Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Alcohol consumption may be associated with risk of colorectal cancer (CRC), but the epidemiological evidence for an association with specific anatomical subsites, types of alcoholic beverages and current *vs.* lifetime alcohol intake is inconsistent. Within the European Prospective Investigation into Cancer and Nutrition (EPIC), 478,732 study subjects free of cancer at enrolment between 1992 and 2000 were followed up for an average of 6.2 years, during which 1,833 CRC cases were observed. Detailed information on consumption of alcoholic beverages at baseline (all cases) and during lifetime (1,447 CRC cases, 69% of the cohort) was collected from questionnaires. Cox proportional hazard models were used to examine the alcohol-CRC association. After adjustment for potential confounding factors, lifetime alcohol intake was significantly positively associated to CRC risk (hazard ratio, HR = 1.08, 95%CI = 1.04–1.12 for 15 g/day increase), with higher cancer risks observed in the rectum (HR = 1.12, 95%CI = 1.06–1.18) than distal colon (HR = 1.08, 95%CI = 1.01–1.16), and proximal colon (HR = 1.02, 95%CI = 0.92–1.12). Similar results were observed for baseline alcohol intake. When assessed by alcoholic beverages at baseline, the CRC risk for beer (HR = 1.38, 95%CI

Grant sponsors: "Europe Against Cancer" Programme of the European Commission (SANCO); Ligue contre le Cancer (France); Société 3M (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale (INSERM); German Cancer Aid; German Cancer Research Center; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; the participating Regional Governments and Institutions of Spain; Cancer Research, UK; Medical Research Council, UK; the Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; the Wellcome Trust, UK; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer; Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Norwegian Cancer Society.

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= 1.08–1.77 for 20–39.9 *vs.* 0.1–2.9 g/day) was higher than wine (HR = 1.21, 95%CI = 1.02–1.44), although the two risk estimates were not significantly different from each other. Higher HRs for baseline alcohol were observed for low levels of folate intake (1.13, 95%CI = 1.06–1.20 for 15 g/day increase) compared to high folate intake (1.03, 95%CI = 0.98–1.09). In this large European cohort, both lifetime and baseline alcohol consumption increase colon and rectum cancer risk, with more apparent risk increases for alcohol intakes greater than 30 g/day.

Key words: alcohol; lifetime exposure; colorectal cancer; prospective study

Colon and rectal cancers accounted for ~9.4% of total worldwide cancer cases in 2002, equivalent to ~1 million new cases.[1] Worldwide, there is at least a 25-fold variation in occurrence of colorectal cancer (CRC), with the highest incidence rates in North America, Australia/New Zealand, Western Europe and Japan (especially in men), and lower rates in Africa and Asia. This variation may be due to differences in diet and lifestyle, which have been estimated to account for a large proportion of CRC cases.[2,3] Alcohol drinking habits are an important contributor to dietary and lifestyle factors and evidence from correlation[4–6] and case–control[7–11] studies suggest that higher alcohol intake may increase CRC risk.

Some data from prospective studies show statistically significant positive CRC risk associations with higher alcohol consumption.[12–18] However, subsite-specific results are either equivocal or suggestive of only a weak association with cancers of the colon, while results for the rectum more consistently suggest an increase in cancer risk at that subsite.[19–21]

In addition, only a few studies have considered CRC risk associated with the consumption of different types of alcoholic beverages.[7–9,22–26] Although a recent pooled analyses of prospective studies reported no clear differences in the effect of alcoholic beverages,[27] beer intake has been related to rectal cancer in many studies,[7–9,22,24–26] while the evidence for its association with colon cancer is less clear. A few studies have reported positive associations between wine or liquor intake and colon cancer,[11,25,28–30] but little information is available for rectal cancer. In addition, CRC risk has been mainly investigated in prospective studies with respect to recent alcohol intake (referred to here as baseline intake), while information on lifetime intake is available in only one prospective study of modest size.[13]

In an attempt to better elucidate the role of alcohol drinking on colorectal carcinogenesis, a study on the association between both lifetime and baseline alcohol intake and risk of colon and rectal cancers, separately and combined, was carried out in the European Prospective Investigation into Cancer and Nutrition (EPIC).[31] EPIC is a cohort with over half a million subjects from 23 centers in 10 Western European countries.

Material and methods

EPIC is a multicenter prospective cohort study designed to investigate the relation between dietary habits, nutritional status and various lifestyle/environmental factors and cancer incidence. The rationale and methods of the EPIC study have been previously discussed in detail.[31] Briefly, the EPIC cohort consists of 23 centers in 10 European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom). Between 1992 and 1998, country-specific dietary questionnaires, standardized lifestyle and personal history questionnaires and anthropometric data were collected from a total of 521,457 subjects (70% women, 30% men), mostly aged from 35 to 70 years. Cohort members signed an informed consent form. Approval for this study was obtained from the relevant ethical review boards of the participating institutions.

