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Abstract Epidemiologic studies suggest that a high intake of fruits and vegetables is associated with decreased risk of cancers of the upper aero-digestive tract. We studied data from 345,904 subjects of the prospective European Investigation into Cancer and Nutrition (EPIC) recruited in seven European countries, who had completed a dietary questionnaire in 1992–1998. During 2,182,560 person years of observation 352 histologically verified incident squamous cell cancer (SCC) cases (255 males; 97 females) of the oral cavity, pharynx, larynx, and esophagus were identified. Linear and restricted cubic spline Cox regressions were fitted on variables of intake of fruits and vegetables and adjusted for potential confounders. We observed a significant inverse association with combined total fruits and vegetables intake (estimated relative risk (RR) = 0.91; 95% confidence interval (95% CI) 0.83–1.00 per 80 g/d of consumption), and nearly significant inverse associations in separate analyses with total fruits and total vegetables intake (RR: 0.97 (95% CI: 0.92–1.02) and RR = 0.89 (95% CI: 0.78–1.02) per 40 g/d of consumption). Overall, vegetable subgroups were not related to risk with the exception of intake of root vegetables in men. Restricted cubic spline regression did not improve the linear model fits except for total fruits and vegetables and total fruits with a significant inverse relation at low intake levels (<120 g/d) for fruits. Dietary recommendations should consider the potential benefit of increasing fruits and vegetables consumption for reducing the risk of cancers of the upper aero-digestive tract, particularly at low intake.

Keywords Upper aero-digestive cancer · Fruits and vegetables · Root vegetables · Prospective study · EPIC · Relative risk

Introduction

About 390,000 new cases of oro-pharyngeal cancer, 160,000 new cases of laryngeal cancer and 412,000 new cases of esophageal cancer occur worldwide each year. This corresponds to approximately 11% of total cancer incidence [1].

Tobacco smoking and alcohol consumption are the major established risk factors for cancers of these sites [2–4]. Furthermore, many observational studies have reported an inverse association between consumption of fruits and vegetables and risk of cancer of the oro-pharynx, larynx and esophagus [5]. The evidence for a decrease in risk due to high fruits and vegetables intake was recently rated by an IARC-expert panel for esophageal cancer as ''probable'' and for cancers of the oro-pharynx and of the larynx as ''possible.'' The assignment of low levels of evidence for a causal relationship despite a consistency in the findings of an inverse association was based on the fact that most studies had used a case–control design prone to recall and selection bias [5]. In addition, the IARC-expert panel expressed the view that analyses on fruits and vegetables intake and cancer risk of the upper

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aero-digestive tract require proper control for tobacco smoking and alcohol drinking since they tend to be related to fruits and vegetable intake. A rigorous control for confounding by these factors has not been done in every study published so far. Thus, studies aiming to contribute substantially to the association between intake of fruits and vegetables and these cancer sites should be prospective in design and have assembled detailed data about tobacco smoking and alcohol drinking habits.

Although most prospective cohort studies have reported an inverse association of fruits or vegetables intake and risk of upper aero-digestive cancer [6–11], the results of these studies are inconsistent regarding the specific group and subgroup of fruits and vegetables.

Therefore we extended a previous preliminary analysis on the relationship between fruits and vegetables intake and the incidence of cancers of the oral cavity, pharynx and esophagus in the European Prospective Investigation into Cancer and Nutrition (EPIC)-study with more cases than in the previous analysis [6] and also included laryngeal cancer. In addition, the current analysis included only histologically verified squamous cell carcinoma (SCC) and also specifically examined several subgroups of vegetables.

Subjects and methods

Study subjects

The EPIC cohort comprises 519,978 study subjects and consists of subcohorts recruited in 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom. Details on the methods of recruitment applied in each center and a description of the study conduct can be found in a supplement describing this study [12]. In most centers, subjects were recruited from the general population residing in a given geographical area, a town or a province. Exceptions were the French center, where female members of the health insurance for state school employees were recruited, the Utrecht (Netherlands) center where women attending a breast cancer screening were recruited, the Ragusa (Italy) center where blood donors and their spouses were recruited and the Oxford (UK) center where mostly vegetarian and health-conscious volunteers were recruited.

Eligible subjects were invited to participate in the study by mail or by personal contact. Those who accepted to participate signed an informed consent form, and diet and lifestyle questionnaires were mailed to these participants to be filled in. In the Spanish centers and in Ragusa, Greece and Naples, interviewer-administered questionnaires were used. Study subjects were then invited to a center for blood collection and anthropometric measurements including height and weight, and to deliver the completed diet and lifestyle questionnaires. In Norway, all information was self-reported, and blood samples were mailed to the coordinating center.

Diet and lifestyle information

Based on results of several methodological studies conducted in the early 1990s [13] diet of the past 12 months was measured by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. Seven countries adopted an extensive self-administered dietary questionnaire which provides data on up to 300–350 food items per country. In Spain and Sicily an interviewer applied dietary questionnaire was used. A food frequency questionnaire and a seven-day dietary record were adopted in the UK and an interview based diet history method combining a questionnaire with a 7-day menu book in Malmö, Sweden. Food intake was calculated by multiplying food frequency and portion size and expressed as grams per day. Food intake data were converted to energy intake by using national food tables.

