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Risk of upper aerodigestive tract cancer and type of alcoholic beverage: a European multicenter case–control study

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Abstract The general relationship between cancers of the upper aerodigestive tract (UADT) and alcohol drinking is established. Nevertheless, it is uncertain whether different types of alcoholic beverages (wine, beer and liquor) carry different UADT cancer risks. Our study included 2,001 UADT cancer cases and 2,125 controls from 14 centres in 10 European countries. All cases were histologically or cytologically confirmed squamous cell carcinomas. Controls were frequency matched by sex, age and centre. Logistic regression models were used to estimate odds ratios (OR) and 95 % confidence intervals (95 %CI) adjusted for age, sex, centre, education level, vegetable and fruit intake, tobacco smoking and alcohol drinking, where appropriate. Risk of beverage-specific alcohol consumption were calculated among 'pure drinker' who consumed one beverage type exclusively, among 'predominant drinkers' who consumed one beverage type to more than 66 % and among 'mixed drinkers' who consumed more than one

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beverage type to similar proportions. Compared to never drinkers and adjusted for cumulative alcohol consumption, the OR and 95 %CI for wine, beer and liquor drinking, respectively, were 1.24 (0.86, 1.78), 1.54 (1.05, 2.27) and 0.94 (0.53, 1.64) among 'pure drinkers' (p value for heterogeneity across beverage types = 0.306), 1.05 (0.76,1.47), 1.25 (0.87,1.79) and 1.43 (0.95, 2.16) among 'predominant drinkers' (p value = 0.456), and 1.09 (0.79, 1.50), 1.20 (0.88, 1.63) and 1.12 (0.82, 1.53) among 'mixed drinkers' (p value = 0.889). Risk of UADT cancer increased with increasing consumption of all three alcohol beverage types. Our findings underscore the strong and comparable carcinogenic effect of ethanol in wine, beer and liquor on organs of the UADT.

Keywords Epidemiology · Cancer · Alcohol · Wine · Beer · Liquor · Head and neck cancer · Upper aerodigestive tract cancer

Background

Alcohol consumption is a well established risk factor for cancers of the upper aerodigestive tract (oral cavity, pharynx, esophagus, larynx) with a known dose–response relationship [1–5]. In several European countries, approximately 44 % of the incidence of upper aerodigestive tract (UADT) cancer is attributable to former and current alcohol consumption among men and 25 % among women [6]. Nevertheless, it is an open question whether drinking different alcoholic beverage types (wine, beer and liquor which are also known as spirits) carry different risks of UADT cancers. Findings from previous epidemiological studies are inconsistent with respect to risk differences by type of alcoholic beverage for the development of UADT cancer [7, 8]. Some studies have reported the highest increased risk of UADT cancer was for wine consumption [9, 10], for beer consumption [11], or for liquor consumption [12–14]. Several studies reported that beer and liquor consumption carry the highest alcohol related risk [15–18], while some other studies found no differences between different types of alcoholic beverage [19–24]. Lack of statistical power to assess less common types of beverage and to detect differences between risks may have influenced these findings. Underreporting or misclassification of consumption of the preferred beverage type could have lead to observations that the most commonly used type of alcoholic beverage in each study had the greatest risk [25]. In addition, it is methodologically very difficult to separate real biological effects out, which are based on higher ethanol concentration or beneficial compounds in specific beverage types, since consumed type of beverage may be collinear with important other traits like sex, tobacco use, education or fruit and vegetable intake [2, 4].

Recently, a large pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium reported comparable risks of oral cavity,

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pharyngeal and laryngeal cancer associated with exclusive consumption of beer and liquor, but a weaker association with exclusive wine consumption at low drinking levels [18]. However, confounding or modification of risk by drinking pattern (such as regular binge drinking, drinking outside of meals and before noon), and high fruit and vegetable intake could not be taken into account. In North Europe, wine consumption is associated with drinking at meals and with a diet rich on fruits and vegetables, whereas beer and liquor consumption are associated with binge drinking [26–28]. However, such associations may differ by country and their influence on risk of UADT cancer is unclear. Another analysis of our data on socioeconomic factors and risk of UADT cancer showed that alcohol consumption was part of the explanation of socioeconomic inequalities [29].

To evaluate the association of drinking different types of alcoholic beverages, we analyzed the data from a large-scale case–control study of UADT cancer in Europe. The purpose of the present analysis was to compare the effect of drinking wine, beer and liquor drinking on the risk of UADT cancer. To control for the confounding by the consumption of the other alcoholic beverages, we evaluated the risk of UADT cancer among 'pure drinkers' who consumed one beverage type exclusively, and among 'predominant drinkers' in whom one beverage type dominated and confounding by other alcoholic beverages may be unlikely. We compared these results with the risk of UADT cancer among 'mixed drinkers' who consumed more than one beverage type in similar proportions and in whom confounding by other alcoholic beverages may be possible. As a secondary aim, we explored the potential modification of these associations by sex, tobacco smoking and fruit and vegetable intake.

Research design and methods

Study design

The Alcohol-Related Cancers and Genetic Susceptibility in Europe (Arcage) study was designed to investigate the role of genetic factors, alcohol drinking, tobacco smoking, and several other suggested risk factors in UADT cancer. The study was initiated by the International Agency for Research on Cancer (IARC) and full details of its design have been previously published [30]. This multi-center case–control study took place in 14 centers in 10 European countries: Zagreb (Croatia), Prague (Czech Republic), Paris (France), Bremen (Germany), Athens (Greece), Dublin (Ireland), Aviano, Padua and Turin (Italy), Oslo (Norway), Barcelona (Spain), Glasgow, Manchester and Newcastle (United Kingdom). Recruitment was conducted from 2002 until 2005 in all centers, except in Paris where a broadly similar case–control study of UADT cancer was already conducted from 1987 to 1992.

The study was approved by the ethical review board of IARC, as well as the respective local boards in participating centers. All subjects provided written informed consent for their participation in the study. Cases were identified by participating hospitals and were men and women with histologically or cytologically confirmed UADT cancer diagnosed within the past 6 months. Eligibility was determined using the International Classification of Diseases, 10th Revision (ICD 10) codes: C00–C10, C12–C13, C14.0, C14.8, C15.0, C15.3–C15.5, C15.8–C15.9, and C32. Since the etiology of salivary gland (ICD 10 codes C07–C08), external lip (ICD 10 codes C00.0–C00.2) and nasopharyngeal (ICD 10 codes C11) cancers differ from that of other UADT cancers, we did not include these cancers. We used the International Classification of Diseases for Oncology, 2nd Edition (ICD–O 2) codes to identify cases of squamous cell carcinoma (SCC): 8051/3, 8052/3, 8070, 8070/3, 8071, 8071/3, 8072/3, 8073/3, 8074/3, 8076/3, 8077/3, 8082/3, 8083/3. All cases in the Paris study center were SCC.

Controls were frequency matched to cases by sex, age (in 5-year intervals) and referral (or residential) area. The three UK centers used population-based controls randomly selected from the same primary practice list as the corresponding case (N = 390), while other centers used hospital controls (N = 1837). Hospital controls were randomly selected from subjects admitted as in- or out-patients in the same hospital as the case. Eligibility of controls included short hospital stay (less than 1 week for the majority of controls) with an admission diagnosis unrelated to alcohol and tobacco, including (1) gastro-intestinal diseases (19.9 %); (2) trauma unrelated to alcohol (16.5 %); (3) ear, eye and mastoid diseases (13.4 %); (4) skin, subcutaneous tissue and musculoskeletal diseases (12.6 %); (5) genito-urinary diseases (10.0 %); (6) respiratory system diseases (9.5 %); (7) nervous system diseases, mental and behavioral disorders (5.4 %); (8) abnormal clinical findings and factors influencing health status (4.4 %); (9) viral infections characterized by skin lesions and blood diseases (3.9 %); (10) circulatory diseases (3.1 %); (11) endocrine and metabolic diseases (1.3 %).

Epidemiological data collection was performed by trained interviewers using a questionnaire which included detailed questions on socio-demographic factors, smoking history, involuntary exposure to tobacco smoke, history of alcohol drinking, personal medical history of diseases associated with UADT cancer, oral cavity health, lifetime occupational history [31] and dietary habits one year prior to the interview based on a semi-quantitative food frequency questionnaire (FFQ). Educational level and number

of years of full-time education were used as measure of socioeconomic status [29]. The Paris center records social class in three categories (worker, clerk, manger) instead of level of education attainment and the Bremen center recorded it in a slightly different way to reflect the education system in Germany (no finished school, finished secondary school, finished secondary school one year longer, finished secondary school for technical college, finished secondary school for university, further finished school, university degree). Both systems were transferred into the used system of education level (primary school/worker, further school/clerk, university/manager).

