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Dietary Intakes of Omega-3, Omega-6 and Fiber and Risk of Rectal Cancer: A Case-Control Study

Payam Hosseinzadeh[1#], Ali Gholami[2,3#], Mahdi Alemrajabi[4], Hasan Ghodsi[5,6], Yasamin Mohammadzade[7], Bahareh Amirkalali[1], Farhad Zamani[1]*

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Abstract

Background: Rectal cancer (RC) is one of the most commonly occurring cancers in Iran in recent years. Dietary intakes of Omega-3 (ω-3), Omega-6 (ω-6), and fiber have been thought to diminish the risk of RC. Therefore, this study was conducted to evaluate the association of dietary ω-3, ω-6, and fiber with the risk of RC.

Methods: In this case-control study, dietary intakes of ω-3 and ω-6 were estimated using a 148-item food frequency questionnaire (FFQ) between 363 people (162 cases, 201 control) aged 20–80 years old. Cases were patients with RC, and controls were healthy people. Odds ratios (OR) and 95% confidence intervals (CI) were assessed using logistic regression models.

Results: According to the multiple logistic regression model with the backward method, dietary fiber intake was inversely associated with RC as a protective factor (OR=0.3; 95%CI= 0.1-0.9; *P*=0.038). Also, it was observed that dietary ω-3 had an inverse borderline association with RC (OR= 0.5; 95%CI= 0.3-1.02; P=0.060), after adjusting for other studied variables. However, the association of ω-6 with RC was not statistically significant (OR=1.1; 95%CI= 0.7-1.8; *P*=0.730).

Conclusion: Although no association between ω-3 and ω-6 intake was observed with the risk of RC, adequate daily intake of dietary fiber may protect us against RC risk.

Keywords: Fiber, ω -3, ω -6, Rectal cancer

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Introduction

For a long time, it was believed that low red meat and high vegetables diet as a source of fiber and sea foods as a source of omega-3 (ω-3) in the Asian population is the reason for the low incidence of Rectal Cancer (RC) (1, 2). This cancer is highly correlated with a Western-style diet characterized by a constellation of dietary components, including lower intakes of fruit and vegetables and higher intakes of red and processed meats, refined grains, sugars, fats, and a higher rate of fatty acids (3, 4). Dietary fiber has been thought to diminish the risk of rectal, although the findings of most of the studies have been conducted on dietary fiber, and the risk of RC has been inconsistent (5, 6). One study showed that fiber can reduce the risk of RC (7). Whereas some recent studies have not shown a protective effect of dietary fiber on RC (5). Nevertheless, several plausible mechanisms have been proposed to explain the hypothesis that dietary fiber reduces the risk of RC, including increased stool bulk and dilution of carcin-

↑*What is "already known" in this topic:*
Rectal Cancer is one of the most commonly occurring cancers in Iran in recent years. Dietary intakes of ω-3, ω-6 and fiber have been thought to diminish the risk of RC.

→*What this article adds:*
The present case-control study suggests that dietary intake of fiber is associated with a decreased risk of rectal cancer.

Corresponding author: *Dr Farhad Zamani, payam.gildrc@gmail.com*

 # The first two authors contributed equally to this work.

1. Gastrointestinal and Liver Diseases Research Center (GILDRC), Iran University of Medical Sciences (IUMS), Tehran, Iran
2. Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran
3. Workplace Health Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran
4. Firoozgar Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
5. Healthy Ageing Research Centre, Neyshabur University of Medical Sciences, Neyshabur, Iran
6. Department of Nursing, Neyshabur University of Medical Sciences, Razavi Khorasan, Neyshabur, Iran
7. Khayyerin-e-salamat Hospital, Qom University of Medical Sciences, Qom, Iran

ogens in the colonic lumen, reduced transit time, and bacterial fermentation of fiber to short-chain fatty acids (8).

