


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 Alemrajabi⁴, Hasan Ghodsi^{5,6}, Yasamin Mohammadzade⁷, Bahareh Amirkalali¹, Farhad Zamani^{1*} 

Received: 19 Dec 2023

Published: 14 Jul 2025

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

Conflicts of Interest: None declared

Funding: None

**This work has been published under CC BY-NC-SA 4.0 license.*

Copyright© Iran University of Medical Sciences

Cite this article as: Hosseinzadeh P, Gholami A, Alemrajabi M, Ghodsi H, Mohammadzade Y, Amirkalali B, Zamani F. Dietary Intakes of Omega-3, Omega-6 and Fiber and Risk of Rectal Cancer: A Case-Control Study. *Med J Islam Repub Iran*. 2025 (14 Jul);39:93. <https://doi.org/10.47176/mjiri.39.93>

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-

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

↑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.

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 than 100 IU/L), Serious acute or chronic heart dis-

ease, Metastatic brain or lung, Bowel obstruction, Kidney problems (Glomerular Filtration Rate \leq 30 or serum creatinine concentrations greater than 1.7 mg/dl), Aids/Hepatitis, Abnormal blood cell count introduced by white blood cell counts greater than 10,000 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 ($P = 0.038$).

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

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

Abbreviations: Body Mass Index (BMI)

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 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.

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-eicosapentanoylethanolamine, 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 C β 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.

Acknowledgment

This study was supported by the Gastrointestinal and Liver Diseases Research Center (GILDRC) and funded by IUMS (IUMS, No: 26713).

Conflict of Interests

The authors declare that they have no competing interests.

References

1. Martin-Fernandez-de-Labastida S, Alegria-Lertxundi I, de Pancorbo MM, Arroyo-Izaga M. Association between nutrient intake related to the one-carbon metabolism and colorectal cancer risk: a case-control study in the Basque Country. *Eur J Nutr*. 2023;62(8):3181-91.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-49.
3. McCullough ML, Giovannucci EL. Diet and cancer prevention. *Oncogene*. 2004;23(38):6349-64.
4. Kim JH, Jun S, Kim J. Dietary intake and cancer incidence in Korean adults: a systematic review and meta-analysis of observational studies. *Epidemiol Health*. 2023:e2023102.
5. Slattery ML, Curtin KP, Edwards SL, Schaffer DM. Plant foods, fiber, and rectal cancer. *The American journal of clinical nutrition*. 2004;79(2):274-81.
6. Pasdar Y, Shadmani FK, Fateh HL, Soleimani D, Hamzeh B, Ghalandari M, et al. The burden of colorectal cancer attributable to dietary risk in Middle East and North African from 1990 to 2019. *Sci Rep*. 2023;13(1):20244.
7. Nomura AM, Hankin JH, Henderson BE, Wilkens LR, Murphy SP, Pike MC, et al. Dietary fiber and colorectal cancer risk: the multiethnic cohort study. *Cancer Causes Control*. 2007;18(7):753-64.
8. Hullsall AG, Sinha R, Liao LM, Freedman ND, Graubard BI, Lofffield E. Whole grain and dietary fiber intake and risk of colorectal cancer in the NIH-AARP Diet and Health Study cohort. *The American journal of clinical nutrition*. 2020;112(3):603-12.
9. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *The Proceedings of the Nutrition Society*. 2008;67(3):253-6.
10. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *The American journal of*

clinical nutrition. 2004;79(6):935-45.

11. Bartram HP, Gostner A, Reddy BS, Rao CV, Scheppach W, Dusel G, et al. Missing anti-proliferative effect of fish oil on rectal epithelium in healthy volunteers consuming a high-fat diet: potential role of the n-3:n-6 fatty acid ratio. *Eur J Cancer Prev*. 1995;4(3):231-7.

