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Alcohol and risk of Barrett's esophagus: a pooled analysis from the international BEACON consortium

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Abstract

Background—Results from studies examining the association between alcohol consumption and the risk of Barrett's esophagus have been inconsistent. We assessed the risk of Barrett's esophagus associated with total and beverage-specific alcohol consumption by pooling individual participant data from five case-control studies participating in the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON).

Methods—For analysis there were 1282 population-based controls, 1418 controls with gastroesophageal reflux disease (GERD) and 1169 patients with Barrett's esophagus (cases). We estimated study-specific odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable logistic regression models adjusted for age, sex, body mass index (BMI), education, smoking status, and GERD symptoms. Summary risk estimates were obtained by random effects models. We also examined potential effect modification by sex, BMI, GERD symptoms and cigarette smoking.

Results—For comparisons with population-based controls, while there was a borderline statistically significant inverse association between any alcohol consumption and the risk of Barrett's esophagus (any vs. none, summary OR=0.77, 95% CI 0.60–1.00), risk did not decrease in a dose-response manner ($p_{trend}=0.72$). Among alcohol types, wine was associated with a moderately reduced risk of Barrett's esophagus (any vs. none, OR=0.71, 95% CI 0.52–0.98); however, there was no consistent dose-response relationship ($p_{trend}=0.21$). We found no

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association with alcohol consumption when cases were compared with GERD controls. Similar associations were observed across all strata of BMI, GERD symptoms and cigarette smoking.

Conclusions—Consistent with findings for esophageal adenocarcinoma, we found no evidence that alcohol consumption increases the risk of Barrett’s esophagus.

Keywords

Esophageal cancer; etiology; risk factors; ethanol

INTRODUCTION

The incidence of esophageal adenocarcinoma continues to rise in the United States and other Western populations (1); median survival time for this cancer remains less than 12 months (2). Efforts to reduce morbidity and mortality from esophageal adenocarcinoma have focused on screening and surveillance for Barrett’s esophagus, a metaplastic condition and the only known precursor to esophageal adenocarcinoma (3). However, these efforts have had very little population-level impact due to under-detection of patients with early esophageal adenocarcinoma and over-detection of indolent Barrett’s esophagus, with resultant uncertainty regarding the effectiveness of periodic surveillance (4).

Better strategies are needed to identify individuals for endoscopic screening for Barrett’s esophagus, to clarify potentially modifiable risk or protective factors and to triage patients with Barrett’s esophagus based on risk of carcinogenic progression. Multiple risk prediction models for Barrett’s esophagus aim to address the former issue (5–9), but none have performed well enough to warrant clinical application, in part due to uncertainty regarding the accuracy of some exposure inputs.

The international Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON; <http://beacon.tlvnet.net/>) is a global resource that has amassed one of the largest and best annotated collections of patients with esophageal adenocarcinoma and Barrett’s esophagus, as well as population-based controls. To date, data from BEACON have been used to better quantify the risk of Barrett’s esophagus conferred by obesity (10) and cigarette smoking (11). However, an outstanding and especially confusing issue is the association between alcohol consumption and the risk of Barrett’s esophagus. Despite previous investigation, it remains unclear whether alcohol consumption is truly associated with risk of Barrett’s esophagus, and whether patients’ alcohol histories may help improve risk stratification for Barrett’s esophagus. Results from previous studies of alcohol and Barrett’s esophagus are conflicting, with some studies reporting positive associations with moderate to heavy total and/or beverage-specific consumption (12–15), and others reporting inverse associations (16–20). However, many of these studies used different exposure categorizations, did not evaluate alcohol subtypes, or had limited power to evaluate interactions between alcohol and other risk factors. Therefore, we pooled individual participant data from five Barrett’s esophagus case-control studies participating in BEACON to comprehensively evaluate the association between alcohol consumption and the risk of Barrett’s esophagus.

METHODS

Study population

The five case-control studies participating in BEACON used for this analysis were: the Study of Digestive Health (Brisbane, Australia) (18); the Factors Influencing the Barrett's/Adenocarcinoma Relationship (FINBAR) study (Ireland) (16); the Epidemiology and Incidence of Barrett's Esophagus study (Kaiser Permanente Northern California) (17); the Study of Reflux Disease (western Washington State) (21); and the Epidemiologic Case-Control Study of Barrett's Esophagus (Chapel Hill, North Carolina). The Institutional Review Boards or Research Ethics Committees of each institution approved the acquisition and pooling of data for the present analysis. Participants provided written informed consent to take part in the studies. Full details of recruitment and participation are provided in the primary papers (16–18, 21).

