ω-3 PUFA on colon cancer

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Substantial human and animal studies support the beneficial effects of ω-3 polyunsaturated fatty acids (PUFAs) on colonic inflammation and colorectal cancer (CRC). However, there are inconsistent results, which have shown that ω-3 PUFAs have no effect or even detrimental effects, making it difficult to effectively implement ω-3 PUFAs for disease prevention. A better understanding of the molecular mechanisms for the anti-inflammatory and anticancer effects of ω-3 PUFAs will help to clarify their potential health-promoting effects, provide a scientific base for cautions for their use, and establish dietary recommendations.

Keywords: ω-3 PUFAs ; colorectal cancer ; eicosanoids ; cytochrome P450 monooxygenases ; soluble epoxide hydrolase

1. Introduction

There are ~1.8 million new cases of and ~881,000 deaths from colorectal cancer (CRC) every year [1]. It is estimated that ~30% of cancers in developed countries are diet-related [2]. Therefore, it is important to develop effective diet-based prevention strategies to reduce CRC risks. Epidemiological and preclinical data support that ω-3 polyunsaturated fatty acids (PUFAs), such as plant-derived α-linolenic acid (ALA, 18:3ω-3) and marine fish-derived eicosapentaenoic acid (EPA, 20:5ω-3), docosapentaenoic acid (DPA, 22:5ω-3), and docosahexaenoic acid (DHA, 22:6ω-3), may reduce CRC risks, in part, through suppressing colonic inflammation. In contrast, ω-6 PUFAs, such as linoleic acid (LA, 18:2ω-6) and arachidonic acid (ARA, 20:4ω-6), are suggested to exaggerate the development of colonic inflammation and CRC [3][4][5][6][7][8]. This is important because the current Western diet has 30–50-times more ω-6 PUFAs than ω-3 PUFAs. The validation of the beneficial effects of ω-3 PUFAs on CRC will have a significant impact on public health. However, after decades of research, the anti-CRC efficacy of ω-3 PUFAs remains inconclusive, making it difficult to make dietary recommendations or guidelines of ω-3 PUFAs for CRC prevention [9]. The inconsistent results suggest that there could be more complex mechanisms, which may be subject to specific cellular and/or metabolic modulation, involved in the anticancer and anti-inflammatory effects of ω-3 PUFAs. Therefore, it is of critical importance to better understand the mechanisms behind the anticancer and anti-inflammatory activities of ω-3 PUFAs to optimize their use for CRC prevention.

A widely accepted molecular mechanism to explain the potential health-promoting effects of ω-3 PUFAs is that they can compete with ARA (a major ω-6 PUFA) for the enzymatic metabolism catalyzed by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes, leading to reduced levels of ω-6-series metabolites (termed eicosanoids) that are predominately proinflammatory and protumorigenic, and/or increased levels of ω-3-series metabolites, which have less detrimental or even beneficial effects [10][11][12][13]. A recent study showed that there is a high degree of interindividual variability in metabolizing ω-3 PUFAs to generate lipid metabolites [14]. Thus, it is feasible that polymorphisms in the genes encoding the ω-3 PUFA-metabolizing enzymes could affect the metabolism of ω-3 PUFAs, impacting the generation of bioactive lipid metabolites in tissues and contributing to observed mixed results in ω-3 PUFA studies [15]. A better understanding of the interactions of ω-3 PUFAs with their metabolizing enzymes could lead to targeted human studies to better understand the metabolic individuality and nutrition effects of ω-3 PUFAs [15][16].

In this review, we summarize recent studies of ω-3 PUFAs on CRC and colonic inflammation (inflammatory bowel disease (IBD)) and discuss the potential roles of ω-3 PUFA-metabolizing enzymes, notably the CYP enzymes, in mediating the actions of ω-3 PUFAs.

2. Effects of ω-3 PUFAs on CRC and IBD

2.1. Effects of ω-3 PUFAs on CRC

Epidemiological and preclinical studies support the preventive effects of ω-3 PUFAs on CRC. In Table 1, we focus on the recent human studies on ω-3 PUFAs, as well as previous studies that have shown the beneficial effect of the ω-3 PUFAs and have been discussed by other review articles. A meta-analysis demonstrated a small but significant ~12% reduction of CRC risk between the highest and lowest ω-3 PUFA consumption groups [17]. In the VITamins And Lifestyle (VITAL) cohort study, the individuals who routinely took fish oil supplements had lower risks of developing CRC compared with those who did not take supplements [18]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study also showed that increased ω-3 PUFA consumption reduced CRC risks [19]. In a randomized, double-blind, placebo-controlled trial, EPA intake was associated with reduced polyp number and size in familial adenomatous polyposis (FAP) patients [20]. Increased intake of ω-3 PUFAs was also associated with improved disease-free survival in stage III CRC patients [21]. In a phase II double-blind, randomized, placebo-controlled trial, EPA intake increased overall survival in advanced CRC patients undergoing liver resection due to liver metastases (CRCLM) [22]. Together, these studies support the conclusion that ω-3 PUFAs reduce the risks of CRC.