In addition to the dietary questionnaire data obtained from each study participant, a highly standardized reference dietary measurement was taken from an 8% age-stratified random sample of the cohort using a computerized 24-h diet recall method [14, 15]. Detailed 24-h recall consumption data were collected from 36,994 subjects. A description of the intake of fruits and vegetables in these subjects can be found in [16].

The lifestyle questionnaires included questions on education and socioeconomic status, occupation, history of previous illnesses and disorders or surgical operations, lifetime history of tobacco use and consumption of alcoholic beverages, and physical activity. Education was categorized into no school degree, primary school degree, technical/professional school degree, secondary school degree, university degree, and not specified. For analysis we combined primary and technical/professional school degree, and secondary school and university degree as one variable each. Smoking habits were assessed and subjects assigned to the following categories: Never smoking, former smoking with quitting ≥10 years, former smoking with quitting <10 years, former smoking with unknown quit, current smoking with <15, current smoking with ≥15 and <25, current smoking with ≥25 cig/d, and current smoking with unknown quantity. Duration of smoking was also assessed. Current alcohol intake was assessed from baseline consumption values of alcoholic beverages. The information on alcohol beverage consumption at ages 20, 30, and 40 and at baseline was converted into a variable representing the lifetime alcohol intake [17]. Both alcohol intake variables were expressed as g/day.

End-points

The follow-up was based on population cancer registries in seven of the participating countries: Denmark, Italy, Netherlands, Spain, Sweden, United Kingdom and Norway. A combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used in three countries: France, Germany and Greece. Mortality data are also collected from either the cancer registry or mortality registries at the regional or national level. By April 2004, the time period of last cancer update for this analysis, for centers using cancer registry data, censoring dates for complete follow up were at December 1999 (Torino), December 2000 (Asturias, Murcia, Cambridge, Bilthoven), December 2001 (Florence, Varese, Ragusa, Naples, Granada, Navarra, San Sebastian, Oxford, Malmö, Norway), December 2002 (Umeå, Aarhus, Copenhagen) and June 2003 (Utrecht). For the three countries using individually based follow-up, the end of the follow-up was considered to be the date of the last known contact, or date of diagnosis, or date of death, which ever came first. Mortality data were coded following the rules of ICD-10, and cancer incidence data following ICD-Oncology, 2nd version. Information from a death certificate about a cancer was replaced by detailed incidence data from the registry or treating hospital if available.

We included incident primary carcinomas of the oral cavity including the tongue (C01–C06), oropharynx (C09–C10), hypopharynx (C13–C14), esophagus (C15), and larynx (C32) in our study. Carcinomas of the lips, nasopharynx and salivary glands were not considered. Morphology information was used to classify the malignant tumors into SCC (n = 352) and adenocarcinomas (n = 67). For 32 cases detailed histological information was not available or the histological data did not allow a classification.

Final study population

Subjects who reported cancer at any site at baseline examination were excluded from the original study population (n = 22,432). Also, individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age, sex, and body weight [18]) were excluded from the analysis to reduce the impact of implausible extreme dietary values on the analysis (n = 9,685). Further exclusion refers to subjects with missing questionnaire data or missing dates of diagnosis or follow-up, representing 2% of the participants.

For the final statistical analyses we excluded the centers of Norway (n = 35,232) and Greece (n = 25,574) due to the short follow-up period and few cases identified so far, and of France (n = 67,657) due to incomplete case identification routines in this cohort for these cancer sites.

Statistical methods

We considered total fruits and vegetables intake combined, total fruits intake (fresh fruits including citrus fruits, nuts and seeds, mixed fruits, olives), total vegetables intake (leafy, fruiting, root, grain and pod, stalk, and mixed vegetables, cabbages, mushrooms, garlic/onion, sprouts and mixed salads) and intake of the fruit subgroups citrus fruits and nuts and seeds and the vegetable subgroups root, leafy, fruiting, and root vegetables, cabbages, and garlic/onion [16]. Fruits and vegetables intake were analyzed as estimated by the food frequency questionnaires and as predicted after regression calibration. The regression calibration procedure included a correction for systematic over- and under-estimation by the dietary instruments used in the different sub-cohorts and also for random measurement error [19–21]. Predicted intake data were obtained from a linear regression calibration model on the basis of the food item specific 24-h dietary recall values being regressed on the respective dietary questionnaire values, stratified by gender, in the subset of the EPIC-population with available 24-h diet recall information. The regression equation included country, center, weight, height, and age of recruitment. The 24-h recalls were weighted according to day of the week and season of application. Zero consumption values in the dietary questionnaires were excluded from the regression calibration models and kept as zero values and negative values occasionally occurring after regression were set to zero as well. Likewise, energy consumption from fat and non-fat sources were calculated. The intake ranges of categories of predicted intake data corresponded well with the means of the 24-h recalls with only a few exceptions such as the categories of very low intake (<4, <6 or <8 g/d depending on the food item) of some vegetable subgroups (root vegetables, cabbage, leafy vegetables, onions/garlic). For these intake categories, a higher mean intake taking the 24-h recalls existed as suggested by the intake range of the category. The categories of observed intake data did not fit with the mean of the 24-h recalls in more instances than the predicted data, particular for low or high intake. However, the observed intake data assigned more subjects to the upper and lower categories of intake than the predicted intake data.

