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Impact of gender on the association between marital status and head and neck cancer outcomes

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ABSTRACT

Objectives: To determine whether the impact of marital status on head and neck cancer (HNC) outcomes vary by gender.

Methods: The Surveillance, Epidemiology, and End Results 18 database from 2007 to 2014 was queried for eligible cases of HNC (n = 71,799). An interaction term (gender*marital status) was tested for each outcome of interest (cancer-specific survival, stage of presentation, adequate treatment), and when significant ($p < 0.05$), the model was stratified by gender. A competing risks proportional hazards (subdistribution [sd]) model estimated the interaction effect on cancer-specific survival. Logistic regression estimated effect on stage of presentation and treatment type.

Results: There was significant gender*marital status interaction for cancer-specific survival and stage of presentation. While married/partnered patients had the highest survival among both genders, males benefitted more: widowed (male sdHR = 1.41, 95% CI 1.31, 1.52; female sdHR = 1.15, 95% CI 1.06, 1.26), divorced/separated (males: sdHR = 1.39, 95% CI 1.32, 1.46; females: sdHR = 1.17, 95% CI 1.06, 1.28), or never married (males: sdHR = 1.42, 95% CI 1.36, 1.49; females: sdHR = 1.15, 95% CI 1.05, 1.26). When stratified by oropharyngeal cancer vs. non-oropharyngeal HNC, unmarried males had 50–60% increased hazard of death, while no difference was found for females. Unmarried males also had greater odds of presenting with late-stage disease compared with females. No gender*marital status interaction was observed for adequate treatment, although married/partnered survivors had greater odds of receiving adequate treatment.

Conclusions: While there are survival benefits for married patients with HNC, married/partnered males, especially those with oropharyngeal cancer, may benefit more than females.

Introduction

Among the growing number of cancer survivors in the United States are 430,000 head and neck cancer (HNC) survivors [1]. Nonclinical prognostic factors for survival include marital status, a marker for social support [2–7]. Spouses may detect visual or phonetic abnormalities indicative of oral/laryngeal neoplasia, facilitating early diagnosis and treatment in a phenomenon known as "spousal surveillance"[8]. Thus, married patients with HNC are more likely to present at earlier stages, receive definitive surgical treatment, adhere to treatment regimens compared with unmarried patients [2,8–10].

Since both HNC incidence [1] and survival differ by gender [11], prognostic factors for survival, such as marital status, might also differ by gender. While this subject has been explored in both the general population and among cancer survivors [2,6,8,12], differences in the survival benefit of marriage based on the gender of the HNC survivor is yet to be thoroughly described. It is unknown if there are differences in stage of presentation or treatment type received among married HNC survivors based on gender. Understanding the interaction between marital status and gender in HNC survival is important for spousal

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surveillance, and for developing tailored interventions aimed at improving socio-emotional support for survivors.

The objective of this study was to examine the interaction of gender and marital status on three HNC outcomes: stage of presentation, type of treatment received, and disease-specific survival. Specific aims of the study were: (1) to determine whether marital status at diagnosis impacts HNC survival differently based on gender, (2) to understand whether gender impacts the effect of marital status on stage of presentation, and (3) to characterize the effect of gender on the association between marital status and receipt of adequate treatment.

Methods

Data source

Adults (≥18 years) HNC patients diagnosed between 2007 and 2014 were abstracted from the Surveillance, Epidemiology, and End Results (SEER) 18 database [13]. SEER is publicly available and representative of cancer patients in the United States, containing > 8 million tumor records. The database covers about 97% of incident cancers in its registry areas [14], making it a premium quality cancer database in the United States [15,16].

Primary anatomic cancer sites were determined using the International Classification of Disease for Oncology third edition (ICD-O-3) topography codes. HNC was defined as primary cancer of the oral cavity and pharynx (including oropharynx, hypo- and nasopharynx) (C0.00-C14.8), larynx (C32.0–32.9), nasal cavity (C30.0), and sinuses (C31.0–31.9). Patients were included in the analysis only if HNC was their first or only cancer (sequence number 0/1), their HNC had squamous cell histology (ICD-O-3 histology 8050–8076, 8078, 8083, 8084, and 8094), and cause of death was not unknown or reported only from death certificate/autopsy.

Measures

There were three outcomes of interest in this study. First, HNC-specific survival was defined as time after HNC diagnosis during which patients did not die from HNC. The "SEER Cause-specific Death Classification" variable [17], which incorporates number of tumors, site of original tumor, and comorbidities to reduce cause of death misclassification, was used to determine if a patient died from first primary HNC. Second, late-stage HNC was defined as being diagnosed with stage III or IV HNC using American Joint Committee on Cancer (AJCC) 6th edition staging. The third outcome was adequate treatment for HNC. Treatment could consist of radiation (grouped as yes or no/unknown in SEER), chemotherapy (yes, no/unknown), and/or surgery (yes, no, unknown). For patients diagnosed at stages I and II, inadequate treatment was defined as no treatment modality (no/unknown for radiation and chemotherapy) or only chemotherapy. For late-stage patients, inadequate treatment was defined as receiving a single treatment modality (chemotherapy, surgery, or radiation). Otherwise, patients were considered to have received adequate treatment.

