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Fish consumption and gastric cancer within the Stomach cancer Pooling (StoP) Project

Carlotta Franchi[1,2]✉, Ilaria Ardoino[1], Sara Mandelli[1], Linia Patel[3], Claudio Pelucchi[3], Rossella Bonzi[3], M. Constanza Camargo[4], Charles S. Rabkin[4], Linda M. Liao[4], Rashmi Sinha[4], Kenneth C. Johnson[5], Jinfu Hu[6], Zuo-Feng Zhang[7], Domenico Palli[8], Monica Ferraroni[3,9], Eva Negri[3,10], Federica Turati[3], Guo-Pei Yu[11], Nuno Lunet[12,13,14], Samantha Morais[12,13,14], Lizbeth López-Carrillo[15], Shoichiro Tsugane[16,17], Akihisa Hidaka[18], Reza Malekzadeh[19], David Zaridze[20], Dmitry Maximovitch[20], Jesus Vioque[21,22], Sandra Gonzalez-Palacios[21,22], Mary H. Ward[23,24], Nuria Aragonés[22,25], Gemma Castaño-Vinyals[22,26,27,28], Maria Paula Curado[29], Emmanuel Dias-Neto[29], Gerson Shigueaki Hamada[30], Raul Ulises Hernández-Ramirez[31], Mohammadreza Pakseresht[19,32,33], Farhad Pourfarzi[34], Lina Mu[35], Areti Lagiou[36], Pagona Lagiou[37,38], Malaquias López-Cervantes[39], Alberto Dolci[40], Stefania Boccia[41,42], Roberta Pastorino[41], Paolo Boffetta[10,43], Barbara D'Avanzo[1] & Carlo La Vecchia[3]

Gastric cancer is among the most common cancer and cause of cancer death. We conducted a meta-analysis of 25 case–control studies from the Stomach cancer Pooling Project to assess the association between fish or canned fish consumption and the risk of gastric cancer. 10,431 cases and 24,903 controls were available. We found no association between fish consumption and risk of gastric cancer (pooled odds ratios (OR) = 0.99; 95% confidence interval (CI) 0.86–1.13, for at least one serving/week vs none). Geographical differences were found: in Asia an increased intake of fish was associated with a lower stomach cancer risk. In the sensitivity analyses, fish consumption was associated to a lower risk of gastric cancer in models adjusted for family history of gastric cancer (OR = 0.80, 95% CI 0.72–0.89) and Helicobacter Pylori infection (OR = 0.72, 95% CI 0.60–0.88), but not for body mass index or energy intake. Seven studies collected information on canned fish (4525 cases and 8073 controls). No association was found for canned fish (OR = 0.96, 95% CI 0.82–1.13). In conclusion, our results provide evidence that fish and canned fish intake are not associated with gastric cancer risk, although geographical differences have been highlighted, with a lower risk of gastric cancer in Asia.

Keywords Consortium, Fish, Canned fish, Pooled analysis, Stomach neoplasms

[1]Laboratory of Pharmacoepidemiology and Human Nutrition, Department of Health Policy, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri, 2, 20156 Milano, Italy. [2]Italian Institute for Planetary Health (IIPH), Milan, Italy. [3]Branch of Medical Statistics, Biometry, and Epidemiology "G.A. Maccacaro", Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy. [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA. [5]School of Epidemiology and Public Health, Department of Medicine, University of Ottawa, Ottawa, Canada. [6]Harbin Medical University, Harbin, China. [7]Department of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA. [8]Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network, ISPRO, Florence, Italy. [9]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. [10]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. [11]Medical Informatics Center, Peking University, Peking, China. [12]EPIUnit – Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal. [13]Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal. [14]Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal. [15]Mexico National Institute of Public Health, Morelos, Mexico. [16]Division of Cohort Research, National Cancer Center Institute for Cancer Control, Tokyo, Japan. [17]International University of Health and Welfare Graduate School of Public Health, Tokyo, Japan. [18]Division of Epidemiology, National Cancer Center Institute for Cancer Control, Tokyo, Japan. [19]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [20]Department of

Clinical Epidemiology, N.N. Blokhin National Medical Research Center for Oncology, Moscow, Russia. [21]Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernandez (ISABIAL-UMH), Alicante, Spain. [22]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain. [23]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA. [24]Cancer Epidemiology Section, Public Health Division, Department of Health of Madrid, Madrid, Spain. [25]Cancer Surveillance and Registry Unit, Public Health Division, Department of Health of Madrid, Madrid, Spain. [26]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain. [27]Barcelona Institute for Global Health—ISGlobal, Barcelona, Spain. [28]Universitat Pompeu Fabra (UPF), Barcelona, Spain. [29]Centro Internacional de Pesquisa, A. C. Camargo Cancer Center, São Paulo, Brazil. [30]Nikkei Disease Prevention Center, São Paulo, Brazil. [31]Department of Biostatistics, Yale School of Public Health, Yale School of Medicine, New Haven, CT, USA. [32]Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, AB, Canada. [33]Nutritional Epidemiology Group, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, UK. [34]Digestive Disease Research Center, Ardabil University of Medical Sciences, Ardabil, Iran. [35]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA. [36]Department of Public and Community Health, School of Public Health, University of West Attica, Athens, Greece. [37]Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece. [38]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [39]Facultad de Medicina, UNAM, 04510 Coyoacán, Mexico. [40]Research and Development Department, Bolton Food SpA, Milan, Italy. [41]Section of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Roma, Italy. [42]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. [43]Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA. ✉email: carlotta.franchi@marionegri.it

Gastric cancer is the sixth most common diagnosed cancer and the seventh cause of cancer death in the world, with nearly one million new cases and 660,000 deaths in 2022[1]. Over the last decades, gastric cancer incidence and mortality have substantially declined due to a reduced prevalence and a better clinical management of one of its main risk factors, i.e. Helicobacter Pylori (HP) infection[1]. Among modifiable risk factors, diet plays a crucial role. A Mediterranean diet, characterized by a high intake of fruits, vegetables, nuts, legumes, whole grains, extra-virgin olive oil, a moderate intake of poultry, fish and alcohol and a low consumption of red and processed meats, has been associated with a reduced risk of stomach cancer[2]. On the contrary, a diet rich in starches, saturated-fats and foods preserved in salt, or smoked, such as salted or dried fish and pickled vegetables, as well as an excessive alcohol consumption have been directly associated with gastric cancer[3].