The association between fruits and vegetables intake and cancer risk was evaluated using Cox proportional hazard regression (PROC PHREG in SAS). The calculated incident rate ratios were taken as estimates of relative risks. The variables center and age were used as stratum variables to control for differences in questionnaire design, follow-up procedures, and other non-measured center effects, and to be more robust against violation of the proportionality assumption. Age at recruitment was taken as entry time t_0 and age at censoring or age at cancer diagnosis as exit time t_1 in the counting process to derive the estimates of relative risks.

Relative risks were estimated for quintiles of fruits and vegetables and *p*-values for trend across quintiles were obtained by the log likelihood ratio test with the median intake within quintiles as a continuous variable. Models were also fit on a continuous scale for men and women combined and separately for men and women. Gender-specific differences in relative risk estimates were evaluated using an interaction term. If significant, gender-specific models were presented only. Restricted cubic spline regression was used to examine non-linearity of the relative risk function for predicted intake data. Log likelihood ratio statistics was used to evaluate whether the fruits and vegetables variables contribute significantly to the model fit, either for the linear or the restricted cubic spline model, and whether the restricted cubic spline model parameters add significantly to the model fit compared to the linear model. The following knots had been selected separately for each food group on an ad hoc basis taking the number of cases into account: Total fruits and vegetables (130, 200, 300, 420, 580); total fruits (40, 100, 180, 250, 400); citrus fruits (5, 15, 30, 60, 340), total vegetables (90, 120, 150, 180, 230), fruiting vegetables (25, 42, 55, 80, 120), root vegetables (5, 10, 14, 20, 40), leafy vegetables (3, 8, 13, 20, 70), cabbages (5, 13, 17, 23, 40), and onion/garlic (3, 8, 11, 15, 30). Further, for each interval of intake between knots linear spline estimates of relative risk were calculated in order to define the linear risk relation for a specific range of intake. For the graphic display of the non-linear relative risk function the median intake value was taken as the reference. All analyses were adjusted for educational attainment, BMI, smoking habits and lifetime as well as current alcohol consumption at baseline examination. Missing confounder data were considered as separate category. Energy intake was included in all models divided into energy from fat and non-fat sources as in other EPIC-wide analyses [22]. Non-consumer status of fruits or vegetables or specific vegetable subgroups included only a few subjects. Thus, non-consumers were not investigated as a separate intake category for estimated relative risk. However, the non-consumer status information was entered as a separate category in the regression models with continuous intake data for adjustment.

In addition, separate models were fit for smokers and non-smokers and for those with high (men >20 g/d; women >10 g/d) and low lifetime alcohol consumption. Former smokers who had quit less than 10 years ago were classified as smokers and those who had quit at least 10 years ago as non-smokers. The combination of non-smokers and ex-smokers more than 10 years since quitting was done to preserve statistical power. Since lifetime alcohol information was not available for each individual and each center [17] and also detailed smoking information was not provided by some individuals, the stratum specific analyses included less than the total number of cases. Finally, separate relative risk estimates were calculated for the subset of cases occurring within the first 2 years of follow-up and the cases occurring after 2 years of follow-up. Estimated relative risks and two-sided 95% confidence intervals were derived from hazard rate ratios and their standard error. All calculations were done using the SAS Statistical Software, version 9.13, SAS Institute, Cary, NC, USA.

Results

The total number of eligible EPIC study subjects for this analysis included 345,904 persons (130,633 men and 215,271 women). Men were observed for 817,710 person-years and women for 1,364,850 person-years. The 352 SCC cases subdivide into the following sites: Oral cavity and pharynx 164, esophagus 84, and larynx 104 (Table 1).

Table 2 shows the mean predicted intake of fruits and vegetables and specific vegetable subgroups within

Table 1 Description of the distribution of cases by country

Country	Squamous cell carcinoma						Person-years	
	Males			Females			Males	Females
	Oral cav. pharynx	Esophagus	Larynx	Oral cav. pharynx	Esophagus	Larynx		
Italy	7	3	7	6	1	2	74,965	188,379
Spain	15	5	18	4	0	0	100,509	155,304
United Kingdom	10	4	12	4	11	2	117,414	278,951
Netherlands	4	1	5	10	3	2	49,803	180,891
Germany	24	7	9	5	3	1	125,712	163,267
Sweden	13	12	10	5	8	0	174,848	203,976
Denmark	39	18	32	18	8	4	174,458	194,083
Total	112	50	93	52	34	11	817,710	1,364,850

the EPIC cohorts by gender and individual center. Women generally consumed more fruits and vegetables than men in the Northern but less in the Mediterranean countries. There was a South to North gradient in the mean consumption of fruits and vegetables. The highest consumption was found in the Mediterranean centers, consuming about 500–650 g/d on average, followed by the centers in Germany, UK and Denmark consuming about 350–400 g/d. The intake of fruits and vegetables was lowest in the Swedish centers and the Bilthoven center with about 250–300 g/d. There was also a regional gradient in the ratio of fruits to vegetables. This ratio was highest in the Ragusa center with about 2.5 followed by the other Southern European centers with about 1.6–1.8. The other centers showed a nearly equal amount of fruits and vegetables intake. Citrus fruits contributed up to 1/3 to fruit intake in some Mediterranean centers.

