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The Effect of Omega-3 Intake on Colorectal Cancer

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ABSTRACT

Background and Objective: Colorectal cancer is one of the most common cancers among men and women in the world. Of all the risk factors of colorectal cancer, nutritional factors are among the most important and preventable risk factors. Epidemiological studies as well as laboratory evidence have investigated the effect of omega-3 intake in the prevention of colorectal cancer, and considering the contradictory results in this area, the present study was conducted to investigate the effect of this nutrient on colorectal cancer.

Methods: In this systematic review and meta-analysis, eligible studies were carefully and independently searched by two researchers using the keywords "colorectal cancer" or "colon cancer", "Omega 3 fatty acids", "fish oil", "n-3 PUFAs" and "ω-3" in ISI, PubMed, Scopus, ProQuest and Embase databases from 1993 till the end of 2017, and the search was restricted to English language. The abbreviations RR, OR, and HR were extracted with a 95% confidence interval and subjected to statistical analysis based on the random effects model.

Findings: Among 6554 articles, 15 prospective cohort studies were finally included in the research. Despite the lower rate of colorectal cancer in both genders (p=0.394, 95% CI: 0.85-1.06, RR: 0.95) as well as men (p=0.395, 95% CI: 0.79-1.09, RR: 0.93) and women (p=0.583, 0.74-1.17, 95% CI: 0.74-1.17, RR: 0.93) who consumed omega-3, no statistically significant difference was found between consumers and non-consumers.

Conclusion: The results of this study demonstrated that there was no significant relationship between the intake of omega-3 and its subtypes and the incidence of colorectal cancer.

Keywords: *Colorectal, Cancer, Fatty Acids, Omega-3, Fish Oil.*

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Introduction

Colorectal cancer is the third most common cancer in the world, and more than 550,000 people die from colorectal cancer every year (1-3). Colorectal cancer is the third most common cancer among women and the fourth most common cancer among men in the world (4). The prevalence and mortality rates of colorectal cancer are high in developed countries and are growing rapidly in middle- and low- income populations (4). On a global scale, this cancer accounts for 27% of all newly diagnosed cancers and 35% of cancer deaths in the world (2). The highest number of people suffering from this cancer are reported in Europe, North America and Australia, while Africa, South America and Asia have the lowest number of people suffering from this cancer. In the United States, the annual incidence rate of this type of cancer is 134,000 new cases per year, and 55,000 deaths due to colorectal cancer are reported annually, which includes 10% of deaths due to cancer in the United States (5, 6).

The etiology of colorectal cancers is complex and both environmental and genetic factors play a role in it (2). Of all the risk factors of colorectal cancer, nutritional factors are among the most important and preventable risk factors. Omega-3 fatty acids are one of the fats required by the human body, which are abundant in fish or fish oil and have many potential effects in the treatment of various diseases (4, 6). Genetic predisposing factors including familial adenomatous polyposis also increase the risk of colorectal cancer. Other genetic causes such as mutation in specific oncogenes and tumor suppressor genes can also be mentioned. However, the prevalence of these factors is very low and 90% of cases are due to other factors, 50-80% of which are environmental factors. Nutritional habits play an important role here (7).

Apart from the origin of tumorigenesis of cancers, the mechanism of this cancer, similar to most cancers, is inhibition of the immune system, generalized immunosuppression and activation of pro-inflammatory signals, which cause progress, survival, proliferation, invasion, angiogenesis and systemic expansion of tumor tissue (3). During the past few decades, many studies have been conducted to investigate the effects of unsaturated fatty acids in colorectal cancers (4, 8). The available evidence shows that omega-3 fatty acids are useful in preventing inflammatory bowel diseases that lead to cancer and create a balance between the growth of intestinal epithelial cells and their apoptosis (8).

Several studies have shown that Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), as the most important omega-3 fatty acids, inhibit the growth of cancer cells under in vitro conditions and lead to their apoptosis. Other studies have reported the lack of positive and preventive effects of consuming unsaturated fatty acids in preventing colorectal cancers (6).

