VER
Vascular & Endovascular Review

Ingestion Of Omega-6 Fatty Acid And Increased Risk Of Colorectal Cancer- A Systematic Review

Sandeep Krishna. R[1], Sindhu. R[2]*, Gibbson Derick D[3], Lubna Fathima[4], Prabu D[5], Rajmohan M[6], Dinesh Dhamodhar[7]

[1]Undergraduate, SRM Dental college, Ramapuram, Bharathi salai, Chennai.
[2,4] MDS, Senior lecturer, Department of Public health dentistry, SRM Dental college, Ramapuram, Bharathi salai, Chennai.
[3]Postgraduate, Department of Public health dentistry, SRM Dental college, Ramapuram, Bharathi salai, Chennai.
[5]PhD, Head of the Department, Department of Public health dentistry, SRM Dental college, Ramapuram, Bharathi salai, Chennai.
[6,7] MDS, Reader, Department of Public health dentistry, SRM Dental college, Ramapuram, Bharathi salai, Chennai.

***Corresponding Author**
Sindhu R (researchphdsrm@gmail.com), MDS, Senior lecturer, Department of Public health dentistry, SRM Dental college, Ramapuram, Bharathi salai, Chennai.

ABSTRACT

Background: Colorectal cancer is a major disease affecting mankind, with an increasing incidence rate. While extensive research has validated the protective role of omega-3 fatty acids in tumorigenesis, the role of omega6 fatty acids remain ambiguous.

Aim- This systematic review aims to determine whether omega-6 fatty acids acid ingestion has increased risk of colorectal cancer

Objectives- To perform a literature review of the effects of omega-6 fatty acids on colorectal cancer tumorigenesis

Materials and methods- PRISMA analysis was done. A total of 11 articles were included for the study based on inclusion and exclusion criteria to evaluate the evidences from multiple prospective and cohort studies to assess the relationship between omega-6 fatty acid ingestion and increased risk of colorectal cancer.

Result- Evidence shows that there is increased risk of colorectal cancer with excess consumption of omega-6fatty acids and modest consumption of combination of omega-6 and omega-3 counteracts the deleterious effects of omega-6 fatty acids on genesis colorectal cancer.

Conclusion- Several studies included in this review reported association between higher intake of omega-6 fatty acids and increased risk of colorectal cancer. Conversely, some studies report no significant or even inverse associations between omega-6 fatty acid consumption and colorectal cancer risk. This systematic review emphasizes the importance of balancing omega-6 with omega-3 fatty acids, rather than suggesting that omega-6 alone is a significant independent risk factor for colorectal cancer.

KEYWORDS: Colorectal cancer, Omega6 fatty acids, Polyunsaturated fatty acids, Dietary assessments.

How to Cite: Sandeep Krishna. R, Sindhu. R, Gibbson Derick D, Lubna Fathima, Prabu D, Rajmohan M, Dinesh Dhamodhar, (2025) Ingestion Of Omega-6 Fatty Acid And Increased Risk Of Colorectal Cancer- A Systematic Review, Vascular and Endovascular Review, Vol.8, No.17s, 338-346.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in women and third most common in men with an estimated 1.2 million new case Colorectal cancer (CRC) is the second most common cancer in women and third most common in men with an estimated 1.2 million new cases diagnosed1.With 2 million new cases in 2018, the incidence of CRC has doubled globally over the last 10 years and is continuously rising in emerging nations2. More than 700,000 deaths have been reported annually due to CRC. The highest incidence of was reported in Eastern Europe, Asia and South America3.Colorectal cancer is a disorder that occurs in the colon or rectum and is caused by the colon's abnormal proliferation of glandular epithelial cells. The three principal types of CRC are Sporadic, hereditary, and colitis-associated. Environmental and genetic factors determine the risk of developing CRC. Generally, CRC takes 10 to 15 years to grow from a polyp to a malignant tumor4.Many factors are associated with the development of CRC, among them modifiable risk factors such as unhealthy dietary intake, lack of physical exercise, alcohol consumption and smoking are important5.

The two classes of essential fatty acids are omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs)[6]. Linoleic acid (LA) (n−6) (omega-6) and α-linolenic acid (ALA) (n−3) (omega-3) cannot be synthesized by our body, hence they are called as essential fatty acids (EFAs). These fatty acids (FAs) give rise to arachidonic acid (ARA, n−6), eicosapentaenoic acid (EPA, n−3), and docosahexaenoic acid (DHA, n−3) that play important roles in regulating body homeostasis[7].PUFAs are substrates for eicosanoid synthesis, with n-6 fatty acids being converted into pro-inflammatory eicosanoids and n-3 PUFA being converted to anti-inflammatory eicosanoids[8].