Globally, seafood is a part of many diets. Fish in particularly is a known source of long-chain omega-3 polyunsaturated fatty acids (PUFAs), which have anti-inflammatory characteristics and consequently anticarcinogenic effect[4,5]. Several epidemiological studies have focused on the association between fish consumption and the risk of gastric cancer with inconsistent results[6–16]. A sub-category of fish deserving attention is canned fish, which is widely consumed for practical reasons, particularly in Europe and Northern America, especially in the pandemic and post pandemic era[17]. Two large previous case–control studies conducted in Italy found an inverse association between canned fish consumption and the risk of colorectal[18] and gastric cancer[19].

Based on these considerations, the present study aims to evaluate the association between fish and canned fish consumption and the risk of gastric cancer through the analysis of individual participant data from several case control studies conducted worldwide and participating in the 'Stomach cancer Pooling (StoP) Project'[20].

Materials and methods

The Stomach cancer Pooling (StoP) Project

The present study is based on the third release of the dataset of the StoP Project (http://stop-project.org/), a consortium of epidemiological studies of gastric cancer from different world areas[20]. Briefly, the StoP Project aimed at investigating the role of lifestyle, dietary and genetic determinants in the etiology of gastric cancer. Inclusion criteria for study participation are case–control study design (including nested case–control and case-cohort derived from cohort studies), and inclusion of at least 80 cases of incident, histologically confirmed gastric cancer (including both cardia and non-cardia location). The release 3.3 of the StoP Project includes 34 studies and a total of 13,121 cases and 31,420 controls. Questionnaires used for data collection and any other useful information, such as codebooks and labels, were provided from the participating studies. All data were harmonized according to a pre-specified format at the pooling center. Principal investigators of the studies included in the StoP Project agreed to participate in the consortium by providing a signed data transfer agreement and the original dataset (or part of it) to the pooling center. Study procedures were conducted in line with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants involved in the study.

The University of Milan Institutional Review Board provided the ethical approval for the StoP Project (reference 19/15 dated 01/04/2015).

Study population

Out of the 34 case–control studies participating to the StoP Project, 25 reported information about fish consumption and were included in the analyses: four from Italy (Italy 1, Italy 2, Italy 3, Italy 4)[21–24], one from Greece[25], one from Russia[26], one from Portugal[27], two from Spain (Spain 1, Spain 2)[28,29], two from Iran (Iran 1, Iran 2)[9,30], three from China (China 2, China 3, China 4)[31–33], one from Japan[34], one from Canada[35], three from United States of America (USA 1, USA 2, USA 3)[36–38], three from Mexico (Mexico 1, Mexico 2, Mexico 3)[39–41], three from Brazil (Brazil 1, Brazil 2, Brazil 3)[42–44], for a total of 10,431 cases and 24,903 controls. Information about canned fish consumption was collected in 7 of the 25 included studies (Italy 2, Italy 4, Russia, Portugal, Spain 2, Japan, USA 3)[22,24,26,27,29,34,38] for a total of 4525 cases and 8073 controls. Details of included studies are reported in Table S1.

Exposure variables

In each study, the dietary habits of subjects were assessed through food frequency questionnaires (FFQ), including information on usual diet in a period from one to five years before diagnosis (for cases), hospital admission (for hospital-based controls) or recruitment (for population-based controls). Table S2 reports the types of fish and the portion size considered by each study. All fish preparations were included in the analyses and total fish consumption was obtained summing up the frequency of consumption of each type of fish considered in the individual questionnaires. In the FFQs, the frequency of fish consumption was expressed as number of portions per year, month, week or days. All frequencies were harmonized to the average number of servings per week (s/w). Occasional intake (no more than 3 times per month) was coded as 0.5 s/w. Study-specific frequencies of fish consumption were converted into grams/day, according to the information on portion size available in each questionnaire or to country specific nutritional guidelines.

Data analysis

Both a two-stage and a one-stage modeling approach were used to assess the association between fish consumption and the risk of gastric cancer.

Fish consumption was categorized into study-specific tertiles, based on the distribution among the controls or as a dichotomic variable (< 1 s/w and ≥ 1 s/w). Fish intake was also analyzed as a continuous variable (grams/day).

For the two-stage approach, at the first stage the association between fish consumption and gastric cancer risk was assessed by estimating for each study the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) using multivariable unconditional logistic regression models. The models included terms for age (categorized in decennia), sex, social class (categorized as low, intermediate, high, as defined in each original study based on education, income and/or occupation), smoking habits (categorized as never smoker, former smoker, current smoker low, current smoker intermediate and current smoker high), center (for multicentric studies) and when available race/ethnicity (categorized as White, Hispanic/Latino, Black/African American, other). In the second stage, to account for anticipated heterogeneity, pooled effect estimates were computed using a random-effect model, which incorporates both within- and between- study variability[45]. Heterogeneity between studies was evaluated using the Q test statistics and quantified using I^2, the proportion of total variation contributed by between-study variance[46].

In one-stage analysis, generalized linear mixed effect models with logistic link function and random intercept for each study were used to compute the ORs and corresponding 95% CIs. Five models were fit. Model 1 included terms for age groups and sex. Model 2 included age groups, sex and social class. Model 3 included age groups, sex, social class and smoking habits. Model 4 included age groups, sex, social class, smoking habits and alcohol intake. Model 5 included age groups, sex, social class, smoking habits, alcohol and fruit and vegetables intake.

