Risk of Esophageal Adenocarcinoma Decreases With Height, Based on Consortium Analysis and Confirmed by Mendelian Randomization

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BACKGROUND & AIMS: **Risks for some cancers increase with height. We investigated the relationship between height and risk of esophageal adenocarcinoma (EAC) and its precursor, Barrett's esophagus (BE).**

METHODS: **We analyzed epidemiologic and genome-wide genomic data from individuals of European ancestry in the Barrett's and Esophageal Adenocarcinoma Consortium, from 999 cases of EAC, 2061 cases of BE, and 2168 population controls. Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for associations between height and risks of EAC and BE. We performed a Mendelian randomization analysis to estimate an unconfounded effect of height on EAC and BE using a genetic risk score derived from 243 genetic variants associated with height as an instrumental variable.**

RESULTS: **Height was associated inversely with EAC (per 10-cm increase in height: OR, 0.70; 95% CI, 0.62–0.79 for men and OR, 0.57; 95% CI 0.40–0.80 for women) and BE (per 10-cm increase in height: OR, 0.69; 95% CI, 0.62–0.77 for men and OR, 0.61; 95% CI, 0.48–0.77 for women). The risk estimates were consistent across strata of age, education level, smoking, gastroesophageal reflux symptoms, body mass index, and weight. Mendelian randomization analysis yielded results quantitatively similar to those from the conventional epidemiologic analysis.**

CONCLUSIONS: **Height is associated inversely with risks of EAC and BE. Results from the Mendelian randomization study showed that the inverse association observed did not result from confounding factors. Mechanistic studies of the effect of height on EAC and BE are warranted; height could have utility in clinical risk stratification.**

Keywords: Esophageal Cancer; Etiology; Risk Factors; Sex Differences.

Abbreviations used in this paper: **BE, Barrett's esophagus; BEACON, Barrett's and Esophageal Adenocarcinoma Consortium; BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GER, gastroesophageal reflux; GRS, genetic risk score; IV, instrumental variable; OR, odds ratio; SNP, single-nucleotide polymorphism.**

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Esophageal adenocarcinoma (EAC) incidence increased 8-fold in the United States from 1973 to 2008.[1] Incidence is up to 8-fold higher in males than in females[2]; however, incidence rates for EAC continue to increase in both males and females.[1] It is presumed that almost all cases of EAC arise within a metaplastic epithelium of the esophagus known as Barrett's esophagus (BE). Gastroesophageal reflux (GER), obesity, and, to a lesser extent, tobacco smoking are the primary risk factors for EAC and BE.[3–7] On the other hand, CagA-positive *Helicobacter pylori* colonization and regular use of aspirin and nonsteroidal anti-inflammatory drugs are associated with reduced risks.[8–11] A better understanding of risk factors for EAC may allow for both improved risk stratification and better insight into the pathogenesis of this lethal condition.

Recently, attention has focused on the relationship between attained height and cancer. A 2011 meta-analysis of 11 prospective studies found that the risk of all cancers combined increased by 10% and 15% per 10-cm increase in height in males and females, respectively.[12] Indeed, height may explain up to one half of the excess risks for all cancers in males.[13] Furthermore, height also is associated with increased risk of all-cancer mortality.[14] Although height is an independent risk factor and prognostic factor for cancers of the colorectum, breast, endometrium, prostate, ovary, and melanoma, studies have reported an inverse association between height and gastric cancer and with cancers of the head and neck.[14–16]

The association between height and esophageal cancer is unclear. In the largest studies to date, height was not associated with the risk of esophageal cancer in the Million Women Study[12] or with mortality from esophageal cancer in the Emerging Risk Factor Collaboration study.[14] However, the association with height may vary by histologic subtype because EAC and esophageal squamous cell carcinoma (ESCC) have different risk profiles. Height partly may explain the sex difference for EAC, although few studies have considered EAC and ESCC separately in relation to height, and those that have done so were limited by small numbers of cases. Height was associated inversely with risks of EAC and ESCC in one study,[17] whereas in another study height was associated inversely with EAC but not with ESCC.[18] In the National Institutes of Health AARP Diet and Health Study, there was evidence of an inverse association between height and EAC, although this did not reach statistical significance.[19] In a prospective study in the general Norwegian population, a statistically significant inverse association was observed between height and both EAC and ESCC risks in males. In females, a similar relationship (albeit weaker and not statistically significant) was seen for EAC but not ESCC.[20] For BE, there was no association with height in 2 previous studies.[21,22] In this study, we aimed to clarify the association between height and risks of EAC and BE.

We took advantage of epidemiologic and genome-wide genomic data available from a large international consortium of BE and EAC studies—the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, http://beacon.tlvnet.net/). We undertook a pooled analysis of original epidemiologic data from 14 population-based case-control and cohort studies in BEACON to examine the association between height and risks of EAC and BE. Because attained height varies by or is influenced by sex, smoking, socioeconomic status, and various early life exposures, the risk estimates for the height-EAC and height-BE associations obtained from conventional epidemiologic analyses may be confounded. We therefore additionally performed a Mendelian randomization analysis using a genetic risk score (GRS) (derived from 243 single-nucleotide polymorphisms [SNPs] associated with height in European populations) (Wood AR et al, unpublished data, 2013) as an instrumental variable (IV) for height to obtain unconfounded risk estimates for height-EAC and height-BE associations.[23–25] The IV method helps to overcome confounding because alleles are allocated randomly from parents to offspring and are not associated with the wide range of risk factors that may confound the association with height.[23,24,26] Further, the genetic variants are measured reliably and are not affected by disease status or by study design.[27]

Methods

Study Population

Data concerning EAC and BE cases and controls were obtained from 14 epidemiologic studies in BEACON. To avoid confounding from population stratification, we restricted our analyses to individuals of European ancestry (confirmed in samples using principal components analysis) that were included in the recent genome-wide association study conducted by BEACON (Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study).[28] Histologic confirmation of EAC was performed for all EAC studies.[6] Similarly, BE was confirmed histologically via identification of goblet cells in metaplastic columnar epithelium in a biopsy sample taken from the esophagus.[7] A total of 1516 EAC cases, 2416 BE cases, and 2187 controls were available for pooling. We excluded participants with missing information on weight or height (517 EAC cases, 355 BE cases, and 18 controls) and those with extreme values (1 male control with height < 130 cm). Analyses thus were based on 999 EAC cases, 2061 BE cases, and 2168 controls (Table 1). The study was approved by the institutional review boards or research ethics committees of each participating institution.

Statistical Analysis

The exposure and outcome data from the 14 studies were pooled and analyses of the single data set were performed separately for EAC and BE and by sex.