Omega-6 fatty acid is commonly found in meat, poultry, fish and cereals. In milk and its derivatives, it is found in lesser quantities while substantial amounts of the fatty acid are present in oils and fat rich foods[9]. Animal and in vitro studies suggest that n-3 and n-6 PUFA have contrasting effects on cancer development: n-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), suppress tumor carcinogenesis, whereas n-6 PUFA promote development[10]. Some investigations show that Omega 6 fatty acids cause lipid peroxidation which induces reactive species production[11]. These reactive species can act on macromolecules causing DNA damage[12]. Another mechanism is by inducing 17 beta estradiol epoxidation this has been linked to progression of human cancers to the metastatic stage due to loss of cell adhesion[13].They also act as carcinogens by enhancing the genotoxic effects of other compounds[14]. While the protective role of omega 3 fatty acids is well established through extensive research over many years, the role of omega 6 fatty acids has been overlooked. Both subsets of fatty acids are obtained from similar food sources and the implication of omega 6 in pathogenesis of CRC is ambiguous. This systematic review aims to evaluate the relationship between omega6 fatty acids and development of CRC.

MATERIALS AND METHODS

This systematic review shows the effects of omega6 fatty acids in the pathogenesis of CRC, that collects information from major databases including PubMed, Google Scholar and ResearchGate, to collect relevant data.

