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.

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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 lipooxygenase 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,
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[8,17-52] (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
| Ref.          | Year | Country         | Follow-up period | Country/subjects | Cancer site | Fish consumption | Relative risk (95%CI) | Adjustments                           |
|--------------|------|-----------------|------------------|------------------|-------------|------------------|-----------------------|---------------------------------------|
| Willett et al[20] | 1990 | United States   | 6 yr             | 88751 F 150 F    | Colon       | < 1/mo           | 1                     | Age, energy intake, height, parity, vitamin E, vitamin Eage interaction, vitamin A |
| Bostick et al[30] | 1994 | United States   | 6 yr             | 35215 F 212 F    | Colon       | 1/ wk            | 1.29 (0.70-2.40)       | Age, energy intake, alcohol intake, height, vitamin E, vitamin Eage interaction, vitamin A |
| Giovannucci et al[19] | 1994 | United States   | 6 yr             | 47949 M 205 M    | Colon       | 2/ wk            | 0.92 (0.49-1.72)       | Age, energy intake, alcohol intake, height, vitamin E, vitamin Eage interaction, vitamin A |
| Kato et al[22] | 1997 | United States   | 7.1 yr            | 14727 F 100 F    | Colorectal  | Q1 < 1 time/wk   | 0.73 (0.50-1.07)       | Age, education, place of residence   |
| Hsing et al[26] | 1998 | United States   | 20 yr            | 17633 M 145 M    | Colorectal  | 0.8-1.6 time/mo  | 1.1 (0.7-1.9)          | Age, education, gender, municipaliry, smoking |
| Knekt et al[26] | 1999 | Finland         | 24 yr            | 9985 73          | Colorectal  | 1.4 time/mo      | 1.2 (0.7-2.0)          | Age, education, gender, smoking       |
| Pietinen et al[26] | 1999 | Finland         | 8 yr             | 27111 M 185 M    | Colorectal  | 1.5 time/mo      | 1.5 (0.9-2.6)          | Age, education, smoking, BMI, alcohol, physical activity, calcium intake |
| Tiemersma et al[26] | 2002 | The Netherlands | 8.5 yr           | 537 102          | Colorectal  | 0.1-< 2.0 times/wk| 1.1 (0.7-1.9)          | Age, energy intake, alcohol, height   |
| English et al[26] | 2004 | Australia       | 9 yr             | 37112 451        | Colorectal  | 0.5-1.4 times/wk | 0.9 (0.7-1.1)          | Age, energy intake, country of birth, gender, fat, cereal intake |
| Kojima et al[26] | 2004 | Japan           | 9.9 yr           | 107824 457       | Colorectal  | every day        | 0.88 (0.65-1.12)       | Age, family history, BMI, smoking, physical activity, education, alcohol intake, region |
| Sanjoaquin et al[26] | 2004 | United Kingdom  | 17 yr            | 10998 95         | Colorectal  | 0-1 time/wk      | 1.21 (0.71-2.06)       | Age, gender, smoking, alcohol         |
| Larsson et al[27] | 2005 | Sweden          | 13.9 yr          | 61433 F 733 F    | Colorectal  | 0.5-< 1.0 serveings/wk | 0.94 (0.72-1.22)       | Age, energy, education, BMI, alcohol, saturated |
| Lüchentborg et al[26] | 2005 | The Netherlands | 5 yr             | 2948 588         | Colorectal  | ≥ 1 time/wk      | 1.0 (0.74-1.27)        | Age, energy intake, gender, family history, educational, alcohol, education, alcohol intake, region |
| Norat et al[26] | 2005 | 10 European     | 4.8 yr           | 478040 1329      | Colorectal  | 15.2 g/d         | 0.86 (0.65-1.06)       | Age, energy intake, country of birth, gender, fat, cereal intake |
| Engeset et al[26] | 2007 | Norway          | 8 yr             | 63914 F 254 F    | colon       | ≥ 80 g/d         | 0.69 (0.54-0.88)       | Age, daily intake of energy, smoking, fish liver, fruit and vegetable, fiber, fats, sauces |