Interviewers also measured height and weight. If this was not possible, the relevant information was retrieved from medical records or from the participants themselves. They reported weight two years prior to interview and at age 30 years. Body mass index (BMI in kg/m^2) was calculated and categorized using World Health Organization (WHO) standards (<18.5, 18.5–24.9, 25.0–29.9, 30.0+ kg/m^2). BMI at time of recruitment was available for all centers, except for the UK and Dublin study centers. Weights from two years prior to recruitment and at the age of 30 were not recorded in the Paris study center. IARC received all anonymized data from individual study centers and performed quality control checks on missing and inconsistent data.

For the hospital-based centers, the response rate was 90 % among cases (2,137/2,365) and 91 % among controls (2,022/2,221), and for the population-based centers, the response rate was 52 % among cases (363/696) and 29 % among controls (390/1,350). The reasons for refusal to participate were not giving consent (335 cases/1,049 controls), unavailability due to illness, language or incorrect contact information (101/24), physician refusal or confidentiality issues (48/36), death of the subject (68/3) and scheduling conflicts (9/47). In addition, in a few centers patients did not allow any recording of their data, leading to a small underestimation of the response rate. We excluded 196 case subjects and 184 control subjects who did not meet the inclusion criteria of the study protocol, 152 cases with non-SCC, 18 cases with in situ carcinoma and 26 cases with unknown histology. In addition, 108 cases and 102 controls with missing essential exposure or confounding variables (frequency and duration of alcohol drinking, sex, age, duration, frequency and time since cessation of tobacco smoking, education level, fruit and vegetable intake) were excluded from all analyses leaving 2,001 SCC cases and 2,125 controls for analysis. Of these cases, 489 were oral cavity cancers, 623 were pharyngeal cancer cases, 631 were laryngeal cancer cases, 144 were esophageal cancer cases, 107 were overlapping oral cavity/pharyngeal cancer cases and 7 were other overlapping cancer cases of the UADT.

Exposure definitions

Alcohol history and drinking duration:

Never drinkers were defined as individuals who reported not to have drunk wine, beer, aperitifs or hard liquor during their lifetime. Alcohol drinkers were asked questions about the volume of the drinking unit, the frequency and duration of drinking of alcoholic beverages (beer, wine, aperitifs or hard liquors) in different periods over life (alcohol history). Lifetime duration of alcohol drinking in years was calculated by summing over all drinking periods and counting overlapping time periods of alcohol consumption once.

Lifetime number of standardized drinks, alcohol drink-years and drinking frequency:

To calculate the lifetime cumulative consumption for each alcohol type, we multiplied the volume of a unit (in ml) by the number of units consumed per day, the number of drinking days per week, 52 weeks per year and the years of beverage consumption. In the UK study centers, the exact percentages of ethanol, obtained from alcohol product lists, were used. In all other study centers, cumulative consumption of pure ethanol, expressed in ml, was calculated by as the sum, across beverage type, of the product of the beverage-specific lifetime consumption (in ml) and volume percentage of pure ethanol, which were 12 % for wine, 5 % for beer and 40 % for hard liquors and aperitifs. Lifetime number of standardized drinks was then calculated as the cumulative consumption of pure ethanol divided by the mean volume of pure ethanol per drink (18 ml) across all alcoholic beverage types, which corresponds approximately to 330 ml of beer, 150 ml of wine, 36 ml of hard liquor or aperitifs. Alcohol drink-years were calculated as the lifetime number of drinks divided by 365 days. Average number of drinks per day (frequency of alcohol drinking weighted by the length of the drinking period) was obtained by dividing alcohol drink-years by lifetime duration of alcohol drinking in years.

Beverage types and drinking pattern:

Duration, frequency and cumulative consumption were calculated separately for each beverage type and for the combination of two beverage types (wine and beer, wine and liquor, beer and liquor). All drinkers were asked if they had normally drunk during meals one year before interview, between meals or both, and how often they consumed alcohol before noon. Binge drinking variables included exposure frequency and duration in lifetime of drinking large amounts of alcoholic beverages in a short period of time, which was ascertained by asking about consumption of “more than 10

drinks in a couple of hours". Alcohol drinkers were also classified as 'pure drinkers' who consumed one beverage type exclusively, in 'predominant drinkers' who consumed one beverage type under at least two types to more than 66 %, or in 'mixed drinkers' who consumed more than one beverage type to similar proportions (less than 66 %). The cut-point of 66 % was chosen a priory to define 'predominant drinkers'. Never wine drinkers included 'pure beer drinkers', 'pure liquor drinkers', and beer and liquor drinkers ('predominant' and 'mixed'). Never beer drinkers included 'pure wine drinkers', 'pure liquor drinkers', and wine and liquor drinkers ('predominant' and 'mixed'). Never liquor drinkers included 'pure wine drinkers', 'pure beer drinkers', and wine and beer drinkers ('predominant' and 'mixed').

Tobacco history:

Subjects were asked if they had ever smoked cigarettes, cigars, pipes or any tobacco product at least once a week for a year. Variables for cumulative consumption, duration, frequency, age at starting and stopping, and time since starting and stopping were calculated for tobacco (cigarette, cigar and pipe) smoking in a similar way to that described for alcohol consumption. Tobacco smoking products were converted to cigarette equivalents (one cigar equal four cigarette and one pipe equal three and a half cigarettes) [32]. For pack-years of cigarette equivalents, a pack was considered as a standard volume of 20 cigarettes. To adjust at the same time for smoking frequency, smoking duration, smoking status and time since stopped smoking, we created a combined variable of smoking frequency, smoking status and time since stopped smoking. Cut-offs for the categories were taken so near as possible to the median within each group (categories shown in Table 1). Among never smokers, duration of involuntary smoking at home or at work was calculated [33]. Information on smokeless tobacco use was not collected.

The Paris center:

For the Paris center, the average drinking frequency of all types of alcoholic beverages was estimated by dividing the sum of drinks of all beverage types per day by the number of types of alcoholic beverages consumed during this time. We then multiplied the duration of alcohol drinking by the average drinking frequency of the four types of alcoholic beverages to obtain drink-years of alcohol drinking. Duration and cumulative consumption of alcohol were not available by alcohol beverage type for the Paris center. In addition, information on drinking only with meals, drinking before noon, binge frequency and binge duration was not collected in this center. In Paris, the study was restricted to smokers.

Fruit and vegetable consumption:

For FFQ-measured fruit and vegetable consumption, center-specific tertiles were created [34]. Low fruit and vegetable intake (combined) was defined as being in the lowest tertile of one food group and in either the lowest or the middle tertile of the other food group; intermediate fruit and vegetable intake incorporates either both fruit and vegetable intakes in the mid tertile, or in opposite extreme tertiles (i.e., low tertile for fruit intake, high tertile for vegetable intake); and high fruit and vegetable intake as having one intake in the high tertile and the other in the mid or the high tertile [35].

Statistical methods

Differences between the distributions of cases and controls for selected characteristics were evaluated using the Chi-squared test. We calculated odds ratios (OR) and 95 % confidence intervals (CI) using unconditional logistic regression overall and by country. To control for potential confounding, models were where appropriate adjusted for age (<40 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75+ years), sex, center, education level (primary school/worker, further school/clerk, university/manager), vegetable and fruit intake (low intake, mid intake, high intake), smoking duration (continuous), frequency and time since quitting of tobacco (cigarette, cigar and pipe) smoking (former smoker since 16+ years and <18 cig/day, former smoker since 16+ years and 18+ cig/day, former smoker since <16 years and <18 cig/day, former smoker since <16 years and 18+ cig/day, current smoker and <15 cig/day, current smoker and 15–19 cig/day, current smoker and 20–27 cig/day, current smoker and 28+ cig/day), and drinking (continuous) of alcohol (adjusting liquor consumption on wine and beer, beer consumption on wine and liquor, and wine consumption on beer and liquor). In addition, beverage-specific alcohol consumption adjusted for cumulative alcohol consumption (continuous) was calculated using the residual method to adjust for the amount of ethanol content of the specific beverage [36, 37]. In some models where number of observations was sufficient, we adjusted for BMI (18.5, 18.5–24.9, 25.0–29.9, 30.0 kg/m^2) and duration of involuntary tobacco smoking (continuous).