The primary independent variables of interest in analyses included marital status (married/partnered, never married, divorced/separated, widowed, unknown) and gender (male, female). Covariates included in the models were primary HNC anatomic subsite (hypopharynx, larynx, nasopharynx, oral cavity, oropharynx, sinonasal), age at diagnosis, year of diagnosis, race/ethnicity (Hispanic, non-Hispanic (NH) Black, NH White, NH other), insurance status (privately insured, Medicaid, uninsured, unknown), treatment received (surgery, radiation, and/or chemotherapy, with patients coded as no/unknown for radiation or chemotherapy considered not to have received that treatment) (not included for late-stage or adequate treatment outcomes), stage at diagnosis (I, II, III, IV, unstaged/unknown) (not included for late-stage outcome), and county-level median household income.

Analysis

Characteristics of patients who remained alive or died of any cause were compared using Chi-squared tests and t-tests. For males and females, Kaplan-Meier curves for HNC-specific survival were stratified by marital status. Patients who died of non-HNC causes, remained alive, or were lost to follow-up were censored. Significant differences among marital status strata within each gender were determined through log-rank tests with Bonferroni multiple testing adjustments.

Multivariate models examined the interaction between gender and marital status on the three outcomes. A Fine and Gray [18] competing risks proportional hazards model assessed this interaction and the effect of all covariates on HNC-specific hazard of death while treating death from other causes as a competing event. It is important to account for competing causes of death in this population as it has been previously found that the risk of death from a competing cause rather than an index HNC increases by 26% each year after diagnosis of primary HNC [19]. The proportional hazards assumption was assessed using Schoenfeld residuals [18] and was considered to have been met for all independent variables. Binary logistic regression models evaluated the interaction and covariates on late-stage HNC diagnosis. Another binary logistic regression model evaluated the interaction and effect of all covariates (except treatment type) on receipt of adequate treatment.

If a significant gender*marital status interaction was found in any of the three multivariate models, then the models were stratified by gender to examine the impact of marital status on HNC-specific mortality within each gender. If a significant interaction was not found, then the interaction term was removed from the model, the main effects of marital status and gender were included, and the model was not stratified by gender.

Because human papillomavirus (HPV)-related oropharyngeal cancer (a majority of oropharyngeal cancer) is male-dominated, and associated with later stage at presentation but also better survival in general than other HNC [20–23], the proportional hazards model and logistic regression model predicting stage at presentation were also stratified by oropharyngeal and all other HNC. While SEER does not report HPV status, a majority of oropharyngeal cancer is HPV-related [20]. The gender*marital status interaction was then tested in these stratified models while controlling for all previously noted covariates except site for the oropharyngeal-specific models.

The proportional hazards model provided sub-distribution hazard ratios (sdHRs) and 95% confidence intervals (CIs), and the logistic regression models provided adjusted odds ratios (aORs) and 95% CIs. All tests were two-tailed, and alpha was set at 0.05.

Results

Demographics

A cohort of 71,799 patients with HNC was included in analyses. Cohort was predominantly male (76.2%), non-Hispanic White (75.5%), and about half (51.1%) were married/partnered. Most patients (83.0%) received adequate treatment, and 42.9% presented with stage IV HNC (Table 1).

Gender effect on marital status and cause-specific HNC survival

Median all-cause survival for the entire cohort was 84 months (range 0–96 months). Log-rank tests indicated significant HNC-specific survival differences by marital status for males and females ($p < 0.01$). Married/partnered patients (female 96-month survival = 0.68, male = 0.70) had significantly higher survival over follow-up compared to divorced/separated (female = 0.51, male = 0.54), never married (female = 0.61, male = 0.53), and widowed patients (female = 0.50, male = 0.48) (Fig. 1a and b).

The Fine and Gray competing risks proportional hazards model

Table 1
Demographics of adult HNC patients, SEER 18, 2007–2014 (n = 71,799). A disproportionate percentage of patients who died from any cause were divorced/separated, single, and widowed (Chi-square $p < 0.01$).

