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n-3 POLYUNSATURATED FATTY ACID INTAKE AND CANCER RISK IN ITALY AND SWITZERLAND

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Data from a series of case-control studies, conducted in Italy and Switzerland between 1991 and 2001, have been analyzed to evaluate the role of n-3 polyunsaturated fatty acid (PUFA) intake in the etiology of cancer of oral cavity and pharynx (736 cases, 1,772 controls), esophagus (395 cases, 1,066 controls), large bowel (1,394 colon, 886 rectum, 4,765 controls), breast (2,900 cases, 3,122 controls) and ovary (1,031 cases, 2,411 controls). Controls were patients admitted to hospital for acute, non-neoplastic conditions, unrelated to modifications in diet. The multivariate odds ratios (OR) for the highest quintile of n-3 PUFAs compared to the lowest one were 0.5 for oral and pharyngeal cancer, 0.5 for oesophageal cancer, 0.7 for colon cancer, 0.8 for rectal and breast cancer and 0.6 for ovarian cancer; the estimates and the trends in risk were significant for all cancer sites, excluding rectal and breast cancer. The estimates for an increase in n-3 PUFAs of 1 g/week were 0.70 for oral and pharyngeal cancer, 0.71 for oesophageal, 0.88 for colon, 0.91 for rectal, 0.90 for breast and 0.85 for ovarian cancer. All the estimates were statistically significant, excluding that for rectal cancer, and consistent across strata of age and gender. These results suggest that n-3 PUFAs decrease the risk of several cancers.

Key words: *breast cancer; cancer; case-control study; colorectal cancer; n-3 polyunsaturated fatty acid; oesophageal cancer; oral and pharyngeal cancer; ovarian cancer; risk factors*

Ecological studies have suggested inverse relations between fish and n-3 polyunsaturated fatty acid (PUFA) intake and the risk of cancer at several sites,[1–3] but the issue remains open to discussion.[4–6]

Fish and n-3 PUFA intake has been inversely associated with risk of cancer of the oral cavity and pharynx,[7] in most,[6,8–10] but not all studies[11] and in studies of cancer of the esophagus.[6,13–15] Data are inconclusive for colorectal cancer, with at least a cohort[16] and a case-control study[17] showing an inverse association with fish intake, and at least 3 case-control studies finding no relation.[18–20] At least 2 prospective studies, 1 in women[21] and 1 in men (U.S. Male Health Professionals),[22] and 2 case-control studies[6,23] found an inverse relation between colon cancer risk and fish intake, whereas 2 prospective studies showed no relation.[24,25] A case-control study on rectal cancer reported an inverse association with fish consumption.[6]

With reference to breast cancer, a prospective study on Norwegian women reported no relation with overall fish intake, but an inverse association with poached fish;[26] the Nurses' Health Study cohort found no relation between n-3 PUFAs from fish and breast cancer risk,[27] and a study on Swedish women found no association with fish intake.[28] Of 3 case-control studies, 1 from Spain found an inverse association with fish intake,[29] 1 from the U.S. reported an inverse association only in postmenopausal women,[30] and 1 from Italy found no relation.[6] A nested case-control study of the New York University Women's Health Study found that although total PUFAs (n-3 and n-6) were suggestive of a small protection, neither individual n-3 PUFAs nor n-6 ones were related to breast cancer risk.[31] Another study found no association of omega-3 fatty acid intake with a mammographic pattern showing extensive fibrosis, which may be associated with a proliferative process.[32] The information on ovarian cancer is scanty and inconsistent, with 2 case-control studies reporting elevated risk with fish consumption[33,34] and 1 showing an inverse trend.[6]

We have re-analyzed a series of case-control studies on cancer at several sites, conducted in Italy and Switzerland[35–44] to systematically evaluate the role of n-3 PUFA intake in the etiology of cancer at various sites.