ELIGIBILITY CRITERIA

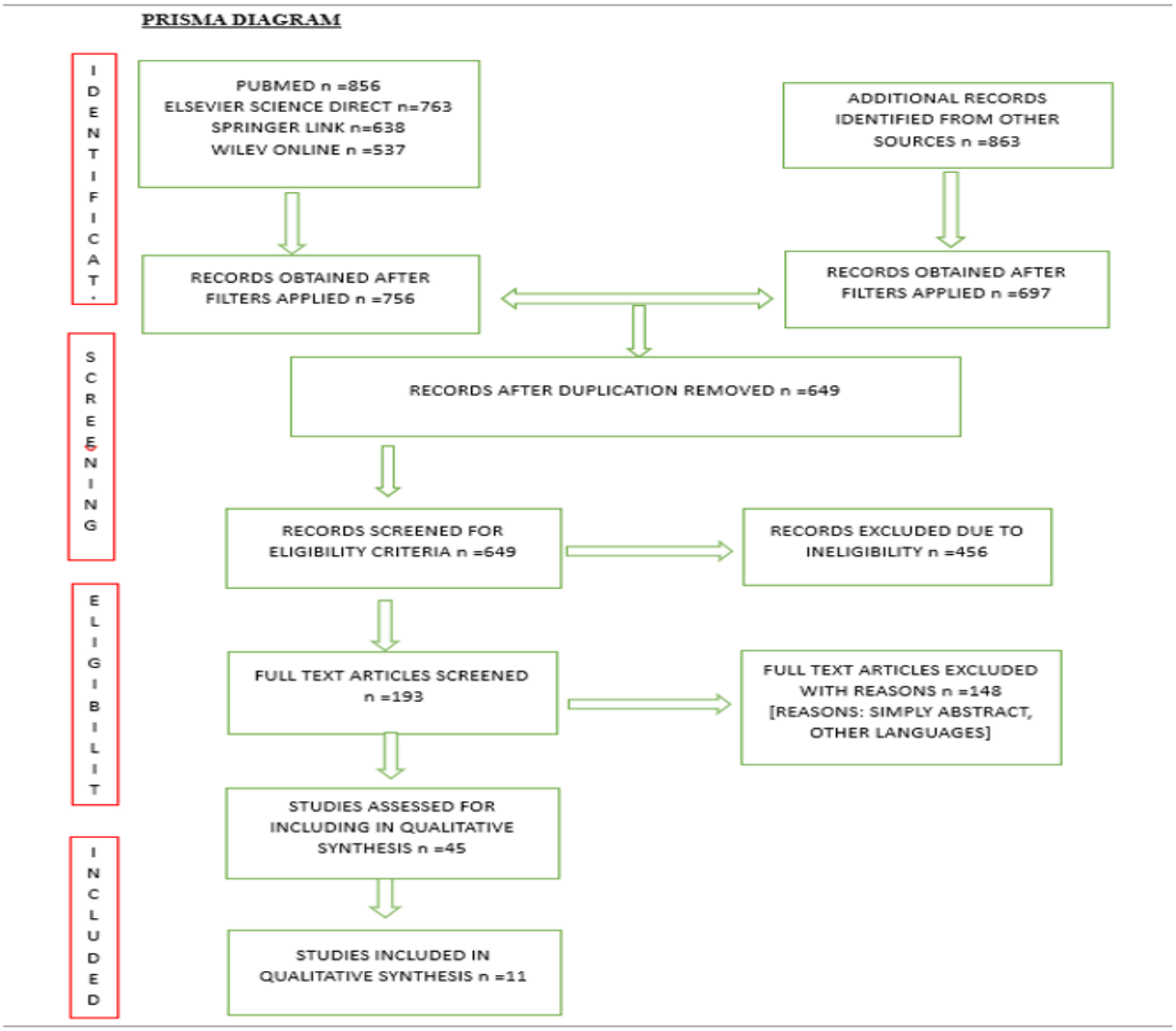
Inclusion Criteria

- Original In vitro, In vivo, Cohort or Prospective studies conducted between 1994-2020, assessing dietary information pertaining to omega6 fatty acids and CRC.
- Articles that provide results such as inflammation, carcinogenesis, immune modulation and tumor inhibition in relation to CRC.

Exclusion Criteria

- Reviews, editorials, case reports, abstract only or preprints.
- Studies published in languages other than English.

FIGURE 1: PRISMA flow diagram for recently conducted systematic reviews that are solely involved in database and registration searches.



RESULTS TABLE 1: CHARACTERISTICS OF THE INTERVENTIONS IN THE INCLUDED STUDIES

S.NO	AUTHOR NAME	STUDY DESIGN	SAMPLE SIZE	INTERVENTION	ANALYSIS
1.	Shin A et al [2020]	Cohort study	48,233	Dietary habits were collected through a food frequency questionnaire (FFQ) Demographics, lifestyle factors, weight, height was collected by self-administered questionnaire.	Not reported
2.	Norat et al [2005]	Prospective study	4,78, 040	Diet over the 12 months before enrollment was measured between 1992 and 1998 by country-specific validated questionnaires. The validity of methods used was established in prior studies using 24-hour urine and blood samples as sources of biomarkers	Health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin was used. Mortality data were collected from the cancer or mortality registries
3.	Engeset D et al [2007]	Cohort study	63 914	Dietary information was collected through food frequency questionnaire	254 cancer cases were reported, all histologically verified. The 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) were used
4.	Spencer EA et al [2010]	Cohort consortium	2575	Each cohort collected dietary information using four-day or seven-day diet diaries. Personal and medical information was collected by interviews or in questionnaires administered prior to completion of the diet diary.	Follow-up for diagnosis of colorectal cancer is provided through record linkage with the Office of National Statistics and local cancer registries, The 9th and 10th Revisions of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) were used

5.	Aglago et al [2020]	Cohort study	476,160	Body weight and height were measured or were self-reported. Questionnaires were used to obtain information on education, smoking and physical activity. Dietary intake was assessed at recruitment by validated center-specific questionnaires. Dietary intakes of LC-PUFAs were estimated using the United States Department of Agriculture (USDA) Nutrient Database,	Incident CRC cases were identified through regional cancer registries or via a combination of methods, including health insurance records, pathology registries. CRC cases were defined according to the International Classification of Diseases for Oncology (ICD-O):
6.	Shin A et al [2011]	Cohort study	1,265,226	Questionnaire and health examination was conducted	Cancer occurrence and death was ascertained from registry databases. Subsites were categorized by international classification of diseases 10th edition.
7.	Cha MC et al [2005]	In vitro study	Not reported	Cultures of normal rat colonic epithelial cells (4D/WT) and those transformed by *v-src* (D/v-src) were supplemented with graded concentrations of DHA or arachidonic acid (AA) alone or in combination with arachidonic acid.	The expression of protein kinase C isoform epsilon was decreased in AA alone supplemented D/v-src cultures but in combination with arachidonic acid decreased only in DHA supplemented 4D/WT cells.
8.	Chao A et al [2005]	Cohort study	148 610	Information was collected through questionnaire	Incident cases were verified by pathological reports
9.	Goldbohm RA et al [1994]	Prospective study	58,279 men and 62,573 women, aged 55-69.	Self-administered food frequency questionnaire	Incidence was by computerized record linkage with PALGA, a national data base of pathology reports.
10.	Hall MN et al [2007]	Prospective case-control study	14,916	A randomized, double-blind, placebo-controlled factorial trial of aspirin and β-carotene supplementation for the primary prevention of cancer and cardiovascular disease.	Annual follow-up questionnaires. Medical records: pathology report, histologic details to confirm the diagnosis. Information on deaths from

				Baseline and follow up questionnaire were conducted for diet and demographic details.	periodic searches of the National Death Index.
11.	Daniel CR et al [2009]	Prospective study	43,108 men and 55,972 women	Self-administered and follow up questionnaires for obtaining information of diet and demographic details	Reported cancers were verified through medical records, registry linkage, or death certificates.

