Ethanol Intake and Risk of Lung Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Within the European Prospective Investigation into Cancer and Nutrition (EPIC), the authors examined the association of ethanol intake at recruitment (1,119 cases) and mean lifelong ethanol intake (887 cases) with lung cancer. Information on baseline and past alcohol consumption, lifetime tobacco smoking, diet, and the anthropometric characteristics of 478,590 participants was collected between 1992 and 2000. Cox proportional hazards regression was used to calculate multivariate-adjusted hazard ratios and 95% confidence intervals. Overall, neither ethanol intake at recruitment nor mean lifelong ethanol intake was significantly associated with lung cancer. However, moderate intake (5–14.9 g/day) at recruitment (hazard ratio (HR) = 0.76, 95% confidence interval (CI): 0.63, 0.90) and moderate mean lifelong intake (HR = 0.80, 95% CI: 0.66, 0.97) were associated with a lower lung cancer risk in comparison with low consumption (0.1–4.9 g/day). Compared with low intake, a high (≥60 g/day) mean lifelong ethanol intake tended to be related to a higher risk of lung cancer (HR = 1.29, 95% CI: 0.93, 1.74), but high intake at recruitment was not. Although there was no overall association between ethanol intake and risk of lung cancer, the authors cannot rule out a lower risk for moderate consumption and a possibly increased risk for high lifelong consumption.

alcohol drinking; cohort studies; ethanol; lung neoplasms

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; ICD-O-2, *International Classification of Diseases for Oncology*, Second Edition.

Smoking is the most important risk factor for lung cancer, being responsible for approximately 90 percent of lung cancer cases (1). Other risk factors include air pollution and occupational hazards, such as exposure to tar and asbestos (1). Suspected risk factors include poor nutrition, such as low consumption of fruits and vegetables, and lack of physical activity (2). Alcohol consumption has already been investigated as a potential risk factor for lung cancer, and a recent pooled analysis of seven prospective cohort studies (3) revealed a non-statistically-significant greater risk of lung cancer for consumption of ≥30 g/day versus none in both men (relative risk = 1.21, 95 percent confidence interval (CI): 0.91, 1.61) and women (relative risk = 1.16, 95 percent CI: 0.94, 1.43). In a meta-analysis, alcohol drinkers had a 19 percent higher risk of lung cancer (95 percent CI: 11, 29) than nondrinkers in cohort studies; the risk was highest in heavy alcohol consumers (≥2,000 g/month) (4). No precise mechanism for the possible lung carcinogenicity of alcohol in humans has been identified yet, but acetaldehyde, the first metabolite of alcohol, is a well-known animal carcinogen and is classified as possibly carcinogenic to humans (5). Additionally, chronic alcohol consumption increases cytochrome P-450 level and microsomal enzyme activity, which may result in accelerated metabolism of tobacco carcinogens (6, 7). Although it seems to be biologically plausible that alcohol consumption increases the risk of lung cancer, it must be taken into account that alcohol consumption is often associated with tobacco smoking and also occupational exposure; thus, effects of alcohol consumption on lung cancer risk might be difficult to separate from effects due to these potential confounders.

In contrast to most previous prospective studies, not only information on alcohol consumption at recruitment but also detailed information on alcohol consumption in the past has been assessed for the majority of subjects who participated in the European Prospective Investigation into Cancer and Nutrition (EPIC). This allowed us to separately determine effects of past and current (i.e., at recruitment) ethanol intake on lung cancer and to examine whether lung cancer risk differs between never drinkers and former drinkers.

MATERIALS AND METHODS

Population

EPIC is a large prospective cohort study being conducted in 23 centers in 10 European countries (France, Italy (Florence, Varese, Ragusa, Turin, Naples), Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), the Netherlands (Bilthoven, Utrecht), the United Kingdom (Cambridge, Oxford), Greece, Germany (Heidelberg, Potsdam), Sweden (Malmö, Umeå), Norway, and Denmark (Aarhus, Copenhagen)). A total of 521,457 participants were recruited for the study. At most of the study centers, participants were recruited from the general population. However, the French cohort encompassed female members of a health insurance plan for school and university employees. Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, and civil servants, as well as the general population. In Utrecht, participants in mammographic screening programs were recruited for the study, and the cohort in Florence also included participants in such screening programs. In Oxford, half of the cohort consisted of "health-conscious" subjects from England, Wales, Scotland, and Northern Ireland. The cohorts of France, Norway, Utrecht, and Naples included women only (8).

Of the 521,457 participants, we excluded prevalent cancer cases ($n = 25{,}868$) and subjects with incomplete follow-up information ($n = 9{,}296$) or with a ratio of energy intake to energy expenditure in the top or bottom 1 percent ($n = 9{,}686$). The current analysis was based on 478,590 EPIC participants.

Exposure assessment

Diet over the previous 12 months was assessed using dietary assessment instruments that had been specifically developed for each participating country (8). Food frequency questionnaires were used in France, Italy, Spain, the United Kingdom, Greece, the Netherlands, Germany, Denmark, Umeå, and Norway. In Malmö, a nonquantitative food frequency questionnaire was combined with a 14-day dietary record on hot meals. Baseline ethanol and energy intakes were calculated from the dietary instruments applied at each study center (8). Participants reported on how many standard glasses of beer and/or cider, wine, sweet liquor, distilled spirits, and fortified wine they had consumed per day or per week during the 12 months prior to recruitment. Ethanol intake was calculated on the basis of average glass volume and ethanol content for each type of alcoholic beverage (9).

