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Journal

The American Journal of Gastroenterology, 119(4)

ISSN

0002-9270

Authors

Low, Eric E

Demb, Joshua

Shah, Shailja C

et al.

Publication Date

2024-04-01

DOI

10.14309/ajg.0000000000002591

Peer reviewed

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Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2025 April 01.

Published in final edited form as:

Am J Gastroenterol. 2024 April 01; 119(4): 635–645. doi:10.14309/ajg.0000000000002591.

Risk of Esophageal Cancer in Achalasia: A Matched Cohort Study Utilizing the Nationwide Veterans Affairs Achalasia Cohort (VA-AC)

Eric E. Low[1,2], **Joshua Demb**[1,2], **Shailja C. Shah**[1,2], **Lin Liu**[1,3], **Ranier Bustamante**[1], **Rena Yadlapati**[2], **Samir Gupta**[1,2,4]

[1]Jennifer Moreno Veteran Affairs San Diego Healthcare System, San Diego, CA, USA

[2]University of California, San Diego Division of Gastroenterology, La Jolla, CA, USA

[3]Division of Biostatistics and Bioinformatics, Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, San Diego, CA, USA

[4]University of California, San Diego Moores Cancer Center, La Jolla, CA, USA

Abstract

Introduction—Achalasia is a postulated risk factor for esophageal cancer (EC); however, EC-associated risk in achalasia is understudied. We aimed to evaluate EC risk among individuals within the nationwide Veterans Affairs Achalasia Cohort (VA-AC).

Methods—We conducted a matched cohort study among US Veterans ≥18 years from 1999–2019. Individuals with achalasia were age- and sex-matched 1:4 to individuals without achalasia. Follow-up continued from study entry until diagnosis with incident/fatal EC (primary outcome), death from non-EC related causes, or end of the study follow up (12/31/2019). Association between achalasia and EC risk was examined using Cox regression models.

Results—We included 9,315 individuals in the analytic cohort (median age 55 years; 92% male): 1,863 with achalasia matched to 7,452 without achalasia. During median 5.5 years follow-up, 17 esophageal cancers occurred (3 esophageal adenocarcinoma (EAC), 12 squamous cell carcinoma (SCC), 2 unknown-type) among individuals with achalasia, compared to 15 esophageal cancers (11 EAC, 1 SCC, 3 unknown-type) among those without achalasia. EC incidence for those with achalasia was 1.4 per 1,000 person-years, and median time from achalasia diagnosis to EC development was 3.0 years (Q1-Q3: 1.3–9.1). Individuals with achalasia had higher cumulative EC

Correspondence: Samir Gupta, MD, MSCS, AGAF, Address: 3350 La Jolla Village Drive, MC 111D, San Diego, CA 92161, s1gupta@health.ucsd.edu Phone: 858.552.8585 ×3280.

Specific author contributions: Eric E. Low[1–6]; Joshua Demb[1,3,5,6]; Shailja C. Shah[3,5]; Lin Liu[5,6]; Ranier Bustamante[2,7]; Rena Yadlapati[1,3,5,8]; Samir Gupta[1–3,5,8]

[1] Study concept and design
[2] Acquisition of data
[3] Analysis and interpretation of data
[4] Drafting of the manuscript
[5] Critical revision of the manuscript for important intellectual content
[6] Statistical analysis
[7] Administrative, technical, or material support
[8] Study supervision

*All authors approved the final manuscript

Guarantor of the article: Samir Gupta, MD, MSCS, AGAF

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incidence at 5, 10, and 15-years follow-up compared to individuals without achalasia, and EC risk was 5-fold higher (hazard ratio 4.6, 95% CI 2.3–9.2).

Discussion—Based on substantial EC risk, individuals with achalasia may benefit from a high index of suspicion and endoscopic surveillance for EC.

Keywords

Manometry; Esophageal motility; Epidemiology; Cancer risk; Outcomes

Introduction

Esophageal cancer is the 5th most common gastrointestinal cancer with an incidence of 4.2 new cases per 100,000 persons per year in the United States (US), and has the second lowest 5-year survival among all cancers, at just 20.6%.[1]

Achalasia is a well-characterized esophageal motility disorder with an incidence of approximately 1 per 100,000 persons per year and a prevalence of 10 per 100,000 persons.[2] Achalasia has been postulated to confer an increased risk for esophageal cancer, both for squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC), compared to the general population without achalasia.[3–8] The hypothesized pathophysiology for higher SCC risk in those with achalasia relates to disrupted esophageal physiology leading to stasis esophagitis, and for EAC, the postulated risk relates to poor clearance of gastroesophageal reflux.[6–8] Diagnosis of esophageal cancer in individuals with already established achalasia may also be delayed, as worsening dysphagia symptoms are often attributed to recurring or deteriorating achalasia.[9] Current American College of Gastroenterology (ACG) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines recommend, independently, against routine endoscopic surveillance for esophageal carcinoma in patients with achalasia based on low and moderate evidence, respectively.[10,11]

Esophageal cancer risk factors and outcomes among individuals with achalasia have been understudied due to a lack of large, validated cohorts with longitudinal follow-up. Currently, there are no large US cohorts evaluating esophageal cancer incidence, stage, and mortality in individuals with achalasia compared to those without achalasia. Our aim was to evaluate the risk of esophageal cancer among individuals with vs without achalasia utilizing a large, nationwide achalasia cohort – the Veterans Affairs Achalasia Cohort (VA-AC)[12] – in order to address existing evidence gaps related to achalasia and subsequent esophageal cancer risk.

Methods

Study Design and Data Sources

We conducted a retrospective matched cohort study of adult US Veterans aged ≥18 years receiving care within the Veterans Health Administration (VHA) between 10/1/1999 and 12/31/2019. The VHA is one of the largest integrated healthcare systems in the US.[13] The VHA electronic health record system allows access to comprehensive longitudinal medical information, including pharmacy files, medical encounters, procedures, imaging, and anthropomorphic data, for all individuals receiving care through the VHA, irrespective

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of geographic location. These data are harmonized and accessible through a unified database called the Corporate Data Warehouse (CDW). The CDW continually undergoes regular quality checks for accuracy to provide rigorous data for clinical research.