	Alive (n = 46639)	Dead (n = 25160)	All patients (n = 71799)	*p*-value
Gender, n (%)				**< 0.01**
Female	10,864 (23.3)	6248 (24.8)	17,112 (23.8)	
Male	35,775 (76.7)	18,912 (75.2)	54,687 (76.2)	
Marital status, n (%)				**< 0.01**
Divorced/separated	5708 (12.2)	4181 (16.6)	9889 (13.8)	
Married/partnered	26,229 (56.2)	10,455 (41.6)	36,684 (51.1)	
Never married	8012 (17.2)	5547 (22.1)	13,559 (18.9)	
Widowed	2927 (6.3)	3324 (13.2)	6251 (8.7)	
Unknown	3763 (8.1)	1653 (6.6)	5416 (7.5)	
Race/ethnicity, n (%)				**< 0.01**
Hispanic	3632 (7.8)	1892 (7.5)	5524 (7.7)	
Non-Hispanic Black	3816 (8.2)	3609 (14.3)	7425 (10.3)	
Non-Hispanic Other	2664 (5.7)	1289 (5.1)	3953 (5.5)	
Non-Hispanic White	35,945 (77.1)	18,281 (72.7)	54,226 (75.5)	
Unknown	582 (1.3)	89 (0.4)	671 (0.9)	
Insurance status, n (%)				**< 0.01**
Insured	36,939 (79.2)	17,398 (69.2)	54,337 (75.7)	
Medicaid	5636 (12.1)	5207 (20.7)	10,843 (15.1)	
Uninsured	2071 (4.4)	1472 (5.9)	3543 (4.9)	
Unknown	1993 (4.3)	1083 (4.3)	3076 (4.3)	
Site, n (%)				**< 0.01**
Hypopharynx	1280 (2.7)	1856 (7.4)	3136 (4.4)	
Larynx	11,118 (23.8)	6520 (25.9)	17,638 (24.6)	
Nasopharynx	1398 (3.0)	836 (3.3)	2234 (3.1)	
Oral cavity	12,202 (26.2)	6863 (27.3)	19,065 (26.6)	
Oropharynx	19,530 (41.9)	8324 (27.3)	27,854 (38.8)	
Sinonasal	1111 (2.4)	761 (3.0)	1872 (2.6)	
Stage, n (%)				**< 0.01**
I	11,508 (24.7)	2770 (11.0)	14,278 (19.9)	
II	5445 (11.7)	2383 (9.5)	7828 (10.9)	
III	6719 (14.4)	3669 (14.6)	10,388 (14.5)	
IV	17,657 (37.9)	13,117 (52.1)	30,774 (42.9)	
Unstaged/unknown	5310 (11.4)	3221 (12.8)	8531 (11.9)	
Treatment, n (%)				**< 0.01**
Chemotherapy only	797 (1.7)	1384 (5.5)	2181 (3.0)	
Radiation and chemotherapy	13,695 (29.4)	7732 (30.7)	21,427 (29.8)	
Radiation only	5278 (11.3)	3021 (12.0)	8299 (11.6)	
Surgery and chemotherapy	352 (0.8)	289 (1.2)	641 (0.9)	
Surgery and radiation	5942 (12.7)	2259 (9.0)	8201 (11.4)	
Surgery only	11,578 (24.8)	3628 (14.4)	15,206 (21.2)	
Surgery, radiation, and chemotherapy	6422 (13.8)	2665 (10.6)	9087 (12.7)	
None	2184 (4.7)	3925 (15.6)	6109 (8.5)	
Unknown	391 (0.8)	257 (1.0)	648 (0.9)	
Adequate treatment, n (%)				**< 0.01**
Adequate treatment	41,559 (89.1)	18,054 (71.8)	59,613 (83.0)	
Inadequate treatment	4689 (10.1)	6849 (27.2)	11,538 (16.1)	
Unknown	391 (0.8)	257 (1.0)	648 (0.9)	
Age at diagnosis, mean (SD)	60.5 (11.4)	65.5 (12.7)	62.3 (12.1)	**< 0.01**
County-level median income, mean (SD)	58423.4 (14577.3)	56073.0 (14322.1)	57599.8 (14531.6)	**< 0.01**

showed that gender modified the association between marital status and HNC-specific mortality ($p < 0.01$). Female patients who were divorced/separated (sdHR = 1.17, 95% CI 1.06, 1.28), never married (sdHR = 1.15, 95% CI 1.05, 1.26), and widowed (sdHR = 1.15, 95% CI 1.06, 1.26) had increased hazard of HNC-specific mortality compared with married/partnered patients. These effects were significantly increased in males, as divorced/separated (sdHR = 1.39, 95% CI 1.32, 1.46), never married (sdHR = 1.42, 95% CI 1.36, 1.49), and widowed (sdHR = 1.41, 95% CI 1.31, 1.52) males had increased hazard of HNC-specific mortality compared with married/partnered males (Table 2).