Table 1 Shows the characteristics of the interventions in the studies that are included. In all the above studies, most of them were carried out with the help of questionnaires, in another study, culture of normal rat colonic epithelial cells and those transformed by *v-src* were supplemented with graded concentrations of DHA alone or in combination with arachidonic acid.

TABLE 2 Characteristics Of Outcome And Resluts In The Included Studies

S.NO	AUTHOR NAME	OUTCOME	RESULT
1	Shin A et al [2020]	A total of 334 cases were ascertained (201=colon, 133=rectal). A high intake of n-6 fatty acids especially linoleic acid, showed an increased risk for colorectal cancer. HR for highest quartile 1.40[95%CI,1.02-1.92] p-trend=0.038	Limited evidence linking omega-3 polyunsaturated fatty acids (PUFAs) with CRC risk. High intake of fish-derived docosahexaenoic acid (DHA) was associated with a decreased risk of rectal cancer. High intake of omega-6 fatty acids, particularly linoleic acid, showed an increased risk of colorectal cancer, especially rectal cancer.
2	Norat et al [2005]	Increasing red and processed meat intake was significantly associated with increasing risk of colorectal cancer [HR] for highest versus lowest intake level= 1.57, 95% confidence interval [CI] = 1.13 to 2.17, *p-trend* = .001 (*p-heterogeneity* = .29)	High intake of red and processed meat was positively associated with an increased risk of colorectal cancer. High fish consumption was inversely associated with colorectal cancer risk. Poultry intake showed no significant association with colorectal cancer risk.
3	Engeset D et al [2007]	There was a significantly higher risk of colon cancer for those in the highest tertile of poached fish consumption (RR 1·46, 95 % CI 1·04, 2·06) The *P*-value for trend was 0·02.	Slight increase in risk was observed for those in the third tertile of poached lean fish consumption. The findings do not support a protective effect of fish consumption against colon cancer
4	Spencer EA et al [2010]	There was very little evidence that intakes of red meat, processed meat, poultry, white fish or fatty fish were associated with risk for colorectal, colon or rectal cancer. The odds ratios for colorectal cancer, compared with the lowest intake group of <25g/day, were 0.81 (95% CI 0.61-1.09), 0.79 (0.59-1.07) and 0.88 (0.65-1.20) for combined intakes of red and processed meat of 25-50,50-75 or more than 75 g per day	Dietary factors may not play a major role in colorectal cancer risk in this population.
5	Aglago et al [2020]	Total fish intake was inversely associated with CRC (HR comparing extreme quintiles HRQ5vs.Q1=0.88, 95%CI=0.80-0.96, Ptrend=0.005) and particularly colon cancer (HRQ5vs.Q1=0.89, 95%CI=0.79-1.00, Ptrend=0.024)	Regular fish consumption at recommended levels was associated with a reduced risk of CRC. Higher intake of total fish, fatty fish, and lean fish significantly lowered CRC risk. Higher dietary intake of long-chain omega-3 PUFA was linked to a 14% lower CRC risk, while a higher ratio of omega-6 to omega-3 intake was associated with increased risk. Plasma levels of n-3 LC-PUFA were not associated with overall CRC risk. The study supports the protective role of fish and n-3 LC-PUFAs in colorectal cancer prevention
6	Shin A et al [2011]	4144 cancer incidents were recorded. More prevalence in older subjects(p<0.001). higher serum total cholesterol resulted in higher incidence (p-trend=0.001 for rectal and p-trend=0.079 for distal colon)	Risk factors varied by cancer subsite and sex. Frequent meat consumption was associated with increased risk of proximal colon cancer in men and rectal cancer in women. The findings suggest that CRC risk factors are heterogeneous depending on cancer location and sex.