Table 1. Recent epidemiological and clinical studies of ω-3 polyunsaturated fatty acid (PUFA) supplementation for the prevention/treatment of colorectal cancer (CRC).

Study	Individuals	*N*	ω-3 PUFA treatment	Dose	Duration	Control treatment	Results	Reference
VITAL prospective cohort	US adults	68,109	Fish oil supplements	N/A	4+days/week for 3+years	no use	↓ CRC risk	Kantor et al., 2014 [18]
EPIC prospective cohort	European adults	521,324	Highest ω-3 PUFAs intake	>470 mg/day	Median 14.9 years	lowest ω-3 PUFAs intake	↓ CRC risk	Aglago et al., 2020 [19]
Randomized, double-blind, placebo-controlled trial	FAP patients	EPA-FFA (n = 28)	EPA-FFA	2 g/day	6 months	Placebo (n = 27)	↓ polyp diameters	West et al., 2010 [20]
CALGB adjuvant chemotherapy trial	stage III colon cancer patients	1011	Highest marine ω-3 PUFAs intake	0.33-0.57 g/day;	>8 years	lowest marine ω-3 PUFAs intake	↑ disease-free survival	Blarigan et al., 2018 [21]
Double-blind, randomised, placebo-controlled trial	CRCLM patients	EPA-FFA (n = 43)	EPA-FFA	2 g/day	12–65 days	Placebo (n = 45)	↑ overall survival; no effect in disease burden and early CRC recurrence rates	Cockbain et al., 2014 [22]

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HPFS and NHS cohort	US adults	123,529	Highest marine ω-3 PUFAs intake	≥ 0.30 g/d (women) ≥ 0.41 g/d (men)	24–26 years	lowest marine ω-3 PUFAs intake	No effect on overall CRC risk; ↑ distal colon cancer risk in men and women; ↓ rectal cancer risk in men	Song et al., 2014 [23]
Randomized, double-blind, placebo-controlled clinical trial	colon cancer patients	ω-3 PUFA (*n* = 21)	ω-3 PUFA intravenous infusion	0.2 g/kg/day	night before and morning after resection surgery	Saline infusions (*n* = 2[illegible])	↑ infectious complications	Bakker et al., 2020 [24]

Abbreviations: VITAL, VITamins And Lifestyle; EPIC, European Prospective Investigation into Cancer and Nutrition; EPA, eicosapentaenoic acid; FFA, free fatty acid; FAP, familial adenomatous polyposis; CALGB, Cancer and Leukemia Group B; CRCLM, colorectal cancer liver metastases; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Consistent with the human studies, recent animal studies also support the beneficial effects of ω-3 PUFAs on CRC (Table 2). Treatment with an ω-3 PUFA mixture or EPA reduced intestinal polyposis formation in a spontaneous intestinal cancer model (using *Apc*$^{Min/+}$ mice) [25][26]. Dietary administration of EPA also decreased tumor incidence and multiplicity in a chemically induced colitis-associated colorectal cancer (CAC) model [27]. In addition, administration of fish oil suppressed the aberrant crypt foci number and adenoma incidence in 1,2-dimethylhydrazine (DMH) or azoxymethane (AOM)-induced CRC models in rats [28][29]. Besides dietary feeding studies using ω-3 PUFAs, previous studies also showed that *fat-1* transgenic mice, which have higher tissue levels of ω-3 PUFAs, have reduced development of CRC in both *Apc* gene mutation-induced CRC model [30] and chemically induced CAC model [31][32].

