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Cereal fiber intake may reduce risk of gastric adenocarcinomas: The EPIC-EURGAST study

Mendez M.A.[1], Guillem Pera[1], Antonio Agudo[1], H. Bas Bueno-de-Mesquita[2], Domenico Palli[3], Heiner Boeing[4], Fátima Carneiro[5], Franco Berrino[6], Carlotta Sacerdote[7], Rosario Tumino[8], Salvatore Panico[9], Göran Berglund[10], Jonas Manjer[11], Ingegerd Johansson[12], Roger Stenling[13], Carmen Martinez[14], Miren Dorronsoro[15], Aurelio Barricarte[16], María J. Tormo[17], José R. Quiros[18], Naomi Allen[19], Timothy J. Key[19], Sheila Bingham[20,21], Jakob Linseisen[22], Rudolf Kaaks[22], Kim Overvad[23], Majken Jensen[23], Anja Olsen[24], Anne Tjønneland[24], Petra H.M. Peeters[25], Mattijs E. Numans[25], Marga C. Ocké[2], Françoise Clavel-Chapelon[26], Marie-Christine Boutron-Ruault[26], Antonia Trichopoulou[27], Eiliv Lund[28], Nadia Slimani[29], Mazda Jenab[29], Pietro Ferrari[29], Elio Riboli[30] and Carlos A. González[1]*

[1]*Department of Epidemiology, Catalan Institute of Oncology, Barcelona (ICO-IDIBELL), Spain*
[2]*Center for Nutrition and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands*
[3]*Molecular and Nutritional Epidemiology Unit, CSPO—Scientific Institute of Tuscany, Florence, Italy*
[4]*German Institute of Human Nutrition, Potsdam-Rehbücke, Germany*
[5]*Institute of Molecular Pathology and Immunology of the University of Porto and Medical Faculty, Porto, Portugal*
[6]*Epidemiology Unit, Istituto Tumori, Milan, Italy*
[7]*University of Torino, Torino, Italy*
[8]*Cancer Registry, Azienda Ospedaliera "Civile M.P. Arezzo," Ragusa, Italy*
[9]*Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy*
[10]*Department of Medical Epidemiology, Karolinska Instututet, Stockholm, Sweden*
[11]*Department of Surgery, Malmö University Hospital, Sweden*
[12]*Department of Nutritional Research, University of Umeå, Sweden*
[13]*Department of Medical Biosciences, University of Umeå, Sweden*
[14]*Andalusian School of Public Health, Granada, Spain*
[15]*Department of Public Health of Guipuzkoa, San Sebastian, Spain*
[16]*Public Health Institute of Navarra, Pamplona, Spain*
[17]*Epidemiology Department, Health Council of Murcia, Spain*
[18]*Public Health and Health Planning Directorate, Asturias, Spain*
[19]*Cancer Epidemiology Unit, University of Oxford, United Kingdom*
[20]*MRC Dunn Human Nutrition Unit, Cambridge, United Kingdom*
[21]*MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, Department of Public Health and Primary Care, University of Cambridge, United Kingdom*
[22]*Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany*
[23]*Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark*
[24]*Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark*
[25]*Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands*
[26]*INSERM, Institut Gustave Roussy, Villejuif, France*
[27]*Department of Hygiene and Epidemiology, Medical School, University of Athens, Greece*
[28]*Institute of Community Medicine, University of Tromso, Norway*
[29]*Nutrition and Hormones Group, International Agency for Research on Cancer, Lyon, France*
[30]*Faculty of Medicine, Division of Epidemiology, Public Health and Primary Care, Imperial College, London, United Kingdom*

Numerous case-control studies suggest dietary fiber may reduce risk of gastric cancer, but this has not been confirmed prospectively. A previous case-control study reported reduced risk of gastric cardia adenocarcinomas associated with cereal fiber, but not with fruit or vegetable fiber. To date, different food sources of fiber have not been examined with respect to noncardia tumors or diverse histologic sub-types. This study prospectively examines associations between fiber from different food sources and incident gastric adenocarcinomas (GC) among more than 435,000 subjects from 10 countries participating in the European Prospective Investigation into Cancer and Nutrition study. Subjects aged 25–70 years completed dietary questionnaires in 1992–98, and were followed up for a median of 6.7 years. About 312 incident GCs were observed. The relative risk of GC was estimated based on cohort-wide sex-specific fiber intake quartiles using proportional hazards models to estimate hazards ratios (HRs) and 95% confidence intervals (CIs). Intakes of cereal fiber, but not total, fruit or vegetable fiber, were associated with reduced GC risk

