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Omega-3 PUFA intake and the risk of digestive system cancers

A meta-analysis of observational studies

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Abstract

Background: A growing number of epidemiological studies have suggested a possible association between long-chain omega-3 polyunsaturated fatty acid (PUFA) intake and the risk of cancers, but the results have been inconsistent. We aimed to conduct a meta-analysis to assess the association of omega-3 PUFA consumption with digestive system cancers.

Methods: Relevant observational studies were identified through a comprehensive search of PubMed, Embase, and the Web of Science through December 2019 and by reviewing the references of the retrieved articles. The relative risks (RRs) of digestive system cancers associated with omega-3 PUFA intake were estimated using a random-effect model and were stratified by region, sex, study design, type of omega-3 PUFAs, smoking status, alcohol consumption, BMI, and physical activity.

Results: Twenty-five studies (8 case–control studies and 17 cohort studies) involving 1,247,271 participants and 23,173 patients with digestive system cancers were included in this analysis. The risk of digestive system cancers decreased by 17% in individuals who consumed omega-3 PUFAs (RR = 0.83, 95% confidence interval (CI), 0.76–0.91). The risk estimates of digestive system cancers varied by cancer sites, study location, study design, type of omega-3 PUFAs, and other confounders (smoking, alcohol consumption, body mass index, and physical activity). Visual inspection of funnel plots and the Begg's and Egger's tests revealed no evidence of publication bias.

Conclusion: The findings show that omega-3 PUFAs should be as a healthy dietary component for the prevention of digestive system cancers. Cancer incidence decreases with increasing omega-3 PUFAs intake for most digestive system cancer sites. The relation between omega-3 PUFAs and digestive system cancers RR is similar among different populations.

Abbreviations: ALA = alpha-linolenic acid, BMI = body mass index, CI = confidence interval, DPA = docosehexaenoie acid, EPA = eicosapentaenoic acid, HR = hazard ratio, OR = odd ratio, PUFA = polyunsaturated fatty acid, RR = relative risk.

Keywords: digestive system cancers, docosahexaenoic acid, omega-3 PUFAs, protective effect

1. Introduction

It has been estimated that by 2020, the number of new cases of cancer will increase to more than 15 million, with the number of deaths increasing to 12 million worldwide.[1] Digestive system cancers are the most common malignant tumors in the world with three million new cases adding each year (accounting for nearly 30% of all cancers).[1] The incidence of digestive system cancers will constantly increase, mainly due to trends in gastric cancer and colorectal cancer.[2] In the majority of developing countries, increasing trends in mortality rates associated with digestive system cancers have also been observed.[3,4]

Although increasing evidence has implicated omega-3 polyunsaturated fatty acids (PUFAs) in delaying the progression of anxiety,[5] cardiovascular disease,[6] and polycystic ovary syndrome,[7] their role in cancer etiology has yet to be established. Some observational epidemiological studies[8–10] have investigated the relationship between long-chain omega-3 PUFAs and the risk of cancers; however, the findings remain controversial. One previous meta-analysis[11] indicated that there was a null association between n-3 PUFAs and the risk of colorectal cancer. However, two systematic reviews of omega-3 PUFAs and cancer risk qualitatively concluded that there is inadequate[12] or limited

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evidence[13] to suggest an association between long-chain omega-3 PUFA intake and the risk of digestive system cancers. However, it had only been restricted to some types of cancer in most of these studies, and some cancer types, such as esophageal and oral cavity/pharynx cancers, were not investigated. Therefore, we conducted this comprehensive systematic review and meta-analysis study, in order to explore the relationship between omega-3 PUFA usage and the risk of digestive system cancers.

2. Methods

2.1. Search strategy

We followed the reporting standards for systematic reviews and meta-analyses of observational studies described in the Observational Studies in Epidemiology (MOOSE) guidelines.[14] For this meta-analysis, three electronic databases including PubMed, Embase, and the Web of Science were used to search from their inception to December 31, 2019, without language restrictions. Reviewing peer-review published articles and computer-aided literature searches using the following search terms with different combinations: ("omega" or "ω-3" or "n-3" or "PUFA" or "fish oil" or "EPA" or "DHA" or "PUFAs" or "eicosapentaenoic acid" or "docosahexaenoic acid" or "linolenic acid" or "docosapentaenoic acid" or "DPA" or "ALA") and ("cancer" or "carcinoma" or "oncology" or "neoplasm") were used to identify the eligible studies. The human studies were restricted in our study. The reference list of any article selected for consideration was manually checked for additional studies.

2.2. Inclusion criteria

We include studies if they met the following criteria:

1. the study was designed using a case-control or cohort;
2. the exposure of interest was omega-3 PUFA intake;
3. the outcome of interest was diagnosed as digestive system cancers or first as digestive system cancers and had died during follow-up in cohort studies;
4. the study reported estimates of odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with 95% confidence intervals (CIs) (or information to calculate those effect sizes).

Only the most recent and informative study was included if the same population were published in multiple reports.

2.3. Data extraction and quality assessment

Two independent authors independently reviewed all the included studies. The following information which was extracted from each study using a data collection form: year of publication, the first author's name, study design, location, number of cases and participants, sex, types of cancer, exposure definition, risk estimates (ORs, RRs, or HRs) and 95% CIs, and covariates adjusted in the analysis. When data were missing, we contacted the authors for detailed information.

Two reviewers independently assessed the study quality by using the Newcastle–Ottawa Scale (NOS) according to the procedures recommended in the Cochrane Handbook of Systematic Reviews.[15] The NOS was a 9-point scale that allocates points on the basis of the process of selection of the cohort study or case–control study (0–4 points), the comparability (0–2 points), and the identification of outcomes or exposures of study participants (0–3 points). We assigned scores of 0–3, 4–6, and 7–9 for low, moderate, and high quality of studies, respectively. Inter-observer agreement (κ) was 0.892. Any disagreement was resolved by review of the manuscript together to reach consensus.