Missing values for confounding variables were imputed with the most frequent categories, according to case/control and sex, when the proportion of missing values was less than 2.5% of each study sample; otherwise, missing values were considered as a separate category. When specific covariates (e.g. alcohol consumption) were not collected within a study, these studies were excluded from the models including that covariate.

Sensitivity analyses were conducted to investigate the robustness of the results by further adjusting regression models for body mass index (BMI), energy intake, family history of gastric cancer and HP infection (one by one). Furthermore, we assessed the influence of individual studies by removing one study at a time and recalculating the pooled ORs from two-stage approach.

Heterogeneity was investigated in stratified analyses by geographic area, age, sex, social class, smoking habits, alcohol consumption, cancer site, family history of gastric cancer, HP infection, energy intake and fruit and vegetables intake. To further discern source of heterogeneity of potential influencing factor, we carried out sub-group meta-analyses, according to the type of fish (shellfish), cooking (fried fish) and preservation (salted, smoked and dried) methods, being this specific information available in the FFQs of an adequate number of studies ($N \geq 5$).

The analyses were conducted using SAS software 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.1 with *meta* package added.

Results

The characteristics of the 10,431 gastric cases and 24,903 controls included in the present analysis is reported in Table 1. The majority of cases and controls were from European studies (40.9% and 42.2%), followed by North American studies (29.4% and 36.1%). Two-thirds of gastric cancer cases were males (65.4%), compared to less than 60% of controls. Cases were also slightly older (median age 65 years, interquartile range (IQR): 57–72) than controls (median age 63 years, IQR: 52–71), and more frequently of lower social class (48.5% vs 36.9%). They had more frequently a history of gastric cancer in first degree relatives (8.7% vs 3.6%) and intermediate-high alcohol consumption (35.9% vs 29.3%).

Fish consumption

Information on fish consumption was available for 9865 cases and 23,495 controls.

Table 2 provides the pooled ORs and the corresponding 95% CIs of gastric cancer according to fish consumption. Fish intake was lower among cases than controls (≥ 1 s/w: 61.7% vs 64.7%). Our results suggest an overall no association among fish consumption and risk of gastric cancer: pooled ORs were 0.88 (95% CI 0.78–0.99) for the intermediate, and 1.04 (95% CI 0.89–1.22) for the highest tertile, compared to the lowest

Variables	Cases		Controls	
	N	%	N	%
Total	10,431		24,903	
Study center (Reference)				
Europe	4269	40.9	10,504	42.2
Italy 1	769	7.4	2081	8.4
Italy 2	230	2.2	547	2.2
Italy 3	160	1.5	444	1.8
Italy 4	1016	9.7	1159	4.6
Greece	110	1.1	100	0.4
Russia	450	4.3	611	2.5
Portugal	692	6.6	1667	6.7
Spain1	441	4.2	3440	13.8
Spain 2	401	3.8	455	1.8
Asia	1706	16.4	2558	10.3
Iran 1	217	2.1	394	1.6
Iran 2	286	2.7	304	1.2
China 2	206	2.0	415	1.7
China 3	711	6.8	711	2.9
China 4	133	1.3	431	1.7
Japan 3	153	1.5	303	1.2
Northern America	3067	29.4	8994	36.1
Canada	1182	11.3	5033	20.2
USA 1	132	1.3	132	0.5
USA 2	170	1.6	498	2.0
USA 3	1583	15.2	3331	13.4
Central-South America	1389	13.3	2847	11.4
Mexico 1	248	2.4	478	1.9
Mexico 2	220	2.1	752	3.0
Mexico 3	234	2.2	468	1.9
Brazil 1	226	2.2	226	0.9
Brazil 2	93	0.9	186	0.7
Brazil 3	368	3.6	737	3.0
Age at diagnosis/interview, years, median (IQR range)	65 (57–72)		63 (52–71)	
Age groups				
< 40	368	3.5	1835	7.4
40–49	931	8.9	3249	13.1
50–59	1980	19.1	4811	19.3
60–69	3560	34.1	7815	31.4
70–79	3100	29.7	6240	25.0
≥ 80	492	4.7	953	3.8
Sex				
Male	6818	65.4	14,409	57.9
Female	3613	34.6	10,494	42.1
Race/Ethnic group□				
White	4484	43.0	13,733	55.2
Black/African American	143	1.4	252	1.0
Asian	542	5.2	983	3.9
Hyspanic/Latinos	104	1.0	146	0.6
Other	181	1.7	261	1.1
Missing	4977	47.7	9528	38.2
Social class				
Low	5058	48.5	9185	36.9
Intermediate	3443	33.0	8905	35.8
High	1660	15.9	6201	24.9
Missing	270	2.6	612	2.4
Tumor site cases				
Continued				

