Early-Onset Appendiceal Cancer Survival by Race or Ethnicity in the United States

Andreana N. Holowatyj,[1,2] Kay M. Washington,[2,3] Safia N. Salaria,[2,3] Christopher H. Lieu,[4] Kamran Idrees,[2,5] and Cathy Eng[1,2]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [2]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee; [3]Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee; [4]Department of Medicine, University of Colorado Denver, Aurora, Colorado; and [5]Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee

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As a rare cancer,[1] little is known about risk factors and etiologies of appendiceal cancer (AC). Overall, the incidence of malignant AC increased 232% between 2000 and 2016 in the United States, with rates rising from older to younger generations.[2] However, rates of appendectomies, a common gastrointestinal surgical procedure that often leads to incident AC diagnosis, remained stable over this period.[2] These findings raise the question of what causes underlie the changing epidemiology and rising burden of cancers among patients younger than 50 years (early-onset cancers),[3,4] including AC. The purpose of this study was to use population-based data to define the burden of AC in young patients, and to compare survival among non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic individuals diagnosed with early-onset AC.

Methods

Cases were identified using the National Institutes of Health/National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program that collects data from population-based cancer registries across the United States, as detailed in the Supplementary Methods. Our analysis included patients age 20 to 49 years with pathologically confirmed AC (C18.1; early-onset AC) between 2000 and 2011 with active follow-up and race/ethnicity classified as NHW, NHB, and Hispanic/Spanish/Latino. Log-rank tests and Cox proportional hazards were used to assess 5-year overall survival (OS)/cancer-specific survival (CSS) (Supplementary Methods).

Results

A total of 1652 AC cases diagnosed in individuals younger than 50 with race/ethnicity categorized as NHW, NHB, and Hispanic were identified from SEER between 2000 and 2011 (Supplementary Table 1A). One-third of young patients were diagnosed with mucinous appendiceal adenocarcinoma (MAA) (n = 560; 33.9%), 16.6% (n = 275) had non-MAA (NMAA), 28.5% (n = 470) had goblet cell, 13.8% (n = 228) had carcinoid, and 7.2% (n = 119) had signet ring cell AC. Histological subtype significantly differed by race/ethnicity, as NMAAs were more frequent among NHB compared with NHW and Hispanic individuals (26.0% vs 15.3% and 16.9%, respectively; $P = .004$, .02, and <.0001, respectively). Among young patients with AC, 319 (19.3%) were diagnosed with advanced stage disease (stage III/IV), and approximately 1 in every 8 patients reported additional cancer diagnoses (12.3%; Supplementary Table 1A).

OS at 5 years after early-onset AC diagnosis was 75.5%, 63.0%, and 75.4% among NHW, NHB, and Hispanic individuals, respectively ($P = .001$; Supplementary Figure 1*A*). CSS at 5 years was 77.0%, 64.5%, and 79.2% among young NHW, NHB, and Hispanic individuals, respectively ($P = .0006$; Supplementary Figure 1*B*). Mean OS/CSS months were lower among NHB individuals with early-onset AC, with this survival disparity observed across all histologic subtypes (Supplementary Table 1B). Among all patients with early-onset AC, NHB individuals demonstrated a significantly higher hazard of overall and AC-specific death compared with NHW individuals in adjusted models (hazard ratio $[HR]_{OS}$ 1.47, 95% confidence interval [CI] 1.10–1.95; HR_{CSS} 1.47, 95%C I 1.10–1.98; Supplementary Table 1C). No increased hazard of death was observed for Hispanic compared with NHW individuals (Supplementary Table 1C).

Stratification of patients by histological subtype revealed pronounced racial disparities in survival for young NHB individuals with MAA ($P_{OS} = .002$ and $P_{CSS} = .001$, respectively; Figure1). Among all young patients with MAA and NMAAs, men experienced significantly worse survival compared with women (Supplementary Table 1D). For young patients with MAAs, NHB individuals experienced significantly worse survival compared with NHW individuals (HR_{OS} 1.96, 95% CI 1.27–3.04; HR_{CSS} 2.04; 95% CI 1.30–3.18), whereas no survival differences were observed between Hispanic and NHW individuals (Supplementary Table 1D). Notably, among young patients with MAAs,

Abbreviations used in this paper: **AC, appendiceal cancer; CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; MAA, mucinous appendiceal adenocarcinoma; NHB, non-Hispanic black; NHW, non-Hispanic white; NMAA, nonmucinous appendiceal adenocarcinoma; OS, overall survival; SEER, Surveillance, Epidemiology and End Results.**