Information on past alcohol consumption was assessed as glass(es) of beverage consumed per week at 20, 30, 40, and 50 years of age. This information was not collected in Naples, Bilthoven, Sweden, and Norway. Information was available for 364,667 participants (76.2 percent of the subjects included in the analysis). To calculate mean lifelong ethanol intake, we used an algorithm that combined information on the duration of alcohol consumption (derived from information on alcohol consumption at different ages) and the amount of alcohol consumed at these different ages. Thus, mean lifelong ethanol intake was determined as a weighted average of the intakes at different ages, with weights equal to the total subject-specific time under investigation. We also collected detailed information on lifetime history of use of tobacco products, including smoking status (current, past, or never smoker), type of tobacco used (cigarettes, cigars, or pipe), number of cigarettes currently smoked per day, and age at which participants had started and, if applicable, quit smoking. Comparability of nondietary questions as well as of questions on past alcohol consumption was ensured by a set of core questions that were similar at all participating centers (8).

Height and weight were measured at all EPIC centers except France, Norway, and Oxford, for which self-reported height and weight were assessed via questionnaire (8).

Outcome assessment

Cancer diagnoses were based on population registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Active follow-up through information obtained from study subjects, next of kin, health insurance records, and cancer and pathology registries was used in France, Germany, and Greece. Mortality data were obtained from either cancer registries or mortality registries at the regional or national level. Participants were censored as follows: December 1999 in Turin; June 2000 in Bilthoven; December 2000 in Asturias, Murcia, and Cambridge; December 2001 in Florence, Varesa, Ragusa, Naples, Granada, Navarra, San Sebastian, Oxford, Malmö, and Norway; June 2002 in France; December 2002 in Umeå, Aarhus, and Copenhagen; and June 2003 in Utrecht. For Germany and Greece, the end of follow-up was considered to be the date of the last known contact, diagnosis, or death, whichever came first.

Cases of lung cancer were defined on the basis of the *International Classification of Diseases for Oncology*, Second Edition (ICD-O-2), and included all invasive cancers that were coded as C34. Histologic information was available for 1,080 of 1,119 lung cancer cases, and this information was used to define three major subgroups by histologic type: adenocarcinoma (ICD-O-2 codes 8140/3, 8230/3, 8250/3, 8251/3, 8260/3, 8310/3, 8480/3, 8490/3, 8481/3, and 8550/3; $n = 366$), squamous-cell carcinoma (ICD-O-2 codes 8052/3, 8070/3, 8071/3, and 8075/3; $n = 234$), and small-cell carcinoma (ICD-O-2 codes 8041/3, 8042/3, 8043/3, 8044/3, 8045/3, and 8246/3; $n = 189$).

Statistical analysis

Cox proportional hazards regression was used to examine the association of ethanol intake with lung cancer, modeling daily ethanol intake as a categorical variable (0, 0.1–4.9, 5–14.9, 15–29.9, 30–59.9, and $\geq$60 g/day). The same categories were used for intake at recruitment and mean lifelong intake. Participants with a low daily ethanol intake of 0.1–4.9 g were used as the reference group to ensure a sufficiently large number of cases in the reference group. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, and time of exit was the age at which participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by sex, center, and age at recruitment in 1-year categories. To adjust for lifelong tobacco smoking, we included current smoking status (never smokers; current cigarette smokers (1–14, 15–24, or $\geq$25 cigarettes/day); former smokers who had stopped $\leq$10 years ago, $>$10–20 years ago, or $>$20 years ago; other smokers (pipe or cigar smokers, occasional smokers); and persons with missing information on smoking) and duration of smoking in 10-year categories ($\leq$10, 11–20, 21–30, 31–40, 41–50, or $>$50 years). We separately adjusted for duration of smoking and amount of smoking instead of using pack-years of smoking. Additionally, weight and height at recruitment (as continuous variables); consumption of fruit, red meat, and processed meat (all continuous); nonethanol energy intake (continuous); physical activity at work, as an indicator of possible exposure to carcinogens at work (nonworker, sedentary occupation, standing occupation, manual work, or unknown); and education (no degree or primary school completed, technical or professional school completed, secondary school completed, university degree, and not specified or missing) were included in the regression models. Trend tests were performed by using the midpoints of the respective alcohol consumption categories to create a continuous variable for the Cox regression model.

To further explore the shape of the risk function, we fitted a Cox proportional hazards model with restricted cubic splines for ethanol intake treated as a continuous variable (10, 11). We specified four knot positions at ethanol intakes

TABLE 1. Case distribution and alcohol consumption by country, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004

