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Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC–EURGAST)

Carlos A. González[1]*, Guillem Pera[1], Antonio Agudo[1], H. Bas Bueno-de-Mesquita[2], Marco Ceroti[3], Heiner Boeing[4], Mandy Schulz[4], Giuseppe Del Giudice[5], Mario Plebani[6], Fátima Carneiro[7], Franco Berrino[8], Carlotta Sacerdote[9], Rosario Tumino[10], Salvatore Panico[11], Göran Berglund[12], Henrik Simán[12], Göran Hallmans[13], Roger Stenling[14], Carmen Martinez[15], Miren Dorronsoro[16], Aurelio Barricarte[17], Carmen Navarro[18], José R. Quiros[19], Naomi Allen[20], Timothy J. Key[20], Sheila Bingham[21], Nicholas E. Day[22], Jakob Linseisen [23], Gabriele Nagel[23], Kim Overvad[24], Majken K. Jensen[24], Anja Olsen[25], Anne Tjønneland[25], Frederike L. Büchner[2], Petra HM. Peeters[26], Mattijs E. Numans[26], Françoise Clavel-Chapelon[27], Marie-Christine Boutron-Ruault[27], Dimitrios Roukos[28], Antonia Trichopoulou[29], Theodora Psaltopoulou[29], Eiliv Lund[30], Corinne Casagrande[31], Nadia Slimani[31], Mazda Jenab[31] and Elio Riboli[31]

[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*
[4]*German Institute of Human Nutrition, Potsdam-Rehbücke, Germany*
[5]*IRIS Research Center, Chiron-Vaccines, Siena, Italy*
[6]*Servizio di Medicina di Laboratorio, Azienda Ospedaliera di Padova, Italy*
[7]*Institute of Molecular Pathology and Immunology of the University of Porto and Medical Faculty, Porto, Portugal*
[8]*Epidemiology Unit, Istituto Tumori, Milan, Italy*
[9]*University of Torino, Italy*
[10]*Cancer Registry, Azienda Ospedaliera "Civile M.P. Arezzo," Ragusa, Italy*
[11]*Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy*
[12]*Department of Medicine, University Hospital Malmö, Lund University Malmö, Sweden*
[13]*Department of Nutritional Research, University of Umeå, Sweden*
[14]*Department of Medical Biosciences, University of Umeå, Sweden*
[15]*Andalusian School of Public Health, Granada, Spain*
[16]*Department of Public Health of Guipuzkoa, San Sebastian, Spain*
[17]*Public Health Institute of Navarra, Pamplona, Spain*
[18]*Epidemiology Department, Health Council of Murcia, Spain*
[19]*Public Health and Health Planning Directorate, Asturias, Spain*
[20]*Cancer Epidemiology Unit, University of Oxford, UK*
[21]*Medical Research Council Dunn Human Nutrition Unit, Cambridge, UK*
[22] *Strangeways Research Laboratory, Cambridge, UK*
[23]*Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany*
[24]*Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark*
[25]*Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark*
[26]*Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands*
[27]*INSERM, Institut Gustave Roussy, Villejuif, France*
[28]*University of Ioannina, Medical School, Ioannina, Greece*
[29]*Department of Hygiene and Epidemiology, Medical School, University of Athens, Greece*
[30]*Institute of Community Medicine, University of Tromso, Norway*
[31]*Nutrition and Hormones Group, International Agency for Research on Cancer, Lyon, France*

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***Correspondence to:** Department of Epidemiology, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain. Fax: +34-932607787.
E-mail: cagonzalez@ico.scs.es
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It is considered that fruit and vegetable (F&V) protect against oesophagus and gastric cancer (GC). However, 2 recent meta-analyses suggest that the strength of association on GC seems to be weaker for vegetables than for fruit and weaker in cohort than in case-control studies. No evidence exists from cohort studies about adenocarcinoma of oesophagus (ACO). In 521,457 men and women participating in the EPIC cohort in 10 European countries, information of diet and lifestyle was collected at baseline. After an average of 6.5 years of follow-up, a total of 330 GC and 65 ACO, confirmed and classified by a panel of pathologists, was used for the analysis. We examined the relation between F&V intake and GC and ACO. A calibration study in a sub-sample was used to control diet measurement errors. In a sub-sample of cases and a random sample of controls, antibodies against *Helicobacter pylori* (Hp) were measured and interactions with F&V were examined in a nested case-control study. We observed no association with total vegetable intake or specific groups of vegetables and GC risk, except for the intestinal type, where a negative association is possible regarding total vegetable (calibrated HR 0.66; 95% CI 0.35–1.22 per 100 g increase) and onion and garlic intake (calibrated HR 0.70; 95% CI 0.38–1.29 per 10 g increase). No evidence of association between fresh fruit intake and GC risk was observed. We found a negative but non significant association between citrus fruit intake and the cardia site (calibrated HR 0.77; 95% CI 0.47–1.22 per 100 g increase) while no association was observed with the non-cardia site. Regarding ACO, we found a non significant negative association for vegetable intake and for citrus intake (calibrated HRs 0.72; 95% CI 0.32–1.64 and 0.77; 95% CI 0.46–1.28 per 100 and 50 g increase, respectively). It seems that Hp infection does not modify the effect of F&V intake. Our study supports a possible protective role of vegetable intake in the intestinal type of GC and the ACO. Citrus fruit consumption may have a role in the protection against cardia GC and ACO.

