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ORIGINAL RESEARCH

Analysis of Race and Gender Disparities in Mortality Trends from Patients Diagnosed with Nasopharyngeal, Oropharyngeal and Hypopharyngeal Cancer from 2000 to 2017

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Background: Squamous cell carcinoma of the nasopharynx, oropharynx and hypopharynx constitutes a majority of head neck malignancies. The incidence-based mortality across different races has been noted to be divergent. This study analyzes the trend in incidence-based mortality from the years 2000 to 2017 amongst both the genders in Caucasian/White and African American/Black patients.

Methods: The Surveillance, Epidemiology, and End Results (SEER) Database was queried to conduct a nation-wide analysis for the years 2000 to 2017. Incidence-based mortality for all stages of nasopharyngeal, oropharyngeal and hypopharyngeal cancer was queried and the results were grouped by race (Caucasian/White, African American/Black, American Indian/Alaskan native and Asian/Pacific Islander) and gender. All stages and ages were included in the analysis. *t*-test was used to determine statistically significant differences between various subgroups. Linearized trend lines were used to visualize the mortality trends of all sub groups.

Results: Across all races, the male to female gender disparity in mortality was ~1:3 in patients with nasopharynx and became worse to ~1:4 and ~1:5 for patients with oropharyngeal and hypopharyngeal cancers, respectively. Notably, the highest incidence-based mortality for nasopharyngeal cancers is seen in Asian/pacific Islander males and a similar peak is noted for hypopharyngeal cancers in African American/Black males. Incidence-based mortality rates (per 1000) for nasopharyngeal, oropharyngeal and hypopharyngeal cancer of all races and both the genders was noted to be divergent.

Conclusion: A significant gender disparity exists in all three pharyngeal cancers across all races. It is unclear if female gender is protective but further study is warranted in a stage-specific and age-specific manner to better understand this disparity.

Keywords: cancer, mortality, race, gender

Introduction

Squamous cells carcinoma (SCC) of the nasopharynx (NPC), oropharynx (OPC), and hypopharynx (HPC) is a common type of head and neck cancer that arises from mucosal surfaces lining the pharynx. SCCs of the pharynx are further classified into nasopharyngeal, oropharyngeal, and hypopharyngeal cancer based on the anatomical landmarks. Cancers at these locations also differ histologically and anatomically and have various causal factors such as tobacco and alcohol use and HPV infection. Cancer of the pharynx is generally asymptomatic in its early stages, often evident

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only once the cancer has advanced. Once symptomatic, patients diagnosed with cancer of the pharynx may experience neck swelling, persistent headaches, congestion, facial pain, and tinnitus. The Center for Disease Control attributes 3% of all cancers diagnosed in the United States per year to cancers of the oral cavity and pharynx.[1] Of head and neck cancers (HNC), tumors of the mouth and oropharynx are some of the most common.[2] It is reported that incidence rates for oral and pharyngeal cancer combined increased during the period of 2007–2016. The age-adjusted incidence of oral cavity and oropharyngeal cancer from 2012 to 2016 in the United States was 11.3 cases per 100,000 persons per year. Hypopharyngeal cancers are more rare, with an incidence rate of only 0.7 cases per 100,000 persons and a lower 5-year survival rate in comparison to oropharyngeal cancer.[3] Like hypopharyngeal squamous cell carcinoma, cancer of the nasopharynx is rare and has an annual incidence rate of 0.7 cases per 100,000 persons in the United States.[4]

