MEDDOCS Open Access Publisher

ISSN: 2639-9229

International Journal of Innovative Surgery

Open Access | Mini-Review

Gender Disparities with Survival of Head and Neck Cancer Patients in the COVID-19 Pandemic

Erick Yuen[1]; Elise E Zhao[1]; Sarah A Imam[2]; Shaun A Nguyen[1]*

[1]Department of Otolaryngology – Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA.

[2]Department of Health and Human Performance, The Citadel, Charleston, South Carolina, USA.

***Corresponding Author(s): Shaun A Nguyen MD**

Professor and Director of Clinical Research, Department of Otolaryngology – Head and Neck Surgery 135 Rutledge Avenue, MSC 550, Charleston, SC 29425, USA.

Tel: 843-792-1356; Email: nguyensh@musc.edu

Received: Dec 16, 2020

Accepted: Feb 05, 2021

Published Online: Feb 08, 2021

Journal: International Journal of Innovative Surgery

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Abstract

To date, the Coronavirus Disease 2019 (COVID-19) pandemic has resulted in over 860,000 confirmed deaths worldwide. Although infection rates between men and women are similar, men have about twice the risk of death from COVID-19, suggesting that biological sex may be a significant determinant of disease severity. A similar trend has been observed in patients with Head and Neck Cancer (HNC), in which male sex is associated with higher incidence-based mortality rates. Prior studies have sought to ascertain whether these disparities are influenced by physiological or social factors. During these unprecedented times, when the delivery of health care is disrupted, a deeper understanding of how these two potential pre-disposing factors, namely male sex and cancer, affect COVID-19 outcomes is warranted. The goal of this commentary is to raise awareness of the complex interplay between biological sex and survival outcomes of patients with COVID-19 and HNC.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has caused profound disruption to the delivery of health care. Many outpatient clinics shut down or restricted visits to emergencies to protect patients and staff from infection. Shortages of personal protective equipment (PPE) and the need to conserve hospital resources for COVID-19 patients resulted in the cancellation and postponement of elective surgeries, including cancer cases. Unfortunately, cancer cases, including Head and Neck Cancer (HNC) cases, are time sensitive. Delayed treatment is associated with higher mortality in patients with HNC [1]. All patients with cancer are more susceptible to severe presentations of COVID-19 compared to patients without cancer [2]. In addition, patients recently treated with chemotherapy or surgery experienced more severe events from COVID-19 [3]. Despite the increased morbidity from COVID-19, surgery or chemoradiation treatment should not be delayed in patient with HNC at low risk of infection [4].

As the pandemic continues to unfold, emerging data suggests that certain populations are at greater risk of poorer COVID-19 outcomes. There is mounting evidence that biological sex may be a predisposing factor [5]. Epidemiological studies

Cite this article: Yuen E, Zhao EE, Imam AA, Nguyen SA. Gender Disparities with Survival of Head and Neck Cancer Patients in the COVID-19 Pandemic. Int J Innov Surg. 2021; 4(1): 1015.

report that although the number of male cases is similar to that of female cases, men have approximately twice the risk of death from COVID-19 [6]. Many theories, such as differences in occupation, lifestyle (including smoking and alcohol use), and medical comorbidities, have been proposed to account for the observed sex disparities in clinical outcomes. Perhaps of greater interest to otolaryngologists is whether biological sex influences outcomes of patients with HNC once infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Sex-related survival disparities among patients with HNC have previously been studied. Although there is no evidence to suggest that male or female sex confers a survival advantage when both groups receive similar cancer care [7], preliminary data shows that certain demographics, such as men and cancer patients, may be more susceptible to severe COVID-19 disease.

There is a limited amount of peer-reviewed, original research studies regarding the impact of biological sex on the management of patients with HNC during the COVID-19 pandemic. However, sex-related health disparities have been identified before the pandemic and may have been amplified as more patients experience disruptions to treatment. The goal of this commentary is to review the existing literature on biological sex as a potential determinant of COVID-19 outcomes and assess its relevance to patients with HNC during the ongoing pandemic.

