Lifetime and baseline alcohol intake and risk of cancer of the upper aero-digestive tract in the European prospective investigation into cancer and nutrition (EPIC) study

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Recent alcohol consumption is an established risk factor for squamous cell carcinoma (SCC) of the upper aero-digestive tract. In contrast, the role of lifetime exposure to alcohol with regard to risk of SCC is not well established. Historical data on alcohol use are available in 271,253 participants of the European Prospective Investigation into Cancer and Nutrition (EPIC). During 2,330,381 person years, 392 incident SCC cases (279 men and 113 women) were identified. Cox regression was applied to model sex-specific associations between lifetime alcohol intake and SCC risk adjusting for potential confounders including smoking. Compared to men who drank 0.1–6.0 g/day alcohol at lifetime, the relative risks (RR) for developing SCC were significantly increased for men who drank 30.1–60.0 g/day (RR 1.65, 95% confidence interval:1.00–2.71), 60.1–96.0 g/day (RR 2.20, 95%CI 1.23–3.95), and >96.0 g/day, (RR 4.63, 95% CI 2.52–8.48), and for former drinkers (RR 4.14, 95%CI 2.38–7.19). These risk estimates did not considerably change when baseline alcohol intake was analyzed. Compared to women who drank 0.1–6.0 g/day alcohol intake at lifetime, the RR were significantly increased for women who drank >30 g/d (RR 6.05, 95%CI 2.98–12.3). Applying similar categories, the relative risk for baseline alcohol intake was 3.26 (95%CI 1.82–5.87). We observed a stronger association between alcohol intake at lifetime and risk of SCC in women compared to men (p for interaction = 0.045). The strong dose-response relation for lifetime alcohol use underscores that alcohol is an important risk factor of SCC of the upper aero-digestive tract throughout life.

Key words: cohort study; epidemiology; squamous cell carcinoma; esophagus; larynx; oral cavity; pharynx

Alcohol consumption is an established behavioral risk factor for several cancer sites including squamous cell carcinoma (SCC) of the upper aero-digestive tract (oral cavity and pharynx, larynx and esophagus).[1] A comprehensive report on this issue was recently released by the World Cancer Research Fund.[2] This systematic analysis of the literature[2] revealed that most of the previous studies are confined to men and most of them had been of a case-control design. Studies in women are difficult to establish for SCC risk due to low incidence in prospective studies[3] and the case-control studies in women are as liable to recall and selection bias as in men. Data from a meta-analysis[4] indicate a somewhat higher risk for esophageal carcinoma in women compared to men drinking the same amount of alcohol, while no such sex-specific differences were revealed for cancers of the oral cavity and pharynx. The systematic analysis of the literature[2] also revealed that in cohort studies data on the cumulative effect of lifetime alcohol consumption is seldom available, as reports are based on the alcohol consumption during a very short period prior to recruitment.

The aim of our study was to provide prospective data on sex-specific associations between lifetime alcohol intake and risk of upper aero-digestive tract SCC in the European Prospective Investigation into Cancer and Nutrition (EPIC) and to compare the findings with data on baseline alcohol consumption. Our study extends our previous investigation[5] in EPIC, a large cohort study including subjects from various geographic regions of Europe with a wide range of drinking habits.

Material and methods

Study population

EPIC is a multicenter prospective cohort study investigating the relationships between diet, lifestyle and environmental factors and the incidence of various types of cancer and other chronic diseases. The cohort consists of 521,457 subjects (70% women, 30%men) mostly aged from 35 to 70 years at time of enrolment recruited in 23 centers in 10 European countries,[6,7] including Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom (UK). For the present study, all prevalent cancer cases at baseline (n = 27,089) were excluded first. In addition, we excluded the cohorts of Norway (n = 35,948) and Greece (n = 26,427) due to the short follow-up period, the French cohorts (n = 69,426) because of incomplete case identification procedures for these cancer sites, the Swedish cohorts (n = 49,622) and the centers of Bilthoven (The Netherlands, n = 21,774) and Naples (Italy, n = 5,056) due to missing information on lifetime alcohol consumption. Thus, subjects for the present study came from 6 countries (n = 286115 subjects) including Italy (centers of Ragusa, Varese, Turin and Florence), Spain (centers of San Sebastian, Navarra, Granada, Asturias, Murcia), the Netherlands (center of Utrecht), the UK (centers of Oxford and Cambridge), Germany (centers of Heidelberg and Potsdam) and Denmark (centers of Aarhus and Copenhagen) (Table I). For the present analyses, we additionally excluded subjects with missing dietary questionnaire data including lifetime alcohol intake and fruit and vegetable intake and individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (n = 14,862) leaving finally 271,253 participants for analyses.