7	Cha MC et al [2005]	Low dose DHA supplementation may enhance araC chemotherapy in colon cancer while protecting normal tissues, possibly through control of PKC signaling pathways.	AraC was toxic to both normal and tumorigenic colon cells, supplementing with low doses of DHA selectively enhanced araC toxicity in tumor cells more than in normal cells. Low-dose DHA could potentially enhance colon cancer chemotherapy efficacy while protecting normal colonic tissue from toxic side effects.
8	Chao A et al [2005]	Higher intake of red and processed meat was associated with higher colon cancer risk in men and women. Higher consumption of poultry and fish was inversely associated with colon cancer risk in women but not men	High consumption of red and processed meat was associated with an increased risk of distal colon cancer. Long-term high consumption of processed meat and high ratio of red meat to poultry and fish raised the risk. Long-term intake of poultry and fish showed an inverse association with colon cancer risk. High red meat consumption was linked to an elevated risk of rectal cancer. These findings support the role of red and processed meats in CRC development and suggest potential protective effects of poultry and fish.
9	Goldbohm RA et al [1994]	A higher consumption of (fresh)meat does not increase the risk of colon cancer	The study found no significant association between overall red meat consumption and colon cancer risk. Pork and lamb consumption were positively associated with increased CRC risk, while beef showed no significant association. These findings suggest that the risk linked to meat consumption may vary by meat type.
10	Hall MN et al [2007]	*n*-6 fatty acids were most strongly inversely associated with colorectal cancer risk when *n*-3 fatty acid levels were low [RR (95% CI) = 0.47 (0.21-1.10)]. nonsignificant inverse associations of blood levels of long-chain *n*-3 and *n*-6 fatty acids with colorectal cancer risk was observed. Results do not support the hypothesis that *n*-6 fatty acids may increase risk of colorectal cancer	Higher blood levels of long-chain omega-3 fatty acids were associated with a decreased risk of CRC among men not using aspirin. Omega-6 fatty acids did not show a clear association with risk. The study suggests that omega-3 fatty acids may have a protective role in CRC development, particularly in the absence of aspirin use.
11	Daniel CR et al [2009]	Total ω-6 intake was inversely related to colorectal cancer risk in men [multivariate relative risk (95% CI) for highest to lowest quartile, 0.81 (0.61-1.07); P_{trend} = 0.07] The ratio of ω-6 to ω-3 intake was not related to colorectal cancer risk in this cohort	Ratio of omega-6 to omega-3 intake was not significantly associated with CRC risk in either men or women. Total omega-6 intake was inversely related to CRC risk in men, while alpha-linolenic acid was associated with increased risk in women. Marine-derived omega-3 intake appeared to be linked with a lower risk in women.

TABLE 2 Shows the characteristics of outcome and results of the included studies. In majority of the studies evidence linking dietary fats and CRC is mixed. High intake of marine omega-3 fatty acids especially DHA, is associated with low CRC risk, whereas high omega-6 intake or high omega-6 to omega-3 ratio increases the risk. High red and processed meat consumption consistently raises CRC risk, while poultry shows no effect. Risk patterns vary by cancer site and sex. DHA also enhances chemotherapy effectiveness while reducing toxicity in normal colonic cells.

TABLE 3 Risk Of Bias Assessment As Included In The Studies

S. No.	Author (Year)	Bias from Randomization Process	Bias due to Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of the Reported Result	Overall Risk of Bias
1	Shin A et al., 2020	Some concerns	Low Risk	Low Risk	Low Risk	Some concerns	Some concerns
2	Norat et al., 2005	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
3	Engeset D et al., 2007	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

S. No.	Author (Year)	Bias from Randomization Process	Bias due to Deviations from Intended Interventions	Bias due to Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of the Reported Result	Overall Risk of Bias
4	Spencer EA et al., 2010	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
5	Aglago et al., 2020	Low Risk	Low Risk	Low Risk	Low Risk	Some concerns	Low Risk
6	Shin A et al., 2011	Some concerns	Low Risk	Low Risk	Low Risk	Some concerns	Some concerns
7	Cha MC et al., 2005	Some concerns	Low Risk	Low Risk	Low Risk	Some concerns	Some concerns
8	Chao A et al., 2005	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
9	Goldbohm RA et al., 1994	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
10	Hall MN et al., 2007	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
11	Daniel CR et al., 2009	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

TABLE 3 Shows the risk of bias assessment as included in the studies: the color Green indicates Low Risk - No or minimal risk of bias; study methods are appropriate and well reported. The color Yellow denotes some concerns - Some aspects are unclear or not fully reported, possibly affecting validity. The color● Red indicates high risk - Major methodological flaws or high potential for bias.

DISCUSSION

This systematic review has compiled findings from multiple prospective cohort studies and large epidemiological investigations examining the relationship between omega-6 fatty acid (n-6 PUFA) intake and the risk of colorectal cancer (CRC). There is an intricate interplay between dietary fatty acids, inflammation, and colorectal carcinogenesis, however the overall evidence remains indefinite.