Methods

Literature review and evidence collection

A review of the English literature was performed by two authors (EY, EEZ), using PubMed/Medline to search for epidemiology, demographics, and news articles on sex-related disparities in the COVID-19 or Head and Neck cancer population. A search strategy was employed with the following search strings: "head and neck cancer OR head and neck" with "biological sex or gender." An independent search was also performed using the following search strings "covid OR covid-19 OR coronavirus" with "biological sex OR gender" in the last year on PubMed and Google. To identify additional sources, the reference lists of relevant articles were hand searched. Results were limited to articles in the English language.

After the completed search, a total list of records was obtained and duplicates removed. A final list of full text articles was then compiled, and one author (EY) independently screened each article.

Table 1: Incidence-based mortality rates (per 1000 people) for nasopharyngeal, oropharyngeal, and hypopharyngeal cancer stratified by sex and race. Data source: Surveillance, Epidemiology, and End Results (SEER) database (2000-2014).

		Nasopharynx	Oropharynx	Hypopharynx
Caucasian	Male	3.2	3.7	7.9
	Female	1.2	1	1.8
African American	Male	5.7	7.9	17.1
	Female	1.9	2	2.6
American Indian/ Alaskan Native	Male	8.2	1.9	7.7
	Female	3.9	0.6	1.1
Asian/Pacific Islander	Male	15.2	1.3	5.5
	Female	4.6	0.3	0.7

Table 2: Incidence and mortality rates (per 100,000 people) for oral cavity and pharyngeal cancers reported in 2017. Data source: Centers for Disease Control and Prevention.

	Sex	Age-Adjusted Rate
Incidence	Male	17.7
	Female	6.3
Mortality	Male	4.0
	Female	1.3

Table 3: Percentage of COVID-19 cases and deaths by sex in selected countries with the highest number of confirmed cases.

	Cases		Deaths		Proportion of deaths in confirmed cases
	Male, %	Female, %	Male, %	Female, %	M: F ratio
Thailand	55.7	44.3	76.0	24.0	2.5
Albania	47.0	53.0	66.0	34.0	2.2
Jamaica	43.4	56.6	60.0	40.0	2.0
Netherlands	38.7	61.3	55.0	45.0	1.9
Peru	55.9	44.1	70.8	29.2	1.9
Dominican Republic	52.0	48.0	66.5	33.5	1.8
Greece	54.5	45.5	67.9	32.1	1.8
Guatemala	61.1	38.9	74.2	25.8	1.8
China	51.1	48.9	63.5	36.2	1.7
Denmark	43.6	56.4	56.5	43.5	1.7
England	43.4	56.6	56.6	43.4	1.7
Spain	43.0	57.0	56.6	43.4	1.7

Sweden	41.6	58.4	54.7	45.3	1.7
Ukraine	41.2	58.8	53.7	46.3	1.7
Belgium	38.8	61.2	50.3	49.7	1.6
Colombia	52.9	47.1	63.8	36.2	1.6
Italy	46.1	53.9	57.6	42.4	1.6
United States	48.4	51.6	53.9	46.1	1.3
Canada	44.7	55.3	45.7	54.3	1.0
Pakistan	74.0	26.0	74.2	25.8	1.0

Data source: Global Health 50/50 M: Male, F: Female

Discussion

HNCs are more than twice as common among men than women [8]. In addition, female sex may be associated with lower incidence-based mortality rates across all pharyngeal cancers (Tables 1-2) [9,10]. Although differences in tobacco smoking, alcohol consumption, and Human Papilloma Virus (HPV) infection are often cited as contributing factors, they do not fully explain this disparity [11]. Studies have previously reported on sex-related disparities among patients with HNC. An analysis of cancer registry data from a California hospital system demonstrated that women with HNC were less likely to receive intensive chemoradiation compared to men. After controlling for variables such as age and medical comorbidities, the ratio of cancer to non-cancer mortality was two times higher for women than men [12]. Taken together, the data suggests that women with HNC may be undertreated. In addition, women are underrepresented in Head and Neck Squamous Cell Carcinoma (HNSCC) chemotherapy clinical trials, whose results direct the National Comprehensive Cancer Network guidelines for chemotherapy use [13]. Due to the complex interplay between biological sex and disease processes in general, this commentary sought to ascertain the differential impact of COVID-19 on men and women worldwide and examine the potential consequences for patients with HNC.

