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In individuals that are genetically predisposed to colon cancer, how does high intake of fish oil compared to low fish oil intake affect the risk of developing colon cancer

Tatiana Mudrenko
University of the Pacific, tatianamudrenko@yahoo.com

In individuals that are genetically predisposed to colon cancer, how does high intake of fish oil compared to low fish oil intake affect the risk of developing colon cancer.

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Tatiana Mudrenko

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Introduction:

Colorectal cancer (CRC) is the fourth most common cancer type in the United States and the third world wide.[1-2] Mortality rates have decreased over the years due to early screening and improvements in treatment; however, the total cancer deaths worldwide are expected to rise. The predicted increase in global CRC deaths is explained not only by population growth and aging but also by risk factors such as lifestyle.[3] Even though colorectal cancer can be genetically inherited, major evidence shows that dietary factors can modify the risk of developing it. Implementing appropriate diet and early screening in individuals who are genetically predisposed to colorectal cancer, can decrease the mortality rate even more. However, there is still a lot of controversy in respect to what should be included in the diet. This literature review looks at how does the high intake of omega 3 Fatty Acids compared to diets low in omega 3 affect the risk of developing colorectal cancer in individuals that are genetically predisposed to it.

What does the literature say?

In order to understand the mechanism of action of Omega 3 Fatty acids, it's important to understand the etiology of CRC. Cyclooxygenase (COX) 1 and 2 have been proven to be involved in development of colorectal cancer. The enzymes promote tumor growth, angiogenesis and metastasis. Individuals that have a genetic mutation, which is often inherited, express higher levels of COX 2 and are at risk for developing colorectal cancer. Even though there is a predisposition to developing colorectal cancer, there seems to be an inflammatory pathway involved in the development of cancer and metastasis. Research shows that chronic intestinal inflammation leads to colorectal cancer. [1-2] A meta-analysis of the current research on the effects of fish oil on the inflammatory mediators in colon cancer was conducted and looked at people 18

years of age and over that were affected by malignant colorectal neoplasms and that used N-3

Polyunsaturated fatty acids as intervention. Current literature shows that colorectal

carcinogenesis involves an inflammatory pathway. The significance of the meta-analysis was

the finding that the consumption of n-3 PUFA by patients with CRC help decrease some

inflammatory mediators. However, the benefits are specific to the duration, the route, and the

dose of the supplementation as well as the type of anti-cancer treatment used (surgery vs

chemotherapy). [4]

Genes modifying the effect of fish on CRC development:

In their cohort study, the researchers followed populations with different polymorphisms

of CRC and aimed to identify the biological mechanisms underlying the CRC by assessing their

diet-gene interaction through blood samples and questionnaires on diet and lifestyle. They

concluded that certain polymorphisms carry a higher risk for CRC and diet has an effect on

certain allele variants but not others. Thus, its effect varies depending on the genetic make-up.

Even though this study supports that fish intake modifies the risk of developing colorectal cancer

in those genetically predisposed, it demonstrates that genetic variability coding for the cancer

may alter the effect of fish. [5]

Evidence from another cohort study showed that fish consumption was associated with a

decreased risk for colorectal cancer with COX 2 genotype. The study looked at the relationship

between consumption of omega 3 PUFA and the risk of CRC. The cohorts from Nurse's Health

Study and the Health Professional's Follow up Study were used in this cohort study. A food

frequency questionnaire was mailed to the participants biennially, looking at the dietary

assessment such as: consumption, how often, and size of portion they consumed certain food and

for how long in the past year.

Later, the researchers looked at the measurement of erythrocyte PUFA, as well as reported cases of CRC. The findings were contradictory of current literature in that no overall association between omega 3 or 6 PUFA intake and the risk of CRC was observed in the general population. However, they did find a reduction of distal colon and rectal cancer with marine omega 3 PUFA but the findings were not significant. The researchers state that a possible explanation of their findings could be due to the fact there tends to be a higher dose of omega-3 FA in the laboratory studies as opposed to a cohort study, which tends to look at the general human consumption. [6]

The researcher continued to follow the cohort and looked at the relationship between consumption of omega 3 PUFA and the risk of CRC. A questionnaire was sent out every 4 years looking at intake of omega 3 PUFA intake and followed up for incident of CRC. The study found that the high intake of omega 3-PUFAs lowered the risk of some types of CRC but not others. However, the effect of omega 3 PUFAs differ for men vs women. This study also shows an association between fish consumption and a decreased risk of development of colorectal cancer. It is consistent with previous research findings by showing the positive effect of omega 3FA on colorectal cancer. [4, 6-7]

Benefits of fish consumption vary between the different cancer types:

To further investigate the discrepancy of the effect of omega-3 FA on certain types of cancers and not others, two systematic reviews looked at the therapeutic role of omega-3 FAs against different types of cancers and looked at its potential mechanism of action. Both of the systematic reviews selected studies with samples that had patients identified with specific types of cancers and consumed Omega 3-FA, and were primary studies. The systematic reviews showed evidence that omega3 PUFAs are effective in cancer management by improving quality

of life, reduces symptoms, improving survival and Omega 3 FA are less toxic and inexpensive. [9-10] After one month of supplementation in the control group, Omega-3 FA was found to inhibit the colorectal atypical crypt foci. However, this benefit was seen in those with breast cancer, pancreatic cancer, CRC, gastric cancer and leukemia, and conflicting results were found with patients with pancreatic cancer and cancer cachexia. Colorectal cancer risk was found to be greater in those that carry the gene variant and did not consumed omega-3 FAs.[8]

Contradictory evidence was found in two meta-analyses that also have looked at the interaction between the n-3 PUFAs intake and the risk of CRC.[10-11] One study went further and looked at whether the association varies by anatomic subsite, by gender, BMI, aspirin use, fiber intake, history of polyps, and genetic risk. In conclusion, this meta-analysis found an increased risk for CRC with: Increasing age, BMI, smoking history, persons consuming >2 alcoholic drinks per week high consumption of red/processed meat intake. A decreased risk of CRC was seen with increasing educational status, physical activity, calcium intake, fiber in- take, and fruit/vegetable intake, aspirin use, hormonal replacement therapy (HRT), and history of sigmoidoscopy/colonoscopy.[10] Both meta-analyses found no association between intake of n-3 PUFA and the risk of CRC, which is consistent with the findings from the cohort study conducted by Song et al. The limitations of these studies were that the cofounding factors were not addressed. However, their strengths are that they had a large number of cases involved. [10-11]

While some studies looked at the therapeutic effect of omega-3 FAs, multiple case-control study were conducted to look at the preventative effect of omega-3 on colorectal tumors, in candidates that are prone to CRC. All of the participants in these trials were histologically confirmed to have CRC. The findings of the statistical analysis were consistent in all four case-control study, which showed that there is a reduce risk of CRC incidence with the intake of

omega 3-PUFA. [12-15] However, these findings varied with different genotypic variants, such as the A allele of XRCC1 and a family history, due to their higher levels of pro-inflammatory mediators, which was consistent with the results of other cohort studies presented.[5, 7, 12-13]

Multiple research data exist that investigate the therapeutic and preventative effect of omega-3 FA in developing colorectal cancer. However, this case-control study has broadened their focus and have looked at the risk factors for early onset of CRC. The researchers have reviewed the data of 3 case-control studies from Italy. The trials included patients with histologically confirmed CRC and looked at their lifestyle, diet and sociodemographic factors as well as family history of CRC. The data review found that the strongest risk factor for CRC is a family history, and that fish consumption had an inverse relationship to CRC. These findings are consistent with the majority of the current literature. The strength of this study is that it is the largest study to include young subjects.

Conclusion:

Even though there is conflicting data on which genotype of colorectal cancer the benefits of fish consumption have a modifying effect on, most of the studies agree that diets high in fish have a protective effect against colorectal cancer. The benefits are also seen among those that are genetically predisposed. According to the above research, the anti-cancer effects of omega 3 PUFA were regulation of apoptosis, anti-inflammatory, anti-thrombotic, anti-proliferative, anti-angiogenic, which all inhibit the cancer growth without any toxic side effects. The current literature supports the value of omega 3 fatty acids in the overall health of patients who are predisposed to or diagnosed with colorectal cancer. It is a useful tool in preventing, and when used in conjunction with chemotherapy even treating colorectal cancer. Due to the fact that those that who are genetically predisposed to CRC have higher intestinal pro-inflammatory mediators,

further research is needed to aid in the therapeutic dose needed to reduce the inflammation to the

level of suppressing the development of colorectal cancer. In addition, further research is needed

in defining the best consumption of omega-3, dietary vs supplements. However, until this

research is conducted and evaluated, according to the current literature it is safe to implement

omega-3 in those predisposed to or diagnosed with colorectal cancers through diets rich in fish as

well as supplementation of omega-3 FAs due to greater benefit to risk ratio. In conclusion,

research shows that high intake of omega 3 Fatty Acids compared to diets low in omega 3

decrease the risk of developing colorectal cancers in individuals that are genetically predisposed

to it.

Reference List:

1. Worldwide data. (n.d.). Retrieved June 30, 2017, from http://www.wcrf.org/int/cancer-facts-figures/worldwide-data

2. Common Cancer Types. (n.d.). Retrieved June 30, 2017, from https://www.cancer.gov/types/common-cancers

3. Araghi M(1), Soerjomataram I(1), Bray F(1), et al. Global trends in colorectal cancer mortality: projections to the year 2035. *International Journal of Cancer*. doi:10.1002/ijc.32055.

