

## Competing causes of death in the head and neck cancer population



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### ABSTRACT

**Purpose/objectives:** The increasing survivorship of head and neck squamous cell carcinoma (HNSCC) comes with a risk of death from other causes, known as competing causes. The demographics of HNSCC are also evolving with increasing incidence of Human Papillomavirus (HPV) associated tumors. This study describes competing causes of death for the HNSCC population compared to the general population and identifies associated risk factors.

**Methods:** Adult patients with first mucosal HNSCC (2004–2011) were identified from the Surveillance, Epidemiology and End Result database. Competing causes of death were compared to reference populations using proportion of deaths and Standardized Mortality Ratios (SMR). A multivariable competing risk survival analysis yielded subdistribution hazard ratios (HR) for competing mortality.

**Results:** Of 64,598 HNSCC patients, 24,602 (38.1%) were deceased including 7142 deaths (29.0%) from competing causes. The most common were cardiovascular disease, lung cancer, and other cancers. All relative mortality rates were elevated, especially liver disease (SMR 38.7; 95% CI: 29.4–49.3), suicide (SMR 37.1; 95% CI: 26.1–48.6), and subsequent primary cancers (SMR 7.5; 95% CI: 6.78–8.32). Demographic and tumor factors independently increased risk of competing mortality, including age (HR per 5 years 1.24; 95% CI: 1.22–1.25), sex (male HR 1.23; 95% CI: 1.16–1.32), race (Black HR 1.17; 95% CI: 1.09–1.26), insurance (uninsured HR 1.28; 95% CI: 1.09–1.50), and marital status (single HR 1.29; 95% CI: 1.21–1.37).

**Conclusion:** Nearly one in three HNSCC patients died from competing causes. When developing long term survivorship regimens for HNSCC patients, clinicians should be familiar with this population's specific risks.

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### Background

It is estimated that 61,760 individuals will be diagnosed with head and neck squamous cell carcinoma (HNSCC) in the United States in 2016, and 13,190 will die from this disease [1]. In addition to death from HNSCC itself, these patients are at risk of dying from other causes. These alternative etiologies are referred to as *competing causes*, with associated risk factors termed *competing risks*, because they compete with the cancer itself to cause death [2–4]. This has become even more relevant due to the improvement in HNSCC prognosis and overall survival in the last three decades

[5], with at least 436,000 current HNSCC survivors in the United States [6].

Competing mortality may result from causes that are common in the general population (e.g. cardiovascular disease); however, HNSCC patients may also experience competing risks specific to this population. For example, these patients have a disproportionate burden of comorbidities [7–10] attributed to tobacco and alcohol use, which increase the risk of secondary cancers of the head and neck, lung, and esophagus, among others [10,11]. The risk of treatment complications is also elevated among HNSCC patients with comorbidities [8,12]. Ultimately, as survivorship trends continue to increase among HNSCC patients [9,13–15], particularly those with HPV-associated cancers [16], the importance of mortality from competing causes will likely increase.

Previous competing-risks studies focused on accurately predicting and measuring patient outcomes resulting from treatment of

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the primary cancer, and several comorbidity indices have been associated with poor oncologic outcomes [7,8,17–20]. Two prior studies focus specifically on competing risk in head and neck cancer [11,21], however each has limitations. Neither study provides a complete list of causes of death, provides comparisons between subsites or standardizes mortality rates to the general population in order to assess the excess burden of death associated with competing causes of death. Identifying patients at high risk for competing mortality and developing targeted preventive interventions is needed as the population of HNSCC survivors increases. As noted in the 2016 American Cancer Society head and neck cancer survivorship guidelines [6], systematic survivorship care should gradually shift from treatment to the management of late treatment effects and general medical care. In this study, we describe the competing causes of mortality in the HNSCC population, compare mortality rates to the general population, and identify risk factors associated with death from these competing causes. This will help inform a more integrated model of HNSCC care that would include management of comorbidities, treatment toxicities, and chronic conditions that increase the risk of death, especially competing deaths, in HNSCC patients.

