load[49]. Commensal bacteria and their constituents have been shown to stimulate Toll-like receptors on tumor-infiltrating myeloid cells and MyD88-mediated production of inflammatory cytokines, such as IL-23. Therefore, IL-23 supported CRC development by activating the release of other cytokines, such as IL-6, IL-17A, and IL-22[71].

### Short-chain fatty acids and bacterial metabolites

A number of studies demonstrated that the gut microbiota was responsible for the production of various bioactive food elements and micronutrients, such as essential vitamins, and the fermentation of dietary fibers and complex carbohydrates, producing short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate

[72-74]. The role of butyrate in colorectal carcinogenesis is controversial[75]. In fact, in *APC<sup>Min/+</sup>; Msh2<sup>-/-</sup>* mice that were also deficient for the DNA mismatch repair gene MutS homolog 2, Belcheva *et al*[76] found that microbial metabolism of carbohydrates into SCFAs, such as butyrate, enhanced the proliferation of tumor-initiated epithelial cells, thus promoting carcinogenesis. In their study, the growth of SCFA-producing bacteria, such as *Clostridiaceae*, *Ruminococcaceae*, and *Lachnospiraceae*, was inhibited by antibiotic therapy or a low-carbohydrate diet, and in turn the number of polyps detected in *APC<sup>Min/+</sup>; Msh2<sup>-/-</sup>* mice was also reduced. On the other hand, many studies have described antineoplastic effects SCFAs, such as the suppression of inflammation, stimulation of apoptosis, and inhibition of cancer cell progression[77]. Nonetheless, further investigation is needed for clarifying the role of butyrate in CRC protection or promotion. Other bacterial metabolites, such as H<sub>2</sub>S, secondary bile acids, and nitric oxide, have been shown to contribute to progression of adenomatous colon polyps to CRC by affecting host metabolism and immunity[78].

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## CURRENT CLINICAL TRIALS

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A growing number of clinical trials have reported an association between gut bacteria and their metabolites and progression of CRC through various mechanisms[79,80]. However, the role of the gut microbiota in the progression and development of CRC is intricate and still not entirely understood, especially in patients with FAP. Currently, only a few clinical trials are recruiting subjects with FAP to determine whether modifying the gut microbiota might influence CRC development[81]. The Memorial Sloan Kettering Cancer Center in New York (United States), is conducting a clinical trial (Clinicaltrials.gov ID: NCT02371135) enrolling patients with Lynch syndrome or other hereditary colonic polyposis syndromes, in order to assess the role of the gut bacteria in CRC development. Investigators collect fecal samples, colon biopsies, and questionnaire responses on diet and lifestyle[82]. A phase 2, randomized, double-blind, placebo-controlled study sponsored by the Tel Aviv Sourasky Medical Center (Israel) is evaluating the efficacy of curcumin supplementation on polyp number and size in patients with FAP (Clinicaltrials.gov ID: NCT03061591)[83].

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## POTENTIAL THERAPEUTIC APPROACHES AND FUTURE DIRECTIONS

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It has been suggested that interventions directed at improving gut dysbiosis in *APC<sup>Min/+</sup>* mice, for instance through probiotics, prebiotics, some antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs), can inhibit the progression of the adenoma-carcinoma sequence, thus reducing the development of CRC[84-86].

### ***Fap-related pouch***

The ileoanal pouch is the surgical procedure of choice for patients with the classical phenotype of FAP[87]. Many studies have shown that the gut microbiota play a key role in the development of pouchitis, as supported by clinical evidence of the benefits of antibiotic therapy[88,89]. Metronidazole, ciprofloxacin, or a combination of both, is usually the initial approach, and it is often effective in chronic pouchitis[90]. A meta-analysis of 21 studies showed that antibiotics induced a significant remission rate (74%) in patients with chronic pouchitis (95% confidence interval: 56-93;  $P < 0.001$ ), whereas the remission rate after administration of biologics was 53% (95% confidence interval: 30-76;  $P < 0.001$ ). Conversely, steroids, bismuth, tacrolimus, and an elemental diet did not result in a significant remission, which was achieved by fecal microbiota transplantation[88]. Probiotics have been shown to be effective in the prevention of pouchitis[91]. Indeed, Shen *et al*[92] showed that administration of a probiotic treatment (*Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Bifidobacterium bifidus*) prevented pouchitis, decreased the Modified Pouch Disease Activity Index score, and reduced fecal pyruvate kinase and calprotectin in FAP patients after restorative proctocolectomy[93].

### ***Probiotics and prebiotics***

Gut microbiota composition and function are considerably modulated by diet[14]. An association between the intake of nondigestible fibers, such as prebiotics, and an abundance of beneficial bacteria in the gut, including *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, *Ruminococcaceae*, and *Roseburia* has been widely reported. Indeed

administration of both probiotics and prebiotics has shown beneficial effects in prevention and reduction of the prevalence of adenomatous colon polyps[94,95]. A metagenomic study by Ni *et al*[96] reported a preventive effect of *Lactobacillus rhamnosus* GG (LGG) on polyp formation in  $APC^{Min/+}$  mice. The results showed that LGG had beneficial effects and reduced polyp development in mice by preserving gut microbial functionality. A study by Urbanska *et al*[97] reported similar results using an orally delivered probiotic formulation that reduced overall intestinal inflammation and the number of polyps in the small intestine of  $APC^{Min/+}$  mice after administration of microencapsulated live *Lactobacillus acidophilus* cells.

### Antibiotics

There is evidence that antibiotic treatment can modify the gut microbiota physiological processes and functions[98]. Some studies showed that shifts in the composition of the intestinal community caused by antibiotics were associated with development of polyps and progression to CRC. Other studies reported a possible protective effect on carcinogenesis[99-101]. A nested case-control study by Dik *et al*[102] reported a significant dose-dependent association between administration of penicillin and quinolone antibiotics and increased risk of CRC development. Another nested case-control study by Boursi *et al*[103] carried out in a large population-based database in the United Kingdom, showed similar results, and concluded that past exposure to several courses of penicillin was associated with a slight increase in CRC risk. A recent study found that long-term treatment of  $APC^{Min/+}$  mice with an antibiotic cocktail composed of vancomycin, neomycin, and streptomycin resulted in gut inflammation with polyposis and cancer progression, perhaps caused by specific changes of the gut microbiota and thinning of the protective mucus layer[104]. On the contrary, Belcheva *et al*[76] observed a decreased number of polyps in both the small and large intestine of C57BL/6  $APC^{Min/+}$ ;  $Msh2^{-/-}$  mice treated with ampicillin, metronidazole, neomycin, and vancomycin. The gut microbiota in  $APC^{Min/+}$ ;  $Msh2^{-/-}$  mice might affect the development of CRC at an early stage, thus acting as a tumor initiator. These contrasting results suggest that the changes of gut bacteria caused by antibiotic treatment can be either detrimental or beneficial in a context-dependent way[105]. Further studies are needed to investigate the role of specific antibiotics in modulating the microbiota response and the relationship with colorectal carcinogenesis.

