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Diet and upper-aerodigestive tract cancer in Europe: The ARCAGE study

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There is suggestive, but inconclusive, evidence that dietary factors may affect risk of cancers of the upper aerodigestive tract (UADT). In the context of the alcohol-related cancers and genetic susceptibility in Europe study, we have examined the association of dietary factors with UADT cancer risk. We have analyzed data from 2,304 patients with UADT cancer and 2,227 control subjects recruited in 14 centers in 10 European countries. Dietary data were collected through a semi-quantitative food frequency questionnaire that also assessed preferred temperature of hot beverages. Statistical analyses were conducted through multiple logistic regression controlling for potential confounding variables, including alcohol intake and smoking habits. Consumption of red meat (OR per increasing tertile = 1.14, 95% CI: 1.05–1.25), but not poultry, was significantly associated with increased UADT cancer risk and the association was somewhat stronger for esophageal cancer. Consumption of fruits (OR per increasing tertile = 0.68, 95% CI: 0.62–0.75) and vegetables (OR per increasing tertile = 0.73, 95% CI: 0.66–0.81) as well as of olive oil (OR for above *versus* below median = 0.78, 95% CI 0.67–0.90) and tea (OR for above *versus* below median = 0.83, 95% CI 0.69–0.98) were significantly associated with reduced risk of UADT cancer. There was no indication that an increase in tea or coffee temperature was associated with increased risk of UADT overall or cancer of the esophagus; in fact, the association was, if anything, inverse. In conclusion, the results of this large multicentric study indicate that diet plays an important role in the etiology of UADT cancer.
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Key words: diet; upper aerodigestive tract; esophagus; cancer

In the European Union, cancers of the oral cavity, pharynx other than nasopharynx, larynx and esophagus, collectively referred to as cancers of the upper aerodigestive tract (UADT), are responsible, as a group, for ~180,000 new cases per year, more than half of whom die from the disease.[1] Although there has been some limited progress in the treatment, there appears to be a better potential for primary prevention.[2] Regular alcohol consumption and tobacco smoking are established causes of UADT cancer and their combined effects seem to be super-additive.[3–5] There is also evidence that higher consumption of nonstarchy vegetables and fruits is associated with reduced UADT cancer risk. However, the collective evidence regarding these dietary factors has been judged as "probable," but not convincing.[5,6] We have exploited data from a large multicenter European case–control study in order to examine the association of selected dietary factors, including vegetables and fruits, with UADT cancer risk. We have also examined whether the preferred temperature of hot beverages, notably coffee and tea, is related to UADT cancer risk in general, or specifically to cancer of the esophagus. For the latter site, there is limited suggestive evidence for an increased risk following consumption of very hot drinks.[5]

Material and methods

ARCAGE (alcohol-related cancers and genetic susceptibility in Europe) is a multicenter case–control study. The study was approved by the ethical review board of IARC as well as the respective local boards in the 14 participating centers listed in

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TABLE I – THE ARCAGE STUDY: DISTRIBUTION OF UPPER AERODIGESTIVE CANCER CASES BY CENTRE AND SUBSITE

Centre	All cases	By subsite					
		Oral cavity	Pharynx[1]	OP NOS[2]	Larynx	Oesophagus	UADT NOS[3]
CZECH REP-Prague	192	6	67	9	44	64	2
GERMANY-Bremen	287	55	139	6	76	11	0
GREECE-Athens	244	51	21	37	113	22	0
ITALY-Aviano	152	49	46	1	37	19	0
ITALY-Padova	135	26	41	0	51	17	0
ITALY-Turin	167	66	39	2	42	17	1
IRELAND-Dublin	44	8	11	0	5	20	0
NORWAY-Oslo	173	44	65	2	32	30	0
UK-Glasgow	98	17	32	25	19	1	4
UK-Manchester	151	66	52	12	21	0	0
UK-Newcastle	89	19	13	10	23	24	0
SPAIN-Barcelona	195	47	52	3	83	10	0
CROATIA-Zagreb	54	31	21	0	2	0	0
FRANCE-Paris	323	49	102	18	154	0	0
TOTAL	2,304	534	701	125	702	235	7

[1]Excluding nasopharynx.–[2]OP NOS = Oral, pharynx not otherwise specified.–[3]UADT NOS = Upper aerodigestive tract cancer, not otherwise specified.

Table I. All subjects provided written informed consent for their participation in the study.

