Fish consumption and cancer risk[1–3]

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ABSTRACT

Background: Although several studies have investigated the relation between fish consumption and the risk of cardiovascular diseases, less attention has been paid to the relation between fish consumption and cancer risk .

Objective: The relation between frequency of consumption of fish and risk of selected neoplasms was analyzed by using data from an integrated series of case-control studies conducted in northern Italy between 1983 and 1996.

Design: The overall data set included the following incident, histologically confirmed neoplasms: oral cavity and pharynx ($n = 181$), esophagus ($n = 316$), stomach ($n = 745$), colon ($n = 828$), rectum ($n = 498$), liver ($n = 428$), gallbladder ($n = 60$), pancreas ($n = 362$), larynx ($n = 242$), breast ($n = 3412$), endometrium ($n = 750$), ovary ($n = 971$), prostate ($n = 127$), bladder ($n = 431$), kidney ($n = 190$), thyroid ($n = 208$), Hodgkin disease ($n = 80$), non-Hodgkin lymphomas ($n = 200$), and multiple myelomas ($n = 120$). Control subjects were 7990 patients admitted for acute, nonneoplastic conditions unrelated to long-term modifications of diet. Odds ratios (ORs) were computed for subsequent levels of fish consumption compared with no or occasional consumption (<1 serving/wk) by using multiple logistic regression, including terms for several covariates.

Results: There was a consistent pattern of protection against the risk of digestive tract cancers with fish consumption: oral cavity and pharynx, OR = 0.5 for the highest compared with the lowest level of consumption; esophagus, OR = 0.6; stomach, OR = 0.7; colon, OR = 0.6; rectum, OR = 0.5; and pancreas, OR = 0.7. There were inverse trends in risk of larynx (OR = 0.7), endometrial (OR = 0.8), and ovarian (OR = 0.7) cancers and multiple myeloma (OR = 0.5). No pattern of cancer risk in relation to fish consumption was observed for cancers of the liver, gallbladder, breast, bladder, kidney, or thyroid or for lymphomas.

Conclusion: This study suggests that the consumption of even relatively small amounts of fish is a favorable indicator of the risk of several cancers, especially of the digestive tract. *Am J Clin Nutr* 1999;70:85–90.

KEY WORDS Fish consumption, diet, cancer risk, case-control study, humans, Italy

INTRODUCTION

A favorable pattern of decreasing risk related to high consumption of vegetables and fruit and low consumption of red meat and selected foods has been shown for several cancers (1, 2). Less attention, however, has been paid to the role of fish consumption in cancer risk. Some prospective studies have reported an inverse relation between fish consumption and cardiovascular disease (3–5), whereas other have not (6, 7). An inverse relation between total mortality and fish consumption, moreover, suggests that there may be an association between fish consumption and other noncardiac causes of death (8).

Ecologic studies have found inverse correlations between fish consumption and cancer incidence and mortality (9–12). In particular, an inverse correlation between fish consumption for most cancers was apparent in Italy (13). Inverse associations with the risk of various cancers—ie, oral cavity and pharynx (14), larynx (14), esophagus (15, 16), stomach (17), colorectal (18–20), pancreas (21), gallbladder (22), breast (23–25), ovary (26), bladder (27), kidney (28), and thyroid (29)—have been reported from case-control and cohort studies. A recent panel report concluded, based on a comprehensive review of epidemiologic studies, that fish consumption may possibly protect against cancers of the colon, rectum, and ovary (2). To provide information on this issue, we examined systematically the relation between fish consumption and the risk of various cancers by using data from an integrated series of case-control studies conducted in northern Italy.

SUBJECTS AND METHODS

The data were derived from a network of hospital-based case-control studies, the general designs of which were described previously (30). Briefly, recruitment of persons with various cancers and of the corresponding control subjects started between 1983 and 1985 and the present analysis is based on data collected before June 1996; for breast and colorectal cancer, only cases based on data collected until 1991 were included.