### Diet and anti-inflammatory drugs

A number of epidemiological studies have shown an association between diet, inflammation, and cancer, including CRC[106-109]. So far, there is a lack of preventive dietary recommendations for FAP patients. A nonrandomized prospective pilot study carried out on FAP patients showed that a low-inflammatory diet based on the Mediterranean diet pattern decreased gastrointestinal markers of inflammation, such as C-reactive protein and pro-inflammatory cytokines, through a modulation of the gut microbiota composition[110]. Combination treatment with curcumin and quercetin has been reported to reduce the development of adenomas in FAP. This beneficial effect might be a result of their antioxidative, anti-inflammatory, and antiproliferative properties and the maintenance of a diverse gut microbial community[111-113]. Black raspberry powder supplementation in FAP patients significantly decreased the burden of rectal polyps and reduced staining of the mucosal proliferation marker Ki-67, compared with placebo[114]. The results could have a response to beneficial effects of the anthocyanin and fiber content of the raspberries on the diversity and composition of the gut microbiota[115,116]. Administration of berberine, an alkaloid that can be isolated from many plants including barberry (*Berberis vulgaris*), significantly reduced the development of CRC and restored the gut microbiota community in  $APC^{Min/+}$  mice fed a high fat diet[117].

There is evidence that the combination of anti-inflammatory drugs and regular endoscopic surveillance can decrease the risk of new adenomas in the rectal stump of FAP patients[118-120]. Administration of NSAIDs and omega-3 essential fatty acids reduced recurrence[121]. Even though long-term therapy with NSAIDs has been shown to increase gastrointestinal and cardiological risk, the use of omega-3 supplements can be expensive for patients[122,123]. NSAIDs may modify the composition and diversity of gut microbiota by inhibiting or facilitating bacterial growth, inducing bacterial cell death, or affecting bacterial metabolism[123]. The bacterial composition of the gut has been shown to change with the type of NSAID administered[124]. Specific shifts in the microbiota such as an increase in *Coriobacteriaceae* or reduction in *Bifidobacteriaceae* and *Lactobacillaceae* after chronic oral treatment with celecoxib, have been associated with a decrease of polyp burden in  $APC^{Min/+}$  mice[125].  $APC^{Min/+}$  mice treated with aspirin showed a decrease in CRC number and load that depended on the

presence of gut microbes. Of interest, *Lysinibacillus sphaericus* in the gut degraded aspirin, thereby reducing its chemopreventive effects in mice. Stool samples from mice treated with aspirin had increased populations of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and decreased populations of pathogenic bacteria such as *Alistipes finegoldii* and *B. fragilis*[126].

## CONCLUSION

The APC<sup>Min/+</sup> mouse model has been widely used to study the underlying mechanisms of colorectal carcinogenesis in FAP. Several studies demonstrated that gut microbiota dysbiosis as a key factor in colorectal carcinogenesis. Indeed, the intestinal microbial community played an important role in the multistep process of the intestinal adenoma-carcinoma sequence, and changes in the gut microbiota were found to be responsible for mucosal barrier injury, low-grade inflammation, activation of the Wnt pathway, and subsequent progression of adenomas. Recent evidence suggests that the modulation of gut microbiota could be a novel therapeutic target in FAP patients. Administration of probiotics, prebiotics, antibiotics, and NSAIDs can prevent the progression of the adenoma-carcinoma sequence in FAP. However, further study of the role of the gut microbiota in the malignant transformation of colorectal adenoma and how microbe-targeted therapies might be useful in preventing CRC development in FAP is needed.

## REFERENCES

- 1 **Kemp Bohan PM**, Mankaney G, Vreeland TJ, Chick RC, Hale DF, Cindass JL, Hickerson AT, Ensley DC, Sohn V, Clifton GT, Peoples GE, Burke CA. Chemoprevention in familial adenomatous polyposis: past, present and future. *Fam Cancer* 2021; **20**: 23-33 [PMID: 32507936 DOI: 10.1007/s10689-020-00189-y]
- 2 **Jung I**, Gurzu S, Turdean GS. Current status of familial gastrointestinal polyposis syndromes. *World J Gastrointest Oncol* 2015; **7**: 347-355 [PMID: 26600934 DOI: 10.4251/wjgo.v7.i11.347]
- 3 **Leoz ML**, Carballal S, Moreira L, Ocaña T, Balaguer F. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. *Appl Clin Genet* 2015; **8**: 95-107 [PMID: 25931827 DOI: 10.2147/TACG.S51484]
- 4 **Monahan KJ**, Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE, Ilyas M, Kaur A, Lalloo F, Latchford A, Rutter MD, Tomlinson I, Thomas HJW, Hill J; Hereditary CRC guidelines eDelphi consensus group. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut* 2020; **69**: 411-444 [PMID: 31780574 DOI: 10.1136/gutjnl-2019-319915]
- 5 **GBD 2017 Colorectal Cancer Collaborators**. The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2019; **4**: 913-933 [PMID: 31648977 DOI: 10.1016/S2468-1253(19)30345-0]
- 6 **Half E**, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009; **4**: 22 [PMID: 19822006 DOI: 10.1186/1750-1172-4-22]
- 7 **Wang XP**, Fan J. Molecular genetics of supernumerary tooth formation. *Genesis* 2011; **49**: 261-277 [PMID: 21309064 DOI: 10.1002/dvg.20715]
- 8 **Byrne RM**, Tsikitis VL. Colorectal polyposis and inherited colorectal cancer syndromes. *Ann Gastroenterol* 2018; **31**: 24-34 [PMID: 29333064 DOI: 10.20524/aog.2017.0218]
- 9 **Herzig D**, Hardiman K, Weiser M, You N, Paquette I, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes. *Dis Colon Rectum* 2017; **60**: 881-894 [PMID: 28796726 DOI: 10.1097/DCR.0000000000000912]
- 10 **Dinarvand P**, Davaro EP, Doan JV, Ising ME, Evans NR, Phillips NJ, Lai J, Guzman MA. Familial Adenomatous Polyposis Syndrome: An Update and Review of Extraintestinal Manifestations. *Arch Pathol Lab Med* 2019; **143**: 1382-1398 [PMID: 31070935 DOI: 10.5858/arpa.2018-0570-RA]
- 11 **Bülow S**. Results of national registration of familial adenomatous polyposis. *Gut* 2003; **52**: 742-746 [PMID: 12692062 DOI: 10.1136/gut.52.5.742]
- 12 **Vacante M**, Ciuni R, Basile F, Biondi A. Gut Microbiota and Colorectal Cancer Development: A Closer Look to the Adenoma-Carcinoma Sequence. *Biomedicines* 2020; **8** [PMID: 33182693 DOI: 10.3390/biomedicines8110489]
- 13 **Wong SH**, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 690-704 [PMID: 31554963 DOI: 10.1038/s41575-019-0209-8]
- 14 **Pop OL**, Vodnar DC, Diaconeasa Z, Istrati M, Bințișan A, Bințișan VV, Suharoschi R,