Analyses were stratified by smoking status (never, ever), fruit and vegetable intake (low, high = intermediate or high), frequency of binge drinking (<1 time/months, 1+ time/month), before noon drinking (never, ever), between meals drinking (never, ever), cancer site (oral cavity, oral cavity/pharynx NOS, oropharynx, hypopharynx, larynx, esophagus), sex, age, (age <45, age 45–59, age 60–74, age 75+) [38], education level (primary school/worker, further

Table 1 Selected characteristics of case and control subjects (N = Number, % = Percent)

	Never drinker				Only wine drinker				Only beer drinker				Only liquor drinker			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Center																
Prague	4	3.51	5	1.9	3	1.9	6	3.4	24	14.0	19	12.8	3	8.3	4	8.3
Bremen	7	6.14	25	9.7	5	3.1	19	10.9	43	25.0	32	21.5	4	11.1	8	16.7
Athens	19	16.7	35	14	21	13.1	22	12.6	11	6.4	10	6.7	7	19.4	3	6.3
Aviano	1	0.88	11	4.3	25	15.6	26	14.9	1	0.6			1	2.8	1	2.1
Padova	9	7.89	25	9.7	14	8.8	12	6.9	1	0.6					1	2.1
Turin	17	14.9	30	12	24	15.0	37	21.3	2	1.2	8	5.4			2	4.2
Dublin	2	1.75	3	1.2					10	5.8	3	2.0	1	2.8	1	2.1
Oslo	8	7.02	16	6.2	3	1.9	7	4.0	3	1.7	4	2.7			2	4.2
Edinburgh	3	2.63	1	0.4			4	2.3	2	1.2	5	3.4	6	16.7	7	14.6
Manchester	2	1.75	5	1.9	1	0.6	8	4.6	34	19.8	28	18.8	3	8.3	7	14.6
Newcastle	2	1.75	4	1.6	2	1.3	2	1.1	13	7.6	23	15.4	3	8.3	2	4.2
Barcelona	24	21.1	72	28	14	8.8	13	7.5	14	8.1	7	4.7	5	13.9	5	10.4
Zagreb	3	2.63	6	2.3	2	1.3	3	1.7	2	1.2	2	1.3			2	4.2
Inserm	13	11.4	19	7.4	46	28.8	15	8.6	12	7.0	8	5.4	3	8.3	3	6.3
Sex																
Men	40	35.1	110	42.8	115	71.9	101	58.0	151	87.8	124	83.2	21	58.3	25	52.1
Women	74	64.9	147	57.2	45	28.1	73	42.0	21	12.2	25	16.8	15	41.7	23	47.9
Education level																
Primary school/worker	54	47.4	101	39.3	86	53.8	70	40.2	44	25.6	23	15.4	10	27.8	9	18.8
Further school/clerk	49	43.0	132	51.4	63	39.4	93	53.4	122	70.9	119	79.9	25	69.4	34	70.8
University/manager	11	9.6	24	9.3	11	6.9	11	6.3	6	3.5	7	4.7	1	2.8	5	10.4
Smoking duration																
Never	45	39.5	158	61.5	25	15.6	81	46.6	13	7.6	39	26.2	5	13.9	15	31.3
1–9 years	2	1.8	8	3.1	1	0.6	10	5.7	5	2.9	10	6.7			6	12.5
10–19 years	11	9.6	19	7.4	6	3.8	12	6.9	9	5.2	14	9.4			2	4.2
20–29 years	9	7.9	30	11.7	17	10.6	13	7.5	28	16.3	23	15.4	1	2.8	8	16.7
30–39 years	19	16.7	25	9.7	47	29.4	25	14.4	60	34.9	31	20.8	11	30.6	10	20.8
40+ years	28	24.6	17	6.6	64	40.0	33	19.0	57	33.1	32	21.5	19	52.8	7	14.6
Smoking status by frequency and years since quitting																
Former																
16+ years, <18 cig/day	6	5.3	15	5.8	8	5.0	14	8.0	8	4.7	18	12.1	1	2.8	5	10.4
16+ years, 18+ cig/day	2	1.8	10	3.9	9	5.6	12	6.9	10	5.8	10	6.7	2	5.6	1	2.1
<16 years, <18 cig/day	3	2.6	10	3.9	12	7.5	13	7.5	7	4.1	9	6.0	1	2.8	4	8.3
<16 years, 18+ cig/day	7	6.1	12	4.7	18	11.3	12	6.9	13	7.6	15	10.1	2	5.6	5	10.4
Current																
<15 cig/day	15	13.2	14	5.4	25	15.6	22	12.6	16	9.3	21	14.1	4	11.1	7	14.6
15–19 cig/day	12	10.5	19	7.4	25	15.6	5	2.9	42	24.4	13	8.7	6	16.7	5	10.4
20–27 cig/day	12	10.5	7	2.7	18	11.3	5	2.9	28	16.3	18	12.1	10	27.8	3	6.3
28+ cig/day	12	10.5	12	4.7	20	12.5	10	5.7	35	20.3	6	4.0	5	13.9	3	6.3
Fruit and vegetable intake																
Low intake	60	52.6	90	35.0	85	53.1	57	32.8	102	59.3	68	45.6	25	69.4	16	33.3
Mid intake	32	28.1	90	35.0	44	27.5	65	37.4	48	27.9	51	34.2	8	22.2	17	35.4
High intake	22	19.3	77	30.0	31	19.4	52	29.9	22	12.8	30	20.1	3	8.3	15	31.3

Table 1 continued

	Never drinker				Only wine drinker				Only beer drinker				Only liquor drinker			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Drinking frequency																
Never drinker	114	100	257	100												
<1 drink/day					56	35.0	92	52.9	65	37.8	77	51.7	19	52.8	37	77.1
1–2 drinks/day					29	18.1	61	35.1	48	27.9	44	29.5	8	22.2	8	16.7
3–4 drinks/day					23	14.4	12	6.9	28	16.3	22	14.8	5	13.9	3	6.3
5+ drinks/day					52	32.5	9	5.2	31	18.0	6	4.0	4	11.1		

	Wine & beer drinker				Wine & liquor drinker				Beer & liquor drinker				Wine, beer, liquor drinker			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Center																
Prague	19	7.6	33	10.3	5	2.5	7	3.5	46	14.3	26	14.4	46	6.2	62	7.8
Bremen	36	14.3	58	18.1	5	2.5	10	5.0	93	28.9	47	26.1	65	8.8	122	15.3
Athens	19	7.6	35	10.9	34	16.9	17	8.5	9	2.8	11	6.1	87	11.8	61	7.7
Aviano	19	7.6	30	9.4	21	10.4	22	11.1	1	0.3			74	10.0	61	7.7
Padova	24	9.6	28	8.8	18	9.0	12	6.0	2	0.6			59	8.0	52	6.5
Turin	27	10.8	31	9.7	32	15.9	15	7.5	1	0.3	2	1.1	48	6.5	68	8.5
Dublin	1	0.4	5	1.6	3	1.5	1	0.5	9	2.8	4	2.2	4	0.5	1	0.1
Oslo	10	4.0	8	2.5	8	4.0	21	10.6	31	9.6	18	10.0	72	9.7	103	12.9
Edinburgh	3	1.2	3	0.9	3	1.5	13	6.5	36	11.2	13	7.2	31	4.2	43	5.4
Manchester	13	5.2	24	7.5	8	4.0	19	9.5	35	10.9	25	13.9	41	5.5	68	8.5
Newcastle	7	2.8	16	5.0	1	0.5	8	4.0	19	5.9	11	6.1	16	2.2	46	5.8
Barcelona	18	7.2	10	3.1	13	6.5	8	4.0	21	6.5	10	5.6	62	8.4	12	1.5
Zagreb	11	4.4	9	2.8	3	1.5	4	2.0	6	1.9	3	1.7	23	3.1	15	1.9
Inserm	44	17.5	30	9.4	47	23.4	42	21.1	13	4.0	10	5.6	112	15.1	82	10.3
Sex																
Men	196	78.1	260	81.3	154	76.6	135	67.8	298	92.5	168	93.3	654	88.4	681	85.6
Women	55	21.9	60	18.8	47	23.4	64	32.2	24	7.5	12	6.7	86	11.6	115	14.4
Education level																
Primary school/worker	88	35.1	84	26.3	92	45.8	55	27.6	81	25.2	43	23.9	289	39.1	160	20.1
Further school/clerk	148	59.0	203	63.4	93	46.3	111	55.8	229	71.1	130	72.2	405	54.7	521	65.5
University/manager	15	6.0	33	10.3	16	8.0	33	16.6	12	3.7	7	3.9	46	6.2	115	14.4
Smoking duration																
Never	24	9.6	110	34.4	16	8.0	47	23.6	11	3.4	35	19.4	40	5.4	213	26.8
1–9 years	6	2.4	21	6.6	5	2.5	9	4.5	5	1.6	17	9.4	16	2.2	52	6.5
10–19 years	14	5.6	37	11.6	6	3.0	16	8.0	9	2.8	21	11.7	34	4.6	101	12.7
20–29 years	39	15.5	50	15.6	31	15.4	29	14.6	43	13.4	27	15.0	131	17.7	155	19.5
30–39 years	87	34.7	64	20.0	60	29.9	43	21.6	121	37.6	45	25.0	263	35.5	149	18.7
40+ years	81	32.3	38	11.9	83	41.3	55	27.6	133	41.3	35	19.4	256	34.6	126	15.8
Smoking status by frequency and years since quitting																
Former																
16+ years, <18 cig/day	13	5.2	41	12.8	10	5.0	22	11.1	6	1.9	26	14.4	42	5.7	118	14.8
16+ years, 18+ cig/day	11	4.4	27	8.4	9	4.5	14	7.0	7	2.2	9	5.0	25	3.4	82	10.3