The methods of recruitment applied in each center and the study conduct have been described previously.[6] In brief, study subjects were recruited from the general population residing in a given geographical area, town or province. Exceptions were the Utrecht cohort (women attending a breast cancer screening), the Ragusa cohort (blood donors and their spouses) and the Oxford health conscious subcohort (mostly vegetarian and health-conscious volunteers). Eligible subjects were invited to participate in the study by mail or personal contact. Those who accepted, signed an informed consent form and completed questionnaires on their diet, lifestyle and medical history.

End points

Incident cancer cases of the upper aero-digestive tract were identified by population cancer registries in Denmark, Italy, Netherlands, UK and Spain. A combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used in Germany. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Participants were followed from study entry until date of cancer diagnosis of the oral cavity, pharynx, larynx or esophagus or censoring due to death, emigration, loss to follow-up or end of follow-up. For centers using cancer registry data, censoring dates for complete follow up were at December 2005 (San Sebastian), December 2004 (Utrecht, Oxford, Cambridge, Navarra, Asturias, Turin, Ragusa), December 2003 (Florence, Varese, Murcia, Aarhus, Copenhagen), December 2002 (Granada). For Germany using individually based follow-up, the end of the follow-up was considered to be the date of the last known contact, or date of diagnosis, or date of death, whichever came first. Mortality data were coded following the rules of the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10) and cancer incidence data following the 2nd Revision of the International Classification of Diseases for Oncology (ICD-O-2). Incident primary carcinomas of the oral cavity including the tongue (C01–C06), oropharynx (C09–C10), hypopharynx (C13–C14), esophagus (C15) and larynx (C32) were included in our study, while carcinomas of the lips, nasopharynx and salivary glands were not considered cases. Morphology information was used to classify the malignant tumors into SCC and adenocarcinomas. Adenocarcinomas were not considered.

Assessment of alcohol consumption, other dietary and lifestyle information

Diet including alcohol intake over the 12 month before enrolment was measured by center-specific dietary assessment instruments (mainly food frequency questionnaires (FFQ))[6] designed to capture local dietary habits with high compliance.[8] Most centers adopted a self-administered dietary questionnaire including 88–266 food items. In each country, baseline alcohol intake was calculated based on intake of alcoholic beverages reported in the

TABLE I – CHARACTERISTICS OF THE EPIC COHORTS INCLUDED IN THE PRESENT STUDY

Country	Cohort size	Male (%)	Mean follow-up (years)	Squamous cell carcinoma		Never drinker of alcoholic beverages at baseline (%)		Former drinker of alcoholic beverages at baseline (%)		Alocohol intake at age 20 (g/d)		Lifetime alcohol intake (g/d)[2]		Baseline alcohol intake (g/d)[1]	
				Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Italy	39,368	35.3	8.6	21	12	2.0	12.9	2.1	5.0	13.6	2.7	20.5	4.2	23.1	5.1
Spain	39,744	37.8	10.0	62	9	3.7	35.2	10.8	16.7	50.2	9.0	40.6	4.4	30.5	5.2
UK	72,990	29.9	8.6	39	30	1.2	1.9	5.0	3.8	11.0	8.5	10.1	5.6	8.6	5.3
Nether-lands	14,898	–	9.2	–	17	–	10.2	–	6.5	–	3.3	-	5.3	-	5.9
Germany	49,494	43.6	8.3	50	12	0.5	1.5	3.6	2.7	12.3	2.2	19.8	4.4	19.6	5.5
Denmark	54,759	47.8	7.7	107	33	0.4	1.5	1.4	1.2	11.3	4.2	18.1	7.2	22.0	10.3
Total	271,253	36.4	8.6	279	113	1.3	8.9	4.2	5.4	13.7	4.7	18.4	5.3	18.0	6.2

[1]Numbers are medians, among participants with an alcohol intake at baseline > 0.–[2]Numbers are medians, among participants with a lifetime alcohol intake > 0.