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***Correspondence to:** Unit of Nutrition Environment and Cancer, Department of Epidemiology, Catalan Institute of Oncology, Barcelona, Spain. Fax: +34-932-607787. E-mail: cagonzalez@iconcologia.net

[adjusted HR for the highest *vs.* lowest quartile of cereal fiber 0.69, 0.48–0.99]. There was a strong inverse association for diffuse [HR 0.43, 0.22–0.86], but not intestinal type [HR 0.98, 0.54–1.80] tumors. Associations for cardia *vs.* noncardia tumors were similar to those for overall GC, although cardia associations did not reach significance. Cereal fiber consumption may help to reduce risk of GC, particularly diffuse type tumors. Further study on different food sources of fiber in relation to GC risk is warranted to confirm these relationships.

Although several case-control studies suggest dietary fiber may reduce risk of gastric adenocarcinomas (GC),[1–9] the relationship remains uncertain. In addition to inconsistent results from a number of case-control studies,[10,11] a prospective study[12] failed to confirm this relationship, finding no association between total, soluble or insoluble fiber and GC risk. A previous case-control study of adenocarcinoma of the gastric cardia found that fiber from cereals, but not total, fruit or vegetable fiber was associated with reduced odds of adenocarcinoma of the gastric cardia.[8] These results suggest that heterogeneous functional properties of dietary fiber from different food groups[13,14] may partly contribute to the discrepant results in previous studies. To date, associations between gastric cancer and fiber from different food sources have not been prospectively examined with respect to noncardia adenocarcinomas, which are etiologically heterogeneous from those of the gastric cardia, or in tumors of different histological types.

In this study, we examine associations between total, cereal, vegetable and fruit fiber intakes and risk of cardia and noncardia GC of different histologic types in the multi-country European Prospective Investigation into Cancer and Nutrition study (EPIC).

Methods

Details on the EPIC study have been published previously.[15,16] Briefly, EPIC is a prospective study comprising cohorts from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom). A total of 521,457 subjects (70.6% women) aged mainly 35–70 years were recruited between 1992 and 1998, primarily from the general population, with some exceptions, including the use of blood donor volunteers (parts of the Spanish and Italians cohorts), a health conscious/vegan sample (Oxford), women attending breast cancer screenings (Utrecht and Florence) and school employees (France). The project was approved by ethical review boards of the International Agency for Research on Cancer and local participating centers.

Data collection included validated country-specific food frequency questionnaires or dietary histories enquiring about usual intakes in the previous 12 months,[17] blood samples (74% of subjects), anthropometric data, and questionnaires on sociodemographic factors, lifestyles and health history.[15] The mean correlation between questionnaire-based estimates of energy-adjusted dietary fiber and estimates from 12 repeated 24-hr recalls was 0.63.[18] Dietary fiber intakes were based on country-specific food composition tables, which were reviewed to ensure comparability to the association of official analytical chemists (AOAC) fiber definition, which includes lignin and resistant starch.[19]

Incident cancer cases were identified through population cancer registries or active follow-up, depending on the center; deaths were identified from mortality registries. Cases were identified from recruitment through December 31, 1999 or September 30, 2002, depending on the study center, with a median follow-up of 6.7 years. Gastric cancers included tumors coded as C16 in the 10th revision of the international classification of diseases,[20] and were categorized by anatomic location (cardia/noncardia) and using the Lauren histologic type classification (diffuse and intestinal).[21] Tumor classification was reviewed and validated by a panel of pathologists.[21]