We compared patients with Barrett's esophagus (cases) with two separate control groups: GERD controls (i.e., participants who had GERD symptoms or endoscopic evidence of acute esophageal inflammation consistent with GERD) and population-based controls. Five studies provided a GERD control group (see Table 1 ref #11); four studies provided population-based controls (the Chapel Hill study did not have a population-based comparison group). The definition of Barrett's esophagus in each study included endoscopic evidence of columnar mucosa in the tubular esophagus, accompanied by the presence of specialized intestinal metaplasia in an esophageal biopsy. Overall, data were pooled for 1432 population-based controls, 1659 GERD controls, and 1320 cases. Among those participants with available data on alcohol consumption (1376 population-based controls, 1597 GERD controls, and 1257 cases), we restricted our analyses to white non-Hispanic study participants (1282 population-based controls, 1418 GERD controls, 1169 cases) due to low numbers of cases from other ethnic groups (cases: 12 black, 32 Hispanic, 42 other, 2 missing).

Data collection

The main exposure was average daily alcohol consumption (drinks per day). Two studies asked participants to report their 'usual consumption of alcohol' (21), two studies captured alcohol consumption for the period one year (17) or five years before interview (16), and one study assessed usual frequency of consumption of alcohol during the age intervals of 20–29 years, 30–49 years and 50 years (18); for this study we used the average across these intervals for the pooled analysis. The beverage-specific analyses for consumption of beer, wine (red or white), and liquor were conducted using data from four studies (the Chapel Hill study did not collect beverage specific consumption) (16–18, 21).

Individual-level harmonized clinical, demographic, and questionnaire data for each study participant were merged into a single de-identified dataset and included information on study center, case-control status, age at diagnosis (or reference date for controls), sex, ethnicity, body mass index (BMI; weight divided by height squared, kg/m²), education, GERD symptoms status (ever vs. never), and cigarette smoking status (never, former, current) and pack-years (continuous). The data were checked for consistency and

completeness and any apparent inconsistencies were follow-up with individual study investigators.

Statistical analysis

We assessed the association between alcohol consumption (in categories: none, $>0<0.5$, $0.5<1.0$, $1<3$, $3<5$, $5<7$, ≥ 7 drinks/day) and risk of Barrett's esophagus using a two-stage analytic approach (22). In the first stage, study-specific odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were estimated using unconditional logistic regression models adjusted for age (<50 , $50-59$, $60-69$, ≥ 70 years), sex, education (school only, technical college/diploma, university/college), BMI (<25 , $25-29.9$, ≥ 30 kg/m²), smoking status (never, former, current), and GERD symptoms (ever vs. never; population-based control comparisons only). Study-specific analyses for the Chapel Hill study were not adjusted for education. In the second stage, the study-specific adjusted ORs were pooled to create a summary OR, using random effects models. We used the I^2 statistic to assess heterogeneity between studies (23). Larger I^2 values reflect increasing heterogeneity, beyond what is attributable to chance. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate, or high levels of heterogeneity, respectively. The referent group for analyses of total alcohol and beverage-specific consumption was non-drinkers of any alcohol type. For each of the beverage-specific analyses, we adjusted for total alcohol consumption in an attempt to investigate specific effects independent of ethanol content.

We calculated the P -value for trend by fitting alcohol consumption as an ordinal variable and assigning participants the median value for their category of alcohol exposure. Restricted cubic spline models were used to further investigate the continuous association between alcohol consumption and the risk of Barrett's esophagus (24). These models allow for easy visualization of nonlinear associations (25, 26) and were plotted using a linear scale on the x-axis (drinks/day of alcohol) and a logarithmic scale on the y-axis for the OR.

Finally, using the same methodology as for the overall analyses, we conducted stratified analyses by categories of sex, BMI, GERD symptoms, and smoking status to assess potential effect modification. We included an interaction term in the full model to assess the statistical significance of the difference in association across strata. All tests for statistical significance were two-sided at $\alpha=0.05$ and analyses were conducted using Stata 13.0 (StataCorp LP, College Station, TX).