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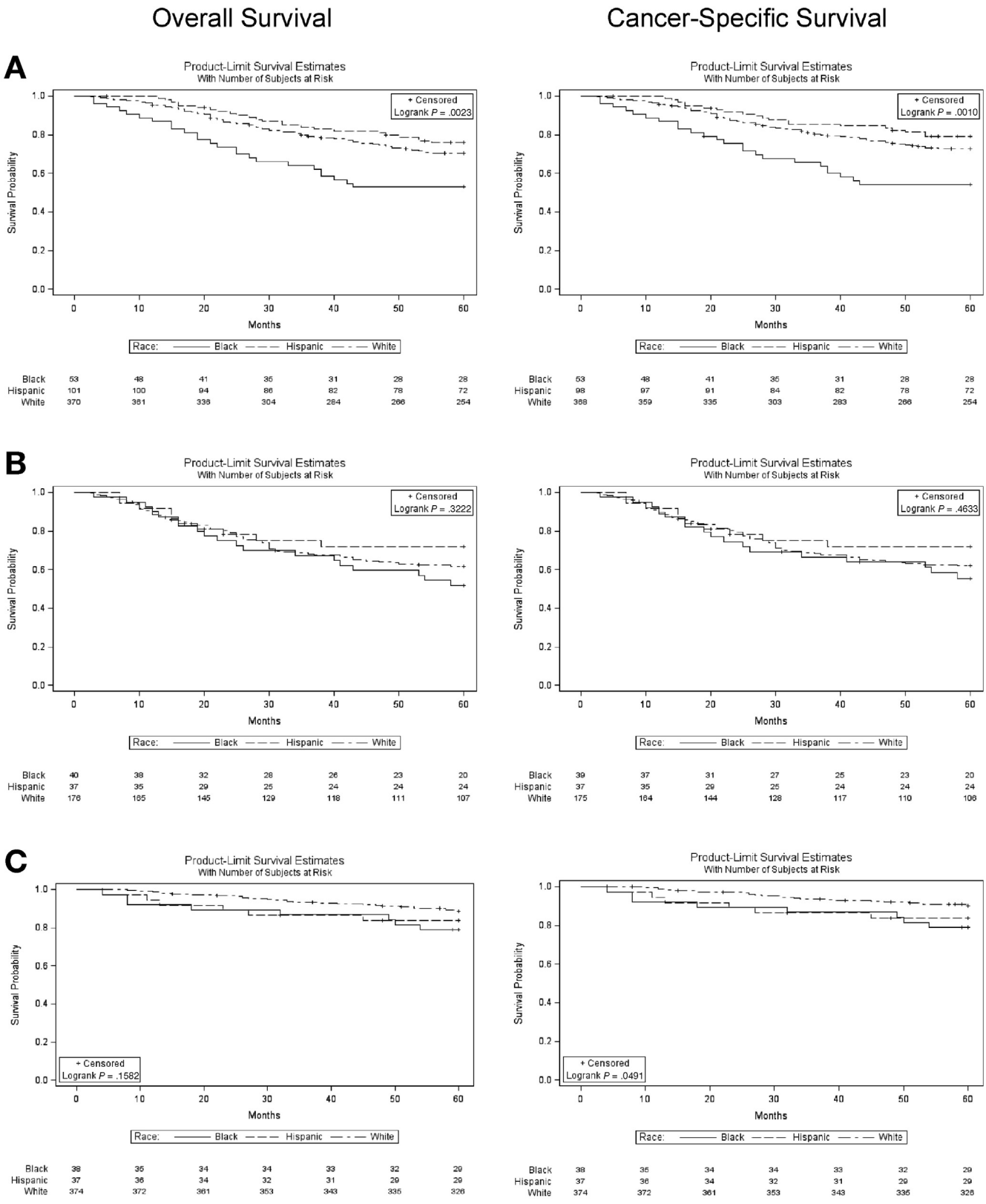

Figure 1. Kaplan-Meier overall (*left*) and cancer-specific (*right*) 5-year survival curves for patients with early-onset (*A*) mucinous adenocarcinomas, (*B*) nonmucinous adenocarcinomas, and (*C*) goblet cell carcinoid tumors of the appendix.

stage and receipt of surgical therapy did not differ between NHW and NHB individuals (Supplementary Table 1E).