In addition to dietary fiber, epidemiologic research demonstrated that polyunsaturated fatty acids (PUFAs) are of particular interest due to their potential role in inflammation-driven rectal carcinogenesis (9). Experimental studies report anti-inflammatory and anticarcinogenic effects in the rectal for ω-3, highest in fish and seed oils, and adverse effects for omega-6 (ω-6) found in commercially popular oils and animal products (10). Despite evidence supporting the ω-6 and ω-3 as a biologically plausible target (11, 12), some studies have generally not found an association with RC (13). Multiple mechanisms of action and molecular targets have been described to explain the anti-inflammatory and anticancer activity of these PUFAs (14). The ω-3 can modulate cyclooxygenase metabolism and reduce the production of several prostanoids, including prostaglandin E2 in cells (15), whilst possibly increasing the production of lipid mediators involved in the resolution of inflammation, such as lipoxins and resolvins, which may have anti-cancer properties (16). Owing to the proposed competitive role of ω-3 and ω-6 through inflammation, the composition of these PUFAs is suggested to be a biologically plausible target. To date, studies investigating the intake of ω-3 and ω-6 PUFAs and risk of RC are limited, and results remain inconsistent (14). Totally, identifying the factors associated with decreased RC incidence among different trace population may help in the prevention of this cancer. Since taking the dietary fiber, ω-3 and ω-6 varies according to the geographical area of each body and can influence the incidence and prevalence of cancer in different persons (17). As, there is few specific research in the Iranian population, which ranks relatively high in the world in terms of the incidence and prevalence of colorectal, we conducted a case-control study to examine the association between dietary ω-3, ω-6 and fiber with RC in Iranian population.

Methods

Study population

This Study is a Case-Control study performed in 363 people (162 cases, 201 control). Recruitment occurred between March 2016 and November 2018. Iranian people were recruited, and besides diet, some variables, including marital status, job status, education, income, physical activity, and body mass index (BMI) were compared between cases and controls. Cases were patients diagnosed with non-metastatic RC who on the chemo-radiation waiting list of the Cancer Institute of Imam-Khomeini and Firoozgar Hospitals in Tehran, Iran. These patients were detected in a parallel phase III clinical trial (Clinical trial number: IRCT2016061118745N8) that was conducted by our research team. The exclusion criteria are explained in the research that was published from the same study. Exclusion criteria for cases were Patients with the age of less than 20 and more than 80 years old. Patients with metastatic cancer of the rectum or a history of colorectal cancer in their family, Liver problems (serum aspartate aminotransferase or alanine aminotransferase concentrations greater than100 IU/L), Serious acute or chronic heart disease, Metastatic brain or lung, Bowel obstruction, Kidney problems (Glomerular Filtration Rate ≤ 30 or serum creatinine concentrations greater than 1.7 mg/dl), Aids/Hepatitis, Abnormal blood cell count introduced by white blood cell counts greater than10,000 cells/L, hemoglobin levels less than 10 mg/dl or platelet counts less than 15,000/mcl or greater than 400,000/mcl, Specific drug regimen or consuming supplements that contained fiber, ω-3 and ω-6, Smoking and/or alcoholic Drinking were excluded from the study (18, 19). Cases were identified from notifications of first diagnoses of RC (International Classification of Diseases 10th revision rubric C19, C20, C21.8) (20). Control subjects applied from cancer-free outpatients at the mentioned hospitals. Frequency matching was performed in this study. In a way that for cases included in the study, controls from the same sex and age groups were selected (Table 1). All participants gave a written consent form prepared by the ethics committee of Iran University of Medical Sciences (IUMS).

The exposures in our study were fiber, ω-3, and ω-6. Omega-3 fatty acids are a family of unsaturated fatty acids whose first double bond is located between the third and fourth carbon in the carbon chain. Omega-3 fatty acids are essential for regulating lipid metabolism and human body activities. But they are not made in the human body.Omega-6 fatty acids are a family of polyunsaturated fatty acids that have in common a final carbon-carbon double bond in the n-6 position, that is, the sixth bond, counting from the methyl end .Dietary fibers are structural and storage polysaccharides of plants along with lignin, which are resistant to enzymatic hydrolysis in the stomach and small intestine and are completely or partially fermented in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and related plant materials. The mean of dietary reference intakes for Fiber, ω-6, and ω-3 is presented in Table 2 (21). Other studied variables include job, marital status, education, income, physical activity, and BMI listed in Table 3.

Data Collection and Nutrient Analyses

Data were collected by using a set of instruments, including a socio-demographic and anthropometric checklist (Table 1). In addition, Participants completed the Iranian version of a standard food frequency questionnaire (FFQ) (22). The validity of our questionnaire's content was previously affirmed based on observations by a panel of experts, item analysis, and reliability measures (23-25). The FFQ included 148 food items, which were assessed for each subject in four frequency categories (daily, weekly, monthly, and yearly). The questionnaires were completed through an interview by trained interviewers who contributed to the project. Nutrient composition data for ω -3, ω-6, and fiber were derived from the NUTRITION4 database as used for the same past articles (26, 27).

