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The importance of delivery rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's and Esophageal Adenocarcinoma Consortium

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Abstract

Background—Cigarette smoking is associated with esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC), and alcohol consumption with ESCC. However, no analyses have examined how delivery rate modifies the strength of odds ratio (OR) trends with total exposure, i.e., the impact on the OR for a fixed total exposure of high exposure rate for short duration compared with low exposure rate for long duration.

Methods—The authors pooled data from 12 case-control studies from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON), including 1,242 (EAC), 1,263 (EGJA) and 954 (ESCC) cases and 7,053 controls, modeled joint ORs for cumulative exposure and exposure rate for cigarette smoking and alcohol consumption, and evaluated effect modification by sex, body mass index (BMI), age and self-reported acid reflux.

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Results—For smoking, all sites exhibited inverse delivery rate effects, whereby ORs with pack-years increased, but trends weakened with increasing cigarettes/day. None of the examined factors modified associations, except for ESCC where younger ages at diagnosis enhanced smoking effects ($P<0.01$). For EAC and EGJA, ORs with drink-years exhibited inverse associations in <5 drinks/day consumers and no association in heavier consumers. For ESCC, ORs with drink-years increased, with trends strengthening with greater drinks/day. There was no significant effect modification, except for EAC and EGJA where acid reflux mitigated the inverse associations ($P=0.02$). For ESCC, younger ages at diagnosis enhanced drinking-related ORs ($P<0.01$).

Conclusions—Patterns of ORs by pack-years and drink-years, delivery rate effects and effect modifiers revealed common as well as distinct etiologic elements for these diseases.

Keywords

alcohol drinking; risk model; smoking

1. Introduction

Cigarette smoking is an established risk factor for esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC), while alcohol consumption is a risk factor only for ESCC [1]. Studies have investigated other potential risk factors, such as obesity, gastroesophageal reflux and diet [1]; however, no previous analysis has considered how delivery rate impacts odds ratio trends (OR) with total exposure for smoking and for drinking.

Studies have typically estimated joint ORs by exposure rate (cigarettes/day [CPD] or drinks/day [DPD]) and exposure duration. Interpretation is however problematic, since ORs with increasing exposure rate for a fixed duration embed effects of increasing total exposure [2]. For example, for 30 years smoking, comparisons of ORs at 20 CPD and 30 CPD include different total exposures, i.e., 30 and 45 pack-years, respectively, where pack-years is the product of mean CPD and years of cigarette smoking. Thus, ORs for exposure rate and duration cannot be interpreted as separate effects. In contrast, we consider total exposure (pack-years or drink-years, defined as the product of mean DPD and years of alcohol consumption) and exposure rate (CPD or DPD), which reformulates analysis in terms of OR trends with total exposure and the modifying effects of delivery rate, where delivery rate represents the relative effects on the OR for an equal total exposure of a high exposure rate for a short duration compared with a low exposure rate for a long duration. For various environmental factors, e.g., cigarette smoking, alcohol consumption and inhaled arsenic, this approach enabled relatively simple characterizations of the joint ORs and generated novel etiologic insights [2–7]. Previous modeling of EAC, EGJA and ESCC data focused on a single factor, CPD or DPD, using splines or general additive models [8,9].

Using pooled data from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), we extend previous analyses of the associations of EAC and EGJA with smoking [10] and alcohol consumption [11], and include additional data on ESCC. Specifically, we consider: (i) trends in ORs by pack-years and drink-years and the influence of CPD and DPD; and (ii) effect modification of smoking patterns and drinking patterns by sex, body mass index (BMI=weight [kg]/height $[m]^2$), occurrence of acid reflux and age, as well as the joint effects of smoking and drinking.

2. Material and methods

2.1 Study data

Data derived from 10 population-based case-control studies [12–21] and two case-control studies nested within cohorts [22–24] of EAC and EGJA (see Table 1 in Cook [10]). We additionally included data from seven BEACON studies which also enrolled ESCC cases [12–15,21–23]. Prior to the implementation of data restrictions (see below), there were 5,427 cases and 12,769 controls available for analysis. For additional study-specific information, see Supplement A.

The population-based studies ascertained amount and duration of cigarette use and smoking status at or within 2 years of diagnosis for cases or the index date for controls. For the two nested case-control studies, the baseline questionnaires administered at cohort enrollment provided exposure variables. The two nested studies ascertained CPD in categories [22,23], while one study ascertained duration of smoking in categories [23]. We assigned midpoint values for the categories. One study did not have duration information [22] which we estimated using either attained age or age at smoking cessation and 17 years as the age at smoking initiation. We minimized the influence of smoking cessation by restricting analysis to never, current and recent (<2 years) former cigarette smokers, thereby omitting 2,183 cases and 4,542 controls who were former smokers.

For alcohol consumption, all studies defined never-drinkers as lifelong abstainers, except four studies which ascertained drinking status one [22,23], five [20] or 20 years [15] before enrollment. We assigned midpoints for one study which collected DPD in categories [23]. Analyses included all subjects, since drinking cessation information was not available for all studies. We standardized DPD by equating one 12 ounce beer, 5 ounce glass of wine and 1.5 ounce of liquor.

Four studies (with 1,859 cases and 6,189 controls) lacked information on duration of alcohol consumption [15,19,20,22], and were not included in drinking analyses. However, we included these studies in smoking analyses by imputing drinking duration. For the eight studies with duration, we cross-classified control drinkers by sex, age (4 levels) and DPD (8 levels) and calculated cell-specific frequencies for duration using cell-specific decile cut-points. For each subject missing duration, we identified the appropriate sex, age and DPD category, randomly sampled a duration category using frequency weights and assigned mean duration. Inference for smoking analyses was similar using either single or multiple imputations, and we therefore present results for a single imputation. Analyses indicated that the inclusion of these four studies did not affect estimates of smoking-related parameters, as results were similar with these studies omitted.

BMI derived from self-reported height and weight, using usual adult weight [12,14,18,19], or, if unavailable, weight one year [13,17,21], five years [20] or 20 years [15] prior to the referent age. One study ascertained weight at age 20 and maximum adult weight (excluding pregnancies), for which we used the latter assuming it better reflected usual adult weight [16]. For the nested case-control studies, we used weight at cohort entry [22,23].