Diet and lifestyle questionnaires

Diet over the 12 months before enrolment was measured by validated country-specific questionnaires[31] designed to capture local dietary habits with high compliance.[32] Most centers adopted a self-administered dietary questionnaire including 88–266 food items. Data on height and weight (self reported in France, Norway and the UK Oxford center; measured elsewhere), alcohol use, smoking status, occupational physical activity and previous illnesses were also collected with lifestyle questionnaires.

For the present study, intake of alcoholic beverages at baseline was calculated from dietary questionnaires,[31] which have previously been validated for alcohol consumption.[32] Subjects reported the number of standard glasses of beer, cider, wine, sweet liquor, distilled spirits or fortified wines consumed per day/week during the 12 months prior to recruitment. In each country, intake was calculated based on the 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 subset of the cohort.[33,34] Due to the great regional specificity of alcohol drinking, alcohol content and glass volumes (particularly according to the type of beverage) were extremely heterogeneous across EPIC countries, thus making it practically unfeasible to identify a unique unit (one drink) of alcohol that was common to all countries.

Information on past alcohol consumption (available for 76.2% of participants) was assessed as glasses of different beverages consumed per week at 20, 30, 40 and 50 years of age.[35] 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.

Endpoints

The follow-up was based on population cancer registries (Denmark, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom; complete up to December 2001) or *via* a combination of methods, including linkage with health insurance records, contacts with cancer and pathology registries, and active follow-up through study subjects and their next-of-kin (France, Germany, Greece; complete up to December 2002). Mortality data were collected from either the cancer or mortality registries at the regional or national level. Currently, vital status is known for 98.4% of all EPIC subjects.

For the present study, colon cancers were defined as tumors in the caecum, appendix, ascending colon and hepatic flexure, transverse colon, splenic flexure (proximal) (C18.0–18.5; International Statistical Classification of Diseases, Injury and Causes of Death, 10th Revision), and descending and sigmoid colon (distal) (C18.6–C18.7), as well as tumors that were overlapping or unspecified (C18.8 and C18.9). Cancer of the rectum included tumors occurring at the rectosigmoid junction (C19) and rectum (C20). CRC is defined as a combination of all the colon and rectal cancer cases. Anal canal tumors were excluded.

Statistical analysis

After exclusions (23,679 with prevalent cancer other than nonmelanoma skin cancer at enrolment; 9,696 in the lowest and highest 1% of the distribution of the ratio of reported total energy intake to energy requirement; 9,350 with missing questionnaire data/diagnosis dates/follow-up data), the total number of subjects included in this analysis was 478,732.

The association between alcohol intake and CRC incidence was evaluated using multivariate Cox proportional hazard models,[36] stratified by study center to control for differences in questionnaires, follow-up procedures and other center-specific effects. Age was used as the primary time variable. To further control for the possible confounding effect of age, models were stratified by age at recruitment in 1-year categories.

TABLE I – COUNTRY-SPECIFIC FREQUENCY OF COLON AND RECTUM CANCER CASES, PERSON-YEARS (PY), AGE-STANDARDIZED COLORECTAL CANCER INCIDENCE RATES (ASR), THE PERCENTAGE OF ALCOHOL NONCONSUMERS AT BASELINE (BNC) AND LIFETIME (LNC), MEANS (10TH–90TH PERCENTILE) OF BASELINE AND LIFETIME ALCOHOL INTAKES (g/day), AND OF BASELINE ALCOHOL FROM WINE, BEER AND SPIRITS AND LIQUORS AT BASELINE (g/day)