RESULTS

The numbers of cases and controls, and summary data for total alcohol consumption by study, are shown in Table 1. Across the studies, 11.3% to 28.8% of population-based controls and 10.8% to 33.6% of GERD controls were non-drinkers. Median total alcohol consumption among population-based controls who were drinkers ranged from 0.4 to 3.0 drinks per day across studies. Cases and controls from the FINBAR study had higher median total alcohol consumption than cases and controls from the other four studies.

All results contrast cases with population-based controls, unless otherwise noted. Overall, there was a borderline statistically significant inverse association between any alcohol consumption and risk of Barrett's esophagus (any vs. non-drinkers, summary OR=0.77, 95% CI 0.60–1.00, $I^2=0\%$). However, while participants who reported typically consuming 3–<5 drinks per day had statistically significant lower risk of Barrett's esophagus (3–<5 drinks per day vs. non-drinkers, summary OR=0.57, 95% CI 0.38–0.86), there were no statistically significant associations with higher levels of alcohol consumption (5–<7 drinks per day, summary OR=0.58, 95% CI 0.30–1.12; 7 drinks per day, summary OR=0.89, 95% CI 0.51–1.55) and we found no evidence for a dose-response relationship ($p_{trend}=0.72$) (Table 2). Study-specific estimates were homogeneous within each of the consumption categories (Figure 1) and the relative risk patterns were generally similar between males (any vs. non-drinkers, summary OR=0.78, 95% CI 0.56–1.08, $I^2=0\%$) and females (any vs. non-drinkers, summary OR=0.76, 95% CI 0.50–1.16, $I^2=0\%$; P -interaction=0.96). Alcohol consumption was not associated with risk of Barrett's esophagus when cases were compared with GERD controls (Table 2; Figure 2). The summary ORs, obtained by pooling study-specific ORs adjusted for similar confounders, were similar to those obtained using an alternate analytic strategy whereby all subjects were analyzed using a single-model (pooled) approach with adjustment for harmonized confounders and study (data not shown). The spline models suggest a nonlinear relationship between total alcohol consumption and risk of Barrett's esophagus (Figure 3).

When we analyzed beverage-specific consumption, there was a statistically significant inverse association with any wine consumption (any vs. non-drinkers, summary OR=0.71, 95% CI 0.52–0.98, $I^2=0\%$), adjusted for total alcohol consumption. However, the test for trend with increasing wine consumption was not statistically significant ($p_{trend}=0.21$). We found no consistent associations between beer, liquor and risk of Barrett's esophagus (Table 3). The results were similar when analyses were not adjusted for total alcohol consumption (data not shown).

We evaluated whether BMI, GERD symptoms, or smoking modified the association between alcohol consumption and risk of Barrett's esophagus (Supplementary Table 1). There was no effect modification of alcohol consumption on the risk of Barrett's esophagus across all categories of each risk factor.

DISCUSSION

In this large pooled analysis, alcohol consumption was not a risk factor for Barrett's esophagus. Compared with controls, average daily consumption of alcohol was moderately lower among cases; however, we found no consistent statistically significant association between alcohol consumption and the risk of Barrett's esophagus and there was no evidence for a dose-response relationship. In beverage-specific analyses adjusted for total alcohol consumption, wine was associated with a moderately reduced risk of Barrett's esophagus. The association between alcohol and Barrett's esophagus was not modified by other factors (including sex, BMI, GERD, and smoking).

Previous studies have reported associations between alcohol and risk of Barrett's esophagus, however results have been conflicting (12–20). One possible explanation for the conflicting findings may be that individual studies have inadequate power to assess this association and are prone to type II error. Summarizing these results into an overall risk estimate using only published data is difficult given the different exposure categories, confounders and analyses used in the published manuscripts. By contrast, in this study, we had access to individual participant data from each of the five contributing studies, allowing us to control for the same set of potential confounders, and standardized categories of alcohol exposure, allowing for more consistent and robust risk estimates. In addition, the large sample size of the consortial approach increased the statistical power to detect associations and interactions.