	No. of cases		Person-years of observation		Nondrinker at recruitment (%)		Ethanol intake at recruitment (median; g/day)*		Mean lifelong ethanol intake (median shown; g/day)*	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
France	—†	40	—†	569,588	—†	12.7	—†	7.6 (2.7–16.8)‡	—†	4.3 (1.1–9.9)
Italy	42	35	75,151	188,691	4.0	22.3	23.6 (6.4–37.1)	5.8 (0.8–14.3)	20.7 (8.3–34.8)	4.3 (1.4–9.8)
Spain	54	13	103,659	163,968	14.2	51.6	29.3 (12.2–52.3)	5.2 (1.5–13.5)	43.0 (22.2–73.1)	5.7 (1.6–12.8)
United Kingdom	62	52	121,141	284,495	6.4	5.9	9.5 (2.8–18.2)	5.0 (1.4–10.5)	10.5 (5.0–19.9)	5.8 (1.8–12.6)
The Netherlands	17	71	50,066	182,050	9.3	16.7	13.6 (5.2–27.4)	5.6 (1.5–14.4)	—†,§	5.7 (2.9–11.4)
Greece	35	3	38,997	55,824	9.2	35.1	12.1 (4.7–25.6)	2.3 (1.2–6.6)	17.9 (7.1–38.9)	1.9 (0.3–6.3)
Germany	106	29	125,746	163,361	4.1	4.2	19.1 (8.6–35.5)	5.8 (2.3–12.4)	19.6 (10.6–33.6)	4.5 (2.1–8.6)
Sweden	95	71	175,655	204,856	7.8	15.2	6.9 (3.0–14.2)	3.3 (1.1–8.3)	—§	—§
Denmark	195	171	174,734	194,151	1.8	2.7	19.8 (10.9–29.9)	9.8 (3.3–17.7)	18.1 (10.4–29.9)	7.2 (3.5–12.6)
Norway	—†	28	—†	108,248	—†	19.0	—†	2.3 (1.0–4.9)	—†,§	—§

* In drinkers.
† There were no male participants in Naples, Utrecht, France, and Norway.
‡ Numbers in parentheses, range.
§ Information on lifelong alcohol consumption was not available for Naples, Bilthoven, Sweden, and Norway.

of 5, 15, 30, and 60 g/day. Other knot positions were specified but did not appreciably change the curves.

We performed subanalyses by histologic type (adenocarcinoma, squamous-cell carcinoma, or small-cell carcinoma), smoking status, and sex. We tested for interaction between sex and ethanol intake by including a cross-product term along with the main-effect terms in the Cox regression model. To test for interaction between smoking status and ethanol intake, we included the categories of ethanol intake as a continuous variable (the same as those we used to test for trend) and smoking categories as a continuous variable (using 0, 1, and 2 for never, former, and current smokers, because these were our stratification variables) and modeled a cross-product term. We additionally included in the models variables for duration of smoking and number of cigarettes smoked per day. The statistical significance of the cross-product term was evaluated by means of the likelihood ratio test. All analyses were conducted using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 1,119 lung cancer cases (606 in men, 513 in women) occurred in 2,980,381 person-years of observation of the entire study population. Adenocarcinomas of the lung were more common in females (39.4 percent of total lung cancer cases) than in males (27.1 percent), whereas squamous-cell carcinomas were diagnosed more often in males (27.9 percent) than in females (12.7 percent). Small-cell carcinomas were as common among females (16.6 percent) as among males (17.3 percent). Median follow-up time was 6.4 years (interquartile range, 4.9–7.7 years). The single largest contribution of lung cancer cases was from the Danish EPIC cohorts (table 1). The Spanish EPIC centers reported the highest percentage of men and women without ethanol intake at recruitment, whereas the lowest percentage was observed at the Danish centers. Spanish men had the highest intake of ethanol at recruitment, followed by men from the Italian cohorts. Among women, the highest intake was observed at the Danish and French EPIC centers.

Current nonconsumers of alcoholic beverages were less likely to be current smokers compared with subjects with the highest intake of alcohol (table 2). In addition, nonconsumers were less likely to have a university degree. Total energy intake (i.e., including energy intake from alcoholic beverages) increased with increasing daily intake of ethanol, but fruit consumption decreased. The baseline characteristics of participants with data on past alcohol consumption were similar to those of the entire cohort (data not shown).

Ethanol intake at recruitment

Nonconsumers of alcohol at recruitment had a higher risk of lung cancer than low consumers (0.1–4.9 g/day) (table 3). This association was attenuated after excluding the first 2 years of follow-up (hazard ratio (HR) = 1.10, 95 percent CI: 0.86, 1.42). The lowest risk of lung cancer was observed among participants with an ethanol intake of 5–14.9 g/day at recruitment (table 3). This association was similar when adjusting for smoking only. Additionally, excluding the first 2 years of follow-up did not appreciably change the result (HR = 0.69, 95 percent CI: 0.56, 0.85). Higher intakes of ethanol at recruitment were not associated with lung cancer risk (table 3). Because we did not observe a statistically significant linear trend (table 3), we tested for heterogeneity between the categories of ethanol intake at baseline; statistically significant heterogeneity was revealed ($p = 0.0005$). The nonparametric regression curve indicated that the association between ethanol intake and lung cancer was

TABLE 2. Baseline characteristics of study participants by total intake of ethanol from alcoholic beverages at recruitment, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004*