A steady decline in the incidence of gastric cancer (GC) and oesophageal cancer (OC) has been observed in most countries in the last decades. However, GC remains the 2nd and OC the 6th most common cause of cancer death, in the world.[1] In contrast, there has been an important increase in adenocarcinoma of oesophagus (ACO) and cardia gastric cancer in USA[2] and Europe,[3] although the rise of cardia cancer is less marked. One explanation for this similar trend is that cardia GC and ACO share, at least in part, some etiological factors such as gastroesophageal reflux disease, Barrett's disease and obesity.[4] Helicobacter pylori (Hp) infection is an established risk factor of non cardia GC, but is not associated with the cardia site,[5] and may reduce the risk of ACO.[6] Tobacco smoking is causally associated with both GC and OC, while fruit and vegetable (F&V) intake are thought to have an important role in gastric and oesophagus carcinogenesis.

A comprehensive review on the effect of F&V intake published in 1997[7] concluded that the evidence of a protective effect is convincing for both GC and OC. Regarding GC, the evidence was particularly convincing for raw vegetables and allium vegetables and citrus fruits. However, this effect remains controversial. Two recent meta-analyses[8,9] have shown that the protective effect seems to be weaker for vegetables than for fruits, and weaker in cohort studies than in case-control studies. These results did not take into account Hp infection, a potentially important effect modifier. Regarding oesophageal cancer, both meta-analyses[8,9] have shown a significant protective effect of F&V in case-control studies, slightly weaker for vegetables than for fruits. The prospective studies conducted so far did not investigate if the association with dietary factors could differ by histological type (adenocarcinoma and squamous cell carcinoma). Furthermore, the potential protective effect of F&V on OC has never been investigated in cohort studies based on Western population.

The aim of this study is to describe the effect of intake of F&V on the risk of GC and ACO in a large cohort study carried out in 10 European countries: the European Prospective Investigation into Cancer and Nutrition (EPIC),[10] which include participants with a wide range of F&V intake.[11] We have also examined in a case-control study nested within the EPIC cohort, whether the association between diet and disease risk was modified by Hp infection.

Material and methods

Study subjects

EPIC is a prospective study designed to investigate the relationships between diet, lifestyle, genetic and environmental factors and the incidence of cancer, carried-out in 23 centers from 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. The study has been described in detail elsewhere.[10] The EPIC cohort consist of 521,457 subjects (368,010 women and 153,447 men), most aged 35–70 years, recruited mostly between 1992 and 1998, usually from the general population residing in a given geographical area, a town or a province. Exceptions were the French cohort based on members of the health insurance of school employees, the Utrecht cohort and the Florence cohort based on women attending breast cancer screening, part of the Italian and Spanish cohort based on blood donors and most of the Oxford cohort based on vegetarian volunteers. Eligible participants gave written informed consent and completed questionnaires on their diet, lifestyle and medical history. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local participating centers. Cancer cases diagnosed before the dietary interview date (138 GC and 22 ACO) and 2,403 subjects lost for follow-up were excluded, as well as subjects from Norway because of the small number of incident cases (2 GC out of 37,203 subjects at risk) and short follow-up.

Diet and lifestyle questionnaires

The usual diet over the previous 12 months was measured at recruitment by country-specific validated questionnaires.[10,12] Most centers adopted a self-administered questionnaire of 88–266 food items. In Greece, all centers in Spain and Ragusa, the questionnaire was administered at a personal interview. Questionnaires in France, Italy, Spain, The Netherlands, Germany and Greece were quantitative, estimating individual average portion size systematically. Those in Denmark, Norway, Naples and Umea were semi-quantitative, with the same standard portion assigned to all subjects. In Malmö, Sweden and United Kingdom, a questionnaire method combined with a food record was used. Lifestyle questionnaires included questions on education, lifetime history of smoking and alcohol intake, occupation, reproductive history and use of hormones, history of previous illnesses and disorders or surgical operations and physical activity.

Follow-up and identification of cancer cases

The follow-up was based on population cancer registries, except in France, Germany and Greece, where a combination of methods, including health insurance records, cancer and pathology hospital registries and active follow-up were used. Mortality data were collected from registries at the regional or national level. Follow-up began at the date of recruitment and ended at either the date of diagnosis of gastric or oesophagus cancer, death or date of the last complete follow-up. A total of 400 incident GC cases and 188 incident OC cases had been reported to the central data-base at IARC for the period up to December 1999 or September 2002, depending on the study center. Cancer of the stomach included cancers coded as C16 according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Validation and confirmation of the diagnosis, classification of tumor site and morphology of tumor (according to ICDO2 Classification and Lauren classification) was carried-out

by a panel of pathologists, including a representative from each participating country and a coordinator (FC). The panel reviewed material provided by the centers (original histological slides and slices obtained from paraffin blocks, as well as original histopathological reports). Among the incidence cases, non-adenocarcinoma oesophagus cancer (121), gastric lymphoma (26) gastric stump cancers (5), other nonadenocarcinoma GC (11) and no otherwise specified malignant neoplasm of the stomach (8) were excluded, so 348 case subjects with gastric adenocarcinoma and 67 case subjects with oesophagus adenocarcinomas were available the analysis. 56 percent of the cases were validated by the panel by histopathological revision of the available material, 24% were classified according to the pathological report and 20% according to information reported from the Cancer Registry to the central database of IARC. The Lauren classification was used for the histological type of GC. Twenty four gastro-oesophageal junction tumors (GEJ) were combined with cardia tumor.

