Cancer Epidemiology 42 (2016) 9–14

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Metabolic syndrome in relation to Barrett's esophagus and esophageal adenocarcinoma: Results from a large population-based case-control study in the Clinical Practice Research Datalink

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ARTICLE INFO

Article history:
Received 28 September 2015
Received in revised form 3 February 2016
Accepted 21 February 2016
Available online xxx

Keywords:
(MeSH): Barrett esophagus
Esophageal Cancer
Metabolic syndrome X
Obesity
Gastroesophageal reflux

ABSTRACT

Gastroesophageal reflux disease (GERD) causes local chronic inflammation that increases risks of Barrett's esophagus (BE) and esophageal adenocarcinoma (EA), yet symptomatic GERD is absent in approximately half of all such patients. Obesity exacerbates GERD and is also a component of metabolic syndrome (MetS). We evaluated the hypothesis that MetS is a GERD-independent mechanism by which obesity is associated with increased risks of BE and EA using data from the UK Clinical Practice Research Datalink. BE cases (n = 10,215) and EA cases (n = 592) were each individually matched to five population controls based on age, sex, and general practice. MetS was defined as occurrence of at least three of the following: obesity, type 2 diabetes, hypertension, and high cholesterol. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. MetS was marginally associated with BE (OR = 1.12, 95%CI 1.00–1.25). Similar effects were found for the individual component factors of obesity, hypertension, and high cholesterol. History of GERD modified the association ($P_{\text{-effect modification}}$ <1E–5), with the MetS-BE association confined to patients without a history of GERD (OR = 1.33, 95%CI 1.12–1.58). No association between MetS and risk of EA was detected in the main or stratified analyses. In this large population-based case-control study, individuals with MetS had a marginally increased risk of BE in the absence of GERD. The systemic inflammatory state (MetS) may represent a reflux-independent inflammatory pathway that increases the risk of BE. MetS did not increase risk of EA in this study population.

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1. Introduction

Chronic inflammation has a central role in the etiology of esophageal adenocarcinoma (EA) and the precursor lesion Barrett's esophagus (BE). Evidence suggests that chronic inflammation triggered by gastroesophageal reflux disease (GERD) not only predisposes to developing BE, but that the ensuing proinflammatory state [1] and oxidative stress [2] have roles in malignant transformation [3].

Although GERD is a key risk factor of EA [4–6], symptomatic GERD is infrequent or absent in 40–48% of people who develop EA [6,7]. Likewise, although GERD is a known risk factor of BE [8–10], more than half of patients diagnosed with BE have an indication for endoscopy other than GERD [11]. These data suggest that other inflammatory mechanisms may exist in the pathogenesis of BE and EA.

Another significant risk factor of BE and EA is abdominal obesity, which causes a state of systemic inflammation, characterized by increased circulating proinflammatory cytokines including C-reactive protein, leptin, interleukin-6, and tumor necrosis factor-alpha. The proinflammatory effects of excess adipose tissue are a hallmark of MetS [12], which itself is a cluster of metabolic disorders that includes abdominal obesity, hypertension, lowered high density lipoprotein (HDL) cholesterol, elevated triglycerides, and elevated fasting glucose [13]. MetS is a better predictor of total mortality than its individual components [14], and may increase the risk of BE [15–18] and EA [19].

Abbreviations: BE, Barrett's esophagus; CPRD, Clinical Practice Research Datalink; EA, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; MetS, metabolic syndrome.

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http://dx.doi.org/10.1016/j.canep.2016.02.008
1877-7821/Published by Elsevier Ltd.

We recently demonstrated that MetS increased risks of BE [18] and EA[1] in an older-aged US population (SEER-Medicare), associations driven by and confined to those without a history of GERD. We proposed that in those without symptomatic GERD, systemic inflammation—represented by MetS—increases the risk for normal esophageal tissues to develop metaplasia and eventually cancer.

The few studies that have evaluated the association of MetS in relation to BE or EA have either not been population-based [15–17], did not include the full age-range of patients [18] or did not investigate potential effect-modification by GERD [19–21]. Therefore, using data collected prospectively in the Clinical Practice Research Datalink (CPRD), which contains longitudinal medical records of virtually all UK primary care events of >8 million subjects of all ages, we investigated MetS in relation to risks of BE and EA separately and evaluated whether GERD was an effect-modifier of these relationships.

