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Title: 1-year Staging Incidence of Esophageal Adenocarcinoma with Enhanced Ethnicity SEER 18 Sampling, 2000-2017

Authors: Eric M. Montminy¹, Meijiao Zhou², Jaya H. Bommireddipally³, Jordan J. Karlitz⁴,⁵, Sachin Wani⁴

1. Division of Gastroenterology, Tulane University School of Medicine; New Orleans, LA 70112
2. Southborough, MA 01776
3. Department of Internal Medicine, Tulane University School of Medicine; New Orleans, LA 70112
4. Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Center; Aurora, CO 80045
5. Division of Gastroenterology and Hepatology, Denver Health Medical Center; Denver, CO 80204

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Correspondence:
Sachin Wani, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
University of Colorado Anschutz Medical Center
Mail Stop F735
1635 Aurora Court, Rm 2.031
Aurora, CO 80045
Phone: 720-848-2746
Fax: 720-848-2749
Email: sachin.wani@cuanschutz.edu

Conflicts of Interest:
These authors disclose the following:
Jordan J. Karlitz, MD
-Serves as consultant to Exact Sciences Corp.
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-Equity position in Gastro Girl
Sachin Wani, MD
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Meijiao Zhou, PhD, MPH
-Senior epidemiologist for Fresenius Medical Care North America

The remaining authors disclose no conflicts.

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All data, figures, and manuscript were available to all authors and not disclosed to other researchers. Data, analytic methods, and study materials are available upon request.

**Ethical Statement:**
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.
Esophageal adenocarcinoma (EAC) incidence rates (IR) are rising in the United States.\(^1\) Additionally, a recent study utilizing the Surveillance, Epidemiology, and End Results Program 9 (SEER 9, sampling approximately 9% of the U.S. population) demonstrated most patients with EAC present with advanced stage (analyzed as regional/distant combined).\(^1\) With rising EAC IRs and increasing EAC risk factor prevalence across all ethnicities, a more granular and comprehensive assessment of EAC staging by age and ethnicity is required as this could impact public health and current screening guidelines for Barrett’s esophagus (BE); the only identifiable premalignant condition for EAC. Current guidelines suggest screening with endoscopy in individuals with chronic gastroesophageal reflux disease with the presence of other risk factors (males, age >50 years, white race, smoking, obesity, and family history of BE/EAC).\(^2\) While white race has been predominantly utilized for profiling EAC risk demographics, this race-based recommendation was recently questioned in a document published by the American Gastroenterological Association.\(^3\) The primary aim of this study was to utilize the SEER 18 database to assess ethnicity and stage stratified trends in EAC IRs and determine differences in distant stage IRs. SEER 18 samples approximately 28% of the U.S. population and has improved ethnicity sampling compared to SEER 9 due to additional urban registries. Compared to prior studies in which age blocks (40-49, 50-59 etc.) were analyzed, we seek to analyze IR changes in one-year age increments over the 2000-2017 SEER 18 dataset. This type of detailed analysis can allow assessment of changes in EAC staging distributions as patients approach index screening age recommendations and thereafter.\(^4\) Additionally, we aimed to utilize rate-ratio analysis to compare distant to localized EAC IRs to gauge stage severity as age progresses.

Using the 2000-2017 SEER 18 dataset, mean 1-year interval age-adjusted EAC IRs per 100,000 person-years (PY) were obtained for ages 40-70 using SEER*Stat (version 8.3.9.1).
IRs were adjusted to the year 2000 U.S. population. SEER 18 was chosen given higher quality datasets and inclusion of more urban/diverse patient populations compared to other SEER registries. EAC IRs were stratified by stage (in situ, localized, regional, and distant) and ethnicity (all ethnicities combined, non-Hispanic white, non-Hispanic black, and Hispanic). Rate-ratios were calculated to determine if each age's distant EAC IR was significantly higher than corresponding localized EAC IRs. Confidence intervals were generated by SEER*Stat with the recommended Tiwari 95% CI option to determine significance. Rate-ratios were considered significant if confidence intervals did not cross 1. Joinpoint Regression Program (version 4.8.0.1) was used to quantify all ethnicities/stages combined EAC IRs annual percent change (APC) trends. For APCs, Monte Carlo permutation method was utilized with standard errors from SEER*Stat to determine significance.