- Gabbianelli R. An Overview of Gut Microbiota and Colon Diseases with a Focus on Adenomatous Colon Polyps. *Int J Mol Sci* 2020; **21** [PMID: 33028024 DOI: 10.3390/ijms21197359]
- 15 **Li L**, Li X, Zhong W, Yang M, Xu M, Sun Y, Ma J, Liu T, Song X, Dong W, Liu X, Chen Y, Liu Y, Ablal Z, Liu W, Wang B, Jiang K, Cao H. Gut microbiota from colorectal cancer patients enhances the progression of intestinal adenoma in Apc<sup>min/+</sup> mice. *EBioMedicine* 2019; **48**: 301-315 [PMID: 31594750 DOI: 10.1016/j.ebiom.2019.09.021]
- 16 **Liang S**, Mao Y, Liao M, Xu Y, Chen Y, Huang X, Wei C, Wu C, Wang Q, Pan X, Tang W. Gut microbiome associated with APC gene mutation in patients with intestinal adenomatous polyps. *Int J Biol Sci* 2020; **16**: 135-146 [PMID: 31892851 DOI: 10.7150/ijbs.37399]
- 17 **Son JS**, Khair S, Pettet DW 3rd, Ouyang N, Tian X, Zhang Y, Zhu W, Mackenzie GG, Robertson CE, Ir D, Frank DN, Rigas B, Li E. Altered Interactions between the Gut Microbiome and Colonic Mucosa Precede Polyposis in APCMin/+ Mice. *PLoS One* 2015; **10**: e0127985 [PMID: 26121046 DOI: 10.1371/journal.pone.0127985]
- 18 **Kostic AD**, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013; **14**: 207-215 [PMID: 23954159 DOI: 10.1016/j.chom.2013.07.007]
- 19 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735 DOI: 10.1016/0092-8674(90)90186-i]
- 20 **Pai SG**, Carneiro BA, Mota JM, Costa R, Leite CA, Barroso-Sousa R, Kaplan JB, Chae YK, Giles FJ. Wnt/beta-catenin pathway: modulating anticancer immune response. *J Hematol Oncol* 2017; **10**: 101 [PMID: 28476164 DOI: 10.1186/s13045-017-0471-6]
- 21 **Valli A**, Rodriguez M, Moutsianas L, Fischer R, Fedele V, Huang HL, Van Stiphout R, Jones D, McCarthy M, Vinaxia M, Igarashi K, Sato M, Soga T, Buffa F, McCullagh J, Yanes O, Harris A, Kessler B. Hypoxia induces a lipogenic cancer cell phenotype via HIF1 $\alpha$ -dependent and -independent pathways. *Oncotarget* 2015; **6**: 1920-1941 [PMID: 25605240 DOI: 10.18632/oncotarget.3058]
- 22 **Newton IP**, Kenneth NS, Appleton PL, N  thke I, Rocha S. Adenomatous polyposis coli and hypoxia-inducible factor-1 {alpha} have an antagonistic connection. *Mol Biol Cell* 2010; **21**: 3630-3638 [PMID: 20844082 DOI: 10.1091/mbc.E10-04-0312]
- 23 **Liu W**, Zhang R, Shu R, Yu J, Li H, Long H, Jin S, Li S, Hu Q, Yao F, Zhou C, Huang Q, Hu X, Chen M, Hu W, Wang Q, Fang S, Wu Q. Study of the Relationship between Microbiome and Colorectal Cancer Susceptibility Using 16SrRNA Sequencing. *Biomed Res Int* 2020; **2020**: 7828392 [PMID: 32083132 DOI: 10.1155/2020/7828392]
- 24 **Valli A**, Morotti M, Zois CE, Albers PK, Soga T, Feldinger K, Fischer R, Frejno M, McIntyre A, Bridges E, Haider S, Buffa FM, Baban D, Rodriguez M, Yanes O, Whittington HJ, Lake HA, Zervou S, Lygate CA, Kessler BM, Harris AL. Adaptation to HIF1 $\alpha$  Deletion in Hypoxic Cancer Cells by Upregulation of GLUT14 and Creatine Metabolism. *Mol Cancer Res* 2019; **17**: 1531-1544 [PMID: 30885992 DOI: 10.1158/1541-7786.MCR-18-0315]
- 25 **B  rtin F**, Mullins CS, Linnebacher M. Mouse models of colorectal cancer: Past, present and future perspectives. *World J Gastroenterol* 2020; **26**: 1394-1426 [PMID: 32308343 DOI: 10.3748/wjg.v26.i13.1394]
- 26 **McIntyre RE**, Buczacki SJ, Arends MJ, Adams DJ. Mouse models of colorectal cancer as preclinical models. *Bioessays* 2015; **37**: 909-920 [PMID: 26115037 DOI: 10.1002/bies.201500032]
- 27 **Irving AA**, Yoshimi K, Hart ML, Parker T, Clipson L, Ford MR, Kuramoto T, Dove WF, Amos-Landgraf JM. The utility of Apc-mutant rats in modeling human colon cancer. *Dis Model Mech* 2014; **7**: 1215-1225 [PMID: 25288683 DOI: 10.1242/dmm.016980]
- 28 **Zeineldin M**, Neufeld KL. More than two decades of Apc modeling in rodents. *Biochim Biophys Acta* 2013; **1836**: 80-89 [PMID: 23333833 DOI: 10.1016/j.bbcan.2013.01.001]
- 29 **Young M**, Ordonez L, Clarke AR. What are the best routes to effectively model human colorectal cancer? *Mol Oncol* 2013; **7**: 178-189 [PMID: 23465602 DOI: 10.1016/j.molonc.2013.02.006]
- 30 **Sobhani I**, Amiot A, Le Baleur Y, Levy M, Auriault ML, Van Nhieu JT, Delchier JC. Microbial dysbiosis and colon carcinogenesis: could colon cancer be considered a bacteria-related disease? *Therap Adv Gastroenterol* 2013; **6**: 215-229 [PMID: 23634186 DOI: 10.1177/1756283X12473674]
- 31 **Sheflin AM**, Whitney AK, Weir TL. Cancer-promoting effects of microbial dysbiosis. *Curr Oncol Rep* 2014; **16**: 406 [PMID: 25123079 DOI: 10.1007/s11912-014-0406-0]
- 32 **Alhinai EA**, Walton GE, Commune DM. The Role of the Gut Microbiota in Colorectal Cancer Causation. *Int J Mol Sci* 2019; **20** [PMID: 31653078 DOI: 10.3390/ijms20215295]
- 33 **Khan AA**, Khan Z, Malik A, Kalam MA, Cash P, Ashraf MT, Alshamsan A. Colorectal cancer-inflammatory bowel disease nexus and felony of Escherichia coli. *Life Sci* 2017; **180**: 60-67 [PMID: 28506682 DOI: 10.1016/j.lfs.2017.05.016]
- 34 **Bleich RM**, Arthur JC. Revealing a microbial carcinogen. *Science* 2019; **363**: 689-690 [PMID: 30765550 DOI: 10.1126/science.aaw5475]
- 35 **Wilson MR**, Jiang Y, Villalta PW, Stornetta A, Boudreau PD, Carr   A, Brennan CA, Chun E, Ngo L, Samson LD, Engelward BP, Garrett WS, Balbo S, Balskus EP. The human gut bacterial genotoxin colibactin alkylates DNA. *Science* 2019; **363** [PMID: 30765538 DOI: 10.1126/science.aar7785]
- 36 **Pleguezuelos-Manzano C**, Puschhof J, Rosendahl Huber A, van Hoek A, Wood HM, Nomburg J, Gurjao C, Manders F, Dalmaso G, Stege PB, Paganelli FL, Geurts MH, Beumer J, Mizutani T,