The first reported cases of SARS-CoV-2 infection originated from Wuhan, China in November 2019. Since then, the novel coronavirus has rapidly disseminated to other countries, resulting in a global outbreak. As of September 3, over 26 million cases and 860,000 deaths have been confirmed worldwide [14]. Globally, 60% of deaths due to COVID-19 occur in men, leading many to speculate the mechanisms by which the novel coronavirus disproportionately affects male patients [15]. There is growing data to suggest that male sex is a risk factor for severe COVID-19 disease. A cohort study of 17 million adults in England, for instance, showed a strong association between male sex and risk of death from SARS-CoV-2 infection [16]. Table 3 shows the percentage of COVID-19 cases and deaths stratified by sex in selected countries with the highest number of confirmed cases [17].

Biological sex has previously been recognized to have a significant impact on the prevalence of infectious diseases among men and women. The prevalence of hepatitis A and tuberculosis, for instance, are significantly higher in men relative to women [18]. In addition, vaccines may be more efficacious in women, who can mount a more robust immune response compared to their male counterparts [19]. On the other hand, social factors have been shown to be the primary determinants of disease severity for some infectious agents, such as Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV). The majority of reported MERS cases, which disproportionately affected older men, originated from Saudi Arabia during the outbreak in 2012. After accounting for age and comorbidity status, one study [20] found that sex did not have a significant impact on fatality rates. Rather, the presence of comorbidities conferred almost a four times greater risk of fatal infection. To account for these conflicting observations, two main hypotheses have been put forth. While one postulates that these disparities are rooted in physiological differences, such as in sex hormone levels and genetic architecture, the second proposes that social and cultural factors have a greater influence [18].

Physiological hypothesis

To examine the merits of the physiological hypothesis, many studies aimed to ascertain the impact of estrogen on COVID-19 outcomes between men and women. Estrogen signaling is believed to serve a protective role against SARS-CoV-2 infection [21]. The hormone 17β-estradiol, a primarily female sex steroid, has been shown to regulate the expression of Angiotensin-Converting Enzyme 2 (ACE2), a key component for SARS-CoV-2 cell entry, in human bronchial epithelial cells [21]. Among female COVID-19 patients receiving systemic estradiol therapy, the fatality risk for women > 50 years of age was reduced by more than 50% compared to non-users in the same age group [22]. The role of hormones in mitigating disease has also been studied in women with HNC [23]. Although there is a paucity of literature on this topic, available evidence suggests that estrogen receptor positivity is associated with improved survival among patients with oropharyngeal cancer [24]. Furthermore, hormone replacement therapy in postmenopausal women has been observed to have a borderline protective effect for HNSCC [25]. In sum, the effects of endogenous and exogenous sex hormones on various disease processes remain understudied and warrant further investigation in these at-risk populations.

In addition to hormonal influences, sex differences in immune phenotype may account for male susceptibility to severe COVID-19 infections. Key variations in immune response to SARS-CoV-2 infection between male and female patients have recently been identified [5]. First, higher levels of several pro-inflammatory cytokines, including IL-8 and IL-18, were observed in male patients. Second, a more robust T-cell response was elicited in female patients compared to their male counterparts. More importantly, a poor T-cell response was associated with worse disease outcomes in infected men [5]. These findings are consistent with those of previous studies suggesting that the immune microenvironment may be vastly different

in male and female HNSCC patients [26]. These differences are clinically relevant, as men and women respond differently to immunotherapy [27]. The literature therefore highlights the need to better understand the impact of biological sex on the physiological response to various disease processes. Furthermore, the development of a sex-based approach for the management of COVID-19 patients, particularly those with comorbid HNC, may be warranted.