We used a matched cohort study design to measure the association between achalasia (exposure) and esophageal cancer risk (primary outcome). Matched cohort designs ensure balance of matched covariate distributions across exposure groups, enabling an *a priori* stratified analysis with a smaller sample size to maximize analytic efficiency.[14] Additionally, matching based on study entry date ensures comparable start to follow-up across exposure groups where temporal secular trends in guidelines and quality of care would be similar.[15,16] Accordingly, we matched individuals with a diagnosis of achalasia[12] to individuals without a diagnosis of achalasia based on the exposed subject's index International Classifications of Diseases (ICD) code date for achalasia (a proxy for achalasia diagnosis date). Matched covariates included sex, year of birth, and the first VA visit date (+/− 180 days). We matched according to the ratio of 1 achalasia subject (exposed) to 4 non-achalasia subjects (unexposed).[17,18] The Supplemental Figure provides a detailed illustration of the match design. The 'MatchIt' package in R version 4.0.2 was used to conduct matching.[19]

Demographic information, anthropometric data, free-text procedure and pathology notes, and relevant dates were compiled from VHA data resources. This was further supplemented with cause-specific mortality information collected from linkage to the National Death Index (NDI).

Achalasia Analytic Cohort

The achalasia analytic cohort included Veterans from a previously validated nationwide cohort of 2,100 individuals with a diagnosis of achalasia between 10/1/1999 and 12/31/2019, called the VA-AC.[12] Briefly, the approach used to identify achalasia cases for the cohort utilized a combination of 3 or more ICD codes in the subject's lifetime plus a Current Procedural Terminology (CPT) code for esophageal manometry. We demonstrated that this approach achieves a positive predictive value of 94% for identifying patients with true achalasia diagnoses as defined by Chicago Classification version 4.0.[12]

Matched Clusters

For each individual with achalasia, we sampled, with replacement, 4 matched individuals without an achalasia diagnosis (i.e. individuals who lacked an ICD code for achalasia as well as a CPT code for esophageal manometry at any time during their VHA care[12]) among those alive in the VA database on the index date of achalasia diagnosis for the corresponding exposed individual. Matching with replacement means a given unexposed (non-achalasia) individual may be used as a match for more than one exposed (achalasia) individual, thus allowing for improved quality of matching and a decrease in potential bias.[20] Each successful matching of 1 individual with achalasia to 4 individuals without achalasia constituted a matched cluster. If an individual with achalasia was not successfully matched to 4 individuals without achalasia based on our matching criteria, then the given individual with achalasia, and the potential matched individuals, were excluded from the analytic cohort. Of the 2,100 individuals in the VA-AC, 1,863 were successfully matched

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to 4 individuals without achalasia and comprise the achalasia analytic cohort in this study. Follow-up of each matched cluster started on index inclusion date. The follow-up ended at the occurrence of the outcome (incident or fatal esophageal cancer) for cases, and was censored at death from a non-esophageal cancer related cause or end of the study observation period (12/31/2019), whichever occurred first. We excluded any individual with esophageal cancer prior to the index date.

Esophageal Cancer Outcomes

Primary outcome was time to incident or fatal esophageal cancer diagnosis on follow up, irrespective of histologic type. Exploratory analyses of outcomes were performed for cancer histology type (SCC vs EAC). All esophageal cancer cases were identified via the CDW Oncology Domain and the NDI. The CDW Oncology Domain contains cancer diagnoses and cancer-specific mortality data from local VA cancer data abstractions.[21] The NDI is a central computerized index of cause-specific death record information maintained by the Centers for Disease Control and Prevention (CDC).[22] All esophageal cancer cases were manually reviewed for verification as well as to determine histology (SCC or EAC), location, and cancer stage. Cases missing histological information were characterized as "unknown histology." Cancer staging was characterized using Surveillance, Epidemiology, End Results Program (SEER) summary stage schema for esophageal cancer.[1] Esophageal cancer-related mortality was also verified with manual chart review. Non-esophageal cancer-related mortality was ascertained via the NDI.

Covariates

Baseline covariates included age, sex, race, ethnicity, body mass index (BMI), and smoking status, and were collected at the study entry date. Lifetime diagnoses of Barrett's esophagus (BE) and candida esophagitis, based on validated administrative claims codes, were also collected for anticipated *post-hoc* analyses.

BMI data were derived based on previously validated algorithms.[23,24] Smoking status was characterized using structured data from the VHA Health Factors database, which categorizes individuals as 'current smokers', 'former smokers' or 'never smokers'.[25] Individuals with BE and/or candida esophagitis were ascertained using combinations of administrative codes (Supplemental Methods).

Statistical Analysis

Univariate analyses to compare individuals with achalasia compared to those without achalasia were conducted using Wilcoxon rank-sum tests or Chi-squared tests for continuous and categorical variables, respectively. Follow-up of each matched cluster started on index date and continued until esophageal cancer diagnosis or censoring event, whichever occurred first. Primary analyses included 5-, 10-, and 15-year cumulative esophageal cancer incidence measures and corresponding 95% confidence intervals (95% CI) derived using Kaplan-Meier estimation. Cumulative incidence rates were compared between individuals with vs without achalasia and used to estimate risk differences. Cox proportional hazard models were used to estimate esophageal cancer hazard ratios (HRs) and corresponding 95% CI, accounting for similar covariate distributions of matched clusters using cluster-specific

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random intercepts.[26] For EAC-specific risk, a logistic regression model was fitted due to the violation of proportional hazards assumption, and odds ratio (OR) and corresponding 95% CI were estimated. Analyses were performed removing esophageal cancer diagnoses within 90 days of index achalasia diagnosis to account for possible pseudoachalasia. Pseudoachalsia is a condition where the esophageal dysmotility characteristic of achalasia is due to a mechanical factor such as an infiltrative malignancy and not attributable to idiopathic degeneration of inhibitory neurons of the esophageal submucosal myenteric plexus.[27] Following our primary analyses, an additional sensitivity analysis was performed removing cancer diagnoses within 1 year of index achalasia diagnosis to account for pseudoachalasia.

Exploratory analyses were subsequently performed to evaluate esophageal cancer risk by histologic type as well as risk of esophageal cancer-related mortality. Additionally, descriptive assessments of treatment outcomes and comorbidity associations were performed after manual review of all esophageal cancer cases.

All analyses were performed using R version 4.0.2 and Statistical Analysis Software (SAS) version 9.4. VHA approved investigators EEL, JD, SS, LL, and SG had full access to data used for this study. All data were securely maintained in the VA Informatics and Computing Interface (VINCI). This research was approved by the local institutional review board at VA San Diego Healthcare System and received exempt status for patient consent.

