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META-ANALYSIS

Fish consumption and risk of gastrointestinal cancers: A meta-analysis of cohort studies

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Abstract

AIM: To assess quantitatively the relationship between fish intake and the incidence of gastrointestinal cancers in a meta-analysis of cohort studies.

METHODS: We searched MEDLINE, Embase, Science Citation Index Expanded, and the bibliographies of retrieved articles. Prospective cohort studies were included if they reported relative risks (RRs) and corresponding 95% confidence intervals (CIs) of various cancers with respect to fish intake. When RRs were not available in the published article, they were computed from the exposure distributions. Two investigators extracted the data independently and discrepancies were resolved by discussion with a third investigator. We performed random-effect meta-analyses and meta-regressions of study-specific incremental estimates to determine the risk of cancer associated with a 20-g/d increment of fish consumption.

RESULTS: Forty-two studies, comprising 27 independent cohorts, met our inclusion criteria. The studies included 2325040 participants and 24115 incident cases of gastrointestinal cancer, with an average follow-up of 13.6 years. Compared with individuals who did not eat, or seldom ate, fish, the pooled RR of gastrointestinal cancers was 0.93 (95%CI: 0.88-0.98) for regular fish consumers, 0.94 (0.89-0.99) for low to moderate fish consumers, and 0.91 (0.84-0.97) for high fish consumers. Overall, a 20-g increase in fish consumption per day was associated with a 2% reduced risk of gastrointestinal cancers (RR = 0.98; 95%CI: 0.96-1.01). In subgroup analyses, we noted that fish consumption was associated with reduced risk of colorectal (RR = 0.93; 95%CI: 0.87-0.99; $P < 0.01$), esophageal (RR = 0.91; 95%CI: 0.83-0.99; $P < 0.05$) and hepatocellular cancers (RR = 0.71; 95%CI: 0.48-0.95; $P < 0.01$).

CONCLUSION: This meta-analysis suggested that fish consumption may reduce total gastrointestinal cancer incidence. Inverse relationships were also detected between fish consumption and specific types of cancers.

Key words: Diet; Cancer prevention; Fish intake; Gastrointestinal cancer

Core tip: Epidemiological studies have revealed associations between fish consumption and cancers of the gastrointestinal tract. After meta-analysis of forty-two studies, comprising 27 independent cohorts, we found that fish consumption might reduce the total incidence of gastrointestinal cancer. A 20-g increase in fish consumption per day was associated with a 2% reduced risk of gastrointestinal cancers. In subgroup analyses, fish consumption was associated with reduced risk of colorectal, esophageal and hepatocellular cancers.

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INTRODUCTION

Gastrointestinal (GI) cancers are the most common types of human tumors[1], and their development has been linked to diet[2,3]. A report published in 2007 by the World Cancer Research Fund and the American Institute for Cancer Research on the relationship between diet and cancer suggested that the consumption of certain types of food may be directly associated with the development of GI cancers[4]. Epidemiological data have shown that in populations with high levels of fish consumption, such as Finnish or Swedish fisherman, the incidence and mortality rates for GI cancers are greatly reduced[5,6].

The diets of most human populations include fish. Fish is an ideal source of fatty acids, which are important components of cell membranes. Fish can also contain high levels of vitamin D and selenium, which may protect against the development of several cancers[7]. Most importantly, fish is a rich source of omega-3 fatty acids, which may protect against GI cancers through their anticarcinogenic and anti-inflammatory effects. Fatty acids regulate the production of proinflammatory prostaglandins and hydroxyeicosatetraenoic acid *via* the cyclooxygenase and lipoxygenase pathways[8]. These pathways play major roles in inflammation, cell proliferation and angiogenesis, each of which represents a key factor in cancer progression. Evidence from animal models and cultured cells indicates that long-chain Ω-3 polyunsaturated fatty acids (PUFAs) could inhibit the progression of cancer[9,10]. Thus, it is likely that the anti-inflammatory properties of fish are important for preventing cancer.

To date, there have been no intervention studies examining the association between fish consumption and the risk of GI cancer. Several epidemiological studies have focused on this association, but their results have been inconsistent[11-13]. Data from case-control studies can be subject to recall bias with respect to fish consumption and selection bias with respect to the control group. Prospective cohort studies that exclude these biases are more useful to identify associations between dietary fish and cancer. We therefore performed a meta-analysis of prospective cohort studies to assess quantitatively the association between fish intake and the risk of GI cancer in humans.

MATERIALS AND METHODS

Literature search

We searched the electronic databases MEDLINE (1966 to May 2013), Embase (1985 to May 2013) and the Science Citation Index Expanded (1945 to May 2013), using the Medical Subject Heading terms fish and gastrointestinal neoplasm, or esophageal neoplasm, or stomach neoplasm, or colorectal neoplasm, or hepatocellular neoplasm, or pancreatic neoplasm. We also reviewed reference lists of retrieved articles to search for additional studies. Only studies published as full-length articles in English were considered.

Inclusion and exclusion criteria

Studies were included if they: (1) had a prospective cohort design; (2) reported relative risks (RRs) or hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) (or data to calculate them) of GI cancer relating to different levels of fresh fish intake; and (3) included the frequency of fish consumption. Studies were excluded if they: (1) had a case-control design; (2) analyzed the consumption of fish oil, salted fish, or fried fish, rather than fresh fish; and (3) did not include the frequency of fish consumption. If multiple published reports from a single cohort were available we included the report with the most information concerning outcome and fish consumption.

Data extraction

Two investigators (XY and JD) extracted the data independently, according to meta-analysis of observation studies in epidemiology (MOOSE) guidelines[14]. Discrepancies were resolved through discussions involving a third investigator (JZ). The following information was extracted from each study: first author's last name, year of publication, country of origin, follow-up period, number of subjects and cases, age at baseline, GI cancer type, frequency of fish intake, outcome assessments, RRs or HRs of cancer and corresponding 95%CI for each category of fish, and covariates that were adjusted during the statistical analysis.

Statistical analysis

The measures of interest were the RRs and corresponding 95%CI for each of the included cohort studies. When RRs were not provided in the published article they were computed from exposure distributions. Different studies used different units for describing fish consumption; therefore, we converted fish consumption into g/d as a standard measure. Some studies reported consumption using qualitative scales (such as low, medium and high), or servings per month, week or day. We transformed these consumption levels into g/d by assuming that a "serving" corresponded to 105 g (the derived average portion size in the Health Professional Follow-Up Study). For studies that did not report CIs, we estimated these values based on the number of cases and controls in each category of exposure.