Studies of Barrett's esophagus help to establish where risk factors act in the pathway to esophageal adenocarcinoma, either in the development of Barrett's esophagus or progression from Barrett's esophagus to cancer. A previous pooled analysis of 11 epidemiological studies of esophageal adenocarcinoma in BEACON found suggestive evidence for an inverse association between alcohol and risk of cancer (27). However, the summary risk estimates were not statistically significant (except for those consuming 0.5–<1.0 drinks/day) and there was no dose-response relationship ($p_{trend}=0.21$). The results of our study of Barrett's esophagus, together with null associations reported for alcohol and risk of progression from Barrett's esophagus to esophageal adenocarcinoma (28, 29), provides strong evidence that alcohol consumption is not a risk factor for developing Barrett's esophagus or progressing from Barrett's esophagus to esophageal adenocarcinoma.

We observed some evidence for an inverse relationship with moderate levels of alcohol consumption. It is possible, however, that this may be due, at least in part, to reverse causation. If people with reflux symptoms tend to avoid drinking alcohol, for example, the apparent protective effect may simply be the result of alcohol avoidance among symptomatic cases. While the associations between alcohol and Barrett's esophagus were not modified by a history of GERD symptoms, we had only self-reported GERD symptoms and the associations were attenuated and not statistically significant when cases were compared with GERD controls. Conversely, one of the component studies found that heavy alcohol consumption at age 21 years (well before diagnosis with Barrett's esophagus) was also inversely associated with risk of Barrett's esophagus (16), which can be interpreted to argue against reverse causality. There are plausible mechanisms by which alcohol — and wine in particular — may protect against Barrett's esophagus, such as from antioxidant resveratrol (30), and reduction in insulin resistance or increased levels of lipoproteins (31). However, as both white wine and red wine have been associated with lower risk of Barrett's esophagus (16, 18), resveratrol is unlikely to explain any inverse association.

This pooled analysis has several important strengths, including its large size and inclusion of multiple largely population-based studies. Furthermore, we defined and constructed each alcohol variable in the same way for each study and adjusted our analyses by a standard set of variables known to be associated with Barrett's esophagus. We found no evidence of between-study heterogeneity or evidence that the associations with alcohol were modified by BMI, GERD symptoms or cigarette smoking.

There are several limitations to this pooled analysis. Most studies ascertained average adult daily consumption, although some studies collected recent consumption and this may have increased the possibility of the reference group of non-drinkers including former drinkers. However, while this would somewhat attenuate the observed associations, it would not explain the inverse association with alcohol. It is possible that our results may be affected by recall and selection bias due to case-control design. However, the possibility of recall bias was minimized as most studies recruited incident cases soon after diagnosis and subjects in some of the studies were blinded regarding the topic of the study. While the FINBAR study included both incident and prevalent cases, the associations observed in FINBAR were similar to other studies that used only incident diagnoses. While our study is the largest to date, we were still unable to examine the association in non-Caucasians and case numbers were still small in some subgroups of the stratified analyses. Finally, we did not adjust our analyses for diet. However, when two of the component studies adjusted for diet, it did not attenuate the associations with alcohol (16, 17).

In contrast to esophageal squamous cell carcinoma, where alcohol is a strong risk factor (27), alcohol consumption is not a risk factor for Barrett's esophagus or esophageal adenocarcinoma. Our findings indicate that alcohol cessation is unlikely to reduce the risk of Barrett's esophagus or esophageal adenocarcinoma. Capturing patients' alcohol histories is therefore unlikely to help improve clinical risk stratification for Barrett's esophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Alcohol consumption is generally thought to confer higher risk of Barrett's esophagus
- However, the results from previously published studies have been inconsistent

2. WHAT IS NEW HERE

- Alcohol consumption is not a risk factor for Barrett's esophagus
- The findings from this large pooled analysis should allay any fears that alcohol consumption increases the risk of developing Barrett's esophagus

Figure 1.

Forest plot of the association between alcohol consumption (drinks/day) and the risk of Barrett's esophagus for comparison with population-based controls. Odds ratios are shown for each category of alcohol consumption relative to non-drinking and are adjusted for sex, age (categorical: <50, 50 to <60, 60 to <70, 70), body mass index (categorical: <25, 25 to 30, 30), education, smoking status (never, former, current), and gastroesophageal reflux symptoms (ever, never).