When stratified by oropharynx and other HNC sites, the gender*-marital status interaction was significant for oropharynx ($p < 0.01$) but not for other HNC sites ($p > 0.05$). For female oropharyngeal patients, there was no significant difference in HNC-specific survival between married/partnered patients and other marital statuses, but for male oropharyngeal patients, divorced/separated (sdHR = 1.50, 95% CI 1.38, 1.63), widowed patients (sdHR = 1.56, 95% CI 1.35, 1.80), and never married (sdHR = 1.60, 95% CI 1.48, 1.73) were more likely to die from HNC compared to married/partnered patients. For other HNC patients, divorced/separated (sdHR = 1.27, 95% CI 1.20, 1.34), never married (sdHR = 1.28, 95% CI 1.21, 1.35), and widowed patients (sdHR = 1.29, 95% CI 1.21, 1.38) were also more likely to die from HNC compared to married/partnered patients (Fig. 2a–c).

Gender effect on marital status and stage of presentation

The multivariate logistic regression model also showed a significant interaction of gender and marital status on late-stage HNC presentation ($p < 0.01$). Females who were divorced/separated (aOR = 1.20, 95% CI 1.08, 1.34), never married (aOR = 1.22, 95% CI 1.10, 1.36), and widowed (aOR = 1.11, 95% CI 1.004, 1.23) were more likely to present with late-stage disease compared with married/partnered females. As in the survival analysis, the effect of gender on the association between marital status and late-stage presentation was also accentuated among males, with divorced/separated (aOR = 1.53, 95% CI 1.43, 1.63), never married (aOR = 1.42, 95% CI 1.34, 1.51), and widowed (aOR = 1.25, 95% CI 1.13, 1.38) men being more likely to present with late-stage disease compared with married/partnered males (Table 2).

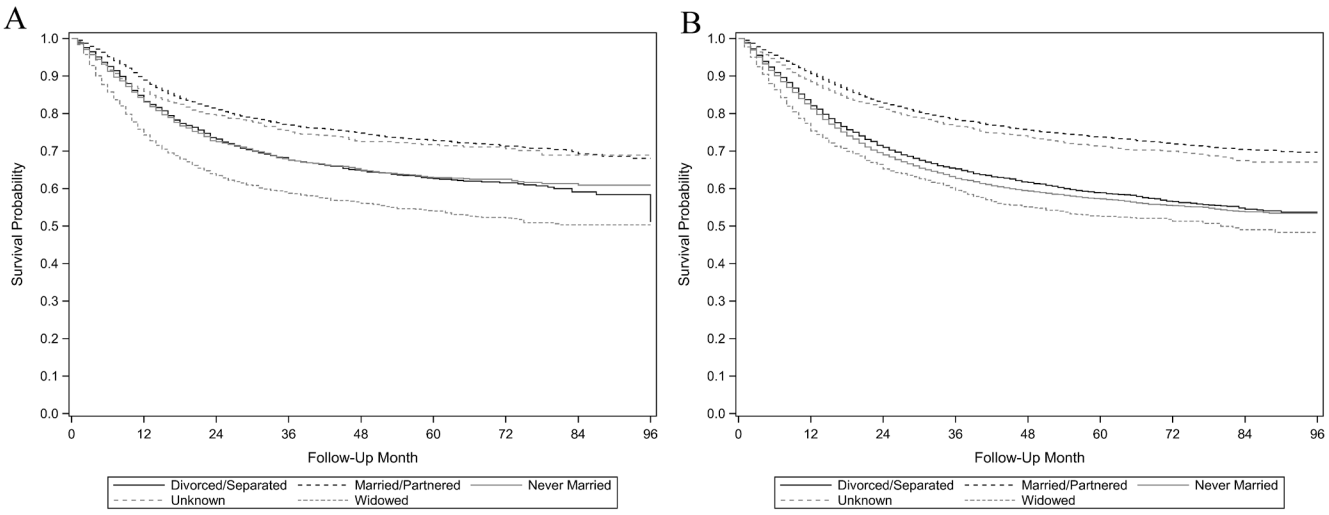

Fig. 1. Title and Legend: Cancer-specific survival curves for HNC by marital status for (A) females and (B) males. Kaplan-Meier curves (A and B) show unadjusted differences in cancer-specific survival of HNC based on marital status (married/partnered, never married, divorced/separated, widowed and unknown). Figure A is female, and B is male. For both genders, log-rank tests indicate that there were significant differences in survival among the marital status groups, with married/partnered having a superior survival rate (Bonferroni $p < 0.01$).