Results

Cohort Characteristics

Of 2,100 patients in the nationwide VA-AC, 1,863 were matched with a ratio of 1:4 to individuals without achalasia from the broader VHA database. The final analytic cohort comprised 9,315 individuals: 1,863 with achalasia matched to 7,452 without achalasia. Median age for the analytic cohort was 55 years (quartile 1–quartile 3 (Q1–Q3): 48–63), and 92% were male.

Compared to individuals without achalasia, individuals with achalasia were more often Black (20% vs 16%), Hispanic (6.7% vs. 4.4%), and current or former smokers (49% vs 39%). Additionally, Veterans with achalasia were more likely to have a diagnosis of BE (2.3% vs 1.3%) and candida esophagitis (3.4% vs 0.1%) at baseline or follow up compared with Veterans without achalasia.

For individuals with achalasia, median age at diagnosis was 55 years (Q1–Q3: 48–63) with a median 5.5 years of follow-up time (Q1–Q3: 2.6–9.5). Most were aged 50–59 years (34%), 65% were White and 57% were overweight or obese. Table 1 provides descriptive data for all covariates between the exposure groups.

Esophageal cancer risk among individuals with vs. without achalasia

Among the 1,863 individuals with achalasia, there were 12,176 total person-years of follow-up time and 17 esophageal cancer diagnoses (3 EAC, 12 SCC, and 2 unknown histology), equating to an incidence of 1.4 cases per 1,000 person-years at risk. In comparison, among

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the 7,452 individuals without achalasia, there were 48,388 total person-years of follow-up time and 15 esophageal cancers (11 EAC, 1 SCC, and 3 unknown histology), equating to an incidence of 0.3 cases per 1,000 person-years at risk. Median time from achalasia diagnosis to esophageal cancer diagnosis was 3.0 years (Q1–Q3: 1.3–9.1), whereas the median time from index study entry date for individuals without achalasia to esophageal cancer development was 4.5 years (Q1–Q3: 1.5–8.5).

Esophageal cancer risk was significantly higher among those with achalasia vs without achalasia: HR 4.58, 95% CI: 2.29–9.18 (Table 2). The Kaplan Meier curve demonstrated higher cumulative incidence of esophageal cancer (Figure 1, based on log-rank test $p<0.0001$) in those with vs without achalasia at 5 years (achalasia: 0.8% [95% CI: 0.3% −1.2%] vs no achalasia: 0.2% [95% CI: 0.1%−0.3%]), 10 years (achalasia: 1.5% [95% CI: 0.6%−2.3%] vs no achalasia: 0.3% [95% CI: 0.1%−0.4%]), and 15 years (achalasia: 2.5% [95% CI: 0.8%−4.1%] vs no achalasia: 0.6% [95% CI: 0.2%−1.0%]) follow-up (Table 2).

Potential influence of smoking on esophageal cancer risk was explored. In univariate analyses, smoking exposure (including former and current smokers) was not a significant risk factor for esophageal cancer (HR for esophageal cancer comparing smoking exposure to never smokers = 2.06, 95% CI 0.85–4.99). In a multivariable analysis evaluating esophageal cancer risk among individuals with achalasia compared to without achalasia adjusting for smoking status, esophageal cancer risk remained higher among those with achalasia versus without achalasia, with a similar magnitude of effect as observed in our primary analysis (HR for esophageal cancer comparing achalasia vs no achalasia, adjusting for smoking status = 4.32, 95% CI: 2.15–8.70).

A sensitivity analysis removing cancer diagnoses within 1 year of index achalasia diagnosis to account for potential additional cases of pseudoachalasia was performed, resulting in 15 esophageal cancer diagnoses (2 EAC, 11 SCC, and 2 unknown histology) among individuals with achalasia. Esophageal cancer risk remained significantly higher among those with achalasia vs without achalasia: HR 4.04, 95% CI: 1.97–8.26.

Esophageal cancer risk by histology type among individuals with vs. without achalasia

There were 12 incident SCC cancers diagnosed among those with achalasia and there was 1 incident SCC cancer diagnosed among those without achalasia. SCC-specific risk was significantly higher among those with achalasia vs without achalasia: HR 47.8, 95% CI: 6.22–367.43.

There were 3 incident EAC cancers diagnosed among those with achalasia and 11 incident EAC cancer diagnosed among those without achalasia. EAC-specific risk was similar among those with achalasia vs without achalasia: OR 1.09, 95% CI: 0.30–3.92.

Patterns of presentation with esophageal cancer and post-hoc analyses

Table 3 provides a detailed timeline for each achalasia esophageal cancer case from index achalasia diagnosis to esophageal cancer development and mortality based on manual chart review. A majority of the esophageal cancers (80% among those with histology available) were SCC in the achalasia cohort, whereas most esophageal cancers (92% among those with

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histology available) were EAC in the non-achalasia cohort. Most esophageal cancers were advanced stage (regional or distant) at diagnosis irrespective of achalasia diagnosis (with achalasia: 83% with SCC and 100% with EAC for those with cancer stage available; without achalasia: 70% with EAC for those with cancer stage available). Table 4.

History of definitive lower esophageal sphincter (LES) therapy (including surgical Heller myotomy, per-oral endoscopic myotomy (POEM), or pneumatic dilation) or esophagectomy preceding cancer diagnosis was common in the achalasia group, specifically noted among 3 of 3 achalasia patients (100%) with EAC, and 5 of 12 achalasia patients (41.7%) with SCC.

Among all 32 individuals with esophageal cancers across the achalasia and non-achalasia groups, 4 (12.5%) had a diagnosis of candida esophagitis preceding their esophageal cancer diagnosis. All 4 individuals with candida esophagitis preceding their esophageal cancer (3 SCC, 1 EAC) diagnosis also had achalasia. There were no diagnoses of candida esophagitis preceding esophageal cancers in individuals without achalasia. Among the remaining 9,283 individuals in our study without esophageal cancer, 67 (0.7%) ever had a lifetime diagnosis of candida esophagitis. We performed a post-hoc analysis of evaluating the risk of esophageal cancer among those with candida esophagitis vs without candida esophagitis. Univariate Cox regression analysis showed esophageal cancer risk was higher among those with candida esophagitis vs without candida esophagitis (HR: 20.59, 95% CI: 6.93–61.12). Median time from candida esophagitis diagnosis to esophageal cancer was 1.8 years (Q1–Q3: 0.3–3.7).