Table 1 continued

	Wine & beer drinker				Wine & liquor drinker				Beer & liquor drinker				Wine, beer, liquor drinker			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<16 years, <18 cig/day	12	4.8	20	6.3	11	5.5	24	12.1	14	4.3	4	2.2	42	5.7	58	7.3
<16 years, 18+ cig/day	17	6.8	21	6.6	33	16.4	22	11.1	22	6.8	15	8.3	87	11.8	51	6.4
Current																
<15 cig/day	40	15.9	40	12.5	19	9.5	21	10.6	52	16.1	34	18.9	103	13.9	100	12.6
15–19 cig/day	40	15.9	23	7.2	29	14.4	18	9.0	64	19.9	22	12.2	118	15.9	56	7.0
20–27 cig/day	41	16.3	18	5.6	33	16.4	18	9.0	82	25.5	19	10.6	121	16.4	57	7.2
28+ cig/day	53	21.1	20	6.3	41	20.4	13	6.5	64	19.9	16	8.9	162	21.9	61	7.7
Fruit and vegetable intake																
Low intake	148	59.0	127	39.7	113	56.2	59	29.6	206	64.0	89	49.4	425	57.4	306	38.4
Mid intake	63	25.1	122	38.1	49	24.4	76	38.2	84	26.1	55	30.6	197	26.6	290	36.4
High intake	40	15.9	71	22.2	39	19.4	64	32.2	32	9.9	36	20.0	118	15.9	200	25.1
Drinking frequency																
Never drinker																
<1 drink/day	78	31.1	172	53.8	53	26.4	98	49.2	66	20.5	67	37.2	133	18.0	287	36.1
1–2 drinks/day	66	26.3	95	29.7	55	27.4	57	28.6	104	32.3	64	35.6	232	31.4	339	42.6
3–4 drinks/day	54	21.5	37	11.6	50	24.9	27	13.6	61	18.9	30	16.7	159	21.5	96	12.1
5+ drinks/day	53	21.1	16	5.0	43	21.4	17	8.5	91	28.3	19	10.6	216	29.2	74	9.3

school/clerk, university/manager), source of control subjects (hospital-based, population-based), country and region (North Europe: Oslo, United Kingdom/Ireland; East Europe: Czech Republic; South Europe: Croatia, Greece, Italy, Spain; West Europe: France, Germany). Heterogeneity by country was examined using the likelihood ratio test, which tested the difference between the log likelihood of the model with the product term, e.g., alcohol drinking and country, and the model without the product term, based on a Chi-squared distribution [39]. We calculated heterogeneity among the ORs of wine, beer and liquor drinking with the method of generalized least squares using the upper covariance bounds, since the reference category for all beverage types was the same group of never drinkers [40].

Results

Table 1 summarizes selected characteristics of case and control subjects in relation to their alcohol consumption. Around 71 % of the control subjects consumed multiple types of alcohol beverages, while 8 % drank only wine, 7 % only beer, 2 % only liquor and 12 % were never drinkers. Among drinkers, median drinks per day were 1.8 among drinkers of more than one type of alcoholic beverage, 1.6 among pure wine drinkers, 1.3 among pure beer drinkers and 0.6 among pure liquor drinkers. Among both cases and controls, never drinkers and pure wine and pure liquor drinkers were more likely to be female compared to drinkers of multiple beverage types and pure beer drinkers. Never drinkers and pure wine drinkers had less education, were more often never smokers and consumed more fruits and vegetables than drinkers of multiple beverage types, pure beer and pure liquor drinkers. Among drinkers, pure wine drinkers had the lowest proportion of frequent binge drinking and alcohol consumption between meals. However, within each consumption group of beverage types, subjects with UADT cancer had higher smoking prevalence, lower educational level and consumed less fruits and vegetables than control subjects.

Compared to never drinkers, the risk of UADT cancer increased for wine, beer and liquor consumption, respectively, with increasing average frequency (Table 2) among 'pure drinkers' (p value for trend of wine and beer consumption <0.001), among 'predominant drinkers' (p value for trend of wine, beer and liquor consumption <0.001), and among 'mixed drinkers' (p value for trend of wine, beer and liquor consumption <0.001). Among 'pure drinkers' of liquor, the point estimates increased, but the numbers of subjects were small and statistically significant increasing trends were not observed. Adjusted with the residual method for total cumulative ethanol-standardized beverage consumption, the OR for ever drinking wine, beer and liquor were similar among 'pure drinkers', among 'predominant drinkers' and among 'mixed drinkers'. Compared to never drinkers and where appropriate

Table 2 Types of alcoholic beverages and the risk of upper aerodigestive tract cancer overall and for men and women

	Wine				Beer				Liquor				p^{f}
	Ca	Co	OR	95 % CI	Ca	Co	OR	95 % CI	Ca	Co	OR	95 % CI	value
Never alcohol (114 Ca, 257 Co, = ref.)													
Alcohol drinking frequency													
Drink only this type[a]													
<1 drink/day	55	92	1.49	(0.95, 2.33)	64	77	1.89	(1.18, 3.01)	19	37	0.76	(0.39, 1.51)	0.076
1–2 drinks/day	30	60	0.86	(0.49, 1.50)	46	40	1.99	(1.12, 3.55)	8	6	2.22	(0.65, 7.56)	0.057
3–4 drinks/day	21	13	1.94	(0.88, 4.28)	29	22	1.43	(0.73, 2.81)	5	4	1.38	(0.30, 6.32)	0.796
5+ drinks/day	54	9	7.03	(3.12, 15.84)	33	10	3.82	(1.69, 8.60)	4	1	3.01	(0.30, 30.17)	0.408
P trend				<0.001				<0.001				0.076	
Drink predominantly this type[c,d]													
<1 drink/day	73	153	1.04	(0.69, 1.57)	84	144	1.25	(0.82, 1.91)	40	55	1.30	(0.76, 2.23)	0.726
1–2 drinks/day	93	158	0.98	(0.66, 1.47)	99	128	1.27	(0.82, 1.97)	39	34	1.57	(0.87, 2.83)	0.356
3–4 drinks/day	98	67	2.13	(1.34, 3.39)	66	45	1.81	(1.05, 3.10)	18	5	4.27	(1.40, 13.01)	0.372
5+ drinks/day	100	35	2.99	(1.76, 5.07)	82	23	3.44	(1.89, 6.24)	30	11	2.28	(1.03, 5.03)	0.679
P trend				<0.001				<0.001				<0.001	
Drink this and other types[c,e]													
<1 drink/day	367	596	1.11	(0.80, 1.54)	495	688	1.12	(0.82, 1.54)	571	765	1.05	(0.77, 1.45)	0.947
1–2 drinks/day	126	102	1.25	(0.82, 1.92)	180	88	1.77	(1.16, 2.69)	225	113	1.57	(1.05, 2.33)	0.455
3–4 drinks/day	58	22	1.67	(0.90, 3.13)	57	18	1.74	(0.89, 3.42)	60	24	1.44	(0.78, 2.65)	0.889
5+ drinks/day	37	6	2.61	(0.99, 6.88)	40	12	2.00	(0.90, 4.43)	53	15	1.59	(0.78, 3.24)	0.662
P trend				0.001				<0.001				0.002	
Drinking status adusted for cumulative alcohol consumption													
Drink only this type[b]	160	174	1.24	(0.86, 1.78)	172	149	1.54	(1.05, 2.27)	36	48	0.94	(0.53, 1.64)	0.306
Drink predominantly this type[b,d]	376	419	1.05	(0.76, 1.47)	355	351	1.25	(0.87, 1.79)	135	110	1.43	(0.95, 2.16)	0.456
Drink this and other types[b,e]	588	726	1.09	(0.79, 1.50)	772	806	1.20	(0.88, 1.63)	909	917	1.12	(0.82, 1.53)	0.889
Drink never this type[b]	530	377	1.63	(1.17, 2.28)	397	419	1.13	(0.83, 1.54)	582	644	1.20	(0.89, 1.62)	0.188
Men—drinking status adusted for cumulative alcohol consumption													
Never alcohol (40 Ca, 110 Co, = ref.)													
Drink only this type[g]	115	101	1.84	(1.08, 3.14)	151	124	2.01	(1.19, 3.38)	21	25	1.55	(0.70, 3.42)	0.848
Drink predominantly this type[g,d]	299	318	1.43	(0.88, 2.33)	325	322	1.53	(0.93, 2.51)	103	79	1.88	(1.07, 3.29)	0.727
Drink this and other types[g,e]	488	595	1.40	(0.88, 2.24)	644	659	1.51	(0.96, 2.38)	795	764	1.51	(0.95, 2.40)	0.960