We computed summary RRs for fish consumers *vs* non-consumers and for different levels of consumption by assigning each study-specific RR a weight that was proportional to its precision (*i.e.*, the inverse of the variance derived from the reported 95%CI). To estimate summary RRs for various levels of fish consumption,

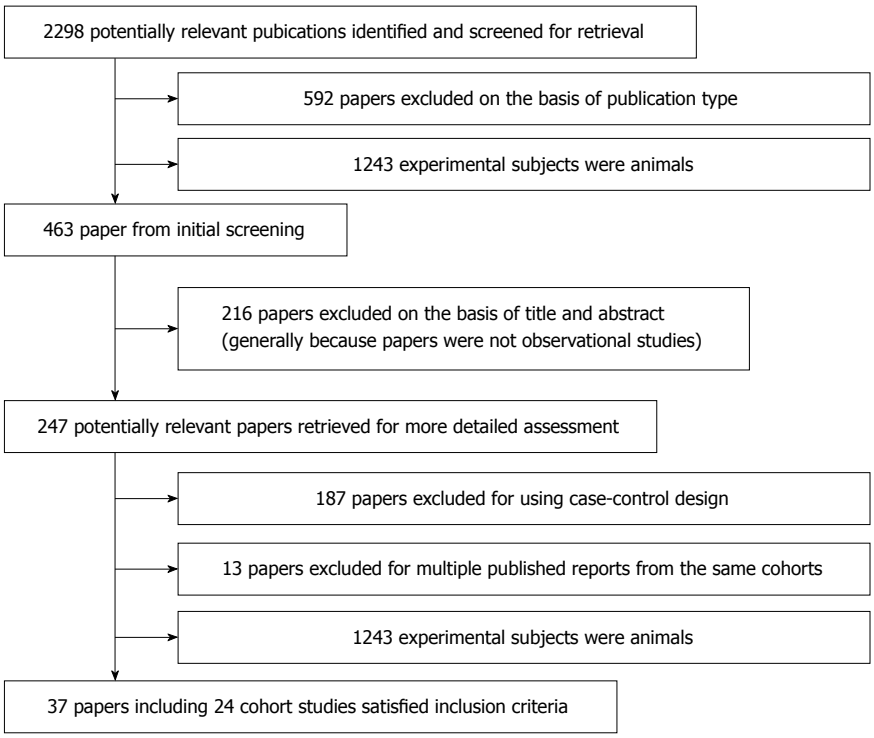

Figure 1 Flow diagram of search strategy and study selection.

we first calculated study-specific estimates for low to moderate consumption and for high consumption. For various GI cancer types, we performed stratified analysis on cancer types associated with more than two cohorts.

Statistical heterogeneity among studies was estimated using Q and I^2 statistics. For the Q statistic, heterogeneity was considered present for $P < 0.1$. We pooled study-specific estimates using both the fixed-effect model and the random-effect model (proposed by DerSimonian and Laird). When significant heterogeneity was found, results from the random-effect model were presented. A sensitivity analysis was also conducted, in which one study at a time was removed and the others analyzed. This allowed us to estimate whether the results could have been dramatically affected by a single study.

For dose-response analysis, we used the method proposed by Greenland and Greenland *et al*[15] to estimate study-specific slopes from the correlated natural logarithm of the RR across categories of consumed fish. For each category, the assigned dose corresponded to the midpoint between upper and lower boundaries. The highest open-ended category was assumed to have the same amplitude of consumption as the preceding category[16]. We then obtained the summary RR for GI cancer risk associated with a 20-g/d increment of consumed fish by pooling study-specific slopes, using the inverse of the corresponding variances as weights.

Finally, publication bias was evaluated through visual analysis of funnel plots and by the Begg's and Egger's tests. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with STATA 9.0; (Stata Corp, College Station, TX).

RESULTS

Using the predefined search strategy we identified 37 publications that were eligible for inclusion in the meta-analysis[5,17-52] (Figure 1). These publications included 27 prospective cohort studies, 2325040 participants, and 24115 cases of GI cancer with an average follow-up of 13.6 years. Characteristics of the included studies are summarized in Table 1. For 225/247 of the reviewed publications the two investigators agreed, without discussion, whether a study was eligible for inclusion (91.1%; $\kappa = 0.852$). Of the 27 cohorts included in the meta-analysis, 10 were conducted in Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom), nine in North America (the United States), seven in Asia (China and Japan), and one in Oceania (Australia).

The estimated RRs of various GI cancers for fish consumers compared with non/low consumers was 0.93 (95%CI: 0.88-0.98) (Figure 2). There was significant heterogeneity between studies ($Q = 80.14$; $P < 0.001$; $I^2 = 67.6\%$). For low to moderate fish consumption, the summary RR was 0.94 (95%CI: 0.89-0.99) (Figure 3), with significant heterogeneity between studies ($Q = 50.29$; $P < 0.003$; $I^2 = 48.3\%$). For high fish consumption, the summary RR was 0.91 (95%CI: 0.84-0.97) (Figure 4), also with significant heterogeneity between studies ($Q = 70.27$; $P < 0.001$; $I^2 = 63.0\%$).

Sources of heterogeneity likely included international differences in fish consumption (*e.g.*, fish type, serving size or cooking methods). To examine the magnitude of the combined RR in each stratum and its respective

Table 1 Summary characteristics of studies included in the meta-analysis

Ref.	Year	Country	Follow-up period	Study subjects	Number of cases	Cancer site	Fish consumption	Relative risk (95%CI)	Adjustments
Willett *et al*[17]	1990	United States	6 yr	88751 F	150 F	Colon	< 1/mo	1	Age
							1-3/mo	1.29 (0.70-2.40)	
							1/wk	0.92 (0.49-1.72)	
							2-4/wk	0.75 (0.35-1.58)	
							⩾ 5/wk	1.06 (0.36-3.12)	
Bostick *et al*[18]	1994	United States	6 yr	35215 F	212 F	Colon	< 1 time/wk	1	Age, energy intake, height, parity, vitamin E, vitamin E*age interaction, vitamin A
							1 time/wk	0.73 (0.50-1.07)	
							1.5 time/wk	0.96 (0.65-1.42)	
							2-2.5 time/wk	0.83 (0.54-1.28)	
							> 2.5 time/wk	0.76 (0.49-1.19)	
Giovannucci *et al*[19]	1994	United States		47949 M	205 M	Colon	8.4 g/d	1	Age, total energy intake
							20.9 g/d	0.85 (0.54-1.33)	
							31.0 g/d	1.05 (0.68-1.61)	
							47.8 g/d	0.80 (0.51-1.26)	
							83.4 g/d	1.06 (0.70-1.60)	
Kato *et al*[20]	1997	United States	7.1 yr	14727 F	100 F	Colorectal	Q1	1	Age, total energy intake, education, place of residence
							Q2	1.01 (0.62-1.67)	
							Q3	0.65 (0.37-1.13)	
							Q4	0.49 (0.27-0.89)	
Hsing *et al*[21]	1998	United States	20 yr	17633 M	145 M	Colorectal	< 0.8 time/mo	1	Age, calories, smoking, alcohol intake, total energy
							0.8-1.6 time/mo	1.1 (0.7-1.9)	
							1.7-4.0 time/mo	1.2 (0.7-2.0)	
							> 4 times/mo	1.5 (0.9-2.6)	
Knekt *et al*[22]	1999	Finland	24 yr	9985	73	Colorectal	Q1	1	Age, energy intake, gender, municipality, smoking
							Q2	1.07 (0.53-2.17)	
							Q3	1.60 (0.81-3.16)	
							Q4	1.11 (0.55-2.28)	
Pietinen *et al*[5]	1999	Finland	8 yr	27111 M	185 M	Colorectal	13 g/d	1	Age, education, smoking, BMI, alcohol, physical activity, calcium intake
							26 g/d	1.1 (0.7-1.6)	
							40 g/d	0.8 (0.5-1.3)	
							68 g/d	0.9 (0.6-1.4)	
Tiemersma *et al*[23]	2002	The Netherlands	8.5 yr	537	102	Colorectal	0-1 time/mo	1	Age, gender, center, total energy intake, alcohol, height
							1-4 time/mo	1.1 (0.7-1.9)	
							> 4 times/mo	0.7 (0.4-1.3)	
English *et al*[24]	2004	Australia	9 yr	37112	451	Colorectal	< 1 times/wk	1	Age, energy intake, country of birth, gender, fat, cereal intake
							1.0-1.4 times/wk	0.9 (0.7-1.2)	
							1.5-2.4 times/wk	0.9 (0.7-1.1)	
							⩾ 2.5 times/wk	0.9 (0.7-1.2)	
Kojima *et al*[25]	2004	Japan	9.9 yr	107824	457	Colorectal	0-2 times/wk	1	Age, family history, BMI, smoking, physical activity, education, alcohol intake, region
							3-4 times/wk	0.88 (0.65-1.12)	
							every day	0.96 (0.71-1.16)	
Sanjoaquin *et al*[26]	2004	United Kingdom	17 yr	10998	95	Colorectal	0 times/wk	1	Age, gender, smoking, alcohol
							0-1 time/wk	1.21 (0.71-2.06)	
							⩾ 1 time/wk	1.17 (0.71-1.92)	
Larsson *et al*[27]	2005	Sweden	13.9 yr	61433 F	733 F	Colorectal	< 0.5 servings/wk	1	Age, energy, education,
							0.5-< 1.0 servings/wk	0.94 (0.72-1.22)	BMI, alcohol, saturated
							1.0-< 2.0 servings/wk	1.21 (0.94-1.55)	fat, calcium, fruits and vegetables, whole-grain
							⩾ 2 servings/wk	1.08 (0.81-1.43)	foods, red meat, poultry
Lüchtenborg *et al*[28]	2005	The Netherlands	5 yr	2948	588	Colorectal	0 g/d	1	Age, energy intake, gender, family history of colorectal cancer, smoking, BMI
							4.6 g/d	1.13 (0.84-1.41)	
							15.2 g/d	0.86(0.65-1.06)	
							29.4 g/d	1.00 (0.74-1.27)	
Norat *et al*[29]	2005	10 European countries	4.8 yr	478040	1329	Colorectal	< 10 g/d	1	Age, energy intake, gender, height, weight, occupational physical dietary fiber, alcohol, center
							10-20 g/d	0.88 (0.74-1.06)	
							20-40 g/d	0.86 (0.72-1.02)	
							⩾ 80 g/d	0.69 (0.54-0.88)	
Engeset *et al*[30]	2007	Norway	8 yr	63914 F	254 F	Colon	< 70.8 g/d	1	Age, daily intake of energy, smoking, fish liver, fruit and vegetables, fiber, fats, sauces
							70.8-117 g/d	0.93 (0.66-1.31)	
							> 117 g/d	1.28 (0.90-1.81)	

