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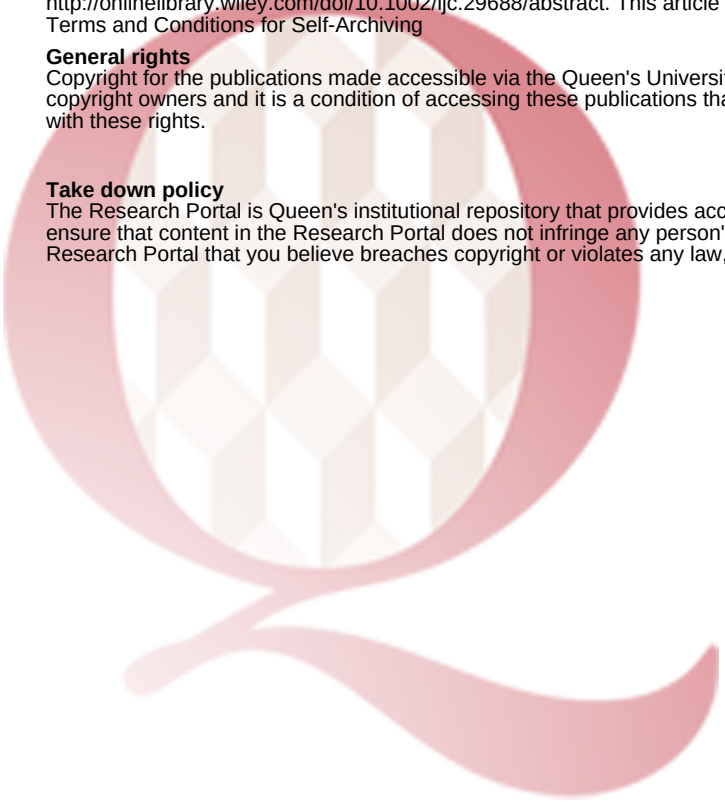

Age-specific risk factor profiles of adenocarcinomas of the esophagus: a pooled analysis from the international BEACON consortium

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Novelty & Impact: Incidence in esophageal adenocarcinoma has increased sharply among all age groups; however one disconcerting trend is the increasing proportion of advanced-stage tumors occurring at younger (< 50 years) as opposed to older ages. The relative rarity of these malignancies has precluded prior studies from assessing risk factors across age groups. Pooling data from 8 case-control studies we found that recurrent heartburn/regurgitation and obesity were appreciably stronger risk factors for early-onset EA relative to older age-categories.

Abbreviations: EA, esophageal adenocarcinoma; EGJA, esophagogastric junction adenocarcinoma; BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval.

Keywords (MeSH terms): risk factors; esophageal cancer; case-control studies; obesity; age of onset

Abstract

Esophageal (EA) and esophagogastric junction (EGJA) adenocarcinoma have been steadily increasing in frequency in younger people, however the etiology of these cancers is poorly understood. We therefore investigated associations of body- mass index (BMI), cigarette smoking, alcohol consumption, gastroesophageal reflux, and use of non-steroidal anti-inflammatory drugs (NSAIDs) in relation to age-specific risks of EA and EGJA. We pooled individual participant data from eight population-based, case-control studies within the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). The analysis included 1,363 EA patients, 1,472 EGJA patients, and 5,728 control participants. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for age-specific (<50, 50–59, 60–69, ≥70 years) cancer outcomes, as well as interactions by age. BMI, smoking status and pack-years, recurrent gastroesophageal reflux, and frequency of gastroesophageal reflux were positively associated with EA and EGJA in each age group. Early-onset EA (<50 years) had stronger associations with recurrent gastroesophageal reflux (OR=8.06, 95%CI: 4.52, 14.37; $P_{effect\ modification}$=0.01) and BMI ($OR_{BMI\ \geq 30\ vs.\ <25}$=4.19, 95%CI: 2.23, 7.87; $P_{effect\ modification}$=0.04), relative to older age groups. In contrast, inverse associations of NSAID use were strongest in the oldest age group (≥70 years), although this apparent difference was not statistically significant. Age-specific associations with EGJA showed similar, but slightly weaker patterns and no statistically significant differences by age were observed. Our study provides evidence that associations between obesity and gastroesophageal reflux are stronger among earlier onset EA cancers.

Introduction

Incidence of esophageal adenocarcinoma (EA) and esophagogastric junction adenocarcinoma (EGJA) has increased sharply in Western populations [1, 2] among all age groups [3-5]. Survival has remained particularly poor, with five-year survival less than 20% [6]. A particularly disconcerting aspect is the growing proportion of advanced-stage tumors that occur at early-onset (< 50 years), as opposed to later-onset [7-9], with most recent estimates from SEER indicating approximately 8.2% of EAs/EGJAs are diagnosed in US individuals less than 50 years of age. Understanding whether and how risk factor profiles vary by age could provide evidence-based information that may inform clinical practice, as well as provide etiologic insight.