A history of alcohol consumption and smoking is the major risk factors for cancer of the pharynx. Chronic exposure of epithelial linings in the pharynx to irritants in alcohol and tobacco results in the development of malignant lesions. Harris et al revealed in their study that the majority of patients with oral and oropharyngeal cancer drink alcohol and smoke tobacco.[5] Patients who both consume large quantities of alcohol and smoke are two to three times more at risk of developing oral and oropharyngeal cancer. Both risk factors indicate a dose-responsive relationship to pharyngeal cancer.[6] In addition to regular alcohol and tobacco use, infection of the Epstein-Barr virus specifically is highly associated with cancer of the nasopharynx. Male individuals and those over the age of 54 are also at risk of developing nasopharyngeal cancer and other cancers of the head and neck.[7] Although not necessary, Human Papilloma Virus strain 16 (HPV 16) infection is a sufficient cause of head and neck cancer and has a causal relationship with cancer of the oropharynx, conferring up to a 15 fold increased risk of developing the cancer.[8,9] Risk factors for hypopharyngeal cancer include tobacco use, alcohol consumption, male gender, and age over 65 years. Studies have also shown that exposure to asbestos results in a significant increase in risk of developing cancer of the hypopharynx.[10]

Although reports note varied rates in pharyngeal cancers primarily due to differences in alcohol consumption and use of tobacco and other chewed products, racial and gender disparities in mortality are present. It has been shown that African American/Blacks have a lower combined 5-year survival rate from cancer of the oral cavity and oropharynx in comparison to Caucasians/Whites.[11] As Black race has been shown to be associated with worse survival and prognosis in patients with cancers of the pharynx, this may provide a public health interventional opportunity to address racial disparity and cancer outcomes. Furthermore, studies have shown a disparity in outcomes of pharyngeal cancers between the male and female genders, with males experiencing greater risk of developing the cancer and poorer survival rates.[12,13] Given this disparity, it is imperative to consider factors such as race and gender in addition to confounding variables such as tumor stage, environmental factors, and age when analyzing incidence-based mortality trends between different subgroups.

As literature regarding influences of race and gender on mortality and outcome from cancer of the pharynx is sparse, there is a need to assess the disease in the context of these variables. Using data from the Surveillance, Epidemiology, and End Results (SEER) Database from 2000 to 2017, this study aims to analyze incidence-based mortality trends from cancers of the nasopharynx, oropharynx, and hypopharynx between male and female genders and amongst the races of Caucasian/White, African American/Black, American Indian/Alaskan Native, and Asian/Pacific Islander. A goal of this study is to assess how demographic factors impact prognosis of pharyngeal cancers and corroborate or counter previous studies to better understand variables that influence incidence-based mortality. The study thereby aims to promote targeted diagnostic and treatment strategies for certain populations of individuals. This study was presented in the form of an abstract at ASCO 2019.

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER) Database was used to gather incidence-based mortality data from all stages of squamous cell carcinoma of the nasopharynx, oropharynx, and hypopharynx from 2000 to 2017. SEER is a National Cancer Institute (NCI) database and source of cancer incidence, survival, and statistics in the United States. SEER collects its data on patient demographics, primary tumor site, tumor morphology, and incidence from cancer registries that extend to 34.6% of the US population. This national database has de-identified patient data and is publicly

available, hence it was deemed to be exempt from IRB approval.

Study Population

Incidence-based mortality of patients of both genders and all and stages of pharyngeal squamous cell carcinoma were included in this study. Patient demographic information such as age and race were included in analysis. This study queried its data and categorized patients to 4 racial/ethnic groups: Caucasian/White, African American/Black, American Indian/Alaskan native, and Asian/Pacific Islander.

Outcomes

Incidence-based mortality rates from nasopharyngeal, oropharyngeal, and hypopharyngeal cancers were analyzed based on gender (male or female) and the four racial/ethnic groups. Incidence-based mortality rate was defined as the number of deaths due to these cancers among the total number of diagnosed patient cases in SEER regions.

Statistical Analysis

t-test was used to determine statistical significance in male to female gender and racial disparities between the aforementioned subgroups. Linearized trend lines were used to compare mortality trends between males and females and across all four racial groups for nasopharyngeal, oropharyngeal, and hypopharyngeal squamous cell carcinomas. Statistical significance was defined as a P-value <0.05.