Shin A et al., 2020 (Swedish Women's Lifestyle and Health Cohort) stated that there were no significant association between total omega-3 or omega-6 fatty acid intake and colorectal cancer risk, though marine-derived omega-3s showed a slight inverse trend. This study is based on a Large, prospective female cohort with robust follow-up and registry linkage which proved to be advantageous. Limitations of the study are Dietary intake based on self-report, potential confounding and limited generalizability to other populations. Future aspects of the study include the use of repeated dietary measures and biomarker validation for fatty-acid intake to confirm trends[15]. Norat T et al., 2005 (EPIC Study) stated that high consumption of red and processed meat increased CRC risk, whereas fish intake was associated with reduced risk. It is a multi-country prospective cohort, large sample, and diverse dietary habits. Limitations include Heterogeneity in dietary assessment and residual confounding by cooking methods and lifestyle. Future aspects of the study include the use of harmonized biomarker-based studies to clarify mechanisms related to cooking practices and meat processing[16]. Engeset D et al., 2007 (NOWAC Study) stated there were no clear association between total fish consumption and colon cancer risk, although fatty fish intake showed a possible protective trend. It is a Large female cohort with registry linkage and national dietary patterns. It however it uses single baseline dietary assessment and there's a possibility of underestimation of fish subtypes. Future aspects of the study include pooled analyses with other Scandinavian cohorts to strengthen statistical power[17].

Spencer EA et al., 2010 (UK Dietary Cohort Consortium) stated there were no significant associations between poultry or fish and CRC, but high red and processed meat intake was linked with increased risk. This study Pooled UK cohorts which increased statistical power and had uniform analysis methods. It However it showed Variation in dietary questionnaires across cohorts and potential confounding from overall dietary pattern. Future aspects include interactions with Fiber and antioxidant intake to refine risk estimates[18]. Aglago EK et al., 2020 (Large European Cohort) stated that higher consumption of fish and long-chain n-3 PUFAs (EPA, DHA) was associated with reduced colorectal cancer risk. The study used a very large European dataset with detailed fatty-acid exposure metrics. Limitations were due to observational design with residual confounding and fish preparation types that were not fully detailed. Future aspects include the Use of genetic or metabolomic approaches to confirm causal pathways for marine n-3 PUFAs[19]. Shin A et al., 2011 (Korean Population Study) stated Meat consumption was associated with higher rectal cancer risk, while fish intake had no significant effect and that risk varied by tumour site. The study Provides insight into Asian dietary patterns and site-specific risks. Cultural dietary differences and FFQ accuracy may limit comparability with Western cohorts. Future aspects include Examination of genetic and microbiome influences on site-specific dietary effects[20]. Cha MC et al., 2005 (In vitro study on DHA) stated that Low-dose DHA protected normal colonic epithelial cells from araC-induced cytotoxicity, supporting anti-inflammatory and protective mechanisms. The study provided mechanistic evidence linking omega-

3 (DHA) to cellular protection against damage. It However the In vitro design limits extrapolation to human populations. Animal and human studies assessing DHA's role in preventing colon epithelial injury could provide future developments to the study[21]. Chao A et al., 2005 (U.S. Cohort, JAMA) stated that high red and processed meat intake significantly increased colorectal cancer risk however fish intake showed no consistent association. It is a Large U.S. population-based cohort with rigorous adjustment for confounders. Self-reported diet and unmeasured lifestyle factors of the study might bias results. Studies separating effects of cooking temperature and heme iron content are warranted for future developments in this particular study[22]. Goldbohm RA et al., 1994 (Dutch Cohort Study) stated that there was a positive association between meat consumption and colon cancer risk, especially for processed meat. Early prospective evidence guided subsequent dietary research. Limitations of the study included outdated dietary assessment tools and evolving meat processing methods since 1990s.Future aspects of the study include using modern dietary instruments and extended follow-up periods[23]. Hall MN et al., 2007 (Biomarker Study, U.S.) stated that higher blood levels of long-chain n-3 PUFAs were associated with reduced CRC risk, particularly among aspirin users. Biomarker-based exposure reduces recall bias and strengthens biological inference. However Single blood measurement conducted in this study may not capture long-term fatty-acid status. Future aspects include repeated biomarker assessments and randomized trials testing combined n-3 and aspirin interventions[24].