According to the studies regarding the consumption of unsaturated fatty acids, especially omega-3 and its effects on colorectal cancers and the contradictory results that have been presented, a systematic review is necessary to reach a comprehensive conclusion. Therefore, considering the importance of the subject, this systematic review was conducted with the aim of determining the role of omega-3 in patients with colorectal cancer.

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Methods

After approval by the Ethics Committee of Babol University of Medical Sciences with the code MUBABOL.REC.1396.79, this systematic review and meta-analysis was conducted by searching for articles related to omega-3 intake and the risk of developing colorectal cancer in ISI, PubMed, Scopus, ProQuest and Embase from 1993 until the end of 2017 with the restriction of English language. This search was done in the above databases by searching based on keywords colorectal cancer or colon cancer, Omega 3 fatty acids, fish oil, n-3 PUFAs and ω-3. Moreover, reference lists of relevant articles, review articles, and meta-analyses were also searched to find additional relevant articles. All the resulting articles were entered into the EndNote software and duplicate articles were omitted.

Inclusion and exclusion criteria of primary studies: Studies in which the relationship between omega-3 intake and the risk of colorectal cancer were investigated and included Hazard risk (HR), Relative risk (RR) and Odds risk (OR) were included in the study. Other inclusion criteria were: interventional studies, use of n-3 PUFAs and its subtypes, colorectal cancers (colon cancer or rectal cancer). If the criteria existed or their existence was ambiguous, the full version of the article was prepared and reviewed.

Data extraction: Two researchers independently extracted data in a blinded way based on a pre-designed questionnaire and recorded it in a specially designed form. Any disagreement in this field was resolved by discussion between the researchers who entered the data, and in case of no consensus, they consulted a third researcher. This form contains general information about the article (author, year of publication and country), type of study, country, mean age of people, gender, weight, race, history of cancer, history of omega-3 consumption and OR, HR and RR indices.

Quality assessment of studies: The quality of studies that were eligible to enter the systematic review was independently assessed by two researchers based on the Newcastle-Ottawa Quality Assessment Scale, and any disagreement was resolved by a third researcher. The articles were classified into different quality levels based on their Methodological Quality Score. Then, among the articles whose scientific principles were confirmed, the articles with high validity were selected. In the absence of such articles, articles with medium validity were selected for statistical analysis. In this study, after searching the mentioned keywords in the above databases and omitting similar articles, 6554 articles were selected (Diagram 1).

After reading the abstract of the articles and initial assessments and omitting the irrelevant articles, the full version of 4150 articles was prepared and reviewed. No new article was added by searching the references of related articles. Then, 306 existing articles were evaluated based on two dimensions of the scientific principles of the study and the validity of the methodology and at this stage, 291 articles were omitted and 15 articles were selected for statistical analysis (Table 1).

Data analysis method: All statistical analyses were performed using Comprehensive Meta-Analysis software. Heterogeneity between studies was evaluated using I-squared statistic (I^2) and based on the above index number, Random Effects Model or Fixed Effects Model was used to combine all articles. Forest Plot was used for graphical assessment of the combination of articles. Publication bias was evaluated based on the Funnel chart and Egger's statistical test, and $p<0.05$ was considered significant.