	Country	Colon	Rectum	PY	ASR[1]	LNC	Lifetime alcohol	BNC	Baseline alcohol	Wine	Beer	Spirits/ liquors
Men	Italy	44	17	75,049	132	1.9[2]	24 (3–48)[2]	4.2	24 (1–53)	21 (0–46)	1 (0–3)	2 (0–5)
	Spain	40	26	103,602	92	3.7	51 (7–106)	14.5	38 (4–84)	30 (0–71)	3 (0–10)	4 (0–14)
	United Kingdom	93	35	121,094	102	1.2	15 (2–32)	6.4	14 (1–35)	6 (0–12)	6 (0–21)	2 (0–3)
	The Netherlands	11	11	50,089	116	–[3]	–[3]	9.8	20 (1–45)	4 (0–11)	11 (0–31)	4 (0–11)
	Greece	7	7	38,997	25	4.5	30 (2–71)	10.1	19 (2–45)	10 (1–26)	3 (0–10)	5 (0–15)
	Germany	58	53	125,589	112	0.5	28 (5–55)	4.3	26 (3–57)	9 (0–23)	16 (0–42)	2 (0–4)
	Sweden	72	69	175,352	91	–[3]	–[3]	9.4	11 (1–26)	3 (0–8)	5 (1–11)	3 (0–8)
	Denmark	123	103	174,444	120	0.3	23 (6–45)	1.8	32 (5–72)	11 (0–32)	18 (1–44)	3 (0–8)
	All	*448*	*321*	*864,217*	*104*	*1.6*	*27 (4–58)*	*6.9*	*23 (2–54)*	*11 (0–32)*	*9 (0–23)*	*3 (0–7)*
Women	France	164	21	569,226	38	10.7	8 (0–18)	14.0	13 (1–30)	10 (0–25)	1 (0–2)	1 (0–2)
	Italy	65	27	188,514	71	12.5[2]	7 (1–18)[2]	22.6	11 (0–25)	9 (0–23)	1 (0–2)	1 (0–1)
	Spain	40	15	163,849	49	35.9	8 (1–19)	52.8	10 (1–26)	8 (0–22)	2 (1–6)	0 (0–1)
	United Kingdom	93	56	284,300	65	1.8	9 (0–21)	5.9	8 (0–26)	5 (0–12)	2 (0–4)	1 (0–3)
	The Netherlands	100	46	181,870	82	10.6[2]	8 (2–18)	18.4	10 (1–26)	5 (0–14)	1 (0–2)	2 (0–4)
	Greece	6	5	55,811	31	28.7	5 (0–13)	35.3	5 (1–12)	3 (0–9)	1 (0–2)	1 (0–2)
	Germany	45	16	163,230	55	1.7	7 (1–15)	4.9	10 (1–24)	7 (0–18)	2 (0–7)	1 (0–1)
	Sweden	84	52	204,609	77	–[3]	–[3]	17.6	6 (0–16)	3 (0–8)	2 (0–5)	1 (0–2)
	Denmark	107	78	193,947	86	1.4	10 (2–20)	2.6	15 (1–37)	9 (0–32)	4 (0–9)	1 (0–4)
	Norway	32	12	108,259	85	–[3]	–[3]	20.6	4 (1–9)	3 (0–5)	1 (0–2)	–
	All	*736*	*328*	*2,113,616*	*83*	*10.6*	*8 (1–19)*	*16.9*	*10 (1–24)*	*7 (0–19)*	*2 (0–4)*	*1 (0–2)*

Mean and percentile values calculated for drinkers only.
[1]Age-standardized incidence rates (per 100,000) were computed using 5-years categories in the common age band between 50 to 69 years, and the European standard population.–[2]Information on lifetime consumption non available for part of the cohort.–[3]Information on lifetime consumption non available.

Baseline and lifetime alcohol daily intakes were modeled as continuous and categorical variables (0, 0.1–4.9, 5–14.9, 15–29.9, 30–59.9, >60 g/day), using the group 0.1–4.9 g/day as reference to ensure a sufficiently large number of cases. Analyses with men and women combined were stratified by gender to control for differences in alcohol drinking behavior.

All models included the following variables: energy intake from nonalcohol sources at baseline (to partially control for errors in alcohol estimation[37]), weight (tertiles), height (tertiles) physical activity (inactive, moderately inactive, moderately active, active, unknown), smoking status (never, former, current, unknown), education level (no degree/primary school, technical or professional school, secondary school, university degree, not specified/missing). The progressive inclusion of dietary fiber, calcium, folate, fish and meat in the statistical model did not alter the magnitude or confidence interval of the results and so no adjustments were made for these variables.

Models evaluating lifetime alcohol consumption were further adjusted by duration of alcohol drinking, time since quitting and an indicator variable for former and current drinkers (for lifetime alcohol in continuous only).[38]

Models evaluating baseline wine, beer and spirits intake were further adjusted for energy coming from alcohol sources other than the one under evaluation. In addition, associations restricted to pure drinkers of one beverage only were evaluated by excluding drinkers of more than 2 g/day of any other beverages.

Overall significance of hazard ratios (HR) was tested by *p*-values for Wald χ^2 with degrees of freedom equal to the number of categories minus one. Tests for trend were computed by modeling alcohol intake as a continuous variable. Potential nonlinear associations between lifetime and baseline alcohol intake were evaluated by using restricted cubic spline models and the associated likelihood ratio test, as well as by visual inspection.[39] However, no evidence of departure from linearity was observed.

To evaluate whether the association with alcohol intake was modulated by folate intake, interaction terms between center and center-specific tertiles of folate intake were included in the model, and significance assessed. For these evaluations adjustment for fiber intake was also performed. Interactions with smoking status were tested in the same way.