- Miao Y, van der Linden R, van der Elst S; Genomics England Research Consortium, Garcia KC, Top J, Willems RJL, Giannakis M, Bonnet R, Quirke P, Meyerson M, Cuppen E, van Boxtel R, Clevers H. Mutational signature in colorectal cancer caused by genotoxic pks<sup>+</sup> E. coli. *Nature* 2020; **580**: 269-273 [PMID: [32106218](#) DOI: [10.1038/s41586-020-2080-8](#)]
- 37 **Cognoux A**, Delmas J, Gibold L, Fais T, Romagnoli C, Robin F, Cuevas-Ramos G, Oswald E, Darfeuille-Michaud A, Prati F, Dalmasso G, Bonnet R. Small-molecule inhibitors prevent the genotoxic and protumoural effects induced by colibactin-producing bacteria. *Gut* 2016; **65**: 278-285 [PMID: [25588406](#) DOI: [10.1136/gutjnl-2014-307241](#)]
- 38 **Lucas C**, Salesse L, Hoang MHT, Bonnet M, Sauvanet P, Larabi A, Godfraind C, Gagnière J, Pezet D, Rosenstiel P, Barnich N, Bonnet R, Dalmasso G, Nguyen HTT. Autophagy of Intestinal Epithelial Cells Inhibits Colorectal Carcinogenesis Induced by Colibactin-Producing *Escherichia coli* in Apc<sup>Min/+</sup> Mice. *Gastroenterology* 2020; **158**: 1373-1388 [PMID: [31917256](#) DOI: [10.1053/j.gastro.2019.12.026](#)]
- 39 **Irrazabal T**, Thakur BK, Kang M, Malaise Y, Streutker C, Wong EOY, Copeland J, Gryfe R, Guttman DS, Navarre WW, Martin A. Limiting oxidative DNA damage reduces microbe-induced colitis-associated colorectal cancer. *Nat Commun* 2020; **11**: 1802 [PMID: [32286276](#) DOI: [10.1038/s41467-020-15549-6](#)]
- 40 **Lv Y**, Ye T, Wang HP, Zhao JY, Chen WJ, Wang X, Shen CX, Wu YB, Cai YK. Suppression of colorectal tumorigenesis by recombinant *Bacteroides fragilis* enterotoxin-2 *in vivo*. *World J Gastroenterol* 2017; **23**: 603-613 [PMID: [28216966](#) DOI: [10.3748/wjg.v23.i4.603](#)]
- 41 **Attene-Ramos MS**, Wagner ED, Gaskins HR, Plewa MJ. Hydrogen sulfide induces direct radical-associated DNA damage. *Mol Cancer Res* 2007; **5**: 455-459 [PMID: [17475672](#) DOI: [10.1158/1541-7786.MCR-06-0439](#)]
- 42 **Dahmus JD**, Kotler DL, Kastenber DM, Kistler CA. The gut microbiome and colorectal cancer: a review of bacterial pathogenesis. *J Gastrointest Oncol* 2018; **9**: 769-777 [PMID: [30151274](#) DOI: [10.21037/jgo.2018.04.07](#)]
- 43 **van Elsland D**, Neeffjes J. Bacterial infections and cancer. *EMBO Rep* 2018; **19** [PMID: [30348892](#) DOI: [10.15252/embr.201846632](#)]
- 44 **Bhatt AP**, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. *CA Cancer J Clin* 2017; **67**: 326-344 [PMID: [28481406](#) DOI: [10.3322/caac.21398](#)]
- 45 **Richard ML**, Liguori G, Lamas B, Brandi G, da Costa G, Hoffmann TW, Pierluigi Di Simone M, Calabrese C, Poggioli G, Langella P, Campieri M, Sokol H. Mucosa-associated microbiota dysbiosis in colitis associated cancer. *Gut Microbes* 2018; **9**: 131-142 [PMID: [28914591](#) DOI: [10.1080/19490976.2017.1379637](#)]
- 46 **Yu LC**, Wei SC, Ni YH. Impact of microbiota in colorectal carcinogenesis: lessons from experimental models. *Intest Res* 2018; **16**: 346-357 [PMID: [30090033](#) DOI: [10.5217/ir.2018.16.3.346](#)]
- 47 **Alto NM**, Orth K. Subversion of cell signaling by pathogens. *Cold Spring Harb Perspect Biol* 2012; **4**: a006114 [PMID: [22952390](#) DOI: [10.1101/cshperspect.a006114](#)]
- 48 **Lahiani A**, Yavin E, Lazarovici P. The Molecular Basis of Toxins' Interactions with Intracellular Signaling via Discrete Portals. *Toxins (Basel)* 2017; **9** [PMID: [28300784](#) DOI: [10.3390/toxins9030107](#)]
- 49 **Tomkovich S**, Yang Y, Winglee K, Gauthier J, Mühlbauer M, Sun X, Mohamadzadeh M, Liu X, Martin P, Wang GP, Oswald E, Fodor AA, Jobin C. Locoregional Effects of Microbiota in a Preclinical Model of Colon Carcinogenesis. *Cancer Res* 2017; **77**: 2620-2632 [PMID: [28416491](#) DOI: [10.1158/0008-5472.CAN-16-3472](#)]
- 50 **Yang Y**, Weng W, Peng J, Hong L, Yang L, Toiyama Y, Gao R, Liu M, Yin M, Pan C, Li H, Guo B, Zhu Q, Wei Q, Moyer MP, Wang P, Cai S, Goel A, Qin H, Ma Y. *Fusobacterium nucleatum* Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating Toll-Like Receptor 4 Signaling to Nuclear Factor- $\kappa$ B, and Up-regulating Expression of MicroRNA-21. *Gastroenterology* 2017; **152**: 851-866.e24 [PMID: [27876571](#) DOI: [10.1053/j.gastro.2016.11.018](#)]
- 51 **Wu Y**, Wu J, Chen T, Li Q, Peng W, Li H, Tang X, Fu X. *Fusobacterium nucleatum* Potentiates Intestinal Tumorigenesis in Mice via a Toll-Like Receptor 4/p21-Activated Kinase 1 Cascade. *Dig Dis Sci* 2018; **63**: 1210-1218 [PMID: [29508166](#) DOI: [10.1007/s10620-018-4999-2](#)]
- 52 **Chen T**, Li Q, Wu J, Wu Y, Peng W, Li H, Wang J, Tang X, Peng Y, Fu X. *Fusobacterium nucleatum* promotes M2 polarization of macrophages in the microenvironment of colorectal tumours via a TLR4-dependent mechanism. *Cancer Immunol Immunother* 2018; **67**: 1635-1646 [PMID: [30121899](#) DOI: [10.1007/s00262-018-2233-x](#)]
- 53 **Rubinstein MR**, Baik JE, Lagana SM, Han RP, Raab WJ, Sahoo D, Dalerba P, Wang TC, Han YW. *Fusobacterium nucleatum* promotes colorectal cancer by inducing Wnt/ $\beta$ -catenin modulator Annexin A1. *EMBO Rep* 2019; **20** [PMID: [30833345](#) DOI: [10.15252/embr.201847638](#)]
- 54 **Dejea CM**, Fathi P, Craig JM, Boleij A, Taddese R, Geis AL, Wu X, DeStefano Shields CE, Hechenbleikner EM, Huso DL, Anders RA, Giardiello FM, Wick EC, Wang H, Wu S, Pardoll DM, Housseau F, Sears CL. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. *Science* 2018; **359**: 592-597 [PMID: [29420293](#) DOI: [10.1126/science.aah3648](#)]
- 55 **Chung L**, Thiele Orberg E, Geis AL, Chan JL, Fu K, DeStefano Shields CE, Dejea CM, Fathi P, Chen J, Finard BB, Tam AJ, McAllister F, Fan H, Wu X, Ganguly S, Lebid A, Metz P, Van