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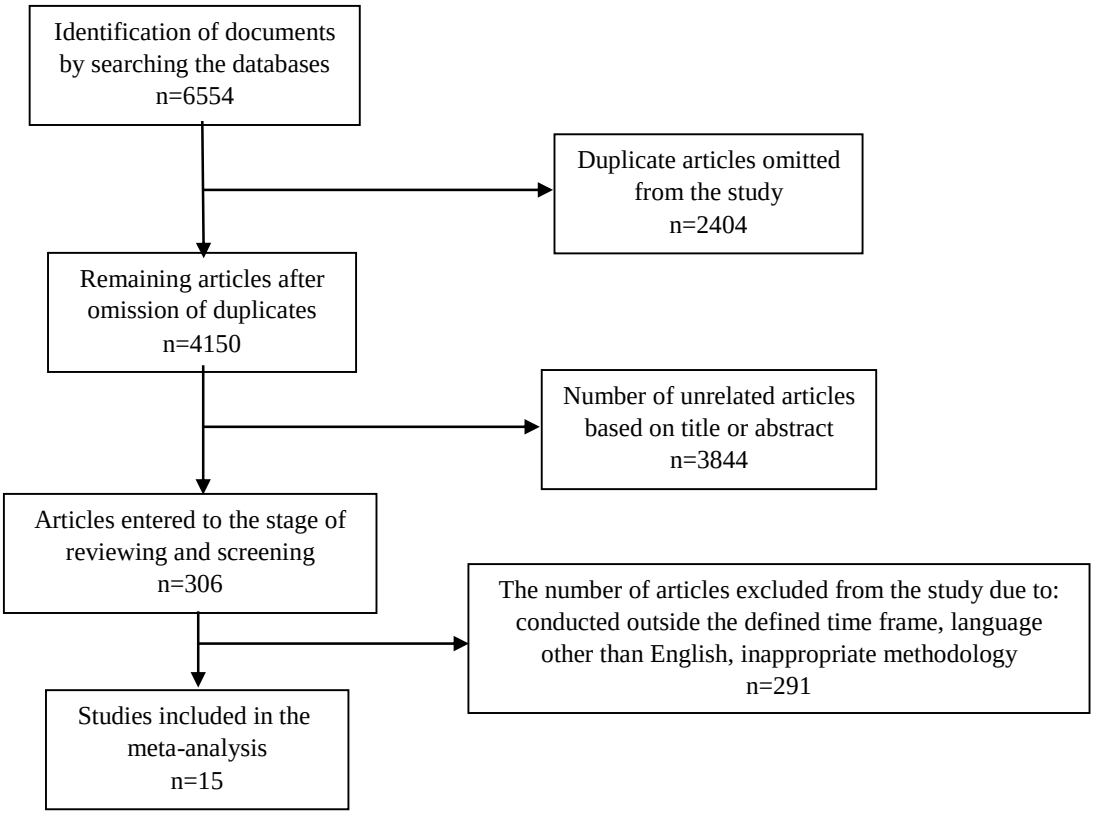


Diagram 1. The screening process and selection of studies for meta-analysis of the effect of omega-3 on colorectal cancer

Table 1. Characteristics of the studies included in the meta-analysis of the effect of omega-3 on colorectal cancer

Name of author and year of publication	Country	Follow-up period (years)	Number of patients	Population	Quality score
Butler - 2009	Singapore	8.9	903	61321	6
Daniel - 2009	The United States	6	869	99140	6
Bostick - 1993	The United States	4	212	35215	4
Hall - 2008	The United States	22	500	22071	8
Kantor - 2013	The United States	6	488	68109	6
Kobayashi - 2004	Japan	4	705	88658	7
Sasazuki - 2011	Japan	3.9	1268	88574	8
Terry - 2001	Sweden	11	460	61463	4
Lin - 2004	The United States	7.8	202	37547	7
Kato - 2009	The United States	1.7	100	14727	7
Oba - 2006	Japan	8	112	30221	4
Pietinen - 1999	Finland	8	185	27111	4
Murff - 2009	China	11	396	73242	4
Song - 2014	The United States	12	2486	123529	5
Kraja - 2015	Netherlands	6.14	222	7983	6

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Results

Among the 930,085 studied people, a total of 8,886 cases (0.96%) of colorectal cancer were reported during the follow-up period. The prevalence of colorectal cancer in the reviewed studies was reported to be 0.04-2.24% and the follow-up period of these patients was 4-9.8 years in the mentioned studies. The results of this secondary study show that the incidence of colorectal cancer in general and gender-specific was lower in the population that consumed omega-3 (Diagram 2), but it was not statistically significant (p=0.394, 95% CI: 0.85-1.06, RR: 0.95). The level of heterozygosity observed in this case was zero. Evaluation of publication bias by Funnel chart and Egger's test showed that the mentioned bias does not exist.