Details on the study design are given elsewhere.[7] The study was conducted from 2002 to 2005 in all centers but Paris, where recruitment took place from 1987 to 1992, with a protocol similar, though not identical, to that use in the other centers. Incident cases were identified from participating hospitals and were histologically or cytologically confirmed. Eligible cases were classified under specific ICD-O codes and included cancer of the oral cavity, pharynx (excluding nasopharynx), larynx and esophagus. In each center, controls were frequency-matched to cases by sex, age (in 5-year groups) and referral (or residence) area. In the UK centers, population controls were randomly chosen from the same community medical practice list as the corresponding cases. Specifically, for each case, a total of 10 controls were selected, matched by age and sex. Potential controls were approached in random order and, in case on nonparticipation of the first potential control, the second 1 was approached and so on, until 1 agreed to participate. In the remaining centers, hospital controls were used to facilitate the collection of blood samples. Only controls with a recently diagnosed disease were accepted and the admission diagnoses related to alcohol, tobacco or dietary practices were excluded. Eligible control admission diagnoses included (*i*) endocrine and metabolic, (*ii*) genito-urinary, (*iii*) skin, subcutaneous tissue and musculoskeletal, (*iv*) gastro-intestinal, (*v*) circulatory, (*vi*) ear, eye and mastoid and (*vii*) nervous system diseases as well as (*viii*) plastic surgery cases and (*ix*) trauma patients. The proportion of controls within a specific diagnostic group could not exceed 33% of the total in any particular center. Overall, the most common diagnoses among controls were gastrointestinal diseases (by protocol, appendicitis, anal fissure and fistula, perianal abscess, ischiorectal abscess, cholangitis) (19.2%), trauma (14.7%) and diseases of the ear, eye and mastoid (13.4%). In France, by center-specific protocol, never-smokers were not included among the cases or controls.

Cases and controls underwent identical personal interviews during which a lifestyle questionnaire was completed. The questionnaire included information on socio-demographic variables as well as the detailed smoking and alcohol drinking histories. Anthropometric measures were also recorded.

Dietary habits were assessed using a semi-quantitative food frequency questionnaire, specifically developed for ARCAGE, recording the frequency (per month, per week or per day, as appropriate) of consumption of 22 food items or groups that have been previously reported to be related to UADT cancer risk. Information on coffee and tea consumption and the temperature at which these beverages were consumed was also collected. In the Athens center, an extensive semi-quantitative food frequency questionnaire of more than 100 food items and drinks, frequently used in the past in case–control studies in Greece,[8] was used and the information was subsequently condensed to the ARCAGE basic diet questionnaire, by summing up frequency of consumption of the component foods of particular food groups. In France, the questionnaire was applied before the launching of ARCAGE and focused on vegetables, fruits and coffee. Therefore, the dietary variables in the French center overlapped with those of the ARCAGE basic diet questionnaire, but were not identical and information on total meat intake, cooked vegetables, tea and olive oil was not recorded. The ARCAGE questionnaire was not all inclusive and relied on frequency of consumption rather than on quantities consumed. It has not been formally validated, because it does not allow estimation of total energy intake, which is a prerequisite for formal validation studies.

For the statistical analyses, all UADT cancer cases were grouped together, because they are considered to share common etiological factors in tobacco smoking, consumption of alcoholic beverages and diet. Simple cross-tabulations were used to examine the distribution of cases and controls by center, gender as well as broad categories of level of education, tobacco smoking and alcohol drinking. For age, height and body mass index 2 years before diagnosis (BMI), mean values and standard errors were calculated. With respect to frequency of consumption of selected dietary variables, medians and quartiles of frequency of consumption, in times per week, were estimated per center, gender and case–control status.

The association of dietary variables with UADT cancer was assessed by comparing the distribution of cancer cases and controls by aggregating, over all centers, marginal (from cases and controls combined),[9] center-specific tertiles. We used multiple logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for UADT cancer by tertile of consumption (categorically, using the lowest tertile as baseline), in order to assess whether there is a monotonic relation between the exposure and log odds of the outcome, as well as by increasing tertile of consumption of the food items or groups. In all models, we adjusted for center through stratification and we also controlled for age (in years, continuous), gender, BMI 2 years before diagnosis (ordered in center-specific quintiles), height (in cm, continuous), education level (categorical: primary as baseline, further education but not university level, university education), alcohol consumption (never drinkers, former drinkers, current drinkers; for former and current drinkers further control was undertaken for drink-years, that is average number of drinks per day multiplied by years of drinking, as an ordered variable with 1 = <20, 2 = 20–39, 3 = 40–59, 4 = 60–79 and 5 = 80+ drink-years) and smoking status (never smokers, former smokers, current smokers; for former and current smokers further control was undertaken for