FFQ. Subjects reported the number of glasses of beer, cider, wine, sweet liquor, distilled spirits or fortified wines consumed during the 12 month prior to recruitment. Country-specific intake was calculated based on estimated average glass volume and ethanol content for each type of alcoholic beverage, using information collected in highly standardized 24-hr dietary recalls from a random subset of the cohort.[9,10]

Lifetime alcohol use was assessed as glasses of different beverages consumed at 20, 30, 40, 50 years of age and at baseline.[11] Average lifetime alcohol intake was determined as a weighted average of intake at different ages, with weights equal to the time of individual exposure to alcohol at different ages.

Never drinkers were defined as subjects who did not report any consumption of alcoholic beverages at all points during their lifetime, while those who reported alcohol consumption at ages 20, 30, 40 or 50 years, but not during the 12 month prior to the recruitment were categorized as former drinkers in both analyses on lifetime and baseline alcohol intake.

Baseline information on other lifestyle variables was obtained from standardized questionnaires including questions on education, socio-economic status, medical history, physical activity, smoking status and lifetime history of tobacco smoking. Height and weight were measured at recruitment, with exception of the Oxford cohort where health conscious subjects self-reported their height and weight.

Statistical analysis

Cox proportional hazards models[12] were used to analyze the association between alcohol intake and SCC incidence for both sexes combined and for sex specific strata. The analyses used the stratification option to control for center effects related to follow up procedures and questionnaire design and to control for age at recruitment in one-year categories. Age was used as the primary time variable in all Cox regression models. Time at entry was age at baseline, exit time was age when participants were diagnosed with SCC cancer of the upper-aerodigestive tract, died, were lost of follow-up, or were censored at the end of the follow-up period, whichever came first. The models were adjusted for duration of smoking (continuous), smoking status (former smoking with quitting ≥ 10 years, former smoking with quitting < 10 years, former smoking with unknown quit, current smoking with < 15, current smoking with ≥ 15 and < 25, current smoking with ≥ 25 cig/day, and current smoking with unknown quantity), education (Non and primary school, technical professional school, secondary school, university degree, missing), body-mass-index (continuous), and fruit and vegetable intake (continuous), and sex (where appropriate).

Associations between baseline and lifetime alcohol consumption and risk of SCC of upper aero-digestive tract were analyzed on a continuous scale (increments: 10 g/day) with addition of dummy variables for never and former drinkers. Gender specific differences in risk estimates were evaluated by interaction terms.

To test whether the associations of alcohol intake with cancer of the upper aero-digestive tract differ between esophageal cancer, larynx cancer and cancer of the oral cavity and pharynx we also evaluated these relationships for baseline and lifetime alcohol intake in a common regression model using the data augmentation method described by Lunn and McNeil.[13,14] In this analysis, each subject has a separate observation for each outcome. We assumed different associations of covariates with the 3 outcomes by including interaction terms between each covariate with type of outcome in each model.

Furthermore, alcohol consumption at baseline, at age of 20 and during lifetime was modeled using the following categories: never-drinker, former drinker, 0.1–6.0 (reference), 6.1–18.0, 18.1–30.0, >30.1–60.0 g/day. In men, the highest category was further divided into 30.1–60.0, 60–96.0 and >96.0 g/day.