2.4. Statistical analysis

RRs were used to measure the associations between omega-3 PUFAs and the risk of digestive system cancers, and HRs were considered equivalent to RRs. We combined the case–control and cohort studies in the primary meta-analysis as ORs and RRs provide similar estimates of risk when the outcome was rare.[16,17] Studies reported by different populations or by types of cancer were regarded as independent reports.

A random-effects model was used to estimate the pooled RRs for the relationship between omega-3 PUFAs and the risk of digestive system cancers,[18] if heterogeneity was detected, or the fixed-effects model was used otherwise. The heterogeneity across studies was assessed with I^2 statistic, where value of 25% or less, near 50%, and near 75% or greater as having low, moderate, and high degrees of heterogeneity, respectively.[19] The Egger's and Begg's tests and inspecting the symmetry of funnel plots were adopted to evaluate publication bias, as recommended by the Cochrane handbook.[20,21] Subgroup analyses were conducted to explore the potential sources of heterogeneity, and were stratified by exposure measurement, study design, sex, study location, cancer site, smoking status, alcohol consumption, body mass index (BMI), and physical activity were conducted to assess the robustness of the results. Additionally, the differences among subgroups were tested using meta-regression analysis (using STATA "metareg" command). Sensitivity analyses were conducted to assess the influence of any single study on the pooled RRs. All statistical analyses were conducted with Stata version 13.0.

3. Results

3.1. Literature search

Figure 1 shows the process of the identification of eligible studies. Of the 5224 articles that were identified, 35 articles qualified for full-text evaluation. Among these articles that underwent full-text review, six articles were duplicate reports from the same study population, eight articles were unmatched with the study exposure, and four studies were added from reference lists ultimately, 25 studies[8–10,22–43] with 28 independent reports were included in the meta-analysis.

3.2. Study characteristics

Table 1 presents the details of the 25 studies. Overall, data were available from 1,247,271 participants, including 23,173 cases with the following 6 cancer types: oral cavity/pharyngeal cancer (n = 736), esophageal cancer (n = 395), large bowel cancer (n = 2,280), pancreatic cancer (n = 1,132), hepatocellular carcinoma (n = 1,071), and colorectal cancer (n = 16,421). Most studies were performed in North America or Europe[9,10,22–27,29,30,33–35,37,38,40,42]; seven studies were conducted in Asia,[8,28,31,32,36,39,43] and one was an international study.[41] In total, four studies reported results for women only,[33,40,42,43] two studies reported results for men only,[9,41] six studies[26,27,35,36,38,39] reported results for men and women separately, and 13 studies reported results for both men and women combined.[8,10,22–25,28–32,34,37] The average NOS score of the included studies was 7.8 (ranging from 5 to 9).