Results

The average incidence-based mortality rates per 1000 individuals for nasopharyngeal (NPC), oropharyngeal (OPC), and hypopharyngeal (HPC) cancer across all four races and both the genders are shown in Table 1. There is evidence of a male to female gender disparity in mortality across all races. The male to female ratio in mortality from NPC is approximately 3:1. This gender disparity worsens when comparing mortality rates between genders for OPC and HPC. The approximate male to female ratio in mortality rates for patients with OPC and HPC are 4:1 and 5:1, respectively. African Americans/Blacks, particularly males, experience the highest mortality rates for OPC and HPC when compared to other races. However, one of the highest incidence-based mortality across all three cancer types, races, and genders is noted in Asian/Pacific Islander males with NPC, with a rate of ~14.3 deaths per 1000 individuals.

Similarly, African American/Black males have a similar peak in incidence-based mortality from HPC with a rate of ~15.2 deaths per 1000 individuals (Figure 1). Although Asian/Pacific Islanders with NPC experience the highest average mortality rates from 2000 to 2017, this population has the lowest mortality rates from OPC and HPC for both genders across all races (Figures 2 and 3). While Asian/Pacific Islanders had the greatest increase in mortality rates from NPC between 2000 and 2017, Caucasian/Whites and American Indians/Alaskan Natives experienced the greatest rise in mortality rates from OPC and HPC from 2000 to 2017, respectively.

Discussion

This study is a population-based analysis of trends in incidence-based mortality rates from all stages of cancers of the nasopharynx (NPC), oropharynx (OPC), and hypopharynx (HPC) in the United States. Patients of both genders and all ages with NPC, OPC, and HPC were identified utilizing the SEER database from years 2000–2017. We evaluated mortality based on variables such as race and gender. Review of both racial and gender disparities in pharyngeal cancers is uncommon in the literature. This study is one of the few studies that address such factors in incidence-based

Table 1 Average Incidence-Based Mortality Rates (per 1000) from 2000 to 2017 for NPC, OPC, and HPC Across Race and Gender (* p < 0.05)

		Nasopharynx	Oropharynx	Hypopharynx
Caucasian/White	**Male**	3	3.4	7.3*
	Female	1.1	1	1.7
African American/Black	**Male**	5.7	7.5	15.2*
	Female	1.8	1.8	2.3
American Indian/Alaskan Native	**Male**	7.3*	1.7	6.6
	Female	3.6	0.5	0.7
Asian/Pacific Islander	**Male**	14.3*	1.1	4.9
	Female	4.2	0.3	0.7