The Institutional Review Board or Research Ethics Committee for each study approved data collection and, if required, participation in the pooling.

2.2 Statistical models

We used binary logistic regression to estimate ORs for each category of smoking and alcohol consumption, as appropriate. For continuous pack-years, d, and CPD, x, the standard logistic model with exponentially increasing ORs across the full exposure range provided a

poor fit to the data. We therefore fitted the model OR(z, d, x) = exp(α z) OR(d, x), where α and z were vectors of adjustment parameters and covariates, respectively, and

$$\mathrm{OR}(d, x)=1+\beta\, d\, g(x) \quad (1)$$

where β represented the excess odds ratio per pack-year (EOR/pack-year) and g(.) described variations of the EOR/pack-year with CPD, i.e., changes in strength with delivery rate [2,4]. After assessing alternatives, we set $g(x)=\exp\{\phi_1 \ln(x) + \phi_2 \ln(x)^2\}$, with g(0)=0. ORs by pack-years were approximately linear within a CPD category, i.e., $\mathrm{OR}(d) = 1 + \gamma_i\, d$ for the i^{th} CPD category, where γ_i was the EOR/pack-year. We compared the fitted $\beta\, g(x)$ with the γ_i estimates from the model:

$$\mathrm{OR}(d, x)=1+\sum\nolimits_i \gamma_i\, d_i \quad (2)$$

where d_i equaled d within the i^{th} CPD category and zero otherwise.

We also used model (1) for continuous drink-years and DPD after preliminary analysis revealed approximately linear relationships for ORs by drink-years within DPD categories. For ESCC, we used the same g(.). For EAC and EGJA, variations with DPD were complex and we modeled g(.) with restricted cubic splines (Supplement B), with the Akaike Information Criterion (AIC) advising on the number and placement of knots [25].

We considered effect modification by a categorical factor (f) with levels 1,…,S using

$$\mathrm{OR}(d, x, f)=1+\sum\nolimits_s \beta_s\, d_s\, g_s(x_s) \quad (3)$$

where distinct β_s parameters and g_s (.) functions replaced β and g(.), and where d_s equaled d and x_s equaled x within level s and zero otherwise. We used deviances to compare model fit and evaluate whether effect modification derived from total exposure (different β's), exposure rate (different g(.)'s) or both. Starting with model (3), we constrained the β's and/or g(.) functions to be equivalent across f and examined degradation in model fit. This approach, in contrast to starting with model (1) and enlarging the model, allowed the evaluation of the interaction of f and one factor (e.g., pack-years) while minimizing influence of the interaction of f and its closely related correlate (e.g., CPD).

Software for polytomous regression under model (1) to evaluate differences in the magnitude of associations between smoking and alcohol consumption across the three disease outcomes (EAC, EGJA, ESCC) was not available. As an alternative, we created one dataset with three "strata" consisting of EAC cases and controls, EGJA cases and controls and ESCC cases and controls and applied model (3) to test homogeneity across outcome. The approach was anti-conservative, since controls were replicated, but was generally comparable to use of categorical variables and standard polytomous logistic regression.

Analyses adjusted for the cross-classification of study (12 levels), age (<60, 60–64, 65–69, 70+ years) and sex, and for education (less than high school, high school graduate, more than high school, missing/not available) and BMI (<25, 25–29.9, 30.0–34.9, 35.0+ kg/m^2). For smoking analyses, we further adjusted for drink-years and DPD categories, and for drinking analyses we adjusted for pack-years and CPD categories. Since results were similar, we did not adjust for race or occurrence of acid reflux, which was available in five studies only.

Cigarette smoking analyses included 927, 990 and 915 cases of EAC, EGJA and ESCC, respectively, 7,431 controls for EAC and EGJA and, due to fewer studies, 6,212 controls for ESCC. Alcohol consumption analyses included 1,103, 1,118 and 896 cases, respectively, and 5,719 controls for EAC and EGJA and 3,973 controls for ESCC.

Previous analyses of cigarette smoking suggested that <10 CPD smokers increased model instability due to a limited range for pack-years. We therefore repeated analyses in never and 10+ CPD smokers, which included 89.7% of cases and 89.1% of controls. For alcohol consumption, the relatively few heavy drinkers were highly influential. We repeated analyses in never and ≤10 DPD drinkers, which included 94.6% of cases and 98.4% of controls.

We fit the various models using the Epicure computer package[26].

3.0 Results

3.1 Marginal and joint odds ratios by pack-years and cigarettes/day

ORs by pack-years increased significantly for all outcomes, with ESCC exhibiting the strongest association (Table 1). Adjusted for pack-years, ORs by CPD increased, leveled, then even decreased, suggesting variations with delivery rate. The test of no linear trend with CPD rejected only for ESCC, although a test of no linear-quadratic variation rejected for EAC (P=0.02) and EGJA (P=0.05).

For joint categories of pack-years and CPD, ORs relative to never-smokers increased approximately linearly with pack-years within CPD categories (Figure 1). Four of 15 tests rejected linearity at the 0.05-level (for EAC <10 CPD, for EGJA 20–29 and 40+ CPD, and for ESCC 40+ CPD). A sensitivity analysis revealed that after omitting two studies [17,21] only one of 15 tests rejected linearity (for EGJA 20–29 CPD), consistent with expectation.

The EOR/pack-year estimates from model (2), i.e., slopes, were generally larger for ESCC than for EAC and EGJA, which were themselves similar (Table 2). EOR/pack-year estimates (square symbol) and the fitted model (1) (solid line) declined at higher CPDs, indicating a decreasing strength of association (Figure 2). For each outcome, the variation of the pack-years association with CPD, g(.), was significant (Supplement Table C1).

Cigarette smoking patterns for EAC, EGJA and ESCC differed significantly (P<0.01) (Table C1). Relative to model (3) with outcome-specific β_s and $g_s(.)$, there was less degradation in fit with common β (P=0.09 and P=0.17 in the full and restricted data, respectively) than with common g(.) (P=0.04 and P=0.07), suggesting the greater EORs for ESCC derived from differential smoking rate effects, g(.). A similar evaluation indicated homogeneity of smoking-related parameters for EAC and EGJA (P=0.63) (not shown).