2. Methods

2.1. Data source

The CPRD, formerly known as the General Practice Research Database (GPRD), is one of the world's largest primary care electronic medical record databases. The CPRD contains longitudinal medical records of health care events including diagnoses, referrals, prescriptions, diagnostic testing, and lifestyle information for participating primary care practices and linkage to cancer registries in the UK since 1989. In addition, as part of the UK healthcare system, medical diagnoses and treatments at locations other than the General Practice are reported back to such and electronically-recorded in the CPRD. Diagnoses in the CPRD are identified by READ codes and generally have high validity, especially for chronic diseases including cancer [22–24]. The database has been described in extensive detail elsewhere [25].

2.2. Study population

Our study included all people without type 1 diabetes in the CPRD from 01/01/1992 through 05/30/2012. All subjects were required to have a minimum of three years of up-to-standard medical history in the CPRD prior to diagnosis of BE, esophageal cancer, or match date for controls. Two case groups were defined: BE and EA cases. Five population controls were incidence density matched to each BE case and, separately, to each EA case based on date of diagnosis (exact), birth year, sex, year of entry in CPRD (same as case or earlier), and general practice, with replacement between risk-sets. For cases, the date of diagnosis was deemed the "index" date. Controls were assigned the index date of their matched case.

2.3. Case definitions

BE was defined as one or more instances of the Read Code J101611. BE cases were excluded if they had one or more instances of the non-specific "Barrett's ulcer" (J102500) prior to BE or if BE was reported by the patient at an initial GP visit (i.e. history of BE prior to start of patient record) in order to reduce the possibility of contamination of the incident BE case group with prevalent cases. Those with a history of cancer (except non-melanoma skin cancer) prior to BE were excluded. Those diagnosed with esophageal cancer within six months after their initial BE diagnosis were also excluded because this short time interval infers concurrent diagnoses, and incident esophageal cancer is a distinct case group in this study design. We also conducted a sensitivity analysis in which the BE case definition required two or more BE diagnosis codes for inclusion.

Individuals with an esophageal cancer READ code were identified as potential EA cases. Since there are two major histologies of esophageal cancer, squamous cell and adenocarcinoma, each with distinct localization and etiologies, we required either a prior diagnosis of BE or a READ histology code (BB5.00; BB5.11; BB52.00) for "adenocarcinoma" ±one month from the esophageal cancer diagnosis date. EA cases were excluded if a READ histology code for "squamous cell" was recorded within one month of the esophageal cancer diagnosis date.

2.4. Control definition

Potential population control subjects for the BE and EA case groups were excluded if they had any instance of BE (J101611) or "Barrett's ulcer" of the esophagus (J102500) prior to their index date or if BE was reported by the patient and documented at an initial GP visit (i.e. history of BE).

All potential controls were required to be cancer-free (excluding non-melanoma skin cancer) up to their index date and not diagnosed with esophageal cancer during the six months following their index date (as a balance to the BE case group selection criterion).

2.5. Definition of metabolic syndrome

MetS was defined using the U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [26] which is the presence of at least three of the following conditions: abdominal obesity, hypertension, lowered HDL cholesterol, elevated triglycerides, and elevated fasting glucose. Waist and hip size are not available in the CPRD. However the International Diabetes Federation suggests that if body mass index (BMI) is $\geq$30 kg/m^2, central obesity can be assumed, thus we used this as a surrogate measure [27]. Type 2 diabetes was used to indicate "elevated fasting glucose" and was assessed using the READ codes for diagnosis. High cholesterol, which is a composite of elevated triglycerides and elevated low-density lipoprotein (LDL) cholesterol, was used to indicate "elevated triglycerides". HDL cholesterol was not specified in the CPRD data and thus lowered HDL cholesterol was not used in our definition of MetS. This approach is similar to analyses conducted in SEER-Medicare data, which also does not capture lowered HDL cholesterol [18]. A subject was considered exposed to either high cholesterol or hypertension if he or she received both a diagnostic READ code for the condition and a prescription for an appropriate medication. The date of the treatment was considered the first date of exposure. An individual was considered exposed to MetS at the first date on which three or more conditions were present within the individual's exposure window of opportunity, explained further below.

2.6. Definition of gastroesophageal reflux (GERD)

GERD-related READ codes for "heartburn", "esophagitis", "reflux", "reflux and esophagitis", and "peptic ulcer of the esophagus" were used to define GERD. In a sensitivity analysis, we restricted the analysis to subjects who received at least four prescriptions for anti-GERD medications (e.g., proton pump inhibitors [PPIs], H2 receptor antagonists [H2RAs]), regardless of documentation of a GERD-related READ code.

[1] Manuscript submitted for publication.