A total of 23,386 EAC cases were reported over 2000-2017. Regarding all ethnicities combined (Figure 1a), distant EAC had the highest IR for every age except age 70 when regional IR was higher (regional 4.2/100,000PY vs. distant 3.9/100,000PY). Furthermore, distant EAC IRs remained significantly higher than localized IRs at every age. Amongst subgroups, non-Hispanic white EAC IRs (Figure 1b) demonstrated the highest peak distant stage IR (age 67-69, 5.9/100,000PY). Non-Hispanic white distant stage IR was higher than non-Hispanic black (Figure 1c) and Hispanic IRs (Figure 1d) at each corresponding age except for age 40 (0.2/100,000PY). Non-Hispanic white and Hispanic distant IRs were significantly higher than localized IRs at nearly all corresponding ages. Non-Hispanic black IRs displayed numerically predominantly distant stage EAC as age progressed, although confidence intervals were wide. Regarding APC in all ethnicities/all stages combined (Supplemental Figure 1), APC increased the fastest from age 40 to 49 (19.7%, p<0.05). From age 49-61, APC significantly increased, though at less of a rate, 11.4% (p<0.05), and less so from age 61 to 70 (5.4%, p<0.05).
The results of this study demonstrate predominant distant stage EAC as age progresses from age 40 to 70 over 2000-2017 except in non-Hispanic black patients. Our findings are unique in that they are the first to report EAC stage analysis in 1-year intervals utilizing the SEER 18 expanded racial/ethnic sampling. Our analysis also shows distant EAC is significantly increased compared to localized disease starting prior to age 50 (the typical index screening age for BE), particularly in all ethnicities combined and non-Hispanic white subgroups. Because distant EAC predominates prior to age 50 and persists thereafter in most subgroups, current screening recommendations and efforts to identify at-risk patients are potentially missing early-stage EAC. Predominant distant EAC throughout our entire population and substantially rising APCs as index screening approaches (though low overall absolute IRs) suggests that a renewed effort similar to recent colorectal cancer initiatives may be necessary for earlier detection. In addition, the substantial increase in APC values even among EAC cases age >50 years suggests failure in identification of at-risk patients through current screening strategies.

With expanding US Hispanic populations and predominantly distant disease in this subgroup, improved outreach efforts are needed to identify at-risk Hispanic individuals for BE/EAC through endoscopic or non-invasive screening modalities. Unlike other published guideline statements, the 2019 American Society for Gastrointestinal Endoscopy Barrett’s esophagus screening guidelines do not reference white race when profiling BE/EAC risk and represents a paradigm shift in EAC risk stratification. Given Hispanic ethnic heterogeneity and 20% of Hispanic patients identifying as white, Hispanic heritage impact on EAC risk remains unclear with epidemiologic data alone. Hence, this guideline change should not alone be considered endorsement of universally screening Hispanic populations for now.
Limitations include a case-controlled analysis and inability to characterize nomenclature bias impacts on in situ stage distribution. Regarding low in situ IRs throughout all subgroups, SEER registries only report an in situ case if labeled as “carcinoma in situ” (outdated term) and does not count cases labeled high-grade dysplasia. We suspect a degree of nomenclature bias is present, but confirmatory studies are required. Currently, national cancer organizations are putting forth recommendations to address this bias.⁹

With more evidence of predominantly distant stage EAC across all ages and ethnicities, future efforts need to refine the current paradigm of BE screening to improve population-level EAC outcomes.
References


FIGURE LEGEND

Figure 1. SEER 18 1-year Staging Incidence in Age 40-70 in All Ethnicities Combined (a), Non-Hispanic White (b), Non-Hispanic Black (c), and Hispanic (d) patients. Stages include distant (red), regional (blue), localized (purple), and in situ (green). Alpha indicates rate ratio of distant IR is significantly higher than localized IR with p<0.05.