THE CONSIDERATION OF DIET QUALITY IN HEAD AND NECK CANCER INCIDENCE AND SURVIVAL

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department Epidemiology of the Gillings School of Global Public Health.

Chapel Hill
2021

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ABSTRACT

Veeral M. Saraiya: The consideration of diet quality in head and neck cancer incidence and survival
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The treatment of head and neck squamous cell carcinoma (HNSCC) often results in significant morbidity and healthcare costs. Tobacco use and alcohol consumption along with the human papillomavirus (HPV) are the major risk factors for HNSCC, though HPV is more strongly associated with HNSCC of the oropharynx than with HNSCC of other anatomical sites. Food groups and individual nutrients have been studied with respect to HNSCC, but few have studied the relation between the *a priori* hypothesis-driven indexes of overall diet quality and HNSCC.

We used data from the Carolina Head and Neck Cancer Epidemiology (CHANCE), a large population-based case control study of HNSCC to explore associations between overall diet quality and HNSCC incidence and survival. The self-reported dietary data captured from a validated food frequency questionnaire were used to construct three *a priori* diet indexes of diet quality: Healthy Eating Index 2005 (HEI-2005), Mediterranean Diet Score (MDS), and a derivative of the MDS, MDS-HNC which we developed and introduced based on the diet-HNSCC literature. Using these measures of diet quality, we aimed to 1) characterize the association between diet quality and HNSCC incidence and 2) characterize the association between diet quality and HNSCC survival. We further sought to explore heterogeneity of the

association by anatomic site, HPV tumor positivity, race, body mass index (BMI), alcohol use, and cigarette smoking.

In our analysis, we found that diet quality was inversely associated with HNSCC incidence and positively associated with survival. We also observed effect measure modification by BMI and by alcohol for the association between diet quality and HNSCC incidence, as well as the association between diet quality and HNSCC survival. Our findings suggest that diet quality prior to diagnosis is associated with lower HNSCC incidence and prolonged survival.

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AFRT	Accelerated fractionation radiotherapy
AHEI	Alternate Healthy Eating Index
AJCC	American Joint Committee on Cancer
BRFSS	Behavioral Risk Factor Surveillance System
CCR	Carolina Cancer Registry
CDKN2A	cyclin-dependent kinase inhibitor 2A
CFA	Confirmatory Factor Analysis
CHANCE	Carolina Head and Neck Cancer Epidemiology study
CI	Confidence Interval, Confidence Interval
CRT	Conventional radiotherapy
CVD	Cardiovascular disease
DDS	Diet diversity score
DM2	Diabetes mellitus type 2
DMV	Division of Motor Vehicles
DNA	Deoxyribonucleic acid
DQS	Diet Quality Scores
EFA	Exploratory Factor Analysis
EGF	Endothelial growth factor
EGFR	Endothelial growth factor receptor
FFQ	Food Frequency Questionnaire
HEI	Healthy Eating Index
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard Ratio

IARC	International Agency for Research on Cancer
IGF	Insulin-like growth factor
IHC	Immunohistochemistry
INHANCE	International Head and Neck Cancer Epidemiology
INK4a	Inhibitor of cyclin dependent-kinase 4a
IRBIS	Institutional Review Board IS
kg	Kilogram
LIN	Laryngeal intra-epithelial neoplasia
LOH	Loss of heterozygosity
LRT	Likelihood Ratio Test
m^2	Meter-squared
MAR	Missing at random
MCAR	Missing completely at random
MDS	Mediterranean
MDS-HNC	HNSCC-specific Mediterranean Diet Score
MUFA	Monounsaturated Fatty Acids
NC	North Carolina
NDI	National Death Index
NMAR	Not missing at random
OCSCC	Oral cavity squamous cell carcinoma
OPC	Oropharyngeal carcinoma
OR	Odds Ratio
PCA	Principal Components Analysis
PCR	Polymerase Chain Reaction
PDGF	Platelet-derived growth factor