TABLE II – THE ARCAGE STUDY: FREQUENCY OF CONSUMPTION (IN TIMES PER WEEK) OF THE INDICATED FOOD ITEMS OR GROUPS

	Cases	Controls
CZECH REP-Prague	n = 192	n = 187
All meat	8.1 (6.0–10.5)	7.4 (5.7–10.2)
Fish	0.5 (0.2–1.0)	0.5 (0.2–1.0)
All vegetables[1]	5.0 (3.0–7.0)	6.0 (3.0–14.0)
Fruit	5.0 (2.0–10.0)	7.0 (3.0–14.0)
Tea	14.0 (5.0–21.0)	14.0 (7.0–21.0)
Coffee	10.0 (7.0–14.0)	14.0 (7.0–21.0)
Olive oil	0.0 (0.0–1.8)	0.0 (0.0–3.0)
GERMANY-Bremen	n = 287	n = 328
All meat	10.0 (7.0–13.0)	9.2 (5.0–12.2)
Fish	1.0 (0.5–1.0)	1.0 (0.5–1.0)
All vegetables[1]	4.0 (2.0–7.0)	5.0 (3.0–7.0)
Fruit	3.0 (2.0–7.0)	7.0 (3.0–7.0)
Tea	1.7 (0.0–14.0)	3.0 (0.0–21.0)
Coffee	21.0 (7.0–35.0)	14.0 (7.0–28.0)
Olive oil	0.0 (0.0–3.0)	2.0 (0.0–6.0)
GREECE-Athens	n = 244	n = 194
All meat	5.6 (3.6–8.3)	4.6 (2.9–6.6)
Fish	1.0 (0.5–2.0)	1.0 (0.7–2.0)
All vegetables[1]	21.0 (14.0–28.0)	21.0 (14.0–28.0)
Fruit	14.0 (7.0–21.0)	14.0 (7.0–21.0)
Tea	0.1 (0.0–1.0)	0.1 (0.0–1.0)
Coffee	14.0 (7.0–21.0)	14.0 (7.0–14.0)
Olive oil	14.0 (11.0–18.0)	14.0 (12.0–21.0)
ITALY-Aviano	n = 152	n = 151
All meat	7.0 (5.0–9.0)	6.2 (4.7–8.1)
Fish	1.0 (0.5–1.0)	1.0 (0.5–1.0)
All vegetables[1]	7.0 (6.0–14.0)	14.0 (7.0–14.0)
Fruit	7.0 (3.0–14.0)	14.0 (7.0–14.0)
Tea	0.0 (0.0–2.0)	0.5 (0.0–7.0)
Coffee	14.0 (7.0–21.0)	14.0 (7.0–21.0)
Olive oil	12.5 (2.0–17.0)	14.0 (7.0–21.0)
ITALY-Padova	n = 135	n = 130
All meat	7.5 (4.5–10.0)	6.7 (4.7–9.0)
Fish	1.0 (0.2–2.0)	1.0 (0.5–2.0)
All vegetables[1]	7.0 (5.0–7.0)	7.0 (7.0–14.0)
Fruit	7.0 (3.0–7.0)	7.0 (7.0–14.0)
Tea	0.2 (0.0–3.0)	0.5 (0.0–3.0)
Coffee	14.0 (7.0–21.0)	14.0 (7.0–14.0)
Olive oil	14.0 (14.0–28.0)	14.0 (10.8–21.0)
ITALY-Turin	n = 167	n = 198
All meat	7.1 (5.1–10.0)	7.0 (4.7–9.2)
Fish	1.0 (0.2–2.0)	1.0 (0.5–2.0)
All vegetables[1]	7.0 (5.0–14.0)	14.0 (7.0–14.0)
Fruit	7.0 (4.0–14.0)	14.0 (7.0–14.0)
Tea	0.0 (0.0–2.0)	0.2 (0.0–3.0)
Coffee	14.0 (7.0–21.0)	14.0 (7.0–21.0)
Olive oil	14.0 (10.0–17.0)	14.0 (14.0–22.8)
IRELAND-Dublin	n = 44	n = 19
All meat	6.7 (4.4–9.0)	5.5 (2.5–7.5)
Fish	1.0 (0.5–2.0)	1.0 (0.5–1.0)
All vegetables[1]	7.0 (4.3–7.0)	7.0 (3.0–14.0)
Fruit	3.0 (1.0–7.0)	7.0 (3.0–7.0)