12. Chapkin RS, Davidson LA, Ly L, Weeks BR, Lupton JR, McMurray DN. Immunomodulatory effects of (n-3) fatty acids: putative link to inflammation and colon cancer. *The Journal of nutrition*. 2007;137(1 Suppl):200S-4S.

13. Nkondjock A, Shatenstein B, Maisonneuve P, Ghadirian P. Specific fatty acids and human colorectal cancer: an overview. *Cancer Detect Prev*. 2003;27(1):55-66.

14. Cockbain AJ, Toogood GJ, Hull MA. Omega-3 polyunsaturated fatty acids for the treatment and prevention of colorectal cancer. *Gut*. 61(1):135-49.

15. Aglago EK, Huybrechts I, Murphy N, Casagrande C, Nicolas G, Pischon T, et al. Consumption of Fish and Long-chain n-3 Polyunsaturated Fatty Acids Is Associated With Reduced Risk of Colorectal Cancer in a Large European Cohort. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2020;18(3):654-66 e6.

16. Ishida T, Yoshida M, Arita M, Nishitani Y, Nishiumi S, Masuda A, et al. Resolvin E1, an endogenous lipid mediator derived from eicosapentaenoic acid, prevents dextran sulfate sodium-induced colitis. *Inflamm Bowel Dis*. 16(1):87-95.

17. Micha R, Khatibzadeh S, Shi P, Fahimi S, Lim S, Andrews KG, et al. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ*. 348:g2272.

18. Hosseinzadeh P, Javanbakht M, Alemrajabi M, Gholami A, Amirkalali B, Sohrabi M, et al. The Association of Dietary Intake of Calcium and Vitamin D to Colorectal Cancer Risk among Iranian Population. *Asian Pacific journal of cancer prevention : APJCP*. 2019;20(9):2825-30.

19. Zamani F, Khalighfar S, Kalhori MR, Poorkhani A, Amirani T, Hosseinzadeh P, et al. Expanding CYLD protein in NF- κ B/TNF- α signaling pathway in response to *Lactobacillus acidophilus* in non-metastatic rectal cancer patients. *Med Oncol*. 2023;40(10):302.

20. Bassett JK, Severi G, Hodge AM, Baglietto L, Hopper JL, English DR, et al. Dietary intake of B vitamins and methionine and colorectal cancer risk. *Nutr Cancer*. 65(5):659-67.

21. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. *Journal of the American Dietetic Association*. 2002;102(11):1621-30.

22. Nanri A, Shimazu T, Ishihara J, Takachi R, Mizoue T, Inoue M, et al. Reproducibility and validity of dietary patterns assessed by a food frequency questionnaire used in the 5-year follow-up survey of the Japan Public Health Center-Based Prospective Study. *J Epidemiol*. 22(3):205-15.

23. Kelishadi R, Pour MH, Sarraf-Zadegan N, Sadry GH, Ansari R, Alikhassy H, et al. Obesity and associated modifiable environmental factors in Iranian adolescents: Isfahan Healthy Heart Program - Heart Health Promotion from Childhood. *Pediatr Int*. 2003;45(4):435-42.

24. Kelishadi R, Pour MH, Zadegan NS, Kahbazi M, Sadry G, Amani A, et al. Dietary fat intake and lipid profiles of Iranian adolescents: Isfahan Healthy Heart Program-Heart Health Promotion from Childhood. *Prev Med*. 2004;39(4):760-6.

25. Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. *Journal of epidemiology*. 20(2):150-8.

26. Hosseinzadeh P, Djazayeri A, Mostafavi S-A, Javanbakht MH, Derakhshanian H, Rahimiforushani A, et al. Brewer's yeast improves blood pressure in type 2 diabetes mellitus. *Iranian journal of public health*. 42(6):602.

27. Hosseinzadeh P, Javanbakht MH, Mostafavi S-A, Djalali M, Derakhshanian H, Hajianfar H, et al. Brewer's yeast improves glycemic indices in type 2 diabetes mellitus. *International journal of preventive medicine*. 4(10):1131.