## Methods

### Data source

Patients were identified from the publicly available Surveillance, Epidemiology, and End Results (SEER) 13 database (<http://seer.cancer.gov/data/access.html>) [22]. This database is the largest and most comprehensive available in SEER for standardized mortality ratio (SMR) analysis. SEER 13 covered 13.4% of the United States' population from 1992 to 2011 [23]. HNSCC patients were defined as adults aged  $\geq 20$  years diagnosed from 2004 to 2011 with primary squamous cell carcinoma of upper aerodigestive

track (ICD-O-3: C00.0–C06.9, C09.0–C14.8, and C30.0–C32.9). Squamous cell carcinomas were identified by ICD-O-3 histologic codes: 8052/3–8078/3 and 8083/3–8084/3. To allow comparison to other populations treated by head and neck surgeons, cohorts were collected with thyroid (ICD-O-3 code: C73.9) and salivary gland (ICD-O-3 code: C07.9, C08.0–C08.9) cancers using the same inclusion/exclusion criteria.

Patients were excluded for unknown survival status, previous malignant tumors, or information limited to death certificates only (Fig. 1). SEER\*stat (Calverton, MD, version 8.2.1) [22] was used to calculate Standardized Mortality Ratios (SMRs) based on United States Census Bureau mortality data (1969–2014). [24] Data were exported to R version 3.2.3 [25] for risk modelling. Statistical significance was set at  $p < 0.05$  and 95% confidence intervals were reported.

### Demographics and causes of death

Descriptive statistics were used to examine tumor characteristics, demographic variables, and survival time. Competing causes of deaths based on National Center of Health Statistics (NCHS) categories were obtained from the SEER variable “COD rec (HIV group w/oth infectious)” and summarized into 18 categories. Deaths from second primary malignancies, including those in the head and neck, were considered competing causes. Individual competing causes are presented as a percentage of total competing deaths. Causes of death in the general population were calculated using SEER\*stat based on data from the National Vital Statistics System [26]. These data were derived from all death certificates and approximate a population without HNSCC-related mortality since HNSCC is an uncommon in general population (0.4% of deaths in 2013) [24]. For cause of death comparisons, individuals aged  $< 40$  were removed as 97.5% of our HNSCC sample was  $\geq 40$  years at the time of diagnosis. However, for the subsequent SMR and survival analyses all patients  $\geq 20$  years are included.

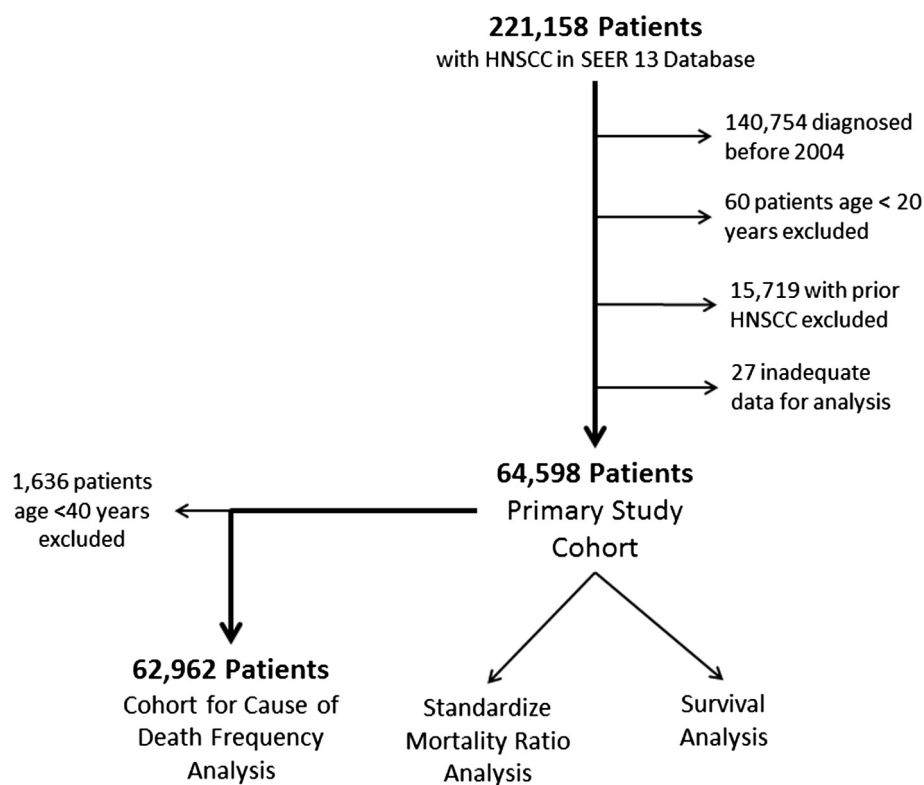


Fig. 1. Study cohort selection. HNSCC: Head and Neck Squamous Cell Carcinoma. SEER: Surveillance, Epidemiology and End Result.

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