To detail the joint effects of alcohol consumption and smoking, relative risks (RR) were calculated for categories of total lifetime alcohol consumption (0.1–30.0, 30.1–60.0, >60.0 g/day in men, 0.1–18.0, >18 g/day in women) cross-classified by smoking status (never-smoker, ex-smoker, smoker at recruitment <15 cig/day, ≥15 cig/day). Furthermore, we performed stratum-specific analyses of alcohol intake on a continuous scale for nonsmokers (defined as never-smokers or former smokers quit $\geq$ 10 years before recruitment) and smokers (defined as current smokers or former smokers who quit $<$ 10 years before recruitment). Interaction between smoking status and alcohol consumption was tested by using the likelihood ratio test for models with and without the respective interaction term.

All analyses were run using SAS Statistical Software, version 9.13 (SAS Institute, Cary, NC). All p-values presented are 2-sided, and those <0.05 were considered statistically significant.

Results

The final sample consisted of 98,505 men and 172,748 women contributing a total of 2,330,381 person-years. Among these participants, 279 cases of SCC of the upper aero-digestive tract were identified in men and 113 in women (Table I). Men generally consumed more alcohol and were less likely to be non-drinkers than women at baseline (Table I). Important baseline characteristics according to never, former and current drinkers are presented in Table II. In both men and women, never smokers were more likely to be never drinkers than current or past smokers. Remarkably, only about 3% of highly educated women were never drinkers, compared to about one fifth of women with lower education. Never drinkers were more frequent among obese subjects than among normal weight participants.

First, the associations between baseline and lifetime alcohol consumption and risk of SCC of upper aero-digestive tract were analyzed on a continuous scale in multivariable adjusted models (Table III). On the basis of baseline alcohol intake the risk increases per 10 g increase were 1.14 (95% CI 1.11–1.18) in men, 1.23 (1.11–1.36) in women, and 1.15 (1.12–1.18) for both sexes

TABLE II – FORMER, CURRENT AND LIFETIME ALCOHOL CONSUMPTION ACCORDING TO MAIN CHARACTERISTICS FOR MEN AND WOMEN

	Men					Women				
	Never-drinker (%)[2]	Former drinker (%)	Current drinker (%)	Baseline alcohol intake (g/d)	Lifetime alcohol intake (g/d)	Never-drinker (%)	Former drinker (%)	Current drinker (%)	Baseline alcohol intake (g/d)	Lifetime alcohol intake (g/d)
Age at recruitment <50 years	1.6	4.2	94.2	16.4	19.6	9.6	4.7	85.7	5.8	5.8
Age at recruitment ≥50 years	1.1	4.2	94.7	18.8	17.8	8.3	6.0	85.7	6.4	5.1
Education										
No school degree or primary school	1.7	7.1	91.2	21.4	22.2	19.0	11.0	70.0	5.1	4.2
Technical, professional or secondary school	1.3	3.7	95.0	17.2	18.0	5.3	3.5	91.2	6.4	5.6
University degree	0.9	2.0	97.1	17.5	17.0	3.2	2.4	94.4	7.6	7.2
Smoking										
Never	2.0	3.5	94.5	13.3	13.6	11.4	5.8	82.8	5.3	4.4
Past	0.8	4.5	94.7	18.6	19.1	4.0	4.5	91.5	7.2	6.7
Current < 15 cig/d	0.9	3.8	95.3	23.8	23.6	7.5	5.0	87.5	8.1	6.4
Current ≥ 15 cig/d	1.4	5.3	93.3	25.0	25.0	7.6	6.2	86.2	8.9	7.3
BMI <25	1.1	3.6	95.3	15.7	15.5	5.4	3.8	90.9	6.7	5.9
25 ≥ BMI <30	1.4	4.3	94.4	19.1	19.2	10.6	6.6	82.8	5.9	5.0
BMI ≥ 30	1.6	5.3	93.1	21.1	23.1	17.4	9.1	73.5	3.8	3.9
Fruit and vegetable intake <320g/d	0.8	3.5	95.7	18.0	17.0	4.9	4.8	90.3	7.1	6.1
320 g/d ≥Fruit and vegetable intake <480 g/d	1.2	3.7	95.1	16.7	17.2	7.0	4.1	88.8	6.1	5.3
Fruit and vegetable intake ≥480g/d	2.1	5.6	92.3	20.7	23.0	15.9	8.4	75.7	5.2	4.5