Hall *et al*[31]	2008	United States	22 yr	21406 M	500 M	Colorectal	< 1 time/wk 1-< 2 time/wk 2-< 5 time/wk ⩾ 5 times/wk	1 0.88 (0.65-1.20) 0.82 (0.61-1.10) 0.63 (0.42-0.95)	Age, smoking, BMI, multivitamin use, history of diabetes, random assignment to aspirin or placebo, vigorous exercise, alcohol, red meat intake
Lee *et al*[32]	2009	China	7.4 yr	73224 F	394 F	Colorectal	< 20 g/d < 33 g/d < 49 g/d < 74 g/d ⩾ 74 g/d	1 1.2 (0.9-1.5) 1.2 (0.8-1.6) 1.5 (1.1-1.9) 1.3 (0.9-1.9)	Age, education, income, survey season, tea consumption, NSAID use, energy intake, fiber intake
Sugawara *et al*[33]	2009	Japan	8 yr	39498	566	Colorectal	0-26.2 g/d 26.3-53.3 g/d 53.4-96.3 g/d ⩾ 96.4 g/d	1 1.04 (0.79-1.39) 1.11 (0.81-1.53) 1.07 (0.78-1.46)	Age, BMI, family history of cancer, history of stroke, hypertension, myocardial infarction and diabetes mellitus, education, marital status, job status, smoking, alcohol, time spent walking, total calories, fruit and vegetables
Spencer *et al*[34]	2010	United Kingdom		2575	579	Colorectal	< 1 g/d 1 < 15 g/d 15 < 30 g/d ⩾ 30 g/d	1 0.89 (0.71-1.08) 1.10 (0.90-1.30) 0.78 (0.62-0.95)	Age, height, weight, smoking, energy, alcohol, dietary fiber
Daniel *et al*[35]	2011	United States	9 yr	492186	6979	Colorectal	3.6 g/1000 kcal 7.0 g/1000 kcal 9.9 g/1000 kcal 13.4 g/1000 kcal 21.4 g/1000 kcal	1 0.97 (0.90-1.04) 0.92 (0.85-0.99) 0.93 (0.86-1.00) 0.95 (0.88-1.03)	Red meat intake, age, sex, education, marital status, family history of cancer, race, BMI, smoking status, frequency of vigorous physical activity, MHT in women, intake of alcohol, fruit, vegetables, and total energy
Nomura *et al*[36]	1990	United States	19 yr	7990 M	150	Gastric	⩽ 1 time/wk 2-4 times/wk ⩾ 5 times/wk	1 1.4 (1.0-1.9) 0.9 (0.5-1.8)	Age
Ngoan *et al*[37]	2002	Japan	10.5 yr	13250	116	Gastric	⩽ 2-4 times/mo 2-4 times/wk ⩾ 1 time/d	1 0.90 (0.40-2.20) 0.90 (0.30-2.10)	Sex, age, smoking smoking, processed meat, liver, cooking or salad oil, sui-mono, pickled food
Sauvaget *et al*[38]	2005	Japan	20 yr	38576	1270	Gastric	> 2 times/wk 2-4 times/wk ⩾ 5 times/wk	1 1.09 (0.96-1.23) 1.16 (0.97-1.39)	Sex, sex-specific age, city, radiation dose, sex-specific smoking habits, education level
Tokui *et al*[39]	2005	Japan	11 yr	110792	859	Gastric	⩽ 1-2 times/mo 1-2 times/wk 3-4 times/wk ⩾ 1 time/d	1 0.85 (0.61-1.19) 0.90 (0.65-1.26) 0.95 (0.68-1.33)	Age
Larsson *et al*[40]	2006	Sweden	18 yr	61433	156	Gastric	< 1.2 servings/wk 1.2-1.9 servings/wk ⩾ 5 servings/wk	1 0.97 (0.64-1.46) 1.14 (0.75-1.72)	Age, education, body mass index, intake of total energy, alcohol, fruits and vegetables
Zheng *et al*[41]	1993	United States	20 yr	17633 M	57	Pancreatic	Q1 Q2 Q3 Q4	1 1.2 (0.5-3.0) 2.0 (0.8-4.7) 1.4 (0.6-3.7)	Age, smoking index, alcohol index, total calories
Stolzenberg-Solomon *et al*[42]	2002	Finland	13 yr	27111 M	163 M	Pancreatic	⩽ 17.9 g/d > 17.9 and ⩽ 27.7 g/d > 27.7 and ⩽ 38.6 g/d > 38.6 and ⩽ 55.8 g/d > 55.8 g/d	1 1.22 (0.75-1.97) 1.14 (0.70-1.86) 1.07 (0.65-1.76) 0.91 (0.54-1.52)	Energy intake, age and years of smoking