Tea	28.0 (21.0–42.0)	28.0 (0.0–35.0)
Coffee	0.0 (0.0–7.0)	0.0 (0.0–7.0)
Olive oil	0.0 (0.0–2.0)	0.0 (0.0–2.0)
NORWAY-Oslo	n = 173	n = 184
All meat	4.5 (3.0–7.4)	4.5 (2.8–7.2)
Fish	2.0 (1.0–2.0)	2.0 (1.0–3.0)
All vegetables[1]	7.0 (4.0–7.0)	7.0 (5.0–7.0)
Fruit	5.0 (2.0–7.0)	7.0 (5.0–7.0)
Tea	1.0 (0.0–4.0)	2.0 (0.2–7.0)
Coffee	21.0 (7.0–42.0)	14.0 (7.0–28.0)
Olive oil	1.0 (0.0–4.3)	1.2 (0.0–4.0)
UK-Glasgow	n = 98	n = 91
All meat	7.5 (6.0–10.2)	6.3 (4.9–8.1)
Fish	1.0 (1.0–1.0)	1.0 (0.5–2.0)
All vegetables[1]	5.0 (3.0–7.0)	7.0 (4.0–7.0)
Fruit	2.0 (0.5–7.0)	7.0 (3.0–7.0)
Tea	21.0 (6.0–42.0)	28.0 (14.0–35.0)
Coffee	14.0 (0.4–28.0)	7.0 (0.1–21.0)
Olive oil	0.0 (0.0–1.0)	1.1 (0.0–4.0)
UK-Manchester	n = 151	n = 186
All meat	6.2 (4.5–9.0)	6.0 (4.5–7.5)
Fish	1.0 (0.5–2.0)	1.0 (1.0–2.0)
All vegetables[1]	7.0 (3.0–7.0)	7.0 (4.0–7.0)
Fruit	4.0 (1.0–7.0)	7.0 (3.0–7.0)
Tea	21.0 (0.5–35.0)	21.0 (7.0–42.0)
Coffee	14.0 (1.0–28.0)	7.0 (1.0–22.8)
Olive oil	0.0 (0.0–2.0)	2.0 (0.0–4.0)
UK-Newcastle	n = 89	n = 113
All meat	6.0 (4.5–9.1)	5.5 (4.0–8.0)
Fish	1.0 (1.0–2.0)	1.0 (1.0–2.0)
All vegetables[1]	6.0 (3.0–7.0)	7.0 (4.0–7.0)
Fruit	3.0 (1.0–7.0)	7.0 (3.5–7.0)
Tea	21.0 (0.7–35.0)	21.0 (5.0–35.0)
Coffee	14.0 (1.0–28.0)	14.0 (1.0–28.0)
Olive oil	0.0 (0.0–1.5)	2.0 (0.0–6.0)
SPAIN-Barcelona	n = 195	n = 166
All meat	9.0 (5.0–12.7)	6.0 (5.0–9.3)
Fish	1.0 (1.0–3.0)	1.0 (1.0–2.0)
All vegetables[1]	3.0 (1.0–7.0)	4.0 (1.0–7.0)
Fruit	7.0 (1.0–7.0)	7.0 (7.0–14.0)
Tea	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Coffee	14.0 (7.0–21.0)	7.0 (7.0–14.0)
Olive oil	28.0 (14.0–47.0)	14.0 (14.0–56.1)
CROATIA-Zagreb	n = 54	n = 46
All meat	6.4 (4.9–8.0)	5.5 (4.3–7.0)
Fish	0.6 (0.2–1.0)	0.5 (0.5–1.0)
All vegetables[1]	4.0 (3.0–7.0)	4.0 (3.0–5.0)
Fruit	2.0 (1.0–3.0)	3.0 (1.2–5.0)
Tea	0.5 (0.0–3.0)	0.5 (0.1–2.0)
Coffee	14.0 (7.0–21.0)	14.0 (7.0–22.8)
Olive oil	0.0 (0.0–0.2)	0.0 (0.0–0.2)
FRANCE-Paris	n = 323	n = 234
All meat	No information	
Fish	1.0 (0.5–3.0)	1.0 (0.5–3.0)
All vegetables[1]	4.9 (2.6–8.2)	9.6 (5.2–15.0)
Fruit	3.9 (1.6–10.0)	9.0 (4.0–12.0)
Tea	No information	
Coffee	21.0 (14.0–28.0)	21.0 (14.0–28.0)
Olive oil	No information	