Source: Yu XF et al. Fish consumption and gastrointestinal cancers. | Issue 41 | November 7, 2014 | Volume 20 | 15401
### Hall et al. [31] 2008 United States 22 yr 21406 M 500 M Colorectal

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 1 time/wk  | 1           | Age, smoking, BMI, multivitamin use, history of diabetes, random assignment to aspirin or placebo, vigorous exercise, alcohol, red meat intake |
| 1-< 2 time/wk| 0.88 (0.65-1.20) |                                                                    |
| 2-< 5 time/wk| 0.82 (0.61-1.10) |                                                                    |
| ≥ 5 times/wk | 0.63 (0.42-0.95) |                                                                    |

### Lee et al. [32] 2009 China 7.4 yr 73224 F 394 F Colorectal

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 33 g/d     | 1           | Age, education, income, survey season, tea consumption, NSAID use, energy intake, fiber intake |
| < 49 g/d     | 1.2 (0.9-1.5) |                                                                    |
| < 74 g/d     | 1.2 (0.8-1.6) |                                                                    |
| ≥ 74 g/d     | 1.3 (0.9-1.9) |                                                                    |

### Sugawara et al. [33] 2009 Japan 8 yr 39498 566 Colorectal

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 20 g/d     | 1           | Red meat intake, age, sex, education, marital status, family history of cancer, race, BMI, smoking status, frequency of vigorous physical activity, NHT in women, intake of alcohol, fruit, vegetables, and total energy |
| < 33 g/d     | 0.88 (0.65-1.20) |                                                                    |
| < 49 g/d     | 0.82 (0.61-1.10) |                                                                    |
| ≥ 50 g/d     | 0.63 (0.42-0.95) |                                                                    |

### Spencer et al. [34] 2010 United Kingdom 2575 579 Colorectal

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 1 g/d      | 1           | Age, height, weight, smoking, energy, alcohol, dietary fiber                     |
| 1 < 15 g/d   | 0.89 (0.71-1.08) |                                                                    |
| 15 < 30 g/d  | 1.10 (0.90-1.30) |                                                                    |
| ≥ 30 g/d     | 0.78 (0.62-0.95) |                                                                    |

### Daniel et al. [35] 2011 United States 9 yr 492186 6979 Colorectal

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 1.2 g/1000 kcal | 1 | Age, sex-specific age, smoking, processed meat, liver, cooking or salad oil, suimono, pickled food |
| 1.2-1.9 g/1000 kcal | 0.97 (0.85-0.99) | Age, sex-specific smoking habits, education level                                    |
| > 2 g/1000 kcal | 1.16 (0.97-1.39) |                                                                    |

### Nomura et al. [36] 1990 United States 19 yr 7990 M 150 Gastric

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| ≤ 1 time/wk  | 1           | Sex, age, smoking, smoking, processed meat, liver, cooking or salad oil, suimono, pickled food |
| 1-< 2 time/wk| 1.4 (1.0-1.9) |                                                                    |
| 2-< 5 time/wk| 0.9 (0.5-1.8) |                                                                    |
| ≥ 5 times/wk | 0.90 (0.60-2.20) |                                                                    |

### Ngoan et al. [37] 2002 Japan 10.5 yr 13250 116 Gastric

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| ≤ 2-4 times/mo| 1 | Age, sex-specific smoking habits, education level                                    |
| 2-4 times/wk | 1.09 (0.96-1.23) |                                                                    |
| ≥ 5 times/wk | 1.16 (0.97-1.39) |                                                                    |

### Sauvaget et al. [38] 2005 Japan 20 yr 38576 1270 Gastric

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 1 time/d   | 1           | Race, BMI, smoking status, age, sex, education, marital status, family history of cancer, frequency of vigorous physical activity, NHT in women, intake of alcohol, fruit, vegetables, and total energy |
| 1-< 2 times/wk| 0.90 (0.50-0.20) |                                                                    |
| 2-4 times/wk | 1.11 (0.93-1.33) |                                                                    |
| ≥ 5 times/wk | 1.14 (0.93-1.40) |                                                                    |