In addition to the orthotropic CRC tumor models discussed above, ω-3 PUFAs have also been shown to inhibit CRC in xenograft and metastasis models. Our recent study showed that administration of an ω-3 PUFAs-enriched diet inhibited MC38 (murine colon adenocarcinoma cell) tumor growth in a murine xenograft model [33]. Consistent with our result, fish oil- or DHA-rich diets attenuated tumor burden and aggressivity in HCT-116 or SW620 (both are human colon cancer cells) xenograft tumor models in nude mice [34][35][36]. In a MC-26 colon cancer cell-induced CRC metastasis model, treatment of EPA suppressed liver metastases in BALB/c mice [37]. In a CC531 colon cancer cell-derived liver metastasis model in rats, administration of an ω-3 PUFAs-rich diet, reduced hepatic tumor incidence and burden [38]. Moreover, ω-3 PUFAs could be used to enhance the actions and reduce the toxicity for anticancer drugs. The coadministration of oxaliplatin and DHA synergistically inhibited HCT-116 xenograft tumor growth in nude mice [31]. Overall, these results support the anti-CRC effects of ω-3 PUFAs.

Human and animal studies also support that the dietary intake of ω-3 PUFAs-rich foods, such as fish, flaxseed, and walnuts, reduces the risks of CRC. In the EPIC cohort study, the consumption of ω-3 PUFAs-rich fish was linked with lower risks of developing CRC . Stage III CRC patients who regularly consumed dark fish (≥1 time per week) had increased disease-free survival rates and lower cancer recurrence/motility risks compared to those who did not . Consistent with the human studies, the administration of a flaxseed-rich diet reduced aberrant crypt foci formation in both proximal and distal colon in an AOM-induced CRC model in rats [39]. The intake of a walnut-added diet also attenuated tumor growth in a HT29 cell-induced CRC xenograft model in mice [40]. ω-3 PUFAs could exhibit beneficial effects via regulating microbiota during CRC. The administration of EPA increased the abundance of *Lactobacillus* in a CAC cancer model in mice . The intake of EPA and DHA mixture could also increase the levels of *Bifidobacterium, Roseburia*, and *Lactobacillus* in humans [41]. Though more studies are needed to determine the extent to which food components, besides ω-3 PUFAs, contribute to the observed anti-CRC effects, these results further support the beneficial effects of ω-3 PUFAs on CRC.

Though many studies support the beneficial effects of ω-3 PUFAs on CRC, there are inconsistent results from animal and human studies. Some reports, in fact, have shown that ω-3 PUFAs had no effect [42][43] or even detrimental effects on the development of CRC [44][45] (Table 1–2). The Health Professionals Follow-Up Study (HPFS) and Nurses' Health Study

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(NHS) cohort studies showed that ω-3 PUFA intake had no effect on overall CRC risks and even increased distal colon cancer risk in certain individuals. The supplementation of ω-3 PUFAs had no effect on the recurrence or survival rate in stage III colon cancer patients [46]. Moreover, in a randomized, double-blind, placebo-controlled clinical trial, compared with saline infusion, intravenous infusions of ω-3 PUFAs worsened the infectious complications in CRC patients undergoing colon resection. Other postoperative complications were also reported in CRC patients who received ω-3 PUFAs after surgery [47]. Animal studies also showed that the treatment of fish oil exacerbated *Helicobacter hepaticus*-induced colitis and adenocarcinoma in SMAD3-deficient mice [45]. These inconsistent results make it difficult to effectively implement ω-3 PUFAs to reduce the risks of CRC.

Table 2. Preclinical studies of ω-3 PUFA supplementation for the prevention/treatment of CRC.

Model	Species	ω-3 PUFA treatment	Dose	Duration	Control treatment	Results	Reference
Apc$^{Min/+}$ mouse	C57BL/6 mouse	Fish oil	12% in diet	10 weeks	Standard diet with soybean oil	↓ intestinal polyp growth	Notarnicola et al., 2017 [25]
Apc$^{Min/+}$ mouse	C57BL/6 mouse	EPA-FFA	2.5% or 5% in diet	12 weeks	AIN-93G diet with soybean oil	↓ polyp number and load in both small intestine and colon.	Fini et al., 2010 [26]
Apc$^{Min/+}$ mouse	C57BL/6 mouse	Endogenous ω-3 PUFA synthesis by transgene of *fat-1*		20 weeks	*Apc*$^{Min/+}$ mice on standard diet with safflower oil	↓ intestinal polyposis	Han et al., 2016 [30]
AOM/DSS-induced CRC model	C57BL/6 mouse	Endogenous ω-3 PUFA synthesis by transgene of *fat-1*		16 weeks	Wild-type mice on standard diet	↓ Tumor number	Han et al., 2016 [31]
AOM/DSS-induced CRC model	C57BL/6 mouse	Endogenous ω-3 PUFA synthesis by transgene of *fat-1*		11 weeks	Wild-type mice on AIN-93G diet with safflower oil	↓ incidence and growth rate	Nowak et al., 2007 [32]
AOM/DSS-induced CRC model	C57BL/6 mouse	EPA-FFA	1% in diet	15 weeks	AIN-93G diet with corn oil	↓ tumor multiplicity, incidence and maximum tumor size	Piazzi et al., 2014 [27]