	Nondrinkers	Ethanol consumption at recruitment (g/day)				
		0.1–4.9	5–14.9	15–29.9	30–59.9	≥60
			Males			
No. of participants	9,172	30,096	38,611	29,430	25,368	10,121
Age (years)	54.3 (47.1–61.6)†	51.5 (43.1–60.0)	52.4 (44.5–59.7)	53.0 (46.4–59.2)	53.0 (47.1–58.6)	53.2 (47.8–58.2)
Smoking status (%)						
Never smoker	33.4	39.1	34.5	27.7	21.9	16.0
Current smoker						
1–14 cigarettes/day	8.8	8.3	8.7	9.9	10.7	10.7
15–24 cigarettes/day	11.1	7.7	8.2	9.0	11.4	15.2
≥25 cigarettes/day	6.6	3.7	3.4	4.5	6.8	13.7
Former smoker						
For <10 years	14.4	11.3	12.2	14.2	15.0	14.2
For ≥10 years	19.1	19.7	22.4	24.6	23.3	18.2
Other smoking‡	6.6	10.2	10.7	10.0	10.9	12.1
Education (%)						
Completion of primary school	40.4	27.8	25.3	24.2	25.8	32.6
University degree	14.8	22.8	28.5	30.9	28.6	22.4
Height (cm)	172.0 (167.0–177.0)	180.0 (170.0–175.0)	175.5 (170.5–180.0)	175.0 (170.0–180.0)	174.6 (170.0–179.5)	174.0 (169.0–179.0)
Weight (kg)	78.5 (71.2–86.8)	78.8 (71.5–87.0)	79.5 (72.6–87.1)	80.0 (73.0–87.7)	80.5 (73.6–88.2)	82.2 (74.6–90.3)
Body mass index§	26.6 (24.2–29.2)	25.8 (23.6–28.2)	25.8 (23.8–28.2)	26.1 (24.1–28.4)	26.4 (24.4–28.8)	27.1 (24.8–29.7)
Energy intake (kcal/day)	2,263 (1,828–2,768)	2,195 (1,784–2,670)	2,295 (1,901–2,749)	2,427 (2,037–2,878)	2,569 (2,174–3,026)	2,910 (2,465–3,431)
Red meat intake (g/day)	46.8 (24.3–74.6)	37.9 (18.8–67.1)	47.9 (25.2–79.5)	57.0 (31.2–89.0)	65.5 (36.1–96.1)	74.9 (45.3–108.4)
Processed meat intake (g/day)	29.2 (9.6–56.9)	28.9 (11.3–51.6)	33.4 (14.9–56.9)	36.9 (17.6–63.1)	37.6 (19.0–63.4)	41.3 (22.7–69.1)
Fruit intake (g/day)	205.0 (102.0–372.8)	173.9 (92.9–319.9)	167.7 (94.3–295.8)	166.8 (93.3–297.2)	153.8 (78.8–286.9)	123.4 (51.8–264.1)
			Females			
No. of participants	53,783	138,113	89,229	36,172	16,353	2,142
Age (years)	51.9 (45.7–59.2)	50.2 (44.0–57.0)	51.0 (44.9–57.2)	51.5 (45.8–57.5)	52.4 (47.3–57.7)	51.7 (46.8–57.0)
Smoking status (%)						
Never smoker	60.9	49.9	44.9	370	29.4	22.7
Current smoker						
1–14 cigarettes/day	9.3	11.0	10.7	12.1	13.2	12.1
15–24 cigarettes/day	5.7	5.7	6.2	7.2	12.0	17.6
≥25 cigarettes/day	1.6	1.1	1.2	1.9	4.2	9.7
Former smoker						
For <10 years	6.1	8.3	9.3	10.0	11.1	9.8
For ≥10 years	7.9	13.1	15.7	16.6	16.5	13.8
Other smoking‡	8.5	11.0	12.1	15.3	13.7	14.3
Education (%)						
Completion of primary school	35.4	22.2	17.5	16.6	14.9	15.1
University degree	12.9	20.4	27.9	30.8	31.0	36.5
Height (cm)	160.0 (155.0–164.6)	162.5 (158.0–167.2)	163.0 (158.5–168.0)	162.5 (158.0–167.0)	163.0 (159.0–168.0)	163.5 (160.0–168.0)
Weight (kg)	66.0 (58.5–74.9)	64.2 (57.6–72.1)	63.2 (57.2–70.0)	62.7 (57.0–69.8)	63.5 (57.5–70.3)	64.5 (58.0–72.3)
Body mass index	25.7 (22.8–29.5)	24.2 (21.8–27.2)	23.7 (21.6–26.4)	23.6 (21.6–26.2)	23.7 (21.6–26.3)	24.0 (21.8–26.7)
Energy intake (kcal/day)	1,807 (1,482–2,192)	1,811 (1,495–2,181)	1,943 (1,624–2,315)	2,073 (1,735–2,456)	2,152 (1,815–2,554)	2,414 (2,017–2,883)
Red meat intake (g/day)	33.0 (17.1–54.3)	28.0 (13.8–51.1)	34.4 (16.1–59.9)	41.7 (19.2–67.1)	49.4 (25.6–74.1)	50.5 (24.1–77.1)
Processed meat intake (g/day)	19.0 (6.7–35.8)	22.0 (9.2–39.1)	22.3 (10.4–39.3)	24.4 (12.4–41.7)	24.0 (12.5–41.5)	28.3 (14.4–48.5)
Fruit intake (g/day)	253.5 (141.5–397.1)	215.8 (124.1–337.1)	214.9 (128.1–326.4)	206.6 (121.4–315.8)	177.7 (96.5–284.2)	139.7 (66.7–250.4)

* All data presented are median values and interquartile ranges unless otherwise specified.
† Numbers in parentheses, interquartile range.
‡ Occasional smokers, cigar smokers, or pipe smokers.
§ Weight (kg)/height $(m)^2$.