3.2 Marginal and joint odds ratios by drink-years and drinks/day

Using binary logistic regression ORs for EAC and EGJA by drink-years were <1.0, while ORs by DPD adjusted for drink-years were about 1.0 for <5 DPD and >1.0 for 5+ DPD (Table 1). These patterns, based on marginal effects, suggested a protective association with drink-years in low DPD consumers but a deleterious association in high DPD consumers. For ESCC, ORs by drink-years increased significantly. After adjustment for drink-years, ORs by DPD increased. Although the test of no linear trend did not reject (P=0.39), the test of no linear-quadratic trend did reject (P<0.01).

For joint categories of drink-years and DPD, ORs relative to never-drinkers increased approximately linearly with drink-years within DPD categories (Figure 3). Two of 15 tests

(for EGJA 5.0–9.9 and ESCC 10+ DPD) significantly rejected linearity. For EAC and EGJA, ORs with drink-years declined in <5 DPD categories. For the five categories, p-values for a test of no trend with drink-years were <0.01, 0.06, 0.33, 0.85 and 0.30 for EAC, respectively, and 0.10, <0.01, 0.04, 0.62 and <0.01 for EGJA.

Expanding DPD categories and fitting model (2), there were inverse associations with drink-years for <5 DPD drinkers (Table 3 and Figure 4), with EOR/drink-year estimates (×10) increasing monotonically from −0.085 to 0.016 for <20 DPD for EAC and from −0.046 to 0.002 for <7 DPD for EGJA. Applying model (1), there were significant associations with alcohol consumption for EAC (P=0.06) and for EGJA (P=0.03), with DPD significantly modifying the EOR/drink-year estimates (P=0.04 and P=0.02) (Table C3).

For ESCC, EOR/drink-year estimates tended to increase with DPD then decrease (Table 3 and Figure 4). We fitted model (1) with $g(x)=\exp\{\phi_1 \ln(x) + \phi_2 \ln(x)^2\}$ for all data and with $g(x)=\exp\{\phi_1 \ln(x)\}$for ≤10 DPD since inclusion of $\ln(x)^2$ did not improve fit (P=0.94). For all data, the 3-parameter model (β, ϕ_1 and ϕ_2) underestimated the EOR/drink-year at lower DPD (solid line), while the 2-parameter model (β and ϕ_1) provided a good fit for ≤10 DPD (dash line).

3.3 Effect modification of cigarette smoking and alcohol consumption excess odds ratios

Using model (3), we evaluated effect modification of cigarette smoking ORs by sex, BMI, age, acid reflux and drink-years. For EAC and EGJA, there was no significant effect modification (Tables 2 and C2). For ESCC, there was significant modification by attained age, with smoking patterns enhanced at younger ages (P=0.01) (Figure C1). The enhancement at younger ages derived primarily from the interaction of CPD and age (P=0.03) and not pack-years and age (P=0.57) (Table C2). There was a suggestion of enhanced smoking effects at lower BMIs (Table 2, P=0.08, with P=0.06 in the restricted data), but relationships were not consistent across CPD categories.

We evaluated effect modification of ORs for alcohol consumption (Tables 3 and C4). For EAC and EGJA, we found no significant effect modification by sex, BMI, age or pack-years, but did observe a suggested modification by acid reflux (P=0.03 for EAC and P=0.14 for EGJA). EOR/drink-year estimates for <7 DPD categories were greater for those reporting acid reflux, except in the <1 DPD category for EAC, suggesting acid reflux mitigated the inverse drink-years association (Table 3). Combining EAC and EGJA cases, acid reflux significantly modified alcohol consumption patterns (P=0.02) (not shown). For ESCC, there was significant modification only by attained age, with drinking patterns enhanced at younger attained ages (P<0.01) (Figure C2). The modification of ORs by sex in the restricted data (P=0.05), which was suggested in Table 3, was due to <1 DPD drinkers and omission of those subjects resulted in P=0.37 for the test of homogeneity. Finally, BMI significantly modified drinking patterns (P=0.04), but results were not consistent, with reduced EOR/drink-year estimates for 30+ BMI subjects but only in <5 DPD categories.

3.4 Consistency of smoking and drinking results by study

Using model (3) within the restricted data, tests of homogeneity of smoking effects across studies did not reject for EAC (p=0.08) or for EGJA (p=0.13), but did reject for ESCC (p=0.02). The latter test was influenced by one study (23), which, when omitted, resulted in no rejection of homogeneity (p=0.16) (not shown). ORs for ESCC by pack-years for the Kaiser-Permanente Study (23) were smaller than the other studies, and may have been influenced by the few ESCC smokers (70 of 92 total ESCC cases) and the limited number of distinct values for pack-years due to the use of category mid-points for duration and CPD.

Using model (3) with a restricted cubic spline for g(.), tests for homogeneity of drinking effects for EAC and for EGJA across studies did not reject (p=0.99 and p=0.98, respectively). Seven BEACON studies contributed cases for ESCC analyses. With the additional requirement of information for duration of drinking, ESCC analyses were limited to four studies (12–14, 21). The test of homogeneity of drinking effects was rejected (p<0.01), although it was not rejected (p=0.24) after omitting the Australian study (21). The Australian study had a similar pattern of increasing EOR/drink-year estimates for ESCC; however, the EOR/drink-year parameter (β) was lower.

4.0 Discussion

Our analysis of BEACON data revealed distinct associations for EAC, EGJA and ESCC with cigarette smoking and alcohol consumption and differential effect modification. For cigarette smoking, each outcome exhibited similar inverse delivery rate patterns above 10–15 CPD, whereby for equal pack-years smoking more CPD for shorter duration was less deleterious than fewer CPD for longer duration. This pattern has occurred consistently with smoking-related cancers, including lung, oral cavity, pharynx, larynx, bladder, kidney, liver and pancreas [2,3,5,7,27], and may reflect saturation of activation pathways [28–30], increased detoxification [31] or enhanced DNA repair [32,33]. These patterns may also have reflected CPD-dependent inhalation, whereby heavier smokers inhaled less vigorously and thereby ingested fewer carcinogens per cigarette. However, a sensitivity analysis based on the association between urinary cotinine and CPD for a smoking and lung cancer study concluded that CPD-dependent inhalation did not explain the inverse delivery rate pattern [34].