Daniel CR et al., 2009 (U.S. Prospective Cohort) stated that high omega-6 intake was linked to a slightly increased CRC risk, whereas omega-3 intake appeared protective, a higher omega-6 to omega-3 ratio correlated with greater risk. It is a large cohort examining both omega-3 and omega-6 simultaneously, allowing ratio-based interpretation. There are possible residual confounding and misclassification of dietary fats. Future aspects include emphasis on biomarker-based studies and mechanistic exploration of lipid metabolism in colorectal tumorigenesis[25]. Daniel et al. (2009) observed a notable increased risk in CRC with higher dietary n-6 PUFA intake in men. Similarly, Hall et al. (2007) explored blood levels of long-chain PUFAs and found that elevated arachidonic acid was associated with increased risk of CRC. Eight out of eleven included studies showed low risk and three studies had some concerns in risk of bias assessment thereby validating the reliability of the included studies.
Some studies reported evidence of increased risk of colorectal cancer with excess consumption of omega-6fatty acids and modest consumption of combination of omega-6 and omega-3 counteracts the deleterious effects of omega-6 fatty acids on genesis colorectal cancer. The overall limitations of these studies on fish, omega 3/6 fatty acid ingestion, and CRC risk include issues with dietary assessment accuracy, heterogeneity in populations, residual confounding, and measurement bias, limited generalizability and short follow-up duration.

CONCLUSION

Evidence recorded by the articles included in this review does not establish a clear association between omega-6 fatty acid intake and CRC risk. While some studies suggest a modest increase in risk with higher omega-6 intake, others report null or inverse findings. The variability in outcomes is due to differences in dietary assessment methods, population characteristics, and confounding factors. Evidence remains consistent for the protective effects of omega-3 fatty acids rather than harmful effects from omega-6 fatty acids. Further research should incorporation of biomarker-based exposure measures and mechanistic analyses to clarify causal pathways in future research will help in development of our understanding on role of omega 6. Importance of balancing omega-6 with omega-3 fatty acids should be emphasized, rather than suggesting that omega-6 alone is a significant independent risk factor for CRC

REFERENCES:

1. 1.Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69–90. PMID: 21296855.
2. 2.Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Przegl Gastroenterol.* 2019;14(2):89–103. doi:10.5114/pg.2018.81072.
3. 3.Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683–691. doi:10.1136/gutjnl-2015-310912.
4. 4.Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges, risk factors, preventive and treatment strategies. *Cancers (Basel)*. 2022;14(7):1732. doi:10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939.
5. Carr PR, Weigl K, Jansen L, Walter V, Erben V, Chang-Claude J, Brenner H, Hoffmeister M. Healthy lifestyle factors associated with lower risk of colorectal cancer irrespective of genetic risk. *Gastroenterology*. 2018;155(6):1805-1815.e5. doi:10.1053/j.gastro.2018.08.044. PMID: 30201362; PMCID: PMC6279591.
6. Food and Nutrition Board, Institute of Medicine. Dietary fats: total fat and fatty acids. In: *Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids*. Washington (DC): National Academies Press; 2002. p. 422-541.
7. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: dietary sources, metabolism and significance – a review. *Life Sci.* 2018;203:255-267. doi:10.1016/j.lfs.2018.04.049.
8. Schmitz G, Ecker J. The opposing effects of n−3 and n−6 fatty acids. *Prog Lipid Res*. 2008;47(2):147-155. doi:10.1016/j.plipres.2007.12.004.
9. Meyer BJ, Mann NJ, Lewis JL, Milligan GC, Sinclair AJ, Howe PRC. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. Lipids. 2003 Apr;38(4):391-8. doi: 10.1007/s11745-003-1074-0. PMID: 12848284.
10. Liput KP, Lepczyński A, Ogłuszka M, Nawrocka A, Poławska E, Grzesiak A, Ślaska B, Pareek CS, Czarnik U, Pierzchała M. Effects of Dietary n-3 and n-6 Polyunsaturated Fatty Acids in Inflammation and Cancerogenesis. Int J Mol Sci. 2021 Jun 28;22(13):6965. doi: 10.3390/ijms22136965. PMID: 34203461; PMCID: PMC8268933.