TABLE 1
Distribution of cases of selected cancers and of control subjects according to sex and age: Milan, Italy (1983–1996)

	Male				Female				
	<45 y	45–54 y	55–64 y	65–74 y	<45 y	45–54 y	55–64 y	65–74 y	Total
Oral cavity and pharynx	9	53	64	26	2	7	15	5	181
Esophagus	13	64	122	59	6	9	24	19	316
Stomach	37	103	165	151	29	56	104	100	745
Colon	34	74	152	163	41	78	143	143	828
Rectum	17	50	119	102	24	31	78	77	498
Liver	27	58	148	84	18	22	36	35	428
Gallbladder	3	4	12	8	2	7	8	16	60
Pancreas	16	62	87	64	8	22	49	54	362
Larynx	10	45	117	59	0	2	5	4	242
Breast	—	—	—	—	794	1034	951	633	3412
Endometrium	—	—	—	—	38	147	306	259	750
Ovary	—	—	—	—	200	305	312	154	971
Prostate	1	10	53	63	—	—	—	—	127
Bladder	7	43	159	152	4	6	25	35	431
Kidney	16	22	58	36	8	6	27	17	190
Thyroid	31	15	13	4	80	25	26	14	208
Hodgkin disease	23	9	11	6	20	5	5	1	80
Non-Hodgkin lymphomas	19	26	39	35	18	24	22	27	200
Multiple myeloma	3	12	21	25	5	12	10	32	120
Total	266	650	1340	1037	1297	1788	2146	1625	10 149
Control subjects	683	859	996	682	1089	1173	1403	1105	7990

Trained interviewers identified and questioned patients admitted to teaching and general hospitals in the area under surveillance for selected cancers and for a wide spectrum of other acute, nonneoplastic conditions. All interviews were conducted during the hospital stay. On average, <3% of eligible cases and control subjects refused to be interviewed. The same study design, criteria of enrollment of cases and control subjects, and interview setting were adopted for all the diseases studied, and all the questionnaires contained a basic structured section, including sociodemographic factors and general characteristics and habits (tobacco smoking and alcohol and coffee consumption). Furthermore, patients were asked to indicate the weekly frequency of consumption of selected indicator foods (for 14–37 items) during the year before cancer diagnosis or hospital admission (for control subjects). All questionnaires included the same item in reference to fish consumption, after the time frame was defined, thus making possible a combination of data from various studies in relation to this issue and major covariates of interest. The following question was asked: "During the year previous to the onset of your disease, which was your average weekly intake of fish?" The response recorded was the number of servings per week, including a code for <1 serving/wk. The reproducibility of the dietary section of the questionnaire was satisfactory (31).

The cases studied were patients younger than 75 y who were admitted to the National Cancer Institute and the Ospedale Maggiore of Milan (which includes the 4 largest teaching and general hospitals in the Milan area) with histologically confirmed incident (ie, diagnosed within the year before interview) cancers of the oral cavity and pharynx ($n = 181$), esophagus ($n = 316$), stomach ($n = 745$), colon ($n = 828$), rectum ($n = 498$), liver ($n = 428$), gallbladder ($n = 60$), pancreas ($n = 362$), larynx ($n = 242$), breast ($n = 3412$), endometrium ($n = 750$), ovary ($n = 971$), prostate ($n = 127$), bladder ($n = 431$), kidney ($n = 190$), and thyroid ($n = 208$); Hodgkin disease ($n = 80$); non-Hodgkin lymphomas ($n = 200$); and multiple myeloma ($n = 120$).

The control group included 7990 patients (3220 males and 4770 females) aged <75 y admitted for a wide spectrum of acute conditions in the same hospitals where cases were identified; no matching procedure was applied. Patients with malignant tumors, digestive tract diseases, or disorders related to alcohol consumption or tobacco smoking or that might have induced a long-term modification of diet were excluded. Control subjects were admitted for traumatic conditions (32%), nontraumatic orthopedic disorders (17%), acute surgical conditions (29%), and other miscellaneous diseases (22%), such as ear, nose, throat, skin, and dental disorders. The median age of the comparison group was 55 y and the distribution of cases and control subjects according to sex and age is given in **Table 1**.

Frequency of fish consumption was categorized into 3 levels: no or occasional consumption (<1 serving/wk), 1 serving/wk, and ≥2 servings/wk. Odds ratios (ORs) were computed for subsequent levels of fish consumption by using unconditional multiple logistic regression analysis, with no or occasional consumption as the referent category (32). Tests for trend for levels of fish consumption were based on the likelihood ratio test between the models with and without a linear term for fish consumption (32). Intake frequency was also introduced as a continuous variable to obtain an estimate of the OR of one average serving per week. Occasional consumption was coded as 0.5. All the models included terms for age, sex, area of residence, education, alcohol consumption, tobacco smoking, and body mass index. The study protocol was revised and approved by the ethical committees and directors of the hospitals involved, and participants gave informed consent.