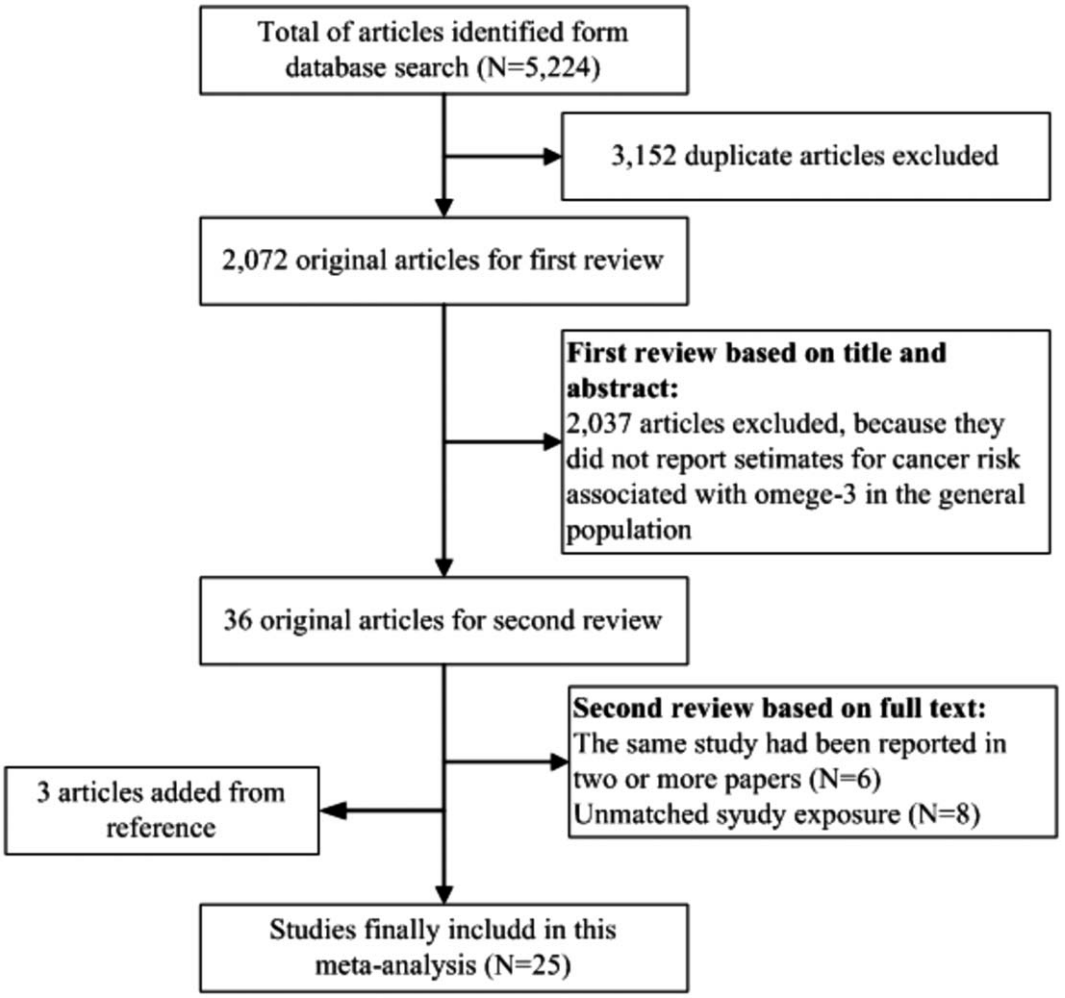

Figure 1. Flow chart of identification of relevant observational studies of omega-3 PUFA intake in relation to digestive system cancers.

3.3. Omega-3 PUFAs and the risk of digestive system cancers

Comparing participants in the highest omega-3 PUFA group with those in the lowest omega-3 PUFA group, the multivariable-adjusted RR for total digestive system cancers was 0.83 (95% CI: 0.76–0.91). There was high heterogeneity across studies (I^2 = 58.0%).

The decreased risks were statistically significant for 4 cancer types: colorectal cancer (RR = 0.89; 95% CI: 0.81–0.98; I^2 = 53.6%), oral cavity/pharyngeal cancer (RR = 0.50; 95% CI: 0.33–0.76), esophageal cancer (RR = 0.50; 95% CI: 0.33–0.76) and large bowel cancer (RR = 0.70; 95% CI: 0.57–0.86). There were no statistically significant associations between omega-3 PUFAs and pancreatic cancer (RR = 0.71; 95% CI: 0.45–1.13; I^2 = 70.2%) or hepatocellular carcinoma (RR = 0.83; 95% CI: 0.62–1.11; I^2 = 9.5%).

3.4. Subgroup analyses

Primary subgroup investigations for digestive system cancers were stratified by region, sex, study design, and type of omega-3 PUFAs; smoking status, alcohol consumption, BMI, and physical activity were controlled or not in the models to examine the stability of the primary results and explore the sources of potential heterogeneity (Table 2). The differences between n-3 PUFA and in relation to digestive system cancers risk were observed in gender and study design subgroups (P values for meta-regression $< .05$). However, no significant interactions were found for other stratified variables (all P values for interaction $> .05$).

There was a lower risk of digestive system cancers in the case–control studies than in the cohort studies (the pooled RR was 0.69 [95% CI: 0.61–0.78] in the case–control studies and the pooled RR was 0.94 [95% CI: 0.87–1.02] in the cohort studies) (Table 2).

The impact of omega-3 PUFAs on the risk of digestive system cancers appeared to be great in the combined sample of men and women (men: RR = 1.02; 95% CI: 0.80–1.30; women: RR = 0.93; 95% CI: 0.84–1.03; combined: RR = 0.79; 95% CI: 0.70–0.89). A decreased risk of digestive system cancers associated with omega-3 PUFA use was also identified in North America and Europe (North America: RR = 0.84; 95% CI: 0.77–0.92; Europe: RR = 0.76; 95% CI: 0.63–0.92). However, no statistically significant association was found in Asian countries (RR = 0.96; 95% CI: 0.84–1.10) (Fig. 2).

Table 1

Characteristics of included studies.

Study source	Sex	Study period	Source of subjects	No. of case	No. of control/ cohort size	Definition of exposure	Cancer site	Adjustment for covariates	Study quality
Case-control studies									
Tavani A,[22] 2005, Italy and Switzerland	M/F	1991–2001	Population from Italy and Switzerland	736	1,772	Intake of n-3 PUFA: 1st: 0.47–0.55 (g/week); 2nd: 0.83–0.89 (g/week); 3rd: 1.06–1.28 (g/week); 4th: 1.46–1.89 (g/week);	Oral cavity/ pharynx	Age, sex, study center, education, body mass index (BMI), energy intake, alcohol, and smoking	6
				395	1,006	Intake of n-3 PUFA: 1st: 0.47–0.55 (g/week); 2nd: 0.83–0.89 (g/week); 3rd: 1.06–1.28 (g/week); 4th: 1.46–1.89 (g/week);	Esophagus	Age, sex, study center, education, BMI, energy intake, alcohol, and smoking	
				2280	4,765	Intake of n-3 PUFA: 1st: 0.47–0.55 (g/week); 2nd: 0.83–0.89 (g/week); 3rd: 1.06–1.28 (g/week); 4th: 1.46–1.89 (g/week);	Large bowel	Age, sex, study center, education, BMI, energy intake, alcohol, smoking, and physical activity	
				2280	9,530	Intake of n-3 PUFA: 1st: 0.47–0.55 (g/week); 2nd: 0.83–0.89 (g/week); 3rd: 1.06–1.28 (g/week); 4th: 1.46–1.89 (g/week);	Colon and rectum	Age, sex, study center, education, BMI, energy intake, alcohol, smoking, and physical activity	
Gong Z,[23] 2010, US	M/F	1995–1999	Population from San Francisco Bay Area	532	1,701	Intake of Long-chain omega-3 fatty acids Q1: < 0.12 (g/day); Q2:0.12–0.22 (g/day); Q3:0.22–0.33 (g/day); Q4:≥0.33 (g/day);	Pancreatic cancer	Age in 5-year groups, sex, and total energy intake; race, education, BMI, history of diabetes, smoking, physical activity, and alcohol consumption	7
Polesel J,[24] 2007, Italy	M/F	1999–2002	Population from Italy	185	412	Intake of Polyunsaturated fatty acids: Mean ± SD:11.4 ± 4.3 (g/day); Tertile 1: None Tertile 2: None Tertile 3: None	Hepatocellular carcinoma	Gender, age, centre, education, place of birth, hepatitis viruses, drinking habits, maximal lifetime alcohol intake, and energy intake	8
Kim S,[25] 2010, US	M/F	2001–2006	The North Carolina Colon Cancer Study II	929	943	Intake of n-3 PUFA: Q1: < 1.27 (g/day) Q2: 1.27–1.72 (g/day) Q3: 1.72–2.31 (g/day) Q4: ≥2.31 (g/day)	Colorectal cancer	Age, race, sex, daily energy intake, and offset term. years of education, endoscopic screening in the past 10 years, red meat intake, vitamin E intake, and body mass index 1 year prior	9
Kato I,[26] 2010, US	M/F	2003–2005	Population from Metropolitan Detroit Tri-County	1163	1,501	Intake of n-3 PUFA: Median (Quartile range): 1.97 (1.66–2.41)(g/day);	Colorectal cancer	Gender, age, gender, specimen type (blood vs others), total calcium and dietary fiber intake, physical activities in their 30s, body mass	7