The intake of fruiting vegetables followed the regional gradient observed for fruits and vegetables. Leafy vegetables were consumed in higher amounts in the centers in Italy and Spain but also in Germany and the Netherlands. Root vegetables were consumed in higher amounts in the German and UK centers and also in the centers of Sweden and Denmark. Onions/garlic were consumed most in the Spanish centers, and the highest intake of cabbage were found in the centers of the UK, the Netherlands, and Germany.

Means and percentages of important covariates that may confound the association of fruits and vegetables intake and SCC over the range of predicted intake categories are shown in Table 3. Subjects who never smoked and who had no school education were more common in higher categories of intake of fruits and vegetables, while the percentage of current smokers and subjects with primary/technical professional school education was lower.

The association between intake of fruits and vegetables and risk of SCC was first evaluated for quintiles of intake of fruits and vegetables. The observed and predicted data of the overall study population were classified into quintiles of increasing intake and the relative risk for SCC estimated from multivariate Cox regression models. First, the observed data were evaluated. Significant trends across quintiles were seen for most of the investigated fruits and vegetables groups and subgroups with the exception of fruiting vegetables, leafy vegetables and onion/garlic. Compared to the lowest quintile, the category of the highest intake showed significantly lower relative risk estimates for SCC in case of total fruits (0.63; 95% CI: 0.42–0.96), total vegetables (0.55; 0.36–0.84), root vegetables (0.64; 95% CI: 0.43–0.95), and cabbages (0.56; 95% CI: 0.34–0.92). Table 4 shows the results for the predicted data. The lowest compared to the highest quintile showed the following mean intake (g/d) values: Total fruits and vegetables 197.4 vs. 617.0, total fruits 80.8 vs. 403.7, citrus fruits 4.5 vs. 104.4, total vegetables 99.8 vs. 239.2, fruiting vegetables 35.2 vs. 119.8, root vegetables 5.4 vs. 35.8, leafy vegetables 5.0 vs. 38.8, cabbages 3.3 vs. 34.3, and onions/garlic 4.2 vs. 21.9. The trend across quintiles was still significant for total fruits and vegetables and total fruits. Intake of total vegetables and vegetable subgroups did not show a significant trend with the exception of root vegetables. A significant reduction in risk for the highest quintile compared to the lowest quintile was also not seen for intake of vegetables.

Analyses on a continuous scale followed the quintile analyses. Statistical models were first fit for men and women combined and it was evaluated whether significant interactions between food intake and gender exist. Table 5 shows the association between predicted intake of fruits and vegetables and the risk for SCC of the upper aero-digestive tract. A significant interaction was observed for root vegetables (p-value for interaction 0.029). Thus, no combined analysis is shown for this food group. The analysis revealed a significant inverse association between intake of total fruits and

Table 2 Mean daily intake of fruits, vegetables, and specific vegetable subtypes (g/d) by gender and EPIC center after regression calibration

Center	Fruits & vegetables		Fruits		Citrus fruits		Vegetables		Fruiting vegetables		Root vegetables		Leafy vegetables		Onion, garlic		Cabbages	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Florence	612	510	397	316	61	58	216	193	109	93	11	12	28	23	4	10	17	12
Varese	565	489	352	331	85	71	213	157	81	72	12	10	35	30	10	6	14	7
Ragusa	593	499	422	357	82	54	170	144	77	64	1	5	32	29	13	9	9	11
Turin	645	588	405	357	62	65	240	231	116	117	11	14	40	36	13	13	17	16
Naples	–	444	–	274	–	66	–	170	–	88	–	9	–	20	–	5	–	21
Asturias	477	436	322	319	44	51	146	110	65	48	7	5	22	18	21	14	14	11
Granada	553	523	336	311	91	102	216	208	142	141	6	8	29	24	23	20	1	1
Murcia	692	628	418	373	148	122	272	254	166	146	12	11	29	30	37	43	7	11
Navarra	548	524	311	335	92	98	241	191	106	90	5	4	80	57	18	10	2	4
S. Sebastian	627	558	384	337	101	77	239	216	114	102	9	12	45	33	30	23	4	7
Cambridge	302	337	149	170	25	35	147	165	44	57	26	28	5	9	8	10	29	34
Oxford HC[a]	394	385	198	190	39	27	196	197	72	87	27	22	10	15	15	10	27	26
Oxford GP[a]	360	370	174	188	40	28	190	187	65	78	27	21	10	14	12	9	30	27
Bilthoven	281	277	149	151	35	34	132	127	45	45	9	11	23	20	12	11	23	22
Utrecht	–	347	–	215	–	52	–	132	–	46	–	13	–	23	–	8	–	25
Heidelberg	316	362	151	195	21	22	167	167	70	70	17	18	20	22	8	7	20	23
Potsdam	383	417	233	251	30	38	151	167	73	83	15	21	8	10	8	5	24	25
Malmö	254	290	130	163	27	33	123	127	55	61	18	16	8	11	7	6	10	9
Umeå	205	265	105	146	25	39	101	120	48	56	16	21	9	10	9	8	8	15
Aarhus	304	380	177	236	30	40	130	146	45	55	21	27	9	11	16	12	17	18
Copenhagen	279	330	136	186	23	39	145	146	55	58	20	24	11	10	13	11	17	19