TABLE III – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) OF SQUAMOUS CELL CARCINOMA OF THE UPPER AERO-DIGESTIVE TRACT BY 10G INCREASE OF DAILY BASELINE AND LIFETIME ALCOHOL INTAKE

	Cases	Baseline alcohol intake		Lifetime alcohol intake	
		Unadjusted RR per 10 g/increase	RR[1]per 10 g/increase	Unadjusted RR per 10 g/increase	RR[1]per 10 g/increase
Men					
Upper aero-digestive tract	279	1.19 (1.16–1.22)	1.14 (1.11–1.18)	1.14 (1.11–1.16)	1.10 (1.08–1.13)
Oral Cavity/Pharynx	126	1.26 (1.20–1.32)	1.15 (1.10–1.20)	1.21 (1.13–1.30)	1.09 (1.06–1.12)
Larynx	101	1.14 (1.09–1.19)	1.08 (1.03–1.14)	1.12 (1.09–1.16)	1.08 (1.05–1.12)
Esophagus	52	1.20 (1.16–1.25)	1.22 (1.15–1.29)	1.12 (1.09–1.15)	1.18 (1.10–1.27)
Women					
Upper aero-digestive tract	113	1.30 (1.19–1.42)	1.23 (1.11–1.36)	1.41 (1.28–1.56)	1.29 (1.16–1.43)
Oral Cavity/Pharynx	62	1.33 (1.16–1.52)	1.18 (1.04–1.33)	1.39 (1.20–1.60)	1.26 (1.07–1.49)
Larynx	16	1.37 (1.15–1.63)	1.38 (1.10–1.73)	1.55 (1.26–1.89)	1.32 (0.93–1.89)
Esophagus	35	1.27 (1.13–1.43)	1.31 (1.12–1.53)	1.41 (1.24–1.62)	1.35 (1.13–1.60)

[1]Models are adjusted for the duration of smoking, former smoking with quitting ≥ 10 y, former smoking with quitting < 10 y, former smoking with unknown quit, current smoking with < 15, current smoking with ≥ 15 and < 25, current smoking with ≥ 25 cig/d, and current smoking with unknown quantity, education, fruit and vegetable intake, and body-mass-index, neverdrinker and former drinker.

combined. On the basis of lifetime alcohol intake the risk increases per 10 g increase were 1.10 (1.08–1.13) in men, 1.29 (1.16–1.43) in women, and 1.10 (1.08–1.13) for both sexes combined. The interaction term for baseline alcohol intake and sex was nonsignificant ($p = 0.14$), whereas the interaction term for lifetime alcohol intake and sex was significant ($p = 0.045$) (data not shown in a table).

Both baseline and lifetime alcohol intake are related to an increased risk of cancer at the various anatomic locations of the upper aero-digestive tract in both men and women (Table III). In men, the multivariable adjusted RR for SCC per 10 g increase in baseline alcohol intake was higher for esophageal SCC compared to laryngeal SCC ($p_{diff} = 0.003$), whereas no significant differences were found between cancers of the esophagus and the oral cavity or pharynx as well as between larynx and oral cavity/pharynx cancers. For high lifetime alcohol intake, the risk of esophagus cancer was higher than the risk of oral cavity/pharynx cancer ($p_{diff} = 0.01$) as well as larynx cancer ($p_{diff} = 0.01$) in men, with no such differences in women based on multivariable adjusted models.

Table IV depicts sex-specific RR of SCC by categories of alcohol intake at age 20, lifetime and baseline and alcohol intake. Risk estimates based on baseline and lifetime alcohol did not considerably differ in men. In men, but not in women, high alcohol intake during young adulthood (age 20 years) was already strongly related to an increased SCC risk. Strong dose-response relations were observed between lifetime exposure and risk in both sexes. When using mild drinkers (0.1–6.0 g/day lifetime or baseline) as the reference category, male never drinkers were not at an increased risk of SCC, while former drinkers had a 3- to 4-fold higher risk. In women, our data are suggestive of increased SCC risk in never drinkers compared to those who drank 0.1–6.0 g/day at baseline or during lifetime, although not all risk estimates reached statistical significance.