TABLE 3. Association between ethanol intake and lung cancer, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004

Category of ethanol intake (g/day)	Intake at recruitment						Mean lifelong intake		
	All participants (n = 479,590; 1,119 cases)			Subgroup* (n = 364,667; 887 cases)					
	No. of cases	HR†,‡	95% CI†	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Nondrinker	146	1.22	0.99, 1.50	90	1.10	0.85, 1.42	30	1.01	6.67, 1.50
0.1–4.9	310	1.00		232	1.00		228	1.00	
5–14.9	232	0.76	0.63, 0.90	181	0.73	0.60, 0.89	229	0.80	0.66, 0.97
15–29.9	169	0.83	0.68, 1.01	141	0.81	0.66, 1.01	201	0.99	0.80, 1.22
30–59.9	184	0.95	0.78, 1.16	166	0.91	0.73, 1.13	117	0.87	0.67, 1.13
≥60	78	0.86	0.66, 1.14	77	0.86	0.65, 1.14	82	1.29	0.93, 1.74
p-trend		0.31			0.51			0.12	

* Only those participants with information on past alcohol consumption.

† HR, hazard ratio; CI, confidence interval.

‡ All results were stratified by age (1-year categories), sex, and study center. Hazard ratios were adjusted for smoking status and smoking duration, height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), physical activity at work (five categories), and total nonethanol energy intake (continuous).

nonlinear (p for nonlinearity = 0.04), with the lowest risk of lung cancer appearing among moderate consumers of alcoholic beverages (figure 1).

We did not observe statistically significant interaction between smoking and ethanol intake at baseline (table 4), although we noted some differences in risk by smoking status. A statistically significantly lower risk for moderate ethanol intake at recruitment as compared with low intake was observed in former and current smokers but not in never smokers (table 4). Among current smokers, we examined whether the associations differed when including number of cigarettes smoked per day and years of smoking as continuous variables instead of categorical variables as was done in the regular analysis, but the associations did not change materially (data not shown). Among men, a very high daily intake of ethanol at recruitment (≥100 g/day) was not associated with an increased risk of lung cancer (based on 12 cases in the high-consumption group; HR = 0.61, 95 percent CI: 0.32, 1.18). We did not examine this association among women, because few women consumed such high amounts of ethanol per day (there were no cases in the high-consumption group). No statistically significant heterogeneity in the association between ethanol intake and lung cancer was observed between countries (data not shown).

Mean lifelong ethanol intake

Use of data on mean lifelong ethanol intake, which were available for 76 percent of the cohort, allowed us to investigate the long-term effect of alcohol consumption on lung cancer risk and to differentiate never drinkers from former drinkers. Among men, 27 percent of nondrinkers at recruitment were lifelong abstainers (i.e., lifelong nondrinkers); in the remaining men, 23 percent had a mean lifelong ethanol intake of 0.1–4.9 g/day, 16 percent had 5–14.9 g/day, 12 percent had 15–29.9 g/day, 11 percent had 30–59.9 g/day, and 11 percent had ≥60 g/day. Sixty-eight percent of female nondrinkers at recruitment were lifelong nondrinkers; of the remaining women, 24 percent had a mean lifelong ethanol intake of 0.1–4.9 g/day, 6 percent had 5–14.9 g/day, 1.2 percent had 15–29.9 g/day, 0.3 percent had 30–59.9 g/day, and 0.2 percent had ≥60 g/day. Compared with persons who always consumed alcoholic beverages, never drinkers did not have a higher risk of lung cancer (HR = 1.08, 95 percent CI: 0.73, 1.60), but the risk was higher in former drinkers (HR = 1.30, 95 percent CI: 0.99, 1.71). Those current drinkers who had not consumed alcoholic beverages in the past had a nonsignificantly lower risk of lung cancer than drinkers who had always consumed alcohol (HR = 0.74, 95 percent CI: 0.53, 1.03).

Lifelong nondrinkers did not have an elevated risk of lung cancer in comparison with low consumers (table 3). A moderate mean lifelong ethanol intake was associated with a lower risk of lung cancer compared with low intake. A mean lifelong ethanol intake of ≥60 g/per day was related to a non-statistically-significantly higher risk of lung cancer in comparison with low consumers (table 3). Similar to what was seen for ethanol intake at baseline, we noted statistically significant heterogeneity between the categories of mean lifelong ethanol intake (p = 0.02). The nonparametric regression curve indicated a J-shaped association between mean lifelong ethanol intake and lung cancer, although the p value from the test for nonlinearity was not statistically significant (p = 0.22) (figure 2).

There was no statistically significant interaction between smoking behavior and mean lifelong ethanol intake (table 4). However, a high mean lifelong ethanol intake tended to be associated with an increased risk of lung cancer, especially in former smokers. Men with a mean lifelong ethanol intake of ≥100 g/day had a nonsignificantly higher risk of lung