Among all 32 individuals with esophageal cancer across the achalasia and non-achalasia groups, 3 (9.4%) had a diagnosis of BE preceding their esophageal cancer diagnosis. All 3 individuals with BE preceding their esophageal cancer diagnosis had EAC per histology. One individual with BE and EAC was in the achalasia cohort and 2 individuals with BE and EAC were in the non-achalasia cohort. Among the remaining 9,283 individuals without esophageal cancer, 134 (1.4%) had a lifetime diagnosis of BE. In multivariable analysis adjusting for BE, esophageal cancer risk remained higher among those with achalasia versus without achalasia, with a similar magnitude of effect as observed in the primary analysis [HR (achalasia vs no achalasia, adjusted for BE): 4.40, 95% CI: 2.19–8.84].

Esophageal cancer-related mortality

Esophageal cancer-related mortality was high, irrespective of achalasia diagnosis, but was higher in Veterans diagnosed with achalasia [16 esophageal cancer-related deaths out of 17 esophageal cancers (94%)] compared to Veterans without achalasia [11 esophageal cancer-related deaths out of 15 esophageal cancers (73%)] (Table 4). Median time from achalasia diagnosis to esophageal cancer-related death was shorter 4.6 years (Q1–Q3: 2.3–10.7), compared to those without achalasia (6.3 years, Q1–Q3: 1.5–11.0). Median time from esophageal cancer diagnosis to esophageal cancer-related mortality among those with achalasia was 0.6 years (Q1–Q3: 0.4–1.1) compared to 1.9 years (Q1–Q3: 1.3–2.2) for those without achalasia. 5-year relative survival of esophageal cancer at time of cancer diagnosis among those with achalasia was 0%, compared to 11% for those without achalasia. Table 4.

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Discussion

Achalasia diagnosis was associated with a 4.6-fold increased risk of esophageal cancer in our large national cohort study of 1,863 individuals with achalasia matched to 7,452 individuals without achalasia. 10-year cumulative incidence of esophageal cancer was equivalent to 1 esophageal cancer case in every 67 individuals with achalasia compared to 1 esophageal cancer case in every 333 individuals without achalasia. Upon manual review of each esophageal cancer case within our achalasia cohort, the following patterns were notable: (1) nearly all esophageal cancer cases were SCC (80% among those with histology available), (2) most esophageal cancers were advanced stage at diagnosis (83% with SCC and 100% with EAC, for those with cancer stage available), (3) the 5-year relative survival of esophageal cancer was 0%, and (4) several esophageal cancer diagnoses were preceded by a diagnosis of candida esophagitis (24%).

Our findings confirm and extend prior work in several ways (Table 5). Current understanding of achalasia as a risk factor for esophageal cancer largely stems from studies used in two recently published meta-analyses.[3,4] Tustumi et al (2017) pooled results from 40 studies (spanning 17 countries, with data collection ranging from 1956 to 2016) reporting on incidence of esophageal cancer in achalasia. Based on pooled analyses, SCC incidence was 3.12 cases per 1,000 person-years and EAC incidence was 0.21 cases per 1,000 person-years among individuals with achalasia.[4] Gillies et al (2019) pooled results from 16 studies (11 countries, with data collection ranging from 1933 to 1992) and estimated the incidence rate of esophageal cancer in achalasia to be 1.36 (95% CI 0.56–2.51) cases per 1,000 person-years.[3] Modern application of these meta-analyses can be challenging, particularly since the majority of studies from both meta-analyses predated the 21st century. Individuals diagnosed with achalasia from earlier studies may have not satisfied the more rigorous definitions of achalasia based on current guidelines.[2] The algorithm for achalasia diagnosis used in the present study was validated using rigorous manometric and clinical criteria, as described for the VA-AC cohort; achalasia manometric criteria defined in the Chicago classification version 4.0 were satisfied for 78% of individuals on chart review.[10]

A more recently published study performed by Harvey et al (2019), examined esophageal cancer risk among those with vs without achalasia using a nationwide primary care database in the United Kingdom.[5] Similar to our study, Harvey et al utilized a matched cohort design matching 2,369 individuals with achalasia with 3,865 controls from 1/2006 to 12/2015. Mean follow-up time was 6.1 years for achalasia cases and 6.4 for controls. They found that the esophageal cancer incidence rate ratio (IRR) was higher among individuals with achalasia compared to controls (IRR 5.22 (95% CI: 1.88–14.45),[5] which is similar to the HR reported in our cohort. Their reported cumulative incidence of esophageal cancer among individuals with achalasia vs without achalasia (10-year cumulative esophageal cancer incidence for achalasia was 0.08% vs. 0.002% in those without achalasia),[5] however, was lower than what our study suggests (1.5% cumulative incidence at 10-years among those with achalasia compared to 0.3% in those without achalasia). Veteran characteristics and an enrichment of risk factors, namely a higher proportion of males, obesity, and current smokers, might explain the higher incidence in our cohort compared to the UK cohort.

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Compared to the most contemporary studies,[7,8] our study showed a similar incidence rate. Incidence of esophageal cancer found in a multicenter retrospective study of achalasia patients in Japan (Sato et al, 2021) was 0.8 cases per 1,000 person-years (mean follow-up was 3.1 years);[8] and incidence of esophageal cancer found in a prospective study of achalasia patients in Italy (Zagari et al, 2021) was 2.4 cases per 1,000 person-years (mean follow-up was 15.5 years).[7] In our study, median follow-up time after achalasia diagnosis was 5.5 years and incidence of esophageal cancer among those with achalasia was 1.4 cases per 1,000 person-years at risk. Cumulative incidence of esophageal cancer in individuals with achalasia increased from 0.8% at 5 years to 1.5% at 10 years and 2.5% at 15 years and supports that individuals with achalasia may benefit from a high index of suspicion and endoscopic surveillance for esophageal cancer.