28. Huang YC, Jessup JM, Forse RA, Flickner S, Pleskow D, Anastopoulos HT, et al. n-3 fatty acids decrease colonic epithelial cell proliferation in high-risk bowel mucosa. *Lipids*. 1996;31 Suppl:S313-7.

29. Michels KB, Edward G, Joshupura KJ, Rosner BA, Stampfer MJ, Fuchs CS, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst*. 2000;92(21):1740-52.

30. Tabatabaei SM, Fritsch L, Knuiman MW, Boyle T, Iacopetta BJ, Platell C, et al. Meat consumption and cooking practices and the risk of colorectal cancer. *Eur J Clin Nutr*. 65(6):668-75.

31. Sato Y, Tsubono Y, Nakaya N, Ogawa K, Kurashima K, Kuriyama S, et al. Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. *Public Health Nutr*. 2005;8(3):309-14.

32. Yang G, Shu XO, Li H, Chow WH, Cai H, Zhang X, et al. Prospective cohort study of soy food intake and colorectal cancer risk in women. *The American journal of clinical nutrition*. 2009;89(2):577-83.

33. Peters U, Sinha R, Chatterjee N, Subar AF, Ziegler RG, Kulldorff M, et al. Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. *Lancet*. 2003;361(9368):1491-5.

34. Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, et al. Dietary fibre intake and risks of cancers of the colon and rectum in the European prospective investigation into cancer and nutrition (EPIC). *PLoS One*. 7(6):e39361.

35. Sheng T, Shen RL, Shao H, Ma TH. No association between fiber intake and prostate cancer risk: a meta-analysis of epidemiological studies. *World J Surg Oncol*. 13:264.

36. Barbosa MV, Dos Santos MP, Leite JA, Rodrigues VD, de Pinho NB, Martucci RB. Association between functional aspects and health-related quality of life in patients with colorectal cancer: can handgrip strength be the measure of choice in clinical practice? *Support Care Cancer*. 2023;31(2):144.

37. Papas MA, Giovannucci E, Platz EA. Fiber from fruit and colorectal neoplasia. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2004;13(8):1267-70.

38. Howe HL, Wu X, Ries LA, Cokkinides V, Ahmed F, Jemal A, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. *Cancer*. 2006;107(8):1711-42.

39. Haggard FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg*. 2009;22(4):191-7.

40. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, et al. Structure of dietary measurement error: results of the OPEN biomarker study. *Am J Epidemiol*. 2003;158(1):14-21; discussion 2-6.

41. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.

42. Lewis JE, Soler-Vila H, Clark PE, Kresty LA, Allen GO, Hu JJ. Intake of plant foods and associated nutrients in prostate cancer risk. *Nutr Cancer*. 2009;61(2):216-24.

43. DiNicolantonio JJ, O'Keefe J. The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Autoimmune Diseases, Asthma, and Allergies. *Mo Med*. 2021;118(5):453-9.

44. D'Angelo S, Motti ML, Meccariello R. omega-3 and omega-6 Polyunsaturated Fatty Acids, Obesity and Cancer. *Nutrients*. 2020;12(9).

45. Serini S, Donato V, Piccioni E, Trombino S, Monego G, Toesca A, et al. Docosahexaenoic acid reverts resistance to UV-induced apoptosis in human keratinocytes: involvement of COX-2 and HuR. *The Journal of nutritional biochemistry*. 22(9):874-85.

46. Navarro SL, Neuhauser ML, Cheng TD, Tinker LF, Shikany JM, Snetselaar L, et al. The Interaction between Dietary Fiber and Fat and Risk of Colorectal Cancer in the Women's Health Initiative. *Nutrients*. 8(12).