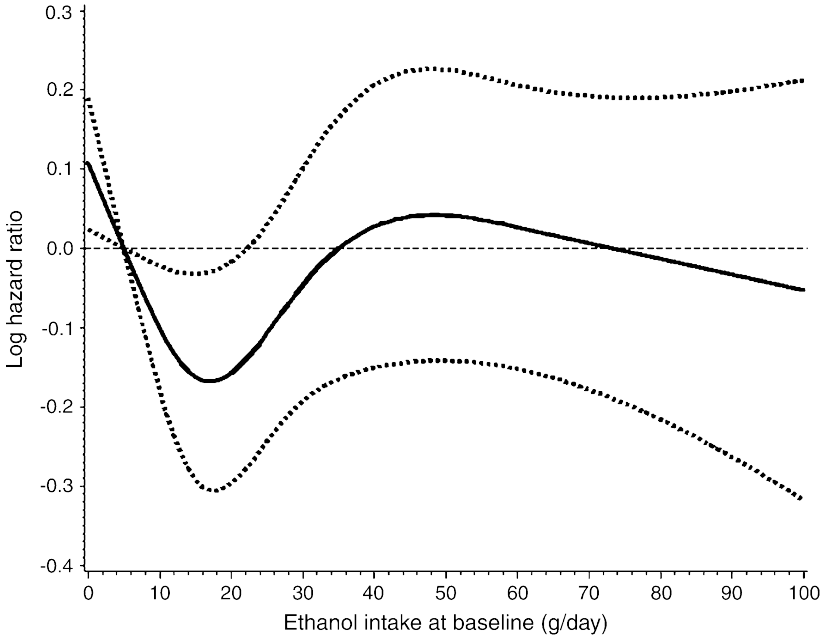

FIGURE 1. Nonparametric regression curve for the relation between ethanol intake at recruitment and lung cancer, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004. Solid line, effect estimate; dotted lines, 95 percent confidence interval.

cancer (HR = 1.71, 95 percent CI: 0.91, 3.25) than men with low consumption.

Histologic subtypes

Nondrinkers at recruitment had a higher risk of squamous-cell carcinoma of the lung than persons with a low ethanol intake at recruitment (table 5). Neither a moderate ethanol intake (5–14.9 g/day) nor a high ethanol intake (≥60 g/day) at recruitment was positively associated with any subtype of lung cancer.

Concerning mean lifelong ethanol intake, the risk of squamous-cell carcinoma was statistically significantly lower in the moderate-intake group (5–14.9 g/day) than in the low-intake group. The risk of adenocarcinomas and possibly also small-cell carcinomas tended to be higher in the highest categories of mean lifelong ethanol intake as compared with low intake.

DISCUSSION

In this prospective cohort study, we relied on two definitions of ethanol intake. The first one referred to ethanol intake at recruitment, that is, recent intake only. The second one was calculated from ethanol intake in the past and at recruitment. We observed a lower risk of lung cancer in participants with a moderate ethanol intake (5–14.9 g/day) when compared with participants who consumed 0.1–4.9 g/day. This was seen for ethanol intake at recruitment as well as mean lifelong ethanol intake. Persons with a mean lifelong ethanol intake of ≥60 g/day (approximately five drinks per day) had a nonsignificant 29 percent higher risk of lung cancer compared with subjects with a low mean lifelong intake of 0.1–4.9 g/day. No such association was seen for ethanol intake at recruitment. Lifelong nonconsumption of alcoholic beverages was not associated with lung cancer risk in this cohort.

Only a few studies have examined the association of lifelong ethanol intake with lung cancer risk. No statistically significant association between lifelong exposure to alcohol and lung cancer was seen in two US case-control studies (12, 13). Years of drinking were related to the risk of lung cancer in a Turkish case-control study (14) but not in a US cohort study (15).

The association between ethanol intake and lung cancer was evaluated in several prospective studies; some investigators observed an elevated risk of lung cancer among subjects who consumed alcohol (4, 16–21), whereas others did not (22–26). In some studies, positive associations were confined to subgroups of the study population (e.g., men (15, 27), participants with a low vitamin A intake (28), heavy smokers (15), or nonsmokers (29)). In a meta-analysis, ethanol intake of ≥2,000 g/month (~67 g/day) was associated with an elevated risk of lung cancer (4). In a pooled analysis of seven cohort studies (including 3,137 lung cancer cases), a nonsignificantly higher risk was seen for an intake of ≥30 g/day compared with no intake (3).

In addition to the suspected carcinogenic effect of acetaldehyde, chronic alcohol consumption increases cytochrome P-450 level and microsomal enzyme activity, which can accelerate the activation of carcinogens (6, 7). Ethanol might act in the later stages of carcinogenesis (19, 30, 31). However, the effect of ethanol on the lung might be cumulative;

TABLE 4. Association of ethanol intake at recruitment and mean lifelong ethanol intake with lung cancer, by smoking status and sex, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004

Category of ethanol intake (g/day)	Smoking status									Sex					
	Never*			Former†			Current‡			Men§			Women§		
	No. of cases	HR¶	95% CI¶	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Baseline intake															
Nondrinker	14	0.64	0.33, 1.23	41	1.45	0.97, 2.16	90	1.27	0.97, 1.67	61	1.13	0.82, 1.56	85	1.26	0.96, 1.65
0.1–4.9	44	1.00		84	1.00		181	1.00		121	1.00		189	1.00	
5–14.9	27	0.93	0.56, 1.53	69	0.71	0.51, 0.98	133	0.75	0.59, 0.95	118	0.70	0.54, 0.91	114	0.79	0.62, 1.01
15–29.9	9	0.67	0.32, 1.41	43	0.70	0.47, 1.03	117	0.92	0.71, 1.18	108	0.76	0.58, 0.99	61	0.90	0.67, 1.21
30–59.9	3	0.55	0.17, 1.83	41	0.86	0.57, 1.29	139	1.00	0.78, 1.27	128	0.85	0.65, 1.11	56	1.08	0.79, 1.49
≥60	0			12	0.87	0.46, 1.67	66	0.90	0.66, 1.24	70	0.81	0.59, 1.11	8	0.87	0.42, 1.82
p-interaction					0.64							0.58			
Mean lifelong intake															
Nondrinker	7	0.53	0.22, 1.23	8	1.91	0.88, 4.18	15	1.00	0.57, 1.75	9	1.41	0.68, 2.92	21	0.87	0.54, 1.41
0.1–4.9	43	1.00		53	1.00		124	1.00		57	1.00		171	1.00	
5–14.9	14	0.45	0.25, 0.84	74	1.08	0.75, 1.57	139	0.78	0.60, 1.00	106	0.75	0.54, 1.05	123	0.83	0.65, 1.05
15–29.9	6	0.62	0.26, 1.50	55	1.29	0.85, 1.96	139	0.93	0.71, 1.21	135	0.90	0.65, 1.25	66	1.09	0.81, 1.47
30–59.9	1	0.37	0.05, 2.98	32	1.29	0.77, 2.16	84	0.77	0.56, 1.06	104	0.82	0.58, 1.16	13	0.89	0.50, 1.59
≥60	1	1.23	0.11, 13.6	15	1.73	0.86, 3.45	66	1.15	0.79, 1.66	80	1.21	0.82, 1.77	2	1.32	0.32, 5.48
p-interaction					0.22							0.87			