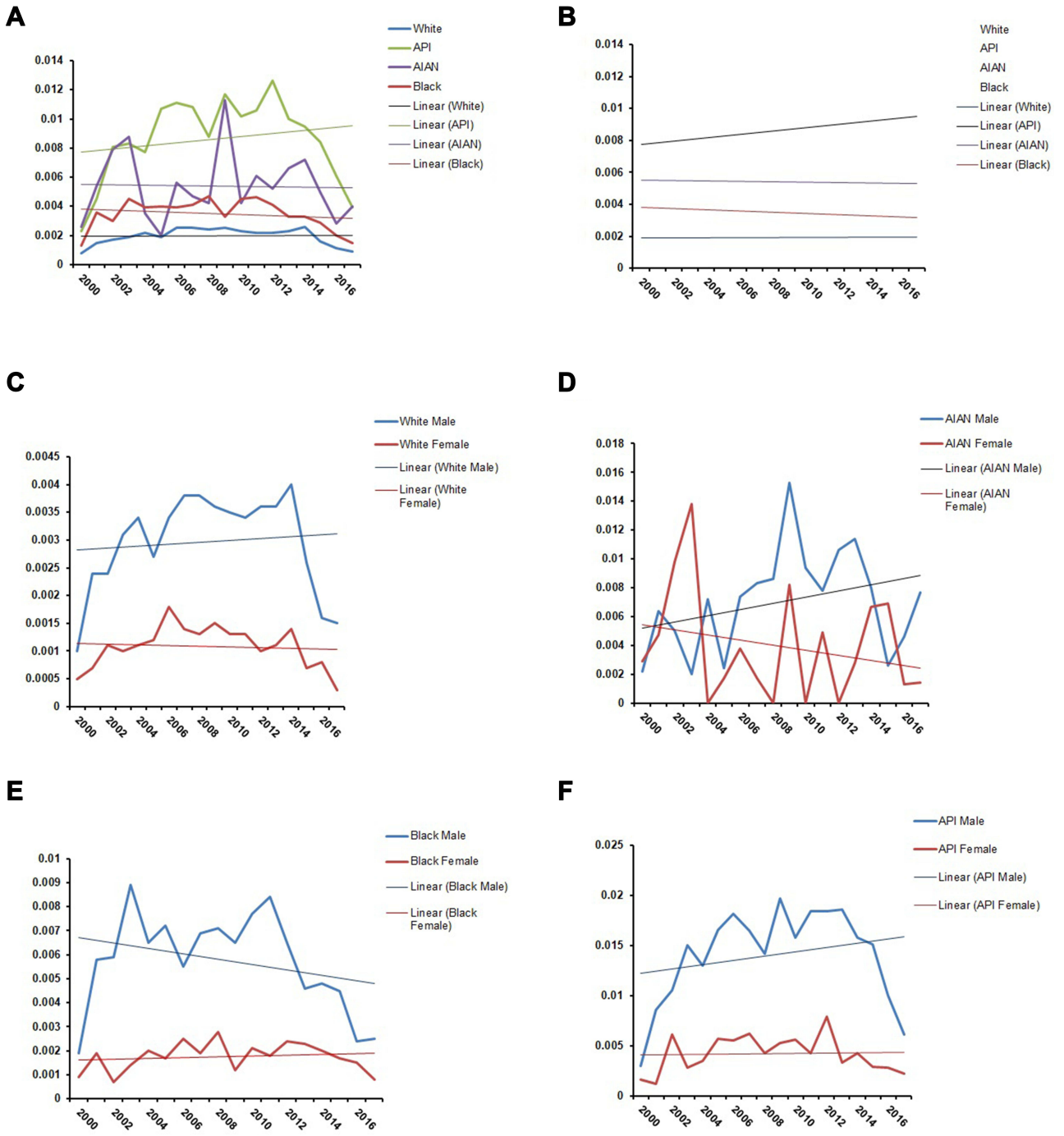

Figure 1 Mortality trends of nasopharyngeal cancer (NPS) with respect to race and gender: (**A**) Trends by race, (**B**) Linearized trends by race; (**C**) Trends by gender in Caucasians; (**D**) Trends by gender in American Indian/Alaskan Natives; (**E**) Trends by gender in African Americans and (**F**) Trends by gender in Asian/Pacific Islanders.

mortality from these cancers. It supports previous study findings that head and neck cancers lead to mortality disproportionately in males and the African American/Black population.

This study shows that Asian/Pacific Islanders (APIs) had the highest incidence-based mortality rates from NPC during the period of 2000 to 2017. Of note, cancer was the leading cause of death in APIs in the United States in 2007.[14] It has been found that APIs have the highest death rates for some of the less common cancers, particularly those associated with infectious agents, such as nasopharynx, liver, and stomach.[15] Among the Chinese in particular, several studies have proposed that the Epstein-Barr virus (EBV), smoked fish products, and genetic