(*continued*)

Table 1
(continued).

Study source	Sex	Study period	Source of subjects	No. of case	No. of control/ cohort size	Definition of exposure	Cancer site	Adjustment for covariates	Study quality
								index, family history of colorectal cancer, pack-years of cigarette smoking and postmenopausal hormone use (women), highest education achieved and NSAID use	
Nkondjock A,[27] 2003, Canada	M/F	1989–1993	Population from French-Canadians	402	668	Intake of n-3 PUFA: Q1: < 1.46 (g/day); Q2: 1.46–2.04 (g/day); Q3: 2.05–2.92 (g/day); Q4: > 2.92 (g/day);	Colorectal cancer	Age, BMI, physical activity marital status, history of colorectal cancer in first degree relatives	8
Kimura Y,[28] 2007, Japan	M/F	2000–2003	The Fukuoka Colorectal Cancer Study	782	793	Median intake of n-3 PUFA: Q1: 1.99 (g/day); Q2: 2.55 (g/day); Q3:2.92 (g/day); Q4: 3.29 (g/day); Q5: 3.94 (g/day);	Colorectal cancer	Age, sex, residential area, body mass index, 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium, and dietary fiber.	9
Theodoratou E,[29] 2007, Scotland	M/F	1999–2006	Study of Colorectal Cancer in Scotland	1455	1,455	Intake of n-3 PUFA: Q1: 0–1.85 (g/day) Q2: 1.86–2.27 (g/day) Q3: 2.28–2.81 (g/day) Q4: > 2.82 (g/day)	Colorectal cancer	Family history of colorectal cancer, total energy intake (residual method), total fiber intake, alcohol intake, use of nonsteroidal anti-inflammatory drugs, smoking, BMI, and physical activity, intake of total fatty acids (energy adjusted)	7
Cohort studies									
Hidaka A,[8] 2015, Japan	M/F	1995–2010	The Japan Public Health Center-based Prospective Study	449	82,024	Intake of n-3 PUFA: Lowest: 2.2 (1.8–2.6) (g/day); Second: 2.7 (2.3–3.1) (g/day); Third:3.2 (2.8–3.6) (g/day); Highest:4.0 (3.5–4.7) (g/day)	Pancreatic cancer	Age and sex, BMI, smoking, alcohol consumption, physical activity, energy, red/processed meat, family history of pancreatic cancer, and history of diabetes mellitus.	9
He K,[30] 2013, US	M/F	2000–2008	The VITAL Cohort Study	151	66,616	Intake of LC-PUFA: Tertile 1: < 0.123 (g/day); Tertile 2:0.123–0.286 (g/day); Tertile 3:≥0.287 (g/day)	Pancreatic cancer	Age, gender, ethnicity, and education; BMI, physical activity, smoking status, alcohol consumption, diabetes mellitus, family history of pancreatic cancer, NSAID use, and dietary intakes of fruits, vegetables, dairy products, red/processed meat, and calories	9
Koh WP,[31] 2016, China	M/F	1993–2010	Singapore Chinese Health Study	488	63,257	Intake of n-3 PUFA:Q1: 0.40 ± 0.10 (% kcal/d); Q2: 0.49 ± 0.10 (% kcal/d);	Hepatocellular carcinoma	Age, sex, dialect, year of interview, educational level, BMI, smoking status, alcohol use, coffee drinking	9

(*continued*)

Table 1

(continued).