The analysis sample excluded: prevalent gastric or esophageal tumors self-reported by subjects at recruitment (160); all incident nonadenocarcinoma gastric tumors including gastric lymphomas, (26) gastric stump cancers, (5) other nonadenocarcinoma gastric cancers (11) and otherwise unspecified malignant neoplasms of the stomach (8); incident esophageal tumors (188); subjects lost to follow-up (2,403); subjects from the Norwegian cohort with only 2 incident GC cases, and from the Greek cohort which lacked data on fiber intakes (63,285); subjects lacking dietary data, including data on fiber intakes(10,257); and subjects in the extreme 1% of the energy intake *vs.* basal metabolic rate ratio.(9,436) The final analysis sample included 435,678 subjects without GC at entry, among whom 312 incident cases of GC were subsequently identified, including 91 cardia (19 at the gastro-esophageal junction [GEJ]) and 154 noncardia tumors, with 67 designated as unknown or mixed. The histological review designated 104 tumors as intestinal and 106 as diffuse, with 102 cases categorized as mixed, unknown or unclassified.

Cox proportional hazards models were used to estimate hazards ratios (HRs) with 95% confidence intervals for the association between fiber intakes and GC risk. Fiber intakes were analyzed as sex-specific quartiles using both density variables (/100 kcals) and as absolute amounts adjusted for energy, with similar results (data not shown). Men and women were combined as no significant sex differences were observed. Models were stratified by age (1-year interval) and center. Final models, which closely resembled results adjusting only for age, sex and study center, also included height,

TABLE I – INTAKES OF DIETARY FIBER FROM DIFFERENT FOOD SOURCES AMONG SUBJECTS WITH AND WITHOUT INCIDENT GASTRIC ADENOCARCINOMA (GC): EPIC-EURGAST

	At risk (n = 435,366)				Incident GC (n = 312)			
	Mean	(SD)	Median	25/75th percentile	Mean	(SD)	Median	25/75th percentile
Total fiber								
Men	24.38	(9.17)	23.10	18.15/29.04	22.86	(9.23)	22.11	16.09/27.21
Women	22.95	(8.00)	21.90	17.42/27.22	21.69	(6.95)	21.10	17.02/25.66
Fiber types								
Cereal fiber								
Men	11.05	(6.11)	9.97	6.83/14.05	10.02	(5.79)	8.74	5.78/12.97
Women	8.08	(4.49)	7.27	4.95/7.27	7.57	(4.88)	6.28	4.63/9.70
Fruit fiber								
Men	4.03	(3.85)	2.96	1.57/5.26	3.95	(4.26)	2.49	1.45/5.38
Women	4.92	(3.61)	4.23	2.45/9.26	5.24	(3.43)	4.79	2.67/6.86
Vegetable fiber								
Men	3.80	(2.70)	3.19	1.96/4.96	3.73	(3.25)	3.01	1.59/4.57
Women	5.05	(3.26)	4.33	2.74/6.62	4.31	(2.92)	3.69	2.42/5.48

Total fiber also includes fiber from potatoes, legumes and other foods. Fiber intakes shown in grams. Fiber intakes/100 kcals obtained dividing absolute intakes shown by mean energy intakes ÷ 100 [mean (sd) energy intakes 2420 (666) kcals in men and 1979 (545) kcals in women].

weight, education level and smoking status, as well as for other types of fiber in the fiber subtype models. Adjusting for other potential confounders (physical activity levels; history of cardiovascular disease or diabetes; intakes of cereal foods, vegetables, citrus fruit,[22] meat,[23] alcohol, beta-carotene and vit E,[24] vitamin C,[25] and estimated endogenous nitrosamine levels (ENOCs)[26] had no meaningful effect, and these variables were excluded. Interactions with smoking status, meat intakes, endogenous nitrosamine levels and vitamin C were examined but were not significant, although the sample size was small and potentially lacking in power for detecting interactions. Models were run for all cases and tumors diagnosed after the first 2 years of follow-up, with similar results. Excluding subjects with cardiovascular disease or diabetes (n = 97,903), or with other prevalent cancers at baseline (n = 20,739, 4.8% of the sample) had no meaningful effect (not shown). Similarly, including nonadenocarcinoma gastric tumors (n = 50) had no effect (not shown). To assess possible effects of different definitions or analytic methods for estimating fiber content across countries, we also ran models using country- and sex-specific quartiles *vs.* sample-wide sex-specific quartiles, and obtained similar results. In supplementary models, a 24-hr recall collected from a participant subset in each country was used to calibrate dietary fiber intakes across centers and reduce measurement error.[27] Because the calibration method requires continuous variables, these models examined risk associated with a 1 SD increase in fiber intakes.