RESULTS

The distribution of cases and multivariate ORs and 95% CIs of selected cancers according to the level of fish consumption are shown in **Table 2**. There was a consistent pattern of protection

against the following digestive tract cancers: oral cavity and pharynx, esophagus, stomach, colon, rectum, ovary, and pancreas. All of the trends in risk were significant, except for gallbladder, possibly because of the small number of cases for this site. There were significant inverse trends in risk of larynx and endometrial cancer and multiple myeloma. There were nonsignificant trends in risk of cancers of the gallbladder, prostate, kidney, and Hodgkin and non-Hodgkin lymphomas. No pattern of risk in relation to fish consumption was evident for breast, liver, bladder, and thyroid cancer. The pattern was similar when fish consumption was considered as a continuous variable (increment of 1 serving/wk).

The pattern of cancer risk in relation to fish consumption (≥1 serving/wk compared with no or occasional consumption) was examined further in separate strata of selected covariates. The pattern of protection against digestive tract cancers was consistent across age, sex, education, smoking, alcohol consumption, and body mass index strata (**Table 3**) and no appreciable effect modification or heterogeneity was found.

DISCUSSION

This study showed a consistent inverse relation between fish consumption and risk of gastrointestinal cancers. The strength of the association varied among sites, but it was consistent across the main covariates studied.

A detailed discussion of the biological mechanisms underlying the possible influence of fish consumption in cancer risk goes beyond the scope of this study. Animal studies indicate that essential fatty acid consumption may influence the risk of developing cancer. Fat from fish contains ≈20–25% saturated fatty acids, and fish and fish oil are a rich source of n–3 fatty acids and the fat-soluble vitamins A and D (33, 34). The n–3 fatty acids are important components of cell membranes (35) and appear to have antiinflammatory effects and inhibit in vitro the growth of colon, breast, and prostate cancers (36–43). Although our questionnaire did not distinguish between types of fish and hence data on n–3 fatty acid consumption were not available, good correlations between adipose fatty acid composition and food-frequency data have been reported (44, 45).

An inverse association between colon cancer and n–3 fatty acid consumption from fish has been reported in epidemiologic studies (18, 19, 46). Bartram et al (47) suggested that n−3 fatty acid consumption per se was less important than n−3 fatty acid consumption expressed as a proportion of total fat. Caygill and Hill (12), from an ecologic analysis of colorectal cancer mortality in 24 European countries, suggested that the apparent protective effect of fish and fish oil consumption was lower than that of fish or fish oil consumption as a proportion of animal fat or of animal minus fish or total fat.

There is little support for a protective effect of fish consumption against breast and prostate cancer risk (2). Although correlational studies have suggested an inverse association in terms of incidence and mortality (10, 12), most studies of breast cancer, including the Nurses' Health Study (48) and studies of large cohorts from New York (49) and Norway (23), showed no relation (50). With reference to prostate cancer, no apparent relation with fish consumption or n–3 fatty acid intake has been shown in published studies (50–52). Direct associations of fish intake and cancer risk have also been reported, but refer to specific circumstances. Exposure to salted fish, particularly as a weaning food, is an important correlate of risk of nasopharyngeal cancer in cer-

TABLE 2
Odds ratios and 95% CIs of selected cancers according to fish consumption: Milan, Italy (1983–1996)