Study source	Sex	Study period	Source of subjects	No. of case	No. of control/ cohort size	Definition of exposure	Cancer site	Adjustment for covariates	Study quality
						Q3: 0.54 ± 0.12 (% kcal/d); Q4: 0.64 ± 0.23 (% kcal/d);		status, baseline history of self-reported diabetes, total energy and dietary protein.	
Sawada N,[32] 2012, Japan	M/F	1990–2001	Japan Public Health Center–Based Prospective Study	398	90,296	Intake of n-3 PUFA: Lowest:1.95 (g/day); Second:2.65 (g/day); Third: 3.18 (g/day); Fourth: 3.77 (g/day); Highest:4.80 (g/day)	Hepatocellular carcinoma	Age, area, sex, smoking status, alcohol frequency, BMI, past history of diabetes mellitus, and intake of coffee, soy foods, vegetables, protein, and iron.	8
Navarro SL,[33] 2016, US	F	1993–2010	Women's Health Initiative	1952	134,017	Median intake of n-3 PUFA: Q 1: < 0.80 (g/day); Q 2: 0.80–1.09 (g/day); Q 3: 1.09–1.41 (g/day); Q 4: 1.41–1.90 (g/day); Q 5: > 1.90 (g/day)	Colorectal cancer	Total energy intake, age, BMI, education, family history of colorectal cancer, history of colonoscopy, current NSAID use, alcohol intake (continuous), smoking history (never, former, current), physical activity, ever use of hormone therapy, folate, calcium, and red meat intake, and study component and CT randomization assignment and treatment arm.	8
Song M,[10] 2016, USA	M/F	1984–2010	Nurses' Health Study, Health Professionals Follow-up Study	2504	125,172	Intake of n-3 PUFA: Q1: < 0.15 (g/day); Q2: 0.15–0.24 (g/day); Q3: 0.24–0.34 (g/day); Q4: ≥0.35 (g/day)	Colorectal cancer	Age, sex and calendar year of current questionnaire cycle, family history of colorectal cancer, history of endoscopy, pack-years of smoking before age 30, current smoking status, BMI, physical activity, multivitamin use, regular use of aspirin or non-steroidal anti-inflammatory drugs, alcohol consumption, calcium intake, and Alternative Healthy Eating Index .	8
Kraja B,[34] 2015, Netherland	M/F	1990–2004	The Rotterdam Study	222	4,967	Intake of n–3 PUFAs: Tertile 1:1.0 ± 0.5 (g/day); Tertile 2:1.1 ± 0.5 (g/day); Tertile 3:1.1 ± 0.5 (g/day)	Colorectal cancer	Age, gender, energy-adjusted DF intake, and Dutch Healthy Diet index (excluding PUFA, fish, SFA, and DF components).	8
Kantor ED,[35] 2014, US	M/F	2000–2008	The VITAL Study	488	68,109	Intake of EPA + DHA: Quartile 1: < 0.08 (g/day) Quartile 2: 0.08–0.16 (g/day) Quartile 3: 0.16–0.29 (g/day) Quartile 4: ≥0.29 (g/day)	Colorectal cancer	Age, sex, race/ethnicity, education, BMI, energy intake, MET-hours per week of moderate/vigorous activity, alcohol intake, smoking history, multivitamin use, calcium intake, dietary fiber intake, fruit and vegetable intake, red/	9

(*continued*)

Table 1
(continued).

Study source	Sex	Study period	Source of subjects	No. of case	No. of control/ cohort size	Definition of exposure	Cancer site	Adjustment for covariates	Study quality
								processed meat intake, aspirin use, non-aspirin NSAID use, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy, history of polyps, hormone replacement therapy, cardiovascular disease, memory loss, use of cholesterol-lowering drugs, and omega-6 (linoleic +arachidonic) intake	
Sasazuki S,[36] 2011, Japan	M/F	1995–2006	Japan Public Health Center-based prospective study	1268	88,574	Intake of n-3 PUFA (women): Q1:2.0 (g/day); Q3:3.1 (g/day); Q5: 4.7 (g/day); Intake of n-3 PUFA (men): Q1: 1.7 (g/day); Q3: 2.0 (g/day) Q5: 4.8 (g/day)	Colorectal cancer	Age, area, BMI, smoking status, alcohol drinking, past history of or medication use for DM, METs, screening for CRC, total calorie, intake of calcium, vitamin D, fiber and red meat	8
Weijenberg MP,[37] 2007, Netherland	M/F	1986–1993	Netherlands Cohort Study	531	120,852	Median intake of n-3 PUFA: Q 1:11.6 (g/day) Q 2:16.0 (g/day) Q 3:20.9 (g/day) Q 4:29.9 (g/day)	Colorectal cancer	Age, sex, BMI, smoking, energy intake, and family history of colorectal cancer	7
Hall MN,[9] 2008, US	M	1995–2006	Physicians' Health Study (PHS).	500	21,409	Intake of n-3 PUFA: Tertile 1: < 1 Time per Week; Tertile 2: 1-2 Times per week; Tertile 3: 2-5 Times per week; Tertile 4:≥5 Times per week	Colorectal cancer	Age, smoking, BMI, multivitamin use, history of diabetes, random assignment to aspirin or placebo, vigorous exercise, alcohol intake), and quartile of red meat intake	7
Daniel CR,[38] 2009, US	M/F	1999–2005	Cancer Prevention Study (CPS)-II Nutrition Cohort	869	99,080	Intake of n-3 PUFA (women): Q1: 0.07 (g/day); Q4: 0.31 (g/day); Intake of n-3 PUFA (men): Q1: 0.08 (g/day); Q4: 0.33 (g/day)	Colorectal cancer	Age, energy, HRT (in women only), recreational physical activity, NSAID use, colorectal screening, BMI, and red and processed meat, low-fat dairy, fruit, and vegetable intake	9
Butler LM,[39] 2009, Singapore	M/F	1993–2005	Singapore Chinese Health Study	961	61,321	Intake of n-3 PUFA (women): Q1: 0.40 (g/1000 kcal); Q2: 0.48 (g/1000 kcal); Q3: 0.53 (g/1000 kcal); Q4: 0.59 (g/1000 kcal); Intake of n-3 PUFA (men): Q1: 0.38 (g/1000 kcal);	Colorectal cancer	Age at interview (year), dialect group), interview year (1993–1995, 1996–1998), diabetes at baseline (no, yes), smoking history, body mass index), alcohol intake, education), any weekly physical activity, first degree	9

(*continued*)

Table 1

(continued).