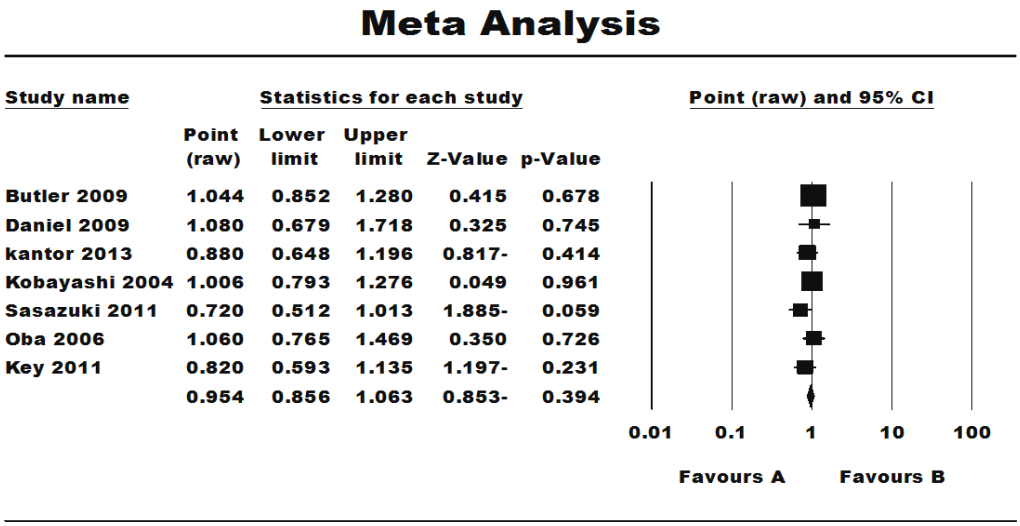


Diagram 2. Forest plot of the relative risk of colorectal cancer in omega-3 consumers

During the follow-up period that varied from 4 to 22 years, 3787 (0.75%) cases of colorectal cancer were reported in a population of 501,633 men in 13 studies. All the articles included in this study have examined the incidence of men separately based on the RR index. The prevalence of these types of cancer among the reviewed studies in the male population was reported to be 0.04-1.84% (Diagram 3). The results of the data analysis show that the incidence of colorectal cancer was lower among men who consumed omega-3; however, it was not statistically significant (p=0.395, 95% CI: 0.79-1.09, RR: 0.93) and the heterogeneity level was moderate (I-squared statistic= 58). Evaluation of publication bias by Funnel chart and Egger's test did not show any bias (p=0.769).

In 6 studies, the female population was examined separately in terms of colorectal cancer, according to which, in a population of 327,722 women, 1587 subjects (0.48%) were diagnosed with colorectal cancer during the follow-up period, and this follow-up period ranged from 4 to 9.8 years. The prevalence of colorectal cancer in these studies among the female population was reported between 0.04-1.84% (Diagram 4). Although the incidence of colorectal cancer among women who consumed omega-3 was lower than others, this difference was not statistically significant (p=0.583, 95% CI: 0.74-1.17, RR: 0.93). Considerable heterogeneity was found (I-squared statistic= 61), and the evaluation of publication bias did not reveal any bias (p=0.725).

