Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis CME

Siddharth Singh, MD,[1,*] Palaniappan Manickam, MD,[2,*] Anita V. Amin, MD,[2] Niharika Samala, MD,[2] Leo J. Schouten, MD,[3] Prasad G. Iyer, MD, MS,[1] Tusar K. Desai, MD[2]

Rochester, Minnesota, USA

Background: The natural history of low-grade dysplasia (LGD) in patients with Barrett's esophagus (BE) is unclear.

Objective: We performed a systematic review and meta-analysis of studies that reported the incidence of esophageal adenocarcinoma (EAC) and/or high-grade dysplasia (HGD) among patients with BE with LGD.

Design: Systematic review and meta-analysis of cohort studies.

Patients: Patients with BE-LGD, with mean cohort follow-up $\geq$2 years.

Main Outcome Measurements: Pooled incidence rates with 95% confidence intervals (CI) of EAC and/or BE-HGD.

Results: We identified 24 studies reporting on 2694 patients with BE-LGD, with 119 cases of EAC. Pooled annual incidence rates of EAC alone and EAC and/or HGD in patients with BE-LGD were 0.54% (95% CI, 0.32-0.76; 24 studies) and 1.73% (95% CI, 0.99-2.47; 17 studies). The results were stable across study setting and location and in high-quality studies. Substantial heterogeneity was observed, which could be explained by stratifying based on LGD/BE ratio as a surrogate for quality of pathology; the pooled annual incidence rates of EAC were 0.76% (95% CI, 0.44-1.09; 14 studies) for LGD/BE ratio $<$0.15 and 0.32% (95% CI, 0.07-0.58; 10 studies) for LGD/BE ratio $>$0.15. The annual rate of mortality not related to esophageal disease in patients with BE-LGD was 4.7% (95% CI, 3.2-6.2; 4 studies).

Limitations: Substantial heterogeneity was observed in the overall analysis.

Conclusion: The incidence of EAC among patients with BE-LGD is 0.54% annually. The LGD/BE ratio appears to explain the variation observed in the reported incidence of EAC in different cohorts. Conditions not related to esophageal disease are a major cause of mortality in patients with BE-LGD, although additional studies are warranted. (Gastrointest Endosc 2014;79:897-909.)

Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IR, incidence rate; LGD, low-grade dysplasia.

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*Drs Singh and Manickam contributed equally to the article.

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Current affiliations: Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota (1), Department of Internal Medicine, William Beaumont Hospital/Oakland University School of Medicine, Royal Oak, Michigan, USA (2), Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, The Netherlands (3).

Reprint requests: Tusar K. Desai, MD, Division of Gastroenterology, Oakland University William Beaumont School of Medicine, 3535 W. 13 Mile Road, Suite 202, Royal Oak, MI 48073.

Barrett's esophagus (BE) is a well-identified precursor for esophageal adenocarcinoma (EAC).[1] The risk of EAC in patients with BE is highly variable, and presence and grade of dysplasia are key predictors of risk of progression to EAC. Although the estimated annual risk of EAC in patients with nondysplastic BE is 1 in 300 patients,[2] the corresponding risk in patients with BE with high-grade dysplasia (HGD) is 1 in 15 patients.[3] The risk of progression to EAC in patients with BE with low-grade dysplasia (LGD) is poorly estimated, with annual incidence rates ranging from <0.2% to more than 3% annually in large studies alone.[4,5] A previous meta-analysis of 16 studies (including surgical series) had estimated the annual incidence rate of EAC in patients with BE-LGD to be 1.6%, with considerable heterogeneity.[6] However, since then, several large, population-based studies have been published, with reported lower incidence of EAC in these patients.[7,8] It is important to accurately estimate the incidence of EAC as well as causes of mortality in patients with BE-LGD to decide on appropriate treatment and surveillance strategy.

One of the reasons for wide variability in the reported risk of EAC in patients with BE-LGD is significant interobserver variability in the diagnosis of LGD among pathologists, with most cases of LGD being mistaken for nondysplastic or "indefinite for dysplasia" BE, especially in the presence of esophageal inflammation.[9] Hence, it is likely that in for studies in which the diagnosis of LGD was made liberally (ie, a high proportion of patients in the cohort were diagnosed with BE-LGD), observed EAC incidence would be low (because several patients with nondysplastic BE with its associated low risk of progression to EAC may have been misclassified as having BE-LGD). In contrast, for studies in which a stringent diagnosis of BE-LGD is made, the estimated risk of progression to EAC may be higher. One surrogate of the presence of selection bias and quality of pathology may be estimating a ratio of LGD to BE (LGD/BE), that is, the proportion of patients with LGD in the entire BE cohort. Population-based studies estimate a prevalence rate of BE-LGD of approximately 13% to 15%.[10,11]

Hence, to better understand the risk of EAC and/or HGD in patients with BE-LGD as well as to estimate the rate of mortality from conditions not related to esophageal disease in these patients, we performed a systematic review and meta-analysis of cohort studies addressing this question. Moreover, we also estimated differences in the risk of EAC based on LGD/BE ratio and identified BE-related factors associated with risk of progression to EAC, reported in the literature.

Take-home Message

- The annual incidence of esophageal adenocarcinoma (EAC) and EAC and/or high-grade dysplasia in patients with Barrett's esophagus/low-grade dysplasia (BE-LGD) is 0.54% and 1.73%, respectively. The risk of progression to EAC is dependent on the LGD/BE ratio (proportion of patients with LGD in the entire BE cohort); the estimated rate is 0.76% if the ratio is <0.15 and 0.32% if the ratio is >0.15. This may serve as a surrogate for quality of pathology.
- The annual rate of mortality from causes not related to esophageal disease is high (4.7%) in patients with BE-LGD. Surveillance strategies in patients with BE-LGD may need to be reconsidered, especially in light of high causes of mortality not related to esophageal disease.

METHODS

Search strategy

We conducted a systematic literature search of MEDLINE (1966 to December 31, 2012) and EMBASE (1988 to December 31, 2012) for all relevant articles on the risk of EAC in patients with BE. Key words used in the search included a combination of "Barrett's esophagus," "Barrett's neoplasia," "Barrett's epithelium," or "intestinal metaplasia" and "esophageal cancer," "esophageal adenocarcinoma," or "esophageal neoplasia." The search was restricted to the studies in human participants published in the English language in peer-reviewed journals. Two authors (A.V.A. and T.K.D.) independently reviewed the title and abstract of studies identified in the primary search, to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria (details later). The full text of the remaining articles was examined to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus, and in discussion with a coauthor (S.S.). Next, the bibliographies of the selected articles as well as systematic and narrative review articles on the topic were manually searched for additional articles. Conference proceedings, which did not undergo peer review, were excluded from our analysis. In case of missing information, attempts were made to contact the authors with specific questions regarding their studies.

Study selection

In this meta-analysis, we included cohort studies that met the following specific criteria: (1) specified number of patients with biopsy-proven BE-LGD; (2) reported mean follow-up of a minimum of 2 years after the diagnosis of BE-LGD; and (3) specified number of patients with BE-LGD who developed EAC and/or HGD, along with the total person-years of follow-up for the subset of patients with BE-LGD or the mean/median follow-up of the BE-LGD or the entire BE cohort. Only cases of EAC and/or HGD that occurred >6 months after diagnosis were included. We excluded the following: (1) case-control studies, cross-sectional studies, and case series; (2) studies with a minimum follow-up of <2 years; and (3) studies that provided insufficient data to allow estimation of the incidence rate (IR) of EAC and/or HGD. We also excluded surgical series