PLS	Partial Least Squares
PTEN	Phosphatase and tensin homolog
Rb	Retinoblastoma
RERI	Relative Excess Risk Due to Interaction
RFS	Recommended food score
ROS	Reactive oxygen species
RRR	Reduced Rank Regression
SAS	Statistical Analysis System
SES	Socioeconomic Status
SFA	Saturated Fatty Acid
SoFAAS	Calories from solid fats, alcoholic beverages, and added sugars
SSN	Social security number
TNM	Tumor Node Metastasis
UADT	Upper aerodigestive tract
USA	United States of America
USDA	United States Department of Agriculture
VEGF	Vascular-endothelial growth factor
WHO	World Health Organization

CHAPTER 1: REVIEW OF THE LITERATURE AND AIMS (SIGNIFICANCE AND INNOVATION)

1.1 What is head and neck cancer?

1.1.1 Definition

Head and neck cancer, also referred to as cancer of the upper aerodigestive tract (UADT) [1], broadly encompasses a variety of malignancies that arise in the head and neck region of the human body [2]. Skin, brain, ocular, thyroid, salivary gland, and tissue-specific tumors like sarcomas and lymphomas, can all be classified as head and neck cancers. [3] This dissertation will not review these malignancies nor will it concern cancer of the lips, paranasal sinuses, nasal cavity, or nasopharynx, as these malignancies each have a distinct natural history and etiology and were not included in the study on which this dissertation is based. Instead, focus will be given to tumors of the head and neck that have been historically considered together because of a common squamous cell histology [2–9]and risk factor profile typified by tobacco and alcohol consumption [4, 8]. Tumors of the head and neck of interest are broadly classified anatomically as cancers of the oral cavity, pharynx, and larynx [10].

1.1.2 Review of anatomy of key HNSCC sites

For a schematic of head and neck anatomy, the reader is encouraged to review Figure 1-1. The oral cavity is the anterior most subdivision of the aerodigestive tract, separated from the oropharynx by a ring formed by the soft palate, the anterior tonsillar pillars, and the circumvallate papillae [10].The oral cavity extends from the lip to the junction of the hard and soft palate and is bounded anteriorly by the lips, laterally by the buccal mucosa, superiorly by the

superior alveolar ridges and hard palate, and inferiorly by the inferior alveolar ridge and the mylohyoid muscle. The lip, the floor of the mouth, the buccal mucosa, the oral tongue, the retromolar triangle, the upper and lower alveolar ridges, and the hard palate are further subdivisions of the oral cavity [7, 10].

The oropharynx is located immediately posterior to the oral cavity [7, 10]and contains the tonsils, and tonsillar pillars, which form part of the boundary of the oropharynx (Figure 1-1). The oropharynx is inferior to the nasopharynx and becomes contiguous with the hypopharynx at the superior aspect of the hyoid bone inferiorly. The oropharynx is bounded anteriorly by a plane formed by the circumvallate papillae, the anterior tonsillar pillars, and the soft palate, posteriorly by the posterior pharyngeal wall, and laterally by the palatine tonsils and the anterior and posterior tonsillar pillars. The retropharyngeal space is located behind the oropharynx and is a common nodal site for both squamous cell carcinoma and nasopharyngeal carcinoma. The base of the tongue/lingual tonsils, the palatine tonsils, the posterior pharyngeal wall, and the soft palate are four common subdivision of the oropharynx [10].

The hypopharynx is contiguous with and immediately inferior to the oropharynx [7, 10]. This region composes the space surrounding the larynx and laryngopharynx (Figure 1-1). The hypopharynx is formed by the lateral and posterior pharyngeal walls and extends from the level of the hyoid bone superiorly to the esophageal inlet inferiorly. The hypopharynx is bounded superiorly by the hyoid bone, glossoepiglottic, and pharyngeoepiglottic folds, and inferiorly by the inferior margin of the cricoid cartilage and cricopharyngeus muscle. The postcricoid mucosa and posterior cricoarytenoid muscle form the anterior margin, while the posterior mucosa with the middle and inferior constrictor muscles form the posterior margin. The pyriform sinuses, the

posterior wall, and the post-cricoid region form three important subdivisions of the hypopharynx [10].