Statistical methods

The proportional hazard model (Cox regression) was used for the analyses of the cohort data. The analysis was stratified by center to control for potential confounding due to differences in follow up procedures and questionnaire design. Age was used as the time scale variable in all models. Entry time was defined as age at recruitment and final time as age of diagnosis (cases) or age at censoring (at risk subjects). All models were adjusted for sex, height, weight, educational level, alcohol intake (g/day) at baseline, status of smoking (never, former and current), daily cigarette smoking (in current smokers only), work physical activity (no activity, sedentary, standing, manual and heavy manual), leisure physical activity (as METS-hour/week), energy intake (Kcal/day) and consumption of red and processed meat (g/day). Vegetable and fresh fruit intakes from the dietary questionnaires were estimated in grams per day. The list of specific vegetables included in each sub-group of vegetables is shown in the appendix. Dried fruits and fruit and vegetable juices consumption were excluded. Juices were quantified in liquid form and it was difficult to pool together the amount of consumption, moreover, their intake in the EPIC cohort was very low (less than 10% of total fruits and vegetables consumption).[11] Intake was analyzed as continuous variables (increment of 100 g/d for groups and of 50 or 10 g/d for subgroups) and as categorical variables, by EPIC-wide sex-specific quartiles for GC and tertiles for ACO. Categorical variables were scored from 1 to 4 (or to 3) and trend tests were calculated on these scores. Separate analyses were done for men and women. No important differences emerged and only the results for both sexes combined are presented in this report. Subsequent analyses were run after the exclusion of cases diagnosed during the first 2 years of follow-up.

Nested case-control study

A nested case-control study within the EPIC cohort, including 241 GC, 47 ACO with available stored blood samples and 1,141 controls, was used to examine whether the association between F&V intake and cancer risk was modified by Hp infection. For each subject with a new incidence of GC, with available blood sample, diagnosed during the follow-up period, 4 control subjects were randomly selected from the cohort, matched by sex, age group (±2.5 y), center and date of collection of blood samples (±45 days), from those at risk at the time of diagnoses of each case. Controls already selected for GC cases were used also for ACO cases, following the same matching criteria (except blood collection date). Laboratory measurements of Hp antibodies were performed in all cases and selected controls. The odds ratio for association of fruits and vegetables in infected and non-infected subjects was estimated by multiple unconditional logistic regression, including matching variables in the model. Interaction terms between fruits and vegetable intake and Hp infection were tested by the likelihood ratio test.

Laboratory assays

Blood samples (30 ml) were collected for most of the subjects at recruitment. Quantification of anti-Hp antibodies in plasma stored sample (0.5 ml straw) of all cases and controls included in the nested study was done by ELISA, using the lysate of the Hp CCUG strain. Briefly, various dilutions of plasma samples (starting dilution 1:200) were incubated with the Hp lysate in solid phase (1 μg/ml). After 1 hr and extensive washings, plates were incubated with an alkaline phosphatase-conjugated polyclonal affinity purified goat anti-human IgG (Sigma chemical Co, St Louis, MO). After 3-hr incubation and further washings, the enzymatic reaction was revealed by addition of *p*-nitrophenylphosphate as a substrate. Hp-specific IgG antibody titres were expressed as ELISA Units (EU), and were determined by interpolation relative to a standard curve constructed by a serial dilution of a standard positive control. A cut-off value of 100 EU was defined using serum samples from individuals negative for *H. pylori* infection as determined by clinical, microbiological and serological assays (Western blotting). Serum samples giving EU values above 100 were considered as positive for anti-*H. pylori* IgG antibodies. In previous experiments, this assay exhibited specificity and sensitivity higher than 90%.

Calibration of the dietary data

A second dietary measurement was taken from an 8% random sample of the cohort (36,994 participants), using a very detailed computerized 24-hr diet recall (24HR) method[13] to calibrate dietary measurements across countries and to correct for systematic

TABLE I – DESCRIPTION OF THE EPIC COHORT

Country	Cohort sample	Person–Years	Stomach adenocarcinoma[1]					Oesophagus adenocarcinoma	Mean daily intake (g/day)[2]			
			Gastric[3]	Gastric[3]	Non cardia	Intestinal[3]	Diffuse[3]		Vegetables		Fresh fruit	
									Men	Women	Men	Women
France[4]	74,504	625,111	11	4	4	3	3	0	–	215.5	–	232.5
Italy	47,531	280,660	52	8	31	26	16	2	218.7	185.1	377.5	320.1
Spain	41,413	276,962	32	6	21	13	13	0	222.2	198.1	346.2	337.2
United Kingdom	87,352	466,049	52	21	23	13	9	25	170.0	178.3	159.8	182.6
The Netherlands	40,047	249,585	29	9	9	6	12	4	132.2	130.5	137.5	183.0
Greece	26,856	100,514	16	2	4	4	9	0	256.9	207.4	220.3	209.4
Germany	53,030	309,303	44	10	24	15	23	2	158.7	172.4	196.8	213.5
Sweden	53,769	419,151	59	17	34	23	27	13	112.3	124.5	125.9	159.1
Denmark	57,016	382,701	53	24	16	13	8	21	138.1	146.8	145.0	193.0
Total	481,518	3,110,034	348	101	166	116	120	67	169.3	171.5	209.2	222.0

[1]Non-adenocarcinoma (45) and gastric stump (5) cancers have been excluded.–[2]GEJ included. Cardia and non-cardia classifications do not include undetermined (75) or mixed (6) localisations. Intestinal and diffuse classifications do not include undetermined (94), unclassified (14) or mixed (4) morphologies.– [3]Based on the 24HR questionnaire of the calibration study participants (13437 men and 21674 women).–[4]Only women. Study centers per country: France (North-East, North-West, South, South coast), Italy (Florence, Varese, Ragusa, Turin, Naples), Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), United Kingdom (Cambridge, Oxford (general and health conscious population)), The Netherlands (Bilthoven, Utrecht), Germany (Heidelberg, Potsdam), Sweden (Malmo, Umea), Denmark (Aarhus, Copenhagen).