| | Fish consumption (servings/wk) | | | Odds ratio (95% CI)[1] | | | |
| | | | | | | Continuous | |
	<1	1	≥2	1 Serving/wk	≥2 Servings/wk	(increment 1 serving/wk)	χ^2 (trend)
		n					
Oral cavity and pharynx	89	68	24	0.8 (0.6, 1.2)	0.5 (0.3, 0.9)	0.8 (0.7, 1.0)	6.8[2]
Esophagus	159	103	54	0.7 (0.5, 0.9)	0.6 (0.4, 0.9)	0.8 (0.7, 0.9)	10.2[2]
Stomach	341	271	133	0.8 (0.7, 1.0)	0.7 (0.5, 0.8)	0.8 (0.7, 0.9)	13.0[2]
Colon	404	278	146	0.7 (0.6, 0.8)	0.6 (0.5, 0.7)	0.8 (0.7, 0.9)	27.8[2]
Rectum	232	199	67	0.8 (0.7, 1.0)	0.5 (0.3, 0.6)	0.7 (0.7, 0.9)	24.8[2]
Liver	168	159	101	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	0.9 (0.8, 1.1)	0.1
Gallbladder	22	29	9	1.2 (0.7, 2.2)	0.6 (0.3, 1.4)	0.8 (0.6, 1.1)	0.6
Pancreas	174	116	72	0.7 (0.5, 0.9)	0.7 (0.5, 1.0)	0.9 (0.8, 1.0)	5.6[2]
Larynx	120	80	42	0.7 (0.5, 1.0)	0.7 (0.4, 1.0)	0.8 (0.7, 1.0)	5.5[2]
Breast	1230	1362	820	1.1 (0.9, 1.2)	1.0 (0.8, 1.1)	1.0 (0.9, 1.0)	0.1
Endometrium	352	227	170	0.6 (0.5, 0.8)	0.8 (0.6, 0.9)	0.9 (0.8, 1.0)	9.7[2]
Ovary	396	349	226	0.9 (0.7, 1.0)	0.7 (0.6, 0.9)	0.9 (0.8, 0.9)	9.3[2]
Prostate	54	53	20	1.0 (0.6, 1.4)	0.7 (0.4, 1.1)	0.8 (0.7, 1.0)	2.0
Bladder	153	165	113	1.1 (0.9, 1.4)	1.4 (1.0, 1.8)	1.0 (0.9, 1.1)	5.1[2]
Kidney	78	71	41	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)	1.0 (0.8, 1.1)	0.4
Thyroid	65	83	60	1.2 (0.8, 1.6)	1.1 (0.7, 1.6)	0.9 (0.8, 1.1)	0.2
Hodgkin disease	35	30	15	0.8 (0.5, 1.3)	0.7 (0.4, 1.4)	0.9 (0.7, 1.2)	1.1
Non-Hodgkin lymphoma	83	83	34	1.0 (0.8, 1.4)	0.7 (0.5, 1.1)	1.0 (1.0, 1.1)	1.1
Multiple myeloma	57	48	15	0.9 (0.6, 1.3)	0.5 (0.3, 0.9)	0.9 (0.7, 1.1)	4.2[2]
Control subjects	3045	3094	1849	—	—	—	—

[1] Estimates from multiple logistic regression equations including terms, when required, for age, sex, area of residence, education, smoking, alcohol consumption, and body mass index. The reference category is no or occasional consumption of fish (<1 serving/wk).
[2] $P < 0.05$.

TABLE 3
Odds ratios of selected cancers according to fish consumption (< 1 serving/wk compared with ≥ 1 serving/wk) and selected covariates: Milan, Italy (1983–1996)[1]