Country-specific analyses were also performed to evaluate the association between alcohol (continuous) and CRC risk. To test for heterogeneity of associations across countries, a meta-analytical approach was used to compute χ^2 statistics and associated *p*-values ($p_{heterogeneity}$). Meta-regression was used to explore heterogeneity of risks across countries.[40]

Since undiagnosed disease at baseline may have led to changes in alcohol intake, models excluding the first 2 years of follow-up were also run for baseline alcohol consumption, by cancer site and gender. All analyses were performed using SAS.[41] All tests were two tailed and statistical significance was assessed at the 5% level.

Results

Out of a total of 478,732 participants (2,977,833 person-years), 1,833 CRC cases (95% histologically confirmed) were identified in a mean follow-up time of 6.2 years. Of these cancers, 1,184 were located in the colon (proximal colon = 476; distal colon = 528; overlapping/unspecified = 180) and 649 in the rectum.

Table I presents country- and sex-specific frequencies of colon and rectal cancer cases with complete information. Age-standardized incidence rates (50–69 years) were 20% (Sweden) to 100% (Germany) higher in men than women. CRC incidence rates in EPIC are in line with country-specific rates observed in Europe.[42] Lifetime alcohol was 17% higher than baseline intake in men but was similar in women. Overall, beer and wine represent about 40 and 50% of total alcohol intake in men, and 70 and 20% in women. These patterns of consumption were consistent across countries in women, while consumption was more heterogeneous across countries in men.

Total energy intake was strongly related to alcohol intake (Table II). In subjects with a consumption of >60 g/day of alcohol, mean total energy intake was 25% (men) and 33% higher (women) than in nondrinkers. However, mean total energy from nonalcohol sources was 0.1% (men) and 4.0% (women) higher in drinkers than nondrinkers.

Average lifetime alcohol intake

Compared to the reference category of exposure (0.1–4.9 g/day), relatively higher HRs were observed among heavy drinkers

TABLE II – STUDY SUBJECTS CHARACTERISTICS BY CATEGORIES OF BASELINE ALCOHOL INTAKE (COUNTRY-ADJUSTED MEANS ± SD)

	Baseline alcohol intake					
	Nonconsumers	0.1–4.9	4.9–14.9	15–29.9	30–59.9	>60
Men						
Subjects in each category	9,811	30,197	37,256	29,551	25,412	10,624
Alcohol at baseline (g/day)	0 ± 0	2 ± 1	10 ± 3	22 ± 4	42 ± 8	83 ± 24
Age (years)	54 ± 9	51 ± 10	51 ± 9	51 ± 9	52 ± 9	52 ± 8
Height (m)	173 ± 7	174 ± 7	175 ± 7	175 ± 7	175 ± 7	175 ± 7
Weight (kg)	80 ± 13	80 ± 12	81 ± 12	81 ± 11	81 ± 12	82 ± 13
Body-mass index (kg/m^2)	27 ± 4	27 ± 4	26 ± 3	26 ± 3	27 ± 3	27 ± 4
Total energy (Kcal)	2,321 ± 686	2,307 ± 640	2,377 ± 619	2,477 ± 616	2,595 ± 619	2,898 ± 664
Energy from nonalcohol (Kcal)	2,320 ± 685	2,290 ± 640	2,308 ± 618	2,324 ± 614	2,301 ± 614	2,320 ± 633
Ever smokers (%)	63	56	61	70	75	83
Women						
Subjects in each category	56,944	131,213	91,662	36,338	17,454	2,270
Alcohol at baseline (g/day)	0 ± 0	2 ± 1	9 ± 3	21 ± 4	39 ± 7	76 ± 17
Age (years)	54 ± 9	50 ± 9	51 ± 9	51 ± 8	51 ± 8	51 ± 8
Height (m)	161 ± 6	162 ± 6	162 ± 6	163 ± 6	163 ± 6	162 ± 6
Weight (kg)	68 ± 13	67 ± 12	66 ± 11	65 ± 10	66 ± 11	68 ± 11
Body-mass index (kg/m^2)	26 ± 5	26 ± 4	25 ± 4	25 ± 4	25 ± 4	26 ± 4
Total energy (Kcal)	1,838 ± 517	1,876 ± 501	1,962 ± 493	2,041 ± 498	2,179 ± 509	2,439 ± 555
Energy from nonalcohol (Kcal)	1,838 ± 517	1,863 ± 500	1,899 ± 492	1,898 ± 497	1,907 ± 507	1,905 ± 549
Ever smokers (%)	32	40	45	50	59	66

for cancers of the rectum (1.33, 95%CI 0.91–1.94 and 2.59, 95%CI 1.62–4.13, for 30–59.9 and >60 g/day, respectively, $p_{trend} < 0.01$), and the distal colon (1.56, 95%CI 1.03–2.38 and 2.22, 95%CI 1.20–4.13, $p_{trend} = 0.03$), compared to the proximal colon (0.87, 95%CI 0.53–1.43 and 1.22, 95%CI 0.59–2.51, $p_{trend} = 0.71$) (Table III). This was consistent for men and women (data not shown). The CRC risk associations of time since quitting drinking (inverse association) and duration of drinking (positive association) were not statistically significant (data not shown).