Previous studies have reported greater smoking-related ORs for ESCC than for EAC and EGJA [1]; however, our analysis went further and suggested that these differences derived from delivery rate effects, i.e., different g(.) functions, and not pack-years, i.e., similar β's. This implied that factors which stochastically influence pathways that predispose towards a specific histology were not related to the carcinogenic impact of lifetime cigarette consumption but to the relative modulating influence of delivery rate. In particular, the greater smoking-related ORs for ESCC derived from heightened responsiveness to differing delivery rates.

Studies have linked increased alcohol consumption with ESCC, as well as cancers of the oral cavity, pharynx, larynx, liver, colon/rectum and breast [35]. This association may derive from the ethanol metabolite acetaldehyde, a possible human carcinogen (Group 2B) [36], which may increase reactive oxygen species [37] or enhance cell permeability to environmental carcinogens, e.g., tobacco smoke [35,38]. Our analysis observed a direct delivery rate pattern for ≤10 DPD, whereby the drink-years association strengthened with increasing DPD, suggesting that alcohol-related causal mechanisms were not rate limited. Above 10 DPD, the drink-years association weakened, a pattern which also occurred for oral cavity, pharyngeal and laryngeal cancers [4,5]. However, interpretation of results for heavy drinkers may be problematic, since data at extreme levels of daily consumption were limited and potentially subjected to increased misclassification. Nevertheless, the decreasing strength of the drink-years association above 10 DPD was consistent, suggesting that this "reduced potency" or "wasted exposure" pattern may not be an artifact.

In contrast to ESCC, studies of EAC and EGJA and alcohol consumption have been less definitive, with reports of a decreasing association[14,16,39], no association[9,14,15,17,22,40–43] and an increasing association[13,39,44,45]. A recent BEACON analysis of EAC and EGJA reported suggestive evidence of an inverse association in modest drinkers[11]. Our modeling found a significant inverse association

with drink-years, but limited mainly to <5 DPD consumers, with no association in heavier drinkers. We think it unlikely that increasing misclassification of DPD greatly influenced the diminution of the inverse drink-years association. Assuming duration was accurate, increasing DPD misclassification should have induced progressively greater curvilinearity of the drink-years association, a pattern we did not observe (Figure 3).

Healthy lifestyle factors may have confounded results for EAC and EGJA through a link to moderate drinking and reduced consequences of insulin resistance or elevated serum lipids and lipoproteins or increased antioxidants [11]. However, alcohol-related ORs were similar in never and current smokers and within BMI categories (not shown), which argues against lifestyle confounding.

We evaluated effect modification of smoking ORs by sex, BMI, age, acid reflux and drink-years and drinking ORs by sex, BMI, age, acid reflux and pack-years. For EAC, only the occurrence of acid reflux significantly modified ORs for alcohol consumption. For <7 DPD, inverse associations with drink-years were greater in those without reflux (P=0.01 for the test of no association) than with reflux (P=0.29), suggesting acid reflux may dissipate any health benefits from lower DPD. A similar pattern occurred for EGJA, with a significant inverse drink-years association among those without (P=0.05), but not with (P=0.77), acid reflux, although homogeneity was not rejected. This result needs corroboration, since information on acid reflux in the pooled data were limited [19,46–48].

For ESCC, we found evidence of effect modification by BMI, with ORs for smoking and drinking enhanced for those under 30 BMI. Confounding by reverse causation (disease-related weight loss) may have influenced results[49]; however, such effects are thought weak for most cancers[50] and moreover reverse causation would had to have been outcome specific. In BEACON, the OR for ESCC by BMI <25 relative to 25+ was OR=1.27 (95% confidence interval [CI] 0.98, 1.65) and OR=1.44 (95% CI 1.22, 1.69) in never and ever smokers, respectively, an association consistent with other ESCC studies [13,23,42,51,52], as well as studies of lung[53–56], oral cavity, pharyngeal and laryngeal cancers[5,57]. In addition, the enhancement of ORs for smoking and drinking at lower BMIs was also observed for oral cavity and pharyngeal cancers[5]. In contrast, ORs for EAC and EGJA increased with greater BMI (not shown), and BMI did not modify smoking and drinking ORs. Mechanisms that link lower BMIs with increased ORs for ESCC, lung, oral cavity and pharynx cancers and with enhancement of smoking-related and drinking-related ORs are unknown[57], but may involve altered caloric absorption and utilization, greater oxidative stress or altered DNA repair[57–60].

We found no effect modification of smoking ORs by drinking or drinking ORs by smoking, indicating consistency with a multiplicative joint association. This agreed with most previous studies [12,14,43,45,61], although not all [9].

Our analysis had several strengths. We pooled original data from 12 studies conducted in diverse settings, while similarities of study instruments allowed substantial harmonization of variables for smoking, alcohol consumption and other important risk factors. The large numbers of case patients increased our power to assess main effects, as well as more subtle patterns, such as delivery rate effects and effect modifiers, and variations by histology and site. The use of pooled data also enabled the direct assessment of the consistency of the observed associations across independent studies.

Limitations in our results included potential recall bias from the retrospective collection of information for the 10 case-control studies, although this was balanced by data from two case-control studies which were nested in cohorts and which used data ascertained at

enrollment and prior to disease incidence. Consistency of results across studies and differential patterns by outcome types suggested that recall bias was not substantial.

In summary, smoking-related ORs exhibited an inverse delivery rate pattern, whereby for equal pack-years smoking more CPD for shorter duration was less deleterious than smoking fewer CPD for longer duration. For EAC and EGJA, there was a significant inverse association with drink-years in <5 DPD drinkers, primarily in those reporting no acid reflux, and no association in heavier drinkers. For ESCC, there was an increasing OR trend with drink-years, which strengthened with greater DPD in light and moderate drinkers. Although consistent across studies, our results require further confirmation, but provide important guidance for the development of more directed hypotheses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BEACON	Barrett’s Esophagus and Esophageal Adenocarcinoma Consortium
CDP	cigarettes per day
CI	confidence interval
DPD	drinks per day
EAC	esophageal adenocarcinoma
EGJA	esophagogastric junctional adenocarcinoma