Behavioral hypothesis

In contrast, proponents of the behavioral hypothesis favor differences in social factors, pre-existing conditions, and gender-segregated occupational exposures as the most probable explanations to account for the sex disparities in COVID-19 outcomes. Smoking, and to a lesser extent alcohol consumption, have been examined as potential predisposing factors for SARS-CoV-2 infection. Although regional variations exist, smoking and alcohol use prevalence are higher among adult men than women worldwide [28]. In 2018, 288 million men compared to 12.6 million women in China were smokers [29,30]. In the United States, 15.6% of adult men versus 12% of adult women were estimated to use tobacco products [31]. In addition to being the single largest risk factor for HNC, early evidence suggests that tobacco use increases ACE2 expression in the lungs [32], representing a possible mechanism in which a social behavior, rather than biological sex, predisposes to poorer COVID-19 outcomes. Furthermore, alcohol consumption not only constitutes another major risk factor for HNC, but has also been linked to an elevated risk of developing severe COVID-19 disease. According to the European World Health Organization (WHO), alcohol use weakens the immune system, with heavy consumption associated with an increased risk of Acute Respiratory Distress Syndrome (ARDS) [33]. The significant overlap in social factors and medical comorbidities between male patients with HNC and COVID-19 support the behavioral hypothesis, in which sex-related disparities are related less so to biological differences. However, as the current literature studying the association between these factors and the incidence and severity of COVID-19 is scant, with some finding no connection [34,35], conclusive remarks cannot be made at this interval.

Impact of COVID-19 on patients with HNC

The COVID-19 pandemic affected many patients' access to treatment. Otolaryngologic procedures are considered at high risk of generating aerosol and COVID-19 transmission. To protect staff and patients from aerosol exposure, institutions delayed surgeries but attempted to proceed with time sensitive HNC resection. Unfortunately, some patients with HNC inevitably experienced surgery delay as a recent survey showed that some institutions temporarily suspended free flap surgery [36]. An increase in the overall treatment time and the postoperative time to radiation have been shown to increase mortality [37,38]. Further interruption to chemoradiation is expected during the pandemic when patients become infected. Since these therapies may increase morbidity from COVID-19, patients who test positive or are at high risk of infection are recommended to delay treatment as clinicians are forced to balance the two risks [4]. Male patients with HNC are more likely to have comorbidities, which is associated with reduced survival in both HNC and COVID-19 [39,40]. Poorer health at baseline in combination with reduced access to health care place male patients with HNC at a higher risk of complications from both COVID-19 and delayed HNC treatment. Although data on outcomes has yet to become available, these patients are likely to fare poorly.

Limitations

This commentary is limited by data availability. Worldwide, many countries do not report reliable data for COVID-19 patients. For example, reports of COVID-19 in indigenous communities are limited to anecdotal news articles. As these populations live in isolated communities and lack access to health care, it is difficult to assess the impact of COVID-19 in these settings. Regarding patients with HNC, little is known about the association of biological sex with treatment outcomes from pre-pandemic times. Increased reporting of biological sex in published studies will allow for an improved understanding of the factors contributing to the observed disparities.

References

1. Liao DZ, Schlecht NF, Rosenblatt G, Kinkhabwala CM, Leonard JM. et al. Association of Delayed Time to Treatment Initiation With Overall Survival and Recurrence Among Patients With Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population. JAMA Otolaryngol Head Neck Surg. 2019; 145: 1001-1009.
2. Dai M, Liu D, Liu M, Zhou F, Li G, et al, Patients with Cancer Appear More Vulnerable to SARS-CoV-2. A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020; 10: 783-791.
3. Liang W, Guan W, Chen R, Wang W, Li J, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020; 21: 335-337.
4. Chaves ALF, Castro AF, Marta GN, Junior GC, Ferris RL, Giglio RE, et al., Emergency changes in international guidelines on treatment for head and neck cancer patients during the COVID-19 pandemic. Oral Oncol. 2020: 107; 104734.
5. Takahashi T, Ellingson MK, Iwasaki A. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. 2020.
6. Bhopal SS, Bhopal R. Sex differential in COVID-19 mortality varies markedly by age. The Lancet. 2020; 396: 532-533.
7. Roberts JC, Li G, Reitzel LR, Wei Q, Sturgis EM, et al. No evidence of sex-related survival disparities among head and neck cancer patients receiving similar multidisciplinary care: a matched-pair analysis. Clin Cancer Res, 2010; 16: 5019-5027.
8. Siegel RL, Miller KD, Jemal A, Cancer statistics. CA: A Cancer Journal for Clinicians. 2017; 67: 7-30.
9. Badin K, Kapoor AN, Guddati AK. Analysis of race and gender disparities in mortality trends from patients diagnosed with nasopharyngeal, oropharyngeal and hypopharyngeal cancer from 2000 to 2014. Journal of Clinical Oncology. 2019; 37: 17533-17533.
10. United States Cancer Statistics: Data Visualizations. Centers for Disease Control and Prevention.; Available from: https://gis.cdc.gov/Cancer/USCS/DataViz.html.
11. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev, 2009; 18: 541-550.
12. Goodwin PM. Gender Disparity in Head & Neck Cancer Treatment, Outcomes. Oncology Times. 2018. 40: 34.
13. Benchetrit L, Torabi SJ, Tate JP, Mehra S, Osborn HA, et al. Gender disparities in head and neck cancer chemotherapy clinical trials participation and treatment. Oral Oncol, 2019; 94: 32-40.