TABLE II – DISTRIBUTION OF FACTORS ACCORDING TO QUARTILES OF INTAKE OF TOTAL VEGETABLES AND FRESH FRUIT[1]

	Total vegetables intake (g/d)		Fresh fruit intake (g/d)		Whole cohort
	Lowest *vs.* highest quartile		Lowest *vs.* highest quartile		
	1	4	1	4	
Age (y)	51.2	52.0	50.4	52.2	51.7
Alcohol intake (g/d)	4.8	5.7	7.4	4.2	6.0
BMI (kg/m^2)	25.5	25.7	25.2	26.1	25.5
Ever tobacco smoker (%)	53.0	45.3	57.3	44.3	49.2
Secondary school (%)	39.9	54.0	44.0	49.2	48.9
Leisure physical activity (MET-hrs/week)	84.4	82.6	78.6	87.7	82.7
Manual activity at work (%)	13.6	10.9	12.7	12.4	11.8
Energy intake (kcal/d)	1940	2293	1976	2304	2136
Red meat intake (g/d)	42.1	48.6	47.8	47.3	47.2
Processed meat intake (g/d)	37.2	22.7	36.7	23.8	31.6

All continuous variables are expressed as mean, but alcohol intake as median.–[1]Intake from EPIC dietary questionnaires.

over- or under-estimation of dietary intakes.[14,15] The 24HR values of these 36,994 cohort participants were regressed on the main dietary questionnaire values for vegetables and fruits. Zero consumption values in the main dietary questionnaires were excluded in the regression calibration models (0% to 8% of the participants depending on the food variable) and a zero was directly imputed as a corrected value. Weight, height, age of recruitment and center were included as covariates, and data was weighted by day of the week and season of the year on which the 24HR was collected. Country and sex-specific calibration models were used to obtain individual predicted values of dietary exposure for all participants. Cox regression models were then run using the predicted (calibrated) values for each individual on a continuous scale. The standard error of the de-attenuated coefficient was calculated with bootstrap sampling in the calibration and disease models consecutively.[15] For all analyses p-value < 0.05 were considered statistically significant.

Results

There have been 3,110,034 person-year in 6.5 average years of follow-up since 1991 and 348 stomach and 67 oesophagus adenocarcinomas were identified, according to the diagnoses criteria (Table I). According to the site, 101 (29%) cancers were located in the cardia (including 24 in the GEJ), 166 (48%) in the distal part of the stomach and for 81 (23%) cases sub-site was unknown. According to the Lauren classification, 116 were classified as intestinal, 120 as diffuse, 4 as mixed, 14 as unclassified and 94 as undetermined. Individuals from whom no dietary information was available (12 cases and 6,486 non-cases) and study subjects (8 cases and 9,426 non-cases) in the top and bottom 1% of the ratio of energy intake to estimated energy requirement were excluded from the analysis.[16] The final sample, therefore, was 330 GC (56% men) and 65 ACO (77% men). Table I shows mean of F&V intakes by countries, based on 24-hour diet recall data. Baseline characteristics of the participants according to intake of F&V are reported in Table II. Table III shows the mean intakes of F&V, within each EPIC-wide quartile. Mean intake of total vegetable in the upper quartile was more than 2-fold higher than in the lowest, while for fruit intake it was almost 5-fold in men and almost 3-fold in women.

Table IV shows the hazard ratio (HR) of GC and ACO according to total vegetable intake. There was no evidence of association with GC risk. Controlling for measurement error (calibrated HR) did not substantially change the results. In the categorical analysis of tumor by site, there seemed to be a positive association with cardia cancer. However, this association was not observed in the

ANNEX 1, TABLE III – MEAN INTAKE (G/DAY) OF FRUITS AND VEGETABLES BY QUARTILES[1]

	Men (study wide quartiles).								Women (study wide quartiles).							
	1		2		3		4		1		2		3		4	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Vegetables (total)	0–94	108.9	94–151	147.6	151–248	177.1	248–2377	249.9	0–123	117.3	123–195	156.0	195–298	197.6	298–2979	237.5
Leafy vegetables (except cabbages)	0–5	6.5	5–12	11.8	12–29	20.2	29–1074	41.8	0–10	8.7	10–23	17.6	23–57	26.6	57–687	46.3
Fruiting vegetables	0–29	40.1	29–51	57.6	51–89	77.3	89–1470	129.0	0–39	44.7	39–65	64.0	65–104	84.9	104–1496	114.8
Root vegetables	0–6	8.6	6–13	11.5	13–30	15.3	30–841	26.5	0–9	9.4	9–22	14.8	22–42	21.9	42–974	32.7
Cabbages[2]	0–5	11.1	5–14	16.3	14–31	21.9	31–969	26.5	0–7	10.5	7–19	16.4	19–37	20.4	37–1247	27.5
Onion, garlic[3]	0–4	8.0	4–11	10.6	11–24	16.2	24–325	25.7	0–4	6.2	4–10	9.2	10–22	12.4	22–328	18.9
Fresh fruit (total)	0–81	70.0	81–155	149.3	155–287	229.8	287–4302	347.9	0–126	116.5	126–222	190.2	222–339	247.5	339–4702	326.1
Citrus fruit	0–8	10.3	8–21	20.4	21–66	41.5	66–2038	96.0	0–12	20.4	12–37	27.3	37–79	48.1	79–2487	80.8

[1]Ranges are based on food frequency questionnaires (FFQ), and the mean was estimated from the 24HR data from the calibration study. For France and Spain, an important amount of vegetables was classified as "VEGETABLES, not specified." This quantity has been distributed according to the 24HR distribution of specific vegetables into the FFQ specific subgroups. For Spain, an important amount of fruits was classified as "FRUITS, not specified." The FFQ intake of citrus fruit has been corrected then using the distribution of intake in the 24HR.–[2]Umea excluded.–[3]France and Umea excluded.