Table 2 continued

	Wine				Beer				Liquor				p^f
	Ca	Co	OR	95 % CI	Ca	Co	OR	95 % CI	Ca	Co	OR	95 % CI	value
Drink never this type[g]	470	317	2.20	(1.37, 3.55)	290	260	1.57	(0.99, 2.50)	462	484	1.64	(1.04, 2.56)	0.495
Women—drinking status adusted for cumulative alcohol consumption													
Never alcohol (74 Ca, 147 Co, = ref.)													
Drink only this type[g]	45	73	0.81	(0.47, 1.4)	21	25	0.82	(0.38, 1.80)	15	23	0.74	(0.31, 1.79)	0.981
Drink predominantly this type[g,d]	77	101	0.98	(0.57, 1.68)	30	29	1.29	(0.62, 2.68)	32	31	1.56	(0.75, 3.24)	0.540
Drink this and other types[g,e]	100	131	1.10	(0.65, 1.85)	128	147	1.20	(0.73, 1.99)	114	153	0.98	(0.58, 1.65)	0.841
Drink never this type[g]	60	60	1.14	(0.64, 2.05)	107	159	0.90	(0.56, 1.44)	120	160	0.90	(0.57, 1.41)	0.762

Ca Cases, *Co* controls, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for center, sex, age, education level, smoking duration, smoking status by frequency and years since quitting, fruit & vegetable intake

[b] Adjusted for center, sex, age, education level, smoking duration, smoking status by frequency and years since quitting, cumulative alcohol consumption, fruit & vegetable intake

[c] Adjusted for center, sex, age, education level, smoking duration, smoking status by frequency and years since quitting, fruit & vegetable intake, drinking frequency of other types

[d] Drink predominantly this type = drink 66 % or more of this beverage type cumulative over lifetime

[e] Drink this and other types = drink less than 66 % of this beverage type cumulative over lifetime

[f] *p* value for heterogeneity among the odds ratios of the three beverage types

[g] Adjusted for center, age, education level, smoking duration, smoking status by frequency and years since quitting, cumulative alcohol consumption, fruit & vegetable intake

adjusted for the consumption of other beverage types, the ORs for alcohol drinking of 3+ drinks/day wine, beer and liquor, respectively, were 4.01 (CI: 2.22, 7.25), 2.08 (1.20, 3.63) and 1.74 (0.49, 6.15) among 'pure drinkers' (*p* value for heterogeneity across beverage types = 0.146), were 2.51 (CI: 1.67, 3.78), 2.32 (1.46, 3.67) and 2.76 (1.40, 5.42) among 'predominant drinkers' (*p* value for heterogeneity across beverage types = 0.902), and were 1.89 (CI: 1.07, 3.32), 1.71 (0.97, 3.03) and 1.42 (0.84, 2.38) among 'mixed drinkers' (*p* value for heterogeneity across beverage types = 0.707).

When we adjusted for frequency of drinking among alcohol drinkers, the associations disappeared for drinking duration of wine, beer and liquor (results not shown). Adjustment for duration of involuntary smoking or BMI did not change the association between wine, beer and liquor consumption and risk of UADT cancer. In addition, there was no difference in our findings after adjusting for individual fruit and vegetable intake variables versus the combined fruit and vegetable intake variable. The risk of UADT cancer for frequency were similar for drinking wine, beer and liquor (Table 2). All heterogeneity tests comparing these risks across the three alcohol beverage types were not statistically significant. The association between UADT cancer and consumption of different types of alcoholic beverages were consistent by country (Fig. 1a–c). Forest plots and heterogeneity tests across country for never wine, never beer and never liquor drinkers did not reveal any heterogeneity (*P* for heterogeneity among never wine drinkers = 0.509, among never beer drinkers = 0.758 and among never liquor drinkers = 0.653).

Risks of UADT cancer in relation to drinking of wine, beer and liquor were assessed stratified by sex (Table 2). For consumption of all alcohol beverage types, we observed a slightly higher risk of UADT cancer among men compared to women. Adjusted with the residual method for total cumulative ethanol-standardized beverage consumption, these associations did not differ between wine, beer and liquor consumption. When we stratified the analysis by organ within the UADT, most OR were approximately twofold higher for pharyngeal cancer than for oral cavity, esophagus and laryngeal cancer among women, but OR were similar among men (Table 3). Adjusted with the residual method for total cumulative ethanol-standardized beverage consumption, the OR for ever drinking wine, beer and liquor were similar among 'pure drinkers', among 'predominant drinkers' and among 'mixed drinkers' for all organs of the UADT among men and among women.