EOR	excess odds ratio
ESCC	esophageal squamous cell carcinoma
OR	odds ratio

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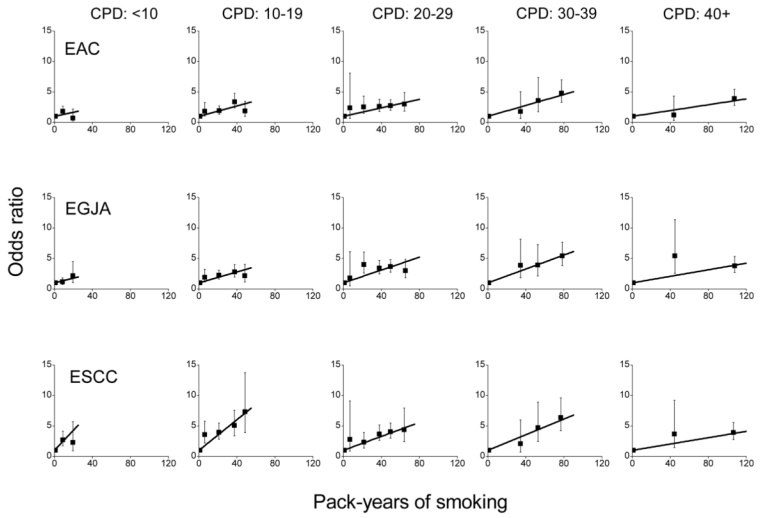

Figure 1.

Odds ratios for esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC) by categories of pack-years of cigarette smoking and number of cigarettes smoked per day (CPD) (solid symbol) and fitted linear models in pack-years (see text). Bars represent 95% confidence intervals. Data for never and current cigarette smokers from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON).

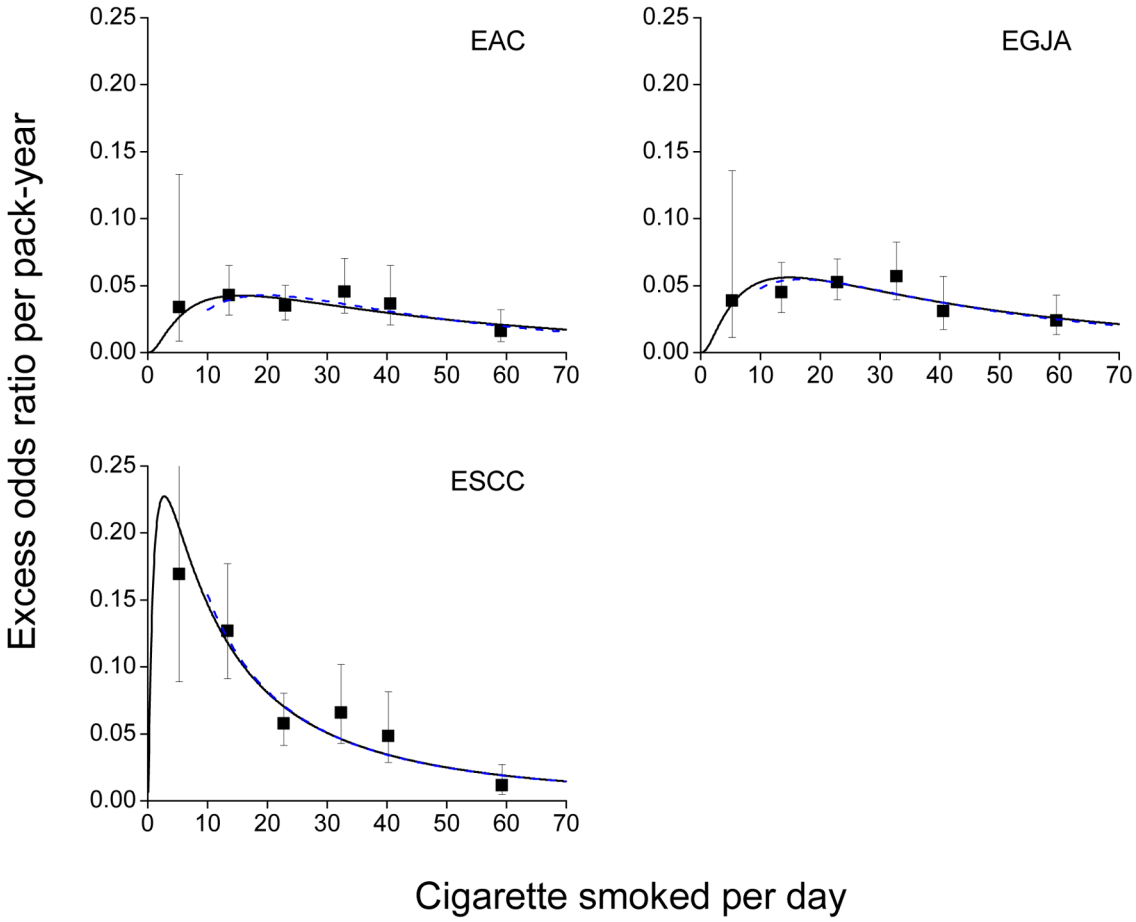

Figure 2.

Estimated excess odds ratios per pack-year for esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC) within categories of cigarettes per day (CPD) (square symbol), plotted at the category-specific mean CPD, and model (1) fitted to all data (solid line) and to never and 10+ CPD smokers (dash line). Bars represent 95% confidence intervals. Data for never and current cigarette smokers from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON).

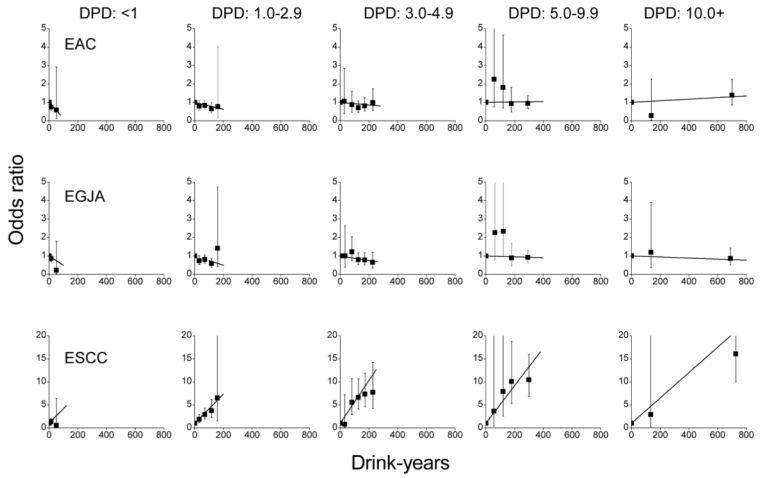

Figure 3.