### Tokai et al. [39] 2005 Japan 11 yr 110792 859 Gastric

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| ≤ 1-2 times/mo| 1 | Age, education, body mass index, intake of total energy, alcohol, fruits and vegetables |
| 1-< 2 times/wk| 0.85 (0.61-1.19) |                                                                    |
| 2-4 times/wk | 0.90 (0.65-1.26) |                                                                    |
| ≥ 1 time/d   | 0.95 (0.68-1.33) |                                                                    |

### Larsson et al. [40] 2006 Sweden 18 yr 61433 156 Gastric

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| < 1.2 servings/wk | 1 | Age, education, body mass index, intake of total energy, alcohol, fruits and vegetables |
| 1.2-1.9 servings/wk | 0.97 (0.64-1.46) |                                                                    |
| ≥ 5 servings/wk  | 1.14 (0.75-1.72) |                                                                    |

### Zheng et al. [41] 1993 United States 20 yr 17633 M 57 Pancreatic

| Intake       | RR (95% CI) | Health Factors                                                                 |
|--------------|-------------|---------------------------------------------------------------------------------|
| ≤ 17.9 g/d   | 1           | Age, smoking, index, alcohol index, total calories                               |
| > 17.9 and ≤ 27.7 g/d | 1.22 (0.75-1.97) |                                                                    |
| > 27.7 and ≤ 38.6 g/d | 1.14 (0.70-1.86) |                                                                    |
| > 38.6 and ≤ 55.8 g/d | 1.07 (0.65-1.76) |                                                                    |
| > 55.8 g/d   | 0.91 (0.54-1.52) |                                                                    |
Yu XF et al. Fish consumption and gastrointestinal cancers

Michaud et al. 2003 United States 18 yr 88802 F 178 FM Pancreatic < 4/mo 1 pack-years of smoking, BMI, history of diabetes mellitus, caloric intake, height, physical activity, menopausal status, Age, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, energy intake

Nöthlings et al. 2005 United States 7 yr 190545 482 Pancreatic 1.1 3.8 6.4 9.8 0.85 (0.70-1.03) 0.84 (0.69-1.03) 0.90 (0.74-1.10) 0.88 (0.58-1.34) 1.52 (0.96-2.40) 0.87 (0.77-0.99) 0.94 (0.98-1.00)

Larsson et al. 2006 Sweden 17 yr 61433 F 172 Pancreatic 17.3 0.91 (0.75-1.11) 1 Age, education, BMI, smoking, intakes of total energy, alcohol, energy-adjusted folate, Age, area, pack-years of smoking

Lin et al. 2006 Japan 11 yr 110792 300 Pancreatic 0-2/mo 1 1.21 (0.60-1.81) 0.98 (0.43-1.53)

Heinen et al. 2009 Netherlands 13.3 yr 120852 350 Pancreatic 0-10 g/d 1.22 (0.89-1.67) 10-20 g/d 1.02 (0.75-1.38)

Rohrmann et al. 2012 10 European countries 16 yr 477202 865 Pancreatic 20 g/d 0.88 (0.58-1.34) 1.05 (0.75-1.47) 1.13 (0.90-1.41) 1.07 (0.81-1.41) 1.16 (0.92-1.47)

Kusrlo et al. 1998 Japan 15 yr 220272 440 Esophageal 1-3 times/mo or less 1 Age, prefecture, occupation, sex

Kjaerheim et al. 1998 Norway 24 yr 10960 M 71 M Esophageal < monthly 1-5 times/mo or more 1.1 (0.9-1.3)

Kurozawa et al. 2004 Japan 12 yr 110792 401 Liver 60 g/d 1.09 (0.81-1.47) 1.16 (0.92-1.47) 1.13 (0.90-1.41) 1.02 (0.80-1.31) 1.05 (0.83-1.32) 1.13 (0.90-1.41)

