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Poor oral health affects survival in head and neck cancer

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ABSTRACT

Introduction: Poor oral health has emerged as a risk factor for squamous cell carcinoma of the head and neck (HNSCC) but its impact on survival has not been examined. We sought to estimate the impact of oral health indicators on survival in a population-based HNSCC cohort.

Materials and methods: Cases (n = 1381) and age-, sex- and race-matched controls (n = 1396) were participants in the Carolina Head and Neck Cancer Epidemiologic Study (CHANCE). Vital status was determined via linkage with the National Death Index. Survival was considered at 5 years post-diagnosis or study-enrollment for controls. Oral health was assessed using self-reported indicators including frequency of routine dental exams and tooth brushing. We used Kaplan-Meyer analyses and Cox regression to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results: Routine dental visits during the preceding 10 years were associated with decreased mortality risk (> 10 visits: HR = 0.6, 95% CI = 0.4–0.8) after adjusting for confounders. This effect was most pronounced for oral cavity cancer—(e.g., > 10 visits: HR = 0.4, 95% CI = 0.2–0.9). Dental visits were also positively associated with survival among controls. No other routine health screening (e.g., eye exams) was associated with survival.

Conclusion: We found significant associations between markers of oral health and survival among both HNSCC cases and controls. This association was most pronounced for sites closer to the dentition. Oral health may have a direct effect on tumor biology due to the associated immune or inflammatory response. It may also represent a proxy for wellness or unmeasured social determinants of health.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) contributes substantially to the global burden of cancer [1–3]. It is the sixth most common cancer worldwide [4], and the fifth most common cancer in the United States, affecting approximately 40,000 new patients each year [1]. It encompasses cancers of the oral cavity, oropharynx, and larynx among others. While the mortality rate for HNSCC has improved recently, it still has poorer survival rates than some other common malignancies such as breast, cervical, and colorectal cancers [5,6]. The traditional risk factors for HNSCC have also been shown to affect survival [7–11]. These include tobacco and alcohol consumption, p16 status, demographics, and socioeconomic status [2,7–10,12–14].

Poor oral health has recently been recognized as a risk factor for HNSCC [15–18]. Specifically, oral health indicators including good oral hygiene, daily tooth brushing and annual dental visits have been linked to modestly reduced HNSCC risk. Although the mechanisms underlying this postulated association have not been elucidated, oral biofilm-induced conditions, like periodontitis, can confer a substantial systemic and local (i.e., oral cavity) inflammatory burden [19–22], which can alter both the behavior of tumors and the resulting immunological response. Moreover, good dental health can also be a marker for general wellness and health-promoting behaviors that likely influence cancer risk and survival [23].

In spite of the accumulating evidence regarding oral health and HNSCC risk, very little information exists on the possible influence of oral health on HCSCC survival. To address this knowledge gap, we carried out this analysis aiming to estimate the impact of oral health indicators on survival in a large population-based HNSCC cohort. We also examined the association by HNSCC site (i.e., oral, laryngeal, pharyngeal) and the relationship of routine dental exams with other behaviors-measures of wellness (e.g., routine physical exams, eye exams, colonoscopies) as predictors of HNSCC survival.

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Methods

Study population

Data for this analysis was obtained from the Carolina Head and Neck Cancer Epidemiology Study (CHANCE); a population based-based case-control study in North Carolina [16,18]. Cases were eligible to participate in CHANCE if they had been diagnosed with a first primary squamous cell carcinoma of the oral cavity, pharynx, or larynx between January 1, 2002, and February 28, 2006; were ages 20 to 80 years at diagnosis; and resided in a 46-county region in central North Carolina. Our inclusion criteria was squamous cell carcinoma of the head and neck; all other diagnoses were excluded (i.e. patients with benign tumors, carcinomas *in situ*, and papillary or adenoid cystic carcinomas). There were 1381 cases in CHANCE. The control group (n = 1396) was identified through the North Carolina Department of Motor Vehicle records, and those individuals were frequency-matched with cases on age, race, and sex. The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Exposure assessment

Oral health was assessed by trained nurse-interviewers using a structured questionnaire during an in-home visit for both cases and controls [16,18]. Cases were interviewed soon after cancer diagnosis (the average time between diagnosis and interview was 5.3 months) and they were specifically asked about their oral health and care before cancer diagnosis. Self-reported oral health variables collected via the interview included: (1) frequency of dental visits in the past 10 years; (2) the number of natural teeth lost, excluding third molars and teeth extracted for orthodontic reasons; (3) frequency of tooth brushing during each participant's adult life; (4) history of tooth mobility or "teeth loose in their socket" because of disease; and (5) gum disease diagnosed by a dentist. The number of dental visits in the past 10 years was chosen as the primary oral health indicator, as it was previously the oral health variable most strongly associated with increased cancer incidence [16,18]. In addition, it was likely the most reliable metric of oral health that could be collected by the trained interviewers.