SUBJECTS AND METHODS

Data were obtained from an integrated series of hospital-based case-control studies with the same design, questionnaire and inclusion criteria.[35–44] Information was collected between 1991 and 2001 and studies were conducted in several areas of northern Italy (greater Milan, the provinces of Pordenone, Padua, Udine and Gorizia, the urban area of Genoa and the province of Forlì), central (the provinces of Rome and Latina) and southern Italy (the urban area of Naples). Studies on oral cavity/pharynx, esophagus, colorectum and breast were conducted also in the Swiss Canton of Vaud.

The case-control studies included incident, histologically confirmed cases of cancer. The first study was on cancer of the oral cavity and pharynx was conducted between 1991 and 1997 in Pordenone, Udine, Rome, Latina and in Switzerland, and included 736 cases, (median age 57 years) and 1,772 controls (median age 57 years). The second study was on cancer of the esophagus, was conducted between 1992 and 1999 in Milan, Pordenone, Padua, Udine and Switzerland, and included 395 cases (median age 60 years) and 1,066 controls (median age 60 years). The third study was on cancer of the large bowel, was conducted between 1992 and 2001 in Milan, Pordenone, Gorizia, Genoa, Forlí, Rome, Latina, Naples and Switzerland, and included 1,394 cases of colon cancer (median age 62 years), 886 cases of rectal cancer (median age 63 years) and 4,765 controls (median age 58 years). The fourth study was on breast cancer, was conducted between 1991 and 2001 in the same areas of the third study, and included 2900 cases (median age 55 years) and 3,122 controls (median age 56 years). The fifth study was on cancer of the ovary, was conducted between 1992 and 1999 in Milan, Pordenone, Gorizia, Padua, Udine, Rome, Latina and Naples, and included 1,031 cases (median age 56 years) and 2,411 controls (median age 57 years). Controls were patients admitted to hospital for a wide spectrum of acute non-neoplastic

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conditions (overall 23% had traumas, 27% non-traumatic orthopedic disorders, 24% acute surgical conditions, and 26% miscellaneous other illnesses). All cases and controls were <80 years old, and were identified and questioned by trained interviewers during their hospital stay, in a network of teaching and general hospitals in the areas under surveillance. The proportion of refusals was less than 5% among cases and controls in all Italian centers and about 15% in Switzerland.

Interviewers used a structured questionnaire including information on socio-demographic factors, anthropometric variables, smoking, alcohol and other lifestyle habits, a problem-oriented medical history, physical activity and history of cancer in relatives. Information on diet referred to the previous 2 years and was based on a food frequency questionnaire, including 78 foods or food groups.[45,46] Information on fish included weekly frequency of consumption and portion size of 3 items: mixed Mediterranean fish and seafood, including clams, mussels (0.94 g of n-3 PUFAs per portion); other fish, including cuttlefish, octopus, squid (0.49 g of n-3 PUFAs per portion); and canned tuna, mackerel and sardines (0.34 g of n-3 PUFAs per portion). Content in n-3 PUFAs (including eicosapentaenoic and docosahexaenoic acids) and total energy intake were computed using tables of food composition,[47,48] taking into account the differences in food habits between Italy and Switzerland. In the Italian studies the mean national composition of fish dishes (including shrimp, cuttlefish, squid, mussels, clams and other seafood) was based on the mean national consumption figures and was used to obtain the coefficient for computing n-3 PUFA.[49] In the Swiss studies the coefficients were calculated on the basis of local consumption (from unpublished sources). The correlation coefficient (r) for reproducibility of questions on fish was 0.59[45] and that for validity of n-3 PUFAs was 0.64.[46]

Data analysis

Odds ratio and the corresponding 95% confidence intervals (CI) for subsequent quintiles of n-3 PUFA intake were derived using unconditional multiple logistic regression[50] (in unmatched studies, *i.e.*, breast, ovarian and colorectal cancers) or conditional one (in studies matched on age, gender and study center, *i.e.*, upper aero-digestive tract cancers). Frequency of n-3 PUFA intake was also introduced as a continuous variable; this model gave an estimate of the OR relative to an increase of 1 g of consumption per week. All regression models included terms for age, sex, study center, education, body mass index and energy intake. Further adjustments were made for parity (breast and ovarian cancer), alcohol drinking and smoking habits (upper aero-digestive tract and large bowel cancer) and physical activity for large bowel cancer.