We identified hypothesis-generating patterns on manual chart review of esophageal cancer cases. First, most esophageal cancer cases among those with achalasia were SCC. Although the pathophysiology of SCC in those with achalasia is not well understood, the proposed mechanism for SCC development relates to esophageal food stasis.[26,27] Food stasis in turn may lead to lactic acid production from bacterial overgrowth and slow continuous chronic inflammation which damages esophageal epithelium and promotes dysplastic changes.[26,27] Secondly, in *post-hoc* review, we found a 20-fold increased risk of esophageal cancer in those with candida esophagitis compared to those without candida esophagitis. All those with candida esophagitis preceding their cancer diagnosis also had achalasia. Higher risk of esophageal cancer has been linked with a hereditary condition called chronic mucocutaneous candidiasis (CMC) which results in recurrent candida esophagitis.[28,29] Candidiasis has been proposed to induce carcinogenesis by mechanisms such as nitrosamine production,[30–32] acetaldehyde production,[33–35] and pro-inflammatory cytokine production resulting in epithelial damage.[36–38] It is interesting to speculate whether the candida infection precipitated the development of SCC seen in our Veterans with achalasia, or if the candida is a bystander and related to esophageal stasis and achalasia. Even if candida is not a causative factor for esophageal cancer, the presence of candida may be an important clinical finding that suggests severe stasis and therefore prompt a heightened concern for future cancer risk. More studies are needed to understand if there is a true causal link between candidiasis and carcinogenesis. Thirdly, in our review of esophageal cancer cases, we identified that a significant proportion with achalasia had definitive LES therapy (i.e. surgical Heller myotomy, POEM, or pneumatic dilation) or esophagectomy preceding cancer diagnosis, including 100% (3 of 3) achalasia patients who had EAC, and 41.7% (5 of 12) who had SCC. All incident EAC cases observed in a prospective study by Zagari et al also underwent definitive LES therapy (surgical myotomy) prior to esophageal cancer development.[7] We postulate definitive disruption to the LES could lead to gastroesophageal reflux, which, in combination with poor esophageal clearance and stasis, could contribute to EAC and even possibly SCC pathogenesis. If definitive LES therapy is indeed related to esophageal cancer risk,[39,40] this may have implications for post-LES treatment surveillance, however more research is needed to better characterize this association.

To the best of our knowledge, this study is the first large US population-based cohort analysis of esophageal cancer risk among those with achalasia. Our study has several strengths. First, we designed a rigorous matched cohort design, ensuring rates of follow

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up within the VHA as well as balanced distribution of age, sex, and length of VHA medical record between the exposure groups. Additionally, we used a previously validated cohort of individuals with achalasia as our achalasia analytic cohort, which is one of the largest population-based cohorts to date.[10] We also reviewed all esophageal cancer cases for each exposure group for verification; details regarding location, stage, and diagnosis date were available for a majority of cases, as well as details regarding achalasia surgical and endoscopic interventions.

Our study is not without limitations. Reflective of the VHA population, a large proportion of the subjects in this study were male and non-Hispanic White individuals, which may limit the generalizability of findings to women and other racial and ethnic groups. Additionally, index ICD code encounter may not reflect the true diagnosis date for all individuals as some individuals may have been diagnosed outside of the VHA system. Detailed information regarding esophageal diameter (a proxy for esophageal stasis) was not available and could not be studied in the context of candidiasis. Additionally, it was not possible to adequately evaluate the duration from symptom onset to diagnosis or treatment symptoms since symptoms were not consistently reported in the reviewed medical documentation. Time-interval estimates could not be determined for subjects who had lower esophageal sphincter disruption/therapy prior to the start of study follow up within our cohort. Evaluation of esophageal cancer risk by achalasia sub-type was not feasible as data regarding achalasia sub-type was not consistently available. Small sample size precluded precise analysis of LES treatment as a risk factor for esophageal cancer. Additionally, due the few numbers of esophageal cancer cases overall, Cox proportional hazard model were conducted as univariate models with a single independent exposure variable. Our study design mitigated confounding by age, sex, and length of VHA care by matching based on these variables. Lastly, small case numbers limited the ability to make strong conclusions based on histologic type. The relative distribution of SCC and EAC cases observed in the achalasia cohort suggests the overall esophageal cancer risks observed in our study may be best attributable to increased risk for SCC rather than EAC.

Conclusion

Using a large, US-based cohort of Veterans with achalasia, we demonstrated that achalasia diagnosis was associated with a 4.6-fold increased risk of incident/fatal esophageal cancer and 5-year overall survival was 0%. Currently there are no guidelines for surveillance endoscopy in those with achalasia, due to limited high-quality data assessing the risk of esophageal cancer in achalasia. Our findings suggest that individuals with achalasia may benefit from a high index of suspicion and endoscopic surveillance for esophageal cancer, particularly in those with candida esophagitis or prior definitive LES therapy. More studies are needed to determine the optimal timing for surveillance for esophageal cancer in individuals with achalasia as well as to better understand the pathophysiology linking achalasia and esophageal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Funding support:

T32 NIH Grant 5T32DK007202-44 (Ghosh, PI); NIH P30 DK120515 (Schnabl, Eckmann, PIs), NIH K23 DK125266 (Yadlapati, PI), VA ICX002027A (Shah, PI); AGA Research Scholar Award (Shah, PI); NIH/NCI K99 CA 267181-01A1 (Demb, PI); NIH/NCI 5 R37 CA 222866-02 (Gupta, PI). There were no funding sources or study sponsors which influenced the study design, collection, analysis, and interpretation of the data or the writing of the report.

Potential competing interests:

EEL: None declared

JD: None declared

SS: Consultant Phathom Pharmaceuticals, RedHill Biopharma

LL: None declared

RB: None declared

RY: Consultant: Medtronic (Institutional), Ironwood Pharmaceuticals (Institutional), Phathom Pharmaceuticals, StatDataLink, Medscape; Research support: Ironwood Pharmaceuticals; Advisory Board with Stock Options: RJS Mediagnostix

SG: Consultant: Guardant Health; InterVenn; Geneoscopy; CellMax Life; Research support: Freenome; Epigenomics

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WHAT IS KNOWN

- Achalasia is a postulated risk factor for esophageal cancer.
- There are no guidelines for esophageal cancer screening for individuals with achalasia.

WHAT IS NEW HERE

- Esophageal cancer risk is 4.6-fold higher in individuals with achalasia compared to those without achalasia, most likely specific to increased risk for esophageal squamous cell carcinoma.
- Observed 5-year overall survival of esophageal cancer was 0% in those with achalasia.