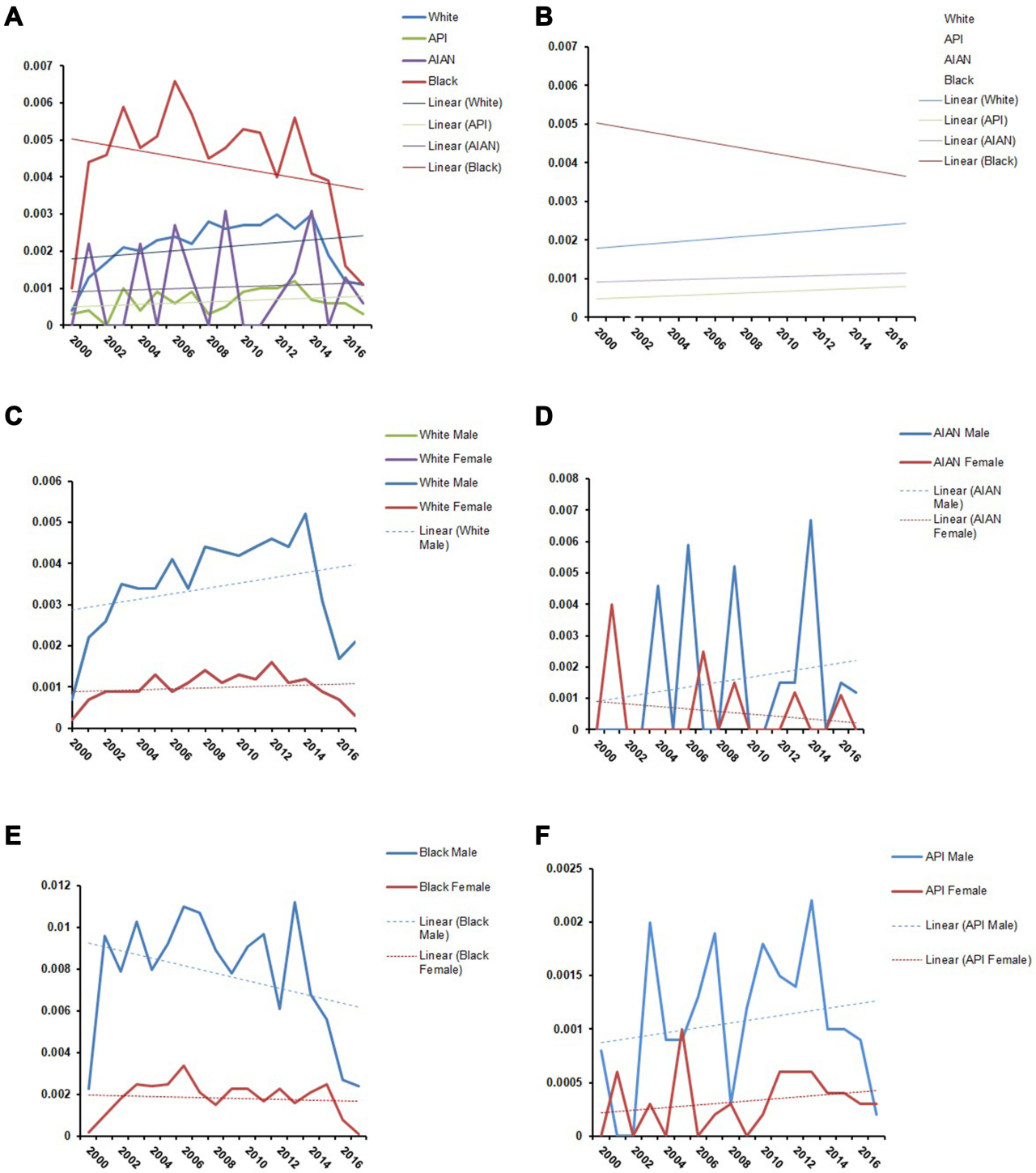

Figure 2 Mortality trends of oropharyngeal cancer (OPC) with respect to race and gender: (**A**) Trends by race, (**B**) Linearized trends by race; (**C**) Trends by gender in Caucasians; (**D**) Trends by gender in American Indian/Alaskan Natives; (**E**) Trends by gender in African Americans and (**F**) Trends by gender in Asian/Pacific Islanders.

predispositions are associated with higher rates of NPC in the API population.[16,17] High prevalence of smoking and alcohol consumptions in Asian countries, especially amongst males, could also contribute to the high mortality rates from NPC with male preponderance. The Global Adult Tobacco Survey reported that 63% of men in China smoked in the year 2010.[18]