Results

Cereal foods were the major source of dietary fiber, contributing about 40% of total fiber intakes (Table I). Fruits and vegetables were also major sources of dietary fiber. In multivariate models, there was a significant inverse relationship between GC risk and cereal fiber intakes (HR for highest *vs.* lowest quartile 0.69; 95 % CI: 0.48–0.99; p trend 0.01) (Table II). The association was somewhat nonlinear, with similar HRs in the top 2 quartiles of intake. Neither total fiber, nor fiber from fruits or vegetables, was associated with overall GAC risk.

After stratifying by histologic type, a linear inverse association with cereal fiber was observed for diffuse tumors (HR for highest *vs.* lowest quartile 0.43, 0.22–0.86) (Table III). There was no clear association with intestinal type tumors. Stratifying by anatomical location showed inverse associations for both cardia and noncardia tumors. For noncardia tumors, associations reached significance only in the third quartile, and were slightly higher and borderline nonsignificant in the top quartile. Associations for cardia tumors did not reach significance, perhaps because of the small number of cases. Total, vegetable and fruit fiber did not appear to be meaningfully associated with tumor subtypes, particularly after multivariate adjustment.

Results excluding subjects diagnosed in the first 2 years of follow-up were similar to findings based on the entire cohort, with a strong and significant reduction in risk of diffuse type tumors associated with cereal fiber intakes (HR 0.44, 0.22–0.86 for the top quartile of intake; other results not shown). In the calibrated models, cereal fiber intakes were also significantly associated with reduced risk of diffuse tumors (HR per 1 SD increase 0.50, 0.25–0.99). Other results from the calibrated models were consistent with the uncalibrated analysis, but associations were not significant (not shown).

Discussion

Data from this large multicountry European cohort study suggest a possible protective effect of cereal fiber, but not total, vegetable or fruit fiber, for GC. We have only studied fiber in foods which means that our results cannot be extrapolated to dietary supplements containing fiber. The finding of protective effects limited to fiber from cereal foods is consistent with a Swedish case-control study[8] which found inverse associations between intakes of

TABLE II – INTAKES OF DIETARY FIBER FROM DIFFERENT FOOD SOURCES AND RISK OF INCIDENT GASTRIC ADENOCARCINOMA (GC): EPIC-EURGAST

	Q1[1]		Q2			Q3			Q4			p-trend
	No. of cases/at risk		No. of cases/at risk	HR	95% CI	No. of cases/at risk	HR	95% CI	No. of cases/at risk	HR	95% CI	
Total fiber[1]	88/107,334		71/109,093	0.82	(0.60, 1.13)	86/109,418	1.03	(0.75, 1.40)	67/109,521	0.89	(0.63, 1.26)	0.82
Fiber types												
Cereal fiber	98/108,022		84/108,725	0.87	(0.64, 1.17)	64/109,168	0.63	(0.45, 0.88)	67/109,451	0.69	(0.48, 0.99)	0.01
Vegetable fiber	97/108,545		73/109,007	0.90	(0.65, 1.23)	74/108,998	0.75	(0.54, 1.06)	68/108,816	0.90	(0.64, 1.28)	0.95
Fruit fiber	80/108,841		76/108,870	0.79	(0.57, 1.08)	68/108,866	0.90	(0.65, 1.25)	88/108,789	1.00	(0.6, 1.46)	0.41

Estimated using multivariate cox proportional hazards models stratified by age and center using age as the time-scale variable, adjusted for sex, height, weight, education level, smoking status, as well as for other types of fiber in the fiber sub-type model. HR, hazard ratio; CI, 95% confidence interval; Q1–Q4, quartiles 1–4 of fiber intakes.
[1]Sex-specific cohort wide quartiles. Quartiles of Intake/100 Kcals.