Statistical analysis

We used SPSS for Windows (Version X9. Chicago, SPSS Inc.) to analyze the data. We used the univariate analysis to investigate the association between studied variables and RC. After adjusting the effect of studied variables, we evaluated the association between dietary intakes of ω -3, ω-6, and fiber with RC by multiple logistic regression models with the backward method. The significance level was set at $P<0.2$ in univariate analyses and $P<0.05$ for multiple analyses. The odds ratios and 95% confidence intervals (CI) reported for evaluated variables (28).

Results

Among 200 cases who agreed to participate in this study, 38 participants were excluded from our investigation, and finally, 162 patients with RC and 201 controls were included in the analysis. The patients' demographic and lifestyle characteristics are displayed in Table 1. The mean age of cases and controls were 59.2±12 and 49.4±13 years old, respectively. The majority of cases were men (58%) and overweight or obese (66%). Only about 40% of our study population had adequate intake levels for ω-3, based on Table 2.

Based on the univariate analysis, job status, educational years, income, physical activity, BMI, and ω-6 had a significant difference between cases and controls (Table 3).

We used the multiple logistic regression model with the backward method to evaluate the independent effect of the dietary intake of fiber, ω-3, and ω-6 on the RC. According to this model, after adjusting for other factors, RC was only significantly associated with fiber intake ($P=0.038$). The association between RC and dietary ω-3 was not statistically significant, although this association is prone to be almost significant ($P=0.060$). Also, no association between the risk of rectal cancer and dietary intakes of ω-6 was found ($P=0.730$, Table 4).

Table 1. Characteristics of study population (N=363)

Variable		Case (N=162) n	Case %	Control (N=201) N	Control %
Age	< 30 years old	9	5.6	21	10.4
	30-39 years old	22	13.6	28	13.9
	40-49 years old	37	22.8	38	18.9
	50-59 years old	43	26.5	58	28.9
	60-69 years old	41	25.3	45	22.4
	≥ 70 years old	10	6.2	11	5.5
Sex	Female	68	42	93	46.3
	Male	94	58	108	53.7
Job	Active	114	71	167	83
	Passive	48	29	34	17
Marital Status	Single/Widow/Divorced	45	27	53	26
	Married	117	73	148	74
Education	< 12 years	89	57	137	70
	≥ 12 *years*	73	43	64	30
Income	< 500$ per month	65	41	101	51
	≥ 500$ per month	97	59	100	49
Physical Activity	Light	134	82	96	48
	Moderate and more	28	18	105	52
BMI	<25	56	34	56	28
	≥ 25	106	66	145	72

Abbreviations: Body Mass Index (BMI)

Table 2. The mean of Dietary Reference Intakes (DRI's) for Fiber, ω-6 and ω-3 (21)

Gender	Age groups	Fiber	ω-6	ω-3
Male	20-50 years old	38	17	1.6
	>50 years old	30	14	
Female	20-50 years old	25	12	1.1
	>50 years old	21	11	

The values are reported in (g/day)

Table 3. Odds Ratio (OR) estimates of RC based on the univariate logistic regression

Variable		Case (n=162)	Control (n=201)	OR (%95 CI)	*P*-value
Job	Active	114	167	2.1 (1.3-3.4)	0.004
	Passive	48	34		
Marital Status	Single/Widow/Divorced	45	53	0.9 (0.6-1.5)	0.764
	Married	117	148		
Educational years	< 12 years	89	137	1.8 (1.1-2.7)	0.010
	≥ 12 *years*	73	64		
Household Income	< 500$	65	101	1.5 (0.9-2.3)	0.054
	≥ 500$	97	100		
Physical Activity	Light	134	96	0.2 (0.1-0.3)	<0.001
	Moderate and more	28	105		
BMI*	<25	56	56	0.7 (0.5-1.1)	0.169
	≥ 25	106	145		
Fiber	Inadequate	30	46	1.3 (0.7-2.2)	0.309
	Adequate	132	155		
ω-3	Inadequate	91	118	1.1 (0.8-1.7)	0.627
	Adequate	71	83		
ω-6	Inadequate	59	95	1.6 (1.02-2.4)	0.038
	Adequate	103	106		

Abbreviations: Body Mass Index (BMI).
P-value≤0.2 is statistically significant.

Table 4. Adjusted analysis of Dietary intakes of fiber, ω-3, and ω-6 based on Backward multiple logistic regression model

Variables	Beta	OR (95%CI)	*P*-value
Fiber	-1.065	0.3 (0.1-0.9)	0.038
ω-3	-0.591	0.5 (0.3-1.02)	0.060
ω-6	0.08	1.1 (0.7-1.8)	0.730

Abbreviations: Confidence interval (CI).
P-value≤0.05 is statistically significant.