	Age				Sex		Education		Tobacco smoking		Alcohol consumption		Body mass index (kg/m^2)	
	<45 y	45–54 y	55–64 y	65–74 y	Male	Female	<7 y	≥7 y	No	Yes	No	Yes	<25 y	≥25 y
Oral cavity and pharynx	0.8	0.7	0.8	0.7	0.8[2]	0.8	0.8[2]	0.9	0.9	0.8[2]	0.9	0.8[2]	0.9	0.6[2]
Esophagus	0.4	0.6	0.6[2]	0.7	0.6[2]	0.8	0.6[2]	0.7[2]	0.4[2]	0.7[2]	0.6	0.6[2]	0.7[2]	0.5[2]
Stomach	0.9	0.7[2]	0.8[2]	0.7[2]	0.7[2]	0.8[2]	0.7[2]	0.8	0.8[2]	0.8	0.8	0.7[2]	0.8[2]	0.6[2]
Colon	0.5[2]	0.8	0.5[2]	0.8	0.7[2]	0.6	0.6[2]	0.6[2]	0.6[2]	0.7[2]	0.8	0.6[2]	0.7[2]	0.7[2]
Rectum	0.9	0.7	0.7[2]	0.7[2]	0.7[2]	0.8	0.7[2]	0.8	0.8[2]	0.7[2]	0.7	0.7[2]	0.7[2]	0.8
Liver	1.0	0.8	1.1	1.0	0.9	1.2	1.0	1.0	1.0	1.1	1.8[2]	0.8	1.0	1.0
Gallbladder	—	1.1	0.9	0.8	1.1	1.0	1.1	0.9	1.1	1.5	0.9	1.0	0.9	1.2
Pancreas	0.5	0.8	0.7[2]	0.7[2]	0.6[2]	0.8	0.5[2]	0.9	0.8	0.7	0.6[2]	0.7[2]	0.7[2]	0.6[2]
Larynx	—	0.7	0.6[2]	0.7	0.7[2]	—[3]	0.6[2]	0.7	—[3]	0.6[2]	—[3]	0.7[2]	0.8	0.5[2]
Breast	1.2	1.2	0.9	1.0	—	1.0	1.0	1.2[2]	1.0	1.1	1.1	1.0	1.1	0.9
Endometrium	1.3	0.7	0.7[2]	0.6[2]	—	0.7	0.7[2]	0.8	0.7[2]	0.6[2]	1.0	0.6[2]	0.7[2]	0.7[2]
Ovary	1.0	1.0	0.8[2]	0.7	—	0.9	0.8[2]	0.9	0.9	0.9	1.0	0.8[2]	0.9	0.8
Prostate	—	0.7	0.9	0.9	0.9	—	0.8	0.9	0.6	0.8	1.4	0.8	1.0	0.8
Bladder	1.0	1.2	1.2	1.1	1.3[2]	0.7	1.0	1.3	1.4	1.2	1.1	1.2	1.0	1.4[2]
Kidney	1.4	1.0	0.8	0.8	1.0	0.7	0.8	0.9	0.9	0.9	1.0	0.9	0.8	1.1
Thyroid	1.2	1.3	2.2[2]	0.9	1.4	1.2	1.6	1.1	1.4	1.1	1.1	1.4	1.3	1.3
Hodgkin disease	0.6	0.8	1.0	0.9	0.9	0.6	0.9	0.7	0.8	0.6	—[3]	1.2	1.1	1.3
Non-Hodgkin lymphoma	1.2	1.1	1.9	0.7	0.8	1.0	0.9	0.9	1.1	0.8	0.8	0.9	0.8	1.0
Multiple myeloma	0.9	1.0	0.5[2]	0.7	0.8	0.7	0.8	0.6	0.8	0.4[2]	1.0	0.6[2]	0.6[2]	0.9

[1] Values were derived by using multiple logistic regression equations including, when required, terms for age, sex, and area of residence.
[2] $P < 0.05$.
[3] Convergence not attained.

tain parts of China, but this effect is attributed to nitrosamines, bacterial mutagens, or genotoxic substances derived from an inefficient preservation process (53). A high intake of fish and seafood has also been suggested to increase the risk of thyroid cancer in Hawaii and Norway, but this increase, if real, may be specific to the thyroid and attributable to iodine excess in certain coastal populations (54). The present results, therefore, are in broad agreement with the available evidence on the issue.

With reference to possible limitations of this study, the potential confounding effect of several covariates—including education, body mass index, area of residence, alcohol consumption, and tobacco smoking—was controlled for in the analysis. Allowance for fruit and vegetable intakes did not materially modify the risk estimates. The results were consistent across the major identified covariates of interest as well as when different periods of recruitment for cases and control subjects were taken into account in the logistic regression models. Limitations of the food-frequency questionnaire pertaining to most cancer sites precluded the definition of a measure of total energy intake. However, allowance for total energy (55) was possible for gastric, colon, and rectal cancers and did not materially modify any of the risk estimates. Residual confounding cannot, however, be excluded because fish consumption could be a marker for a more favorable dietary pattern, a healthier lifestyle, or both.

With reference to possible selection bias, cases and control subjects were identified in the major teaching and general hospitals of the area under surveillance, and the participation of cases and control subjects was almost complete. Potential information bias was minimized by using similar interview settings; additionally, the questionnaire was tested for reproducibility (31) and there was no reason to assume different recalls of fish consumption on the basis of disease status. Although several dietary factors were consid-

ered, the food-frequency questionnaire contained a limited number of items and thus we cannot exclude that some other dietary factors associated with fish consumption could have accounted for the observed associations. However, indirect support for the existence of a real association between fish consumption and gastrointestinal cancers comes from the observation that such an inverse relation was neither systematically observed in all cancer sites nor with respect to other foods, such as meat, milk, and cereals (56).

In conclusion, the results of this study suggest that, in addition to the potential beneficial effect of fish consumption on cardiovascular disease risk (5), the intake of even relatively small amounts of fish is a favorable indicator of the risk of several digestive tract cancers, notably colon and rectal cancer, which are among the leading causes of cancer mortality in developed countries. ☘

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