Median (and quartiles) by center, gender and upper aerodigestive tract cancer case/control status.
[1]Potatoes excluded.

pack-years as an ordered variable with 1 = <20, 2 = 20–39, 3 = 40–59, 4 = 60–79 and 5 = 80+ pack-years). Drink-years and pack-years among ex- and current-users were assessed as ordinal variables to avoid disproportional influence of a few individuals with extreme values. Statistical analyses were conducted using the SPSS 16.0 statistical software.

Results

A total of 2,304 cases (1,861 men and 443 women) of UADT cancer and 2,227 controls (1,661 men and 566 women) were included in the analysis probing the association of dietary variables with risk of UADT cancer. Table I shows the distribution of UADT cancer cases per center and subsite. There were 534 cases of cancer of the oral cavity, 826 of pharyngeal (excluding nasopharyngeal) cancer, 702 of laryngeal cancer, 235 of cancer of the esophagus and 7 cases of nonotherwise-specified UADT cancers. This distribution reflects the case mix in the participating hospital(s) and cannot be used to ascertain proportional distributions in the underlying populations.

Table II shows the frequency of consumption (median and quartiles) of food items or groups that have been reported in some or several previous investigations to be related to UADT cancer risk. Among controls, there are no clear patterns with respect to meat or fish consumption, but frequency of intake of vegetables and fruits was somewhat higher in southern European centers. Frequency of intake of vegetables and fruits was particularly high in Athens, which could be due in part to the use of an extensive food frequency questionnaire, although international databases do point to a higher intake of vegetables and fruits in Greece.[10] Tea consumption was low in all but in the U.K. centers and Dublin, whereas the opposite was true with respect to coffee intake. The most striking difference between centers in Mediterranean *versus* non-Mediterranean countries concerns olive oil, which is regularly consumed in the former and only exceptionally in the latter. Frequency of consumption of indicated food items or groups differed very little between men and women (data not shown), implying that the difference in energy intake between genders is mostly accounted for by portion size.

Table III shows the distribution of ARCAGE cases and controls by marginal, center-specific tertiles of frequency of consumption of the indicated food items or groups. These tertiles are not gender-specific because, as indicated, frequencies of intake were generally similar between genders. This table allows an inspection of differential patterns of intakes of the indicated food groups, as well as coffee and tea, between cases and controls, although these comparisons are not adjusted for gender, age or lifestyle variables. It should be noted that for fruit juice, tea and olive oil, 2 rather than 3 categories are shown, because the respective distributions were too skewed to allow calculations of tertiles. An additional distribution for tea and coffee refers to preferred temperature of intake of these beverages. There is evidence that intake of all forms of meat except poultry is associated with increased risk of UADT cancer, whereas intake of fish appears to be unrelated to this risk. There is also evidence that overall consumption of vegetables or fruits, as well as olive oil and perhaps tea is inversely associated with UADT cancer risk. Finally, there is evidence that, contrary to expectation, higher temperature of tea or coffee intake is not associated with increased risk for cancer of UADT, if anything the association appears to be inverse. As indicated, however, these associations are not adjusted for nondietary potential confounders.

In Table IV, results concerning the indicated food items or groups are evaluated in relation to UADT cancer risk, stratified by center and also controlling for age, gender, height, BMI, educational level and, in detail, tobacco smoking and alcohol consumption. Results are presented both categorically, using the first tertile as baseline, as well as by increasing tertile of consumption. Whereas meat overall is derived from the addition of component meat categories, vegetables overall and fruits overall represent distinct items in the questionnaire and are not derived from the addition of the component vegetables and fruits, respectively (which explains mild deviations in the respective point estimates of the odds ratio). A number of important associations are evident in this table and, reassuringly, in virtually all instances, significant trends are also reflected in monotonic changes across the 3 tertiles. In contrast to poultry, increased consumption of all forms of red meat is significantly or suggestively associated with increased UADT cancer risk, with no evidence of significant heterogeneity among the indicated different types of red meat ($p > 0.30$). For red meat overall, the OR contrasting the third to the first tertile was 1.31 (95% CI: 1.09–1.57). When we limited the analysis to esophageal cancer, for which there is prior suggestive evidence of an increased risk in relation to higher red meat intake,[5] the association was stronger (OR contrasting the third to the first tertile was 1.69 with 95% CI: 1.12–2.55). Higher consumption of fruits overall (OR contrasting the third to the first tertile = 0.48 with 95% CI: 0.40–0.58) and vegetables overall (OR contrasting the third to the first tertile = 0.53 with 95% CI: 0.43–0.67), though not cooked vegetables and pulses, was significantly associated with reduced risk of UADT cancer. Olive oil, whether in salads or in cooking, was also significantly inversely associated with UADT cancer risk (OR contrasting frequency of consumption above *versus* below median = 0.78 with 95% CI: 0.67–0.90). Among nonalcoholic beverages, coffee appears unrelated to risk, whereas there is evidence that increasing frequency of intake of tea is associated with reduced disease risk (OR contrasting frequency of consumption above *versus* below median = 0.83 with 95% CI: 0.69–0.98).