[a]HC = Health conscious GP = General population

Table 3 Cohort characteristics by ranges of predicted intake of total fruits and vegetables

	Intake of fruits and vegetables				
	Predicted intake ≤240	Predicted intake 241–320	Predicted intake 321–400	Predicted intake 401–480	Predicted intake >480
Total energy intake (lipids) *Mean* [*kcal/d*]	870	797	767	747	791
Total energy intake (without lipids) *Mean* [*kcal/d*]	1,410	1,348	1,328	1,332	1,455
BMI *Mean* [kg/m^2]	25.9	25.6	25.6	25.8	26.5
Gender *Frequency* (*% male*)	58.3	38.5	29.0	24.8	38.7
Smoking *Frequency* %					
Never	36.8	44.3	48.6	51.5	50.0
Former ≥10 years ago	20.2	24.2	25.2	23.5	23.4
< 10 years ago	4.3	4.4	4.1	3.7	4.1
Unknown quit	2.0	1.9	1.9	1.4	0.9
Current < 15 cig/d	14.0	11.5	10.2	10.8	11.8
15–24 cig/d	14.8	9.1	6.9	6.5	6.6
≥25 cig/d	5.1	2.7	1.9	1.8	2.2
Unknown quantity	2.1	1.5	0.9	0.6	0.6
Unknown	0.7	0.5	0.3	0.3	0.6
Duration of smoking (Smokers only) *Mean* [*years*]	18.7	14.2	12.1	11.5	12.2
Education *Frequency* %					
Non	0.3	0.8	2.0	5.0	10.5
Primary school or Techn. prof. school	63.0	56.6	50.5	46.1	43.5
Secondary school or University degree	36.0	39.8	42.6	44.3	43.7
Not specified	0.8	2.9	5.0	4.7	2.2
Lifetime alcohol intake *Mean* [*g/d*]	17.5	14.1	12.3	11.6	15.1
Alcohol intake *Mean* [*g/d*]	15.9	13.7	12.6	11.9	13.8

vegetable and the incidence rate of SCC (RR = 0.91; 95% CI: 0.83–1.00 for 80 g/d). The relative risk estimates for total fruits and total vegetables were nearly significant. In men, an increase of intake of fruits and vegetables by 80 g/day was associated with a decrease in the incidence rate of SCC by 12% (95% CI: 2–21%) and an increase of total vegetable by 40 g/day with an decrease of 17% (95% CI: 1–29%). Root vegetable intake was inversely related to estimated relative risk (RR = 0.76; 95% CI: 0.64–0.90 for 8 g/d). Borderline significant associations were observed for total fruits, fruiting vegetables and cabbages. In women, no significant associations between intake of fruits and vegetables and risk of SCC were found. We also investigated whether the subgroup nuts and seeds relate to risk of SCC. The obtained estimates of relative risk of this subgroup of fruits were all non significant with point estimates slightly above 1 (data not shown). Total fruits minus nuts and seeds showed nearly identical estimates of relative risk as total fruits. Thus, we kept the food group total fruits as previously defined. Analyses with the observed data on a continuous scale obtained similar results as with the predicted data with the exception of fruiting vegetables. Significant results were obtained for total fruits and vegetables (RR = 0.94; 95% CI: 0.90–0.99 per 80 g/d),

Table 4 Estimates of relative risk[a] and 95% confidence intervals (CI) for SCC of the upper aero-digestive tract for quintiles of predicted fruits and vegetables intake

	RR (95% CI)					*p* for trend
	1. quintile	2. quintile	3. quintile	4. quintile	5. quintile	
Total fruits and vegetables	1	0.64 (0.46–0.89)	0.67 (0.46–0.97)	0.61 (0.40–0.94)	0.60 (0.37–0.99)	0.035
Total fruits	1	0.63 (0.45–0.88)	0.67 (0.46–0.96)	0.68 (0.46–1.02)	0.60 (0.38–0.97)	0.041
Citrus fruits	1	0.90 (0.66–1.24)	0.56 (0.38–0.83)	0.84 (0.59–1.19)	0.76 (0.51–1.13)	0.129
Total vegetables	1	0.92 (0.67–1.27)	1.14 (0.80–1.61)	0.86 (0.56–1.32)	0.80 (0.49–1.31)	0.459
Fruiting vegetables	1	0.89 (0.65–1.21)	0.90 (0.63–1.28)	0.85 (0.56–1.30)	0.72 (0.42–1.25)	0.249
Root vegetables	1	0.97 (0.68–1.38)	0.88 (0.61–1.27)	0.67 (0.44–1.01)	0.65 (0.41–1.01)	0.020
Leafy vegetables	1	0.82 (0.59–1.13)	0.88 (0.61–1.26)	0.83 (0.53–1.31)	0.87 (0.50–1.49)	0.562
Cabbages	1	1.01 (0.71–1.43)	0.79 (0.53–1.17)	0.71 (0.45–1.11)	0.89 (0.55–1.42)	0.412
Onion, garlic	1	1.03 (0.70–1.52)	0.98 (0.65–1.47)	0.96 (0.63–1.48)	1.17 (0.73–1.86)	0.447