TABLE IV – TOTAL VEGETABLES, TOTAL FRESH FRUIT AND CITRUS INTAKE AND THE RISK OF STOMACH AND OESOPHAGUS ADENOCARCINOMA

Site/type	Cases number	Quartiles[1]				Calibrated (per 100 g[2])
		2	3	4	*p*	HR (C195%)
		HR (C195%)	HR (C195%)	HR (C195%)	trend	
Stomach						
Total vegetables	330	1.14 (0.85–1.52)	0.82 (0.58–1.16)	1.15 (0.78–1.70)	0.99	0.91 (0.65–1.28)
Total fresh fruit		1.17 (0.87–1.58)	0.85 (0.61–1.19)	0.99 (0.68–1.42)	0.51	1.04 (0.91–1.20)
Citrus		0.86 (0.64–1.17)	0.67 (0.48–0.93)	0.88 (0.63–1.24)	0.21	0.96 (0.77–1.22)
Cardia						
Total vegetables	94	1.25 (0.68–2.28)	1.53 (0.81–2.89)	1.88 (0.91–3.90)	0.08	0.99 (0.50–1.97)
Total fresh fruit		1.38 (0.81–2.34)	0.72 (0.38–1.37)	0.96 (0.48–1.91)	0.46	1.02 (0.80–1.30)
Citrus		0.72 (0.42–1.23)	0.60 (0.33–1.07)	0.62 (0.32–1.19)	0.08	0.77 (0.47–1.22)
Non-cardia						
Total vegetables	159	1.15 (0.77–1.73)	0.77 (0.47–1.28)	1.12 (0.64–1.97)	0.87	0.96 (0.60–1.52)
Total fresh fruit		0.81 (0.53–1.56)	0.70 (0.44–1.11)	0.85 (0.51–1.42)	0.39	1.03 (0.85–1.26)
Citrus		1.01 (0.65–1.57)	0.73 (0.45–1.18)	1.10 (0.68–1.78)	0.96	1.08 (0.82–1.40)
Intestinal						
Total vegetables	109	1.03 (0.63–1.69)	0.79 (0.44–1.42)	0.89 (0.44–1.79)	0.55	0.66 (0.35–1.22)
Total fresh fruit		0.84 (0.49–1.44)	0.75 (0.42–1.32)	0.86 (0.46–1.61)	0.55	1.02 (0.82–1.28)
Citrus		0.91 (0.53–1.57)	0.67 (0.38–1.19)	0.95 (0.53–1.69)	0.60	1.01 (0.73–1.40)
Diffuse						
Total vegetables	116	1.38 (0.85–2.22)	1.03 (0.57–1.88)	1.40 (0.70–2.81)	0.49	1.18 (0.69–2.03)
Total fresh fruit		1.23 (0.75–2.03)	0.95 (0.55–1.65)	0.68 (0.35–1.31)	0.22	0.97 (0.74–1.29)
Citrus		0.99 (0.60–1.63)	0.58 (0.32–1.04)	0.95 (0.53–1.68)	0.46	0.79 (0.50–1.28)
Oesophagus						
Total vegetables	65	0.88 (0.48–1.63)	0.71 (0.34–1.48)	Tertiles instead of quartiles	0.36	0.72 (0.32–1.64)
Total fresh fruit		0.67 (0.37–1.22)	0.94 (0.49–1.80)	Tertiles instead of quartiles	0.75	0.84 (0.60–1.17)
Citrus		0.56 (0.30–1.03)	0.73 (0.39–1.37)	Tertiles instead of quartiles	0.22	0.77 (0.46–1.28)

[1]For oesophagus, tertiles have been used instead of quartiles, due to the small sample. The cut-points of the total vegetables tertiles are the following (men-women): (111.53–145.53 and 207.15–257.45) The cut-points of the total fresh fruit tertiles are the following (men–women): (102.09–157.22 and 234.29–292.36).The cut-points of the citrus tertiles are the following (men–women): (10.68–17.43 and 43.40–60.71). Quartiles and tertiles are full cohort sex-specific.–[2]For citrus scale is per 50 g. Full cohort analysis: Stratified by center and age. Adjusted by sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, red meat intake and processed meat intake.

calibration model. We observed a negative non significant association with the intestinal type (calibrated HR 0.66; 95% CI 0.35–1.22 for an increase of 100 g/day). Results were quite consistent between Northern and Southern European countries (data not shown). Regarding ACO, a non significant negative association with total vegetables intake was observed. The calibrated HR was 0.72 (95% CI 0.32–1.64) for an increase of 100 g/day of total vegetable intake, there was, however, no evidence of log-linear dose response. In relation with specific types of vegetables (Table V), we found a borderline significant negative association (*p* for trend 0.06) between onion and garlic intake and intestinal GC risk. The HR for the highest *versus* the lowest category of consumption was 0.47 (95% CI 0.21–1.05). The calibrated HR was 0.70 (95% CI 0.38–1.29) for an increase of 10 g/d of onion and garlic intake. We observed also a border-line non significant negative association of leafy vegetables intake (*p* for trend 0.07) for ACO.