Because the frequencies of intake of tea and coffee are inversely associated, we have evaluated whether there is mutual confounding in the association of these 2 variables with UADT risk. Controlling for coffee intake reduced the OR contrasting frequency of consumption above *versus* below median for tea to 0.82 (95% CI: 0.69–0.98), whereas controlling for tea intake reduced the OR contrasting third to first tertile for coffee from 1.03 (95% CI: 0.87–1.23) to 0.96 (95% CI: 0.79–1.16). We have also included red meat overall, vegetables overall and fruits overall, as well as the nondietary variables (including alcohol) indicated in the footnote of Table IV in a separate multiple logistic regression model. There was evidence of modest mutual confounding between vegetables overall and fruits overall. Thus, the OR contrasting third to first tertile for vegetables overall increased to 0.80 (95% CI: 0.61–1.05), whereas the odds ratio for fruits increased to 0.58 (95% CI: 0.47–0.72). There was practically no change in the odds ratio for red meat overall after controlling for both vegetables overall and fruits overall (OR contrasting third to first tertile = 1.33 with 95%

TABLE III – THE ARCAGE STUDY: DISTRIBUTION OF UPPER AERODIGESTIVE TRACT CANCER CASES AND CONTROLS, BY MARGINAL CENTER-SPECIFIC[1] TERTILES OF FREQUENCY OF CONSUMPTION OF THE INDICATED DIETARY VARIABLES

	Tertiles		
	1	2	3
All meat			
Cases	589 (29.7)	653 (33.0)	739 (37.3)
Controls	745 (37.4)	668 (33.5)	580 (29.1)
Red meat and cold cuts			
Cases	581 (29.3)	638 (32.2)	762 (38.5)
Controls	772 (38.7)	667 (33.5)	554 (27.8)
Poultry			
Cases	957 (48.3)	612 (30.9)	412 (20.8)
Controls	854 (42.8)	629 (31.6)	510 (25.6)
Fish			
Cases	993 (43.1)	804 (34.9)	507 (22.0)
Controls	922 (41.4)	791 (35.5)	514 (23.1)
All vegetables[2]			
Cases	1086 (47.1)	971 (42.1)	247 (10.7)
Controls	744 (33.4)	1119 (50.2)	364 (16.3)
Fresh green vegetables			
Cases	939 (47.4)	667 (33.7)	375 (18.9)
Controls	674 (33.8)	804 (40.3)	515 (25.8)
Cooked green vegetables			
Cases	927 (46.8)	543 (27.4)	511 (25.8)
Controls	801 (40.2)	617 (31.0)	575 (28.9)
All fruit			
Cases	1113 (48.3)	815 (35.4)	376 (16.3)
Controls	639 (28.7)	988 (44.4)	600 (26.9)
Fresh fruit juice[3]			
Cases	1036 (52.3)	945 (47.7)	
Controls	929 (46.6)	1064 (53.4)	
Tea[3]			
Cases	717 (36.2)	1264 (63.8)	
Controls	585 (29.4)	1408 (70.6)	
Coffee			
Cases	934 (40.5)	712 (30.9)	658 (28.6)
Controls	1029 (46.2)	709 (31.8)	489 (22.0)
Temperature of tea or coffee[4]			
Cases	1005 (53.0)	703 (37.1)	189 (10.0)
Controls	885 (46.1)	794 (41.4)	241 (12.6)
Olive oil in salads and cooking[3]			
Cases	1227 (61.9)	754 (38.1)	
Controls	1007 (50.5)	986 (49.5)	

[1]Data from Paris included only for all vegetables, all fruits, fish and coffee; on account of this and some missing values data do not always add up.–[2]Potatoes excluded.–[3]Median cut off (distribution too skewed to allow calculation of tertiles).–[4]Temperature stands for 1 = warm, 2 = hot, 3 = very hot.

TABLE IV – THE ARCAGE STUDY: LOGISTIC REGRESSION-DERIVED ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR UPPER AERODIGESTIVE TRACT CANCER BY CENTER-SPECIFIC TERTILE OF FREQUENCY OF CONSUMPTION OF THE INDICATED FOOD ITEMS OR GROUPS[1]