Furthermore, African American/Black individuals of both genders had the highest mortality from both OPC and HPC across all races. A retrospective cohort study

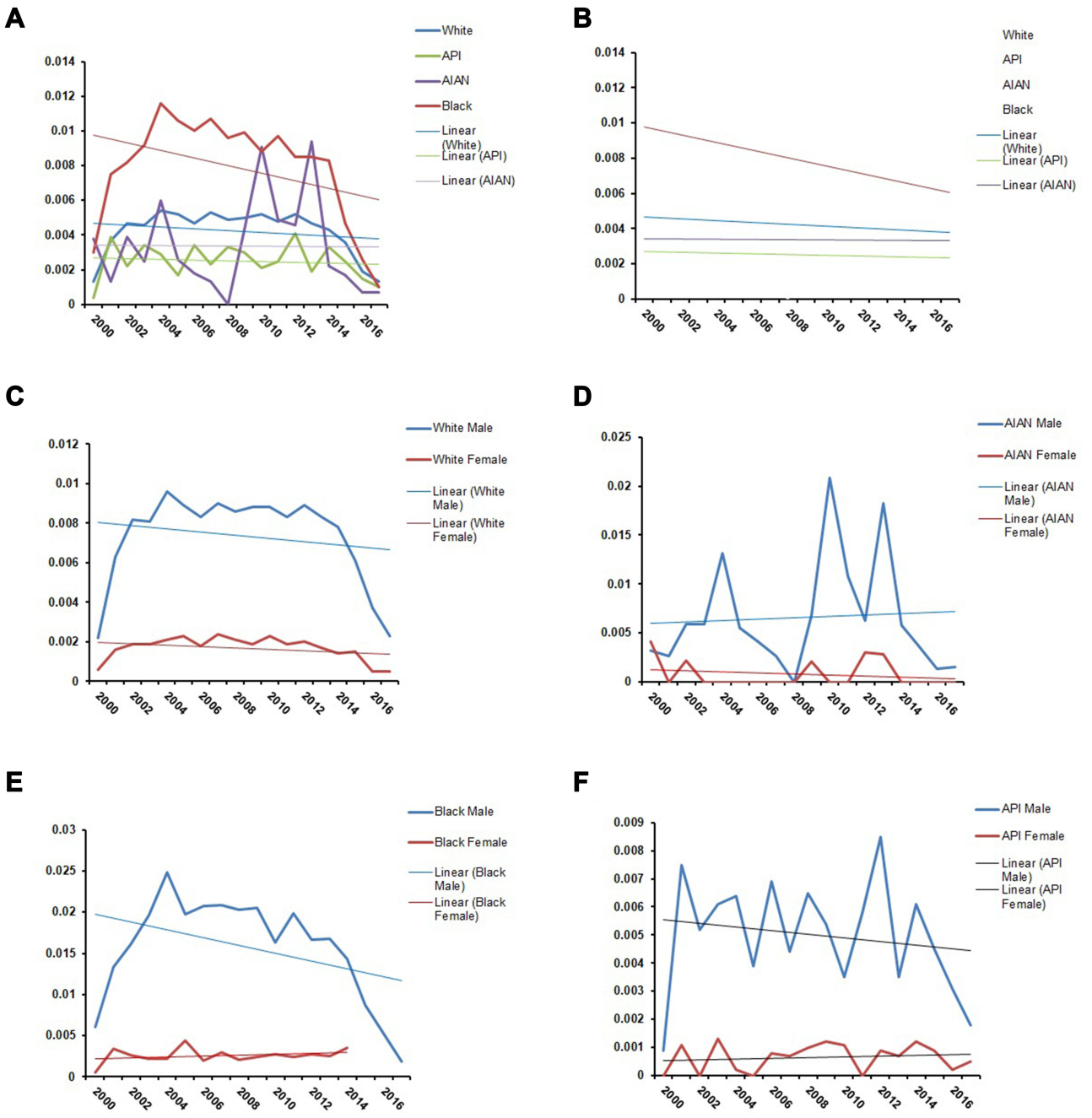

Figure 3 Mortality trends of hypopharyngeal cancer (HPC) with respect to race and gender: (**A**) Trends by race, (**B**) Linearized trends by race; (**C**) Trends by gender in Caucasians; (**D**) Trends by gender in American Indian/Alaskan Natives; (**E**) Trends by gender in African Americans and (**F**) Trends by gender in Asian/Pacific Islanders.