There was no evidence of association between total fresh fruit intake and GC risk (Table IV). We did not observe changes by histological type or subsite. Results were quite consistent between Northern and Southern European countries (results not shown). Regarding ACO, a non significant negative association was observed in the calibrated model (HR 0.84; 95% CI 0.60–1.17 for an increase of 100 g/day of fresh fruit intake). We have observed a negative, but not significant association between citrus fruit intake and cardia GC (Table IV). The HR for the highest *versus* lowest quartile of intake was 0.62; 95 % CI 0.32–1.19, with a borderline significant linear trend (*p* 0.08). The effect seems to be present in all levels of consumption, although it seems to be weaker in the calibrated model. On the contrary, there was no evidence of association with noncardia GC. Results were quite consistent between Northern and Southern European countries (results not shown). No differences between diffuse and intestinal histological types were observed. A non significant negative association was observed between citrus fruit intake and ACO (Table IV). The calibrated HR was 0.77 (95% CI 0.46–1.28) for an increase of 50 g/day. We explored the effect of F&V intake after excluding cases diagnosed in the first 2 years of follow-up and overall we did not observe important changes in any of the studied associations (data not shown).

In a case-control study nested within the EPIC cohort, we examined whether the association between F&V and cancer risk was modified by Hp infection (Table VI). The ORs of the calibrated intake of total vegetable, fresh fruit and citrus fruit on the GC and OCA risk among Hp infected and non infected subjects were relatively similar. We observed only a statistically significant interaction term for fresh and citrus fruits and stomach cancer, but their individual effect were not statistically significant.

Discussion

This is the largest cohort study presenting results on F&V intake and the incidence of GC in Western countries and the first on ACO. It is also the first cohort study investigating the association of GC risk with F&V, taking into account markers of Hp infection. The results presented in our paper are based mostly on histologically confirmed adenocarcinoma cases that have been validated by a panel of pathologists. Regarding GC, we observed no evidence of association with fresh fruit intake or with total vegetable intake, even though a protective effect of total vegetables and onion and garlic (allium vegetables) was suggested for the intestinal type. The association with onion has been observed previously by other European cohort, but only for the noncardia GC.[17] We observed a negative, although no significant association between citrus fruit intake and the GC risk restricted to the cardia site of the stomach. The negative association between cardia GC and citrus fruit is in agreement with the role of vitamin C in gastric carcinogenesis by the inhibition of nitrosamines endogenous formation and scavenging of potentially mutagenic oxidative free radicals.[7] Our findings on F&V intake are relatively consistent

ANNEX 2, TABLE V – INTAKE OF SPECIFIC VEGETABLES AND THE RISK OF STOMACH AND OESOPHAGUS ADENOCARCINOMA

Food	Site/type	Cases number	Quartiles[1] 2 HR	2 (CI 95%)	3 HR	3 (CI 95%)	4 HR	4 (CI 95%)	*p* trend	Calibrated (per 100 g) HR	(CI 95%)
Leafy veg. (except cabbages)	Stomach	330	0.96	(0.71–1.31)	1.11	(0.80–1.55)	1.19	(0.79–1.81)	0.36	1.01	(0.88–1.16)
	Cardia	94	0.95	(0.53–1.69)	1.54	(0.85–2.78)	1.50	(0.69–3.26)	0.15	0.94	(0.68–1.31)
	Non-cardia	159	0.84	(0.54–1.31)	0.98	(0.61–1.57)	1.15	(0.64–2.08)	0.71	0.99	(0.82–1.19)
	Intestinal	109	0.97	(0.56–1.67)	1.19	(0.68–2.10)	0.69	(0.33–1.46)	0.64	0.88	(0.68–1.14)
	Diffuse	116	0.98	(0.58–1.65)	1.00	(0.56–1.77)	1.50	(0.75–2.98)	0.38	1.10	(0.88–1.36)
	Oesophagus	65	0.82	(0.46–1.46)	0.35	(0.12–1.04)	Tertiles instead of quartiles		0.07	0.75	(0.42–1.34)
Fruiting veg.	Stomach	330	1.02	(0.76–1.38)	1.05	(0.76–1.44)	0.93	(0.63–1.36)	0.83	0.98	(0.92–1.04)
	Cardia	94	1.01	(0.58–1.75)	1.15	(0.65–2.04)	0.89	(0.42–1.86)	1.00	0.98	(0.87–1.11)
	Non-cardia	159	0.99	(0.64–1.52)	0.97	(0.61–1.53)	1.04	(0.62–1.75)	0.94	1.00	(0.92–1.08)
	Intestinal	109	1.01	(0.61–1.67)	0.81	(0.46–1.40)	0.65	(0.33–1.27)	0.18	0.92	(0.82–1.03)
	Diffuse	116	1.30	(0.78–2.15)	1.10	(0.63–1.93)	0.95	(0.49–1.85)	0.89	1.01	(0.92–1.11)
	Oesophagus	65	1.08	(0.62–1.89)	0.81	(0.39–1.70)	Tertiles instead of quartiles		0.68	0.94	(0.81–1.09)
Root veg.	Stomach	330	0.96	(0.70–1.30)	1.08	(0.79–1.49)	1.03	(0.72–1.46)	0.73	0.97	(0.86–1.10)
	Cardia	94	0.68	(0.36–1.30)	1.14	(0.63–2.05)	1.15	(0.61–2.16)	0.41	1.05	(0.90–1.22)
	Non-cardia	159	0.78	(0.50–1.22)	1.01	(0.64–1.59)	0.95	(0.57–1.58)	0.99	0.92	(0.73–1.16)
	Intestinal	109	0.77	(0.45–1.30)	0.86	(0.50–1.49)	0.81	(0.44–1.51)	0.53	0.85	(0.63–1.15)
	Diffuse	116	1.34	(0.79–2.27)	1.75	(1.02–3.00)	1.32	(0.70–2.48)	0.19	1.05	(0.89–1.27)
	Oesophagus	65	0.82	(0.42–1.58)	0.69	(0.35–1.37)	Tertiles instead of quartiles		0.29	0.89	(0.69–1.14)
Cabbages (Umea excluded)	Stomach	331	0.95	(0.68–1.32)	0.95	(0.66–1.35)	0.83	(0.55–1.28)	0.46	1.00	(0.83–1.20)
	Cardia	89	0.82	(0.42–1.61)	1.03	(0.53–2.02)	1.25	(0.60–2.62)	0.46	1.19	(0.94–1.50)
	Non-cardia	150	0.92	(0.58–1.47)	0.92	(0.55–1.53)	0.59	(0.30–1.16)	0.20	1.00	(0.78–1.29)
	Intestinal	102	0.77	(0.43–1.39)	0.95	(0.51–1.78)	1.27	(0.63–2.53)	0.55	1.33	(1.09–1.63)
	Diffuse	109	1.07	(0.62–1.83)	1.03	(0.57–1.85)	0.82	(0.40–1.70)	0.68	0.73	(0.50–1.07)
	Oesophagus	61	0.98	(0.48–2.04)	0.78	(0.34–1.82)	Tertiles instead of quartiles		0.58	0.86	(0.59–1.24)
Onion. garlic (Umea & France excluded)	Stomach	300	0.94	(0.69–1.29)	0.87	(0.60–1.25)	0.77	(0.50–1.20)	0.25	0.89	(0.62–1.28)
	Cardia	85	0.71	(0.38–1.33)	0.85	(0.43–1.66)	0.88	(0.40–1.95)	0.79	0.84	(0.39–1.82)
	Non-cardia	146	1.12	(0.72–1.73)	1.14	(0.69–1.89)	1.02	(0.54–1.92)	0.83	1.04	(0.67–1.63)
	Intestinal	99	0.64	(0.37–1.10)	0.65	(0.35–1.21)	0.47	(0.21–1.05)	0.06	0.70	(0.38–1.29)
	Diffuse	106	1.35	(0.82–2.24)	1.20	(0.63–2.28)	1.64	(0.77–3.47)	0.23	1.30	(0.75–2.23)
	Oesophagus	61	0.80	(0.41–1.56)	1.27	(0.59–2.73)	Tertiles instead of quartiles		0.55	1.54	(0.72–3.28)