Baseline alcohol intake

The results between baseline alcohol and CRC risk (1.09, 95%CI 1.05–1.13 for 15 g/day increase) were similar to those for average lifetime intake (Table IV). Higher HRs were observed for rectum (1.11, 95%CI 1.05–1.17 for 15 g/day increase) than colon cancer (1.07, 1.02–1.12), although the difference was not statistically significant ($p_{heterogeneity} = 0.31$). In addition, higher risks were observed for distal colon cancer (1.68, 95%CI 1.08–2.62 for >60 g/day), whereas no relation was observed for the proximal colon (0.92, 95%CI 0.51–1.66). Nondrinkers and exdrinkers showed similar risks to moderate drinkers.

The association between baseline alcohol intake and CRC was consistent in the 2 genders, with higher risks observed in the rectum (men: 1.11, 95%CI 1.04–1.17; women: 1.20, 95%CI 0.97–1.49, for a 15 g/day increase) than colon (men: 1.04, 0.98–1.10; women: 1.10, 0.96–1.26). HRs computed after exclusion of the first 2 years of follow-up were similar to estimates from the whole follow-up time (data not shown).

The association between baseline alcohol intake and cancer was borderline heterogeneous across countries in the colon ($p_{heterogeneity} = 0.06$), but not in the rectum ($p_{heterogeneity} = 0.81$), while for lifetime intake no evidence of heterogeneity was observed in the colon ($p_{heterogeneity} = 0.24$), and rectum ($p_{heterogeneity} = 0.32$). Using meta-regression, the percentage of nonconsumers was the only significant predictor of colon cancer risks.

Alcoholic beverages

Moderately higher colon cancer HRs were observed for baseline beer intake (1.33, 95%CI 0.96–1.84 for 20–39 g/day *vs.* 0.1–2.9 g/day) than wine (1.11, 95%CI 0.89–1.39) (Fig. 1). Similar associations were observed in the rectum for beer (1.45, 95%CI 0.99–2.12 for 20–39 g/day *vs.* 0.1–2.9 g/day) and wine (1.40, 95%CI 1.05–1.86). Overall, these associations were not significantly different by cancer subtypes or alcoholic beverages. Spirit and liquor intake were associated, although nonsignificantly, to rectal cancer (1.27, 95%CI 0.96–1.69 for >5 g/day *vs.* 0.1–1.9 g/day).

Alcohol was more strongly associated to cancer in current smokers (1.23, 95%CI 1.12–1.36 for 15 g/day increase) than never smokers (1.15, 95%CI 1.03–1.28) or former smokers (1.11, 0.97–1.28), but overall interaction was not statistically significant ($p_{heterogeneity} = 0.41$). The association between baseline alcohol and CRC was stronger in individuals with low folate intake (Table V), with a borderline significant interaction ($p_{heterogeneity} = 0.06$). This observation was consistent for men and women (results not shown).

Discussion

In the EPIC study, both lifetime (23% increase in risk) and baseline (26% increase in risk) alcohol intake were significantly associated to CRC incidence for alcohol intakes of 30–59.9 g/day compared to 0.1–4.9 g/day.

Experimental animal models indicate that alcohol by itself is not carcinogenic,[43] but several indirect mechanisms, such as generation of carcinogenic metabolites, have been proposed for alcohol-associated colorectal carcinogenesis. The most important metabolite appears to be acetaldehyde, a known carcinogen,[19] which is derived from the oxidation of ethanol by dehydrogenases in the colorectum and other organs.[44] Acetaldehyde is known to be present in high concentration in the large intestine after alcohol consumption and may either act directly to cause cellular injury and gene mutations,[44] or indirectly by decreasing glutathione levels and the elimination of free radicals.[45] In addition, acetaldehyde has been shown to increase the rate of cellular proliferation, a biomarker of cancer risk, in the rectal mucosa.[46]

In this study, consistent with the results of a meta-analysis of case–control and prospective studies,[20] a gradient of increasing associations was observed from the proximal to the distal colon followed by the rectum. However, it must be noted that in the present study, the subsite specific risks were not significantly different from each other, in agreement with findings of a pooled analysis of prospective studies,[27] and a recent meta-analysis based on cohort studies.[19] Several previous prospective studies have reported that associations with alcohol occur predominantly in the rectum,[15–17,22,47,48] although some others have reported elevated risks associated with colon cancer only.[12,17,19,49]

It has been observed that acetaldehyde concentrations are higher in the distal colon and rectum than in the proximal colon,[46] perhaps because distal colonic contents are less diluted. Thus, the