Variables	Cases		Controls	
	N	%	N	%
Cardia	1780	17.1		
Fundus of stomach	182	1.7		
Body of stomach	701	6.7		
Pyloric antrum	1010	9.7		
Pylorus	96	0.9		
Lesser curvature of stomach	276	2.6		
Greater curvature of stomach	133	1.3		
Overlapping sites of stomach	311	3.0		
Stomach unspecified	2096	20.1		
Non-cardia, unspecified	2281	21.9		
Missing	1565	15.0		
Diagnosis of controls				
Traumas/sprains			1243	5.0
Other orthopedic problems			738	3.0
Acute surgical condition			566	2.3
Ophthalmology			346	1.4
ORL			82	0.3
Other conditions			893	3.6
Missing			21,035	84.4
Smoking habits				
Never smoked	4248	40.7	11,191	44.9
Former smoker	3369	32.3	7654	30.8
Current smoker low	644	6.2	1904	7.6
Current smoker intermediate	972	9.3	2078	8.3
Current smoker high	795	7.6	1486	6.0
Missing	403	3.9	590	2.4
Alcohol, Overall consumption (gr/day)*				
Never	2758	26.4	7059	28.4
Low (≤ 12)	2401	23.0	7536	30.3
Intermediate (> 12 and ≤ 47)	2456	23.6	5108	20.5
High (> 47)	1283	12.3	2200	8.8
Missing	1533	14.7	3000	12.0
History of stomach cancer in first degree relatives†				
No	4305	41.3	11,104	44.6
Yes	909	8.7	901	3.6
Missing	5217	50.0	12,898	51.8
Helicobacter test‡				
Negative	883	8.5	1716	6.9
Positive	1935	18.5	5155	20.7
Uncertain	121	1.2	67	0.3
Missing	7492	71.8	17,965	72.1
Vegetables and fruit intake∫				
Low	3181	30.5	6914	27.8
Intermediate	3254	31.2	7807	31.3
High	3401	32.6	8441	33.9
Missing	595	5.7	1741	7.0
Continued				

Variables	Cases		Controls	
	N	%	N	%
Energy intake, KCAL/day[¥]				
Low	2091	20.1	4726	19.0
Intermediate	2229	21.4	4863	19.5
High	2449	23.5	4716	18.9
Missing	3662	35.0	10,598	42.6

Table 1. Distribution of gastric cancer cases and controls according to study center, sex, age, and other selected covariates. IQR: Interquartile Range; USA: United States of America. [☐]Variable not collected for studies: Italy 1, Italy 3, Italy 4, Greece, China 2, Iran 1, China 3, China 4, Portugal, Mexico 1, Mexico 2, Mexico 3, Japan 3. *Variable not collected for studies: Iran 2, China 3 and China 4. [†]Variable not collected for studies: Canada, China 3, Mexico 1, Mexico 2, Mexico 3, USA 3. [‡] Variable not collected for studies: Italy 1, Italy 2, Italy 4, Greece, Canada, China 3, USA1, Mexico 2, USA 2, USA 3. [∫]Variable not collected for studies: China 4, Mexico 3. [$] Variable not collected for studies: Italy 4, Greece, China 3. [¥] Variable not collected for studies: Italy 1, Italy 3, Canada, China 2, Iran 1, China 4, USA 1, Brazil 1, Brazil 2, Brazil 3.

	Cases		Controls		
	N	%	N	%	OR (CI 95%)[1]
Fish consumption	9865		23,495		
Tertiles					
Never or low	3689	37.4	8673	36.9	1.00
Intermediate	3140	32.1	7766	33.1	0.88 (0.78–0.99)
High	3036	30.5	7056	30.0	1.04 (0.89–1.22)
Dichotomic					
Never or less than 1 serving/week	3773	38.3	8302	35.3	1.00
At least 1 serving/week	6092	61.7	15,193	64.7	0.99 (0.86–1.13)
Continuous					
10 g/day increment					1.01 (0.99–1.02)
Canned fish consumption	4459		8001		
Tertiles					
Never or low	1901	42.6	3521	44.0	1.00
Intermediate	1221	27.4	2075	25.9	0.89 (0.69–1.16)
High	1337	30.0	2405	30.1	0.96 (0.88–1.05)
Dichotomic					
Never or less than 1 serving/week	3483	78.1	6005	75.1	1.00
At least 1 serving/week	976	21.9	1996	24.9	0.96 (0.82–1.13)
Continuous					
10 g/day increment					1.03 (1.00-1.05)

Table 2. Distribution of gastric cancer cases and controls according to fish and canned fish consumption and Odds Ratios and corresponding 95% CIs from the two-stage analysis. [1]Pooled ORs were computed using random-effects models. Study specific ORs were adjusted, when available for age, sex, race/ethnic group, social class, smoking habits and study center for multicentric studies.

tertile, showing substantial heterogeneity across studies (I^2: 65.7% and I^2: 78.3% respectively). No association as well emerged when fish intake was analyzed as continuous variable. When removing one study at a time, the ORs remains almost stable varying between 0.87 (95% CI 0.77–0.99) and 0.99 (95% CI 0.85–1.15) for the intermediate vs lowest tertile, and between 0.88 (95% CI 0.78–0.99) and 1.07 (95% CI 0.92–1.24) for the highest vs the lowest tertile, indicating that no study significantly influenced the general results.

Figure 1 reports the study-specific and pooled ORs for fish consumption as dichotomous variable (≥ 1 vs < 1 s/w) and risk of gastric cancer from the two-stage analysis. Four studies (Portugal, China 2, China 4, Iran 1)[9,27,31,33] found an inverse association, with a variable effect size, ORs ranging from 0.50 to 0.30. Instead, five studies (Italy 4, Canada, USA 2, Mexico 3, Brazil 3)[24,35,37,41,44] found an increased risk of gastric cancer, with ORs ranging from 1.16 to 3.45 among individuals consuming ≥ 1 s/w. The remaining 16 studies (Italy 1, Italy 2, Italy 3, Greece, Russia, Spain 1, Spain 2, China 3, Iran 2, Japan 3, USA 1, USA 3, Mexico 1, Mexico 2, Brazil 1, Brazil 2)[21–23,25,26,28–30,32,34,36,38–40,42,43] did not find a significant association between fish consumption and risk of gastric cancer. Among those, 5 studies (Italy 2, Spain 1, USA 3, Mexico 2, Brazil 1)[22,28,38,40,42] found null association