TABLE III – FIBER INTAKES FROM DIFFERENT FOOD SOURCES AND RISK OF ANATOMICAL AND HISTOLOGICAL SUB-TYPES OF GC: EPIC-EURGAST

	Histologic subtypes						Anatomical subtypes					
	Diffuse (n = 106)			Intestinal (n = 104)			Cardia (n = 91)			Noncardia (n = 154)		
	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Total fiber												
Lowest quartile	31	1.00		32	1.00		22	1.00		51	1.00	
2nd quartile	24	0.83	(0.49, 1.44)	26	0.85	(0.50, 1.44)	23	1.13	(0.63, 2.06)	29	0.61	(0.39, 0.98)
3rd quartile	31	1.17	(0.69, 1.97)	23	0.82	(0.47, 1.45)	24	1.25	(0.68, 2.29)	46	1.01	(0.66, 1.54)
Highest quartile	20	0.87	(0.47, 1.60)	23	0.92	(0.50, 1.67)	22	1.34	(0.71, 2.54)	28	0.66	(0.39, 1.10)
p for trend			0.98			0.71			0.34			0.36
Cereal fiber												
Lowest quartile	34	1.00		35	1.00		30	1.00		50	1.00	
2nd quartile	32	0.92	(0.56, 1.50)	25	0.74	(0.44, 1.25)	22	0.76	(0.43, 1.34)	46	0.97	(0.64, 1.46)
3rd quartile	25	0.67	(0.39, 1.17)	18	0.61	(0.33, 1.10)	20	0.63	(0.34, 1.15)	27	0.57	(0.35, 0.94)
Highest quartile	15	0.43	(0.22, 0.86)	26	0.98	(0.54, 1.80)	19	0.67	(0.35, 1.28)	31	0.69	(0.41, 1.16)
p for trend			0.01			0.61			0.16			0.04
Fruit fiber												
Lowest quartile	28	1.00		25	1.00		25	1.00		42	1.00	
2nd quartile	25	0.82	(0.47, 1.42)	24	0.85	(0.48, 1.51)	25	1.05	(0.60, 1.85)	35	0.73	(0.47, 1.16)
3rd quartile	27	0.88	(0.50, 1.53)	24	0.74	(0.41, 1.34)	22	0.91	(0.50, 1.67)	31	0.60	(0.37, 0.97)
Highest quartile	26	0.77	(0.42, 1.41)	31	0.85	(0.46, 1.56)	19	0.81	(0.42, 1.57)	46	0.75	(0.46, 1.23)
p for trend			0.44			0.54			0.47			0.20
Vegetable fiber												
Lowest quartile	35	1.00		38	1.00		21	1.00		53	1.00	
2nd quartile	27	0.91	(0.54, 1.53)	24	0.65	(0.38, 1.10)	16	0.80	(0.41, 1.58)	37	0.80	(0.52, 1.24)
3rd quartile	27	1.15	(0.67, 2.00)	24	0.77	(0.44, 1.34)	27	1.50	(0.80, 2.80)	34	0.90	(0.57, 1.44)
Highest quartile	17	1.15	(0.58, 2.30)	18	0.71	(0.36, 2.39)	27	1.65	(0.81, 3.35)	30	1.00	(0.58, 1.74)
p for trend			0.58			0.38			0.06			0.99

Quartiles of intakes/100 kcals. Multivariate models stratified by age and center using age as the time-scale variable, adjusted for sex, height, weight, education level, smoking status, as well as for other types of fiber in the fiber sub-type model. HR, hazard ratio; CI, 95% confidence interval; Q2–Q4, quartiles 2–4 of fiber intakes.

cereal fiber, but not fruit or vegetable fiber, for adenocarcinomas of the gastric cardia. In our study, associations with gastric cardia did not reach statistical significance, perhaps in part due to the relatively small number of cases at this site in our sample.