When stratified by oropharynx and other HNC sites, the gender*-marital status interaction was not significant for oropharynx ($p > 0.05$) but was for other HNC sites ($p < 0.05$). Among oropharyngeal patients, divorced/separated (aOR = 1.33, 95% CI 1.18, 1.49) and never married patients (aOR = 1.25, 95% CI 1.12, 1.39) were more likely to present with late stage cancer than married/partnered patients. For other HNC sites, female who were divorced/separated (aOR = 1.14, 95% CI 1.01, 1.30), never married (aOR = 1.18, 95% CI 1.04, 1.33), and widowed patients (aOR = 1.15, 95% CI 1.03, 1.29) were more likely to be diagnosed with late stage HNC. These effects were increased among male other HNC patients (divorced/separated aOR = 1.63, 95% CI 1.51, 1.76; never married aOR = 1.52, 95% CI 1.41, 1.63; widowed aOR = 1.34, 95% CI 1.20, 1.49).

Gender effect on marital status and adequate treatment

The multinomial logistic regression did not show any significant interaction between gender and marital status on odds of receiving adequate treatment for HNC ($p > 0.05$). Removing the interaction term from the model, we found that, irrespective of gender, patients who were divorced/separated (aOR = 0.78, 95% CI 0.73, 0.83), never married (aOR = 0.58, 95% CI 0.55, 0.62), and widowed (aOR = 0.67, 95% CI 0.62, 0.73) patients were less likely to have received adequate treatment compared with married/partnered patients (Table 2). Non-Hispanic Black patients were 15% less likely than non-Hispanic Whites to receive adequate treatment (aOR = 0.85, 95% CI 0.79, 0.91). Also, compared with patients with private insurance, patients on Medicaid (aOR = 0.71, 95% CI 0.67, 0.75) or uninsured (aOR = 0.65, 95% CI 0.59, 0.71) were less likely to receive adequate treatment. Also, compared to patients diagnosed with stage I HNC, those diagnosed with stages II (aOR = 0.67, 95% CI 0.59, 0.76), III (aOR = 0.10, 95% CI 0.09, 0.11), and IV (aOR = 0.11, 95% CI 0.10, 0.12) were less likely to receive adequate treatment. Having oropharynx cancer was favorable for receiving adequate treatment, as other head and neck sites were less likely to receive adequate treatment in comparison (aOR range 0.84–0.67) (Table 2).

Discussion

This study aimed to determine the impact of gender on the association between marital status and cause-specific survival, stage of presentation, and treatment type for HNC survivors. We found that while both unmarried males and females were more likely to die from HNC compared to those married within their gender, and the impact of marital status on survival was greater among males than females. We also found that unmarried males and females were more likely to present with late-stage disease compared to married males and females, which was also more pronounced in males. There was no significant difference in receiving adequate treatment between females and males, but patients who were not married at diagnosis were less likely to receive adequate treatment than married patients. This differential benefit of marital status on survival based on gender among HNC survivors is a novel finding, and it necessitates further exploration of the underlying mechanism of supportive care in HNC survivorship.

While both married male and female survivors benefit from their marital status, we found a differential in cancer-specific survival based on gender, with males benefitting more than females. Unmarried males were more likely to be diagnosed with late-stage disease and have a higher hazard of death from HNC compared with unmarried females. This finding may relate to spousal influence on adoption of healthy behaviors, as well as support to quit harmful risk factors associated adverse outcomes [24]. Males consume more tobacco and alcohol than females, regardless of marital status [4,25,26,28,29], and this greater exposure to these major risk factors for HNC among males may partly explain the survival differential based on gender. Women tend to have a greater influence on their partner's health than men because women exert more effort to control their spouses' health habits [24,30]. Takagi et al. postulates that a wife's non-smoking status tended to "spillover" in their male spouses [31]. For a malignancy like HNC, known to be more emotionally traumatic and distressing than other cancers [32], the support received by male survivors to adopt healthier lifestyles and have a positive outlook may explain their greater survival benefit from being married.

This finding of a differential impact of marital status on cancer-specific survival based on gender might be driven mostly by oropharyngeal cancer. Female oropharyngeal cancer patients did not appear to benefit from being married from cancer-specific survival standpoint, and there was no significant difference in survival between female patients who were married/partnered, never married, divorced/separated, or widowed. In contrast, male patients with oropharyngeal significantly benefitted from being married and had better cancer-specific survival. In fact, when compared to those married or partnered, risk of death was increased up to 50–60% for male patients who were divorced/separated, or widowed, or never married. We also found that

Table 2
Proportional hazards model estimating HNC-specific survival stratified by gender. sdHR = sub-distribution hazard ratio, CI = confidence interval, aOR = adjusted odds ratio.