- Meerbeke SW, Huso DL, Wick EC, Pardoll DM, Wan F, Wu S, Sears CL, Housseau F. Bacteroides fragilis Toxin Coordinates a Pro-carcinogenic Inflammatory Cascade *via* Targeting of Colonic Epithelial Cells. *Cell Host Microbe* 2018; **23**: 203-214.e5 [PMID: 29398651 DOI: 10.1016/j.chom.2018.01.007]
- 56 **Goodwin AC**, Destefano Shields CE, Wu S, Huso DL, Wu X, Murray-Stewart TR, Hacker-Prietz A, Rabizadeh S, Woster PM, Sears CL, Casero RA Jr. Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis. *Proc Natl Acad Sci USA* 2011; **108**: 15354-15359 [PMID: 21876161 DOI: 10.1073/pnas.1010203108]
- 57 **He Z**, Gharaibeh RZ, Newsome RC, Pope JL, Dougherty MW, Tomkovich S, Pons B, Mirey G, Vignard J, Hendrixson DR, Jobin C. *Campylobacter jejuni* promotes colorectal tumorigenesis through the action of cytolethal distending toxin. *Gut* 2019; **68**: 289-300 [PMID: 30377189 DOI: 10.1136/gutjnl-2018-317200]
- 58 **Li Y**, Kundu P, Seow SW, de Matos CT, Aronsson L, Chin KC, Kärre K, Pettersson S, Greicius G. Gut microbiota accelerate tumor growth *via* c-jun and STAT3 phosphorylation in APCMin/+ mice. *Carcinogenesis* 2012; **33**: 1231-1238 [PMID: 22461519 DOI: 10.1093/carcin/bgs137]
- 59 **Nalbantoglu I**, Blanc V, Davidson NO. Characterization of Colorectal Cancer Development in Apc (min/+) Mice. *Methods Mol Biol* 2016; **1422**: 309-327 [PMID: 27246043 DOI: 10.1007/978-1-4939-3603-8\_27]
- 60 **Wu S**, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis *via* activation of T helper type 17 T cell responses. *Nat Med* 2009; **15**: 1016-1022 [PMID: 19701202 DOI: 10.1038/nm.2015]
- 61 **Rhee KJ**, Wu S, Wu X, Huso DL, Karim B, Franco AA, Rabizadeh S, Golub JE, Mathews LE, Shin J, Sartor RB, Golenbock D, Hamad AR, Gan CM, Housseau F, Sears CL. Induction of persistent colitis by a human commensal, enterotoxigenic Bacteroides fragilis, in wild-type C57BL/6 mice. *Infect Immun* 2009; **77**: 1708-1718 [PMID: 19188353 DOI: 10.1128/IAI.00814-08]
- 62 **Toprak NU**, Yagci A, Gulluoglu BM, Akin ML, Demirkalem P, Celenk T, Soyletir G. A possible role of Bacteroides fragilis enterotoxin in the aetiology of colorectal cancer. *Clin Microbiol Infect* 2006; **12**: 782-786 [PMID: 16842574 DOI: 10.1111/j.1469-0691.2006.01494.x]
- 63 **Dai Z**, Zhang J, Wu Q, Chen J, Liu J, Wang L, Chen C, Xu J, Zhang H, Shi C, Li Z, Fang H, Lin C, Tang D, Wang D. The role of microbiota in the development of colorectal cancer. *Int J Cancer* 2019; **145**: 2032-2041 [PMID: 30474116 DOI: 10.1002/ijc.32017]
- 64 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]
- 65 **Chen J**, Pitmon E, Wang K. Microbiome, inflammation and colorectal cancer. *Semin Immunol* 2017; **32**: 43-53 [PMID: 28982615 DOI: 10.1016/j.smim.2017.09.006]
- 66 **McClellan JL**, Davis JM, Steiner JL, Day SD, Steck SE, Carmichael MD, Murphy EA. Intestinal inflammatory cytokine response in relation to tumorigenesis in the Apc(Min/+) mouse. *Cytokine* 2012; **57**: 113-119 [PMID: 22056354 DOI: 10.1016/j.cyto.2011.09.027]
- 67 **Guo P**, Tian Z, Kong X, Yang L, Shan X, Dong B, Ding X, Jing X, Jiang C, Jiang N, Yu Y. FadA promotes DNA damage and progression of Fusobacterium nucleatum-induced colorectal cancer through up-regulation of chk2. *J Exp Clin Cancer Res* 2020; **39**: 202 [PMID: 32993749 DOI: 10.1186/s13046-020-01677-w]
- 68 **Rubinstein MR**, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/ $\beta$ -catenin signaling *via* its FadA adhesin. *Cell Host Microbe* 2013; **14**: 195-206 [PMID: 23954158 DOI: 10.1016/j.chom.2013.07.012]
- 69 **Arthur JC**, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansson JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012; **338**: 120-123 [PMID: 22903521 DOI: 10.1126/science.1224820]
- 70 **Grivnenkov SI**, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, Taniguchi K, Yu GY, Osterreicher CH, Hung KE, Datz C, Feng Y, Fearon ER, Oukka M, Tessarollo L, Coppola V, Yarovinsky F, Cheroutre H, Eckmann L, Trinchieri G, Karin M. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature* 2012; **491**: 254-258 [PMID: 23034650 DOI: 10.1038/nature11465]
- 71 **Mager LF**, Wasmer MH, Rau TT, Krebs P. Cytokine-Induced Modulation of Colorectal Cancer. *Front Oncol* 2016; **6**: 96 [PMID: 27148488 DOI: 10.3389/fonc.2016.00096]
- 72 **Rowland I**, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr* 2018; **57**: 1-24 [PMID: 28393285 DOI: 10.1007/s00394-017-1445-8]
- 73 **Conlon MA**, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 2014; **7**: 17-44 [PMID: 25545101 DOI: 10.3390/nu7010017]
- 74 **Holscher HD**. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes* 2017; **8**: 172-184 [PMID: 28165863 DOI: 10.1080/19490976.2017.1290756]
- 75 **Bultman SJ**, Jobin C. Microbial-derived butyrate: an oncometabolite or tumor-suppressive metabolite? *Cell Host Microbe* 2014; **16**: 143-145 [PMID: 25121740 DOI: 10.1016/j.chom.2014.07.011]
- 76 **Belcheva A**, Irrazabal T, Robertson SJ, Streutker C, Maughan H, Rubino S, Moriyama EH, Copeland JK, Surendra A, Kumar S, Green B, Geddes K, Pezo RC, Navarre WW, Milosevic M,