Odds ratios for esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC) by categories of drink-years and number of drinks per day (DPD) (solid symbol) and fitted linear models in drink-years (see text). Bars represent 95% confidence intervals. Data from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON).

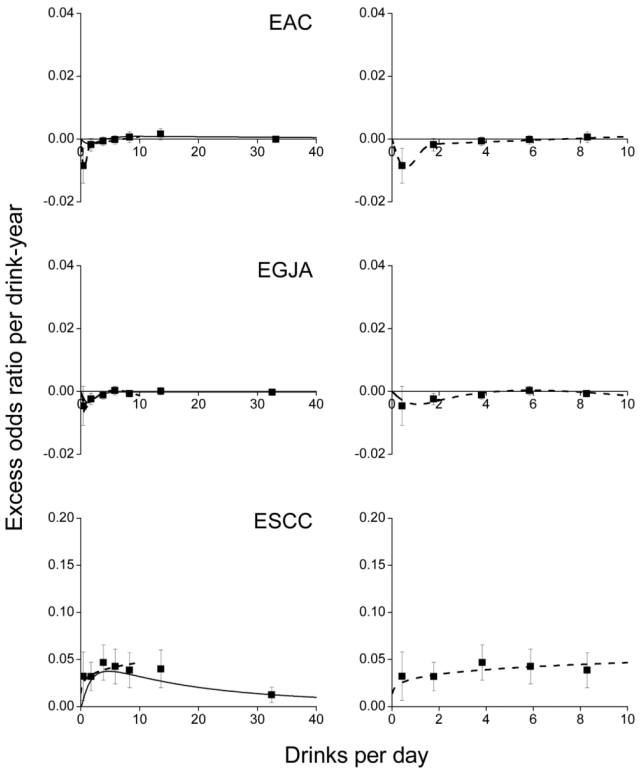

Figure 4.

Estimated excess odds ratios per drink-year for esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma (EGJA) and esophageal squamous cell carcinoma (ESCC) within categories of drinks per day (DPD) (square symbol), plotted at the category-specific mean DPD, for all data (left panels) and for #10 DPD (right panels). Bars represent 95% confidence intervals. For EAC and EGJA, model (1) included DPD effects estimated by restricted cubic splines with four interior knots at 0.2, 0.5, 3.0 and 10.5 DPD for EAC and at 0.1, 1.0, 2.0 and 7.0 for EGJA (solid line), and at 0.1, 0.3, 1.3 and 2.0 DPD for EAC and at 0.1, 0.2, 2.0 and 9.8 for EGJA for never and #10 DPD drinkers (dash line). For ESCC, model (1) included DPD effects defined by an exponential function (see text) fitted to all data (solid line) and to restricted data (dash line). Note the aspect ratio for EAC and EGJA panels was 2-times the aspect ratio for the ESCC panels. Data from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON).

Table 1

Odds Ratios (OR) with 95% Confidence Intervals (CI) By Cigarette Smoking And Alcohol Consumption By Disease Type. Data From The Barrett's Esophagus And Esophageal Adenocarcinoma Consortium (BEACON).

	Cases [a]			Controls		OR	95% CI	OR	95% CI	OR	95% CI
Variable	**EAC**	**EGJA**	**ESCC**	**EAC/EGJA**	**ESCC**	**EAC**		**EGJA**		**ESCC**	
Pack-years of smoking [b]											
0	411	393	203	4,587	3,720	1.00 [c]		1.00 [c]		1.00 [c]	
1–29	61	47	67	596	527	1.66	1.1–2.4	1.24	0.8–1.8	2.63	1.8–4.0
30–39	73	108	121	608	529	1.45	0.8–2.5	1.87	1.1–3.1	2.69	1.6–4.6
40–49	117	135	166	485	407	2.22	1.2–4.0	2.01	1.1–3.5	3.93	2.2–7.1
50–59	104	144	178	684	630	1.92	1.0–3.6	1.93	1.1–3.5	4.62	2.5–8.5
60+	161	163	180	471	399	2.77	1.4–5.6	1.86	1.0–3.6	5.63	2.7–11.7
P for no linear trend [d]						<0.01		<0.01		<0.01	
Cigarettes/day [e]											
1–9	46	35	43	315	254	1.00 [c]		1.00 [c]		1.00 [c]	
10–19	140	141	198	955	825	1.30	0.8–2.2	1.29	0.8–2.1	1.42	0.9–2.3
20–29	178	245	281	1,067	978	1.33	0.7–2.4	1.82	1.0–3.2	0.89	0.5–1.6
30–39	73	100	91	206	170	1.65	0.8–3.4	2.59	1.5–5.0	1.03	0.5–2.1
40+	79	76	99	301	265	1.34	0.6–2.9	2.12	1.0–4.3	0.71	0.3–1.5
P for no linear trend						0.40		0.35		(<0.01)	
Drink-years [f]											
0	146	143	44	1,054	579	1.00 [c]		1.00 [c]		1.00 [c]	
1–49	468	480	181	2,697	1,847	0.74	0.6–0.9	0.86	0.7–1.1	1.31	0.9–1.9
50–99	198	209	131	882	666	0.77	0.5–1.1	0.93	0.6–1.3	2.18	1.3–3.8
100–149	96	103	114	436	347	0.60	0.4–0.9	0.68	0.4–1.0	2.96	1.6–5.3
150–199	60	70	107	231	191	0.62	0.4–1.1	0.62	0.4–1.0	3.52	1.8–6.9
200+	135	113	319	419	343	0.67	0.4–1.2	0.49	0.3–0.9	3.82	1.9–7.8
P for no linear trend						(0.22)		(0.34)		<0.01	
Drinks/day [g]											
0.1–1.0	376	386	140	2,149	1,491	1.00 [c]		1.00 [c]		1.00 [c]	

	Cases [a]			Controls		OR	95% CI	OR	95% CI	OR	95% CI
Variable	**EAC**	**EGJA**	**ESCC**	**EAC/EGJA**	**ESCC**	**EAC**		**EGJA**		**ESCC**	
1.0–2.9	309	314	197	1,520	1,112	1.09	0.8–1.4	0.88	0.7–1.1	1.32	0.9–1.9
3.0–4.9	130	142	188	547	439	1.27	0.8–1.9	1.24	0.8–1.8	2.15	1.3–3.6
5.0–9.9	104	105	199	332	269	1.56	0.9–2.7	1.90	1.1–3.2	2.74	1.5–5.2
10+	38	28	128	117	83	1.87	0.9–3.7	1.74	0.9–3.4	4.12	2.0–8.4
P for no linear trend						0.90		0.60		0.39	

[a] Includes esophageal adenocarcinoma (EAC), esophagogastric junctional adenocarcinoma, (EGJA), and esophageal squamous cell carcinoma (ESCC) cases. There were fewer controls for ESCC cases, since cases enrolled in seven studies only. ORs obtained from standard binary logistic regression adjusted for study/center, education, age, sex.