11. Pai R, Soreghan B, Szabo IL, Pavelka M, Baatar D, Tarnawski AS. Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. Nat Med. 2002;8(3):289-93.
12. Ting AH, McGarvey KM, Baylin SB. The cancer epigenome—components and functional correlates. Genes Dev. 2006;20(23):3215-31.
13. Yu FL, Greenlaw R, Fang Q, Bender W, Yamaguchi K, Xue BH, et al. Studies on the chemopreventive potentials of vegetable oils and unsaturated fatty acids against breast cancer carcinogenesis at initiation. Eur J Cancer Prev. 2004 Jun;13(3):239-48.
14. Kinnunen PK, Koiv A, Lehtonen JY, Rytomaa M, Mustonen P. Lipid dynamics and peripheral interactions of proteins with membrane surfaces. Chem Phys Lipids. 1994 Apr;73(3):181-207.
15. Shin A, Cho S, Sandin S, Lof M, Oh MY, Weiderpass E. Omega-3 and -6 Fatty Acid Intake and Colorectal Cancer Risk in Swedish Women's Lifestyle and Health Cohort. Cancer Res Treat. 2020 Jul;52(3):848-54. doi: 10.4143/crt.2019.550. Epub 2020 Mar 6. PMID: 32138465; PMCID: PMC7373878.
16. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst. 2005 Jun 15;97(12):906-16. doi: 10.1093/jnci/dji164. PMID: 15956652; PMCID: PMC1913932.
17. Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. Br J Nutr. 2007 Sep;98(3):576-82. doi: 10.1017/S0007114507721487. Epub 2007 Apr 10. Erratum in: Br J Nutr. 2008 Mar;99(3):696. PMID: 17419892.
18. Spencer EA, Key TJ, Appleby PN, Dahm CC, Keogh RH, Fentiman IS, Akbaraly T, Brunner EJ, Burley V, Cade JE, Greenwood DC, Stephen AM, Mishra G, Kuh D, Luben R, Mulligan AA, Khaw KT, Rodwell SA. Meat, poultry and fish and risk of colorectal cancer: pooled analysis of data from the UK dietary cohort consortium. Cancer Causes Control. 2010 Sep;21(9):1417-25. doi: 10.1007/s10552-010-9569-7. Epub 2010 May 1. Erratum in: Cancer Causes Control. 2011 Sep;22(9):1351. PMID: 20437091.
19. Aglago EK, Huybrechts I, Murphy N, Casagrande C, Nicolas G, Pischon T, Fedirko V, Severi G, Boutron-Ruault MC, Fournier A, Katzke V, Kühn T, Olsen A, Tjønneland A, Dahm CC, Overvad K, Lasheras C, Agudo A, Sánchez MJ, Amiano P, Huerta JM, Ardanaz E, Perez-Cornago A, Trichopoulou A, Karakatsani A, Martimianaki G, Palli D, Pala V, Tumino R, Naccarati A, Panico S, Bueno-de-Mesquita B, May A, Derksen JWG, Hellstrand S, Ohlsson B, Wennberg M, Van Guelpen B, Skeie G, Brustad M, Weiderpass E, Cross AJ, Ward H, Riboli E, Norat T, Chajes V, Gunter MJ. Consumption of Fish and Long-chain n-3 Polyunsaturated Fatty Acids Is Associated with Reduced Risk of Colorectal Cancer in a Large European Cohort. Clin Gastroenterol Hepatol. 2020 Mar;18(3):654-666.e6. doi: 10.1016/j.cgh.2019.06.031. Epub 2019 Jun 25. PMID: 31252190.
20. Shin A, Joo J, Bak J, Yang HR, Kim J, Park S, Nam BH. Site-specific risk factors for colorectal cancer in a Korean population. PLoS One. 2011;6(8): e23196. doi: 10.1371/journal.pone.0023196. Epub 2011 Aug 10. PMID: 21853085; PMCID: PMC3154290.
21. Cha MC, Lin A, Meckling KA. Low dose docosahexaenoic acid protects normal colonic epithelial cells from araC toxicity. BMC Pharmacol. 2005 Mar 23; 5:7. doi: 10.1186/1471-2210-5-7. PMID: 15788091; PMCID: PMC1079882.
22. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, Rodriguez C, Sinha R, Calle EE. Meat consumption and risk of colorectal cancer. JAMA. 2005 Jan 12;293(2):172-82. doi: 10.1001/jama.293.2.172. PMID: 15644544.
23. Goldbohm RA, van den Brandt PA, van 't Veer P, Brants HA, Dorant E, Sturmans F, Hermus RJ. A prospective cohort study on the relation between meat consumption and the risk of colon cancer. Cancer Res. 1994 Feb 1;54(3):718-23. PMID: 8306333.
24. Hall MN, Campos H, Li H, Sesso HD, Stampfer MJ, Willett WC, Ma J. Blood levels of long-chain polyunsaturated fatty acids, aspirin, and the risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2007 Feb;16(2):314-21. doi: 10.1158/1055-9965.EPI-06-0346. PMID: 17301265.
25. Daniel CR, McCullough ML, Patel RC, Jacobs EJ, Flanders WD, Thun MJ, Calle EE. Dietary intake of omega-6 and omega-3 fatty acids and risk of colorectal cancer in a prospective cohort of U.S. men and women. Cancer Epidemiol Biomarkers Prev. 2009 Feb;18(2):516-25. doi: 10.1158/1055-9965.EPI-08-0750. Epub 2009 Feb 3. PMID: 19190143.