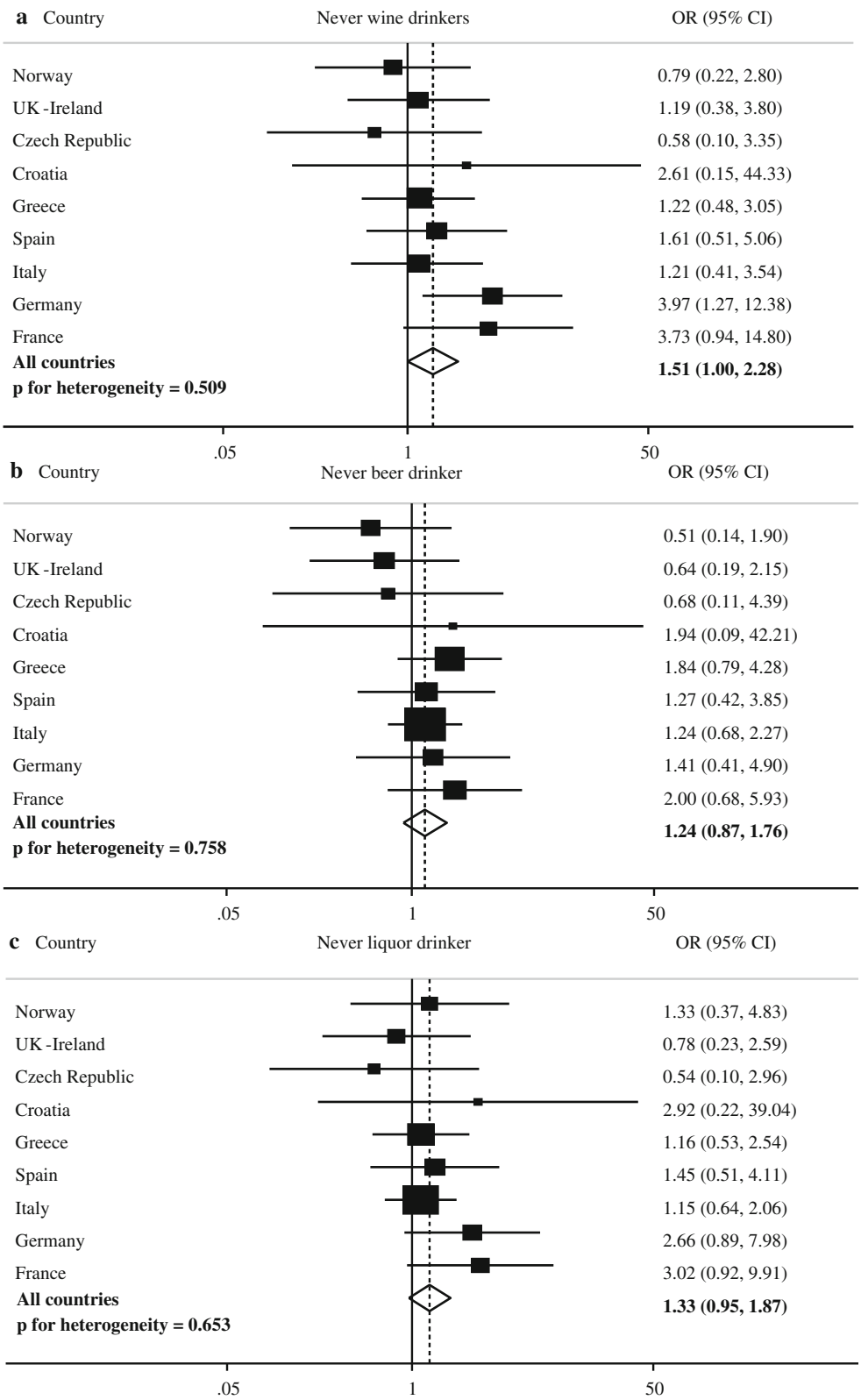

Fig. 1 **a–c** Never drinkers of wine (**a**), beer (**b**) and liquor (**c**) and the risk of upper aerodigestive tract cancer adjusted for sex, age, education level, smoking duration, smoking status by frequency and years since quitting, cumulative alcohol consumption, fruit and vegetable intake

The pattern of associations across beverage types did not differ by age group, education level, sources of control subjects or geographical region (results not shown). In analyses stratified by smoking status, the associations between UADT cancer risk and wine, beer and liquor consumption were suggested to be most time stronger

Table 3 Alcohol drinking status adjusted for cumulative alcohol consumption and the risk of the upper aerodigestive tract cancer subsites for men and women

	Wine				Beer				Liquor				p^a
	Ca	Co	OR		Ca	Co	OR		Ca	Co	OR		value
Men—drinking status adusted for cumulative alcohol consumption													
Oral cavity													
Never alcohol (6 Ca, 110 Co, = ref.)													
Drink only this type[b]	23	101	2.59	(0.94, 7.17)	39	124	3.58	(1.33, 9.61)	3	25	1.64	(0.34, 7.86)	0.694
Drink predominantly this type[b,c]	73	318	2.12	(0.82, 5.46)	68	322	2.57	(0.98, 6.73)	21	79	2.97	(1.03, 8.58)	0.891
Drink this and other types[b,d]	107	595	2.06	(0.82, 5.2)	160	659	2.45	(0.99, 6.09)	185	764	2.52	(1.01, 6.28)	0.945
Drink never this type[b]	107	317	3.78	(1.49, 9.61)	51	260	2.08	(0.81, 5.33)	107	484	2.63	(1.07, 6.48)	0.660
Pharynx													
Never alcohol (9 Ca, 110 Co, = ref.)													
Drink only this type[b]	25	101	1.71	(0.70, 4.22)	59	124	2.45	(1.07, 5.63)	11	25	3.16	(1.05, 9.44)	0.670
Drink predominantly this type[b,c]	98	318	2.13	(0.93, 4.87)	143	322	2.07	(0.92, 4.65)	35	79	1.88	(0.77, 4.59)	0.977
Drink this and other types[b,d]	199	595	2.07	(0.94, 4.59)	237	659	1.97	(0.9, 4.28)	307	764	1.93	(0.88, 4.22)	0.992
Drink never this type[b]	191	317	2.58	(1.17, 5.7)	82	260	1.74	(0.79, 3.82)	152	484	1.88	(0.88, 4.03)	0.751
Esophagus													
Never alcohol (2 Ca, 110 Co, = ref.)													
Drink only this type[b]	6	101	2.11	(0.36, 12.3)	11	124	1.68	(0.29, 9.63)		25			0.856
Drink predominantly this type[b,c]	15	318	0.79	(0.16, 3.95)	33	322	1.32	(0.26, 6.73)	9	79	3.55	(0.64, 19.55)	0.441
Drink this and other types[b,d]	35	595	1.61	(0.33, 7.81)	34	659	1.27	(0.28, 5.86)	55	764	1.15	(0.24, 5.37)	0.953
Drink never this type[b]	37	317	2.56	(0.5, 13.05)	15	260	1.76	(0.35, 8.77)	31	484	1.65	(0.35, 7.68)	0.918
Larynx													
Never alcohol (23 Ca, 110 Co, = ref.)													
Drink only this type[b]	61	101	2.01	(1.02, 3.94)	41	124	1.56	(0.77, 3.15)	7	25	1.41	(0.48, 4.18)	0.799
Drink predominantly this type[b,c]	113	318	1.28	(0.68, 2.41)	78	322	1.12	(0.58, 2.19)	37	79	2.08	(0.98, 4.38)	0.422
Drink this and other types[b,d]	146	595	1.18	(0.64, 2.19)	213	659	1.36	(0.75, 2.45)	246	764	1.34	(0.73, 2.44)	0.932
Drink never this type[b]	131	317	2.00	(1.07, 3.73)	141	260	1.47	(0.81, 2.65)	171	484	1.51	(0.84, 2.70)	0.716
Women—drinking status adusted for cumulative alcohol consumption													
Oral cavity													
Never alcohol (34 Ca, 147 Co, = ref.)													
Drink only this type[b]	17	73	0.65	(0.30, 1.39)	7	25	0.85	(0.28, 2.59)	5	23	0.77	(0.22, 2.70)	0.915
Drink predominantly this type[b,c]	28	101	0.81	(0.38, 1.72)	9	29	1.35	(0.46, 3.93)	10	31	1.58	(0.54, 4.60)	0.522

Table 3 continued

	Wine				Beer				Liquor				p^a
	Ca	Co	OR		Ca	Co	OR		Ca	Co	OR		value
Drink this and other types[b,d]	37	131	1.36	(0.66, 2.80)	46	147	1.08	(0.55, 2.13)	37	153	0.83	(0.40, 1.70)	0.615
Drink never this type[b]	18	60	1.09	(0.47, 2.49)	38	159	0.79	(0.41, 1.50)	48	160	0.89	(0.48, 1.63)	0.823
Pharynx													
Never alcohol (12 Ca, 147 Co, = ref.)													
Drink only this type[b]	17	73	2.21	(0.88, 5.54)	10	25	2.03	(0.66, 6.29)	4	23	0.92	(0.21, 4.01)	0.586
Drink predominantly this type[b,c]	26	101	2.30	(0.91, 5.79)	14	29	2.69	(0.92, 7.88)	12	31	2.63	(0.86, 8.05)	0.970
Drink this and other types[b,d]	43	131	2.30	(0.95, 5.59)	49	147	2.52	(1.06, 5.97)	44	153	2.18	(0.89, 5.33)	0.972
Drink never this type[b]	24	60	2.18	(0.86, 5.52)	39	159	2.18	(0.95, 4.99)	47	160	1.94	(0.87, 4.33)	0.973
Esophagus													
Never alcohol (10 Ca, 147 Co, = ref.)													
Drink only this type[b]	5	73	0.65	(0.17, 2.46)	2	25	0.06	(0.01, 1.16)	5	23	2.82	(0.41, 19.21)	0.095
Drink predominantly this type[b,c]	13	101	0.61	(0.16, 2.30)	3	29	2.05	(0.30, 14.00)	2	31	0.81	(0.09, 7.58)	0.588
Drink this and other types[b,d]	7	131	0.46	(0.11, 1.95)	14	147	0.64	(0.16, 2.52)	14	153	0.48	(0.12, 1.93)	0.937
Drink never this type[b]	9	60	1.12	(0.26, 4.85)	15	159	0.74	(0.23, 2.32)	13	160	0.59	(0.19, 1.81)	0.789
Larynx													
Never alcohol (18 Ca, 147 Co, = ref.)													
Drink only this type[b]	6	73	0.44	(0.12, 1.59)	2	25	0.25	(0.04, 1.72)	1	23	0.11	(0.01, 1.48)	0.619
Drink predominantly this type[b,c]	10	101	0.48	(0.13, 1.74)	3	29	0.43	(0.08, 2.37)	7	31	1.23	(0.26, 5.72)	0.572
Drink this and other types[b,d]	12	131	0.44	(0.13, 1.42)	19	147	0.64	(0.20, 2.05)	19	153	0.63	(0.19, 2.07)	0.879
Drink never this type[b]	9	60	0.43	(0.11, 1.62)	15	159	0.44	(0.15, 1.30)	12	160	0.34	(0.11, 1.01)	0.937