	Fine and Gray Model				Late Stage at Presentation Model				Adequate Treatment Model	
	Female		**Male**		**Females**		**Males**		**Female and Male**	
	sdHR	**95% CI**	**sdHR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Sex (ref = Female)	–	–	–	–	–	–	–	–		
Male	–	–	–	–	–	–	–	–	0.99	0.93, 1.04
Marital status (ref = Married/partnered)										
Divorced/separated	1.17	1.06, 1.28	1.39	1.32, 1.46	1.20	1.08, 1.34	1.53	1.43, 1.63	0.78	0.73, 0.83
Never married	1.15	1.05, 1.26	1.42	1.36, 1.49	1.22	1.10, 1.36	1.42	1.34, 1.51	0.58	0.55, 0.62
Unknown	0.92	0.80, 1.06	1.00	0.92, 1.09	0.68	0.58, 0.79	0.93	0.85, 1.03	0.61	0.56, 0.67
Widowed	1.15	1.06, 1.26	1.41	1.31, 1.52	1.11	1.00, 1.23	1.25	1.13, 1.38	0.67	0.62, 0.73
Race/ethnicity (ref = Non-Hispanic White)										
Hispanic	1.02	0.90, 1.15	1.17	1.10, 1.25	1.18	1.03, 1.35	1.22	1.13, 1.33	0.93	0.85, 1.00
Non-Hispanic Black	1.18	1.07, 1.30	1.26	1.20, 1.33	2.05	1.81, 2.34	1.75	1.63, 1.89	0.85	0.79, 0.91
Non-Hispanic Other	1.07	0.94, 1.22	1.14	1.05, 1.24	0.98	0.85, 1.14	1.16	1.05, 1.28	1.01	0.91, 1.12
Insurance status (ref = Insured)										
Medicaid	1.31	1.21, 1.43	1.46	1.39, 1.53	1.56	1.41, 1.73	1.80	1.68, 1.92	0.71	0.67, 0.75
Uninsured	1.43	1.24, 1.64	1.43	1.33, 1.53	1.70	1.41, 2.05	1.72	1.55, 1.92	0.65	0.59, 0.71
Unknown	1.06	0.90, 1.26	1.06	0.95, 1.17	0.81	0.64, 1.03	0.86	0.75, 0.99	0.47	0.41, 0.54
Stage (ref = I)										
II	1.71	1.48, 1.96	2.09	1.91, 2.29	–	–	–	–	0.67	0.59, 0.76
III	2.67	2.33, 3.05	3.44	3.15, 3.75	–	–	–	–	0.10	0.09, 0.11
IV	3.87	3.42, 4.39	5.71	5.26, 6.19	–	–	–	–	0.11	0.10, 0.12
Unstaged/unknown	1.89	1.65, 2.17	2.64	2.41, 2.89	–	–	–	–	–	–
Site (ref = Oropharynx)										
Hypopharynx	1.32	1.14, 1.53	1.76	1.64, 1.89	1.30	1.03, 1.65	0.99	0.86, 1.13	0.73	0.67, 0.80
Larynx	0.96	0.88, 1.05	1.36	1.30, 1.43	0.33	0.30, 0.37	0.11	0.10, 0.11	0.67	0.64, 0.71
Nasopharynx	1.11	0.93, 1.33	1.69	1.53, 1.87	0.75	0.62, 0.92	0.31	0.27, 0.35	0.73	0.64, 0.83
Oral cavity	1.29	1.18, 1.40	1.73	1.63, 1.82	0.27	0.25, 0.29	0.12	0.11, 0.12	0.69	0.65, 0.74
Sinonasal	1.04	0.87, 1.24	1.67	1.48, 1.88	0.44	0.37, 0.54	0.20	0.17, 0.22	0.84	0.73, 0.97
Treatment (ref = Surgery only)										
Chemotherapy only	3.69	3.09, 4.40	3.00	2.72, 3.32	–	–	–	–	–	–
None	4.84	4.26, 5.50	3.82	3.52, 4.14	–	–	–	–	–	–
Radiation and chemotherapy	1.82	1.61, 2.06	1.34	1.24, 1.44	–	–	–	–	–	–
Radiation only	2.29	2.02, 2.61	1.80	1.66, 1.95	–	–	–	–	–	–
Surgery and chemotherapy	2.20	1.60, 3.03	1.77	1.51, 2.08	–	–	–	–	–	–
Surgery and radiation	1.41	1.24, 1.60	0.96	0.88, 1.05	–	–	–	–	–	–
Surgery, radiation, and chemotherapy	1.55	1.36, 1.77	1.10	1.02, 1.20	–	–	–	–	–	–
Unknown	3.09	2.34, 4.09	1.98	1.65, 2.38	–	–	–	–	–	–
Age at diagnosis	1.03	1.02, 1.03	1.02	1.02, 1.03	1.00	1.00, 1.00	0.99	0.99, 0.99	0.96	0.96, 0.96
Year of diagnosis	0.96	0.94, 0.97	0.96	0.95, 0.97	1.02	1.01, 1.04	1.03	1.02, 1.04	1.01	1.00, 1.02
County-level median income	1.00	1.00, 1.00	1.00	1.00, 1.00	1.00	1.00, 1.00	1.00	1.00, 1.00	1.00	1.00, 1.00