[b] Never and current cigarette smokers. ORs additionally adjusted for BMI, drink-years, DPD and CPD. ORs by pack-years at the referent category of <10 CPD smokers, based on a logistic main effects model for the two factors.

[c] Referent category.

[d] P-value for one degree of freedom chi-square test of no trend. Parentheses denote negative trend.

[e] Never and current cigarette smokers. ORs additionally adjusted for BMI, drink-years, DPD and pack-years.

[f] All data, omitting subjects with missing drink-years. ORs additionally adjusted for BMI, pack-years, CPD and DPD. ORs by drink-years at the referent category of <1.0 DPD drinkers, based on a multiplicative logistic model for main effects.

[g] All data, omitting subjects with missing drink-years. ORs additionally adjusted for BMI, pack-years, CPD and drink-years.

Table 2

Estimated Excess Odds Ratio (EOR) Per Pack-Year By Categories Of Cigarettes/Day (CPD), Overall And By Levels Of Potential Effect Modifiers [a]. Data For Never And Current Cigarette Smokers From The Barrett's Esophagus And Esophageal Adenocarcinoma Consortium (BEACON).

		Cigarettes/day							
Modifier	**Level**	**<10**	**10–19**	**20–29**	**30–39**	**40–49**	**50+**	**P [b]**	**P [b,c]**
		Esophageal adenocarcinoma carcinoma cases and controls							
None		0.034	0.043	0.035	0.045	0.036	0.016		
Sex	Females	0.066	0.062	0.102	0.084	0.052	0.000	0.17	0.21
	Males	0.025	0.039	0.029	0.042	0.034	0.017		
BMI [d]	<25	0.028	0.034	0.036	0.060	0.022	0.035	0.51	0.36
	25–29	0.020	0.062	0.039	0.037	0.055	0.012		
	30+	0.085	0.027	0.025	0.039	0.043	0.006		
Age	<55	0.021	0.055	0.040	0.069	0.027	0.023	0.64	0.80
	55–64	0.028	0.054	0.031	0.047	0.058	0.005		
	65+	0.042	0.028	0.033	0.028	0.023	0.023		
Acid reflux	No	0.000	0.047	0.026	0.050	0.046	0.017	0.57	0.69
	Yes	0.031	0.066	0.025	0.034	0.050	0.035		
Drink-yrs	Never	0.127	0.057	0.022	0.145	0.195	0.005	0.14	0.79
	<50	0.016	0.027	0.046	0.035	0.038	0.031		
	50–99	0.000	0.051	0.035	0.028	0.015	0.013		
	100+	0.150	0.068	0.025	0.050	0.033	0.009		
		Esophagogastric junctional adenocarcinoma cases and controls							
None		0.039	0.045	0.053	0.057	0.031	0.024		
Sex	Females	0.083	0.060	0.101	0.077	0.109	0.069	0.09	0.08
	Males	0.027	0.041	0.045	0.053	0.026	0.019		
BMI	<25	0.015	0.057	0.056	0.067	0.024	0.038	0.03	0.28
	25–29	0.127	0.043	0.053	0.047	0.042	0.017		
	30+	0.000	0.023	0.050	0.065	0.034	0.018		
Age	<55	0.000	0.045	0.062	0.079	0.031	0.020	0.32	0.36
	55–64	0.053	0.054	0.077	0.045	0.061	0.039		
	65+	0.049	0.041	0.033	0.054	0.013	0.011		
Acid reflux	No	0.051	0.070	0.062	0.058	0.041	0.023	0.29	0.36

		Cigarettes/day							
Modifier	**Level**	**<10**	**10–19**	**20–29**	**30–39**	**40–49**	**50+**	**P** *b*	**P** *b,c*
	Yes	0.027	0.043	0.082	0.088	0.032	0.115		
Drink-yrs	Never	0.000	0.095	0.088	0.141	0.083	0.031	0.06	0.09
	<50	0.061	0.037	0.047	0.050	0.022	0.029		
	50–99	0.000	0.028	0.080	0.041	0.018	0.014		
	100+	0.030	0.042	0.029	0.049	0.032	0.019		
	Esophageal squamous cell carcinoma case and controls								
None		0.169	0.127	0.058	0.066	0.048	0.012		
Sex	Females	0.168	0.170	0.056	0.037	0.199	0.008	0.65	0.79
	Males	0.168	0.111	0.056	0.070	0.042	0.012		
BMI	<25	0.192	0.154	0.066	0.083	0.045	0.012	0.08	0.06
	25–29	0.188	0.119	0.057	0.042	0.062	0.012		
	30+	0.000	0.031	0.025	0.077	0.054	0.012		
Age	<55	0.314	0.319	0.106	0.091	0.078	0.007	0.01	<0.01
	55–64	0.135	0.131	0.051	0.060	0.077	0.028		
	65+	0.151	0.071	0.048	0.067	0.024	0.012		
Acid reflux	No	0.205	0.186	0.094	0.063	0.060	0.012	0.45	0.39
	Yes	0.194	0.142	0.073	0.053	0.202	0.086		
Drink-yrs	Never	0.012	0.168	0.000	0.065	0.003	0.011	0.19	0.12
	<50	0.155	0.156	0.073	0.044	0.081	0.015		
	50–99	0.000	0.200	0.156	0.176	0.049	0.042		
	100+	0.141	0.083	0.036	0.049	0.041	0.006		

[a]Estimates of EOR/pack-year based on linear odds ratios by pack-years relative to never-smokers within CPD categories.