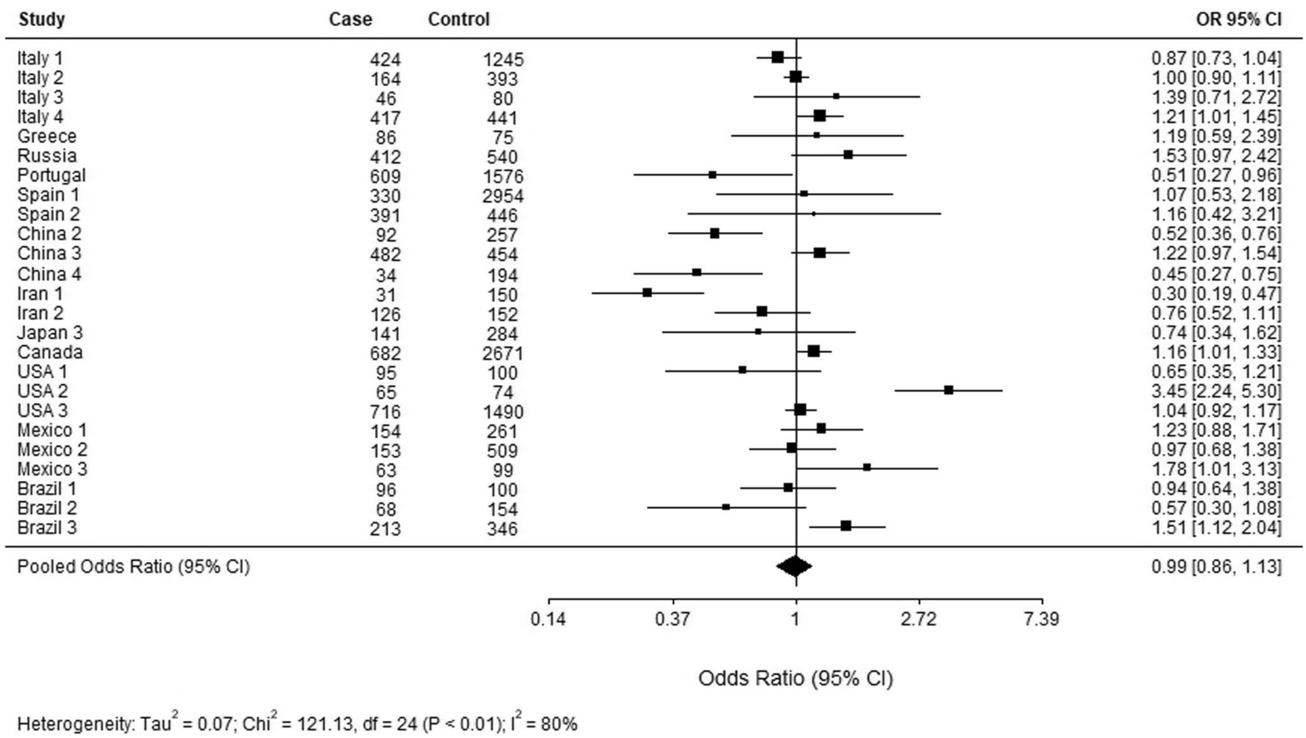

Fig. 1. Study-specific and pooled odds ratios and corresponding 95% confidence intervals of gastric cancer risk for fish consumption (≥1 serving/week vs <1 serving/week).

with ORs ranging from 0.94 to 1.07. The pooled OR for ≥ 1 serving/week vs < 1 serving/week was 0.99 (95% CI 0.86–1.13, I^2 = 80%), indicating an overall null association.

Table 3 gives the ORs and 95% CIs from the one-stage analysis. These results were similar in all the models when adjusting for an increasing number of risk factors. Moreover, they were consistent with those from the two-stage analysis with ORs further shrinking versus the null (OR = 0.93, 95% CI 0.87–0.99 for the intermediate and OR = 1.05, 95% CI 0.99–1.12 for the highest tertile vs the lowest), reinforcing the main conclusion of the lack of association. Even, when fish consumption was analyzed as a continuous variable the ORs were overlapping to those pointed out from two-stage analysis.

Canned fish consumption

Out of the 25 studies included, seven (Italy 2, Italy 4, Russia, Portugal, Spain 2, Japan, USA 3)[22,24,26,27,29,34,38] collected information on canned fish for a total of 4525 cases and 8073. The distribution of sex, age and other selected characteristics in cases and control was similar as that observed in studies on total fish (Table S3). Information about canned fish consumption was available for 4459 cases and 8001 controls. Canned fish consumption was lower among cases than controls (≥ 1 s/w: 21.9% vs 24.9%) (Table 2).

When comparing tertiles of consumption, the pooled ORs were 0.89 (95% CI 0.69–1.16), for the intermediate and 0.96 (95% CI 0.88–1.05) for the highest, compared to the lowest tertile (Table 2) with substantial heterogeneity only in the first comparison (I^2: 69.5% and I^2: 0% respectively). When leaving out one study at a time, the ORs remains almost stable varying between 0.82 (95% CI 0.65–1.05) and 1.00 (95% CI 0.86–1.16) for the intermediate, and between 0.94 (95% CI 0.86–1.03) and 0.98 (95% CI 0.89–1.07) for the highest vs the lowest tertile, so that no study significantly affected the results.

Figure 2 reports the study-specific and pooled ORs for canned fish consumption as dichotomous variable (≥ 1 vs < 1 s/w) and risk of gastric cancer. In three studies an OR lower than one was found (Italy 2, Italy 4, Portugal)[22,24,27], suggesting that canned fish consumption was associated with a lower risk of gastric cancer, although it reached statistical significance only in two of them (Italy 2, Portugal) reporting a modest effect[22,27]. One study (USA 3)[38] reported an OR close to 1 showing a null association, while three studies reported ORs higher than one (Russia, Spain 2, Japan, USA 3)[26,29,34,38], thus highlighting an increased risk of gastric cancer but with a weak effect, not statistically significant. The pooled OR was 0.96 (95% CI 0.82–1.13) with a moderate heterogeneity (I^2 = 59.3%).