The larynx extends from the hyoid bone to the inferior aspect of the cricoid cartilage [7]. The larynx is divided into the supraglottis, the glottis, and the subglottis (Figure 1-1). The supraglottis includes the epiglottis, arytenoid cartilages, the aryepiglottic folds, and the false vocal cords. Just inferior is the true glottis, containing the true vocal cords and five millimeters of space inferior to the true vocal cords. The supraglottis and glottis are very distinct subsites of the larynx with different vascular and lymphatic supplies and patterns of tumor spread. The subglottis is the region just inferior to the glottis, extending inferiorly to the cricoid cartilage.

1.1.3 Natural History of HNSCC

1.1.3.1 Oral cavity cancer

Oral cavity squamous cell carcinomas (OCSCC) often remain asymptomatic prior to diagnosis and, as a consequence, identifying and quantifying the prevalence of precursor lesions is difficult. Notwithstanding, leukoplakias and erythroplakias, which are clinical entities, represent histological changes in the oral mucosa, and that may include hyperplasia, dysplasia, and *in situ* carcinoma, are recognized OCSCC precursor lesions [11–13]. The propensity for malignant change to invasive carcinoma from these premalignant lesions varies, depends on histology and length of follow-up [14], and is often difficult to predict [9].

The World Health Organization (WHO) defines leukoplakia as a white patch or plaque that cannot be removed, is not attributable to a specific cause of disease, and requires a biopsy for histologic examination [15–17]. Oral leukoplakia is typically found in middle-aged and older men and has a prevalence that increases over the life course and is estimated in the general population to be between less than one and five percent [18].

In the oral cavity, leukoplakia occurs most frequently on the lip vermillion, buccal mucosa, and gingiva and displays a wide array of clinical phenotypes that may range from homogenous thin white plaques with well-defined borders to thick, almost verrucous lesions [9]. In an investigation of 3300 biopsy specimens of intraoral white lesions [19], approximately 20% showed some degree of epithelial dysplasia and about three percent showed a frank invasive tumor.

An important consideration regarding these OCSCC precursor lesions is understanding their propensity for malignant transformation; however, because these lesions are often asymptomatic and change over time, with some increasing in size and severity and others decreasing in size or even disappearing, it becomes difficult to find pool of leukoplakia cases to follow over time to estimate valid and generalizable malignant transformation proportions. Despite these limitations, some investigations have suggested that the overall percentage of leukoplakias that exhibits malignant transformation is between 3.6 and 17.5 percent [12, 16, 20–22] with lesions of the floor of the mouth, tongue, and lower lip associated with higher rates of dysplasia [18, 23] and, with the exception of the lower lip, demonstrating higher probabilities of malignant transformation [18, 19, 23]. Dysplasia, carcinoma in situ, and frank invasion have been documented to occur in 42% of oral leukoplakia specimens taken from the floor of the mouth [19].

Like leukoplakia, erythroplakia is a clinical entity that is identified by exclusion and is defined as a red lesion of the oral cavity that cannot be removed, is not attributable to a specific cause, and requires a biopsy for specific examination [9]. When this well-demarcated, velvety-red plaque or patch contains within itself or is surrounded by white areas, it is termed erythroleukoplakia [9]. Erythroplakia is rare with an estimated prevalence of 0.2 to 0.8 percent

[24] and occurs most commonly in middle-aged men [9]. Compared to leukoplakia, erythroplakia is more suggestive of invasive disease as most lesions show some degree of dysplasia [9]. It has been estimated that up to 50 percent of oral erythroplakia are invasive OCSCC, 40 percent are carcinoma in situ, and nine percent have mild-to-moderate dysplasia [12, 25, 26].