A number of risk factors for EA and EGJA have been identified—irrespective of age at diagnosis. Increased risk is associated with male sex, white race, hiatal hernia [10-12], gastroesophageal reflux [10, 13], obesity [14], and cigarette smoking [15, 16]. Inverse associations with usage of nonsteroidal anti-inflammatory drugs (NSAIDs) [17] and moderate alcohol consumption [18] have also been observed. Few studies have conducted age-specific risk factor analyses for EA and EGJA. One study suggested that obesity is more strongly associated with risk of EA among younger patients (<50 years) [19] while another reported that obesity among patients was associated with younger median age at diagnosis [20]. Given the relative rarity of these malignancies prior studies have been limited in size, which has precluded detailed investigations across multiple age groups. Therefore, we leveraged the large sample size in the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) and comprehensively

evaluated risk factors by age at diagnosis, particularly focusing on early-onset (<50 years) disease.

Methods

Study Population

The BEACON consortium was formed in 2005 by an international group of investigators [21-33]. Consortium data consist of population-based case-control and cohort studies of EA, EGJA and Barrett's esophagus. The large total amount of consortium data enable the conduct of etiological studies of these conditions with excellent statistical power.

For this analysis, we included eight case-control studies that provided data from both EA and EGJA patients: the nationwide Australian Cancer Study (esophageal cancer component) [32], Factors Influencing the Barrett's Adenocarcinoma Relationship (FINBAR) Study [21], nationwide Swedish Esophageal and Cardia Center Study (SECC) [28], Larynx/Esophagus/Oral cavity (LEO) Study [29], Los Angeles County Multi-ethnic Study [33], Nebraska Health Study II [31], Population Health Study [22], and the United States (US) Multi–Center Study [27]. Details about source populations, case definitions, recruitment procedures, participants, and study designs have been reported previously [21-34].

The main outcomes of interest were age-specific groups of EA and EGJA patients; particularly early-onset disease (<50 years) given that risk factor profiles for this rarer group are poorly understood. Subjects were limited to those of white non-Hispanic ancestry, because of relatively small numbers of non-white or Hispanic patients (26 black, 89 Hispanic, 42 other race or ethnic groups). The eight studies together provided

2,835 patients (1,363 EA, 1,472 EGJA) and 5,728 controls for analysis. Data acquisition and data pooling were approved by the Institutional Review Board or Research Ethics Committee of each participating institution included in the study.

Study Variables

Included studies provided information on age at diagnosis for case patients, age at interview for controls, sex, education, usual adult body mass index (BMI: weight divided by square of height [kg/m^2]), alcohol consumption, cigarette smoking, and study center (for multi-center studies). Studies or their subsets also included information on reported heartburn and regurgitation [21, 27, 28, 32, 33], and NSAID usage [21, 27, 32, 33]. Detailed information on exposure harmonization and detailed analyses of these risk factors has been reported previously for BMI [14], alcohol consumption [18], cigarette smoking [16, 34], heartburn/regurgitation [15], and NSAIDs use [17]. The categories for age at diagnosis were selected *a priori* based on convenient cut-points (<50, 50–59, 60–69, ≥70 years) for ease of interpretation.

Statistical Analysis

Primary exposure variables of interest included BMI, alcohol consumption, cigarette smoking, heartburn and regurgitation, and NSAID usage. Because of the small number of early-onset esophageal cancer diagnoses in each study (Table 1), we pooled data for our analysis, rather than using a 2-step meta-analytic approach as in most prior BEACON studies that have focused on a single exposure in relation to cancer diagnosed at any age and include larger case groups, such as BMI [14], alcohol [18], smoking [34], or gastroesophageal reflux [15]. Multivariable logistic regression models were used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for the

association between each primary exposure variable and each outcome (EA or EGJA) stratified by age (diagnosis for cases, interview for controls; <50, 50–59, 60–69, ≥70 years). Covariates included in the multivariable logistic regression models (if not assessed as primary exposure variables) included age (continuous), sex, study, study-center (for multicenter studies), education (< or ≥ high school), BMI (continuous), ever regular consumption of alcohol, and smoking status (never, current, former), as these variables are either of primary interest or known to be associated with these malignancies and thus potential confounders [35].

As previously noted, a subset of studies also included information on the following risk factors: heartburn, regurgitation or both as recurrent symptoms (≥ weekly frequency: yes/no) and frequency of heartburn, regurgitation or both (never, <monthly, monthly to <weekly, weekly to <daily, ≥daily) and regular NSAID use (ever/never; including aspirin usage and non-aspirin NSAID usage).