- Wilson BC, Girardin SE, Wolever TMS, Edelmann W, Guttman DS, Philpott DJ, Martin A. Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. *Cell* 2014; **158**: 288-299 [PMID: 25036629 DOI: 10.1016/j.cell.2014.04.051]
- 77 Gill PA, van Zelm MC, Muir JG, Gibson PR. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. *Aliment Pharmacol Ther* 2018; **48**: 15-34 [PMID: 29722430 DOI: 10.1111/apt.14689]
- 78 O'Keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 691-706 [PMID: 27848961 DOI: 10.1038/nrgastro.2016.165]
- 79 Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. *Nat Rev Microbiol* 2017; **15**: 465-478 [PMID: 28529325 DOI: 10.1038/nrmicro.2017.44]
- 80 Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014; **12**: 661-672 [PMID: 25198138 DOI: 10.1038/nrmicro3344]
- 81 Leavitt J, Saleh N. The Microbiome and Colorectal Cancer: Current Clinical Trials. *Oncology (Williston Park)* 2019; **33**: 78 [PMID: 30784035]
- 82 Stadler Z. Memorial Sloan Kettering Cancer Center. Metagenomic Evaluation of the Gut Microbiome in Patients With Lynch Syndrome and Other Hereditary Colonic Polyposis Syndromes. [accessed 2021 Feb 5]. In: ClinicalTrials.gov [Internet]. New York (NY): U.S. National Library of Medicine. Available from: <https://clinicaltrials.gov/ct2/show/NCT02371135> ClinicalTrials.gov Identifier: NCT02371135
- 83 Kariv R. Turmeric Supplementation on Polyp Number and Size in Patients With Familial Adenomatous Polyposis. [accessed 2021 Feb 5]. In: ClinicalTrials.gov [Internet]. Tel Aviv: U.S. National Library of Medicine. Available from: <https://clinicaltrials.gov/ct2/show/NCT03061591> ClinicalTrials.gov Identifier: NCT03061591
- 84 Fong W, Li Q, Yu J. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene* 2020; **39**: 4925-4943 [PMID: 32514151 DOI: 10.1038/s41388-020-1341-1]
- 85 Dutta D, Lim SH. Bidirectional interaction between intestinal microbiome and cancer: opportunities for therapeutic interventions. *Biomark Res* 2020; **8**: 31 [PMID: 32817793 DOI: 10.1186/s40364-020-00211-6]
- 86 Perillo F, Amoroso C, Strati F, Giuffrè MR, Díaz-Basabe A, Lattanzi G, Facciotti F. Gut Microbiota Manipulation as a Tool for Colorectal Cancer Management: Recent Advances in Its Use for Therapeutic Purposes. *Int J Mol Sci* 2020; **21** [PMID: 32751239 DOI: 10.3390/ijms21155389]
- 87 Möslein G. Surgical considerations in FAP-related pouch surgery: Could we do better? *Fam Cancer* 2016; **15**: 457-466 [PMID: 27194409 DOI: 10.1007/s10689-016-9904-6]
- 88 Segal JP, Ding NS, Worley G, McLaughlin S, Preston S, Faiz OD, Clark SK, Hart AL. Systematic review with meta-analysis: the management of chronic refractory pouchitis with an evidence-based treatment algorithm. *Aliment Pharmacol Ther* 2017; **45**: 581-592 [PMID: 28008631 DOI: 10.1111/apt.13905]
- 89 Batista D, Raffals L. Role of intestinal bacteria in the pathogenesis of pouchitis. *Inflamm Bowel Dis* 2014; **20**: 1481-1486 [PMID: 25046009 DOI: 10.1097/MIB.0000000000000055]
- 90 Gionchetti P, Calafiore A, Riso D, Liguori G, Calabrese C, Vitali G, Laureti S, Poggioli G, Campieri M, Rizzello F. The role of antibiotics and probiotics in pouchitis. *Ann Gastroenterol* 2012; **25**: 100-105 [PMID: 24714229]
- 91 Kousgaard SJ, Michaelsen TY, Nielsen HL, Kirk KF, Albertsen M, Thorlacius-Ussing O. The Microbiota Profile in Inflamed and Non-Inflamed Ileal Pouch-Anal Anastomosis. *Microorganisms* 2020; **8** [PMID: 33092101 DOI: 10.3390/microorganisms8101611]
- 92 Shen B, Achkar JP, Connor JT, Ormsby AH, Remzi FH, Bevins CL, Brzezinski A, Bambrick ML, Fazio VW, Lashner BA. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis Colon Rectum* 2003; **46**: 748-753 [PMID: 12794576 DOI: 10.1007/s10350-004-6652-8]
- 93 Tomasz B, Zoran S, Jarosław W, Ryszard M, Marcin G, Robert B, Piotr K, Lukasz K, Jacek P, Piotr G, Przemysław P, Michał D. Long-term use of probiotics Lactobacillus and Bifidobacterium has a prophylactic effect on the occurrence and severity of pouchitis: a randomized prospective study. *Biomed Res Int* 2014; **2014**: 208064 [PMID: 24579075 DOI: 10.1155/2014/208064]
- 94 Drago L. Probiotics and Colon Cancer. *Microorganisms* 2019; **7** [PMID: 30823471 DOI: 10.3390/microorganisms7030066]
- 95 Liong MT. Roles of probiotics and prebiotics in colon cancer prevention: Postulated mechanisms and in-vivo evidence. *Int J Mol Sci* 2008; **9**: 854-863 [PMID: 19325789 DOI: 10.3390/ijms9050854]
- 96 Ni Y, Wong VH, Tai WC, Li J, Wong WY, Lee MM, Fong FL, El-Nezami H, Panagiotou G. A metagenomic study of the preventive effect of Lactobacillus rhamnosus GG on intestinal polyp formation in Apc<sup>Min/+</sup> mice. *J Appl Microbiol* 2017; **122**: 770-784 [PMID: 28004480 DOI: 10.1111/jam.13386]
- 97 Urbanska AM, Bhatena J, Cherif S, Prakash S. Orally delivered microencapsulated probiotic formulation favorably impacts polyp formation in APC (Min/+) model of intestinal carcinogenesis. *Artif Cells Nanomed Biotechnol* 2016; **44**: 1-11 [PMID: 25060720 DOI: 10.3109/21691401.2014.898647]
- 98 Kennedy EA, King KY, Baldrige MT. Mouse Microbiota Models: Comparing Germ-Free Mice and Antibiotics Treatment as Tools for Modifying Gut Bacteria. *Front Physiol* 2018; **9**: 1534