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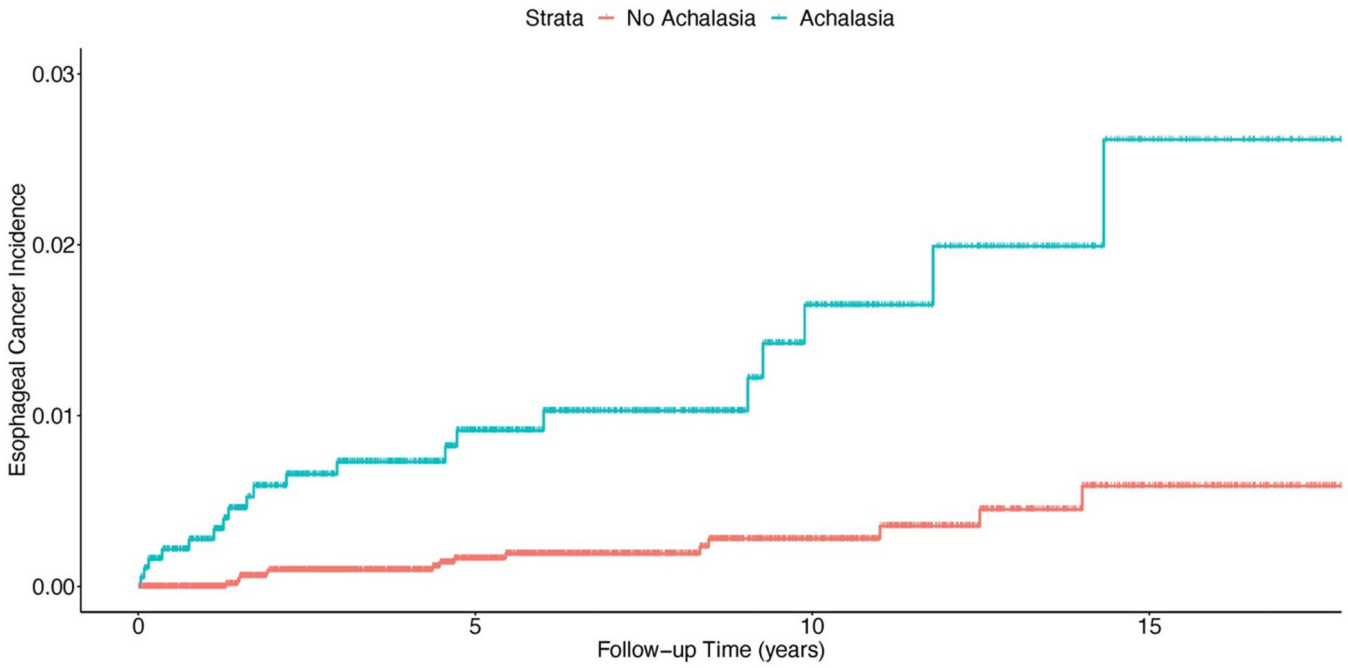

Figure 1.

Cumulative Incidence of Esophageal Cancer

Kaplan Meier curve demonstrating cumulative incidence at 5-, 10- and 15-year time points. Incidence at each time point was significantly higher for individuals with achalasia compared to individuals without achalasia.

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Table 1.

Cohort Characteristics

	Achalasia N = 1863	**No Achalasia N = 7452**
Age, median (Q1–Q3)	55.0 (48.0 – 63.0)	55.0 (48.0 – 63.0)
Males, n (%)	1722 (92.4)	6888 (92.4)
Race/Ethnicity, n (%)		
Asian/Pacific Islander	23 (1.2)	113 (1.5)
Black	377 (20.2)	1163 (15.6)
Hispanic	124 (6.7)	325 (4.4)
Missing	107 (5.7)	948 (12.7)
Multiracial/Other	25 (1.3)	157 (2.1)
White	1207 (64.7)	4746 (63.7)
BMI, median (Q1–Q3)	28.6 (25.1 – 32.9)	28.6 (25.4 – 32.6)
Smoking Status, n (%)		
Current	530 (28.5)	1589 (21.3)
Former	386 (20.7)	1288 (17.3)
Never	555 (29.8)	2395 (32.1)
Missing	392 (21.0)	2180 (29.3)
Barrett's Esophagus, n (%)	43 (2.3)	94 (1.3)
Candida Esophagitis, n (%)	64 (3.4)	7 (0.1)
Follow up Time in years, median (Q1–Q3)	5.5 (2.6 – 9.5)	5.5 (2.6 – 9.4)

*All variables are significant with p-value <.0001, except Age (Matched), Sex (Matched), and BMI which were not statistically significant at alpha=0.05

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Table 2.

Esophageal cancer risk among individuals with vs without achalasia, VA-Achalasia Cohort, 10/1999 to 12/2019

	Esophageal Cancer Cases			Cumulative Incidence (%)			Risk^
	Squamous Cell Carcinoma	Adenocarcinoma	Unknown Histology	5-year (95% CI)	10-year (95% CI)	15-year (95% CI)	Unadjusted HR (95% CI)
Achalasia	12	3	2	0.8 (0.3, 1.2)	1.5 (0.6, 2.3)	2.5 (0.8, 4.1)	4.58 (2.29, 9.18)
No Achalasia	1	11	3	0.2 (0.1, 0.3)	0.3 (0.1, 0.4)	0.6 (0.2, 1.0)	-

^Risk was derived from a univariate Cox regression model, including matching strata variable as random intercept; reported HR p-value was <0.0001

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Table 3.

Timeline from Achalasia Diagnosis to Esophageal Cancer Diagnosis among all 17 Esophageal Cancer Cases