	OR 2nd tertile	95% CI	OR 3rd tertile	95% CI	OR (trend)	95% CI	*p* for trend
Red meat overall[2]	1.16	0.97–1.39	1.31	1.09–1.57	1.14	1.05–1.25	0.004
Beef[2]	1.04	0.87–1.23	1.08	0.90–1.30	1.04	0.95–1.14	0.406
Pork[2]	1.08	0.91–1.27	1.29	1.05–1.58	1.13	1.02–1.25	0.019
Other red meat(lamb etc)[2]	0.92	0.78–1.09	1.17	0.95–1.43	1.05	0.95–1.16	0.300
Cold cuts[2]	1.08	0.90–1.29	1.26	1.05–1.51	1.12	1.02–1.22	0.016
Poultry[2]	0.95	0.80–1.13	0.87	0.72–1.05	0.93	0.85–1.03	0.149
Fish	1.12	0.95–1.32	1.10	0.92–1.32	1.06	0.97–1.15	0.236
Vegetables overall[3]	0.73	0.63–0.85	0.53	0.43–0.67	0.73	0.66–0.81	<0.001
Raw green vegetables[2]	0.82	0.69–0.97	0.73	0.60–0.89	0.85	0.77–0.94	0.001
Cooked green vegetables[2]	0.90	0.76–1.07	1.09	0.92–1.31	1.04	0.95–1.13	0.435
Carrots	0.81	0.69–0.95	0.66	0.55–0.78	0.81	0.74–0.89	<0.001
Fresh tomatoes	0.79	0.68–0.92	0.71	0.60–0.85	0.84	0.77–0.91	<0.001
Pulses[2],[4]					1.09	0.93–1.28	0.271
Fresh juice[2],[4]					0.91	0.77–1.06	0.216
Fruit overall	0.62	0.53–0.73	0.48	0.40–0.58	0.68	0.62–0.75	<0.001
Apples and pears[2]	0.85	0.72–1.01	0.73	0.60–0.89	0.85	0.78–0.94	0.002
Citrus fruit[2]	0.82	0.69–0.98	0.78	0.65–0.93	0.88	0.80–0.96	0.006
Bananas	0.86	0.73–1.01	0.78	0.66–0.93	0.88	0.81–0.96	0.003
Berries[2]	0.67	0.56–0.79	0.63	0.53–0.76	0.79	0.72–0.87	<0.001
Plums, peaches, apricots[2]	0.76	0.64–0.91	0.79	0.66–0.95	0.89	0.81–0.97	0.010
Kiwi[2]	0.78	0.65–0.94	0.61	0.52–0.73	0.78	0.72–0.85	<0.001
Tea[2],[4]					0.83	0.69–0.98	0.032
Coffee	1.02	0.87–1.19	1.03	0.87–1.23	1.02	0.93–1.11	0.716
Temperature[2] 1 = warm, 2 = hot, 3 = very hot	0.78	0.65–0.92	0.67	0.52–0.86	0.81	0.72–0.91	<0.001
Olive oil overall[2,4]					0.78	0.67–0.90	0.001
Olive oil in salads[2,4]					0.84	0.70–1.00	0.051
Olive oil for cooking[2,4]					0.65	0.55–0.78	<0.001

Results categorically, using the first tertile as baseline, and ordered by increasing tertile (trend).
[1]Adjusted for center through stratification and also controlled for age (in years, continuous), gender, BMI (ordered in center-specific quintiles), height (in cm, continuous), education level (categorical: primary-baseline, further education but not university level, university education), alcohol consumption (never drinkers, former drinkers, current drinkers; for former and current drinkers further control for drink-years was undertaken), smoking status (never smokers, former smokers, current smokers; for former and current smokers further control for pack-years was undertaken).–[2]Food item not recorded in the Paris center.–[3]Potatoes excluded.–[4]Center-specific median used as cut-off point; for these items: above *vs*. below median.

CI: 1.10–1.59). Finally, we repeated the analysis using center-and-gender-specific tertiles, instead of center-specific tertiles, but the results were essentially unchanged.

There was no evidence in our data that an increase in the preferred temperature of tea or coffee is associated with increased risk of UADT cancer. In fact, the association was, if anything, inverse (OR contrasting very hot to warm = 0.67 with 95% CI: 0.52–0.86). When we limited the analysis to esophageal cancer, for which there is prior suggestive evidence of increased risk in relation to higher drink temperature,[5] the corresponding OR was 0.89 (95% CI: 0.51–1.55).

As indicated, population controls were used in the 3 UK centers, as opposed to hospital controls in the remaining centers, so we repeated the analyses separately for these 2 groups of centers, controlling for individual center within each of the 2 groups. In the group of UK centers (338 cases and 390 controls), the ORs (95% CI) contrasting third to first tertile were 1.19 (0.76–1.86) for red meat overall, 0.57 (0.29–1.10) for vegetables overall and 0.50 (0.28–0.89) for fruits overall. In the group of remaining centers (1,966 cases and 1,837 controls), the corresponding values were 1.33 (1.09–1.63) for red meat overall, 0.53 (0.42–0.68) for vegetables overall and 0.47 (0.39–0.58) for fruits overall. It appears that the results are fairly consistent irrespectively of the nature of controls used (*p* for heterogeneity >0.50 in all 3 instances). However, tea is infrequently used in continental Europe, so the respective results rely heavily on the UK centers. In the French center (323 cases and 234 controls), meat, tea and olive oil consumption was not assessed and the gradient appeared sharper with respect to vegetables overall (OR contrasting third to first tertile 0.19, 95% CI: 0.12–0.33) and fruits overall (OR contrasting third to first tertile 0.23, 95% CI: 0.14–0.39).