Table 3 reported the ORs and 95% CIs from the one-stage analysis. No association was found between consumption of canned fish and the risk of gastric cancer. The OR for the intermediate consumption was 0.91 (95% CI 0.81–1.03) and that for the highest was 0.98 (95% CI 0.90–1.06) compared to the lowest tertile in the fully adjusted model.

	Cases		Controls						
	N	%	N	%	OR (CI 95%)[1]	OR (CI 95%)[2]	OR (CI 95%)[3]	OR (CI 95%)[4]	OR (CI 95%)[5]
Fish consumption	9865		23,495						
Tertiles									
No or Low	3689	37.4	8673	36.9	1.00	1.00	1.00	1.00	1.00
Intermediate	3140	31.8	7766	33.1	0.89 (0.84–0.95)	0.92 (0.86–0.97)	0.91 (0.86–0.97)	0.91 (0.86–0.97)	0.93 (0.87–0.99)
High	3036	30.8	7056	30.0	1.01 (0.95–1.07)	1.05 (0.99–1.11)	1.04 (0.98–1.11)	1.03 (0.96–1.09)	1.05 (0.99–1.12)
Dichotomic									
Never or less than 1 serving/week	3773	38.3	8302	35.3	1.00	1.00	1.00	1.00	1.00
At least 1 serving/week	6092	61.7	15,193	64.7	1.02 (0.97–1.08)	1.06 (1.00–1.12)	1.05 (0.99–1.11)	1.06 (1.00–1.13)	1.08 (1.02–1.15)
Continuous									
10 g/day increment					1.00 (0.99–1.01)	1.00 (1.00–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (1.00–1.01)
Canned fish consumption	4459		8001						
Tertiles									
No or Low	1901	42.6	3521	44.0	1.00	1.00	1.00	1.00	1.00
Intermediate	1221	27.4	2075	25.9	0.89 (0.79–1.00)	0.90 (0.80–1.01)	0.90 (0.80–1.02)	0.90 (0.80–1.01)	0.91 (0.81–1.03)
High	1337	30.0	2405	30.1	0.94 (0.87–1.03)	0.96 (0.88–1.05)	0.96 (0.88–1.04)	0.95 (0.87–1.04)	0.98 (0.90–1.06)
Dichotomic									
Never or less than 1 serving/week	3483	78.1	6005	75.1	1.00	1.00	1.00	1.00	1.00
At least 1 serving/week	976	21.9	1996	24.9	0.94 (0.86–1.04)	0.96 (0.88–1.06)	0.96 (0.87–1.05)	0.95 (0.86–1.04)	0.97 (0.89–1.07)
Continuous									
10 g/day increment					1.03 (0.98–1.08)	1.03 (0.98–1.08)	1.03 (0.98–1.08)	1.03 (0.98–1.08)	1.04 (0.99–1.10)

Table 3. Distribution of gastric cancer cases and controls according to fish and canned fish consumption and Odds Ratios and corresponding 95% CIs from the one-stage analysis. [1]Adjusted for age groups and sex (Fish N = 33,360 Canned fish N = 12,460). [2]Adjusted for age groups, sex and social class (Fish N = 33,360 Canned fish N = 12,460). [3]Adjusted for age groups, sex, social class, smoking habits (Fish N = 33,360 Canned fish N = 12,460). [4]Adjusted for age groups, sex, social class, smoking habits, alcohol intake (Fish N = 30,950 Canned fish N = 12,460) excluded studies: Iran 2, China 3, China 4. [5]Adjusted for age groups, sex, social class, smoking habits, alcohol intake, fruit and vegetables intake (Fish N = 30,671 Canned fish N = 12,460) excluded studies: Iran 2, China 3, China 4, Mexico 3.

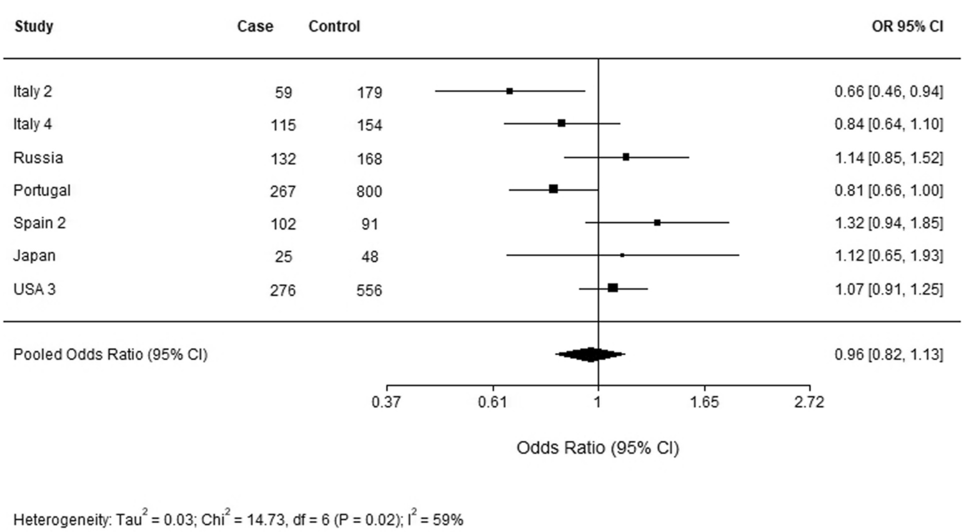

Fig. 2. Study-specific and pooled odds ratios and corresponding 95% confidence intervals of gastric cancer risk for canned fish consumption (≥1 serving/week vs <1 serving/week).

Sensitivity analyses

Tables S4–S7, in the supplementary materials, report the results of sensitivity analyses conducted in studies collecting information about BMI, energy intake, family history of gastric cancer and HP test, respectively.

