

Taller Adults May Have Lower Risk of Esophageal Adenocarcinoma

April 21, 2014

JM Kocarnik

Taller adult height has been associated with increased risk for several cancer types. Physiologically, this increased risk may stem from either higher cell turnover, mediated by growth factors or steroid hormones, or from simply having a larger number of cells. Height is also considered a proxy measure for various exposures that affect cancer risk. Esophageal adenocarcinoma, a subtype of esophageal cancer, is eight times more common in men than women, suggesting that height may be a risk factor for this cancer. In a recent study published in *Clinical Gastroenterology and Hepatology*, Drs. Aaron Thrift and Thomas Vaughan in the Public Health Sciences Division report that greater height is actually associated with a decreased risk of esophageal adenocarcinoma. Previous studies have not found an association between esophageal cancer and height, though they did not evaluate whether this relationship varied by histologic subtype. The authors followed-up this surprising finding using a Mendelian randomization analysis, which further supported this inverse association.

To evaluate the effect of height on cancer risk, the authors utilized data from 14 studies participating in the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). The self-reported adult heights of roughly 2000 Barrett's Esophagus and 1000 esophageal adenocarcinoma cases were compared with that of 2200 controls. Using traditional epidemiologic methods, the authors found that the risks for both conditions were significantly lower in both men and women with greater height (see figure). For each 10 cm increase in height, risk of esophageal adenocarcinoma was 30% lower in men and 43% lower in women. A similar reduction in risk with greater height was also seen for Barrett's Esophagus, a precursor condition of the esophagus that precedes almost all cases of esophageal adenocarcinoma. These inverse associations remained consistent across strata of various risk factors for these conditions, including body mass index, weight, smoking status, and gastroesophageal reflux.

While the consistency of these findings was reassuring, it remained possible that these results were not due to height, but instead reflective of confounding factors such as childhood nutrition, illness, and other early life exposures that might impact adult height. To address this issue, the authors

additionally evaluated these relationships using Mendelian randomization methods. Said lead author Thrift, "this analytic approach allows investigators to test whether an association between a traditional risk factor (e.g. height) and an outcome (e.g. esophageal adenocarcinoma) may be the result of confounding by other factors, or may indeed be an independent association." Because these genetic variants are randomly allocated at birth, they are not associated with other potentially confounding factors. As such, demonstration of an association between the genetic risk score characterizing the exposure and the outcome of interest provides confirmatory evidence of the relationship between the exposure and the outcome.

The authors created a weighted genetic risk score that acts as an instrumental variable representing the predicted height, rather than using self-reported height. This risk score was calculated by combining genotype information from 243 height-related genetic variants, weighted by the effect size of their previously identified association with height. Though not statistically significant themselves, the results of the genetic risk score analyses for height and esophageal adenocarcinoma risk were similar to the epidemiologic results: for each 10 cm increase in height, risk of esophageal adenocarcinoma was 27% lower in men and 37% lower in women. A similar reduction in risk with greater height was again seen for Barrett's Esophagus, and statistical tests showed no significant difference between the effect estimates of the epidemiologic and Mendelian randomization analyses. From this, said Thrift, "we conclude that height is inversely associated with risk of esophageal adenocarcinoma, both in men and women, and that this association is not due to confounding from known risk factors or bias."

While these results provide epidemiologic evidence of an association, the mechanism through which greater height might lower esophageal adenocarcinoma risk is not known. The authors hypothesize that shorter stature might create greater intra-abdominal pressure, which may promote development of a hiatal hernia and subsequent gastroesophageal reflux. Alternatively, perhaps shorter persons may more easily become obese than taller people. Certainly, additional research will be needed to further characterize these risks. In the meantime, said Thrift, "we believe that our findings have potential clinical utility in risk stratification models for esophageal adenocarcinoma and its precursor, Barrett's esophagus, and we are planning to incorporate height into existing risk models for these diseases."

Other PHS investigators contributing to this project were Drs. Lynn Onstad and Brian Reid.

Citation:

[Thrift AP, Risch HA, Onstad L, Shaheen NJ, Casson AG, Bernstein L, Corley DA, Levine DM, Chow WH, Reid BJ, Romero Y, Hardie LJ, Liu G, Wu AH, Bird NC, Gammon MD, Ye W, Whiteman DC, Vaughan TL.](#) 2014. Risk of esophageal adenocarcinoma decreases with height, based on consortium analysis and confirmed by Mendelian randomization. *Clin Gastroenterol Hepatol* 2014 Feb 12. doi: 10.1016/j.cgh.2014.01.039. [Epub ahead of print]

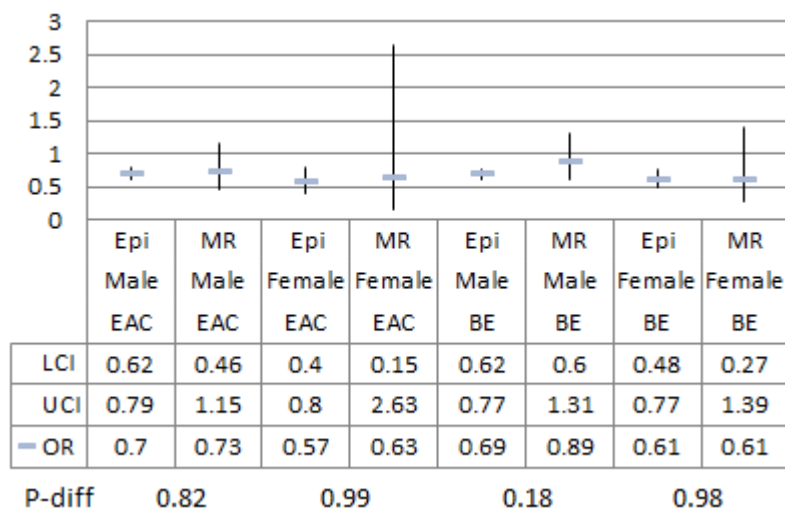


Image provided by Dr. Jonathan Kocarnik

Comparison of odds ratio (OR) and 95% confidence interval (LCI – UCI) estimates of the association between height and esophageal adenocarcinoma (EAC) or Barrett’s esophagus (BE), stratified by sex, as evaluated using traditional epidemiologic (Epi) or Mendelian randomization (MR) approaches (P-diff > 0.05 depicts no statistical difference between ORs from these two methods).