[a]Adjusted for: age, gender, center, BMI, energy from fat sources, energy from non-fat sources, education, smoking status categories, duration of smoking (years), alcohol drinking at recruitment (g/d), lifetime alcohol drinking (g/d), non-consumer status (0/1)

Table 5 Estimates of relative risk[a] and 95% confidence intervals (CI) for SCC the upper aero-digestive tract for predicted intakes of fruits and vegetables

Food group (g/day)	Men		Women	Men, women combined
Total fruits and vegetables (per 80 g/d)	0.88 (0.79–0.98)		0.96 (0.79–1.15)	0.91 (0.83–1.00)
p for interaction with gender		0.864		
Total fruits (per 40 g/d)	0.96 (0.91–1.02)		0.98 (0.86–1.12)	0.97 (0.92–1.02)
p for interaction with gender		0.526		
Citrus fruits (per 8 g/d)	0.93 (0.78–1.11)		1.23 (0.95–1.61)	0.98 (0.85–1.13)
p for interaction with gender		0.966		
Total vegetables (per 40 g/d)	0.83 (0.71–0.99)		0.93 (0.74–1.18)	0.89 (0.78–1.02)
p for interaction with gender		0.410		
Fruiting vegetables (per 40 g/d)	0.81 (0.58–1.12)		0.88 (0.59–1.33)	0.89 (0.69–1.14)
p for interaction with gender		0.371		
Root vegetables (per 8 g/d)	0.76 (0.64–0.90)		0.96 (0.82–1.12)	–
p for interaction with gender		0.029		
Leafy vegetables (per 8 g/d)	1.03 (0.92–1.14)		0.90 (0.66–1.23)	1.03 (0.94–1.13)
p for interaction with gender		0.113		
Cabbages (per 8 g/d)	0.91 (0.76–1.09)		1.08 (0.88–1.32)	0.98 (0.86–1.12)
p for interaction with gender		0.257		
Onion, Garlic (per 8 g/d)	1.04 (0.79–1.36)		1.20 (0.73–1.97)	1.04 (0.82–1.31)
p for interaction with gender		0.255		

[a]Adjusted for: age, gender (if appropriate), center, BMI, energy from fat sources, energy from non-fat sources, education, smoking status categories, duration of smoking (years), alcohol drinking at recruitment (g/d), lifetime alcohol drinking (g/d), non-consumer status (0/1)

total vegetables (0.94; 95% CI: 0.89–0.99 per 40 g/d), fruiting vegetables (RR = 0.88; 95% CI: 0.78–0.98 per 40 g/d) and root vegetables (RR = 0.94; 95% CI: 0.90–0.98 per 8 g/d). A borderline significant result was seen for total fruits (RR = 0.98; 95% CI: 0.95–1.01 per 40 g/d). The remaining relative risk estimates were close to 1 and in case of cabbage, a significant interaction with gender existed with significant relative risks estimates below 1 for men (RR = 0.93; 95% CI: 0.88–0.99 per 8 g/d) and above 1 for women (RR = 1.06; 95% CI: 1.02–1.10 for 8 g/d).

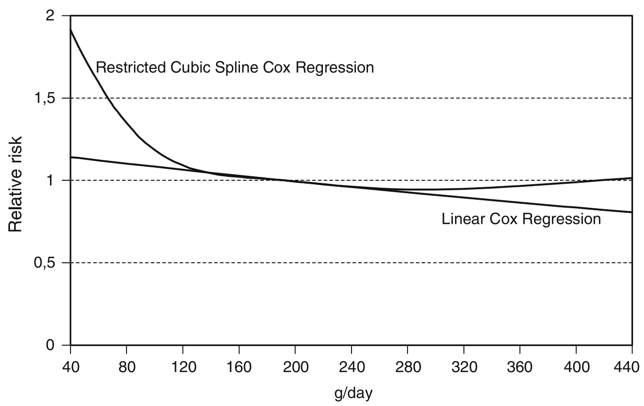

Fig. 1 Estimated relative risk of squamous cell cancer (SCC) for intake of total fruits (restricted cubic spline and linear risk functions)

Next we tested the predicted data for non-linearity using restricted cubic spline regression. The likelihood ratio tests revealed that only in case of total fruits and vegetables and total fruits the spline model obtained a significant better model fit compared to the linear model (p = 0.015 and 0.012). The form of the non-linear relation for total fruits is displayed in Fig. 1. In addition, for comparison, the linear risk function from the Cox regression is also shown. In the low range of fruit intake up to 120 g/d, a higher intake of fruits was significantly inversely associated with relative risk, while in the higher range of intake above 120 g/d the risk relation was completely flat and no benefit in terms of relative risk was seen with higher intake. The risk relation of intake of total fruits and vegetables with SCC taking the restricted cubic spline regression model showed a similar pattern as with total fruits. First, a significant inverse relative risk relation up to an intake of 300 g/d was seen and subsequently a flat relationship.

We next grouped the EPIC centers into those with low and those with high mean total fruits intake using Table 2 and the consumption values for men. The 10 centers from Southern Europe formed the high intake group with more than 300 g/d intake on average and the remaining centers located in Middle, Western, and Northern Europe and having around 150 g/d intake the low intake group. The estimated relative risk for intake of fruits and SCC was 1.01 (95% CI: 0.96–1.06) for each increase by 40 g/d for the centers with the high intake and 0.95 (95% CI: 0.90–0.99) for the centers with the low intake. The result of the center-specific analysis confirmed the non-linearity of the risk relation for total fruits. For total vegetables the respective estimates of relative risk were 0.95 (95% CI: 0.87–1.04) for the high intake centers and 0.94 (95% CI: 0.88–1.00) for the low intake centers.