When adjusting for BMI (Italy 1, Italy 2, Italy 4, Greece, Canada, China 2, Iran 1, Iran 2, China 3, USA 1, Portugal, Japan 3, USA 2, USA 3, Brazil 3)[9,21,22,24,25,27,30–32,34–38,44], and for energy intake (Italy 2, Italy 4, Greece, Russia, Iran 2, China 3, Portugal, Spain 2, Mexico 1, Mexico 2, Mexico 3, Japan 3, USA 2, USA 3)[22,24–27,29,30,32,34,37–41] results remain almost unchanged both for fish and canned fish consumption (Tables S4 and S5).

After adjusting for family history of GC (Italy 1, Italy 2, China 2, Iran 1, Iran 2, China 4, USA 1, Spain 1, Brazil 1, Brazil 2, Japan 3, USA 2)[9,21,22,28,30,31,33,34,36,37,42,43] fish consumption was associated to lower risk of gastric cancer, with an increasing trend according to fish intake (OR = 0.82, 95% CI 0.74–0.91 for intermediate; and OR = 0.78, 95% CI 0.69–0.87 for high intake compared to the lowest intake) (Table S6). After adjusting for HP infection (Iran 1, Japan 3, Mexico 1, Brazil 1, Brazil 2)[9,34,39,42,43] fish consumption was still associated to lower risk of gastric cancer (OR = 0.72, 95% CI 0.60–0.88 for > 1 vs < 1 s/w), but no trend was highlighted (Table S7). On the contrary, not conclusive results were obtained for canned fish consumption in both analyses (Tables S6 and S7).

Stratified and sub-group analyses

When analyzing fish consumption according to geographic area, an inverse association between fish consumption and risk of gastric cancer was found in Asian studies, with ORs of 0.81 (95% CI 0.69–0.94) for intermediate and 0.75 (95% CI 0.63–0.89) for high fish intake. An increased risk of gastric cancer was found for high fish intake in studies from Central-South America (OR 1.49, 95% CI 1.25–1.78).

The association of fish and canned fish consumption with gastric cancer risk was also analyzed across strata of sociodemographic, lifestyle and clinical variables, according to one-stage analysis (Tables S8 and S9). There was no evidence for interaction among risk factors and fish or canned fish consumption.

Results from sub-group analyses according to type of fish, cooking and preservation methods are showed in the supplementary Tables S10 to S12. Overall, no association was found between shellfish and gastric cancer, with negligible differences among geographic areas (Table S10). No association was found between salted/smoked fish with the risk of gastric cancer (Table S11), with results from one-stage and two-stage analysis providing consistent findings and not appreciable differences among geographic areas (not shown), although in two studies from Asia (Iran1 and Japan3)[9,34] the highest consumption of salted/smoked fish was associated with a reduced risk of gastric cancer with respect to the lowest (OR = 0.63, 95% CI 0.43–0.92). No study from South-America were included, due to the very low consumption of this kind of fish. On the contrary, high consumption of fried fish was associated with an increased risk of gastric cancer, although with weak effect size (OR = 1.18, 95% CI 1.04–1.33) (Table S12), with unchanged results from one-stage and two-stage approaches. This association was stronger, and mainly driven by two studies from North America (USA1 and USA3)[36,38]. In South America, a strong association has also been highlighted in the only one study (Brazil3)[44] that reported this information, but it was excluded due to the high number of missing. No study from Asian countries reported this item.

Discussion

This pooled analysis is one of the largest ever conducted investigating the association of fish consumption and gastric cancer. It found no overall association between fish and canned fish consumption and gastric cancer risk, although geographical differences have been highlighted with an inverse association in Asia and a positive one in Central-South America. The estimates were consistent between one stage and two stage approaches and were not modified by adjustment for the major potential confounding factors. Likewise, analyses in strata of sociodemographic characteristics and lifestyle habits (smoking and alcohol intake) did not suggest any significant interaction. Only high fried fish consumption was associated with increased risk of gastric cancer.

Previous studies assessing the association between fish consumption and gastric cancer found inconsistent results. Some of these found an inverse association, with a reduction of the risk ranging from about 30% up to 60%[7–9]. In a review of 15 case–control and two cohort studies, Wu et al. (2011) found a non-significant reduced risk (OR = 0.87, 95% CI 0.81–1.07) for high fish consumption[13]. The meta-analysis of Fang et al. (2015) that investigate association among several dietary factors and risk of gastric cancer, based on seventy-six prospective cohort studies, found no association among total fish consumption and gastric cancer (OR = 1.08, 95% CI 0.92–1.26) in ten studies which included this exposure[47]. Similarly, a meta-analysis of cohort studies of gastrointestinal cancers and fish consumption, including five studies of gastric cancer, reported a relative risk of 1.04 (95% CI 0.97–1.10) for 20 g/day increment of fish consumption[48].

Other than type of food, also cooking and preservation methods may be linked to increased risk of developing cancer and gastric cancer, particularly due to direct contact with gastric mucosa.

Concern was raised by several observations in relationship to salted fish, given its high content of salt which is a recognised risk factor for gastric cancer. The above cited meta-analysis of Fang et al. in 2015 found a direct association of salted fish with gastric cancer risk in 11 studies[47]. This finding was confirmed by a recent umbrella review including 49 studies[10]. However, a meta-analysis of cohort studies showed no association of salted fish consumption with gastric cancer risk and mortality[14]. Even our findings confirmed no association between salted and smoked fish consumption and gastric cancer, with no geographical differences, but a limited number of studies was included. Previous results of a large meta-analysis from the same StoP consortium found an increased risk of gastric cancer among subjects with high consumption of salted and salt preserved foods and/or salty taste preferences, though the association was less robust with total sodium intake[49].