Figure 2.

Forest plot of the association between alcohol consumption (drinks/day) and the risk of Barrett's esophagus for comparison with GERD controls. Odds ratios are shown for each category of alcohol consumption relative to non-drinking and are adjusted for sex, age (categorical: <50, 50 to <60, 60 to <70, 70), body mass index (categorical: <25, 25 to 30, 30), education (except UNC), and smoking status (never, former, current).

Figure 3.

Restricted cubic spline models of the relationship between total alcohol consumption and risk of Barrett's esophagus for comparisons with (A) population-based controls and (B) GERD controls. Plots are restricted to alcohol consumption between 0 and 10 drinks per day for clarity and consistency.

Table 1

Characteristics of the five studies participating in the analysis

Study	Location	Population Controls				GERD Controls				Barrett's esophagus Cases			
		Non-drinkers n (%)	Drinkers n (%)	Alcohol use *		Non-drinkers n (%)	Drinkers n (%)	Alcohol use *		Non-drinkers n (%)	Drinkers n (%)	Alcohol use *	
FINBAR	Northern Ireland and Republic of Ireland	75 (28.8)	185 (71.2)	3.0, 0.8–6.7		68 (29.6)	162 (70.4)	1.9, 0.7–4.7		76 (34.2)	146 (65.8)	1.7, 0.7–6.5	
KPNC	Northern California, USA	65 (24.3)	203 (75.7)	0.4, 0.1–1.1		84 (33.2)	169 (66.8)	0.6, 0.1–1.7		86 (31.0)	191 (69.0)	0.4, 0.0–1.3	
Study of Digestive Health	Brisbane, Queensland, Australia	64 (11.3)	500 (88.7)	1.2, 0.5–2.6		31 (10.8)	257 (89.2)	0.9, 0.4–2.2		37 (10.3)	322 (89.7)	1.2, 0.5–2.9	
Study of Reflux Disease	Washington, USA	29 (15.3)	161 (84.7)	0.9, 0.3–2.2		62 (16.8)	308 (83.2)	0.9, 0.4–2.0		26 (15.3)	144 (84.7)	1.1, 0.4–2.3	
UNC-Chapel Hill	North Carolina, USA	-	-	-		93 (33.6)	184 (66.4)	0.0, 0.0–1.0		42 (29.8)	99 (70.2)	0.0, 0.0–1.0	

Numbers of cases and controls listed are those with alcohol data after restricting to white participants.

* Number of drinks/day: median, interquartile range.

Table 2

Adjusted ORs and 95% CIs for the associations between alcohol consumption and risk of Barrett's esophagus, overall and stratified by sex

Drinks/day	BE Cases vs. Population Controls			BE Cases vs. GERD Controls		
	Controls	Cases	OR ^a (95% CI)	Controls	Cases	OR ^a (95% CI)
All						
None	233	227	Referent	342	269	Referent
Any	1049	801	0.77 (0.60–1.00)	1076	900	0.90 (0.73–1.11)
>0–<0.5	319	260	0.85 (0.64–1.14)	407	318	1.02 (0.80–1.30)
0.5–<1.0	166	115	0.73 (0.50–1.05)	167	115	0.70 (0.49–0.99)
1–<3	320	232	0.74 (0.47–1.17)	322	261	0.80 (0.61–1.04)
3–<5	130	92	0.57 (0.38–0.86)	97	96	0.76 (0.51–1.12)
5–<7	52	43	0.58 (0.30–1.12)	14	51	0.89 (0.53–1.50)
7	62	59	0.89 (0.51–1.55)	44	59	1.14 (0.66–1.96)
p-trend			0.72			0.42
Males						
None	128	140	Referent	157	161	Referent
Any	742	611	0.78 (0.56–1.08)	642	681	0.94 (0.68–1.31)
>0–<0.5	163	155	0.87 (0.58–1.29)	179	193	1.07 (0.71–1.64)
0.5–<1.0	97	81	0.76 (0.47–1.24)	94	81	0.78 (0.50–1.22)
1–<3	252	192	0.75 (0.39–1.43)	210	212	0.79 (0.56–1.12)
3–<5	120	87	0.55 (0.34–0.90)	84	91	0.75 (0.48–1.19)
5–<7	52	43	0.59 (0.25–1.36)	33	51	0.96 (0.53–1.73)
7	58	53	0.83 (0.44–1.54)	42	53	0.85 (0.46–1.56)
p-trend			0.63			0.83
Females						
None	105	87	Referent	185	108	Referent
Any	307	190	0.76 (0.50–1.16)	434	219	0.80 (0.57–1.14)
>0–<0.5	156	105	0.81 (0.42–1.56)	45	125	0.85 (0.59–1.24)
0.5–<1.0	69	34	0.72 (0.37–1.40)	73	34	0.72 (0.38–1.35)
1	82	51	0.68 (0.37–1.23)	133	60	0.83 (0.51–1.33)
p-trend			0.84			0.82