As smoking and drinking are the most important risk factors for the SCC of upper aero-digestive tract in a further analysis, we investigated single and combined effects of lifetime alcohol drinking and tobacco smoking on risk of SCC. Although it appeared that lifetime alcohol drinking and tobacco smoking interact to increase the risk of SCC beyond the multiplicative model (Table V), this was not confirmed when the interaction was tested (men: $p = 0.27$, women: $p = 0.49$). Moreover, high alcohol intake increased the risk in both nonsmokers (RR per 10 g increase in lifetime alcohol intake: men: 1.10 (1.01–1.19), women: 1.24 (0.94–1.62)) and smokers (RR per 10 g increase in lifetime alcohol intake: men: 1.12 (1.10–1.15), women: 1.34 (1.18–1.51)) (data not shown in a table).

TABLE IV – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) OF SQUAMOUS CELL CARCINOMA OF THE UPPER AERO-DIGESTIVE TRACT

By categories of daily alcohol intake (g/d)	Alcohol intake at age 20			Lifetime alcohol intake			Baseline alcohol intake		
	Cases	Person (years)	RR (CI)[1]	Cases	Person (years)	RR (CI)[1]	Cases	Person (years)	RR (CI)[1]
Men									
Never	–	–	–	1	11731	0.51 (0.07–3.80)	1	11731	0.44 (0.06–3.24)
Former	–	–	–	36	37022	4.14 (2.38–7.19)	36	37022	3.51 (2.16–5.71)
0	23	89637	1.78 (1.02–3.13)	–	–	–	–	–	–
0.1–6.0	29	183063	Reference	23	125581	Reference	35	167781	Reference
6.1–18.0	75	245282	1.76 (1.14–2.71)	44	252547	0.78 (0.47–1.31)	34	225677	0.68 (0.42–1.09)
18.1–30.0	41	120307	2.17 (1.34–3.52)	46	167215	1.10 (0.65–1.86)	25	135670	0.80 (0.47–1.36)
30.1–60.0	47	111854	2.76 (1.71–4.46)	70	169100	1.65 (1.00–2.71)	63	179163	1.31 (0.85–2.01)
60.1–96.0	26	45431	3.98 (2.26–7.03)	30	50260	2.20 (1.23–3.95)	37	60502	1.66 (1.02–2.71)
>96.0	38	42704	5.24 (2.97–9.25)	32	24823	4.63 (2.52–8.48)	48	20733	4.79 (2.96–7.74)
p for trend			<0.0001			<0.0001			<0.0001
Women									
Never	–	–	–	9	141909	2.22 (0.99–4.99)	9	141909	2.33 (1.02–5.30)
Former	–	–	–	9	87241	2.01 (0.91–4.43)	9	87241	2.07 (0.93–4.63)
0	46	550193	1.12 (0.71–1.77)	–	–	–	–	–	–
0.1–6.0	40	542691	Reference	34	661818	Reference	29	630354	Reference
6.1–18.0	18	289689	1.00 (0.57–1.77)	38	452615	1.67 (1.03–2.69)	34	413762	1.86 (1.12–3.09)
18.1–30.0	6	71298	1.83 (0.75–4.45)	11	110999	1.84 (0.90–3.75)	8	114735	1.29 (0.58–2.89)
>30.0	3	38233	1.64 (0.49–5.52)	12	37522	6.05 (2.98–12.3)	24	104103	3.26 (1.82–5.87)
p for trend			0.2687			<0.0001			0.0009

[1]Models are adjusted for the duration of smoking, former smoking with quitting ≥ 10 y, former smoking with quitting < 10 y, former smoking with unknown quit, current smoking with < 15, current smoking with ≥ 15 and < 25, current smoking with ≥ 25 cig/d, and current smoking with unknown quantity, education, fruit and vegetable intake, and body-mass-index.–[2]*p* for trends were estimated excluding never and former drinkers.