* Results were stratified by age (1-year categories), sex, and study center. Hazard ratios were adjusted for height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), physical activity at work (five categories), and total nonethanol energy intake (continuous).

† Results were stratified by age (1-year categories), sex, and study center. Hazard ratios were adjusted for smoking duration and time since stopping smoking (three categories), height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), physical activity at work (five categories), and total nonethanol energy intake (continuous).

‡ Results were stratified by age (1-year categories), sex, and study center. Hazard ratios were adjusted for number of cigarettes smoked per day (three categories) and smoking duration, height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), physical activity at work (five categories), and total nonethanol energy intake (continuous).

§ Results were stratified by age (1-year categories) and study center. Hazard ratios were adjusted for smoking status and smoking duration, height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), physical activity at work (five categories), and total nonethanol energy intake (continuous).

¶ HR, hazard ratio; CI, confidence interval.

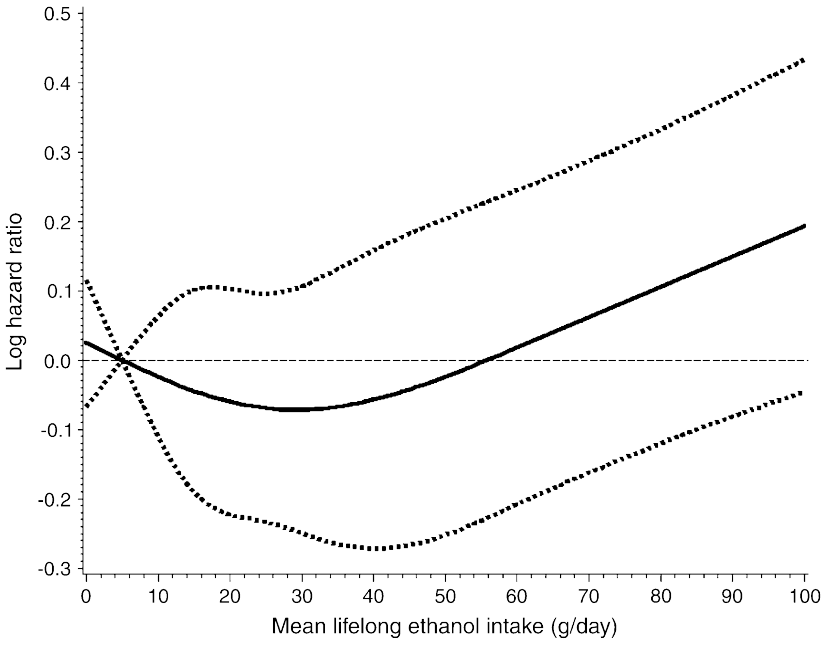

FIGURE 2. Nonparametric regression curve for the relation between mean lifelong ethanol intake and lung cancer, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004. Solid line, effect estimate; dotted lines, 95 percent confidence interval.

thus, assessing ethanol intake only at recruitment could lead to underestimation of the association between ethanol intake and lung cancer (32). Our results hint at a long-term effect of ethanol on lung cancer development, since we noted a positive (though nonsignificant) association of a high mean lifelong ethanol intake with lung cancer. An alternative explanation for the positive association for a high mean lifelong ethanol intake and the lack of such association for ethanol intake at baseline might be a higher risk for heavy drinkers who quit. We observed a nonsignificant higher risk of lung cancer in former drinkers with a high mean lifelong ethanol intake ($\geq$60 g/day) than in light former drinkers (0.1–4.9 g/day) (HR = 2.12, 95 percent CI: 0.61, 7.40).

Nondrinkers at recruitment (but not lifelong nondrinkers) had a higher risk of lung cancer when compared with low consumers. Subjects with symptoms may have stopped drinking alcoholic beverages, thus generating an elevated risk of lung cancer among nondrinkers at recruitment as compared with low consumers. Many nondrinkers at recruitment, especially men, were former drinkers. After we excluded former drinkers from the analysis of ethanol intake at recruitment (which was possible only for the subgroup with information on lifelong alcohol consumption), we no longer observed an increased risk in nondrinkers at recruitment (HR = 1.00, 95 percent CI: 0.67, 1.50) as compared with low consumers. However, lung cancer cases in former drinkers were not diagnosed earlier in follow-up than cases in never or current drinkers.