To assess effect modification by age group, we used the likelihood-ratio statistic to compare nested models of the age-adjusted main-effect data (i.e., not stratified by age) with a model that also included main-effect exposure-age category interaction terms (<50, 50–59, 60–69, ≥70 years; 3df). All analyses were performed using Stata software version 13. All statistical tests were two–sided and P-values less than 0.05 were considered to be statistically significant.

Results

In total, data from 1,363 EA and 1,472 EGJA case patients were available for the analysis (Table 1). Among these subjects, 125 EA and 174 EGJA patients had been

diagnosed at <50 years of age (10.5%), 314 EA and 334 EGJA diagnosed at 50–59 years of age (22.9%), 473 EA and 526 EGJA diagnosed at 60–69 years of age (35.2%), and 451 EA and 438 EGJA patients diagnosed at ≥70 years of age (31.4%). In total, 5,728 population controls—including 790 aged <50 years, 1,286 aged 50–59 years, 1,936 aged 60–69 years, and 1,716 aged ≥70 years—were available for comparison (Table 1). Study participant characteristics by age at diagnosis/interview are shown in Supplementary Table 1.

The overall and age-specific risk factor profiles of EA and EGJA are provided in Tables 2 and 3. Overall we observed an increased risk of EA and EGJA with increasing BMI, whereas alcohol consumption categories up to 3–5 drinks per day, but not more, were inversely associated, each compared with the 0 drinks per day category. Current or former cigarette smoking status were each positively associated with increased risk of both EA and EGJA, and we observed a trend of increasing risks with increasing cumulative exposure to tobacco smoke (pack-years). Recurrent heartburn and/or recurrent regurgitation, and greater frequency of symptoms were associated with increased risk of both cancers. Lastly, we observed inverse associations with use of NSAIDs and aspirin, and a modest inverse association with non-aspirin NSAID usage with EA. In contrast, associations between NSAID use and EGJA were mostly null. These results are similar to individual exposures investigated in prior BEACON studies [14, 15, 17, 18, 34].

We next evaluated age-specific associations of each exposure in relation to EA. Obesity (BMI ≥30) was most strongly associated with early-onset EA (OR=4.19, 95%CI: 2.23, 7.87), with significant differences across age groups ($P_{effect\ modification}$=0.042). The

magnitude of the association was higher in early-onset EA than in later-onset patients. ORs for the other age categories ranged between 2.6–2.8. When we limited our analysis to studies including reflux variables and further adjusted models by recurrent reflux, little difference was seen in the association between BMI and EA in the youngest age group (Supplemental Table 3: OR: 2.1 vs OR: 2.3) and age remained an effect modifier ($P_{effect\ modification}$=0.002).

Alcohol consumption and number of drinks per day showed little to no associations with risk of EA among age groups <50, 50–59, and 60–69 years. However, for the age group ≥70 years the inverse association for regular drinking was stronger and gained nominal statistical significance (OR 0.62, 95%CI: 0.45, 0.85). Similar findings were found for frequency of alcohol consumption, up to and including the 5–<7 drinks per day category. However, tests for effect modification by age were not statistically significant for either ever regularly consuming alcohol ($P_{effect\ modification}$=0.17) or for frequency of alcohol consumption ($P_{effect\ modification}$=0.33).

Current and former cigarette smokers were at increased risk of EA in each age group assessed compared with never-smokers. ORs ranged between 1.81 and 3.75 for former and current smokers. Effect modification by age was observed (P=0.028), yet no obvious linear pattern across age groups was seen. Associations were strongest for 50–59 year olds and weakest for 60–69 year olds, and these differences persisted when pack-years of cigarette smoking was included in the model, albeit the P value for effect modification was slightly attenuated and not statistically significant (P=0.073).

We observed statistically significant positive associations between recurrent gastroesophageal reflux variables (≥ weekly symptoms) and EA risk for all age groups. The strongest associations were observed for early-onset EA, with ORs ranging from 6.62 to 8.06 and age was consistently a significant effect modifier ($P_{effect\ modification}$=0.02–0.04). In contrast, associations between EA and frequency of heartburn and/or regurgitation symptoms were similar across each age groups ($P_{effect\ modification}$=0.16–0.57).

Regular use of NSAIDs and aspirin were inversely associated with EA for the age group ≥ 70 years. For all other age groups assessed, weaker inverse associations of these exposures with EA risk were seen, although most of them were not statistically significant and neither were their tests effect modifications by age (P=0.09–0.12). No substantial differences for regular use of non–aspirin NSAIDs were seen by age group and were not associated.