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DMH-induced CRC model	Wistar rat	Fish oil	18% in diet	36 weeks	AIN-93G diet with soybean oil	↓ number of aberrant crypt foci; ↓ incidence of adenoma	Moreira et al., 2009 [28]
AOM-induced CRC model	F344 rat	Fish oil	10% in diet	26 weeks	AIN-93G diet with mixed lipids	↓ colon tumor incidence and multiplicity	Reddy et al., 2005 [29]
MC38 cell-based xenograft mouse model	C57BL/6	DHASCO Algae oil	8% in diet	5 weeks	AIN-93G diet with corn oil	↓ tumor volume and weight	Wang et al., 2016 [33]
SW620 cell-based xenograft mouse model	Nude mouse	Fish oil	12% by calorie	6 weeks	Standard diet	↓ tumor growth and less aggressive	Bæhren et al., 2008 [34]
HCT116 cell-based xenograft mouse model	Nude mouse	DHA	10mg/kg	every other day for 13 days	Ethanol	↓ tumor size	Jeong et al., 2019 [35]
HCT116 cell-based xenograft mouse model	Nude mouse	DHA	3% in diet	Standard diet with sunflower oil 14 days		↓ tumor growth	Flückiger et al., 2016 [36]
Hℓ pylori-induced CRC mouse model	*SMAD3* deficiency	Fish oil	6% in diet	AIN-93G diet with corn oil 12 weeks		↓ adenocarcinoma formation	Woodworth et al., 2010 [45]

Abbreviations: AIN, American Institute of Nutrition; AOM, azoxymethane; DSS, dextran sodium sulfate; DMH, 1,2-Dimethylhydrazine; i.p., intraperitoneal; SMAD3, mothers against decapentaplegic homolog 3.

2.2. Effects of ω-3 PUFAs on IBD

IBD, which is characterized by chronic inflammation in intestinal tissues, severely impacts the quality of life of the patients. Symptoms include abdominal pain, vomiting, diarrhea, and rectal bleeding. The incidence and prevalence of IBD have risen dramatically in recent decades: In 2015, ~1.3% of US adults (3 million) were estimated to be diagnosed with IBD [48], representing a 50% increase from 1995 (2 million) [49]. To date, there is no cure for IBD, and the current anti-IBD treatments could lead to serious side effects, including infection, bone marrow dysfunction, and organ dysfunction [50]. Therefore, it is important to develop novel preventive strategies to reduce the risks of IBD.

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Human and animal studies support the beneficial effects of ω-3 PUFAs on the development of IBD. The intake of fish oil reduced the abundance and activity of cytotoxic NK cells and improved the disease condition in IBD patients [51]. Fish oil also decreased disease activity index and reduced neutrophil infiltration in ulcerative colitis (UC, a subtype of IBD) patients [52][53]. In animal models, ω-3 PUFAs suppressed T cell transplantation-induced colitis in severe combined immunodeficient (SCID) mice [54]. The treatment of a ω-3 PUFA (using linseed oil)-rich diet reduced the incidence of ovalbumin-induced allergic diarrhea in a food allergy mouse model [55]. The intake of ω-3 PUFAs, especially the EPA, reduced tissue damage and IBD-associated diarrhea, bloody stools, and weight loss in dextran sodium sulfate (DSS)-induced colitis models in mice and rats [56][57][58]. In ischemia-reperfusion (IR) rats, the intake of ω-3 PUFA-attenuated IR-induced mucosal injury in intestine [59]. In addition to the nutritional intervention of ω-3 PUFAs, *fat-1* transgenic mice, which have higher tissue levels of ω-3 PUFAs, have been shown to exhibit reduced colonic inflammation in DSS- or 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis . ω-3 PUFAs mainly exhibit beneficial effects via regulating immune cell infiltration during IBD. The administration of ω-3 PUFAs reduced the colonic infiltration of neutrophils [53][58], macrophages [62], T cells [54], and NK cells [illegible] in IBD mice and patients. Moreover, ω-3 PUFAs have been shown to decrease proinflammatory cytokines (TNF-α, IL-12, IL-1β, iNOS, and/or IL-6), enhance epithelial barrier function, upregulate antioxidative enzymes, and reduce lipid oxidation-derived compounds [54][57][58][59][60][61], and therefore inhibit the development of IBD in mice or rats.