Proliferative verrucous leukoplakia is another pre-malignant lesion of the oral cavity. First reported in a case series by Hansen in 1985 [27], proliferative verrucous leukoplakia is an aggressive premalignant lesion that is characterized by high rates of recurrence and the ability to spread to multiple oral sites. As a subset of oral leukoplakia, proliferative verrucous leukoplakia is thought to be rare, though its incidence and prevalence have yet to be estimated [28]. Nevertheless, case series and case reports of proliferative verrucous leukoplakia together provide a depiction of features common to this disease entity. These descriptive investigations suggest that 70.3 percent of proliferative verrucous leukoplakia lesions display malignant transformation to verrucous carcinoma or squamous cell carcinoma Females have four times the propensity of males of presenting with the condition, and smoking appears to be unrelated to its etiology [29–32].

Malignant lesions of the oral cavity may appear similar in clinical characteristics to the aforementioned pre-malignant conditions. Oral cavity squamous cell carcinoma (OCSCC), for example, may be asymptomatic and not show any signs or symptoms of a pathologic process in early stages [9]. As disease progresses, the lesion may become symptomatic and may be characterized by nonspecific pain, loose teeth, bleeding, difficulty in speech, difficult or painful swallowing, ear pain, nerve dysfunction, the presence of a mass at the primary site, or swollen cervical lymph nodes [9]. OCSCC tumors are typically white, red, or speckled lesions, may be

exophytic or endophytic, and usually display the classic features of central ulceration with indistinct, indurated borders [33–35] The most common sites of OCSCC are the dorsal and lateral borders of the tongue (40 percent), the floor of the mouth (30 percent), the retromolar trigone, the buccal mucosa, and the maxillary and mandibular gingiva [30, 33, 34].

1.1.3.2 Oropharyngeal and Pharynx cancer

Earlier studies of the natural history of oropharyngeal and pharyngeal cancer focused on the structure and function of the pharynx and how its close proximity to lymphatics systems facilitated cancer progression. As pointed out by Lederman, the pharynx functions to transmit the passage of a variety of items ultimately destined for either the alimentary tract by way of the esophagus or the respiratory system by way of the trachea. Lederman discusses “weak” points in the pharynx that are especially susceptible to the spread of cancer originating from pharyngeal tissues [36]. The irregularities of the attachments of the pharyngeal constrictor muscles to the pharyngeal mucosa as well as the passage of blood vessels and nerves between the pharyngeal constrictor muscles are areas of susceptibility through which cancer of the pharynx spreads to distal sites [36]. These and other avenues through which cancer may spread from the pharynx include the proximally situated Eustachian tube, the cleft between the lower border of the inferior pharyngeal constrictor muscle and the superior aspect of the esophagus, the hiatus between the middle and lower pharyngeal constrictor muscles, and the retromolar trigone [36]. The pyramidal space bounded superiorly by the medial pterygoid muscle and laterally by the convergence of the medial aspect of the mandible with the lateral wall of the pharynx is referred to by Lederman as the parapharyngeal space and is a common destination for cancers originating from the tonsils, palate, fauces, and nasopharynx [36].

Oropharyngeal carcinomas (OPC) associated with human papillomavirus (HPV) infection have a presentation and natural history that are distinct from OPCs that are not associated with HPV infection. Notably, HPV-positive OPCs occur almost exclusively at the base of the tongue or tonsillar fossae as opposed to all regions of the oropharynx. Furthermore, Ang and Sturgis summarized that HPV-positive OPCs display a unique TNM classification profile, typified by lower tumor stage that is distinct from profiles that are commonly seen among HPV-negative oropharyngeal carcinomas [37].

The histologic and molecular profile of HPV-positive OPC has also been characterized. Compared to HPV-negative OPC, HPV-positive OPC is typically poorly differentiated and basaloid histologically [38]. Others, however, contend that the basaloid appearance of HPV-related tumors is more a consequence of admixture of tumors that are both HPV- positive and HPV-negative than a true property of HPV-associated OPC [37]. HPV-positive OPC has also been found to display a unique profile of chromosomal defects [39]. Some investigations have identified an HNSCC molecular profile that is similar in nature to that found in cervical squamous cell carcinoma, a tumor that is positive for HPV type-16, has wild-type p53 expression, has perturbed pRb activity, and increased p16 expression [40].