TABLE V – RELATIVE RISKS[1] (RR) AND 95% CONFIDENCE INTERVALS (CI) OF SCC OF THE UPPER AERO-DIGESTIVE TRACT ACCORDING TO CROSS-CLASSIFIED CATEGORIES BY LIFETIME ALCOHOL INTAKE AND CIGARETTE SMOKING

Lifetime alcohol intake (g/d)	Never-smoker		Ex-smoker		Current smoker < 15 cig./d		Current smoker ≥15 cig./d	
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Men								
0.1–30	17	1	33	1.50 (0.83–2.71)	16	2.33 (1.16–4.68)	40	5.76 (3.20–10.36)
30.1–60	3	0.90 (0.26–3.10)	19	3.23 (1.66–6.30)	8	3.55 (1.50–8.37)	37	11.75 (6.44–21.43)
>60	2	1.71 (0.38–7.67)	8	4.24 (1.78–10.12)	16	11.02 (5.17–23.52)	36	22.86 (12.27–42.60)
Women								
0.1–18	24	1	21	1.71 (0.94–3.12)	6	1.43 (0.57–3.57)	20	6.04 (3.20–11.40)
>18	3	1.94 (0.58–6.54)	1	0.59 (0.08–4.37)	4	7.00 (2.34–20.90)	14	17.28 (8.39–35.60)

[1]Relative risks were estimated after cross-classification of participants by categories of alcohol drinking (lifetime) and tobacco smoking using drinkers with mild to moderate alcohol intake as a reference. Never and former drinkers (36 male cases, 5270 male non-cases, 18 female cases, and 24565 female non-cases) and subjects with incomplete information on smoking status (8 male cases, 2100 male non-cases, 2 female cases and 987 female non-cases) were excluded. Cox regression models were stratified by center and age at recruitment and adjusted for education, fruit and vegetable intake, and body-mass-index.

In additional analyses, we explored the role of alcohol for risk of SCC taking the type of beverage into account. In men, the relative risk per 10 g increase in alcohol intake were 1.09 (95% CI 1.04–1.15) for wine, 1.16 (95% CI 1.12–1.21) for beer, and 1.20 (95% CI 1.06–1.37) for liquors. In women, these RRs were 1.11 (95% CI 0.95–1.30) for wine, 1.26 (95% CI 1.06–1.52) for beer, and 1.51 (95% CI 1.10–2.07) for liquors. These analyses showed that alcohol is increasing the risk of SCC independent of source. Interestingly, the risk estimates for alcohol from wine differed significantly from those for alcohol from beer or liquors (p_{diff} =0.03) in men but not in women (p_{diff} = 0.12).

Discussion

This is the first study investigating associations between lifetime alcohol intake and risk of SCC of the upper-aerodigestive tract in a large prospective cohort. In our study, based on the European Prospective Investigation into Cancer and Nutrition, lifetime alcohol consumption was an important risk factor for SCC of the upper aero-digestive tract in both men and women. Interestingly, the risk increasing effect of lifetime alcohol consumption was significantly higher in women compared to men. However, we found significantly increased risks for SCC at the age of 20, for lifetime and baseline alcohol intake in men, and for lifetime and baseline alcohol intake in women. These associations indicate that alcohol intake is an important risk factor throughout lifetime in both men and women.

Compared to most other cohort studies on alcohol consumption and cancer risk,[15–17] EPIC as a multicenter cohort study covers a wide range of alcohol consumption from various beverages and drinking patterns among the participating regions and countries.[10] EPIC provides data on both baseline and lifetime alcohol consumption. To our knowledge, this is the first study investigating baseline and lifetime alcohol consumption in relation to cancer of the upper-aero-digestive tract in a large prospective cohort. Although the validity of absolute measures of retrospective alcohol use might be questionable, relative ranks were shown to be reasonable stable.[18] Furthermore, the trends of past alcohol use based on self-reported alcohol intake in EPIC and on data of per capita consumption were comparable.[11]