Several mechanisms have been postulated in epidemiological studies regarding the association of salted fish and gastric cancer. Firstly, excess salt may act as an irritant to the gastric mucosa, causing atrophic gastritis, increased DNA synthesis, and cell proliferation sequentially increasing susceptibility to mutagenesis or carcinogenesis[50]. Vulnerability to gastric carcinogenesis is in turn exacerbated through a synergistic effect with Helicobacter Pylori infection. HP infection is a major risk factor for gastric cancer[50,51]. Finally, the high-salt intakes can lead to the formation of N-nitroso compounds (NOCs) in the stomach which along with sodium chloride itself are known to be carcinogenic and have been implicated in the development of gastric cancer[52]. Although tinned fish can indeed be high in salt, especially if it's preserved in brine or a salty solution. Interestingly, in our study, overall findings showed that canned fish was not associated to increased risk of stomach cancer. The processing methods used for tinned fish, such as canning and preservation techniques, might mitigate some of the potential risks associated with salt intake. Additionally, many tinned fish products are rich in beneficial nutrients like omega-3 fatty acids, which have been associated with various health benefits, including potential protective effects against certain types of cancer, including gastric cancer[53].

On the contrary, our study found that high fried fish intake is a risk factor for gastric cancer, also after adjusting for several sociodemographic and lifestyle risk factors, and results were consistent among one-stage and two-stage analyses, with only limited heterogeneity. Several epidemiological studies have already reported a positive association between food cooked at high temperatures (by grill, barbecue, or frying, etc.) and the risk of colorectal cancer, however less evidence exists for the gastric cancer. A meta-analysis of 18 studies showed a significant positive association between high level of fried food intake and the risk of gastric cancer (OR = 1.52, 95% CI 1.23–1.87)[54]. Another review reported several studies, supporting that frequent use of cooking oil (such as the case of deep-oil-fried food and street food) was a risk factor for gastric cancer, but using olive oil for frying can protect against gastric cancer[55]. Zhang explained that nitrate converts to nitrite during metabolic processes, and nitrite has been implicated in the development of several cancers. The cooking process modulates the nitrate contents in foods. While boiling process and other cooking methods reduced the nitrate contents, the frying process increased it, so when protein-rich foods and vegetables high in vitamins, minerals, antioxidants and nitrate are fried can increase cancer risk[54].

Geographical differences were highlighted in our work. In particular, in the Asian region, fish consumption was inversely associated with gastric cancer. Limited literature can be found related to this finding. In the above cited meta-analysis of Wu et al., the authors reported an inverse association among fish consumption and gastric cancer in 8 studies from Asia, although the modest effect found was not statistically significant (OR = 0.80, 95% CI 0.54–1.16)[13]. However, we may attempt to contextualize this result. Although, deep-oil-fried foods, that is confirmed to be a risk factor for gastric cancer, can be found in many Asian culinary traditions, its consumption is supposed to be limited. Indeed, such item was not present in any FFQ of the six studies of the three Asian countries included in the StoP consortium[9,30–34].

Moreover, when adjusting for family history or for HP infection, fish intake turned out to be inversely associated to gastric cancer risk. It can be noted that half of the studies, included in our sensitivity analyses, where this information was available came from Asian countries, as well. Indeed, in Asia, high rates of familiar clustering and high prevalence of HP among adults are known[56–58].

Limitations and strengths

Our study has limitations and strengths. A major strength is the large sample size. This study is among the largest ever studied in relation to fish and canned fish intake and gastric cancer. StoP project represents a wide number of countries worldwide, thus giving insight into different fish consumption and overall dietary patterns.

Our study also has limitations. Firstly, our results showed in general a substantial heterogeneity. This heterogeneity can be related to several aspects. Firstly, the questionnaires included different items with a high variability of fish and fish preparations investigated across the studies. They ranged from just one question ("fish in general") to 19 different questions investigating kind of fish, cooking (e.g. grilled, broiled, boiled etc.) and preservation (e.g. salted, smoked, frozen, fresh) methods. We did an attempt to deeply investigate relationship between specific type of fish, cooking and preservation methods. However, the extreme variability in possible preparations forced researchers in the frame of the StoP consortium to jointly gather different cooking and preservation methods. So that, only a limited number of studies with specific data on way of cooking and preservation methods were available for these analyses. Heterogeneity could also be due to different portions size of fish consumption across studies. Secondly, the questionnaires referred to different time frames (recent consumption, rather than consumption in the past two or five years). Moreover, the studies were published in a time span of more than 30 years, therefore reflecting possible dietary habits and styles changing throughout the period.

Another limitation is that we could not include in our final model HP and family history, despite they were recognized risk factors, because they were only available for a subset of the studies. Indeed, on sensitivity analyses, in which we adjusted for family history and HP, consumption of fish, but not canned fish, appeared to have an inverse association with stomach cancer risk.

Conclusions

Given the high incidence and mortality of gastric cancer and the role of diet in predicting such risk[1], elucidating the effect of selected foods remains an important topic. Our results provide convincing evidence that fish and canned fish intake are not associated with gastric cancer. However, the high intake of fried fish is associated to an increased risk, suggesting the cooking methods could play a role as risk factors for stomach cancer.

Data availability

Request to use datasets should be made to the StoP Consortium Steering Committee (http://stop-project.org; stop.project@unimi.it). Further information is available from the corresponding author upon request.

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Author contributions

C.F., I.A., S.M, CLV and B.D. designed the study; I.A., S.M.: carried out statistical analysis.; C.P.: harmonized the data, as part of the Stomach Cancer Pooling (StoP) Project.; L.P., M.C.C., C.S.R., L.M.L., R.S., K.C.J., J.H., Z.F.Z., D.P., M.F., E.N., F.T., G.P.Y., N.L., S.M., L.LC., S.T., A.H., R.M., D.Z., D.M., J.V., S.GP., M.H.W., N.A., G.CV., M.P.C., E.DN., G.S.H., R.U.HR., M.P., F.P., L.M., A.L., P.L., M.LC., S.B., C.LV.: supplied the data, as part of the Stomach Cancer Pooling (StoP) Project.; C.F., I.A.: wrote the manuscript. All authors read and approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to C.F.

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