Sawada et al. 2012 Japan 11.2 yr 90296 398 Liver 35.0 g/d 1 Age, area, sex, smoking status, alcohol frequency, body mass index, past history of diabetes mellitus, and intake of coffee, soy foods, vegetables, 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...
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 PUFA, which may protect against the development of GI cancers. Omega-3 (Ω-3) PUFA is 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 PUFA 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 PUFA are those that relate to eicosanoid biosynthesis and function. Dietary Ω-3 PUFA can be metabolized to prostaglandins, thromboxanes, hydroxyeicosatetraenoic acids and leukotrienes, by the enzymatic activity of COXs and LOXs[35]. Besides eicosanoids, marine Ω-3 PUFA may also be me-
Yu XF et al. Fish consumption and gastrointestinal cancers

| Study ID                   | ES (95%CI) | % weight |
|----------------------------|------------|----------|
| Nomura 1990                | 1.40 (1.00, 1.90) | 1.27     |
| Bostick 1994               | 0.81 (0.58, 1.04) | 3.68     |
| Giovannucci 1994           | 0.93 (0.63, 1.24) | 2.44     |
| Kato 1997                  | 0.77 (0.47, 1.08) | 2.44     |
| Hsing 1998                 | 1.19 (0.79, 1.60) | 1.53     |
| Kinjo 1998                 | 0.90 (0.70, 1.10) | 4.39     |
| Kjaerheim 1998             | 0.73 (0.18, 1.28) | 0.88     |
| Knekt 1999                 | 0.29 (0.76, 1.82) | 0.95     |
| Ngoan 2002                 | 0.90 (0.40, 2.20) | 0.35     |
| Stolzenberg-Solomon 2002   | 1.14 (0.84, 1.45) | 2.44     |
| Tiemersma 2002             | 1.10 (0.70, 1.90) | 0.75     |
| Michaud 2003               | 1.23 (0.85, 1.61) | 1.70     |
| English 2004               | 0.90 (0.70, 1.20) | 3.28     |
| Sanjoaquin 2004            | 1.21 (0.71, 2.06) | 0.60     |
| Nöthlings 2005             | 0.85 (0.73, 0.96) | 7.38     |
| Sauvaget 2005              | 1.09 (0.96, 1.23) | 6.55     |
| Tokui 2005                 | 0.65 (0.53, 0.78) | 6.96     |
| Larsson 2006               | 0.89 (0.73, 1.05) | 5.62     |
| Engeset 2007               | 0.93 (0.66, 1.31) | 2.20     |
| Hall 2008                  | 0.88 (0.65, 1.20) | 2.86     |
| Heinen 2009                | 1.00 (0.86, 1.13) | 6.55     |
| Lee 2009                   | 1.20 (0.96, 1.44) | 3.47     |
| Sugawara 2009              | 1.04 (0.79, 1.39) | 2.50     |
| Spencer 2010               | 0.99 (0.85, 1.12) | 6.55     |
| Daniel 2011                | 0.92 (0.88, 0.96) | 10.48    |
| Rohrmann 2012              | 0.92 (0.82, 1.02) | 8.04     |
| Sawada 2012                | 0.84 (0.63, 1.05) | 4.14     |
| Overall (I² = 48.3%, P = 0.003) | 0.94 (0.89, 0.99) | 100.00   |

Note: weights are from random effects analysis

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.

Fish consumption and colorectal cancer

Colorectal cancer (CRC) is a worldwide problem, with an annual incidence of 1 million cases and an annual mortality of more than 500000 cases. Although some studies have demonstrated an inverse relationship between fish consumption and colorectal cancer, others have not found a clear association. 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, 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. Our meta-analysis of 20 prospective cohort studies revealed a more significant association between fish intake and colorectal cancer risk (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. We therefore investigated associations...
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. 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 seen between fish intake and the risk of stomach cancer. 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. 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/day 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. This may be because highly salted foods, such as salted or smoked fish products, can contain chemical carcinogens. These carcinogens include nitrates and their related compounds, and heterocyclic amines, which have been detected in fish or meat cooked at high temperatures. In addition, 2-chloro-4-methylthiobutanoic acid, which is a mutagen found in salted fish, may be associated with gastric carcinogenesis.