[1]For oesophagus, tertiles have been used instead of quartiles, due to the small sample. Quartiles and tertiles are full cohort sex-specific. Full cohort analysis: Stratified by center and age. Adjusted by sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, red meat intake and processed meat intake.

with the evaluation of the IARC expert panel and the results from cohort studies shown in a recent meta-analysis. In a meta-analysis,[8] based on 17 case-control studies and 5 cohort studies, the estimate effect for the highest *versus* the lowest level of intake was significantly protective in case-control studies, but weak and non significant in cohort studies (RR 0.89; 95% CI 0.75–1.05 for vegetable and RR 0.89; 95% CI 0.73–1.09 for fruit). Furthermore, the protective effect for fruit intake was stronger in studies carried out in Asia than in USA and Europe. Asian countries have higher rates of stomach cancer and higher rates of childhood Helicobacter pylori infection. It has been suggested that the protective effect of F&V could be higher in high risk population. The incidence rate of GC in European countries included in the EPIC study is moderately low, and trends in most of them have shown a drastic decrease in last decades. The expert evaluation[9] showed a strong and significant protective effect for F&V intake in case-control studies, but in cohort studies a weak and significant protective effect was observed for fruit (RR 0.85; 95% CI 0.77–0.95), but not for vegetables (RR 0.94; 95% CI 0.84–1.06). None of them show results comparing cardia and non cardia or by histological type. According to this evidence, cohort studies do not confirm the strong protective effect of F&V intake, suggested by case-control studies on GC. It is well known that case-control studies are potentially affected by selection bias (high participation of highly health conscious and motivated controls), recall bias (cancer cases report their diet differently than healthy controls) and changes in dietary habits in cancer cases because of the first symptoms of the disease.

We did not observe important differences between intestinal and diffuse type, with the exception of the association between vegetables and the intestinal type, although the relative small sample size of each histological type does not allow us to obtain definitive conclusions. The largest European case-control studies[18–20] have shown similar patterns for both histological types, but evidence from cohort studies is lacking and the pathway and features of these histological types is still unknown. A prospective study in Japan[21] found a decreased risk for the consumption of yellow and white vegetables, that was stronger in the intestinal histological type and cardia than in the diffuse type and non-cardia cancer. We observed a negative association of citrus intake restrict to cardia cancer, but we observed no differences in the effect of vegetables, between cardia and non cardia cancer.

Our results support a role of F&V in ACO carcinogenesis. We observed a non-significant negative association for the highest level of total vegetables intake. Our results suggest also a negative, but non significant association for citrus fruits intake. Although the number of ACO cases in our study is relatively small and more cases and more years of follow-up are needed to reach more definitive conclusions, it seems that the effect is weaker than that estimated in a case-control study,[22] which has shown that 32% of adenocarcinoma of oesophagus in a Northern European country could be attributed to the under consumption of F&V. In other study[23] in USA, however, the estimated proportion was lower (15.3%).