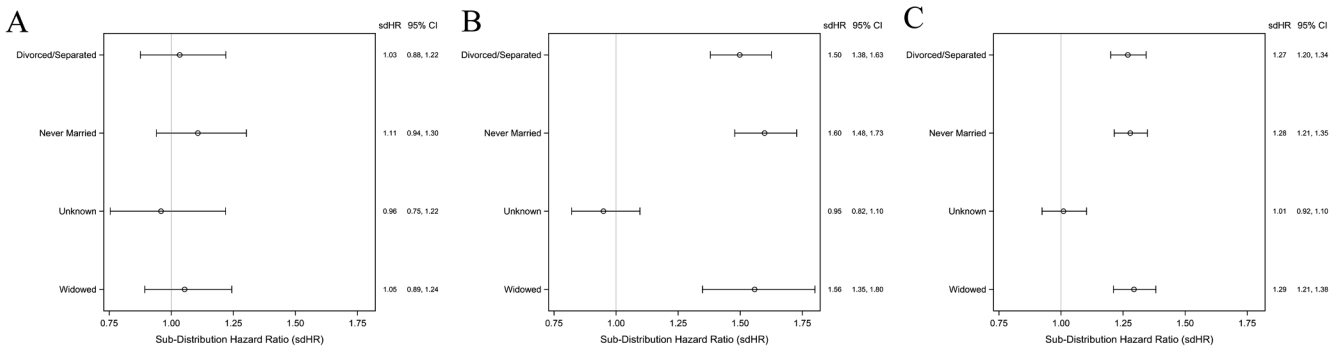

Fig. 2. Title and Legend: Fig. 2. Sub-distribution hazard ratios for the effect of marital status on HNC-specific mortality for oropharynx (stratified by gender) and other HNC sites (not stratified), with married/partnered as reference. Multivariate competing risks proportional hazards models were first stratified by HNC site (oropharynx, other), and a gender*marital status interaction was tested in each site's model. If the interaction was significant, the site-specific model was stratified by gender for that site, and the stratified model included the gender-specific effect of marital status. If the interaction was not significant, the models were not stratified by gender, and the main effects of gender and marital status were included in the multivariate model for that site. For oropharynx, there was a significant gender*marital status interaction ($p < 0.05$); the marital status sub-distribution hazard ratios for (A) females and (B) males are presented here. For other HNC sites, the interaction was not significant ($p > 0.05$); the (C) marital status main effect sub-distribution hazard ratios are presented here.

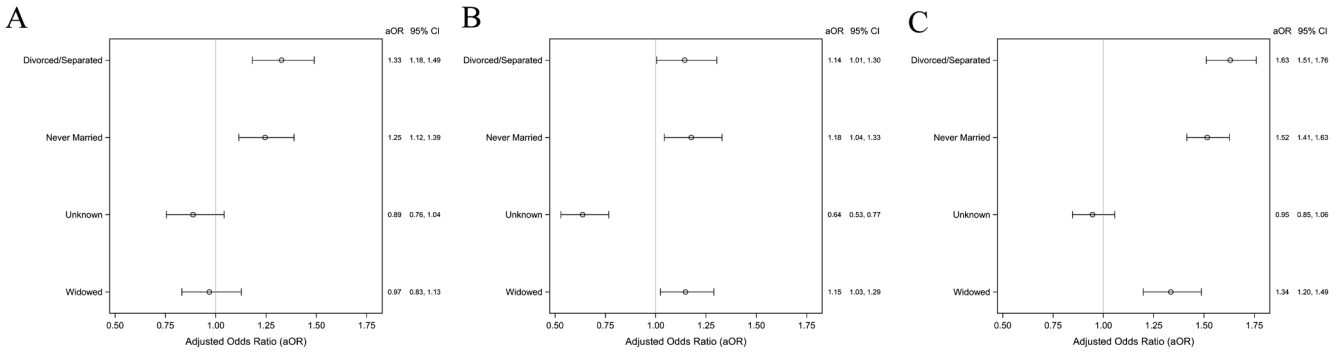

Fig. 3. Adjusted odds ratio for the effect of marital status on stage of presentation for oropharynx and other HNC sites, with married/partnered as reference. Multivariate binary logistic regression models were stratified by HNC site (oropharynx, other), and a gender*marital status interaction was tested in each site's model. If the interaction was significant, the model was stratified by gender for that site, and the stratified model included the gender-specific effect of marital status. If the interaction was not significant, the models were not stratified by gender, and the main effects of gender and marital status were included in the multivariate model for that site. For oropharynx, the gender*marital status interaction was not significant ($p > 0.05$); the (A) marital status main effect adjusted odds ratios are presented here. For other HNC sites, the interaction was significant ($p < 0.05$); the marital status sub-distribution hazard ratios for (B) females and (C) males are presented here.