Since the World Cancer Research Fund/American Institute for Cancer Research report, Lin et al. 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 4 Summary relative risks of gastrointestinal cancer for high fish consumers vs non/lowest consumers from the included studies

| Study ID     | ES (95%CI) | % weight |
|--------------|------------|----------|
|    |            |          |          |
| Nomura 1990 | 0.90 (0.50, 1.80) | 0.96 |
| Bostick 1994 | 0.79 (0.54, 1.05) | 3.85 |
| Giovannucci 1994 | 0.91 (0.62, 1.20) | 3.32 |
| Kato 1997 | 0.49 (0.27, 0.89) | 3.05 |
| Hsing 1998 | 1.48 (0.73, 2.22) | 0.75 |
| Kinjo 1998 | 1.10 (0.90, 1.30) | 4.87 |
| Kjaerheim 1998 | 0.96 (0.15, 1.77) | 0.65 |
| Knekt 1999 | 1.01 (0.43, 1.59) | 1.18 |
| Ngoan 2002 | 0.90 (0.30, 2.10) | 0.53 |
| Stolzenberg-Solomon 2002 | 0.90 (0.67, 1.12) | 4.38 |
| Tiemersma 2002 | 0.70 (0.40, 1.30) | 1.79 |
| Michaud 2003 | 1.05 (0.65, 1.45) | 2.14 |
| English 2004 | 0.95 (0.70, 1.20) | 3.93 |
| Sanjoaquin 2004 | 1.17 (0.71, 1.92) | 1.09 |
| Nöthlings 2005 | 0.91 (0.78, 1.03) | 6.57 |
| Sauvant 2005 | 1.16 (0.97, 1.39) | 4.67 |
| Tokui 2005 | 0.79 (0.66, 0.93) | 6.33 |
| Larsson 2006 | 1.01 (0.85, 1.17) | 5.75 |
| Engeset 2007 | 1.28 (0.90, 1.81) | 1.76 |
| Hall 2008 | 0.73 (0.55, 0.91) | 5.30 |
| Heinen 2009 | 1.02 (0.80, 1.23) | 4.57 |
| Lee 2009 | 1.42 (1.11, 1.73) | 3.05 |
| Sugawara 2009 | 1.09 (0.84, 1.34) | 3.93 |
| Spencer 2010 | 0.78 (0.62, 0.95) | 5.63 |
| Daniel 2011 | 0.86 (0.82, 0.90) | 8.22 |
| Rohrmann 2012 | 0.67 (0.57, 0.77) | 7.14 |
| Sawada 2012 | 0.70 (0.48, 0.91) | 4.57 |
| Overall (I² = 63.0%, P = 0.000) | 0.91 (0.84, 0.97) | 100.00 |