Michaud *et al*[43]	2003	United States	18 yr	88802 F	178 FM	Pancreatic	< 4/mo	1	pack-years of smoking, BMI,
							1/wk	1.42 (1.01-1.98)	history of diabetes mellitus,
							⩾ 2/wk	1.30 (0.86-1.98)	caloric intake, height, physical activity, menopausal status
Nöthlings *et al*[44]	2005	United States	7 yr	190545	482	Pancreatic	1.1	1	Age, ethnicity,
							3.8	0.85 (0.70-1.03)	history of diabetes mellitus,
							6.4	0.84 (0.69-1.03)	familial history of pancreatic cancer,
							9.8	0.90 (0.74-1.10)	smoking status, energy intake
							17.3	0.91 (0.75-1.11)	
Larsson *et al*[45]	2006	Sweden	17 yr	61433 F	172	Pancreatic	⩽ 1.0 servings/wk	1	Age, education,
							1.1 < 1.5 servings/wk	0.88 (0.58-1.34)	BMI, smoking,
							1.5 < 2.0 servings/wk	1.52 (0.96-2.40)	intakes of total energy,
							⩾ 2.0 servings/wk	1.22 (0.77-1.92)	alcohol, energy-adjusted folate
Lin *et al*[46]	2006	Japan	11 yr	110792	300	Pancreatic	0-2/mo	1	Age, area,
							1-4/wk	1.21 (0.60-1.81)	pack-years of smoking
							Almost every day	0.98 (0.43-1.53)	
Heinen *et al*[47]	2009	Netherlands	13.3 yr	120852	350	Pancreatic	0	1	Gender, age, energy, smoking,
							0-10 g/d	1.22 (0.89-1.67)	alcohol, history of diabetes mellitus,
							10-20 g/d	1.02 (0.75-1.38)	history of hypertension, BMI,
							⩾ 20 g/d	1.05 (0.75-1.47)	vegetables, fruit
Rohrmann *et al*[48]	2012	10 European countries	16 yr	477202	865	Pancreatic	0 to <10 g/d	1	Height, weight,
							10 to < 20 g/d	1.13 (0.90-1.41)	physical activity index,
							20 to <40 g/d	1.20 (0.97-1.50)	cigarette smoking, education,
							⩾ 40 g/d	1.16 (0.92-1.47)	history of diabetes, total energy intake
Kinjo *et al*[50]	1998	Japan	15 yr	220272	440	Esophageal	1-3 times/mo or less	1	Age, prefecture,
							1-3 times/wk or less	0.9 (0.7-1.1)	occupation, sex
							4 times/wk or more	1.1 (0.9-1.3)	
Kjaerheim *et al*[49]	1998	Norway	24 yr	10960 M	71 M	Esophageal	< monthly	1	Age, smoking level,
							1-5 times/mo	0.73 (0.18-1.28)	frequency of alcohol consumption,
							⩾ 6 times/mo	0.96 (0.15-1.77)	
Kurozawa *et al*[51]	2004	Japan	12 yr	110792	401	Liver	⩽ 1-2 times/wk	1	Age, gender
							3-4 times/wk	0.34 (0.13-0.55)	
							Almost every day	0.46 (0.16-0.76)	
Sawada *et al*[52]	2012	Japan	11.2 yr	90296	398	Liver	35.0 g/d	1	Age, area, sex, smoking status,
							60.6 g/d	0.83 (0.59-1.17)	alcohol frequency, body mass index,
							82.8 g/d	0.84 (0.59-1.20)	past history of diabetes mellitus,
							109.9 g/d	0.75 (0.51-1.11)	and intake of coffee, soy foods, vegetables,
							160.6 g/d	0.64 (0.41-1.02)	vegetable oil, protein, and iron

test of heterogeneity, we conducted subgroup analyses by gender, GI cancer sites, and geographical regions. The summary RR was 0.95 (95%CI: 0.87-1.02) for men and 0.96 (95%CI: 0.89-1.03) for women when all studies were combined. There was significant heterogeneity for men (Q = 13.97; P = 0.082; I^2 = 42.8%) and women (Q = 27.60; P = 0.001; I^2 = 71.0%).

When stratified by GI cancer sites, fish consumption

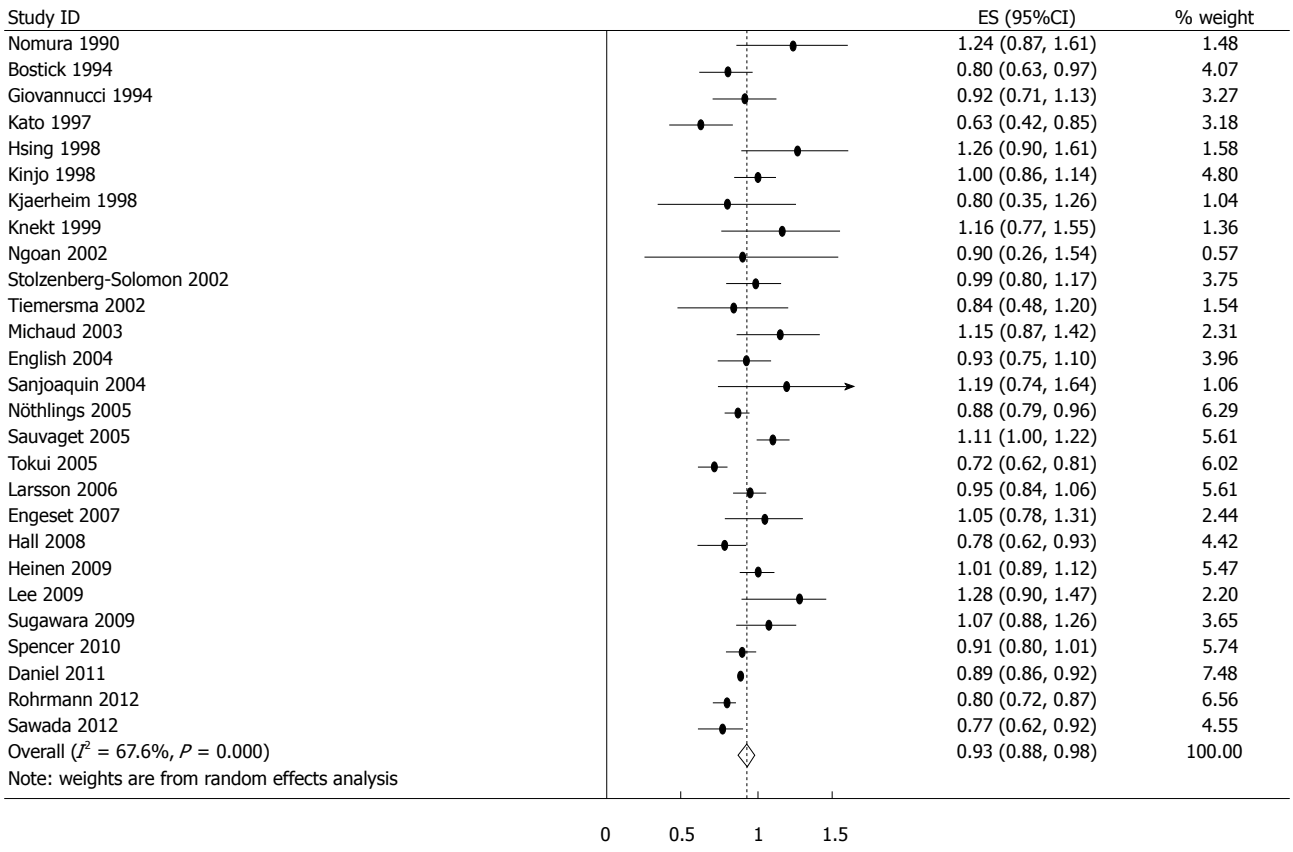

Figure 2 Summary relative risks of gastrointestinal cancer for fish consumers *vs* non/lowest consumers from all included studies. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight; *i.e.*, the inverse of the variance); horizontal lines represent 95%CI; diamonds represent summary relative risk estimates with corresponding 95%CI.

was inversely associated with colorectal 0.93 (0.87-0.99) (Figure 5), colon 0.95 (0.91-0.98), rectal 0.85 (0.75-0.95), esophageal 0.91 (0.83-0.99) and hepatocellular 0.71 (0.48-0.95) cancers. There was no association with stomach and pancreatic cancer. The summary RR for an increment of 20 g of fish per day was 0.98 (95%CI: 0.96-1.01) for all studies combined. Pooled RRs for various GI cancer sites and an increment of 20 g/d of fish consumption (along with their heterogeneity) are listed in Table 2.