- [PMID: 30429801 DOI: 10.3389/fphys.2018.01534]
- 99 **Hale VL**, Chen J, Johnson S, Harrington SC, Yab TC, Smyrk TC, Nelson H, Boardman LA, Druliner BR, Levin TR, Rex DK, Ahnen DJ, Lance P, Ahlquist DA, Chia N. Shifts in the Fecal Microbiota Associated with Adenomatous Polyps. *Cancer Epidemiol Biomarkers Prev* 2017; **26**: 85-94 [PMID: 27672054 DOI: 10.1158/1055-9965.EPI-16-0337]
- 100 **Xu L**, Surathu A, Raplee I, Chockalingam A, Stewart S, Walker L, Sacks L, Patel V, Li Z, Rouse R. The effect of antibiotics on the gut microbiome: a metagenomics analysis of microbial shift and gut antibiotic resistance in antibiotic treated mice. *BMC Genomics* 2020; **21**: 263 [PMID: 32228448 DOI: 10.1186/s12864-020-6665-2]
- 101 **Sánchez-Alcoholado L**, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, Gómez-Millán J, Queipo-Ortuño MI. The Role of the Gut Microbiome in Colorectal Cancer Development and Therapy Response. *Cancers (Basel)* 2020; **12** [PMID: 32486066 DOI: 10.3390/cancers12061406]
- 102 **Dik VK**, van Oijen MG, Smeets HM, Siersema PD. Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study. *Dig Dis Sci* 2016; **61**: 255-264 [PMID: 26289256 DOI: 10.1007/s10620-015-3828-0]
- 103 **Boursi B**, Haynes K, Mamtani R, Yang YX. Impact of antibiotic exposure on the risk of colorectal cancer. *Pharmacoepidemiol Drug Saf* 2015; **24**: 534-542 [PMID: 25808540 DOI: 10.1002/pds.3765]
- 104 **Kaur K**, Saxena A, Debnath I, O'Brien JL, Ajami NJ, Auchtung TA, Petrosino JF, Sougiannis AJ, Depaep S, Chumanevich A, Gummadidala PM, Omebeyinje MH, Banerjee S, Chatzistamou I, Chakraborty P, Fayad R, Berger FG, Carson JA, Chanda A. Antibiotic-mediated bacteriome depletion in *Apc<sup>Min/+</sup>* mice is associated with reduction in mucus-producing goblet cells and increased colorectal cancer progression. *Cancer Med* 2018; **7**: 2003-2012 [PMID: 29624892 DOI: 10.1002/cam4.1460]
- 105 **Leystra AA**, Clapper ML. Gut Microbiota Influences Experimental Outcomes in Mouse Models of Colorectal Cancer. *Genes (Basel)* 2019; **10** [PMID: 31703321 DOI: 10.3390/genes10110900]
- 106 **Ruiz-Canela M**, Bes-Rastrollo M, Martínez-González MA. The Role of Dietary Inflammatory Index in Cardiovascular Disease, Metabolic Syndrome and Mortality. *Int J Mol Sci* 2016; **17** [PMID: 27527152 DOI: 10.3390/ijms17081265]
- 107 **Adjibade M**, Andreeva VA, Lemogne C, Touvier M, Shivappa N, Hébert JR, Wirth MD, Hercberg S, Galan P, Julia C, Assmann KE, Kesse-Guyot E. The Inflammatory Potential of the Diet Is Associated with Depressive Symptoms in Different Subgroups of the General Population. *J Nutr* 2017; **147**: 879-887 [PMID: 28356432 DOI: 10.3945/jn.116.245167]
- 108 **Ryu I**, Kwon M, Sohn C, Shivappa N, Hébert JR, Na W, Kim MK. The Association between Dietary Inflammatory Index (DII) and Cancer Risk in Korea: A Prospective Cohort Study within the KoGES-HEXA Study. *Nutrients* 2019; **11** [PMID: 31652856 DOI: 10.3390/nu11112560]
- 109 **Bodén S**, Myte R, Wennberg M, Harlid S, Johansson I, Shivappa N, Hébert JR, Van Guelpen B, Nilsson LM. The inflammatory potential of diet in determining cancer risk; A prospective investigation of two dietary pattern scores. *PLoS One* 2019; **14**: e0214551 [PMID: 30978193 DOI: 10.1371/journal.pone.0214551]
- 110 **Pasanisi P**, Gariboldi M, Verderio P, Signoroni S, Mancini A, Rivoltini L, Milione M, Masci E, Ciniselli CM, Bruno E, Macciotta A, Belfiore A, Ricci MT, Gargano G, Morelli D, Apolone G, Vitellaro M. A Pilot Low-Inflammatory Dietary Intervention to Reduce Inflammation and Improve Quality of Life in Patients With Familial Adenomatous Polyposis: Protocol Description and Preliminary Results. *Integr Cancer Ther* 2019; **18**: 1534735419846400 [PMID: 31055940 DOI: 10.1177/1534735419846400]
- 111 **Cruz-Correa M**, Shoskes DA, Sanchez P, Zhao R, Hyland LM, Wexner SD, Giardiello FM. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2006; **4**: 1035-1038 [PMID: 16757216 DOI: 10.1016/j.cgh.2006.03.020]
- 112 **Cruz-Correa M**, Hyland LM, Marrero JH, Zahurak ML, Murray-Stewart T, Casero RA Jr, Montgomery EA, Iacobuzio-Donahue C, Brosens LA, Offerhaus GJ, Umar A, Rodriguez LM, Giardiello FM. Efficacy and Safety of Curcumin in Treatment of Intestinal Adenomas in Patients With Familial Adenomatous Polyposis. *Gastroenterology* 2018; **155**: 668-673 [PMID: 29802852 DOI: 10.1053/j.gastro.2018.05.031]
- 113 **McFadden RM**, Larmonier CB, Shehab KW, Midura-Kiela M, Ramalingam R, Harrison CA, Besselsen DG, Chase JH, Caporaso JG, Jobin C, Ghishan FK, Kiela PR. The Role of Curcumin in Modulating Colonic Microbiota During Colitis and Colon Cancer Prevention. *Inflamm Bowel Dis* 2015; **21**: 2483-2494 [PMID: 26218141 DOI: 10.1097/MIB.0000000000000522]
- 114 **Wang LS**, Burke CA, Hasson H, Kuo CT, Molmenti CL, Seguin C, Liu P, Huang TH, Frankel WL, Stoner GD. A phase Ib study of the effects of black raspberries on rectal polyps in patients with familial adenomatous polyposis. *Cancer Prev Res (Phila)* 2014; **7**: 666-674 [PMID: 24764585 DOI: 10.1158/1940-6207.CAPR-14-0052]
- 115 **Pan P**, Lam V, Salzman N, Huang YW, Yu J, Zhang J, Wang LS. Black Raspberries and Their Anthocyanin and Fiber Fractions Alter the Composition and Diversity of Gut Microbiota in F-344 Rats. *Nutr Cancer* 2017; **69**: 943-951 [PMID: 28718724 DOI: 10.1080/01635581.2017.1340491]
- 116 **Kresty LA**, Fromkes JJ, Frankel WL, Hammond CD, Seeram NP, Baird M, Stoner GD. A phase I pilot study evaluating the beneficial effects of black raspberries in patients with Barrett's esophagus. *Oncotarget* 2018; **9**: 35356-35372 [PMID: 30450163 DOI: 10.18632/oncotarget.10457]