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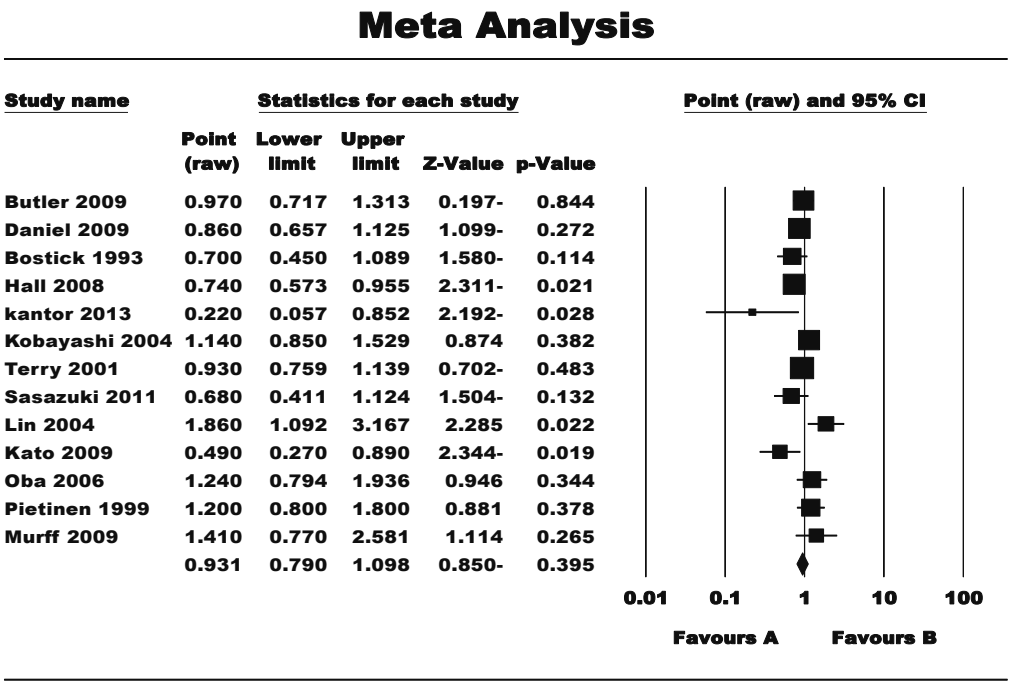


Diagram 3. Forest plot of the relative risk of colorectal cancer in men consuming omega-3

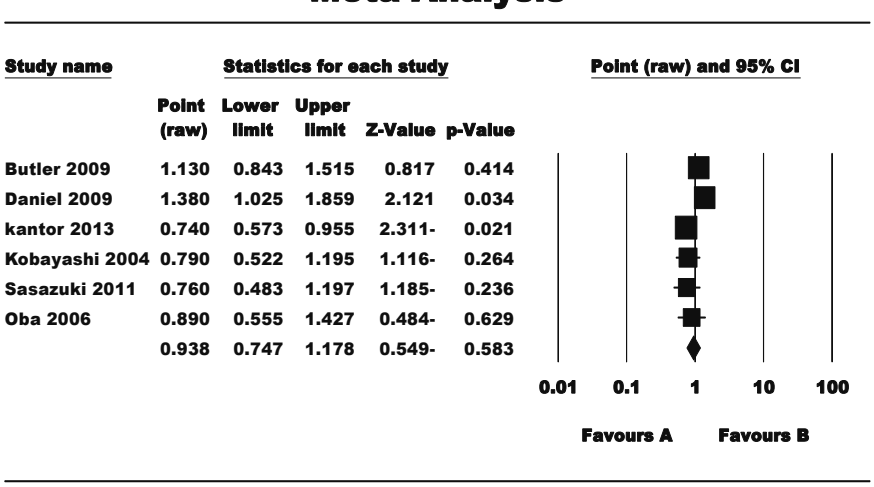


Diagram 4. Forest plot of the relative risk of colorectal cancer in women consuming omega-3

In four studies, the incidence rate of colorectal cancer was reported in the population based on the HR index regardless of gender. In the studied population of 260,942 people, 4099 (1.57%) cases of colorectal cancer were reported during the follow-up period, which ranged from 6 to 14.6 years. In these studies, the prevalence of colorectal cancer in both genders was reported to be 0.07-1.84% (Diagram 5). The results of data analysis show that the incidence of colorectal cancer among people who consumed omega-3 did not have a statistically significant difference with others (p=0.549, 95% CI: 0.82-1.45, HR: 1.09). Considerable heterogeneity was found (I-squared statistic= 49.5) and there was no publication bias (p=0.933).