Study source	Sex	Study period	Source of subjects	No. of case	No. of control/ cohort size	Definition of exposure	Cancer site	Adjustment for covariates	Study quality
						Q2: 0.46 (g/1000 kcal); Q3: 0.51 (g/1000 kcal); Q4: 0.55 (g/1000 kcal);		relative diagnosed with colorectal cancer), and total daily energy intake (kcal).	
Bostick RM,[40] 1994, US	F	1986–1990	The Iowa Women's Health Study cohort	212	35,215	Intake of n-3 PUFA: Q1: < 0.03 (g/day); Q2:0.03-0.05 (g/day); Q3: 0.06-0.10 (g/day); Q4:0.11-0.18 (g/day); Q5: > 0.18 (g/day)	Colon cancer	Age, total energy intake, height, parity, total vitamin E intake, a total vitamin E by age interaction term, and vitamin A supplement intake.	8
Pietinen P,[41] 1999, US and Finland	M	1988–1993	Alpha tocopherol beta carotene cancer prevention study	185	27,111	Medians of intake of n-3 PUFA: Quartile 1:0.2 (g/day); Quartile 2:0.5 (g/day); Quartile 3:0.5 (g/day); Quartile 4:0.7 (g/day)	Colorectal cancer	Smoking year, BMI, alcohol, education, physical activity at work, calcium intake	5
Terry P,[42] 2001, Sweden	F	1987–1990	population-based	460	61,463	Median intake of EPA: Lowest: 0.03 (g/day); Second quartile: 0.05 (g/day); Third quartile: 0.07 (g/day); Highest: 0.09 (g/day); Median intake of DHA: Lowest: 0.08 (g/day); Second quartile: 0.11 (g/day); Third quartile: 0.13 (g/day); Highest: 0.18 (g/day)	Colorectal cancer	Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, and vitamin D. Saturated fat, monounsaturated fat, and polyunsaturated fat	5
Murff HJ,[43] 2009, China	F	1996–2007	Shanghai Women's Health Study (SWHS)	396	73,242	Medians of intake of n-3 PUFA: Q 1:0.64 (g/day); Q 2:0.76 (g/day); Q 3:0.93 (g/day); Q 4:1.13 (g/day); Q 5:1.61 (g/day)	Colorectal cancer	Age, energy intake in kcal, total energy-adjusted n-6 PUFA intake in g/d, energy-adjusted ratio of total n-6 PUFA to n-3 PUFA intake, BMI, current smoker, alcohol use, regular physical activity in past five years, total energy-adjusted red meat intake in g/day, menopausal status, hormone replacement therapy use, multivitamin use and aspirin use.	8

BMI = body mass index, CRC = colorectal cancer, DF = dietary fiber, DM = diabetes mellitus, F = female, HRT = hormone replacement therapy, LC-PUFAs = long-chain (n-3) polyunsaturated fatty acids, M = male, MET = metabolic equivalent task, NSAIDs = Nonsteroidal Anti-inflammatory Drugs, PUFA = polyunsaturated fatty acid, Q = Quartile, SD = standard deviation, SFA = saturated fatty acid, VITAL = VITamins And Lifestyle, US = United States.

Table 2

Subgroup analysis of relative risk of cancers.

	No. of reports	Relative risk	95%CI	I^2	*P* for heterogeneity	*P* for meta-regression
Cancer site						.171
Colorectal	19	0.89	0.81–0.98	53.6%	.004	
Oral cavity/pharynx	1	0.50	0.33–0.76	–	–	
Esophagus	1	0.50	0.33–0.76	–	–	
Large bowel	1	0.70	0.57–0.86	–	–	
Pancreatic cancer	3	0.71	0.45–1.13	70.2%	.035	
Hepatocellular carcinoma	3	0.83	0.62–1.11	9.2%	.331	
Gender*						.037
Men	8	1.02	0.80–1.30	59.1%	.045	
Women	10	0.93	0.84–1.03	0.0%	.564	
Combined	13	0.79	0.70–0.89	61.8%	.000	
Study location						.194
North America	11	0.84	0.77–0.92	0.0%	.469	
Europe	9	0.76	0.63–0.92	78.7%	.000	
Asia	7	0.96	0.84–1.10	7.7%	.423	
Multi-country	1	1.20	0.78–1.85	–	–	
Study design						.001
Case-control	11	0.69	0.61–0.78	42.7%	.065	
Cohort	17	0.94	0.87–1.02	24.1%	.199	
Type of n-3 PUFA†						.150
DHA	10	0.79	0.66–0.93	63.3%	.004	
DPA	4	0.85	0.71–1.01	0.0%	.518	
EPA	10	0.79	0.68–0.91	51.2%	.030	
ALA	10	0.96	0.83–1.10	32.0%	.152	
Controlling smoking in models						.234
Yes	21	0.81	0.73–0.90	59.3	.000	
No	7	0.94	0.78–1.13	43.2	.103	
Controlling drinking in models						.129
Yes	21	0.80	0.72–0.89	59.5	.000	
No	7	0.95	0.81–1.13	39.0	.132	
Controlling BMI in models						.388
Yes	25	0.82	0.75–0.90	55.5	.001	
No	3	0.92	0.54–1.57	74.7	.019	
Controlling physical activity in models						.537
Yes	14	0.81	0.72–0.91	55.5	.012	
No	14	0.86	0.75–0.99	56.9	.004	

* Four studies reported results for women only, two studies reported results for men only, 6 studies reported results for men and women separately, and 13 studies reported results for both men and women combined; therefore, there are 31 reports from 25 articles for gender subgroup.

† Ten articles reported their results by DHA, 4 articles reported results by DPA, 10 articles reported results by EPA, and 10 articles reported results by ALA; therefore, there are 34 reports from 25 articles for type of N-3 PUFA.