4. Mocellin M, Camargo C, Nunes E, Fiates G, Trindade E. Meta-analyses: A systematic review and meta-analysis of the n-3 polyunsaturated fatty acids effects on inflammatory markers in colorectal cancer. *Clinical Nutrition* [serial online]. April 1, 2016;35:359-369. Available from: ScienceDirect, Ipswich, MA. Accessed January 17, 2018.

5. Andersen, V., Holst, R., Kopp, T. I., Tjønneland, A., & Vogel, U. (2013, October 23). Interactions between diet, lifestyle and IL10, IL1B, and PTGS2/COX-2 gene polymorphisms in relation to risk of colorectal cancer in a prospective Danish case-cohort study. Retrieved January 19, 2018, from https://www.ncbi.nlm.nih.gov/pubmed/24194923

6. Song, M., Chan, A. T., Fuchs, C. S., Ogino, S., Hu, F. B., Mozaffarian, D., … Wu, K. (2014). Dietary Intake of Fish, ω-3 and ω-6 Fatty Acids and Risk of Colorectal Cancer: A Prospective Study in U.S. Men and Women. *International Journal of Cancer. Journal International Du Cancer*, *135*(10), 2413–2423. http://doi.org/10.1002/ijc.28878

7. Song, M., Nishihara, R., Cao, Y., Chun, E., Qian, Z. R., Mima, K., … Chan, A. T. (2016). Marine ω-3 polyunsaturated fatty acid intake and risk of colorectal cancer according to tumor-infiltrating T cells. *JAMA Oncology*, *2*(9), 1197–1206. http://doi.org/10.1001/jamaoncol.2016.0605

8. Nabavi, S. F., Bilotto, S., Russo, G. L., Orhan, I. E., Habtemariam, S., Daglia, M., . . . Nabavi, S. M. (2015, July 31). Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. Retrieved January 18, 2018, from https://link.springer.com/article/10.1007%2Fs10555-015-9572-2

9. Eltweri A, Thomas A, Metcalfe M, Calder P, Dennison A, Bowrey D. Review: Potential applications of fish oils rich in omega-3 polyunsaturated fatty acids in the management of gastrointestinal cancer. *Clinical Nutrition*[serial online]. February 1, 2017;36:65-78. Available from: ScienceDirect, Ipswich, MA. Accessed January 17, 2018.

10. Kantor E, Lampe J, Peters U, Vaughan T, White E. Long-Chain Omega-3 Polyunsaturated Fatty Acid Intake and Risk of Colorectal Cancer. *Nutrition & Cancer* [serial online]. May 2014;66(4):716-727. Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed January 17, 2018.

11. Chen, G. C., Qin, L. Q., Lu, D. B., Han, T. M., Zheng, Y., Xu, G. Z., & Wang, X. H. (2015, January). N-3 polyunsaturated fatty acids intake and risk of colorectal cancer: meta-analysis of prospective studies. Retrieved January 18, 2018, from https://www.ncbi.nlm.nih.gov/pubmed/25416450

12. Poomphakwaen, K., Promthet, S., Suwanrungruang, K., Chopjitt, P., Songserm, N., & Wiangnon, S. (n.d.). XRCC1 gene polymorphism, diet and risk of colorectal cancer in Thailand. Retrieved January 18, 2018, from https://www.ncbi.nlm.nih.gov/pubmed/25227862

13. Habermann, N., Ulrich, C. M., Lundgreen, A., Makar, K. W., Poole, E. M., Caan, B., . . . Slattery, M. L. (2012). PTGS1, PTGS2, ALOX5, ALOX12, ALOX15, and FLAP SNPs: interaction with fatty acids in colon cancer and rectal cancer. *Genes & Nutrition,8*(1), 115-126. doi:10.1007/s12263-012-0302-x

14. Tokudome, S., Kuriki, K., Yokoyama, Y., Sasaki, M., Joh, T., Kamiya, T., . . . Okuyama, H. (2015, March). Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. Retrieved January 18, 2018, from https://www.ncbi.nlm.nih.gov/pubmed/25451556

15. Xu, M., Fang, Y., Chen, Y., Lu, M., Pan, Z., Yan, B., . . . Zhang, C. (2015, August 12). Higher freshwater fish and sea fish intake is inversely associated with colorectal cancer risk among Chinese population: a case-control study. Retrieved January 19, 2018, from https://www.nature.com/articles/srep12976

16. Rosato, V., Bosetti, C., Levi, F., Polesel, J., Zucchetto, A., Negri, E., & Vecchia, C. L. (2012, December 08). Risk factors for young-onset colorectal cancer. Retrieved January 19, 2018, from https://link.springer.com/article/10.1007%2Fs10552-012-0119-3