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

[†] Summary OR and 95% CI from random effect models. OR adjusted for sex, age (categorical: <50, 50 to <60, 60 to <70, 70 years), body mass index (categorical: <25, 25 to 30, 30), education (except UNC) and smoking status (never, former, current), where appropriate. Analyses comparing BE cases with population controls were additionally adjusted for gastroesophageal reflux disease symptoms (ever, never).

Table 3

Adjusted ORs and 95% CIs for the associations of beer, liquor and wine with risk of Barrett's esophagus

Drinks/day	BE Cases vs. Population Controls				BE Cases vs. GERD Controls			
	Controls	Cases	OR [†] (95% CI)	I ²	Controls	Cases	OR [†] (95% CI)	I ²
Beer[‡]								
None [§]	233	227	Referent		249	227	Referent	
Any	806	646	0.92 (0.65–1.29)	1	655	646	1.23 (0.89–1.71)	0
>0–<0.5	351	292	0.92 (0.65–1.28)	0	322	292	1.23 (0.89–1.71)	0
0.5–<1.0	116	86	0.94 (0.52–1.68)	0	91	86	1.16 (0.64–2.10)	0
1–<3	171	133	1.19 (0.63–2.23)	10	135	133	1.05 (0.59–1.88)	0
3–<5	93	64	1.20 (0.52–2.74)	0	60	64	1.09 (0.31–3.88)	54
5	75	71	0.94 (0.45–1.99)	9	47	71	0.84 (0.05–15.1)	77
p-trend			0.06				0.93	
Liquor[‡]								
None [§]	233	227	Referent		249	227	Referent	
Any	699	545	0.78 (0.56–1.09)	0	625	545	0.92 (0.67–1.27)	0
>0–<0.5	567	404	0.78 (0.56–1.09)	0	471	404	0.92 (0.67–1.27)	0
0.5–<1.0	68	51	0.73 (0.40–1.33)	0	67	51	0.75 (0.42–1.33)	0
1–<3	49	64	1.18 (0.62–2.24)	0	65	64	1.00 (0.55–1.85)	0
3	15	26	1.43 (0.43–4.81)	0	22	26	1.08 (0.38–3.08)	0
p-trend			0.36				0.32	
Wine[‡]								
None [§]	233	227	Referent		249	227	Referent	
Any	801	545	0.71 (0.52–0.98)	0	611	545	1.16 (0.84–1.60)	0
>0–<0.5	497	347	0.71 (0.52–0.98)	0	376	347	1.16 (0.84–1.60)	0
0.5–<1.0	139	92	0.78 (0.46–1.33)	0	104	92	1.00 (0.58–1.73)	0
1–<3	150	94	0.61 (0.36–1.05)	0	117	94	0.92 (0.53–1.61)	0
3	15	12	0.57 (0.07–4.42)	57	14	12	0.68 (0.20–2.38)	0
p-trend			0.21				0.43	

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

[†]Summary OR and 95% CI from random effect models, OR adjusted for sex, age (categorical: <25, 25 to <30, 30, education, smoking status (never, former, current) and total alcohol consumption (0 to <0.5, 0.5 to <1.0, 1 to <3, 3 to <5, 5 to <7, 7), where appropriate. Analyses comparing BE cases with population controls were additionally adjusted for gastroesophageal reflux disease symptoms (ever, never).

[‡]Beer, liquor and wine were unavailable for the UNC-Chapel Hill study.

[§]Referent group is non-drinkers of any type of alcohol.