Other investigations regarded the role of cancer site. Separate models on a continuous scale with predicted intake data were fit for oral pharynx, esophagus and larynx cancer, men and women combined. For total fruits and vegetables, total fruits, total vegetables, fruiting vegetables, and root vegetables, all point estimates of relative risk were below 1 and in case of root vegetables we observed a significant reduced estimate of relative risk of 0.22 (95% CI: 0.05–0.89 for 8 g/d) for larynx cancer in men. Leafy vegetables, cabbages and onion/garlic show point estimates of relative risks above 1 and below 1 for the separate organ sites.

We further investigated whether risk estimates differ according to smoking status and lifetime alcohol consumption in case of predicted intake of total fruits and vegetables, total fruits, and total vegetables. The stratum of smokers included 234 cases and the stratum of non-smokers 109 cases. Relative risk estimates were similar in each stratum with slightly stronger inverse associations within the stratum of non-smokers than within the stratum of smokers. The interaction term between fruits and vegetables intake and smoking status was non-significant. The estimates of relative risk for high (179 cases) and low (109 cases) lifetime consumption of alcohol were similar in each stratum and none of the interaction terms were significant. As smoking and alcohol drinking are considered as major risk factors we also run models without these confounders and with only one of these variables. With the exception of leafy vegetables and onion/garlic, the estimates of relative risk were much stronger and significant without adjusting for smoking and alcohol drinking. Taking smoking into account revealed estimates of relative risk slightly closer to 1 than taking alcohol consumption. Risk models with only one of the variables for adjustment revealed significant estimates of relative risk for total fruits and vegetables, total fruits, total vegetables, and root vegetables.

We also evaluated whether the relative risk estimates for cases having occurred within the first 2 years ($n = 107$) and those having occurred after 2 years of follow-up ($n = 245$) differed; however, the stratum specific analyses showed no substantial differences between risk estimates for the two groups of subjects.

Discussion

This prospective study with 345,904 subjects and an average follow-up period of 5.8 years corroborates previous findings that higher intake of fruits and vegetables is associated with lower risk of SCC of the upper aero-digestive tract. The analysis identified intake of total fruits and vegetables, and total fruits as well as total vegetables as being significantly or nearly significantly inversely related to risk. Intake of root vegetables was inversely related to risk in men, but not in women. It was also found that the relation between intake of total fruits and risk of SCC follows a non-linear functional form with a strong decrease in relative risk with increasing intake in the range of low intake (< 120 g/d) and no decrease in risk with medium and high intake. A similar risk function with a strong inverse relation up to 300 g/d intake was also observed for total fruits and vegetables. All findings were obtained from risk models that investigated the intake variables without further adjustment for other fruits and vegetables intake variables.

The design of this multicenter study has some features that are important for the interpretation of the results. The variation in intake of fruits and vegetables is large compared to most other cohorts on diet and cancer because several European countries with various dietary traditions were included into the study. The center-specific mean intake of fruits and vegetables across EPIC cohorts varied more than twice from roughly 200 g/d on average to over 500 g/d [16]. This general South to North gradient is reflected in vegetables as well as in fruits intake. Second, cancer rates vary across countries of the EPIC-study with incidence rates of upper aero-digestive tract cancer showing almost 3-fold differences [1]. Thus, our study takes advantage of substantial variation in diet and cancer rates across European countries [21]. Third, we applied linear regression calibration to adjust for center-specific mean intake and random measurement error. Linear regression calibration is often associated with a considerable shrinking of the variation within a center; however, it could be seen that the predicted intake data obtained across the EPIC centers coincide well with the 24-h recall measurements.