RESULTS

Table I shows the OR of cancer at selected sites for the subsequent quintiles of n-3 PUFA intake. Compared to patients with the lowest quintile of intake, the multivariate OR for those with the highest n-3 PUFA intake was 0.5 for oral and pharyngeal cancer, 0.5 for oesophageal cancer, 0.7 for colon cancer, 0.8 for rectal cancer and breast cancer and 0.6 for ovarian cancer; all the estimates were significant, except for cancer of the rectum and breast, which were of borderline significance. The trends in risk were also significant for all cancer sites. The corresponding estimates for an increase in n-3 PUFA consumption of 1 g/week were 0.70 for oral and pharyngeal cancer, 0.71 for oesophageal cancer, 0.88 for colon cancer, 0.91 for rectal cancer, 0.90 for breast cancer and 0.85 for ovarian cancer.

The risk of cancer at selected sites according to an increase of 1 g/week of n-3 PUFA intake was consistent across strata of age, gender, smoking habit and alcohol drinking (Table II).

DISCUSSION

All studies combined in the present analysis are hospital-based, but cases were identified in the major teaching and general hospitals of the areas under surveillance and the participation of cases and controls was similar, thus reducing the scope for selection bias. We excluded from the control group patients admitted to hospital for chronic conditions or digestive tract diseases, which could have affected dietary habits. In a reproducibility study a satisfactory comparability of dietary information was found from subjects interviewed at home and in the hospital.[51] The similar interview setting for cases and controls also provides reassurance against potential information bias,[51] and there is no reason to suspect different selective recall of n-3 PUFA intake on the basis of disease status, as n-3 PUFA or fish intake was not known to affect cancer risk. The food frequency questionnaire was satisfactorily valid and reproducible,[45,46] and indirect support for a real inverse association between n-3 PUFA intake and cancer at several sites comes from the consistent relation across strata of age, sex and the other considered variables. Allowance for main selected potential confounding factors, including energy intake, as indicator of any potential over-reporting by cases, was unable to explain the association observed. The risk estimates adjusted for age, sex and center were not materially different from those obtained with the more complex models. Residual confounding remains, however, plausible, because n-3 PUFA and fish intake could be markers for a more favorable dietary pattern or healthier lifestyle. We cannot exclude that allowance for other variables specific for each cancer site might modify some of the risk estimates, but further allowance for physical activity or exogenous hormones did not materially modify the risk estimates for colorectal, breast or ovarian cancer.

As dietary PUFAs of the n-3 series are rapidly incorporated into cell membranes and profoundly influence several biological responses,[52] multiple mechanisms may be involved in the preventive activity of n-3 PUFAs on cancer risk. These include suppression of neoplastic transformation, cell growth inhibition, influence on the immune system and inflammation,[53,54] enhanced apoptosis and

TABLE I – ODDS RATIOS[1] AND THEIR 95% CONFIDENCE INTERVALS FOR SELECTED CANCERS ACCORDING TO n-3 POLYUNSATURATED FAT (PUFA) INTAKE

Cancer site	Cases/controls (n)	Quintiles of intake					Continuous OR (for an increase of 1g/week)
		2nd	3rd	4th	5th (highest)	x^2, trend (p-value)	
Oral cavity/pharynx[2]	736/1772	0.9 (0.7–1.2)	0.7 (0.5–0.9)	0.6 (0.4–0.8)	0.5 (0.3–0.7)	22.16 (<0.0001)	0.70 (0.60–0.82)
Oesophagus[2]	395/1066	0.8 (0.5–1.2)	0.7 (0.5–1.1)	0.6 (0.4–0.9)	0.5 (0.3–0.7)	12.11 (<0.001)	0.71 (0.57–0.88)
Large bowel[3]	2280/4765	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	17.91 (<0.0001)	0.90 (0.84–0.95)
Colon[3]	1394/4765	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.8 (0.6–0.9)	0.7 (0.5–0.8)	15.59 (<0.0001)	0.88 (0.82–0.95)
Rectum[3]	886/4765	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	6.91 (<0.01)	0.91 (0.84–1.00)
Breast[4]	2900/3122	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	8.56 (<0.01)	0.90 (0.84–0.95)
Ovary[4]	1031/2411	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.8 (0.7–1.1)	0.6 (0.4–0.7)	15.46 (<0.001)	0.85 (0.77–0.93)