gender did not significantly impact stage of presentation for married patients with oropharyngeal cancer but did for the non-oropharyngeal HNC. Spouses might detect changes in voice or hoarseness quicker, and these signs and symptoms of HNC are more common in the non-oropharyngeal subsites [3], whereas the anatomic complexity and location of the oropharynx often prevent more dramatic signs and symptoms [23,33], which might explain why stage of presentation did not differ based on marital status for oropharyngeal cancer. It is therefore plausible to conclude that spousal surveillance may benefit male patients with oropharyngeal cancer post diagnosis and remains critical after initiation of treatment. While this is an important finding from the perspective of supportive care and cancer survivorship among males, it raises questions about alternative support systems besides marriage that could optimize quality of life for female patients with oropharyngeal cancer.

In general, females are significantly more likely to seek and utilize social support networks and affiliate with other support systems, and other non-spousal networks such as friends and other family members, especially under stress, then males [34,35]. Thus, with or without a spouse, females may derive important social support from other important people in their lives, such as their children, or other relatives and friends [36]. Males, on the other hand, tend to rely heavily or exclusively on spouses for social support [36]. Without additional forms of support, unmarried males are at a significant disadvantage and may be unable to cope with major adverse life events, including HNC. This could lead to delay in cancer diagnosis and even treatment, leading to adverse survival outcomes. Future studies should focus on understanding clinical and social profiles of unmarried male HNC survivors to mitigate survivorship disparities in this population.

While married HNC survivors were in general more likely to detect their disease at an earlier stage, married female survivors were significantly more likely to present with early stage disease than males. Previous studies have shown that there are differences in attitudes to health based on gender [36], and that even in healthcare systems that offer equal access to care, female HNC patients are more likely to present earlier than males [37]. We corroborated this finding in our study among married HNC survivors. More studies are needed to elucidate the basis for this finding as stage of presentation is prognostic for overall outcomes in this survivor population.

We did not find any gender differences in the association between marital status and treatment received. However, married survivors were more likely to receive adequate treatment for their stage of presentation than divorced, widowed, and unmarried survivors. Previous studies from the Scandinavia [38] and the United States [8] have suggested that those married might receive more adequate treatment than the unmarried, and this was also confirmed in our study. Since married males and females did not differ significantly in the treatment type received, the survival differences we found may be due to

psychosocial aspects of social support, or factors such as lifestyle changes, or treatment adherence, rather than treatment type received.

Strengths and limitations

This study has several limitations. First, the SEER database only provides marital status at the time of diagnosis. It does not provide information on change of marital status after cancer diagnosis. If being married impacts survival as we have shown in our study, it is reasonable to postulate that change of marital status after cancer diagnosis might equally be impactful on survival. Second, there is lack of information about same-sex marital status versus heterosexual status. This is an important gap in the literature that needs to be filled, since support system is so critical for HNC survival. Third, since this study utilizes retrospective data within the SEER database, causation could not be determined. Fourth, SEER does not include information on HNC risk factors, such as tobacco or alcohol, which are impacted by marital status. Lastly, our definition of adequate treatment may not be appropriate for all HNC cases. SEER does not provide information on extracapsular extension of nodal disease, positive surgical margins, and patient fitness for chemotherapy, which are necessary to determine adequate therapy for individual patients. Also, specific T, N, and M stage HNC may need to receive different treatment options than specified by their I-IV stage.

Despite these limitations, this study contributes to HNC literature by highlighting the differential marital status benefit among married male HNC survivors. Additional research is warranted to further understand this disparity and its impact on HNC survival. From an interventional standpoint, unmarried males HNC should be targeted aggressively with counseling measures and support groups to improve quality of life and overall survival.

Clinical/Public health implications

The fact that marital status impacts survival is important for survivorship care planning, and underscores the need for social support among HNC survivors. A key recommendation in the recent HNC survivorship guideline by the American Cancer Society, and endorsed by the American Society of Clinical Oncology, is that clinicians should include spouses/partners or other caregivers in mainstream HNC survivorship care and support plan.[1,39] However, while being married was associated with increased survival, males and females benefitted differentially. If females do not benefit as much as males from a known nonclinical prognostic factor in HNC survival, there needs to be more studies understanding the mechanism behind this observation, as well as examining female-specific factors associated with HNC survival. Additionally, it is important to develop and test the survival impact of alternate support systems, especially for individuals who are not married, since it is unrealistic to expect every cancer survivor to be married. Finally, future studies should incorporate social support among sexual minority HNC survivors, as more needs to be understood about survivorship in this population.

In conclusion, we show in this retrospective cohort study that social support, in the form of being married, is important for HNC survivors, but different by gender. While being married conferred survival advantages in general, married males, especially those with oropharyngeal cancer, significantly benefited from being married compared with females.

Conflict of Interest

None

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.009.

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