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Discussion

Overall, the results of this study revealed an inverse association between intakes of dietary fiber and RC. No associations were observed between dietary ω-6 and a reduced risk of RC. Considering the p-value=0.06 in the case of ω-3 and RC, there is a borderline association. Previous studies on the intake of fiber and the risk of RC have had inconsistent findings (29, 30). The study in Asia did not support the inverse association between fiber and RC (31). Whereas the protective effect of dietary intake of fiber on RC observed in our study was consistent with some previous findings (32, 33). This protective effect could be due to various mechanisms such as the formation of short-chain fatty acids from fermentation by colonic bacteria, reduction of secondary bile acid production, reduction in intestinal transit time and increase of fecal bulk, and a reduction in insulin resistance (34). It was noted that most of these studies were conducted in Western countries. The Western diet is typically described as being high in fat and low in fiber compared with the Asian diet (35, 36). It is probably leading to more differences between cases and controls. In our study, as the Iranian diet in early decades has changed in Western dietary patterns, cases have less intake of vegetables and legumes as a fiber source, resulting in an increasing rate of RC. So, we observed more significant differences between healthier people as a control group and RC patients.

Fiber is especially vulnerable to confounding factors such as smoking, drinking alcohol, eating red meat, and not being physically active (37). In our study, we exclude smoking and alcohol drinking. The extent to which confounding variables inter-relate and influence the fiber-RC relationship may vary between studies. These differences impact study risk estimates and could explain some of the disparities between our results and other studies (38, 39). Dietary measurement error could also account for the lack of associations observed in some studies (40). The ORs in different studies represent the combination of different types of fiber, such as soluble and insoluble fiber, and fiber from different food sources, which may have different effects on RC, suggesting different associations (35).

We did not find any robust associations between ω-6 fatty acid and RC risk in the present research ,consistent with previous studies (41) and in contrast with research that showed an inverse association (42). The possible mechanisms of the lack of association between omega-6 and colorectal cancer risk reduction are as follows: The increase in the omega-6/3 ratio has paralleled the rise in numerous autoimmune, inflammatory, and allergic diseases. Omega-3s are utilized by the body to resolve and lower inflammation, whereas omega-6 polyunsaturated fatty acids are primarily used for increasing inflammation (43). The metabolic pathways linking ω-6, endocannabinoids, and inflammatory mediators. The syntheses of N-docosahexaenoyl ethanolamine, N-eicosapentanoyl ethanolamine, and anandamide from ω-6 PUFAs, require the activity of N-acetyltransferase (NAT) followed by N-acyl phosphatidylethanolamine-specific phospholipase D. The synthesis of 2-AG from ω-6 PUFAs requires the subsequent activity of phospholipase Cβ and diacylglycerol lipase. The hydrolysis of the endocannabinoids requires the activity of the fatty acid amide hydrolase and monoacylglycerol lipase. The activity of lipoxygenases, cyclooxygenase, and cytochrome P450 enzymes drives the production of inflammation mediators like thromboxanes, leukotrienes, and prostaglandins that refers to the pro-inflammatory role of ω-6 (44). Despite supportive experimental data for ω-3 (14, 45) a relatively significant association was found for ω-3 and RC in our study.

In an overview, there was a similar body of inconsistent literature on the association between fiber, ω-3, and ω-6 with RC (46, 47). Also, as with dietary fiber, while laboratory data consistently show reduced RC risk with marine ω-3 PUFA (48), epidemiologic data are less convincing. Whereas Huang et al., (28) reported reduced RC risk with ω-3 from fish intake, two studies concluded that there is insufficient (49) or limited data (50).

An impressive body of evidence has been obtained in preclinical studies using in vivo colorectal cancer models, consistently supporting the antineoplastic role of ω-3. In these studies, extremely high doses of ω-3 were administered (51, 52). In spite of these data, only very few were in conflict with a protective effect of the ω-3 (53). As our results were based on the DRI, dietary intake of ω-3 was not agreed with high doses ω-3 studies.

Global, regional, and national consumption levels of dietary fats and oils between 1990 and 2010 were studied in a systematic analysis including 266 country-specific nutrition surveys., Based on the results, the global mean intake of ω-3 was 163 mg/day, with tremendous regional variation (from 700 mg/day) and national variation (from 5 to 3886 mg/day); Notably, 100 nations had very low mean consumption (<100mg/day), generally in North Africa and Middle East(17). In the Far East, Middle East and American diets, the amount of fat intake (energy intake, %) and the ratios of saturated fatty acids: monounsaturated fatty acids: PUFAs were 40 to 50 g (20-25%) and 1:1:1, 70 to 80 g (30-35%) and 2:5:2, and 80 to 90 g (35-40%) and 2:2:1, in that order, and this diversity may be closely related to their disease prevalence, including cancers in several sites (54, 55).