It was found that estimated relative risk for total fruits was inversely related to risk in connection with low intake and not with medium and high intake. This was not seen for total vegetables. For total vegetables, there was a borderline significant linear relationship with risk over the whole range of intake. Non-linearity of the relative risk relation is important information because it might have some implications on the interpretation of the previous findings and contains a public health message for subjects with low intake of fruits. If the risk relation between upper aero-digestive cancer and intake of fruits and subsequently of fruits and vegetables combined depends on the intake in a population, studies in areas with low intake of fruits or in groups with low intake will yield a high relative risk estimate and studies with a medium and high intake a low and probably non-significant risk estimate, in particular if the range of intake and size of the study population are small. Thus, published relative risk estimates world-wide need also to vary depending on the intake of the study population. However, since most of the previous studies used crude estimates of food intake or data from food frequency questionnaires without calibration only, valid and precise information of the intake of fruits and vegetables in these study populations might be lacking. Thus we report the findings from other studies so far without intake information and concentrate the discussion on prospective studies. Case–control studies first reported on the inverse relation between intake of fruits and vegetables and risk of SCC, particularly in Europe [23], and thus guided the next generation of observational epidemiological studies, the prospective studies. The study of Kasum et al. [9] investigated 169 incident aero-digestive tract cancers identified within a 14-year follow-up in 34,651 US women and found borderline significant inverse relationships for fruits as well as vegetables intake. The study of Kjaerheim et al. [10] reported relative risk estimates for single food items obtained from 71 cases of upper aero-digestive tract cancers seen within 24 years of follow-up of 10,960 Norwegian men. They found oranges being significantly inversely related to risk, borderline significant results for other fruit items and no relationships with vegetable items. Guo et al. [8] reported relative risk estimates for esophageal cancer from a case–control study nested within the Linxian intervention trial on micronutrients with 29,584 subjects. The authors identified 640 cases during a 5-year follow-up period and found fresh vegetables—but not fresh fruits—to be significantly inversely related to risk. Sauvaget et al. [11] conducted a study on fruits and vegetables intake and cancer mortality on 38,540 subjects of the Life Span Study in Japan. Eighty deaths due to esophageal cancer appeared during an 18-year follow-up being inversely related to intake of fruits but not to green-yellow vegetables. A cohort of 7,995 Japanese-American men reported by Chyou et al. [7] was observed for 24 years with 92 aero-digestive tract cancers identified during follow-up. In their study, fruits consumption was borderline significantly inversely linked with aero-digestive tract cancer. Fresh vegetable items were not assessed in this study. The study of Hirayama [24] reported no relationship between intake of red-yellow vegetables and risk of esophageal cancer but did not estimate fruits consumption in his large prospective study with 265,118 subjects. In contrast to prospective studies, most case–control studies found consistent results with regard to an inverse relationship of fruit and vegetable consumption and risk of upper aero-digestive cancers. The literature on this topic was recently summarized in a systematic way and published in the series of Handbooks of Cancer Prevention [5] with details to each study.

In concordance with other studies [5] we observed in the cross-sectional analysis a lower intake of fruits and vegetables in heavy smokers and a higher intake in non-smokers. This phenomenon leaves the question whether residual confounding affected the observed association of fruits and vegetables with risk of upper aero-digestive cancer. In our analysis we established a rigorous control for the potential confounding by tobacco smoking and alcohol drinking in that various aspects of smoking and alcohol drinking, including continuous variables of alcohol consumption and detailed smoking categories were simultaneously considered in the statistical model as confounders. In addition, educational level, usually a further factor associated with risk for upper aero-digestive cancer, was also taken into account.

A further and for the topic highly relevant question is that of the modifying effect according to smoking status. It can be hypothesized that fruits and vegetables intake might modify the detrimental effect of the strongest risk factor, smoking, and thus being active in smokers only. However, external evidence from case–control studies with upper digestive cancer, conducted in non-smokers and non-alcohol drinkers, suggests that intake of fruits and vegetables is inversely related to risk also in these subgroups of the population [5]. We investigated this issue in our data and concluded that the relative risk estimates do not differ between smokers and non-smokers. We even found some indication that the effect of fruit and vegetables is stronger in non-smokers than in smokers. However, the evaluation of the interaction terms between smoking status and intake of fruits and vegetables in terms of risk of SCC based on a low number of cases which results in low power to detect differences between stratum specific results. Further analyses with larger numbers of cases are required to clarify this issue.

We also analyzed whether the observed inverse association between intake of fruits and vegetables differs with length of follow-up time. We found no indications of a substantial difference in estimated relative risk in cases being diagnosed within the first 2 years after the food consumption measurement compared to cases being diagnosed later in follow-up.

The gender-specific results with a significant inverse risk relation for total fruits and vegetables and total vegetables in men are noteworthy. The number of male cases was about twice the number of female cases despite a much higher number of accrued person-time in the latter group. The excess of male cancers compared to female cancers might, aside the difference in prevalence of other major risk factors such as smoking and alcohol drinking, also refer to the comparatively lower intake of fruits and vegetables in this group, particularly of fruits (Table 2). If we assume a stronger risk relation among low compared to medium and high intake for fruits, the point estimates of relative risk per unit of intake of total fruits or total fruits and vegetables should be larger in men compared to women. This was actually observed as well as the stronger estimated relative risk in the centers with low intake. Similar effects might also guide the findings for vegetables without being statistically noted. However, the gender-specific analyses were hampered by the small number of women which reduced the likelihood of significant findings.

The major hypotheses on the biological mechanisms behind the observed associations and the current evidence from experimental studies are described in detail in a recent IARC-expert report [5]. For example, experimental biomarker studies with fruits and vegetables cover among others enhanced antioxidant function, prevention of oxidative damage and DNA-adduct formation, prevention of nitrosation, and influencing bioactive transformations. Animal experiments were successful in preventing tumors in the oral cavity and esophagus in mice and rats by feeding specific fruits (raspberries, strawberries, blueberries) or vegetables (garlic) [5]. The complex nature of fruits and vegetables and the many substances with cancer preventive activities, often labeled as bioactive plant constituents, biochemicals or phytochemicals, currently do not allow a conclusive statement regarding the mechanisms potentially behind our observation.

We conclude that intake of fruits and vegetables is prospectively linked with reduced risk for SCC of the upper aero-digestive tract of about 9% with each 80 g portion of fruits and vegetables (12% for men; 4% for women), supporting initiatives to increase the consumption of this type of food. We propose to concentrate on messages that motivate subjects particularly to increase low intake.

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