TABLE III – AVERAGE LIFETIME ALCOHOL INTAKE (g/day) AND RISK OF COLORECTAL CANCER IN EPIC

		Nonconsumers	Average lifetime alcohol intake (g/day)						Alcohol intake as continuous variable (15 g/day)	
			0.1–4.9	4.9–14.9	15–29.9	30–59.9	>60	*p*-value*	HR (95%CI)	*p*-value
Colorectum	Person-years	246,448	786,239	701,946	358,149	168,559	64,067			
	Cases	110	433	444	246	140	74			
	HR[1] (95%CI)	0.98 (0.72–1.33)	1.00	1.05 (0.90–1.21)	1.07 (0.89–1.29)	1.23 (0.98–1.55)	1.98 (1.46–2.70)	0.001	1.08 (1.04–1.12)	<0.001
Colon	Cases	83	299	298	156	82	38			
	HR[1] (95%CI)	1.03 (0.72–1.48)	1.00	1.06 (0.88–1.26)	1.07 (0.85–1.34)	1.17 (0.87–1.56)	1.62 (1.07–2.46)	0.374	1.05 (1.00–1.11)	0.057
Proximal Colon	Cases	20	119	117	64	26	13			
	HR[1] (95%CI)	0.79 (0.40–1.57)	1.00	0.98 (0.74–1.30)	1.05 (0.74–1.49)	0.87 (0.53–1.43)	1.22 (0.59–2.51)	0.906	1.02 (0.92–1.12)	0.708
Distal Colon	Cases	46	122	136	64	44	17			
	HR[1] (95%CI)	1.07 (0.62–1.82)	1.00	1.22 (0.92–1.60)	1.08 (0.76–1.54)	1.56 (1.03–2.38)	2.22 (1.20–4.13)	0.097	1.08 (1.01–1.16)	0.025
Rectum	Cases	27	134	146	90	58	36			
	HR[1] (95%CI)	0.85 (0.48–1.52)	1.00	1.02 (0.78–1.32)	1.09 (0.79–1.49)	1.33 (0.91–1.94)	2.59 (1.62–4.13)	0.002	1.12 (1.06–1.18)	<0.001

[1]Hazard ratios estimated in Cox regression model stratified by centre, age and gender, adjusted for duration of alcohol consumption (in years), time since quitting alcohol consumption (in years), an indicator variable for former and current (in continuous only) drinkers, total physical activity index, smoking status, education level, weight (tertiles), height (tertiles), energy from nonalcohol sources at baseline.

*Test for overall significance, according to a χ^2 distribution with 5 degrees of freedom.

TABLE IV – BASELINE ALCOHOL INTAKE (g/day) AND RISK OF COLORECTAL CANCER IN EPIC

		Nonconsumers	Baseline alcohol intake (g/day)						Alcohol intake as continuous variable (15 g/day)	
			0.1–4.9	4.9–14.9	15–29.9	30–59.9	>60	*p*-value*	HR (95%CI)	*p*-value
Colorectum	Person-years	409,104	984,755	803,635	427,241	271,158	81,939	–		
	Cases	224	518	482	275	233	101	–		
	HR[1] (95%CI)	0.99 (0.84–1.17)	1.00	1.05 (0.92–1.19)	1.03 (0.88–1.20)	1.26 (1.06–1.49)	1.64 (1.29–2.08)	<0.001	1.09 (1.05–1.13)	<.001
Colon	Cases	152	348	309	183	139	53			
	HR[1] (95%CI)	0.97 (0.79–1.18)	1.00	1.03 (0.88–1.21)	1.08 (0.89–1.31)	1.21 (0.98–1.50)	1.43 (1.04–1.97)	0.201	1.07 (1.02–1.12)	0.004
Proximal Colon	Cases	52	142	135	79	54	14			
	HR[1] (95%CI)	0.81 (0.58–1.13)	1.00	1.11 (0.87–1.42)	1.20 (0.89–1.61)	1.21 (0.86–1.70)	0.92 (0.51–1.66)	0.323	1.03 (0.95–1.12)	0.442
Distal Colon	Cases	79	155	133	67	65	29			
	HR[1] (95%CI)	1.08 (0.81–1.45)	1.00	0.98 (0.77–1.24)	0.86 (0.63–1.16)	1.22 (0.89–1.67)	1.68 (1.08–2.62)	0.073	1.08 (1.01–1.16)	0.018
Rectum	Cases	72	170	173	92	94	48			
	HR[1] (95%CI)	1.04 (0.78–1.38)	1.00	1.07 (0.86–1.33)	0.94 (0.72–1.23)	1.34 (1.01–1.77)	1.93 (1.35–2.78)	0.003	1.11 (1.05–1.17)	<0.001

[1]Hazard ratios estimated in Cox regression model stratified by centre, age and gender, total physical activity index, smoking status, education level, weight (tertiles), height (tertiles), energy from nonalcohol sources at baseline.