by Megwalu et al supports the significant finding that African American/Black patients with OPC have the worst survival after adjusting for factors like age, sex, and year of diagnosis.[19] This finding may possibly be attributed to worse socioeconomic conditions that hinder access to treatment for these individuals. A similar discovery has been noted with NPC. The Epstein-Barr virus is known to be a primary risk factor for non-keratinizing squamous cell carcinoma of the nasopharynx. Racial disparities are noted for this cancer, with African American/Black males displaying the worst survival across histological subtype.[13] A study by Morse et al similarly noted racial disparities in analysis of oral and pharyngeal cancer. It was found that during the period of 1998–2002, the incidence rate of this cancer was 20% higher in Black males than in White males, with an age-adjusted mortality

rate being 82% greater in Black males.[20] It is of public health relevance to consider reasons for the significantly lower 5-year survival rates in African American/Blacks, particularly males, with pharyngeal cancer. As examined in a comparative study by Shavers et al, a potential explanation for this finding lies in racial/ethnic differences in diagnosis, disease stage, and treatment. When compared to White patients, African American/Black patients are less likely to get cancer-directed treatment or cancer-directed surgery.[21] Concordantly, more unfavorable cancer stages and lower rates of cancer screenings were found in African American/Black individuals.[21] Racial disparity in pharyngeal cancer mortality may as such be attributed to differential rates in early detection. The cancer stage at diagnosis has a strong influence on length of survival, with earlier caught, localized oral and pharyngeal cancers conferring the best chances of 5-year survival.[22]

When compared to the female subgroup, males in this study experienced greater mortality rates for all three pharyngeal cancers. This finding is supported by studies that show meaningful differences between incidence of head and neck cancers (HNC) in men and women. For example, Human Papillomavirus (HVP) infection is a major risk factor of HNC, accounting for 40–80% of OPC cases in the United States.[23] A retrospective study by Mourad et al found that the rate of HPV infection with regard to OPC was significantly higher in men compared to women. The gender disparity of HPV-related OPC indicated a male:female ratio of 4:1.[24] A study by the National Health and Nutrition Examination Survey also notes a gender disparity, with 10.1% of men and 3.6% of women having oral HPV attributable to oropharyngeal cancer.[25] Similar results are shown in studies of NPC, with females conferring the highest 5-year survival estimates compared to males and across racial groups.[13] The American Cancer Society similarly notes that cancer of the larynx and hypopharynx are four times more likely in men than in women.[26] These findings could be due to higher rates of alcohol and tobacco co-use among males than in females.[27]

This study found that APIs had the greatest increase in mortality rates from NPC between 2000 and 2017. The greatest increases in mortality from OPC and HPC during this time frame were in Caucasian/Whites and American Indians/Alaskan Natives (AIAN), respectively. An analysis of HNC incidence from 1995 to 2005 supports this finding, reporting that incidence of HPV-associated cases of HNC increased at the greatest rate in Non-Hispanic White males.[28] This is a significant finding, as the CDC estimates 70% of oropharyngeal cancers are caused by HPV infection.[29] The rise in mortality from OPC from 2000 to 2017 may be the result of the significantly increased prevalence of HPV in the United States.[30] While the incidence of HPV-positive OPC has increased, the incidence of HPV-negative cancers has drastically declined in the United States. The ratio of HPV-positive to negative cases after 1995 was 3.81.[28,30,31] American Indians in the Northern Plains of North and South Dakota, Nebraska, and Iowa reportedly have significantly elevated incidence rates of HNC when compared to the White population, with particularly higher incidence of NPC, as supported in this study. Rates of different cases of HNC in the AIAN population do however vary by region.[32] Studies examining outcome disparity in AIANs with head and neck squamous cell carcinoma have shown that American Indians experience worse survival than Whites. American Indians in South Dakota are reported to have a greater risk of alcohol abuse, smoke, lack access to cancer centers, and present with late-stage disease which may explain the population's relatively high mortality rate from NPC.[33] Further investigation into the relationship of sociodemographic factors and mortality from HPC in the AIAN population during this period is warranted.