[1]Reference category: 1st quintile of PUFA intake (lowest). The upper cut-points for the quintiles of intake (g/week) ranged between 0.47–0.55 for the 1st quintile, 0.83–0.89 for the 2nd, 1.06–1.28 for the 3rd and 1.46–1.89 for the 4th. Italy and Switzerland, 1991–2001.–[2]OR adjusted for age, sex, study centre, education, body mass index, energy intake, alcohol consumption and smoking habit.–[3]OR adjusted for age, sex, study centre, education, body mass index, energy intake, alcohol consumption, smoking habit and physical activity.–[4]OR adjusted for age, study centre, education, body mass index, energy intake, and parity.

TABLE II – ODDS RATIOS AND 95% CI FOR SELECTED CANCERS ACCORDING TO AN INCREASE OF 1 GRAM/WEEK OF n-3 POLYUNSATURATED FAT INTAKE IN STRATA OF SELECTED COVARIATES[1]

Cancer site	Age (years)		Sex		Smoking habit		Alcohol drinking	
	< 60	≥ 60	M	F	Non-smokers	Current smokers	Non-drinkers	Current drinkers
Oral cavity/ pharynx[2]	0.6 (0.5–0.7)	0.9 (0.7–1.1)	0.7 (0.6–0.8)	0.8 (0.6–1.0)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.5 (0.4–0.7)	0.7 (0.6–0.9)
Oesophagus[2]	0.8 (0.6–1.0)	0.7 (0.5–0.9)	0.7 (0.6–0.9)	0.7 (0.3–1.3)	0.6 (0.5–0.9)	0.8 (0.6–1.1)	0.4 (0.2–0.8)	0.8 (0.6–1.0)
Large bowel[3]	0.9 (0.8–0.9)	0.9 (0.9–1.0)	1.0 (0.9–1.0)	0.8 (0.7–0.9)	0.9 (0.8–0.9)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Breast[4]	0.9 (0.8–1.0)	0.9 (0.8–1.0)	—	—	0.9 (0.8–0.9)	1.0 (0.8–1.1)	0.8 (0.8–0.9)	0.9 (0.9–1.0)
Ovary[4]	0.8 (0.7–1.0)	0.8 (0.7–1.0)	—	—	0.8 (0.7–0.9)	0.9 (0.8–1.1)	0.8 (0.6–0.9)	0.9 (0.8–1.0)

[1]Italy and Switzerland, 1991–2001.–[2]OR adjusted for age, sex, study centre, education, body mass index, energy intake, alcohol consumption and smoking habit, when appropriate.–[3]OR adjusted for age, sex, study centre, education, body mass index, energy intake, alcohol consumption, smoking habit (when appropriate) and physical activity.–[4]OR adjusted for age, study centre, education, body mass index, energy intake, and parity.

anti-angiogenicity.[55] Animal studies have shown that diets rich in n-3 PUFA have diminished tumorigenesis,[56] and decrease the number and size of tumors, and increase the time elapsed before appearance of tumors.[57] In the colon n-3 PUFAs may act through the prostaglandin pathway,[58,59] and influence the activity of enzymes and proteins related to intracellular signaling and cell proliferation,[60] and in the breast they suppress cell growth and metastases in mouse models.[61] It is possible, however, that other nutrients or micronutrients in fish are in part responsible of the inverse association.[62]

In conclusion, this investigation points to n-3 PUFA intake as an important potential factor in the nutritional etiology of several common cancers. The favorable effect of n-3 PUFA intake on the cardiovascular system[63,64] indicates that fish can be a preferable substitute for meat intake[65] in the western diet. The finding that an increase of 1 g/week of n-3 PUFA intake significantly lowers the risk of cancer at several sites suggests that the protection on carcinogenesis is exerted also at low doses of n-3 PUFAs derived from fish, as observed also for myocardial infarction.[66]

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