The subgroup analysis indicated that an inverse association was observed in the docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) groups (DHA: RR = 0.79; 95% CI: 0.66–0.93; EPA: RR = 0.79; 95% CI: 0.68–0.91), but not in the docosapentaenoic acid' (DPA) and alpha-linolenic acid (ALA) groups (DPA: RR = 0.85; 95% CI: 0.71–1.01; ALA: RR = 0.96; 95% CI: 0.83–1.10).

We conducted subgroup analysis by lifestyle factors. Additional subgroup analyses of lifestyle factors to assess the effect of smoking status, alcohol consumption, BMI, and physical activity on the digestive system cancers relationship showed no differences.

3.5. Sensitivity analyses

We excluded each study one by one and pooled the results of the remaining included studies. The pooled RR of cancer ranged from 0.82 (95% CI, 0.75–0.89) to 0.85 (95% CI, 0.78–0.93), which indicated that none of the studies substantially changed the combined RR.

3.6. Publication bias

Visual inspection of a funnel plot did not identify substantial asymmetry (Fig. 3). In addition, the Begg's test and Egger's test provided no evidence of publication bias across included studies (Begg's test $P = .477$; Egger's test $P = .334$).

4. Discussion

In this meta-analysis of 25 studies, omega-3 PUFAs exerted a protective effect on the risk of digestive system cancers and was shown to possibly decrease the incident risk of cancers by as much as 17%. Inverse associations were also found between omega-3 PUFAs and the risk of colorectal, oral cavity/pharyngeal, esophageal and large bowel cancers. However, no significant association was observed between the intake of omega-3 PUFAs and the risk of pancreatic and hepatocellular cancers.

There are several potential mechanisms of the anticarcinogenic actions of omega-3 PUFAs. First, omega-3 PUFAs could inhibit the biosynthesis of arachidonic acid-derived eicosanoid, which

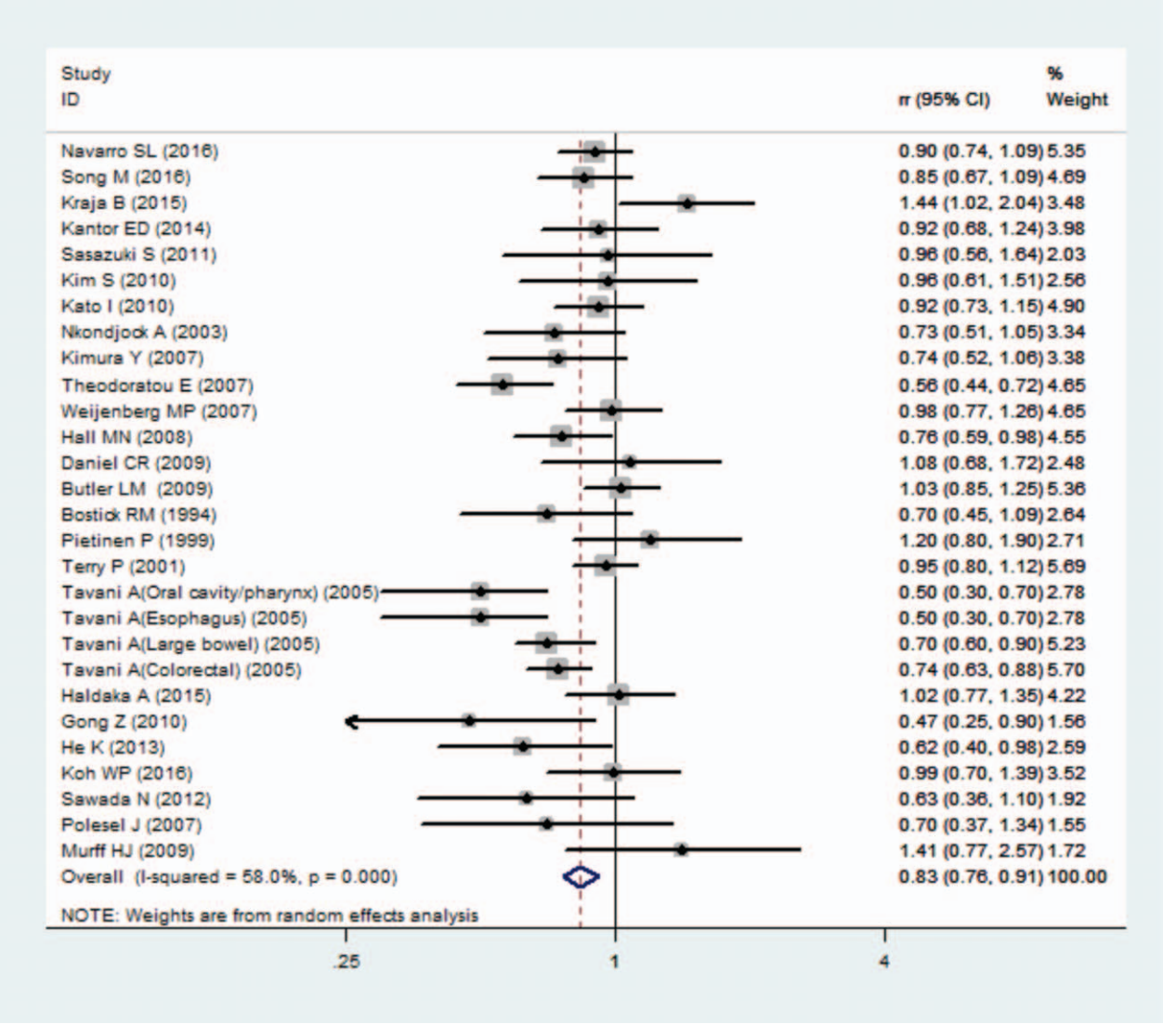

Figure 2. Forest plot for studies of omega-3 PUFA intake in relation to digestive system cancers.