Ca Cases, *Co* controls, *OR* odds ratio, *CI* confidence interval

[a] *p* value for heterogeneity among the odds ratios of the three beverage types

[b] Adjusted for center, age, education level, smoking duration, smoking status by frequency and years since quitting, cumulative alcohol consumption, fruit & vegetable intake

[c] Drink predominantly this type = drink 66 % or more of this beverage type cumulative over lifetime

[d] Drink this and other types = drink less than 66 % of this beverage type cumulative over lifetime

among smokers compared to never smokers for men and for women (Table 4). Across the three beverage types, no major differences in the OR of UADT cancer risk were observed among both smokers and never smokers for men and women. Among men and women with low or high fruit and vegetable intake, the associations between alcohol drinking and risk of UADT cancer were consistent and similar across different beverage types for 'pure drinkers', 'predominant drinkers' and 'mixed drinkers'. Additional informations are given in Online Resource.

Discussion

According to our results the carcinogenic effect of wine, beer and liquor consumption on the risk of UADT cancer is similar. Strong dose–response relationships with risk estimates of beverage consumption were observed for each alcoholic beverage type, after adjusting for other possible confounders. These associations did not differ substantially across 'mixed drinkers', 'predominant drinkers' and 'pure drinkers' after adjusting for the consumption of the other

Table 4 Alcohol drinking status adjusted for cumulative alcohol consumption and the risk of upper aerodigestive tract cancer by smoking status and fruit and vegetable intake for men and women

	Wine				Beer				Liquor				p^c
	Ca	Co	OR		Ca	Co	OR		Ca	Co	OR		value
Men—drinking status adusted for cumulative alcohol consumption													
Never smoker													
Never alcohol (6 Ca, 48 Co, = ref.)													
Drink only this type[a]	9	32	1.96	(0.54, 7.06)	7	30	2.21	(0.55, 8.90)	1	7	1.22	(0.11, 13.62)	0.913
Drink predominantly this type[a, d]	18	86	1.46	(0.46, 4.63)	17	92	1.19	(0.36, 4.00)	1	15	0.56	(0.05, 5.74)	0.764
Drink this and other types[a,e]	25	172	1.07	(0.36, 3.17)	29	178	1.24	(0.43, 3.54)	40	194	1.51	(0.54, 4.25)	0.895
Drink never this type[a]	17	66	1.90	(0.58, 6.22)	16	54	2.53	(0.79, 8.11)	26	141	1.45	(0.49, 4.26)	0.774
Smoker													
Never alcohol (34 Ca, 62 Co, = ref.)													
Drink only this type[a]	106	69	2.75	(1.59, 4.76)	144	94	3.82	(2.21, 6.59)	20	18	2.45	(1.09, 5.46)	0.493
Drink predominantly this type[a,d]	281	232	2.55	(1.54, 4.21)	308	230	3.41	(2.03, 5.71)	102	64	4.38	(2.47, 7.76)	0.271
Drink this and other types[a,e]	463	423	2.74	(1.68, 4.47)	615	481	2.92	(1.82, 4.70)	755	570	3.11	(1.93, 4.99)	0.912
Drink never this type[a]	453	251	4.78	(2.90, 7.88)	274	206	2.58	(1.60, 4.18)	436	343	2.70	(1.68, 4.32)	0.076
Low fruit and vegetable intake													
Never alcohol (22 Ca, 43 Co, = ref.)													
Drink only this type[b]	62	33	2.27	(1.00, 5.17)	89	57	1.87	(0.86, 4.03)	14	7	2.51	(0.72, 8.73)	0.887
Drink predominantly this type[b,d]	180	145	1.43	(0.69, 2.96)	206	150	1.39	(0.67, 2.88)	60	31	2.11	(0.92, 4.83)	0.675
Drink this and other types[b,e]	280	250	1.31	(0.65, 2.64)	376	293	1.27	(0.65, 2.48)	492	348	1.64	(0.83, 3.25)	0.818
Drink never this type[b]	295	146	2.23	(1.09, 4.57)	166	88	1.78	(0.89, 3.56)	266	193	1.75	(0.89, 3.43)	0.838
Higher fruit and vegetable intake													
Never alcohol (18 Ca, 67 Co, = ref.)													
Drink only this type[b]	53	68	1.59	(0.77, 3.28)	62	67	1.98	(0.95, 4.12)	7	18	1.14	(0.37, 3.54)	0.694
Drink predominantly this type[b,d]	119	173	1.45	(0.73, 2.88)	119	172	1.65	(0.82, 3.33)	43	48	1.75	(0.79, 3.86)	0.925
Drink this and other types[b,e]	208	345	1.52	(0.79, 2.93)	268	366	1.81	(0.95, 3.46)	303	416	1.43	(0.75, 2.72)	0.852
Drink never this type[b]	175	171	2.15	(1.11, 4.18)	124	172	1.40	(0.73, 2.68)	196	291	1.52	(0.81, 2.85)	0.583
Women—drinking status adusted for cumulative alcohol consumption													
Never smoker													
Never alcohol (39 Ca, 110 Co, = ref.)													
Drink only this type[a]	16	49	0.58	(0.26, 1.29)	6	9	1.58	(0.45, 5.54)	4	8	3.01	(0.65, 14.04)	0.099
Drink predominantly this type[a,d]	20	52	0.99	(0.46, 2.14)	5	9	1.60	(0.36, 7.02)	5	15	2.27	(0.59, 8.65)	0.516

Table 4 continued

	Wine				Beer				Liquor				p^c
	Ca	Co	OR		Ca	Co	OR		Ca	Co	OR		value
Drink this and other types[a,e]	15	57	1.22	(0.53, 2.82)	24	71	1.12	(0.54, 2.29)	18	68	0.93	(0.42, 2.06)	0.883
Drink never this type[a]	12	23	1.97	(0.74, 5.22)	29	87	0.82	(0.41, 1.63)	36	91	0.84	(0.44, 1.58)	0.267
Smoker													
Never alcohol (35 Ca, 37 Co, = ref.)													
Drink only this type[a]	29	24	1.37	(0.64, 2.96)	15	16	0.92	(0.36, 2.33)	11	15	0.68	(0.25, 1.90)	0.457
Drink predominantly this type[a,d]	57	49	1.40	(0.70, 2.80)	25	20	1.47	(0.62, 3.47)	27	16	2.39	(0.99, 5.76)	0.538
Drink this and other types[a,e]	85	74	1.51	(0.79, 2.91)	104	76	1.93	(1.01, 3.67)	96	85	1.45	(0.77, 2.75)	0.731
Drink never this type[a]	48	37	1.39	(0.68, 2.84)	78	72	1.30	(0.69, 2.43)	84	69	1.32	(0.71, 2.43)	0.986
Low fruit and vegetable intake													
Never alcohol (38 Ca, 47 Co, = ref.)													
Drink only this type[b]	23	24	1.00	(0.42, 2.36)	13	11	0.62	(0.19, 2.07)	11	9	1.38	(0.39, 4.81)	0.623
Drink predominantly this type[b,d]	46	23	1.18	(0.49, 2.82)	21	12	1.68	(0.61, 4.65)	14	4	3.53	(0.86, 14.48)	0.377
Drink this and other types[b,e]	54	37	1.10	(0.49, 2.47)	71	43	1.13	(0.51, 2.48)	67	39	1.22	(0.55, 2.73)	0.979
Drink never this type[b]	38	27	1.25	(0.52, 2.97)	58	43	1.14	(0.54, 2.38)	69	60	0.81	(0.41, 1.62)	0.634
Higher fruit and vegetable intake													
Never alcohol (36 Ca, 100 Co, = ref.)													
Drink only this type[b]	22	49	0.64	(0.30, 1.37)	8	14	0.93	(0.30, 2.84)	4	14	0.45	(0.11, 1.76)	0.699
Drink predominantly this type[b,d]	31	78	0.88	(0.42, 1.86)	9	17	1.16	(0.36, 3.73)	18	27	1.12	(0.43, 2.88)	0.881
Drink this and other types[b,e]	46	94	1.18	(0.56, 2.46)	57	104	1.34	(0.66, 2.74)	47	114	0.90	(0.43, 1.87)	0.716
Drink never this type[b]	22	33	1.15	(0.49, 2.68)	49	116	0.72	(0.37, 1.40)	51	100	0.86	(0.46, 1.63)	0.670