Our results suggested that associations between cereal fiber and GC may be limited to diffuse type tumors. To our knowledge, previous studies have not examined cereal fiber intakes in relation to different histologic subtypes of gastric cancer. Tumors of different histologic type may be etiologically heterogeneous, reflected for example in the lower prominence of multifocal atrophy and metaplasia in the poorly differentiated diffuse tumor type relative to intestinal type tumors.[28] However, reasons for possible differences in risk of different histological types with respect to cereal fiber consumption are unclear. Future studies with larger numbers of cases and more power to examine differences across histologic types are needed to confirm this finding and to explore associations that may explain the underlying mechanisms.

Like a previous prospective study,[12] we did not find associations between total dietary fiber intakes and gastric cancer risk. That study did not find reduced risk of GC associated with either soluble or insoluble fiber, but did not examine effects of fiber from different food sources. Both of these types of dietary fiber are found in different food sources, including cereals, fruits and vegetables. As we were unable to quantify intakes in terms of soluble *vs.* insoluble fiber, we were unable to assess whether associations with these fiber subtypes were also neutral in our population. However, like other prospective studies including the previous study exploring dietary fiber, we observed weak associations with fruit and vegetable consumption.[22,29,30]

In vitro research suggests that components of whole grains, the major source of cereal fiber, may protect against gastric carcinomas by acting as a nitrite scavenger in conditions similar to those that exist in the stomach, potentially countering the carcinogenic effects of *N*-nitroso compounds (NOCs).[31] Consistent with this hypothesized mechanism, we previously reported an increased risk of GC associated with high levels of endogenous NOCs (ENOCs), which were estimated based on reported red meat intakes.[26] We did not observe stronger effects of cereal fiber in subjects with high *vs.* low ENOCs levels [for overall GC, HRs for >median intakes were 0.75 (0.57–0.99) at high and 0.80 (0.52–1.23) at low ENOCs levels, respectively (p-value for ENOC-cereal fiber interaction ns). However, cross-classifying subjects based on ENOCs and cereal fiber intakes, we found that the combination of high cereal fiber with low ENOCs levels appeared to be associated with a greater reduced risk (HR 0.54, 0.38–0.76) than either low ENOCs/low fiber (HR 0.71, 0.52–0.99) or high fiber/high ENOCs (HR 0.71, 0.52–0.98).

As in a number of previous case control studies,[4,5,9,11,32–34] we did not find reduced risk of GC associated with high intakes of cereal foods (*i.e.* breads, rice, pasta; data not shown), suggesting that the reduced risk observed was specific to eating cereal foods with high fiber content, such as cereal products containing whole grains. This is consistent with *in vitro* research, in which reduced nitrosation occurred in the presence of wheat bran but not refined wheat flour.[31] Previous cohort[35] and case-control studies[36–41] have also reported reduced risk of GC associated with consumption of whole grains, but not necessarily with refined grain foods. As details on whole *vs.* refined cereal foods were not uniformly available for all EPIC centers, we were unable to specifically explore effects of whole grain foods. Nonetheless, cereal fiber intakes are more strongly related to whole grain than to overall cereal food consumption.[42]

It is unclear whether specific components of whole grain foods other than fiber may be responsible for any beneficial effects in gastric carcinogenesis. Whole grain also contain antioxidants compounds which may be chemoprotective.[43] We therefore examined whether effects were confounded by dietary antioxidants or alternative nitrate scavengers such as vitamin C, beta-carotene and vitamin E. Adjusting for these compounds did not affect our findings (not shown). Similarly, adjusting for *H. pylori* infection and plasma vitamin C using data from the nested case control study in

which biomarkers were measured[25,44] did not meaningfully affect results (not shown).

In conclusion, this analysis suggests that high intakes of cereal fiber—or perhaps whole grain foods rich in cereal fiber—may help to reduce risk of GC, in particular diffuse type tumors. Given the possibility that fiber intakes may help to reduce risk of other cancers including colorectal tumors,[45] as well as the beneficial associations reported for cardiovascular disease[46] these findings provide an additional basis for continuing to promote consumption of cereal fiber and whole grains. However, given the small sample size, particularly for specific tumor sites and histological types, it is important that these relationships be explored in future studies.

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