Associations were similar for studies from North America, but not from Europe and the Asia-Pacific region. The RR was 0.88 (95%CI: 0.81-0.97) when considering nine North American studies, 0.94 (95%CI: 0.86-1.01) for 10 European studies, and 0.98 (95%CI: 0.81-1.15) for seven Asian studies. No significant differences by sex and cancer-type were found.

There was no indication of publication bias from either visualization of the funnel plot or Egger's (P = 0.287) and Begg's (P = 0.404) (Figure 6) tests. A sensitivity analysis, in which one study was removed at a time, confirmed the stability of our results.

DISCUSSION

Dietary fish can potentially affect the etiology of GI cancers through its effect on multiple biological pathways, including carcinogenesis and apoptosis. For most types of GI cancer, there is significant evidence that the consumption of up to 100 g of fish per day does not elevate cancer occurrence. Through the meta-analysis of cohort studies, we found that regular fish consumers had lower levels of GI cancer than individuals who did not eat or seldom ate fish. This was particularly true for high consumers. Overall, increasing fish consumption by 20 g/d was associated with a 2% reduction in the risk of developing a GI cancer. This suggested that fish intake may reduce GI cancer occurrence in humans.

In addition to vitamin D and selenium, fish is a rich source of PUFAs, which may protect against the development of GI cancers. Omega-3 (Ω-3) PUFAs are essential fatty acids necessary for human health. Studies in human populations have linked high consumption of fish or fish oil to reduced risk of colon, prostate and breast cancer. A number of biological effects that could contribute to cancer suppression by Ω-3 PUFAs have been suggested[53,54]. These effects include alterations in the proliferation, invasion, metastasis and apoptosis of cancer cells.

The most widely studied effects of PUFAs are those that relate to eicosanoid biosynthesis and function. Dietary Ω-3 PUFAs can be metabolized to prostaglandins, thromboxanes, hydroxyeicosatetraenoic acids and leukotrienes, by the enzymatic activity of COXs and LOXs[55]. Besides eicosanoids, marine Ω-3 PUFAs can also be me-

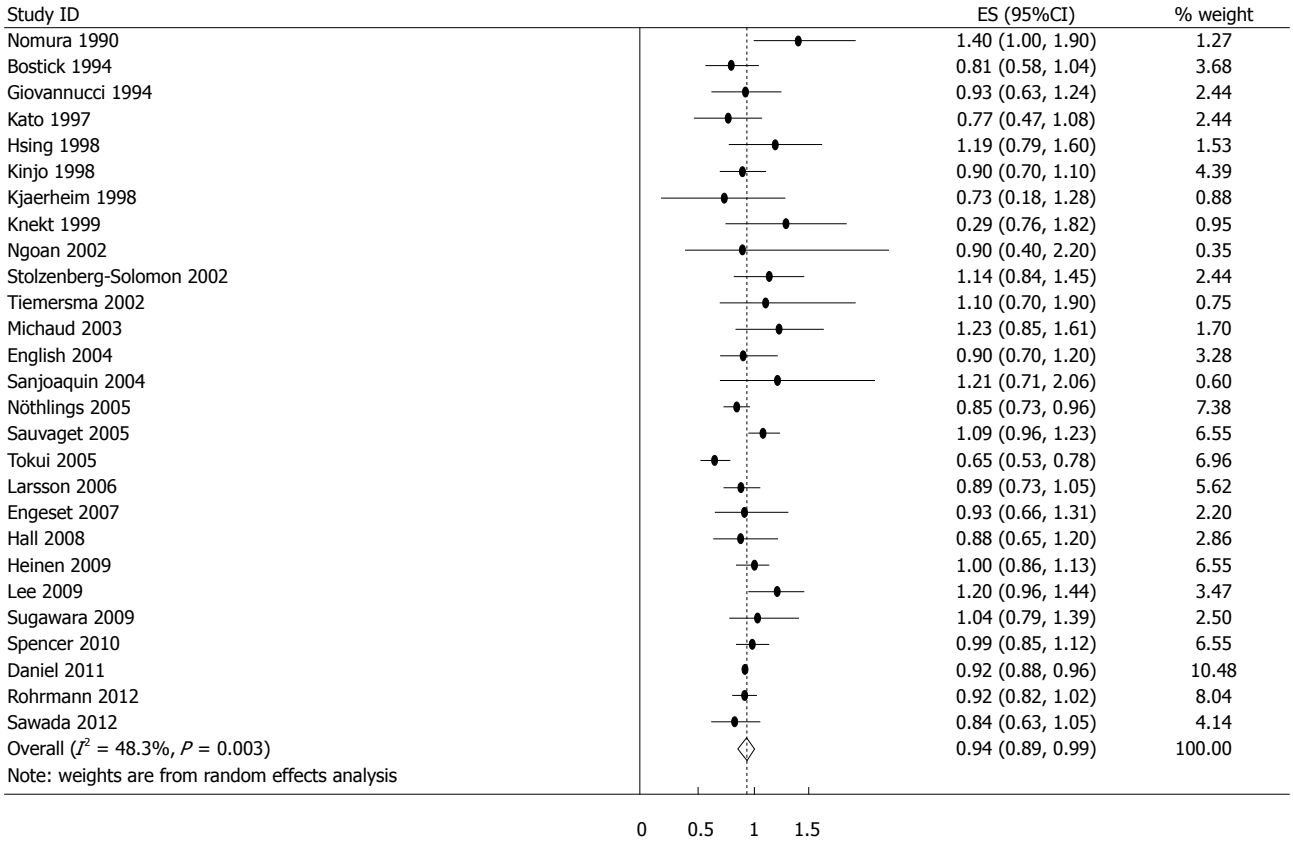

Figure 3 Summary relative risks of gastrointestinal cancer for low to moderate fish consumers *vs* non/lowest consumers from included studies. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight; *i.e.*, the inverse of the variance); horizontal lines represent 95%CI; diamonds represent summary relative risk estimates with corresponding 95%CI.

tabolized to resolvins and protectins. These compounds possess potent anti-inflammatory and immunoregulatory actions[56]. Mounting evidence suggests that inflammation plays a critical role in the development of human cancer[57,58]. Therefore, one of the possible mechanisms for inhibition of tumors by Ω-3 PUFAs is by suppression of inflammation through resolvins.

A number of signaling pathways that are relevant to carcinogenesis and tumor progression are differentially affected by Ω-3 PUFAs. For instance, Ω-3 PUFA products were reported to downregulate and inactivate cellular signaling mediators, including ras, protein kinase C, ERK 1/2[59] and nuclear factor-κB (NF-κB)[60]. Changes in lipid composition of the plasma membrane may affect membrane fluidity and the way growth factors, cytokines and hormones interact with their receptors, and the resulting signal transduction through secondary messengers[61]. A second type of mechanism through which Ω-3 fatty acids may alter cellular signaling is by acting directly as ligands for nuclear receptors, including peroxisome proliferators-activated receptors[62] or retinoid X receptor alpha[63]. Ω-3 PUFAs may also regulate the translation machinery. Eicosapentaenoic acid (EPA) has been reported to affect intracellular homeostasis and inhibit translation initiation, and to preferentially downregulate oncogenes and G1 cyclins[64].

Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of 1 million cases and an annual mortality of more than 500000 cases[65]. Although some studies have demonstrated an inverse relationship between fish consumption and colorectal cancer[20,29], others have not found a clear association[5]. A meta-analysis of prospective cohort studies on colorectal cancer and fish consumption was completed and published in 2007[66]. This analysis revealed an inverse association between the highest levels of fish consumption and the risk of colorectal cancer, although the association was only borderline statistically significant. The pooled RR for the highest compared with the lowest fish consumption category was 0.88 (95%CI: 0.78-1.00) for colorectal cancer incidence (14 studies). A more recent meta-analysis of 22 cohort and 19 case-control studies found that fish intake decreases the risk of colorectal cancer by 12%. The pooled odds ratios of colorectal cancer for the highest *vs* lowest fish consumption in the case-control and cohort studies were 0.83 (95%CI: 0.72-0.95) and 0.93 (95%CI: 0.86-1.01), respectively[67]. Our meta-analysis of 20 prospective cohort studies revealed a more significant association between fish intake and colorectal cancer risk abatement (summary RR = 0.93; 95%CI: 0.87-0.99).

Despite the fact that colon and rectal cancers share many features and are often referred to as "colorectal cancer", these cancer types typically exhibit different characteristics[68]. We therefore investigated associations

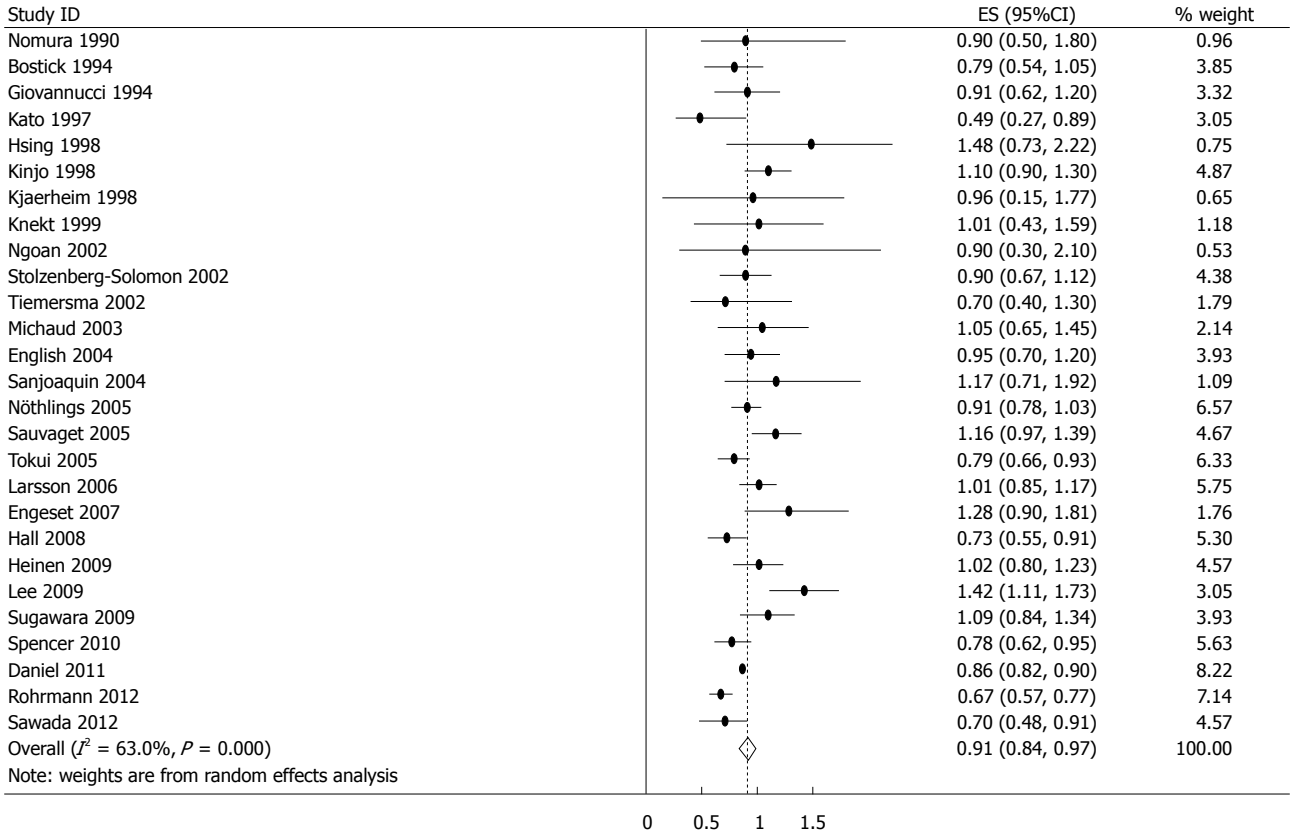

Figure 4 Summary relative risks of gastrointestinal cancer for high fish consumers *vs* non/lowest consumers from the included studies. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight; *i.e.*, the inverse of the variance); horizontal lines represent 95%CI; diamonds represent summary relative risk estimates with corresponding 95%CI.

between fish consumption and colon or rectal cancer. In 12 studies involving colon cancer, fish intake slightly reduced the risk of colon cancer (summary RR = 0.95; 95%CI: 0.91-0.98). In eight studies involving rectal cancer, a significant decrease was found between fish consumption and the risk of rectal cancer (summary RR = 0.85; 95%CI: 0.75-0.95). The different characteristics of colon and rectal cancers may explain why fish consumption more effectively protected against rectal cancer. For example, colon cancers are generally molecularly heterogeneous, whereas rectal cancers tend to arise through a single neoplastic pathway[68]. Further analysis is required to determine the mechanisms underlying the difference in how these two cancer types are affected by fish consumption.

Over the past few decades, gastric cancer mortality has dropped significantly, but it remains a disease with a poor prognosis and high mortality. Among participants in the Japan Collaborative Cohort Study, there was no association was seen between fish intake and the risk of stomach cancer[39]. A meta-analysis of two cohort and 15 case-control studies found no association between fish consumption and the risk of gastric cancer, whether these studies were evaluated together or individually[69]. Our meta-analysis, which included seven cohort studies, also suggested no significant association between fish intake and gastric cancer. However, an increment of 20 g/d of fish influenced the risk of gastric cancer, although the association was only borderline statistically significant. The summary RR was 1.03 (95%CI: 1.00-1.05).

Our current meta-analysis only analyzed data concerning fresh fish consumption, thereby avoiding confounding factors such as fish oil, salted fish or fried fish. However, in the overwhelming majority of cases we could not determine the exact kind of fish consumed or the manner in which the fish was prepared. Although there is no conclusive evidence concerning the association between processed fish consumption and the risk of gastric cancer, many epidemiological studies and reviews have found associations between the consumption of highly salted foods and the risk of gastric cancer[70,71]. This may be because highly salted foods, such as salted or smoked fish products, can contain chemical carcinogens. These carcinogens include nitrites and their related compounds, and heterocyclic amines, which have been detected in fish or meat cooked at high temperatures[22,72]. In addition, 2-chloro-4-methylthiobutanoic acid, which is a mutagen found in salted fish, may be associated with gastric carcinogenesis[73].