Age-specific analyses of EGJA (Table 3) provided generally similar results to those observed for EA (Table 2). Age-specific associations of BMI, alcohol, and gastroesophageal reflux exposures in relation to EGJA were slightly attenuated when compared with those for EA, but were similar in patterns and direction. However, none of these apparent differences were statistically significant. Inverse associations were seen between users of non-aspirin NSAIDs and EGJA in older age groups (60–69 and ≥ 70) compared with non-users. However, unlike the EA analysis, no associations were observed with regular usage of aspirin.

Discussion

In this large pooled analysis of eight population-based case-control studies we found that recurrent heartburn/regurgitation and obesity were appreciably stronger risk factors for early-onset EA relative to older age categories. Conversely, low/moderate alcohol consumption and use of aspirin and NSAIDs were inversely associated with late-onset EA, although effect modifications of these associations by age were not significant. Age-specific associations with EGJA showed similar, but slightly weaker patterns and no statistically significant differences by age were observed.

To our knowledge this is the first pooled analysis aimed to evaluate and compare age-specific risk factor profiles for EGJA and one of only a few for EA. In a prior study of age-specific risk factors of EA (cases: n=356), the authors also found that obesity was associated with a younger age at cancer diagnosis [20]. Our pooled analysis corroborates that finding and provides detailed investigations of the major risk factors across multiple age groups. Although the rise in EA incidence predates the rise in obesity [36], it is still possible that obesity is implicated in more recent increases in EA incidence; as evidenced by the strong associations with BE and EA observed in prior BEACON analyses [37, 38] and other studies [39].

The predominant mechanism by which central adiposity is proposed to increase risk of esophageal cancer is by disrupting the integrity of the lower esophageal sphincter; leading to increased propensity for gastroesophageal reflux [40]. Independent of the "mechanical effect" of central adiposity on cancer risk, proinflammatory effects of excess adipose tissue may increase risk of EA via systemic proinflammatory effects [14,

[40, 41]. In this study we also observed some evidence for an effect of obesity on risk of EA that is independent of reflux symptoms.

No prior study, independent of the studies contributing to this pooled analysis, has investigated age-specific associations between recurrent heartburn/regurgitation and risk of EA. Reflux increases secretion of numerous proinflammatory cytokines such as IL-6 and TNF-α and reactive oxygen species [42-44]. As a recognized hallmark of cancer [45], inflammation induced by reflux is likely to contribute substantially to the development and progression of esophageal adenocarcinoma [46]. Among a subset of the EA patients included in this study, four SNPs in three apoptosis genes (BCL2, CASP8, and TNFRSF10A) were previously identified as significantly associated with early-onset EA (≤55 vs >55 years) [9]. Taken together, one possible explanation for our results is that patients diagnosed with EA at younger ages may have increased likelihood of genetic susceptibility to the deleterious effect of reflux, perhaps having decreased ability to expunge damaged cells via apoptosis. This process could lead to the accumulation of oncogenic mutations in the esophageal cell population, heightening the risk of early-onset EA.

An important strength of our study was the availability of individual participant data from eight population-based, case-control studies, which provided sufficient case numbers required to identify risk factor profiles for early and late-onset disease and to assess effect modification by age. Our exposure variables are believed to have a high degree of reliability, since each was constructed using a unified approach across studies and each exposure in relation to EA and EGJA has been examined and published. Our

overall results corroborate the findings of these prior studies [14, 15, 17, 18, 34] and provide confidence in our statistical approach.

However, several limitations of our analysis should be considered. We have not assessed heritability or genetic factors. These factors could induce differential residual confounding by age at diagnosis, possibly contributing to the effect modification by age effects that we observed [47-50]. The categories for age at diagnosis were selected *a priori* based on convenient cut-points for ease of interpretation, however, similar trends were observed when age-at-diagnosis categories were based on quartiles of age among controls (data not shown). It is important to note that our analysis includes self-reported symptoms of heartburn and regurgitation, yet reflux exposures can occur without apparent symptoms. Symptoms have been shown to correlate with greater severity of acid reflux exposure [51]; nonetheless our results may only apply to people with symptomatic heartburn or regurgitation.

Overall, this study confirms that smoking, obesity, recurrent or frequent heartburn/regurgitation are all associated with increased risk of EA and EGJA across all ages studied. In addition, we found evidence that recurrent heartburn/regurgitation and obesity are more strongly associated with risk of early-onset EA, compared with older age groups. Understanding the mechanisms through which obesity and reflux confer increased risks of esophageal cancer at younger ages might yield important insights for prevention and control of this cancer. Moreover, as the clinical community aims to incorporate more evidence-based health decisions, it is prudent that age-specific risk estimates be considered.

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