Case	Histology	Location	Stage	Achalasia Sub-Type	Timeline to Esophageal Cancer Diagnosis
1	SCC	Lower	Regional lymph node(s) involved only	Unknown	• Index VHA endoscopy status post botulinum toxin injection • EGD performed for worsening dysphagia >15 months following achalasia diagnosis revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred >12 months following esophageal cancer diagnosis
2	SCC	Middle	Regional lymph node(s) involved only	Unknown	• Index VHA endoscopy positive for candida esophagitis (treatment prescribed) • EGD performed for worsening dysphagia >15 months later revealing recurrent candida esophagitis (treatment prescribed) • Gastrostomy tube placed for oropharyngeal and esophageal dysphagia • EGD performed for IDA >3 years following achalasia diagnosis revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
3	SCC	Middle	Distant	Type 1	• Index VHA endoscopy status post pneumatic dilation • EGD performed for worsening dysphagia >6 years following achalasia diagnosis revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <12 months following esophageal cancer diagnosis
4	SCC	Middle	Distant	Type 1	• Index VHA endoscopy • Within 12 months a laparoscopic Heller myotomy was performed with Dor fundoplication • EGD performed for dysphagia >6 months later and pneumatic dilation was performed for a tight wrap • EGD performed for dysphagia >2 years later revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
5	SCC	Upper	Distant	Type 1	• Index VHA endoscopy • Laparoscopic Heller myotomy with Dor fundoplication performed one year later • EGD performed for dysphagia <6 months later and TTS balloon dilation was performed for a tight wrap • EGD performed for worsening dysphagia >6 years after achalasia diagnosis revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred >12 months following esophageal cancer diagnosis
6	SCC	Upper	Regional lymph node(s) involved only	Type 1	• Prior history of laparoscopic Heller myotomy for achalasia • Index VHA endoscopy • EGD performed for worsening dysphagia >5 years later revealing candida esophagitis (treatment prescribed) • EGD performed <6 months later to assess treatment efficacy revealing recurrent candida esophagitis (treatment extended) • EGD performed <6 months following to assess treatment efficacy revealing recurrent candida esophagitis (treatment extended and infectious disease consultation was requested for persistent candida infection) • EGD performed for worsening dysphagia >12 months later revealing **incident esophageal cancer** and recurrent candida esophagitis • Esophageal cancer-related mortality occurred >12 months following esophageal cancer diagnosis
7	SCC	Upper	Distant	Unknown	• Prior history of laparoscopic Heller myotomy for achalasia • Index VHA endoscopy • EGD performed for worsening dysphagia >15 months later revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
8	SCC	Middle	Regional lymph node(s) involved only	Unknown	• Index VHA endoscopy • EGD performed for unintentional weight loss >6 years later revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <12 months following esophageal cancer diagnosis
9	SCC	Middle	Localized	Unknown	• Index VHA endoscopy status post dilation with a through the scope balloon dilator • EGD performed for progressive dysphagia >6 years later revealing **incident esophageal cancer** • Esophageal cancer-related mortality <24 months later

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Case	Histology	Location	Stage	Achalasia Sub-Type	Timeline to Esophageal Cancer Diagnosis
10	SCC	Upper	Regional lymph node(s) involved only	Type 1	• Index VHA endoscopy positive for candida esophagitis (treatment prescribed) • EGD performed <3 months later without evidence of malignancy or candida infection status post botulinum toxin injection • A third EGD was performed for worsening dysphagia <6 months following the previous EGD revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
11	SCC	Middle	Regional by BOTH direct extension and lymph node(s) involved	Type 1	• Index VHA endoscopy with views obstructed by retained food particles • EGD was then performed for repeat assessment for possible pseudoachalasia <3 months following, which was negative for malignancy status post botulinum toxin injection • CT chest was performed >12 years later for shortness of breath, revealing circumferential mid-esophageal thickening involving the trachea with lymphadenopathy • EGD was performed for to evaluate the abnormal imaging findings revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
12	SCC	Unknown	Localized	Type 2	• Index VHA endoscopy status post botulinum toxin injection • Non-esophageal cancer-related mortality occurred >12 months following achalasia diagnosis • Localized, **incident esophageal cancer** was diagnosed on autopsy
13	AC	Lower	Distant	Unknown	• Prior history of distal esophagectomy for refractory achalasia • Index VHA endoscopy • EGD performed for worsening dysphagia <3 years later revealing candida esophagitis (treatment prescribed) • EGD repeated <3 months following to assess for candida treatment efficacy and repeat evaluation of the esophagus due to poor visibility revealing recurrent candida esophagitis and **incident esophageal cancer** • Esophageal cancer-related mortality occurred >12 months following esophageal cancer diagnosis
14	AC	Lower	Unknown	Unknown	• Index VHA endoscopy • Pneumatic dilation performed <3 months following which was complicated by perforation of the esophagus • Esophageal cancer-related mortality occurred >12 months following the perforation, **incident esophageal cancer** was discovered on autopsy
15	AC	Lower	Distant	Type 1	• Prior history of laparoscopic Heller myotomy with Nissen fundoplication for achalasia • Index VHA endoscopy but positive for long segment BE without dysplasia • EGD performed for BE surveillance >12 months later, revealing **incident esophageal cancer** • Esophageal cancer-related mortality occurred <6 months following esophageal cancer diagnosis
16	Unknown	Unknown	Unknown	Type 2	• Index VHA endoscopy • Esophageal cancer-related mortality occurred >12 months later
17	Unknown	Unknown	Unknown	Unknown	• Index VHA endoscopy • Esophageal cancer-related mortality occurred >3 years later

* Unknown achalasia sub-type was based on limited characterization of esophageal swallow physiology.

** Exact times are not provided to protect patient confidentiality.

Abbreviations: BE = Barrett's esophagus; EGD = esophagogastroduodenoscopy; IDA = iron deficiency anemia; TTS = through the scope; VHA = Veterans Health Administration

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Table 4.

Esophageal Cancer Characteristics

	Achalasia	No Achalasia
Squamous Cell Carcinoma	**n = 12**	**n = 1**
Time to incident SCC diagnosis in years, median (Q1–Q3)[a]	6.0 (1.6 – 9.9)	0
Tumor Location, n (%)		
Upper esophagus	4 (33.3)	-
Middle esophagus	6 (50)	-
Lower esophagus	1 (8.3)	-
Unknown	1 (8.3)	1 (100)
SEER Summary Stage, n (%)		
Localized	2 (16.7)	-
Regional lymph node(s) involved only	5 (41.7)	-
Regional by BOTH direct extension and lymph node(s) involved	1 (8.3)	-
Distant	4 (33.3)	1 (100)
Cancer Mortality, n (%)	11 (91.7)	1 (100)
Time to SCC-related mortality in years, median (Q1–Q3)[a]	6.7 (2.3 – 11.8)	14.0
Prior Intervention [*], n (%)		
Surgical Heller myotomy	4 (33.3)	-
Pneumatic Dilation	1 (8.3)	-
Esophageal Adenocarcinoma	**n = 3**	**n = 11**
Time to incident EAC diagnosis in years, median (Q1–Q3)[a]	1.7 (1.3 – 2.2)	4.5 (1.9 – 8.5)
Tumor Location, n (%)		
Lower esophagus	3 (100)	11 (100)
SEER Summary Stage, n (%)		
Localized	.	3 (27.3)
Regional lymph node(s) involved only	.	3 (27.3)
Distant	2 (66.7)	4 (36.4)
Unknown	1 (33.3)	1 (9.1)
Cancer Mortality, n (%)	3 (100)	7 (63.6)
Time to EAC-related mortality in years, median (Q1–Q3)[a]	2.4 (1.4 – 3.3)	6.3 (1.5 – 10.0)
Prior Intervention [*], n (%)		
Surgical Heller myotomy	1 (33.3)	-
Esophagectomy	1 (33.3)	-
Pneumatic Dilation	1 (33.3)	-
Unknown Histology	**n = 2**	**n = 3**
Cancer Mortality, n	2 (100)	3 (100)

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[*] Prior intervention reflects prior achalasia therapy before cancer diagnosis

[^] Time to diagnosis reflects time in years from achalasia diagnosis to the event

[a] Time is in relation to the achalasia diagnosis date (equivalent to the matching date for non-achalasia individuals)

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Table 5.