[b]P-values for chi-square tests of homogeneity of model (3) for continuous pack-years and CPD across levels of modifying factor, based on 3 (2-level modifier) or 6 (3-level modifier) degrees of freedom. Additional test results given in Supplement Table C2.

[c]P-value for data restricted to never and 10+ CPD smokers.

[d]Body mass index.

Table 3

Estimated Excess Odds Ratio (EOR) Per 10-Drink-Years By Categories Of Drinks/Day (DPD), Overall And By Levels Of Potential Effect Modifiers [a]. Data From The Barrett's Esophagus And Esophageal Adenocarcinoma Consortium (BEACON).

		Drinks/day								
Modifier	**Level**	**<1**	**1–2.9**	**3–4.9**	**5–6.9**	**7–9.9**	**10–19.9**	**20+**	**P [b]**	**P [b,c]**
		Esophageal adenocarcinoma carcinoma cases and controls								
None		−0.085	−0.018	−0.007	−0.002	0.006	0.016	−0.001		
Sex	Female	−0.066	0.018	0.069	−0.032	0.699	−0.053	0.000	0.31	0.21
	Males	−0.088	−0.021	−0.008	−0.002	0.003	0.016	−0.001		
BMI [d]	<25.0	−0.090	−0.003	0.022	−0.005	−0.003	0.024	0.001	0.97	0.79
	25–29	−0.086	−0.026	−0.009	−0.008	0.030	0.008	−0.003		
	30+	−0.082	−0.031	−0.032	0.023	−0.011	0.025	−0.030		
Age	<55	−0.116	0.022	0.006	0.043	0.035	−0.005	−0.003	0.47	0.18
	55–64	−0.122	−0.042	−0.014	−0.009	0.031	0.022	−0.002		
	65+	−0.068	−0.013	−0.005	−0.005	−0.009	0.012	0.003		
Acid reflux	No	−0.072	−0.048	−0.024	−0.018	0.000	0.018	0.000	0.72	0.03
	Yes	−0.124	−0.015	−0.004	0.007	−0.008	0.008	−0.005		
Pack-yrs	0	0.024	0.052	0.011	0.056	0.071	0.029	−0.005	0.50	0.10
	<30	−0.050	0.005	0.010	0.001	0.019	0.042	0.009		
	30–44	0.009	−0.003	−0.003	0.019	0.002	0.032	0.003		
	45+	−0.113	−0.025	−0.003	−0.005	0.003	0.008	0.000		
		Esophagogastric junctional adenocarcinoma cases and controls								
None		−0.046	−0.024	−0.012	0.002	−0.007	0.001	−0.003		
Sex	Female	−0.020	−0.015	−0.004	0.054	−0.035	0.071	0.000	0.92	0.98
	Males	−0.049	−0.025	−0.012	0.002	−0.007	0.000	−0.003		
BMI	<25.0	−0.023	−0.027	−0.001	0.022	−0.003	0.001	−0.005	0.04	0.30
	25–29	0.038	0.016	0.003	−0.002	0.014	−0.005	0.000		
	30+	−0.089	−0.025	−0.009	0.021	−0.009	0.068	0.060		
Age	<55	−0.123	−0.041	−0.011	0.002	−0.027	−0.013	−0.003	0.92	0.45
	55–64	−0.067	−0.027	−0.004	0.016	0.022	−0.003	−0.001		
	65+	−0.028	−0.021	−0.015	−0.005	−0.012	0.010	−0.004		
Acid reflux	No	−0.036	−0.039	−0.020	−0.005	−0.002	−0.008	−0.003	0.09	0.14

		Drinks/day								
Modifier	**Level**	**<1**	**1–2.9**	**3–4.9**	**5–6.9**	**7–9.9**	**10–19.9**	**20+**	**P** *b*	**P** *b,c*
	Yes	−0.011	−0.010	0.001	0.015	−0.003	0.009	−0.005		
Pack-yrs	0	0.008	0.009	0.030	0.033	−0.015	0.009	0.023	0.89	0.72
	<30	0.069	0.005	0.005	0.006	0.015	−0.003	−0.005		
	30–44	−0.050	−0.007	−0.015	−0.001	0.006	0.005	−0.003		
	45+	−0.052	−0.025	−0.004	0.012	−0.002	0.006	−0.001		
		Esophageal squamous cell carcinoma case and controls								
None		0.323	0.320	0.468	0.427	0.386	0.400	0.124		
Sex	Female	0.023	0.252	0.287	4.019	0.561 *e*			0.38	0.05
	Males	0.849	0.498	0.694	0.594	0.551	0.559	0.175		
BMI	<25	0.414	0.327	0.476	0.357	0.351	0.372	0.106	0.04	0.06
	25–29	0.359	0.462	0.575	0.608	0.462	0.440	0.143		
	30+	−0.054	0.095	0.307	0.445	0.534	0.618	668.7		
Age	<55	0.072	0.881	1.282	1.224	1.291	1.346	0.286	<0.01	<0.01
	55–64	0.323	0.404	0.624	0.449	0.481	0.334	0.090		
	65+	0.203	0.176	0.236	0.270	0.198	0.261	0.121		
Acid reflux	No	0.134	0.140	0.216	0.203	0.261	0.278	0.087	0.18	0.30
	Yes	0.043	0.019	0.190	0.272	0.111	0.186	0.024		
Pack-yrs	0	0.189	0.195	0.597	0.762	0.416	0.850	0.570	<0.01	0.26
	<30	0.509	0.243	0.409	0.516	0.534	0.531	0.090		
	30–44	0.193	0.231	0.490	0.293	0.457	0.256	0.016		
	45+	0.447	0.623	0.548	0.472	0.347	0.422	0.346		

[a] Estimates of EOR/10 drink-years based on linear odds ratios by drink-years relative to never-drinkers within DPD categories.

[b] P-values for chi-square test of homogeneity of model (3) for continuous drink-years and DPD across levels of modifying factor, based on 3 (2-level modifier), 6 (3-level modifier) or 8 (4-level modifier) degrees of freedom. Additional test results given in Supplement Table C4.

[c] P-value using data restricted to never and ≤ 10 DPD drinkers.

[d] Body mass index.

[e] Includes 7+ DPD.