Survival assessment

CHANCE data were linked to the National Death Index (NDI) based on name, social security number, date of birth, sex, race, and state of residence to identify deaths through December 31, 2013. The NDI is a national file of identified death record information, including cause of death compiled from computer files submitted by State Vital Statistics offices. More than 75% of the CHANCE cases were perfect or near-perfect NDI matches on social security number, date of birth, and sex. The remaining near-matches were confirmed by examining the United States Social Security Death Index and obituaries on newspaper websites. We chose 5-year survival as our endpoint for this study, as after 5 years the initial tumor likely plays a diminished role in their overall survival.

Questionnaire and clinical assessment

Demographic, lifestyle, diet, and other data also were collected during the in-home interview. Potential confounders to be adjusted for in statistical models were selected *a priori* based on their potential association with survival and oral health. These included age, race, gender, education, annual income, smoking and alcohol consumption. In order to assess for HPV-associated cancer, p16 immunohistochemistry was retrospectively performed on a subset patients using a previously described protocol [18]. Smoking was dichotomized at 10 pack-years and alcohol use at 1 drink per week.

Clinical information such as tumor site was abstracted from participants' medical records and reviewed independently by a pathologist and a head neck cancer surgeon. Tumors were classified by site according to International Classification of Diseases for Oncology, third edition, topography codes for the oral cavity (C02.0- C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8, and C06.9), the larynx (C32.0-C32.3, and C32.8-C32.9), the hypopharynx (C13.0, C13.1, C13.2, C13.8, and C13.9), and the oropharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0-C10.4, C10.8, and C10.9).

Statistical analysis

Descriptive statistics were calculated and bivariate testing methods included *t* and chi-squared tests. Overall survival was calculated as time from diagnosis to either date of death due to any cause or censoring on December 31, 2013, whichever came first. Overall and stratified Kaplan-Meier survival plots were constructed. Hazard ratios (HRs) and 95% confidence intervals (CI) for the independent effects of oral health indicators on overall survival were estimated by Cox proportional hazards regression modeling adjusting for sex, age, race, education, income, insurance status, smoking, and alcohol use. Cases and controls were analyzed in both separate analyses and a pooled analysis. For cases, the Cox proportional hazard models were also adjusted for T, N and M classification. Models were run with and without treatment variables (surgery, chemotherapy, and radiation therapy). The proportional hazards assumption for the oral health indicator variables was tested and satisfied.

We tested for site-specific heterogeneity of survival effect estimates with a global Wald chi-squared test using a conservative criterion of $p < 0.2$, and further examined *post hoc* differences between sites using pairwise homogeneity Z-scores and corresponding p-values.[24] STATA 13 (StataCorp, College Station, TX) was used for analyses.

Results

Descriptive information of the CHANCE participants is presented by case/control status and according to receipt of a dental exam during the last 10 years in Table 1. Cases had mean age of 59 years and had mostly high school education or less; affected sites were mostly larynx/hypopharynx (n = 481), followed by oropharynx (n = 327) and oral cavity (n = 164). Almost half (51%) of cases and three-quarters (76%) of controls had a dental exam during the preceding 10 years ($p < 0.001$). Notable differences in dental exam status were found according to most other examined participant characteristics including sociodemographics, behaviors and other oral health indicators; e.g., dental exams were more frequent among whites, more educated and more affluent cases and controls. Lack of dental visits was also associated with other deleterious health behaviors including smoking and alcohol use (among cases), as well as less frequent tooth brushing and increased tooth loss.

During the 5-year follow-up period, there were 578 deaths among cases (survival: 58%; 95% CI = 55–61%) and 146 deaths among controls (survival: 91%; 95% CI = 89–0.92%). Routine dental visits during the preceding 10 years were associated with decreased mortality risk among cancer cases (Fig. 1). After adjustment for confounders, dental visits were associated with almost 40% decreased survival, although no exposure–response gradient was found. When compared with no visits, 1 to 10 visits were associated with a HR of 0.62 for mortality (95% CI = 0.49–0.80) and > 10 visits a HR of 0.63 (95% CI = 0.46–0.89) (Table 2). Adjustment for tumor stage (T, N M) and other oral health indicators (e.g., frequency of tooth brushing, number of lost teeth, the presence of gum disease) did not result in any material change in the HR estimates. The inverse association between visits and mortality differed by cancer site (Fig. 2). Specifically, the reduced HR was most pronounced for oral cavity cancer (e.g., HR = 0.40; 95% CI = 0.17–0.93 for 10+ visits), followed by oropharyngeal cancer and