*Test for overall significance, according to a χ^2 distribution with 5 degrees of freedom.

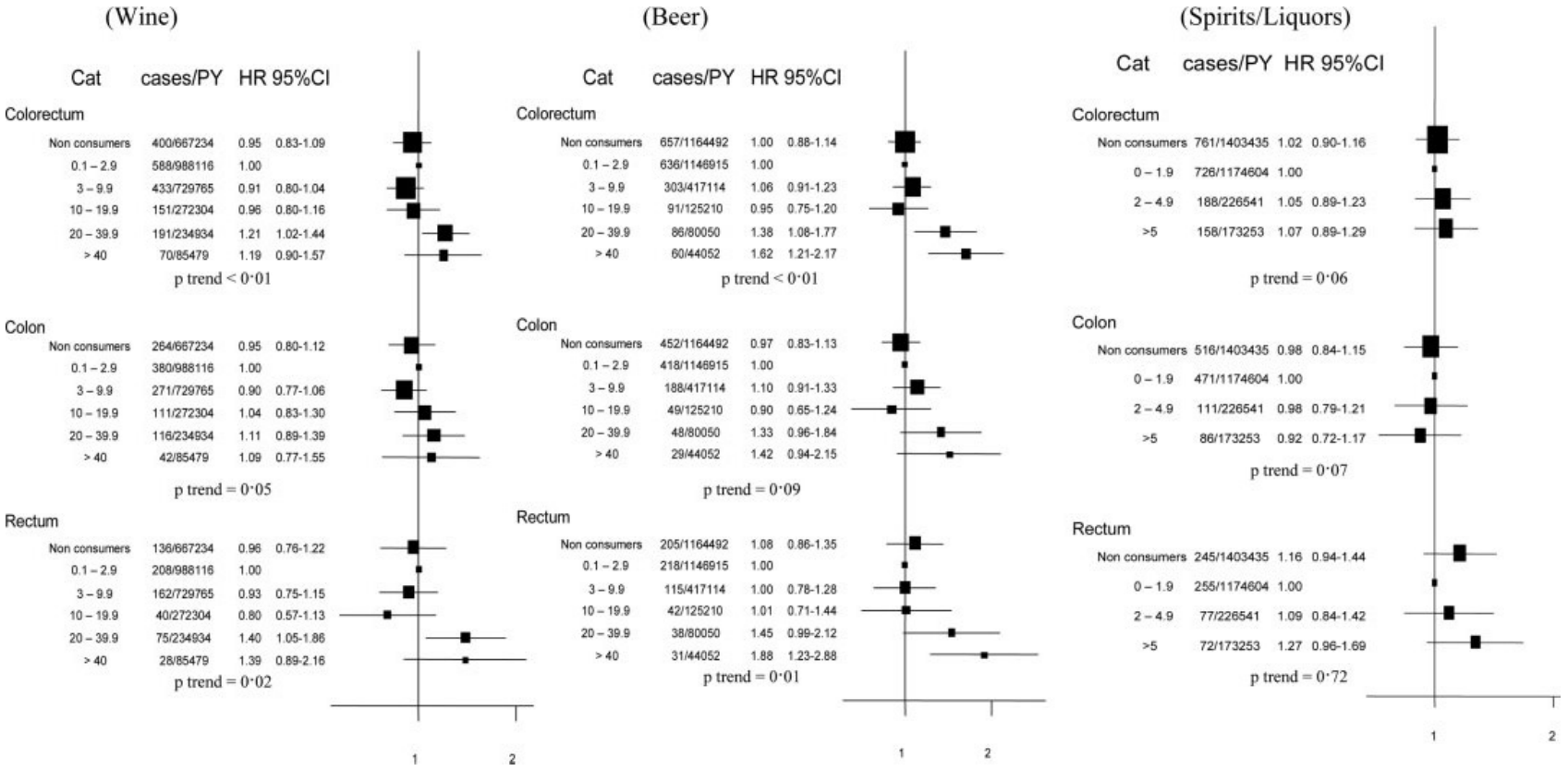

Figure 1 – Intake of baseline wine, beer and spirits/liquors intakes (g/day) and risk of colorectal, colon and rectal cancer (men and women combined). Cox regression models stratified by center, age and gender, adjusted for total physical activity index, smoking status, education level, weight (tertiles), height (tertiles), energy from nonalcohol sources, energy from alcohol without in turn, wine, beer and spirits/liquors.