Since the World Cancer Research Fund/American Institute for Cancer Research report, Lin *et al*[46] studied the association between fish consumption and the risk of pancreatic cancer in a large population-based cohort study in Japan and concluded that fish intake does not

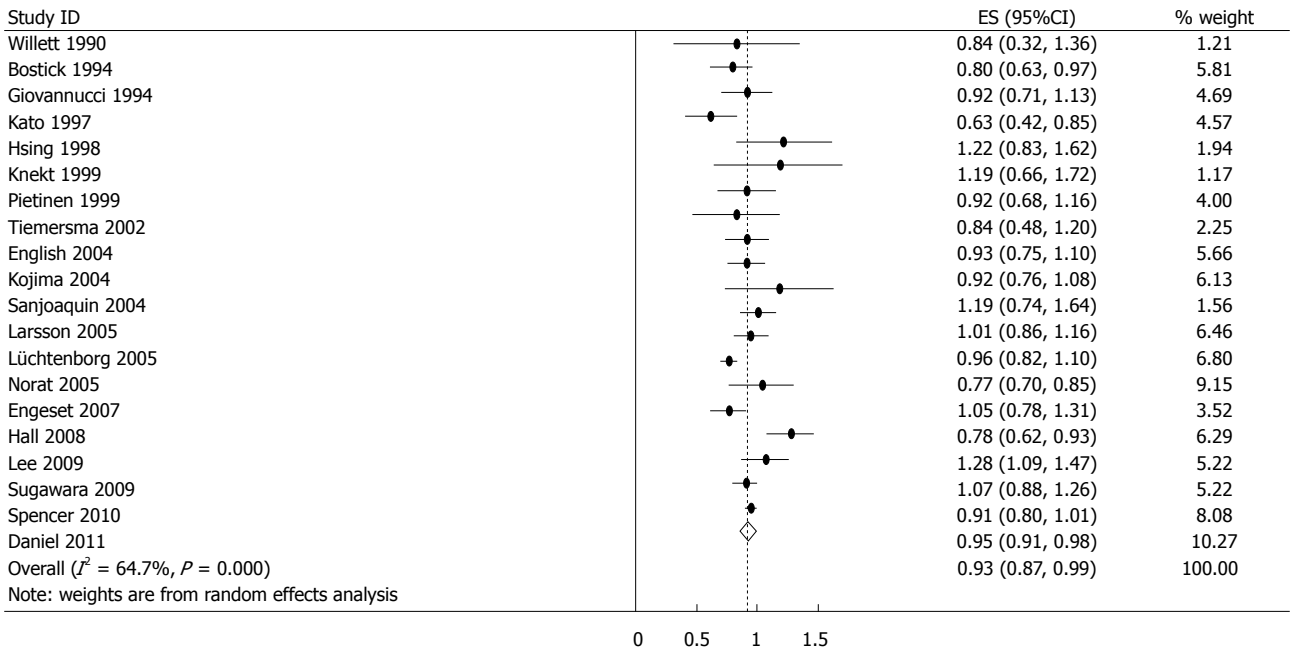

Figure 5 Summary relative risks of colorectal cancer for fish consumers *vs* non/lowest consumers from the included studies. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight; *i.e.*, the inverse of the variance); horizontal lines represent 95%CI; diamonds represent summary relative risk estimates with corresponding 95%CI.

Table 2 Summary relative risk for various cancer sites or different geographical regions and incremental estimates for 20-g/d increment of fish consumption

Cancer sites		Corresponding	Heterogeneity test			RR for 20 g/d
regions		RR (95%CI) for cancer	*Q* value	*P* value	I^2 (%)	Increment of fish
	Total	0.93 (0.88-0.98)	80.14	0.000	67.6	0.98 (0.96-1.01)
	Total male	0.95 (0.87-1.02)	13.97	0.082	42.8	
	Total female	0.96 (0.89-1.03)	27.60	0.001	71.0	
	Low consumption	0.94 (0.89-0.99)	50.29	0.003	48.3	
	High consumption	0.91 (0.84-0.97)	70.27	0.000	63.0	
Colorectum	Total	0.93 (0.87-0.99)	53.85	0.000	64.7	0.99 (0.97-1.01)
	Low consumption	0.95 (0.91-0.98)	13.12	0.832	0.0	
	High consumption	0.91 (0.82-0.99)	55.50	0.000	65.8	
Colon	Total	0.95 (0.91-0.98)	10.53	0.160	33.5	
	Low consumption	0.97 (0.92-1.02)	3.15	0.871	0.0	
	High consumption	0.90 (0.81-0.99)	12.65	0.081	44.7	
Rectum	Total	0.85 (0.75-0.95)	16.66	0.020	58.0	
	Low consumption	0.86 (0.80-0.93)	3.32	0.853	0.0	
	High consumption	0.85 (0.70-0.99)	17.53	0.014	60.1	
Esophagus	Total	0.91 (0.83-0.99)	2.43	0.297	17.6	
	Low consumption	0.90 (0.79-1.02)	0.43	0.807	0.0	
	High consumption	0.95 (0.73-1.17)	4.71	0.095	57.5	
Stomach	Total	1.04 (0.97-1.10)	5.94	0.430	0.0	1.03 (1.00-1.05)
	Low consumption	1.02 (0.94-1.11)	6.75	0.344	11.1	
	High consumption	1.06 (0.96-1.17)	3.06	0.802	0.0	
Liver	Total	0.71 (0.38-1.03)	29.04	0.000	93.1	0.89 (0.84-0.94)
	Low consumption	0.73 (0.34-1.13)	23.75	0.000	91.6	
	High consumption	0.71 (0.48-0.95)	6.60	0.037	69.7	
Pancreas	Total	1.07 (0.96-1.17)	19.49	0.012	59.0	1.02 (0.96-1.08)
	Low consumption	1.05 (0.93-1.17)	15.38	0.052	48.0	
	High consumption	1.04 (0.96-1.11)	8.73	0.366	8.4	
Asia		0.98 (0.81-1.15)	49.49	0.000	87.9	
Europe		0.94 (0.86-1.01)	16.86	0.051	46.6	
North America		0.88 (0.81-0.97)	19.73	0.011	59.5	

decrease the risk of pancreatic cancer. Preliminary results from the Nurses Health Study suggest no inverse association between fish intake and the risk of pancreatic cancer[43]. Our pooled analysis of nine cohort studies also revealed no association between fish consumption and the risk of pancreatic cancer.

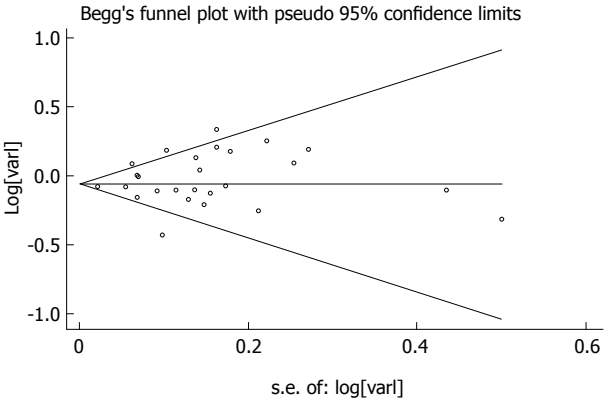

Figure 6 Publication bias in the studies. Begg's funnel plot indicating no publication bias in the studies included in this meta-analysis. No indication of publication bias was noted from either visualization of the funnel plot or from Egger's test.