Further, the opportunity of performing sex-specific analyses is among the strengths of our study. It is, however, important to note the limitations. Even though EPIC is one of the largest studies on cancer and nutrition worldwide, the number of SCC cases of the upper aero-digestive tract remains small, especially in women. This may lead to instable risk estimates particularly in the categorical analyses, for instance alcohol intake at age 20 or cross-classi-

fied analyses on alcohol intake and smoking. Moreover, the very magnitude of the individual and total cohorts, the related lengthy period of subject recruitment and the variety of local facilities have made it impossible to standardize all of the procedures strictly, as would be possible for smaller studies.[6] However, considerably effort has been put into ensuring maximum comparability within and between the cohorts, in particular where dietary information is concerned, by means of the large calibration subsample. Furthermore, we performed all analyses stratified by center.[9,10] Another important risk factor for SCC of the upper aero-digestive tract is infection with human papillomavirus (HPV), particularly type 16.[19] We had no information on HPV16 seropositivity. We also could not consider information on genetic predisposition in our analyses, as these data are not available at this point. It must be kept in mind that the effect of alcohol on SCC risk may be modified by common genetic variants of genes involved in alcohol metabolism, such as ADH1B and ALDH2.[20]

An important result of our study is that former male drinkers carry an increased risk of developing SCC of the upper aero-digestive tract. This result is in line with a recent large pooled analysis on alcohol drinking cessation and esophageal and head and neck cancer.[21]

We found no convincing evidence that the effect of alcohol consumption is modified by tobacco smoking. This furthers the data of previous studies reporting that alcohol drinking and tobacco smoking independently increase the risk of SCC on a multiplicative scale.[22] Furthermore, the independent association of each of the 2 main risk factors is underlined by the pooled-analysis of 15 case-control studies investigating the effect of alcohol consumption in never smokers. Among never users of tobacco, alcohol consumption was associated with an increased risk of head and neck cancer when alcohol was consumed at high frequency (OR for 3 or more drinks per day *vs.* never drinking = 2.04, 95% CI = 1.29–3.21).[23] Nonetheless, in our study the risk estimates for heavy smokers drinking very high amounts of alcohol appeared to be somewhat higher than what would be expected for an independent multiplicative contribution of alcohol and smoking to SCC risk. The numbers of cases with specific combinations of risk factors were rather small, *e.g.*, few never smokers drinking very high amounts of alcohol, in both men and women. Thus, the power to detect an effect modification by smoking and drinking on a multiplicative scale has been low. The effect modification might be investigated more sufficiently after more years of follow-up.

Further, our analysis showed that the use of all types of alcoholic beverages increases risk of SCC although some evidence was found that alcohol from wine might have less detrimental consequences than alcohol from beer and liquors. Studies taking the source of alcohol into account have not produced conclusive data.[22,24] Wine may contain substances that are believed to protect against cancer development including SCC.[25] However, residual confounding can also not be excluded since important life style factors relevant for SCC are associated with beverage type.[26,27]

Sex-specific drinking patterns[10,28] and differences in reporting alcohol intake motivated us to generally conduct sex-specific analyses. We noted higher relative risk estimates in women compared to men drinking the same amount of lifetime alcohol. Such results suggest that women could be more susceptible to alcohol-induced carcinogenesis in the upper aero-digestive tract than men. Higher blood ethanol concentrations in women compared to men[29] and sex-specific differences in alcohol metabolism[30] should be considered. On the other hand, underreporting of the amount of alcohol consumed may be relevant in this context. Although alcohol measurements at baseline have shown relatively high validity and reliability in both men and women,[8] the question of relevant underreporting especially among women cannot be fully excluded. Sex differences in reporting alcohol intake are difficult to circumvent and may constitute a common problem.[31,32] It has been put forward that women are substantially influenced by social norms and stigma when answering questions about their alcohol intake.

In conclusion, our prospective data provide further evidence that alcohol drinking is related to risk of SCC in the upper aero-digestive tract in both men and women. The strong dose-response relation for both baseline and lifetime alcohol intake underlines, that alcohol is an important risk factor throughout life.

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