Note: weights are from random effects analysis.
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 regions  | Corresponding ES (95%CI) for cancer | Heterogeneity test Q value | P value | I² (%) | RR for 20 g/d 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)                   | 30.69                    | 0.002  | 32.1  | 0.94 (0.92-0.96)              |
| Total female          | 0.96 (0.89-1.03)                   | 27.60                    | 0.001  | 71.0  | 0.91 (0.85-0.96)              |
| Low consumption       | 0.94 (0.89-0.99)                   | 50.29                    | 0.003  | 48.3  | 0.91 (0.84-0.97)              |
| High consumption      | 0.91 (0.84-0.97)                   | 70.27                    | 0.000  | 63.0  | 0.87 (0.80-0.94)              |
| Colorectum            | 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                    | 0.852  | 0.0   | 0.91 (0.85-0.96)              |
| High consumption      | 0.91 (0.82-0.99)                   | 55.50                    | 0.000  | 65.8  | 0.86 (0.80-0.93)              |
| Colon                 | 0.95 (0.91-0.98)                   | 10.53                    | 0.160  | 33.5  | 0.93 (0.87-0.99)              |
| Low consumption       | 0.97 (0.92-1.02)                   | 3.13                     | 0.871  | 0.0   | 0.90 (0.81-0.99)              |
| High consumption      | 0.90 (0.81-0.99)                   | 12.65                    | 0.001  | 44.7  | 0.86 (0.80-0.93)              |
| Rectum                | 0.85 (0.75-0.95)                   | 16.66                    | 0.020  | 58.0  | 0.88 (0.80-0.93)              |
| Low consumption       | 0.86 (0.80-0.93)                   | 3.32                     | 0.853  | 0.0   | 0.86 (0.80-0.93)              |
| High consumption      | 0.85 (0.70-0.99)                   | 17.53                    | 0.014  | 60.1  | 0.85 (0.70-0.99)              |
| Esophagus             | 0.91 (0.83-0.99)                   | 2.43                     | 0.297  | 17.6  | 0.89 (0.80-0.99)              |
| Low consumption       | 0.90 (0.79-1.02)                   | 0.43                     | 0.807  | 0.0   | 0.90 (0.79-1.02)              |
| High consumption      | 0.95 (0.73-1.17)                   | 4.71                     | 0.095  | 57.5  | 0.95 (0.73-1.17)              |
| Stomach               | 1.04 (0.97-1.10)                   | 5.94                     | 0.450  | 0.0   | 1.04 (0.97-1.10)              |
| Low consumption       | 1.02 (0.94-1.11)                   | 6.75                     | 0.344  | 11.1  | 1.02 (0.94-1.11)              |
| High consumption      | 1.06 (0.96-1.17)                   | 3.06                     | 0.802  | 0.0   | 1.06 (0.96-1.17)              |
| Liver                 | 1.00 (0.86-1.11)                   | 29.04                    | 0.000  | 93.1  | 0.86 (0.80-0.93)              |
| Low consumption       | 0.73 (0.34-1.13)                   | 23.75                    | 0.000  | 91.6  | 0.73 (0.34-1.13)              |
| High consumption      | 0.71 (0.48-0.95)                   | 6.60                     | 0.037  | 69.7  | 0.71 (0.48-0.95)              |
| Pancreas              | 1.07 (0.96-1.17)                   | 19.49                    | 0.012  | 59.0  | 1.07 (0.96-1.17)              |
| Low consumption       | 1.05 (0.93-1.17)                   | 15.38                    | 0.052  | 48.0  | 1.05 (0.93-1.17)              |
| High consumption      | 1.04 (0.96-1.11)                   | 8.73                     | 0.366  | 8.4   | 1.04 (0.96-1.11)              |
| Asia                  | 0.98 (0.81-1.15)                   | 49.49                    | 0.000  | 87.9  | 0.98 (0.81-1.15)              |
| Europe                | 0.94 (0.86-1.01)                   | 16.86                    | 0.051  | 46.6  | 0.94 (0.86-1.01)              |
| North America         | 0.88 (0.81-0.97)                   | 19.73                    | 0.011  | 59.5  | 0.88 (0.81-0.97)              |

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

Yu XF et al. Fish consumption and gastrointestinal cancers
Yu XF et al. Fish consumption and gastrointestinal cancers

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.

Some study indicated that raw fish intake significantly reduced the risk of pancreatic cancer. Norell et al. 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. 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. Inverse associations between the consumption of white meat or fish and liver cancer have been observed in some studies, but not confirmed in others. Sawada et al. investigated the association between fish and \(\Omega-3\) 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 \(\Omega-3\) PUFA-rich fish or \(\Omega-3\) 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., we observed a 29% reduction in the risk of liver cancer among high consumers of fish.

In clinical trials, dietary supplementation with \(\Omega-3\) PUFAs for 1-3 mo was associated with a decreased release of interleukin-1 and -6. 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, the anti-inflammatory properties of \(\Omega-3\) 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 \(\Omega-3\) PUFA-rich fish may reduce the risk of HCC through the anti-inflammatory effects of \(\Omega-3\) 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.

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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.

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