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Factors associated with increased risk of suicide among survivors of head and neck cancer: A population-based analysis

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ABSTRACT

Objectives: Cancer diagnosis is considered an independent predictor of suicide. We aimed to determine whether gender and human papillomavirus (HPV)-relatedness are associated with increased risks of suicide in the head and neck cancer (HNC) population.

Materials and methods: Adult patients ≥18 years with HNC were selected using the Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2014. Using anatomic sites as proxy, patients were grouped as HPV-related or not HPV-related. Standardized Mortality Ratios (SMRs) were calculated, and association between suicide, gender, HPV-relatedness were estimated as adjusted rate ratios (aRR) using multivariable Poisson regression model.

Results: There were 1036 suicides among 287,901 HNC patients in the study period (63 suicides per 100,000 person-years). Male patients were six times more likely to commit suicide compared to female patients (aRR = 5.74, 95% CI 3.88, 8.50); however, HPV-relatedness did not increase risk of suicide (aRR = 0.87, 95% CI 0.58, 1.29). Compared with white patients, blacks (aRR = 0.20, 95% CI 0.12, 0.33) and Hispanics (aRR = 0.25, 95% CI 0.14, 0.43) were less likely to commit suicide. Additionally, increased risks of suicide were found among the widowed (aRR = 1.48, 95% CI 1.10, 1.99) and divorced/separated (aRR = 1.30, 95% CI 1.00, 1.69), compared with married patients.

Conclusion: Gender, not HPV-relatedness, was associated with risk of suicide in our study. We identified HNC patients more likely to commit suicide as: previously married, white, male, widowed, divorced or separated, ≥70 years. Our findings may be useful clinically in planning personalized cancer care and lifelong surveillance of HNC patients with higher risks of suicide.

Introduction

More than 15 million individuals in the United States are currently living with a cancer diagnosis [1], 430,000 of whom are head and neck cancer (HNC) survivors [2]. The number of HNC survivors is projected to increase mostly due to decreasing smoking rates, decreasing smoking related head and neck cancer, and increasing incidence of human papillomavirus (HPV)-related head and neck cancer [2]. Post-diagnosis, survivors face survival and lifestyle-related comorbidities and competing causes of death, including depression and suicide [3–5]. Among cancer sites that have been associated with suicide, HNC is ranked in the top four [6,7]. Even though they account for less than 3% of the total cancer burden in the United States, two head and neck subsites, pharynx and tongue, contribute 20% of all cancer related suicides among men [8].

Studies have shown differences in the frequency and nature of suicide between men and women [9,10]. However, the only study published exclusively on HNC-related suicide reported standard mortality ratios (SMRs), which compared rates of suicide to the general United States population [11]. There are no known studies describing how the risks of suicide following HNC differ based on gender. It is important to understand if there are gender differences in HNC-associated suicide for future interventions.

Additional gaps in the literature include quantifying the risk of HNC associated suicide due to human papillomavirus (HPV) status. HPV-related head and neck cancer is the fastest growing subset of HNC [12].

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HPV is a sexually transmitted infection, and patients with HPV-related HNC may be anxious, depressed, confused, feel guilty or even stigmatized, and experience confusion over the sexual nature of the disease [13]. These negative emotions also associated with suicide have been expressed by cervical and vulvar cancer patients, which are both HPV-related [14]. Spouses of HNC survivors may question their partners about marital infidelity when they are diagnosed with HPV-related HNC, and HPV-related cancer status has resulted in issues pertaining to sexual desire and intimacy [13,15–17]. While these factors are known to be associated with depression and suicide [15,18], no study has described whether having an HPV-related HNC increases risk of suicide in these patients. With the rapidly increasing incidence of HPV-related HNC, there is a need to understand whether a diagnosis with HPV-related HNC increases risk of suicide. The aim of this study was to evaluate differences in suicide based on gender and HPV-relatedness in HNC patients.

Materials and methods

Data source and study population

Subjects were identified from the Surveillance, Epidemiology, and End Results (SEER) 18 database [19]. SEER is a publicly available, nationally population-based cancer database that contains more than 8 million cancer cases, with data that spans four decades and covers 28% of the United States population [20]. The Saint Louis University IRB determined the study is exempt from an IRB approval as publicly available de-identified data were used. Data were retrieved using SEER*Stat version 8.3.4 (Surveillance Research Program, National Cancer Institute).