47. Kato A, Okada C, Eshak ES, Iso H, Tamakoshi A, Group JS. Association between dietary intake of n-3 polyunsaturated fatty acids and risk of colorectal cancer in the Japanese population: The Japan Collaborative Cohort Study. *Cancer Med.* 2023;12(4):4690-700.
48. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation.* 2021;122(21):2152-9.
49. Calviello G, Serini S, Piccioni E. n-3 polyunsaturated fatty acids and the prevention of colorectal cancer: molecular mechanisms involved. *Curr Med Chem.* 2007;14(29):3059-69.
50. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et biophysica acta.* 1981;4(4):469-84.
51. Bommarreddy A, Zhang X, Schrader D, Kaushik RS, Zeman D, Matthees DP, et al. Effects of dietary flaxseed on intestinal tumorigenesis in Apc(Min) mouse. *Nutr Cancer.* 2009;61(2):276-83.
52. Jia Q, Lupton JR, Smith R, Weeks BR, Callaway E, Davidson LA, et al. Reduced colitis-associated colon cancer in Fat-1 (n-3 fatty acid desaturase) transgenic mice. *Cancer Res.* 2008;68(10):3985-91.
53. Kantor ED, Lampe JW, Peters U, Vaughan TL, White E. Long-chain omega-3 polyunsaturated fatty acid intake and risk of colorectal cancer. *Nutr Cancer.* 2006;66(4):716-27.
54. Tokudome S, Nagaya T, Okuyama H, Tokudome Y, Imaeda N, Kitagawa I, et al. Japanese versus Mediterranean Diets and Cancer. *Asian Pacific journal of cancer prevention : APJCP.* 2000;1(1):61-6.
55. Tu K, Ma T, Zhou R, Xu L, Fang Y, Zhang C. Association between Dietary Fatty Acid Patterns and Colorectal Cancer Risk: A Large-Scale Case-Control Study in China. *Nutrients.* 2022;14(20).
56. John S, Luben R, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. *European journal of gastroenterology & hepatology.* 2005;22(5):602-6.
57. Seyyedsalehi MS, Collatuzzo G, Huybrechts I, Hadji M, Rashidian H, Safari-Faramani R, et al. Association between dietary fat intake and colorectal cancer: A multicenter case-control study in Iran. *Front Nutr.* 2022;9:1017720.
58. Busstra MC, Siezen CL, Grubben MJ, van Kranen HJ, Nagengast FM, van't Veer P. Tissue levels of fish fatty acids and risk of colorectal adenomas: a case-control study (Netherlands). *Cancer Causes Control.* 2003;14(3):269-76.
59. Wang Y, Guan WX, Zhou Y, Zhang XY, Zhao HJ. Red ginseng polysaccharide promotes ferroptosis in gastric cancer cells by inhibiting PI3K/Akt pathway through down-regulation of AQP3. *Cancer Biol Ther.* 2024;25(1):2284849.
60. Sasazuki S, Inoue M, Iwasaki M, Sawada N, Shimazu T, Yamaji T, et al. Intake of n-3 and n-6 polyunsaturated fatty acids and development of colorectal cancer by subsite: Japan Public Health Center-based prospective study. *International journal of cancer.* 2007;129(7):1718-29.
61. Kelishadi R, Gouya MM, Adeli K, Ardalan G, Gheiratmand R, Majdzadeh R, et al. Factors associated with the metabolic syndrome in a national sample of youths: CASPIAN Study. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2008;18(7):461-70.
62. Kabagambe EK, Baylin A, Allan DA, Siles X, Spiegelman D, Campos H. Application of the method of triads to evaluate the performance of food frequency questionnaires and biomarkers as indicators of long-term dietary intake. *Am J Epidemiol.* 2001;154(12):1126-35.
63. Hassanpour Ardekanizadeh N, Mousavi Mele M, Mohammadi S, Shekari S, Zeinalabedini M, Masoummand M, et al. Naturally nutrient rich (NNR) score and the risk of colorectal cancer: a case-control study. *BMJ Open Gastroenterol.* 2023;10(1).
64. Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). *Cancer Causes Control.* 2005;16(3):225-33.