HPV also appears to be an important factor as it relates to survival following OPC diagnosis. In both clinical trials and population-based investigations, individuals with HPV-positive OPC, particularly HPV type 16-positive OPC, had a more favorable time-specific survival hazard when compared to individuals with HPV-negative OPC [41, 42]. HPV-positive OPC's better survival prognosis relative to HPV-negative OPC may be explained by reports that suggest HPV-positive OPC responds more favorably to radiotherapy compared to HPV-negative OPC.

1.1.3.3 Larynx cancer

Dysplasia, or laryngeal intra-epithelial neoplasia (LIN) is characterized by the presence of atypical cytological features in the laryngeal squamous epithelium. LIN features qualitative alterations in a malignant direction in the appearance of the cells. Three subdivisions of LIN, mild, moderate, and severe, are based on the degree of cellular atypia and structural alterations. The initial microscopic change is believed to take place in the basal layer of the epithelium and gradually extends away from the basal layer until it reaches the surface epithelial layer, where it spreads laterally [43].

Carcinoma *in situ* of the larynx is an example of severe LIN in which at least one cell in the lesion has gained the potential to metastasize, but has not yet done so; thus, the basement membrane is still intact. Micro-invasive carcinoma of the larynx, in contrast, is characterized by infiltration of both the basement membrane and underlying stroma indicating that the lesion can spread through proximal lymphatics or vasculature channels. Importantly, many invasive cancers of the larynx do not pass through the stage of carcinoma *in situ* and are invasive from the start [43].

Laryngeal cancer, arising mostly from squamous epithelium, requires many years to reach a clinically apparent phase. Early cancers of the larynx are usually detected in the glottis whereas cancers of the supraglottis and hypopharynx are detected less commonly and usually by accident. Early cancer of the supraglottis is not synonymous with localized cancer as some may characteristically be micro-invasive and metastasize via local lymphatics [43]. Indeed, lymph node metastases have been shown to occur in approximately 20% of T1 early supraglottic cancers [44]. Early supraglottic cancer may be asymptomatic and may be more advanced than it seems. Precise identification of epithelial abnormalities requires excisional biopsy [43]. Early

vocal cord cancer often arises in the anterior half of the vocal cord and the main symptom is hoarseness, but a change in the voice is often inconstant [43]. Ferlito comments that early laryngeal cancers are confined to mucosa, regardless of any lymph node metastases. Importantly, early vocal cord cancer has a high cure rate [43].

Advanced laryngeal carcinomas correspond to stages III and IV of the TNM classification and are further divided into locally advanced laryngeal cancer with no evidence of lymph node involvement, loco-regionally advanced laryngeal cancer with lymph node involvement but no evidence of distant metastases and disseminated laryngeal cancer with lymph node involvement and evidence of distant metastases.

Hypopharyngeal carcinomas will be considered with laryngeal cancers because of the close anatomical proximity of the hypopharynx to the larynx [10]. Investigations of the natural history and outcomes of hypopharyngeal carcinoma suggest that it is typically diagnosed at later stages and among men in their 7th decade of life. Recurrence is very common, and prognosis is generally poor [45–48].

1.1.4 Diagnosis and Staging:

The American Joint Committee on Cancer (AJCC) has established a staging system that incorporates three aspects of tumor growth: extent of the primary tumor (T), involvement of regional lymph nodes (N), and distant metastasis (M) [49].

The TNM staging system is based primarily on clinical examination and describes anatomic extent of the tumor, though it can incorporate diagnostic information captured through imaging modalities if available (Greene, 2002). Information for pathological staging is derived from operative findings and histopathological review and it should be recorded separately [49]. In general, the T stage is relatively similar for each subdivision of head and neck cancer but

varies on anatomical considerations [49]. The N Stage is unique in nasopharyngeal and thyroid cancer, while the M stage is uniform throughout [49].