- 117 **Wang H**, Guan L, Li J, Lai M, Wen X. The Effects of Berberine on the Gut Microbiota in Apc<sup>min/+</sup> Mice Fed with a High Fat Diet. *Molecules* 2018; **23** [PMID: 30205580 DOI: 10.3390/molecules23092298]
- 118 **Kim B**, Giardiello FM. Chemoprevention in familial adenomatous polyposis. *Best Pract Res Clin Gastroenterol* 2011; **25**: 607-622 [PMID: 22122775 DOI: 10.1016/j.bpg.2011.08.002]
- 119 **Tajika M**, Niwa Y, Bhatia V, Tanaka T, Ishihara M, Yamao K. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. *World J Gastroenterol* 2013; **19**: 6774-6783 [PMID: 24187452 DOI: 10.3748/wjg.v19.i40.6774]
- 120 **Vasen HF**, Möslin G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bülow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Järvinen H, Mecklin JP, Møller P, Myrhei T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008; **57**: 704-713 [PMID: 18194984 DOI: 10.1136/gut.2007.136127]
- 121 **West NJ**, Clark SK, Phillips RK, Hutchinson JM, Leicester RJ, Belluzzi A, Hull MA. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 2010; **59**: 918-925 [PMID: 20348368 DOI: 10.1136/gut.2009.200642]
- 122 **Song M**, Lee IM, Manson JE, Buring JE, Dushkes R, Gordon D, Walter J, Wu K, Chan AT, Ogino S, Fuchs CS, Meyerhardt JA, Giovannucci EL; VITAL Research Group. Effect of Supplementation With Marine  $\omega$ -3 Fatty Acid on Risk of Colorectal Adenomas and Serrated Polyps in the US General Population: A Prespecified Ancillary Study of a Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: 108-115 [PMID: 31750855 DOI: 10.1001/jamaoncol.2019.4587]
- 123 **Maseda D**, Ricciotti E. NSAID-Gut Microbiota Interactions. *Front Pharmacol* 2020; **11**: 1153 [PMID: 32848762 DOI: 10.3389/fphar.2020.01153]
- 124 **Rogers MAM**, Aronoff DM. The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clin Microbiol Infect* 2016; **22**: 178.e1-178.e9 [PMID: 26482265 DOI: 10.1016/j.cmi.2015.10.003]
- 125 **Montrose DC**, Zhou XK, McNally EM, Sue E, Yantiss RK, Gross SS, Leve ND, Karoly ED, Suen CS, Ling L, Benezra R, Pamer EG, Dannenberg AJ. Celecoxib Alters the Intestinal Microbiota and Metabolome in Association with Reducing Polyp Burden. *Cancer Prev Res (Phila)* 2016; **9**: 721-731 [PMID: 27432344 DOI: 10.1158/1940-6207.CAPR-16-0095]
- 126 **Zhao R**, Coker OO, Wu J, Zhou Y, Zhao L, Nakatsu G, Bian X, Wei H, Chan AWH, Sung JY, Chan FKL, El-Omar E, Yu J. Aspirin Reduces Colorectal Tumor Development in Mice and Gut Microbes Reduce its Bioavailability and Chemopreventive Effects. *Gastroenterology* 2020; **159**: 969-983.e4 [PMID: 32387495 DOI: 10.1053/j.gastro.2020.05.004]



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