Ca Cases, *Co* controls, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for center, age, education level, fruit & vegetable intake, cumulative alcohol consumption

[b] Adjusted for center, age, education level, smoking duration, smoking status by frequency and years since quitting, cumulative alcohol consumption

[c] *p* value for heterogeneity among the odds ratios of the three beverage types

[d] Drink predominantly this type = drink 66 % or more of this beverage type cumulative over lifetime

[e] Drink this and other types = drink less than 66 % of this beverage type cumulative over lifetime

alcoholic beverages among drinkers who consumed more than one beverage type. Moreover, we did not observe any beverage type specific differences in UADT cancer risk after adjusting with the residual method for total cumulative alcohol consumption.

Our findings of similar UADT cancer risk across beverage types are in line with most previous studies [19–24]. Although the mechanism by which alcohol consumption promotes UADT carcinogenesis is mostly unknown, comparable risks across types of alcoholic beverages support the hypotheses that the common ingredient, ethanol, and its metabolite, acetaldehyde, are the main carcinogenic agents in all alcoholic beverages [41, 42]. Reasons for the small differential in risks of drinking frequency among 'pure drinkers' in our study are not clear. These differences may be chance findings due to the parse data for 'pure drinkers'

and multiple testing of several hypotheses. Residual confounding may have influenced these findings by tobacco smoking or fruit and vegetable consumption because high fruit and vegetable intake and low tobacco use were much more common among pure wine drinkers than among pure beer and pure liquor drinkers. Additionally, we observed a higher risk for wine, beer and liquor consumption among smokers than among never smoker in this analysis which confirms the joint effect between tobacco smoking and alcohol consumption for each beverage type [43–45]. In line with these observations, we did not detect risk differences across alcohol beverage types after stratification by tobacco smoking and fruit and vegetable intake. Therefore, the suggested stronger association with pure beer consumption compared to pure wine consumption may be explained by residual confounding through these variables among this special group of pure beer drinkers with low levels of fruit and vegetable intake and high frequency of current tobacco use and, on the other hand, of pure wine drinkers with high levels of fruit and vegetable intake and low frequency of current tobacco use.

If ethanol concentration influences risk of UADT cancers through increased local exposure of the mucosa, liquor, which has the highest concentration of ethanol, was suggested in some previous epidemiological studies to have a stronger association than the ethanol-content equivalent in wine or beer, particularly when they are consumed undiluted [13, 46]. In contrast, in our study the risk of UADT cancer was broadly similar across different alcohol beverage types. However, since we were not able to distinguish between straight versus diluted liquor consumption, which are both common in our European study population, we cannot exclude the possibility that our risk estimates for liquor drinking may be influenced by this uncontrolled consumption pattern. Wine and beer, on the other hand, are mainly consumed undiluted, and although ethanol concentration in wine is approximately double that in beer, the small differences in associations that we observed between these beverage types was in changing directions. Notably, at low levels of consumption, we observed a greater increased risk of UADT cancer among pure beer drinkers, which are drinkers of alcohol with the lowest ethanol concentration compared to pure wine or pure liquor drinkers. Therefore, differences in ethanol concentration would not explain these observations. However, at high levels of consumption, the risk of UADT cancer was slightly higher among pure wine drinkers than among pure beer drinkers. Thus, ethanol concentration may be a relevant factor, if at all, at very high consumption levels.

Small risk differences across alcohol beverage type have been observed in other studies, suggesting that they may be real [15–18]. There is the possibility that an ingredient other than ethanol, which is present in certain alcoholic beverages, may contribute to UADT cancer risk and such contents might include nitrosamines in beer [1, 47] or higher acetaldehyde content in wine and liquor [48, 49]. Acetaldehyde associated with alcohol consumption has been classified from the IARC as carcinogenic to humans [50]. The residual acetaldehyde concentrations in the saliva after swallowing was estimated to be, on average, 195 μM for beer, 1,387 μM for liquor, 734 μM for wine and 2,417 μM for fortified wine [49]. In contrast, our results did not support a higher risk with wine and liquor consumption compared to beer consumption. However, our groups of beverage types were very wide and acetaldehyde content may differ within one beverage group. Therefore, future studies on UADT cancer risk and alcohol consumption would be necessary to measure more detailed the acetaldehyde content of different alcoholic beverages for estimation of this association.

Alternatively, some alcoholic beverages may contain more protective components, for instance more resveratrol in wine [51, 52]. Concentrations of polyphenols, such as resveratrol, are particularly high in red wine compared to other alcohol beverage types. Ethanol-induced carcinogenesis in many organs has been associated with increased reactive oxygen species and oxidative stress, which damage the DNA and affect DNA repair [53–56], whereas resveratrol had been suggested to be an antioxidant with an anti-inflammatory effect, which may reduce tumor initiation and progression [51, 52]. In accordance with these hypotheses, at low consumption levels we observed a weaker association of UADT cancer risk among lifetime exclusive wine drinkers than exclusive drinkers of other alcoholic beverages. Unfortunately, we had no information on color of wine in our study to evaluate these hypotheses in more detail. However, most of the evidence on protective effects of resveratrol comes from in vitro studies with the native form of resveratrol, whereas the bioavailability of resveratrol in humans is very low due to its rapid metabolism in mammals, which makes protective effects of resveratrol by drinking red wine unlikely [57, 58].

The advantage of focusing on ‘pure drinkers’ of each beverage type isolates exposure to the specific beverage and thus eliminates confounding by other beverage types. However, such ‘pure drinkers’ may have particular characteristics, uncontrolled potential mediators and risk factors that we are not aware, or have not controlled for in any way or in an adequate way, which may lead to confounding. If wine was truly less harmful than beer, we would have expected a similar difference in risk in ‘predominant drinkers’ of these alcoholic beverages, but no differences were found, i.e., predominant wine drinkers has as high a raised risk as predominant beer and liquor drinkers at all consumption levels. Thus, confounding by other risk

factors, which are specific for 'pure drinkers' may be more likely to explain these differences among light and heavy drinkers for UADT cancer.

Our study had several limitations. Recall bias might be possible because the exposures were measured after disease diagnosis. Although we analyzed a large-scale multicenter case–control study, the numbers of subjects and hence statistical power was limited, especially for 'pure drinkers', never smokers, drinkers with high consumption levels of liquor and for the analysis of esophagus cancer. We were missing information on specific type of wine (red vs. white wine), regarding ethanol concentration during consumption (straight or diluted consumption) and content of acetaldehyde. Underreporting and overreporting of the amount of alcohol consumed may be influenced by social norms in Europe and cannot be fully excluded in our analysis. However, we would expect that such non-differential exposure misclassification would bias our results towards the null for never or ever drinking.

On the other hand, our study had several strengths. We had information on education level, fruit and vegetable intake, a complete lifetime history of alcohol consumption and tobacco use, and very detailed information about pattern of drinking, for instance information about alcohol consumption before noon and between meals, and binge drinking. In addition, a dose–response analysis of alcohol exposure is more likely to appear statistically significant if the exposure contrast existing within the study population is large. In our multi-center study, the median of average alcohol exposure and cumulative alcohol exposures received over lifetime differ approximately by a factor 6 between study centers. This large range of exposure levels needed for dose–response analysis is often not available in a single study with small sample size, in particular after stratification by alcohol beverage type. Moreover, our multi-center study avoids problems in comparability because nearly all included centers used the same protocol for exposure assessment and one of two standardized protocols for case–control recruitment (hospital-based controls vs. population-based controls). Finally, no heterogeneity across study type or study center specific results was observed for the alcohol-related risk of UADT cancer across all alcohol beverage types.

This large case–control study underscores the strong and comparable carcinogenic effect of ethanol in wine, beer and liquor on organs of the UADT. Confounding and chance may explain the small differences among the rare group of exclusive lifetime drinkers.

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