TABLE V – BASELINE ALCOHOL INTAKE AND RISK OF CRC, BY TERTILES OF FOLATE INTAKE

Center-specific tertiles of folate	HR[1] (15 g/day)	95%CI	$p_{heterogeneity}$*	Mean alcohol[2] (g/day)	10th–90th percentile[3] (g/day)
Low	1.13	1.06–1.20	0.060	13.8	0.4–34.4
Mid	1.09	1.03–1.15		18.5	0.5–46.6
High	1.03	0.98–1.09		28.3	3.8–50.7

[1]Hazard ratios of baseline alcohol intake modelled as continuous variable in Cox models stratified by centre, age and gender, adjusted for total physical activity index, smoking status, education level, weight (tertiles), height (tertiles), energy from nonalcohol sources, fibre.–[2]Gender- and country-adjusted means of baseline alcohol intake, based on drinkers only.–[3]Gender- and country-adjusted 10th and 90th percentile values of baseline alcohol intake, based on drinkers only.

*p-value for heterogeneity across tertiles of folate intake, according to a χ^2 distribution with 2 degrees of freedom.

mucosa in the distal colon and rectum may be exposed to a greater degree to the carcinogenic effects of acetaldehyde than the mucosa in the proximal colon. Results from some animal studies also suggest an increased risk in the rectum *vs.* the colon,[50] or show comparable tumor burdens throughout the colorectum.[51]

The lifetime and baseline alcohol–CRC associations were consistent in men and women, with very similar and statistically significant dose–response relations. Although some prospective studies have shown a stronger association in men compared to women,[15] the present findings using baseline intake are consistent with those of some other individual prospective evaluations where no gender differences were observed[12,18] and a pooled analysis of prospective studies.[27] However, very limited evidence is available from prospective studies on gender differences by anatomical subsites within the colorectum.

Considering lifetime alcohol exposure, CRC risk was more strongly associated with a higher level of alcohol intake at 40 years of age than at 20 or 30 years (data not shown), possibly suggesting that observed cancer risks reflect more recent consumption. However, the validity of self-reported past alcohol intake is likely to diminish as study subjects recall exposure progressively distant in time, thus attenuating observed associations.

Although measurement errors in individual estimates of alcohol intake are likely to attenuate CRC risk estimates, in the EPIC study, alcohol measurements at baseline have shown relatively high validity and reliability.[32] It has been suggested that the association between alcohol and CRC might be attenuated because study subjects with preclinical disease (*i.e.* undiagnosed CRC, adenomas, polyps) might be more prevalent at the start of the study among nondrinkers than among drinkers.[49] Abstainers over the preceding 12 months from baseline were comprised of both never- and exdrinkers, who may have stopped because of poor health conditions. Here, using the information on lifetime alcohol consumption, the effect of alcohol was examined by evaluating the risk associated to exdrinkers separately, which in the EPIC cohort represents 73% of male and 33% of female nondrinkers at baseline, as well as after exclusion of the first 2 years of follow-up. In both men and women, the risks associated to exdrinkers were very similar to never-drinkers, and the exclusion did not produce appreciable changes in risks (data not shown).

In the present study, different alcoholic beverages were associated to CRC, with slightly higher risks for rectal than colon cancer, although these differences were not significant. Positive associations between beer and rectal cancer had been previously reported,[7–9,22–25] while the significant positive relationship between wine and rectal cancer observed in the present study has been previously reported in only 2 other studies.[23,24] The association between wine, beer and spirits, and CRC was consistent in men and women (data not shown).

Methylation of DNA is a basic element of regulating gene expression in cells. Hypomethylation may increase the risk of CRC *via* loss of control of proto-oncogene activity.[52] The combination of high alcohol and low folate intake could result in lower *S*-adenosylmethionine level resulting in DNA hypomethylation.[53,54] In addition, alcohol may indirectly alter DNA methylation patterns by affecting the intestinal absorption, hepatobiliary metabolism and renal excretion of folate. In this study, although alcohol consumption was higher, and more variation was observed in the top tertile of folate intake (18 g/day of within-center standard deviation in alcohol intake) than in the bottom tertile (14 g/day), the effect of alcohol on CRC incidence was lower for high folate consumption, consistent with previous observations.[30,55] To investigate the role of alcohol on CRC incidence, it is important to take into account not only the detrimental effect of alcohol on folate metabolism, but also the beneficial effect of folate in counteracting the carcinogenic effects of alcohol, but more research is needed to elucidate these complex relations.

In summary, this study has shown a statistically significant positive association between the risk of CRC and higher lifetime and baseline alcohol consumption levels, with more apparent risk increases for alcohol intakes greater than 30 g/day. The relationship was maintained after adjustment for a series of relevant dietary and lifestyle confounding factors, and was not heterogeneous by gender or anatomical subsite. These results lend further validity to the role of alcohol as a potential carcinogen and may be important in the formulation of public health initiatives aimed at the control and limitation of alcohol intake.

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