Epidemiological studies, including cohort studies have also other limitations[24] measurement error of dietary exposure being

TABLE VI – TOTAL VEGETABLES, TOTAL FRESH FRUIT AND CITRUS CALIBRATED[1] INTAKE AND THE RISK OF STOMACH AND OESOPHAGUS ADENOCARCINOMA IN H. PYLORI NOT INFECTED AND INFECTED SUBJECTS

Food	Number of hp−/Hp+ cases[2] Hp staus	Stomach (40/201)			Cardia (22/47)			Non-cardia (12/113)			Intestinal (16/77)			Diffuse (9/82)			Oesophagus (19/28)		
		OR	CI 95%	*p*	OR	CI 95%	*p*	OR	CI 95%	*p*	OR	CI95%	*p*	OR	CI 95%	*p*	OR	CI 95%	*p*
Total vegetables	Not infected	1.53	0.49–4.78	0.41	2.42	0.54–10.8	0.89	0.70	0.03–16.7	0.73	1.17	0.19–7.10	0.81	0.43	<0.001–392.52	0.81	0.69	0.13–3.66	0.15
	Infected	1.11	0.71–1.74		1.42	0.58–3.45		1.25	0.71–2.20		0.88	0.44–1.80		1.22	0.64–2.34		0.59	0.12–2.99	
Total fresh fruit	Not infected	0.72	0.39–1.33	0.013	0.61	0.25–1.47	0.38	0.64	0.14–2.89	0.43	0.81	0.33–1.95	0.19	0.00	<0.001–3.09	0.83	0.61	0.25–1.48	0.47
	Infected	0.98	0.81–1.20		0.76	0.48–1.22		1.10	0.87–1.39		0.90	0.65–1.25		0.90	0.64–1.24		0.79	0.39–1.61	
citrus	Not infected	0.49	0.18–1.33	0.012	0.61	0.17–2.15	0.71	0.47	0.05–4.39	0.10	0.54	0.11–2.54	0.20	<0.001	<0.001–20.90	0.37	0.71	0.17–3.00	0.40
	Infected	0.89	0.64–1.22		0.46	0.20–1.04		1.20	0.82–1.75		0.95	0.59–1.53		0.64	0.36–1.14		0.86	0.40–1.86	

[1]Per 100 g (except for citrus, per 50 g).–[2]Number of Hp− and Hp+ controls is 372 and 769, respectively. p: p for interaction with Hp (likelihood ratio test). Nested analysis: Adjusted by sex, age, center, date of blood extraction (except for oesophagus), height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, red meat intake, processed meat intake and helicobacter pylori infection.

the most important one, which forces us to be cautious in making definitive conclusions. It has been shown that the magnitude of the distortion in the estimated relative risk depends on the ratio between the interindividual variation of intake to the intraindividual measurement error.[25] This means that the relatively wide range of vegetables and fruit intake in the EPIC cohort reduces the potential impact of measurement errors. Also, the use of the calibration approach allowed us to control part of this measurement error. Finally it should be taken into account that the mean levels of F&V intake in our cohort, even in the lowest quartile, were relatively high (109 g/d for men and 117 g/d for women). In the largest case-control study carried-out in Western-Europe, almost 20 years ago, the cut-off for the lowest category of vegetable intake was 2.1 times a month in Sweden,[18] 2.9 times a week in Italy[19] and 47 g/d in Spain.[20] It may be possible that most subjects are above the biological level needed to have a beneficial effect of chemical compound contained in vegetables and fruits. Another potential limitation of our study is that we did not collect information about antecedents on gastric cancer family history. However, a study in Japan[26] designed to assess the influence of this information did not observe differences between lifestyle and risk factors of GC in patients with and without GC family history.

We did not find any evidence that Hp modifies the relationship between F&V and GC and ACO. We observed only a statistically significant interaction term for fresh and citrus fruit and stomach cancer, but the association was not significant. Although the number of not infected cases is small, these results did not support the hypothesis of a stronger protective effects of F&V among infected subjects.[18] As far as we know, the interaction between Hp infection and F&V intake had not been previously analyzed in a cohort study. It was analyzed only in few case-control studies with negative results. It has been found that adjustment by Hp[27] did not change the estimate of F&V effect, and formal test of interaction was not significant in relation with raw vegetables or fruits,[28] vitamin C intake,[29] total antioxidant potential of F&V[30] or vitamin C and beta carotene.[18] Only 1 study observed that Hp infection was a significant risk factor of GC in the low vitamin C intake group but not in the high vitamin C intake group.[31]

In conclusion, gastric and oesophagus cancer are relatively uncommon and despite the large size of the EPIC cohort, comparatively small numbers of cases have been accrued to date. Nevertheless, although not significant, results are suggestive for a protective effect of F&V on GC and ACO. We observed a probable protective effect of citrus fruits on cardia tumor and of total vegetables and allium vegetables intake on the intestinal type of GC. It also suggested a probable protective effect of vegetable and citrus fruit consumption on ACO. Further cohort studies with more cases are needed to confirm these findings. The 5-year survival rate of GC and OC is very low and the identification and better control of risk factors represent the most effective way for reducing the burden of these tumors.

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Appendix

Selected foods included in specific sub-groups of vegetables in the EPIC study.

Leafy vegetables: borage, chard, endive, lettuce, spinach, thistle.

Fruiting vegetables: artichoke, aubergine, cucumber, eggplant, pepper, pumpkin, tomato.

Root vegetables: beetroot, carrot, celery, parsnip, radish, salsify, turnip.

Cabbages: broccoli, Brussels sprouts, cabbage, cauliflower, kale.

Onion-garlic: garlic, young garling, onion, shallot.