Discussion

Our study of survival among 1652 individuals with early-onset AC demonstrates substantial variation by race/ethnicity and histologic subtypes, using data from ~28% of the US population. NHB individuals younger than 50 years had significantly poorer survival after AC diagnosis when compared with young NHW individuals, whereas no survival disparities were observed between Hispanic and NHW individuals. Sex and histological subtype were also independent predictors of survival among young patients, as the most pronounced racial differences were reported between NHB and NHW individuals with MAAs. The reason for this finding may be, to some extent, due to differences in AC biology by race/ethnicity, but currently no studies have examined the burden of AC among young patients or survival *specifically* within this population.

The survival difference observed by race/ethnicity among young patients with AC may be partly attributed to differences in socioeconomic status by race/ethnicity,[5] such as variation in diagnostic/surgical procedures or differential health care access. AC is rare and usually discovered in an acute situation, frequently presenting as appendicitis. NHW individuals often have greater health care access, which may lead to earlier or more accurate diagnosis. This analysis found that NHB individuals with early-onset AC have similar socioeconomic status to young Hispanic individuals, and presumably experience comparable barriers in health care access. Rates of appendectomies have remained stable over the past 2 decades,[2] and although together these factors may impact survival rates among patients with early-onset AC, they do not completely explain the survival difference between NHB individuals and other racial/ethnic groups.

This study also revealed that nearly half of all early-onset cases were appendiceal adenocarcinomas (mucinous/nonmucinous) and that young NHB individuals with MAAs experienced significantly poorer prognosis compared with NHW individuals. As clinical features did not differ between young NHW and NHB individuals diagnosed with MAAs, these findings suggest that specific molecular characteristics of AC may differ by race/ethnicity and may explain survival differences among young patients. Furthermore, men experienced significantly worse survival compared with women among young patients with MAA and NMAA histologies. These results are aligned with previous reports, including a SEER study that observed increased hazard of death in men compared with women with early-onset colorectal adenocarcinoma.[6] These findings suggest that the observed survival benefit among young women with appendiceal adenocarcinoma may be, to some extent, attributable to biological and behavioral differences between men and women.[7,8]

SEER registry data represent the most complete data for characterizing patterns of AC survival. Limitations are acknowledged in the completeness of patient treatment regimens (eg, chemotherapy), and individual-level features (eg, body mass index). The completeness of data on low-grade appendiceal mucinous neoplasms also varies in SEER, as behaviors of low-grade appendiceal mucinous neoplasms can be classified as noninvasive or uncertain (as to benign or malignant). Consequently, it was not possible to assess whether these malignancies may be driving the observed survival differences by race/ethnicity among young patients with MAAs.

To our knowledge, this study represents the first reporting of AC patterns and survival by race/ethnicity among young patients diagnosed in the United States. Given the lack of guidance for systemic therapies among patients with AC, the study of treatment patterns in cohorts with more comprehensive clinical/individual-level information is necessary to determine the extent to which health care access, health behaviors, and potential environmental exposures may contribute to survival differences among young patients with AC. Molecular characterization of tumors in multi-ethnic cohorts is also warranted to examine heterogeneity in AC by racial/ethnic group. Differences in survival by age of disease onset and race/ethnicity can inform the discovery of risk factors and tumor biomarkers, with implications for AC risk assessment, screening and surveillance, and treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.06.011.

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Correspondence
Address correspondence to: Andreana N. Holowatyj, PhD, MS, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, 2525 West End Avenue, Suite 334-G, Nashville, Tennessee 37203. tel. 615-322-0105. e-mail: andreana.holowatyj@vumc.org.

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Nashville, Tennessee; and Mark A. Lewis, MD, Department of Internal Medicine, Intermountain Healthcare, Murray, Utah.

CRediT Authorship Contributions

Andreana Natalie Holowatyj, PhD, MS (Conceptualization: Lead; Data curation: Lead: Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Software: Lead; Supervision: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead). Kay M. Washington, MD, PhD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Supporting; Writing – review & editing: Supporting). Safia N. Salaria, MD (Investigation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting). Christopher H. Lieu, MD (Investigation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting). Kamran Idrees, MD, MSCI (Investigation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting). Cathy Eng, MD (Conceptualization: Equal; Funding acquisition: Equal; Writing – original draft: Supporting; Writing – review & editing: Supporting).

Conflict of Interest

The authors disclose no conflicts.

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