14. Johns Hopkins Coronavirus Resource Center. 2020.

15. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein S, et al., Impact of sex and gender on COVID-19 outcomes in Europe. Biology of Sex Differences. 2020; 11: 29.

16. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature, 2020; 584: 430-436.

17. Global Health 50/50. COVID-19 Sex-disaggregated Data Tracker.

18. Guerra-Silveira, F, Abad-Franch F. Sex bias in infectious disease epidemiology: patterns and processes. PLoS One. 2013; 8: e62390.

19. Fink AL, Engle K, Ursin RL, Tang WY, Klein SL, et al., Biological sex affects vaccine efficacy and protection against influenza in mice. Proceedings of the National Academy of Sciences. 2018; 115: 12477-12482.

20. Yang YM, Hsu CY, Lai CC, Yen MF, Wikramaratna PS, et al. Impact of Comorbidity on Fatality Rate of Patients with Middle East Respiratory Syndrome. Scientific Reports. 2017; 7: 11307.

21. Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, et al, Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2020; 318: L1280-L1281.

22. Seeland U, Coluzzi F, Simmaco M, Mura C, Bourne PE, et al. Evidence for treatment with estradiol for women with SARS-CoV-2 infection. BMC medicine. 2020; 18: 1-9.

23. Hashim D, Sartori S, Vecchia CL, Serraino D, Maso LD, et al., Hormone factors play a favorable role in female head and neck cancer risk. Cancer Med. 2017; 6: 1998-2007.

24. Grsic K, Opacic IL, Sitic S, Milkovic Perisa M, Suton P, et al. The prognostic significance of estrogen receptor β in head and neck squamous cell carcinoma. Oncol Lett, 2016: 12; 3861-3865.

25. Langevin SM, Grandis JR, Taioli E. Female hormonal and reproductive factors and head and neck squamous cell carcinoma risk. Cancer Lett. 2011; 310: 216-221.

26. Li L, Wang XL, Lei Q, Sun CZ, Xi Y, et al. Comprehensive immunogenomic landscape analysis of prognosis-related genes in head and neck cancer. Scientific Reports. 2020; 10: 6395.

27. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, et al., Cancer immunotherapy efficacy and patients' sex: A systematic review and meta-analysis. The Lancet. Oncology. 2018; 19: 737-746.

28. World Bank Group. 2020.

29. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med. 2020; 8: e20.

30. Ceylan-Isik AF, McBride SM, Ren J. Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? Life Sci. 2010; 87: 133-138.

31. Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults in the United States.

32. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med. 2020; 201: 1557-1559.

33. Alcohol and COVID-19: what you need to know. WHO/Europe.

34. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75: 1730-1741.

35. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020; 382: 1708-1720.

36. Patel RJ, Kejner A, McMullen C. Early institutional head and neck oncologic and microvascular surgery practice patterns across the United States during the SARS-CoV-2 (COVID19) pandemic. Head Neck. 2020; 42:1168-1172.

37. Tam M, Wu SP, Gerber NK, Lee A, Schreiber D, et al. The impact of adjuvant chemoradiotherapy timing on survival of head and neck cancers. Laryngoscope. 2018; 128: 2326-2332.

38. Ho AS, Kim S, Tighiouart M, Mita A, Scher KS, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer. 2018; 124: 3154-3162.

39. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020; 55.

40. Stordeur S, Schillemans V, Savoye I, Vanschoenbeek K, Leroy R, et al. Comorbidity in head and neck cancer: Is it associated with therapeutic delay, post-treatment mortality and survival in a population-based study? Oral Oncol. 2020 102: 104561.