While the Western diet has a higher ratio of ω-6 than ω-3, several studies in Iran showed that increasing of Western pattern diet may also result in an increased incidence of many chronic and inflammatory diseases (56, 57). On the other hand, some studies have shown that decreased consumption of ω-3 during life can increase the risk of different kinds of gastrointestinal cancers like RC. According to these findings (55) we hypothesized that intake of ω-6 and ω-3 fatty acids would be more relevant to inflammatory pathways. When intake of ω-3 is sufficiently high, they are preferentially metabolized by shared metabolic and cyclooxygenase enzymes, leading to ‘‘competitive inhibition’’ with ω-6 metabolism. Through this route, this fatty acid may induce alterations of the cell's oxidative status and modulation of oxidative stress-dependent molecular pathways related to cell proliferation, apoptosis, or inflammation(58, 59). Unlike, high intake of ω-6’s, which are far more common in Iranian diets, as we saw in our study, can depress the metabolism of ω-3 fatty acids, leading to an influx of the pro-inflammatory class of eicosanoids (10, 59). Dietary sources are the other plausible reason describing the discrepancies between our findings by some of the studies (18, 60). Dietary sources of ω-3 and ω-6 PUFAs include several common foods. Hence, the effects of ω-6 may be masked by those of ω-3 PUFAs. Furthermore, because these foods are consumed on a daily basis and might have small between-person variabilities, the association, if any, might have been attenuated.

Limitations and strengths of our study

Briefly, the underrepresentation of cases that were ill when at presentation might limit the external validity of results. In addition, limitations of case-control studies using FFQs are recall bias and misclassification bias due to imprecise measures of dietary intake; however, we attempted to limit these problems by careful adjustment, adoption of identical study procedures in cases and controls, use of images of portion sizes and careful instructions to improve accuracy of reporting diet to reduce recall bias. Moreover, we used the FFQ that had been validated (61), and the reliability of that was well-established in Iran (23, 24). Although the FFQ has been validated for fatty acids using biomarkers (62), PUFAs are derived from both endogenous and exogenous sources, suggesting that a combination of dietary assessment and adipose tissue or blood biomarkers may be optimal to address measurement error and risk of misclassification (63). Our research has powers that affect the interpretation of the results. It is possible that the inverse associations between dietary fiber and the risk of RC can result from unmeasured confounding by other dietary or lifestyle factors. Higher intakes of dietary are typically associated with other health behaviors such as higher levels of physical activity, lower prevalence of smoking, overweight, or obesity, and lower intakes of alcohol and red and processed meat (63, 64). Many but not all of these confounders adjusted in our study. All of the cases in our study were specifically RC patients, but in many of the studies, patients were selected among "RC" cases who had cancerous cells in one of the colon or rectum or both of them, and they could not assess cancer risks in rectum separately (46). Although we performed adjustments for a wide range of confounders, we could not rule out the possibility that other unidentified or unmeasured factors could affect the association.

Conclusion

In conclusion, the present case-control study suggests that dietary intake of fiber is associated with a decreased risk of RC risk. Nevertheless, questions still remain about how dietary fiber may be beneficial against RC development and at which stages along the adenoma-carcinoma pathway fiber may act. Alternatively, fiber may only prevent disease progression to RC and not early lesions such as adenoma. In the case of ω-6 there is no association with RC in both cases and controls. More in-depth studies are needed to confirm the relationship between ω-3 and RC. An interesting possibility that may represent the field of future promising research in this area is that ω-3 fatty acid may affect DNA cytosine methylation, the covalent modifications of histones, or the expression of noncoding microRNA, and via these affects the RC. More in-depth studies are needed to confirm the relationship between ω-3 and RC.

Authors' Contributions

PH, AG, and FZ conceived and designed the research. PH, YM and BA collected the data. PH and AG analyzed and/or interpreted data. PH, MA, HG and YM drafted the manuscript. PH, AG, and FZ revised the manuscript critically for important intellectual content. All authors read and approved the final paper.

Ethical Considerations

The study protocol was part of a clinical trial (Ethical code: IR.IUMS.REC.1398.548) that was approved by the IUMS Ethics Committee.

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Conflict of Interests

The authors declare that they have no competing interests.

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