Using SEER data (1973–2014), adult patients ≥18 years with HNC (squamous cell carcinoma) were selected, including oral cavity, oropharynx, nasal cavity, nasal sinuses, nasopharynx, hypopharynx, and larynx subsites. HPV-related HNC was defined using International Classification of Disease for Oncology Version 3 (ICD-0–3) topography codes as primary cancers of the base of tongue (C019), lingual tonsil (C024), palatine tonsil (C090-C099), oropharynx (C100-109), and Waldeyer's ring (C142). This methodology, described by Chaturvedi et al [21], uses anatomic site as a proxy for HPV-relatedness in the absence of data on HPV-tumor status in SEER. Approximating rates of HPV-related HNC based on anatomic proxy is acceptable since about 75% of all tumors found in these sites (oropharynx, base of tongue, lingual and palatine tonsil, and Waldeyer's ring) are HPV-positive [22]. A recent study also showed that in the absence of HPV tumor status, anatomic proxy information is an acceptable surrogate [23]. For this study, the HPV-unrelated group were oral cavity (tongue (C020-023), gum (C030-039), palate (C050-059), other mouth/oral cavity areas (C060-069), lip (C000-009), floor of mouth (C040-049)), hypopharynx (C130-139), sinuses (C310-319), and larynx (C320-329), sites largely associated with tobacco-related HNC. For the main analysis, we excluded overlapping lesion of tongue (C028), tongue NOS (C029), pharynx NOS (C140) from the HPV-related group due to their ill-defined nature as well as controversies about how much these sites have HPV positive tumors. We however ran a sensitivity analysis where the modified the Chaturvedi anatomic proxy methodology described above [21], and included these ill-defined sites as HPV-related [24].

Outcome of interest

The outcome of interest was suicide as a cause of death (COD) among HNC survivors, identified from the ICD COD code in SEER (suicide and self-inflicted injury; ICD 9 codes: 950–959; ICD 10 codes: U03, X60-X84, Y87.0; recode 50220). The assigned COD code used by SEER and its associated cancer registries is acceptable and validated [25]. It is based on an algorithm that captures additional patient related information such as primary cancer site, tumor sequence and comorbidities [26], thus minimizing errors due to misclassifications and allowing a more accurate reporting of actual cause of death among cancer patients [26]. While the SEER's COD information has been validated, there are no specifics in its categorization of "suicide and self-inflicted injury" versus "accidents and adverse effects" [27]. With greater number of accidental deaths recorded among cancer patients relative to suicide [28], it is possible that misclassifications could occur and suicide underreported or misclassified as accidental deaths [27].

Primary independent variables

The primary independent variables were gender and HPV-relatedness. Gender was reported in SEER as categorical variable, male vs. female. HPV-relatedness was determined using the Chaturvedi methodology described earlier which categorized as HPV-related vs. HPV-unrelated HNC [21].

Covariates

Based on the literature on HNC survival and competing causes of death [4,5], we included the following covariates: tumor stage at diagnosis (localized, regional, distant, unknown/unstaged), treatment modality (surgery only, radiation only, chemotherapy only, surgery and radiation, surgery and chemotherapy, radiation and chemotherapy, surgery, radiation, and chemotherapy, none), age at diagnosis (categorized as 18–39, 40–59, 60–69, 70+), race/ethnicity (Hispanic, non-Hispanic [NH] White, NH Black, NH Other [which includes American Indian/Alaska Native, Asian and Native Hawaiian/other Pacific Islander]), and marital status (married, previously married [widowed/divorced/separated], single, and unknown). Lastly, we included county-level median household income data linked to SEER from the US Census Bureau's American Community Survey data as a covariate grouped into quintiles, as individual level SES information was unavailable in the SEER database [4].

Statistical analysis

The bivariate association between patient outcome (committed suicide, non-suicide death, remained alive) and the primary independent variables (gender and HPV-relatedness) was examined using Chi-Squared ($\chi 2$) tests as well as bivariate association between all covariates and patient outcome.

To estimate mortality rate compared to the general United States population, we calculated SMRs based on United States Census Bureau mortality data, using SEER*Stat (Calverton, MD, version 8.2.1).

We estimated the association between suicide, gender, and HPV-relatedness by calculating adjusted rate ratios (aRR) using a multivariable Poisson regression model [29,30]. In the initial model, we determined if an interaction existed between gender and HPV-relatedness while controlling for covariates. Since this interaction effect was not significant ($p = 0.94$), we retained gender and HPV-relatedness in the final model as independent variables. We forced all covariates into the final model regardless of their significance in bivariate analysis, since these covariates have been shown in the literature to be associated with HNC survival [4,5,31].

Finally, we performed a Poisson regression to estimate the relative risk of suicide for each head and neck cancer anatomic subsite. Subsites included the hypopharynx, larynx, nasopharynx, oropharynx, oral cavity, and sinonasal regions. HPV relatedness was not included in this model.

SAS System for Windows, Version 9.4 (SAS Institute Inc, Cary, NC) was used for all analyses, and all statistical tests were two-sided, with $p \leq .05$ considered statistically significant.