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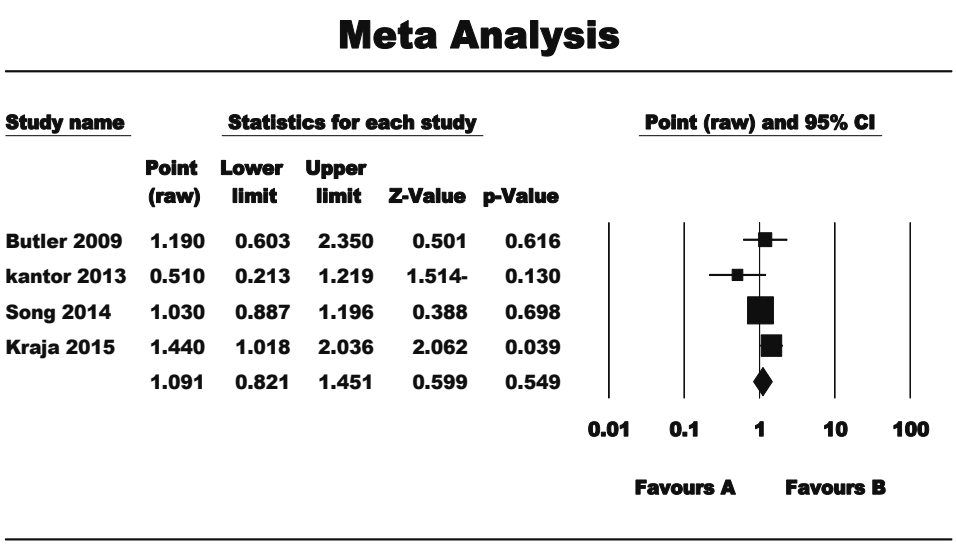


Diagram 5. Forest plot of the risk ratio of colorectal cancer in omega-3 consumers

Discussion

In this systematic review and meta-analysis, 15 studies from seven different countries, all of which were prospective cohorts, were examined. Overall, according to several different studies and different demographic characteristics, no significant relationship was observed between the consumption of omega-3 fatty acids and the risk for colorectal cancers. The results of this secondary study showed that in the studied population, the incidence of colorectal cancer in people who consumed omega-3 was non-significantly lower than the group that did not consume omega-3. These results were in line with the results of a number of studies (9-11) and were contrary to the findings of studies by Kimura et al. (12), Kantor et al. (7) and Michalak et al. (4). Furthermore, Chen et al. in their meta-analysis state that the heterogeneity found in the anatomical location of colorectal cancer among the findings of different articles has demonstrated that the consumption of omega-3 fatty acids reduces the incidence of colon cancer but it is not significant. However, these fatty acids significantly increase the incidence of rectal cancer. They also point to the evidence of possible impact of time on the effect of marine unsaturated fatty acids; consumption of marine unsaturated fatty acids reduces the risk of developing colorectal cancer 10 to 13 years or more before diagnosis (11).