Characteristics of Prior Studies Evaluating Esophageal Cancer Risk in Achalasia

Authors (Year Published)	Design	Data Collection Period and Study Population	Main Findings	Strengths	Limitations
Tustumi et al (2017)	Systematic Review/Meta-analysis	Data collection from 40 pooled studies ranged from 1956–2016, spanning 17 countries. Study inclusion did not require achalasia validation for retrospective studies.	11,978 total individuals with achalasia. Pooled incidence rates of esophageal cancer: SCC - 3.12 cases per 1,000 person-years EAC - 0.21 cases per 1,000 person-years	• Global representation.	• Studies were not included or excluded based on methodologic rigor. • 66.6% of studies had unclear reporting of demographics of the participants. • 54.7% of studies had unclear reporting of clinical information of the participants. • 73.8% of the studies had unclear outcomes or follow up results of cases clearly reported. • Measurements of heterogeneity were not reported among studies. • Most study data was collected prior to 2000, predating the current diagnostic criteria for achalasia.
Gillies et al (2019)	Systematic Review/Meta-analysis	Data collection from 16 pooled studies ranged from 1933 to 1992, spanning 11 countries. Study inclusion did not require achalasia validation for retrospective studies.	4,389 total individuals with achalasia. Pooled incidence of esophageal cancer: 1.36 (95% CI 0.56, 2.51) cases per 1,000 person-years	• Used Bayesian modeling with allowed for all the uncertainty associated with the between-study heterogeneity.	• A few Chagas cases were retained in the meta-analysis. • All study data was collected prior to 2000, predating the current diagnostic criteria for achalasia.
Harvey et al (2019)	Retrospective and Matched Cohort (THIN); UK	Data collection from 2006–2015. Two databases were utilized in the analyses. (1) The Hospital Episode Statistics (HES) – a database of claims codes (ICD-10 and CPT) and demographic information within England (identified as a secondary care database). This database was validated for true diagnoses of achalasia based on patient-level procedure and manometry reports. A single ICD code in the primary position correlated 96% of the time with a true diagnosis based on manual chart review (there were 56 total patients reviewed, and no specific validation criteria were listed). (2) The Health Improvement Network (THIN) – a database of general practices (primary care) covering 6% of the United Kingdom and includes diagnosis codes recorded as Read codes and	HES included 10,509 incident achalasia cases in England. THIN included 711 incident achalasia cases in the UK. Achalasia overall incidence per 100,000 population over the study period: HES: 1.99 (95% CI 1.87–2.11) THIN: 1.53 (95% CI 1.42–1.64) A matched cohort design was performed using the THIN database: 2,369 achalasia patients matched with 3,865 controls. Mean 6.1 years of follow up for achalasia cases and 6.4 for controls. Esophageal cancer incidence rate ratio (IRR) was higher for achalasia subjects compared to controls 5.22 (95% CI: 1.88 to 14.45); p<0.001. Median time from achalasia diagnosis to esophageal cancer diagnosis was 15.5 years (IQR 5.8–26.2).	• Utilized a validated approach to characterize achalasia incidence in the HES database. • Utilized a matched cohort design to measure esophageal cancer incidence and risk.	• Validation of achalasia cases were limited to the HES database. THIN was not validated for achalasia, which was the database used to measure esophageal cancer incidence. • Esophageal cancer cases were not manually reviewed for verification. • Esophageal cancer cases were not distinguished based on histology (ie. SCC vs EAC)

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Authors (Year Published)	Design	Data Collection Period and Study Population	Main Findings	Strengths	Limitations
		demographic information. This database was validated for true diagnoses of achalasia			
Zagari et al (2021)	Prospective Cohort; Italy	Data collected from 566 patients with achalasia from 1973 to 2018 and followed for a mean of 15.5 years since achalasia diagnosis.	20 patients developed esophageal cancer: 15 SCC and 5 EAC. Incidence of esophageal cancer was 2.4 cases per 1,000 person-years. The risk of esophageal cancer was significantly greater than the general population with a standardized incidence ratio (SIR) 104.2, 95% CI 63.7–161). Specifically for SCC the SIR = 126.9 (95% CI 71.0–209.3), and for EAC the SIR = 110.2 (95% CI 35.8–257.2)	• Prospective study with long follow-up period.	• Underpowered to perform multivariable analyses. • Early cases may have not met current guideline criteria for achalasia. • Single center study.
Sato et al (2021)	Retrospective Multicenter Study; Japan	Data collected from 2,714 patients with achalasia and achalasia-related esophageal motility disorders from 2010 to 2019 and followed fosr a mean of 3.1 years since achalasia diagnosis.	24 of the 2,714 patients developed esophageal cancer. Cumulative incidence was 0.8 per 1,000 person-years.	• Multicenter study, with each site contributing over 50 patients with achalasia. • Histology and stage were available for all cancers.	• Relatively short follow-up time. • No cases of EAC were observed. • Underpowered to perform multivariable analyses.
Low et al (Presented Study)	Matched Cohort; USA	Data collection from 1999–2019. The validated, nationwide Veterans Affairs Achalasia Cohort (VA-AC) was utilized for this study.	A matched cohort design was performed using the VA database: 1,866 achalasia patients matched with 7,464 controls. Mean 5.5 years of follow up for both achalasia cases and non-achalasia controls. Esophageal cancer hazard ratio (HR) for achalasia subjects compared to controls was 5.39 (95% CI: 2.76 to 10.54). Median time from achalasia diagnosis to esophageal cancer diagnosis was 3.0 years (Q1–Q3: 1.3–9.1).	• Utilized a previously validated cohort. • Large, population-based study. • Matched cohort design. • All esophageal cancer cases were manually reviewed for verification.	• Veteran population. • Limited female achalasia cases. • Index ICD code for achalasia served as a proxy for achalasia diagnosis and may not reflect the true diagnosis date. • Limited cases of esophageal cancer reduced the power for multivariable analyses.