In contrast to most published studies, we observed a lower risk of lung cancer for moderate ethanol intake than for low intake. In two US studies, the risk of lung cancer was lower among moderate drinkers than among nondrinkers at baseline (21, 33). In the pooled analysis (3), a lower risk of lung cancer for low and moderate drinkers as compared with nondrinkers was observed, which was confined to women. However, there was no inverse association between moderate ethanol intake and lung cancer in two reviews (4, 32). Despite alcohol's detrimental effects on health when consumed in large amounts, several investigations have shown an inverse association of moderate alcohol consumption with mortality, mainly based on the inverse association with coronary heart disease (34). Antiinflammatory effects of moderate ethanol intake are thought to contribute to this effect. Moderate alcohol drinking has been shown to be related to lower plasma concentrations of several systemic biomarkers of inflammation in comparison with no consumption or high consumption (35), as well as reduced oxidative damage (36, 37), and antioxidative components of alcoholic beverages have been discussed for a possible role in tumor promotion and progression (38). Additionally, small quantities of alcohol might be necessary for induction of protective enzymes such as DNA repair enzymes or carcinogen detoxification enzymes (39). Nonlinear associations between alcohol consumption and lung cancer risk have been observed in several studies (21, 33). It is possible that beneficial effects of low-to-moderate alcohol consumption counteract the cancer-promoting function of ethanol and its metabolites. With increasing mean lifelong intake of ethanol, the balance is likely to shift to outweigh these beneficial effects. However, we cannot exclude the possibility that residual confounding due to smoking, passive smoking, or other factors unaccounted for may explain our results.

We adjusted for smoking by taking into account smoking status, smoking amount, and years of smoking. Adjustment

TABLE 5. Association of ethanol intake at recruitment and mean lifelong ethanol intake with carcinoma of the lung, by histologic type, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992–2004

Category of ethanol intake (g/day)	Adenocarcinoma			Squamous-cell carcinoma			Small-cell carcinoma		
	No. of cases	HR*,†	95% CI*	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Baseline intake									
Nondrinker	40	1.14	0.77, 1.67	40	1.85	1.20, 2.87	18	0.90	0.51, 1.57
0.1–4.9	100	1.00		53	1.00		54	1.00	
5–14.9	82	0.90	0.67, 1.22	49	0.83	0.56, 1.24	42	0.81	0.53, 1.22
15–29.9	58	1.06	0.75, 1.50	31	0.78	0.49, 1.25	26	0.69	0.42, 1.12
30–59.9	62	1.27	0.89, 1.80	40	0.96	0.61, 1.50	33	0.87	0.54, 1.40
≥60	24	1.22	0.74, 2.01	21	0.93	0.53, 1.63	16	0.92	0.50, 1.71
p-trend		0.19			0.30			0.85	
Mean lifelong intake									
Nondrinker	9	1.03	0.50, 2.15	6	1.15	0.47, 2.83	2	0.60	0.14, 2.56
0.1–4.9	70	1.00		45	1.00		33	1.00	
5–14.9	72	0.86	0.61, 1.21	43	0.59	0.38, 0.91	43	0.99	0.62, 1.59
15–29.9	69	1.30	0.89, 1.89	42	0.73	0.46, 1.17	32	0.94	0.55, 1.61
30–59.9	35	1.09	0.68, 1.75	29	0.70	0.41, 1.20	23	1.00	0.54, 1.85
≥60	19	1.41	0.76, 2.63	19	0.94	0.49, 1.82	16	1.38	0.66, 2.83
p-trend		0.16			0.87			0.38	

* HR, hazard ratio; CI, confidence interval.

† All results were stratified by age (1-year categories), sex, and study center. Hazard ratios were adjusted for smoking status and smoking duration, height (continuous), weight (continuous), fruit consumption (continuous), red meat consumption (continuous), processed meat consumption (continuous), education (five categories), and total nonethanol energy intake (continuous).

for pack-years of smoking instead of duration and amount of smoking as separate variables did not change the associations between ethanol intake and lung cancer risk. We did not note statistically significant effect modification by smoking status. Therefore, it is unlikely that the higher risk of lung cancer for high mean lifelong ethanol intake might be explained by confounding only. We did not take into account environmental tobacco smoking, because information on environmental tobacco smoking was assessed at only 11 EPIC centers. However, when we restricted our analyses to the 214,964 participants for whom information on exposure to passive smoking was available (exposure at home or at work; yes vs. no), the results did not change appreciably (data not shown).

We cannot rule out the possibility that some subjects misreported their alcohol consumption, especially those with a high intake. However, ethanol intake as calculated from the food frequency questionnaire was highly correlated with intake assessed by means of a 24-hour dietary recall administered in an 8 percent random sample of each cohort. In another study, Friesema et al. (40) also reported a high validity of a food frequency questionnaire in assessing alcohol consumption. If high consumers were falsely categorized as moderate consumers, this would have led to an underestimation of the risk for high consumers. In addition, we cannot exclude the possibility that the association between mean lifelong ethanol intake and lung cancer would change if we had information on this variable for all participants instead of only 76 percent of the cohort. However, it is reassuring that we observed similar results for ethanol intake at recruitment when examining the associations for the complete cohort and the subcohort.

In conclusion, lung cancer risk appears to be lower among moderate consumers of alcohol with a daily ethanol intake of 5–14.9 g/day than among light consumers with an intake of 0.1–4.9 g/day. This was observed for ethanol intake at baseline as well as for mean lifelong ethanol intake. However, high lifelong alcohol consumption might increase the risk of lung cancer, although the association was not statistically significant in this cohort. The implications regarding lifelong ethanol intake warrant confirmation from other studies that also have detailed information on past alcohol consumption.

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