Many laboratory studies point to the antineoplastic activities of omega-3 fatty acids against colorectal cancers based on a mechanism that reduces cell differentiation (13-20). The results of the present study are in contrast with laboratory studies. Ones must note that the amount of omega-3 fatty acids used in laboratory studies is much higher than the amount consumed by humans. Therefore, it is possible that there is a threshold level for the protective effect of omega-3 fatty acids to protect against colorectal cancers. Chen et al. also had similar belief in their study. In their study, by analyzing the dose of omega-3 fatty acids and the response rate, they found that the risk of cancer decreases among people who receive a much higher dose of omega-3 (11). Moreover, we must consider that in many of the studies included in this research, such as

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the 22-year cohort study of by Hall et al. (21), the amount of omega-3 fatty acids consumed by the study subjects was collected based on questionnaire-based data, which is naturally less accurate than laboratory studies with accurate calculation of dosage of omega-3 fatty acids. Baylin et al. have suggested that measuring the blood level of long-chain omega-3 fatty acids may provide a better assessment of long-term omega-3 intake compared to questionnaires on the consumption of different foods (22). Keep in mind that long – term use of omega-3 fatty acids should be considered in the overall dietary pattern of a person. Epidemiological evidence supports the benefits of using fish as the main source of omega-3 fatty acids in the diet for protection against colorectal cancer (23-25). However, even if omega-3 fatty acids are one of the components responsible for this effect in fish, it may also be necessary to use it as part of the structure of other nutrients in fish or other foods for these benefits (11).

On the other hand, there is evidence that points to the harmful effects of the consumption of omega-3 fatty acids or the consumption of fish on the development of colorectal cancers. Griffini et al. have reported in their study that omega-3 fatty acids in the diet increase the metastasis of colon cancer in the rat liver (26). Knekt et al. also state in their study that the use of certain types of fish (such as smoked fish and salted fish) increases the risk of colorectal cancer (27). This phenomenon may be due to the production of N-nitroso compounds (NOCs) in the production process of these foods (27, 28). This may explain the increased risk of colorectal cancers reported among Asian men, who have abundant use of smoked and salted fish, in some articles reviewed in this study.

The results of the present study showed that in the population of men and women separately, the incidence of colorectal cancer in people who consumed omega-3 was lower than the group that did not consume omega-3, but this rate was not significant. In their meta-analysis, Shen et al. have reported this significant difference in the male population, which is contrary to the results of the present study by examining seven prospective cohort studies. However, the results of their study regarding the fact that this difference is not significant in the population of women are in line with the results of the present study (29).

Various studies have pointed out the different effects of consuming omega-3 fatty acids and its subgroups in two different gender groups. For example, the Physicians' Health Cohort Study has reported a significant adverse effect of omega-3 fatty acids on the incidence of colorectal cancers among men, which is not consistent with the results of the present study (21). Nevertheless, Daniel et al. in their cohort study have pointed out the obvious positive effect of these nutrients among the female population (10). In their case study, Kojima et al. state that the serum level of omega-3 fatty acids has a significant inverse relationship with the risk of colorectal cancer among men, but this is not true in the female population (30). A possible explanation in justifying this theory is that female sex hormones may play a role in the etiology of colorectal cancers by affecting the metabolism of fatty acids (29).

It is also possible that different subtypes of omega-3 fatty acids, whose exact amounts have not been evaluated in different studies, are the cause of this discrepancy between different studies. In their study among female population, Daniel et al. observed positive effect of alpha linoleic acid as a subtype of omega-3 fatty acid, while the results of their study show that the consumption of marine omega-3 fatty acids was not associated with the risk of colorectal cancer (10). Shen et al. also state in their study that the EPA subtype

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of omega-3 fatty acids is strongly associated with reduced risk of colorectal cancers, while this does not apply to DHA fatty acids (29, 31). The experimental study of Petrick et al. also showed that the EPA subtype has a greater antitumorigenic effect than DHA among mice (32). Therefore, the lack of accurate evaluation of different subtypes of omega-3 fatty acids among the studies reviewed in this study can justify this discrepancy between different studies.

In summary, the findings of this meta-analysis of prospective cohort studies indicate that, in general, there is no significant association between the omega-3 intake and its subtypes and the risk of developing colorectal cancer. However, the need for other prospective studies is felt to prove this finding.

Ethical considerations: All ethical considerations related to being bias-free in the research stages from article selection to data extraction were considered.

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