There are also inconsistent reports, which have shown that ω-3 PUFAs have no effect or even adverse effects on IBD. In randomized, placebo-controlled trials, ω-3 PUFAs intake has had no effect in improving the recovery of colitis [63][64], and has even enhanced disease activity in UC patients [65]. Moreover, ω-3 PUFAs had no effect on either chemotherapy-induced enterocolitis in acute myeloid leukemia (AML) patients [66] or type 2 diabetes-induced duodenal inflammation in obesity patient [67]. In animal models, the treatment of fish oil has had little effect on DSS- or TNBS-induced colitis in rats [68][69], and has exacerbated the DSS-induced colitis in mice [70]. ω-3 PUFAs have also been shown to exaggerate chemotherapy (5-fluorouracil)-induced small intestine damage in rats [71].

2.3. Potential Reasons for the Mixed Results of ω-3 PUFAs

Overall, the effects of ω-3 PUFAs on CRC and IBD are controversial, making it difficult to effectively use ω-3 PUFAs for disease prevention. There are several possible reasons for the mixed results in ω-3 PUFA studies:

1. Both CRC and IBD are highly heterogeneous diseases, and previous studies have shown that ω-3 PUFAs have varied effects on different types of diseases. The plasma level of ω-3 PUFAs was negatively associated with the risks of proximal colon cancer, but with not distal colon cancer or overall CRC risk . The consumption of ω-3 PUFAs decreased the risks of developing rectal cancer but increased the risks of developing distal colon cancer in men . The administration of fish oil reduced the aberrant crypt foci and adenoma incidence, but not the carcinoma incidence, in a DMH-induced CRC model in rats . It is feasible that ω-3 PUFAs target some specific types of colon carcinogenesis or inflammation, which remains to be better defined.
2. Interindividual genetic variations could also influence the effects of ω-3 PUFAs on CRC and IBD. Many human studies have demonstrated significant interindividual variations in response to ω-3 PUFAs [72][73][74][75][76], which has made it difficult to confirm the efficacy of ω-3 PUFAs. The continuation of the current ω-3 PUFA research paradigms that neglect interindividual variation can be expected to keep generating mixed results and to fail to clarify their effects . Notably, recent research supports that ω-3 PUFA-metabolizing enzymes contribute to the biological actions of ω-3 PUFAs. A recent study showed that there is a high degree of interindividual variability in metabolizing ω-3 PUFAs to generate lipid metabolites . In addition, many studies support the critical roles of ω-3 lipid metabolizing enzymes in the activities of ω-3 PUFAs. For example, Dwyer et al.
3. [75] showed that a diet rich in ω-3 PUFAs decreased, while a diet rich in ω-6 PUAFs increased, the risks of atherosclerosis in the subpopulation carrying a specific 5-LOX genotype but not in the general population. Other studies have also supported that polymorphism in genes encoding lipid-metabolizing genes affect the effects of ω-3 PUFAs on CRC. Notably, in a population-based case-control study, lower DHA consumption is linked to increased CRC risk in individuals with polymorphic variants in the PTGS1 gen[74]The ω-3 PUFAs consumption only increased disease-free survival rate in CRC patients with upregulation of the PTGS2 gene [77]. These results emphasize the need to better understand the roles of lipid metabolism in the actions of ω-3 PUFAs.
4. Contamination and impurities in medication, supplements, and products can potentially compromise the protective effects of ω-3 PUFAs in clinical applications. ω-3 PUFAs are highly unstable and are easily oxidized. Oxidized ω-3 PUFAs release lipid peroxidation/oxidative products, which are cytotoxic and genotoxic to colonic cells [78][79]. Moreover, persistent organic pollutants (POPs) and foreign contaminations in fish oil supplements could exacerbate the colon carcinogenesis by stimulating aberrant crypt foci formation in rats [80]. The use of high-quality ω-3 PUFAs is critical in future human and animal studies to exclude the potential adverse effects from lipid oxidative products and

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contaminations. In addition, multiple studies have shown that the beneficial effects of ω-3 PUFAs, including anti-inflammation [81][82], anti-atherosclerosis [83], and anti-metastasis [84] effects, are dose-dependent. More studies are needed to determine the optimal dose and treatment time to maximize the beneficial effect of ω-3 PUFAs and to establish the official recommended daily intake for the general public and for CRC