Age, environmental factors, education level, and stage of the tumor are also important considering factors in studying mortality from pharyngeal cancers. For instance, a study has revealed that educational attainment influences mortality from oral cavity and pharyngeal cancer. With the exception of Black women, mortality rates for patients with these cancers decreased significantly among men and women with over 12 years of education, regardless of race/ethnicity.[34] This may reflect differing sexual and smoking behaviors among populations of different educational status. Age is also associated with high incidence of mortality from pharyngeal cancer. A study from São Paulo found that patients with advanced age had the worst survival rates, which could be a result of other comorbid complications from aging.[35] Occupational exposure to hazardous elements like asbestos and chlorinated solvents has been recently studied to assess risks of developing pharyngeal cancers. These studies have found that exposure to methylene chloride, a material commonly used in industrial processes like paint stripping, as well as asbestos are associated with an increased risk and significantly

increased risk of hypopharyngeal cancer (HPC), respectively.[10,36]

This study has several limitations. Because this study is retrospective and used a database which could contribute to inherent study bias, we are unable to draw causal relationships from our data. As a result, we must infer potential explanations for our results. We also acknowledge that there may be inconsistencies when comparing data between studies. Certain racial and ethnic groups may have a higher prevalence of comorbid conditions resulting in higher mortality rates. Furthermore, as prevalence and mortality from certain HNCs in the AIAN population vary by region, comparison of data between AIAN and other racial/ethnic groups may be misleading. As reported in previous studies, many individuals in the African American/Black and AIAN populations may have presented with late-stage cancer upon diagnosis which would thereby skew mortality data. This potential lack of consistency in classifying disease stage can make comparisons difficult.

Conclusion

Using the national SEER database, this study analyzes the rates of incidence-based mortality from all stages of cancer of the nasopharynx, oropharynx, and hypopharynx with respect to race/ethnicity and gender of patients between the years 2000 and 2017. Overall, our study indicates varied levels of mortality amongst all races and genders. Across all racial and ethnic groups, there are higher incidence-based mortality rates in males compared to females. The highest level of mortality was found in African/American males diagnosed with hypopharyngeal cancer, with a similar high mortality rate in male Asian/Pacific Islanders with nasopharyngeal cancer. African American/Blacks had the highest mortality rates during this period for both hypopharyngeal and oropharyngeal cancers, while Asian/Pacific Islanders had the highest mortality trends for nasopharyngeal cancer. Our results imply that African American males have some of the worst outcomes in terms of incidence-based mortality from pharyngeal cancers, as supported in the literature. Additional investigation into the relationship between genetic factors and sociodemographic factors like environmental and occupational conditions and racial and gender mortality disparities should be undertaken. Further research conducted on cancer of the hypopharynx in relation to race and gender is warranted, as literature on epidemiology and mortality primarily focus on cancers of the oral cavity, oropharynx, and nasopharynx. This could fill gaps in our knowledge of health disparity and improve individualized healthcare and patient outcomes.

Ethics Statement

This study is based on a publicly available national database which has de-identified patient data with no patient contact or intervention.

Acknowledgments

Preliminary results shown in the study were presented as an abstract at ASCO 2019 and may be found at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.e17533. This manuscript is not under consideration in any other journal. The authors declare that there was no funding for this study. All authors have read the manuscript and agree to the content.

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Disclosure

The authors report no conflicts of interest in this work.

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