resulted in an altered immune response to cancer cells and the modulation of inflammation, metastasis, apoptosis, cell proliferation, and angiogenesis.[44,45] Second, omega-3 PUFAs may affect gene expression, the activity of transcription factors, and signal transduction, which contributed to changes in metabolism and cell growth and differentiation.[46] Third, metabolites of omega-3 PUFAs increased the production of PGE3 and decreased the production of PGE2, which was expected to reduce estrogen-stimulated cell growth. Fourth, free radicals and reactive oxygen species could lead to the production of lipid hydroperoxides, which may further lead to genetic damage and cancer, and omega-3 PUFAs have been shown to decrease the levels of free radicals and reactive oxygen species, thus preventing cancer initiation. Final, PUFAs could reduce the risk of cancer through improving insulin sensitivity and membrane fluidity.[47]

Our subgroup analyses resulted in three valuable and significant findings. First, an interesting finding was that omega-3 PUFAs reduced the risk of digestive system cancers in the case–control studies but not in the cohort studies. One possible explanation for the difference might be that omega-3 PUFAs were assessed only at baseline in cohort studies, and the single baseline exposure assessment of omega-3 PUFA intake might reduce the ability to identify the relationship between omega-3 PUFAs and digestive system cancers. Moreover, cohort studies were more likely to have potential confounding bias, which might bias the statistical power.[48] Second, our results indicated that the strongest reduction in the risk of digestive system cancers associated with omega-3 PUFA intake was found in North American and European countries. However, no statistical significance was found in Asian countries. The reason may be that more than two-thirds of the included studies were performed in North American and European countries, and only a few studies were conducted in Asian countries, of which, 60% were from Japan. This might affect the accuracy of the results. Therefore, more researches are needed to investigate the differences among different countries and regions. Third, we found that the protective effects on digestive system cancers were observed in DHA and EPA but not in DPA or ALA. Muley

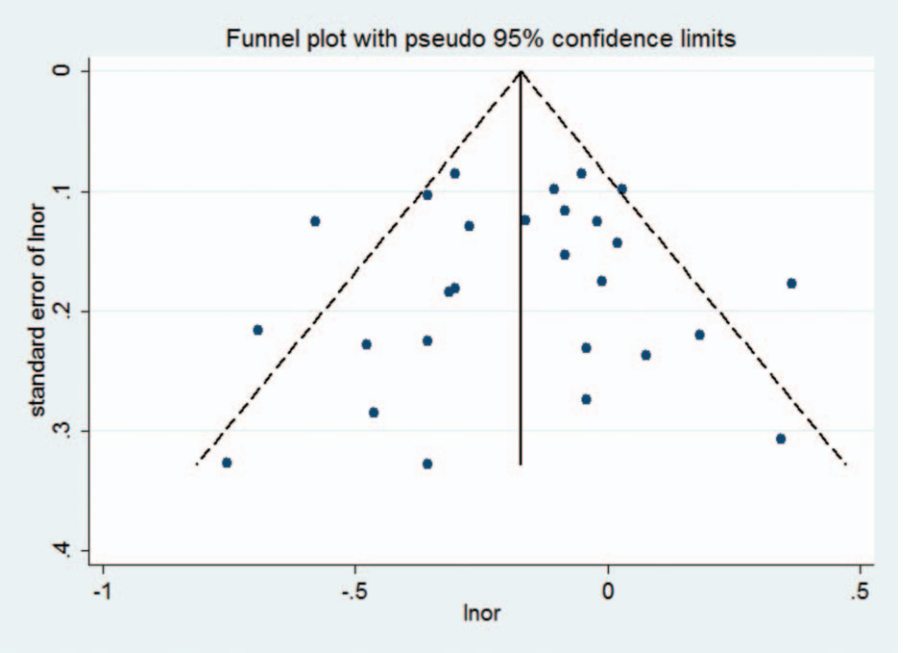

Figure 3. Funnel plot for studies of omega-3 PUFA intake in relation to digestive system cancers.

et al[49] also indicated that marine n-3 PUFA had a better cardioprotective effects. However, the reasons for the discrepancies remain unclear, and additional studies on investigating the underlying mechanism by which these differences arise are clearly warranted.

This meta-analysis had some strength. This is the first evidence showing that omega-3 PUFAs can decrease the risk of colorectal cancer. Additionally, a large sample size provided reliable results with greater precision and statistical power. Moreover, there was no publication bias in the outcomes, showing that the statistical data obtained from the included studies may approximate actual results. Potential limitations did exist, however, which should be noted. Due to the limitation of the included data, we did not conduct a dose–response relationship analysis; thus, the relationship between omega-3 PUFAs and digestive system cancers could not be accurately assessed. In addition, although we established strict inclusion criteria, the different definitions of omega-3 PUFA intake might influence the results.

5. Conclusion

In summary, n-3 PUFA intake is inversely associated with the risk of digestive system cancers, especially colorectal, esophageal, large bowel, and oral cavity/pharyngeal cancers. The association between omega-3 PUFA intake and the risk of cancer might underlie part of the difference in the incidence of cancer across populations. Future studies, particularly studies with a universal definition of omega-3 PUFA intake and prospective studies with larger sample sizes, should be assessed to explore the association between omega-3 PUFAs and the development of digestive system cancers.

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Author contributions

J.W, Y. Z and L. Z conceived and designed the study. J.W and Y. Z carried out the data collection. Y. Z performed the statistical analyses. J.W and Y. Z drafted the manuscript. All authors read and approved the final manuscript. L.Z is the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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