Most of the studies reporting the associations of fish intake with risk of pancreatic cancer were primarily designed to study either the effect of meat or dietary fat consumption. Thus, they focused on total fish rather than different species of fish or different preparation methods. This limitation might contribute to the null findings in the primary studies and this meta-analysis. Fish can be served in many ways, such as fresh, broiled, baked, salted or fried. Fish preparation methods may alter the relation between fish intake and pancreatic cancer by changing the lipid profile and by generating unexpected chemicals with the use of certain cooking methods. Frying was found to considerably reduce the amount of LC-PUFA in fish. Deep-frying could generate trans-fatty acids, oxidized lipids, or food mutagens, such as heterocyclic amines and benzo(a)pyrene, which may promote carcinogenesis and which is associated with elevated pancreatic cancer risk[74,75].

Some study indicated that raw fish intake significantly reduced the risk of pancreatic cancer[76]. Norell *et al*[77] found that fried/grilled fish consumption may attenuate or cancel the potential benefit of fish consumption on pancreatic cancer risk. In a cohort study, researchers conducted a relative thorough separate analysis on both fish preparation methods and fish types[78]. Their results suggested that non-fried fish, but not total fish, intake was inversely associated with incident pancreatic cancer. It might be speculated that mixing all fish species and preparation methods may have masked the potential inverse association of fish intake with pancreatic cancer risk. An extensive analysis of fish species and preparation method with pancreatic cancer risk is needed in the future.

A recent prospective study showed an inverse association between the consumption of white meat, which included fish, and liver cancer[79]. Inverse associations between the consumption of white meat or fish and liver cancer have been observed in some studies[80,81], but not confirmed in others[82,83]. Sawada *et al*[52] investigated the association between fish and Ω-3 PUFA consumption and the incidence of hepatocellular carcinoma (HCC) in a population-based prospective cohort study of 90296 Japanese subjects. They found that consumption of Ω-3 PUFA-rich fish or Ω-3 PUFAs, particularly EPA, docosapentaenoic acid, and docosahexaenoic acid, appears to protect against the development of HCC, even among subjects with HBV and/or HCV infection. Although our meta-analysis did not confirm the findings of Sawada *et al*[52], we observed a 29% reduction in the risk of liver cancer among high consumers of fish.

In clinical trials, dietary supplementation with Ω-3 PUFAs for 1-3 mo was associated with a decreased release of interleukin-1 and -6[84,85]. Given that HCC is an inflammation-related cancer that has a background of chronic inflammation, triggered by exposure to hepatitis virus infection or toxic compounds, such as ethanol[86,87], the anti-inflammatory properties of Ω-3 PUFAs might decrease the risk of HCC. Here, we showed that the risk of HCC was decreased with greater consumption of fish. The intake of Ω-3 PUFA-rich fish may reduce the risk of HCC through the anti-inflammatory effects of Ω-3 PUFAs on chronic hepatitis.

Some limitations concerning our current meta-analysis should be acknowledged. First, as in all observational studies of diet and disease, the possibility of bias and confounding factors cannot be excluded. For example, some subjects may have modified their fish eating habits after the baseline assessment. However, cohort studies, which are less susceptible to bias because of their prospective design, also showed an inverse association between fish consumption and the risk of GI cancers, suggesting that this central finding is not likely attributable to recall and selection bias. Individual studies may have failed to adjust for known and unknown confounding factors. Second, the methods and units of measuring fish intake varied across studies. In some studies, the definitive volumes of fish consumption were not clearly defined and only the lowest and highest categories were reported. Statistical tests showed heterogeneity among studies; therefore, we used the random-effects model, which considers both within- and between-study variation, for pooled RR estimates and dose-response analyses. Third, we used fresh fish as an inclusion criterion to avoid confounding factors associated with fish oil, salted fish and fried fish. Despite this effort, we could not determine the exact kind of fish consumed or the manner in which the fish was prepared. This represents a limitation to our analysis, because a recent article showed that cooking temperature may affect the risk of colorectal cancer[88]. Fourth, we extracted risk estimates that reflected the greatest degree of control for potential confounders. Results based on adjustments for specific confounders were likely different from those based on standard adjustments. Finally, we included only studies published in English. This is because it is difficult for the authors to interpret data presented in different languages. Therefore, publication bias may have occurred,

although such bias was not indicated from visualization of the funnel plot and Egger's test.

In our meta-analysis of 27 prospective cohort studies, fish intake was not associated with harmful effects. Instead, fish consumption may reduce total incidence of GI cancer. Specific inverse associations were detected between fish consumption and colorectal, esophageal and hepatocellular cancers.

COMMENTS

Background

Gastrointestinal cancers are the most common types of human tumors and their development has been linked to diet. A report published by the World Cancer Research Fund and the American Institute for Cancer Research suggested that the consumption of certain types of food may be directly associated with the development of gastrointestinal cancers. Epidemiological data have shown that in populations with high levels of fish consumption, the incidence and mortality rates for gastrointestinal cancers are greatly reduced. However, a comprehensive analysis of this epidemiological evidence has not been performed.

Research frontiers

Fish is an ideal source of fatty acids, which are important components of cell membranes. Fish can also contain high levels of vitamin D and selenium, which may protect against the development of several cancers. Most importantly, fish is a rich source of omega-3 (Ω-3) fatty acids, which may protect against GI cancers through anticarcinogenic and anti-inflammatory effects. Fatty acids regulate the production of proinflammatory prostaglandins and hydroxyeicosatetraenoic acid *via* the cyclooxygenase and lipoxygenase pathways. These pathways play major roles in inflammation, cell proliferation, and angiogenesis, each of which represents a key factor in cancer progression.

Related publications

A meta-analysis of prospective cohort studies on colorectal cancer and fish consumption was completed and published in 2007. This analysis revealed an inverse association between the highest levels of fish consumption and the risk of colorectal cancer. The pooled RR for the highest compared with the lowest fish consumption category was 0.88 (95%CI: 0.78-1.00) for colorectal cancer incidence. A more recent meta-analysis of 22 cohort and 19 case-control studies found that fish intake decreases the risk of colorectal cancer by 12%. The pooled odds ratios of colorectal cancer for the highest *vs* lowest fish consumption in the case-control and cohort studies were 0.83 (95%CI: 0.72-0.95) and 0.93 (95%CI: 0.86-1.01), respectively.

Innovations and breakthroughs

This meta-analysis presents epidemiological evidence for the relationship between fish intake and risk of digestive cancers. We observed an inverse association between fish intake and the risk of digestive cancers. A 20-g increase in fish consumption per day was associated with a 2% reduced risk of gastrointestinal cancers. In subgroup analyses, fish consumption was associated with reduced risk of colorectal, esophageal and hepatocellular cancers. More investigations are needed to determine the biological mechanism of the inverse relationship between fish intake and the incidence of digestive cancers.

Applications

The study results suggest an inverse association between fish intake and the risk of digestive cancers. High fish intake may decrease the risk of colorectal, esophageal and hepatocellular cancers. Increasing fish intake could prevent gastrointestinal cancers.

Terminology

Long-chain Ω-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids necessary for human health. They may protect against cancers through anticarcinogenic and anti-inflammatory effects. PUFAs regulate the production of proinflammatory prostaglandins and hydroxyeicosatetraenoic acid *via* the cyclooxygenase and lipoxygenase pathways. These pathways play major roles in inflammation, cell proliferation and angiogenesis, each of which represent key factors in cancer progression.

Peer review

This review presents a meta-analysis of prospective cohort studies on the association between fish consumption and the risk of gastrointestinal cancers. The authors conclude that fish intake may reduce gastrointestinal cancer incidence. This is an interesting and well written review, on an important topic. The data presented confirm and significantly extend the data already published.

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