Discussion

In the large multicenter ARCAGE case–control study, we found evidence that red meat significantly increases the risk of UADT cancer, the association being apparently stronger for cancer of the esophagus, for which there is supportive prior evidence.[5] Regarding other foods of animal origin, no association was evident with respect to poultry and fish. With respect to plant foods, consumption of fruits and consumption of non-starchy vegetables (but not cooked green vegetables or pulses) were significantly inversely associated with UADT cancer risk. There was no evidence for differential effects by the specific fruit or raw nonstarchy vegetable categories examined. Moreover, consumption of olive oil, either in salads or for cooking, and tea drinking were significantly inversely associated with UADT cancer risk. There was no evidence for an association of this risk with coffee drinking. Temperature of beverages generally consumed warm or hot was unrelated to cancer of the esophagus and was apparently inversely associated with the risk for the remaining UADT cancers.

When viewed in the context of the existing scientific literature,[5,6] our results strengthen the evidence that fruits and non-starchy vegetables convey some protection against UADT cancer and suggest that the evidence applies to fresh rather than cooked plant foods. Red meat has been reported to increase the risk of several forms of cancer, but the evidence for UADT cancer is quite weak,[11] except for cancer of the esophagus.[5] In our data, higher consumption of all examined types of red meat was associated with increased UADT cancer risk, but the association was stronger for cancer of the esophagus. Several mechanisms have been invoked to explain the carcinogenic potential of red meat with respect to various cancer sites, including generation of carcinogenic *N*-nitroso compounds, production of heterocyclic amines and polycyclic aromatic hydrocarbons when meat is cooked in high temperatures, and release of heme iron, which facilitates the production of free radicals.[5] As for tea, it has been reported to be rich in phytochemicals, notably flavonoids,[12] which have been reported to have anticancer properties, so our results suggesting an inverse association with UADT cancer risk are biologically plausible. Previous studies have reported olive oil to be inversely related to cancer of the oral cavity and pharynx,[13] larynx[14] as well as squamous cell esophageal cancer,[15] in line with our results. In contrast, we found no evidence that very hot drinks increase the risk of either cancer of the esophagus or cancer of the remaining UADT sites, in spite of reports that very hot drinks could possibly increase esophageal cancer risk.[5] In fact, our data suggest that increasing beverage temperature, if anything, reduces risk of UADT cancer in sites other than the esophagus, a finding that deserves exploration in future investigations.

Strengths of our investigation are its large sample size, coverage of several populations with very different UADT incidence rates, use of histologically confirmed incident cases and recruitment of controls with diagnoses unrelated to diet as well as to tobacco smoking and alcohol intake. Limitations of the study are those inherent to case control investigations, notably information bias, as well as the use of a limited dietary questionnaire which did not allow for control of energy intake. However, information bias is unlikely to have been substantial, because our results concerning plant food intake were restricted to fresh as opposed to cooked foods, and this distinction is not generally entertained by the public. Moreover, we found an inverse association of UADT cancer risk with hot drinks, in spite of the general perception to the opposite. The combination of center-specific tertiles into a single analysis makes interpretation of the results difficult, as consumption of several of the examined dietary variables varies across centers. However, there is no evidence in the literature that the association between the variables we have examined and UADT cancer risk is anything but monotonic, which justifies combination of tertiles across centers, with adjustment for center. Control for energy intake is important in itself,[16] but also accommodates systematic over- or under-reporting by cases *versus* controls.[17] However, there was no evidence of systematic over- or under-reporting in the results (increased UADT cancer risk was associated with increased red meat intake, but with reduced fresh plant food intake, while there were also several null associations with other foods).

In conclusion, in a large study covering several European populations, we have examined diet in relation to UADT cancer risk, controlling for smoking and drinking patterns, and we have found strong evidence that dietary habits play an important role in the etiology of these cancers. Consumption of fresh nonstarchy vegetables, fruits, olive oil and tea appears to be associated with reduced UADT cancer risk. Consumption of red meat appears to be associated with increased risk of UADT cancer, particularly cancer of the esophagus. We could not confirm the previously reported association of very hot beverages with esophageal cancer risk and in fact, we found evidence that high beverage temperature may be inversely associated with UADT cancer risk.

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