1.1.5 Treatment strategies

The treatment of HNSCC requires consideration of a variety of factors including the TNM classification, stage, and anatomic subtype of the HNSCC tumor as well as the status of the individual diagnosed with HNSCC's general health. Surgery and radiation are the mainstays of management of HNSCC with chemotherapy typically used in a supportive capacity or for circumstances in which surgery or radiotherapy alone cannot be curative [50].

Surgical excision alone may be able to cure early-stage cancer; however, advanced stage cancers, those classified as stage III or IV typically require the combination of treatments, usually in the form of surgery with radiotherapy or radiotherapy with chemotherapy [50].

Conventional radiotherapy (CRT) applied with the intention to cure HNSCC typically delivers a dose of approximately 70 Gray through a series of 35 fractionations over a period of seven weeks [51]. Altered fractionation approaches vary the dose of radiation and length of treatment. Accelerated fractionation radiotherapy (AFRT) typically shortens the length of treatment time, essentially *accelerating* treatment while either maintaining or reducing the total radiation dose delivered through CRT; while, hyper-fractionated radiotherapy (HFRT) increases the total dose of treatment by delivering smaller radiation doses multiple times per day during the course of radiation treatment.

Chemoradiotherapy, the combination of chemotherapy with CRT is another approach used to treat HNSCC; while neo adjuvant chemotherapy is the application of chemotherapy prior to delivery of radiotherapy whereas adjuvant chemotherapy is the application of chemotherapy following radiotherapy [52].

1.2 Head and neck cancer epidemiology

1.2.1 Worldwide:

Oral cavity, other pharynx, and larynx cancers accounted for 599,000 incident cases and 325,000 deaths in 2012 worldwide. [53] High-risk regions for oral cavity cancer include Melanesia (a subregion of Oceania, northeast of Australia), southcentral Asia, western and southern Europe, and southern Africa. Globally, laryngeal carcinoma incidence is highest in southern and Eastern Europe, South America, and western Asia. [53]

Temporal trends in worldwide HNSCC incidence vary by geographic location and anatomic subtype. Despite the variability in trends across geographic regions and HNSCC subtypes, Curado and colleagues' evaluation of HNSCC incidence rate trends showed that between 1975 and 1995, the incidence rates for HNSCC were higher for men than for women, regardless of geographic origin or anatomic subtype. [54]

Among men, incidence rate temporal trends for oral cavity and pharynx HNSCC differed by geography with territories in France, the United States, and Canada showing general declines in oral cavity and pharynx HNSCC over time between 1975 and 1995. Incidence rates from Nagasaki, Japan show an increase in incidence over the same period while those rates from Cali, Colombia in South America have remained stable over time at approximately 10 cases per 100,000 persons [54]. Among these five regions of the world considered, oral cavity and pharynx HNSCC incidence rates among men in France were approximately 50 cases per 100,000 persons higher than the incidence rates for men the next highest region during the period considered [54]. Cali, Colombia had the lowest oral cavity and pharynx HNSCC incidence rates among the five regions considered [54].

Incidence rate trends for larynx HNSCC among men appeared to have peaked to just above 25 cases per 100,000 persons in 1985 in France and then stabilized to just under 25 cases

per 100,000 persons in 1995. Canada and the United States follow a similar downward trend in larynx cancer incidence among men from 1975 to 1995. The larynx HNSCC incidence rates in Cali, Colombia, South America have remained stable while in Japan, incidence of larynx HNSCC among men decreased initially midway between 1985 and 1995 and then had risen thereafter and appeared to be on the rise [54].

Among women, oral cavity and pharynx HNSCC appeared to be on the rise in Canada, France, Colombia, and Japan, while in the USA the incidence rates were generally declining for oral cavity and pharynx cancer from 1975 to 1995. Larynx cancer incidence among women between 1975 and 1995 generally followed an inverted "U" pattern where incidence rates tend to increase steadily, peak, and then decline. As of 1995, it appeared that larynx cancer incidence was declining [54].

1.2.2 United States:

1.2.2.1 Incidence

In 2014, oral cavity and pharynx cancer accounted for an estimated 42,440 incident cases and 8390 deaths in the United States [55]. A total of 12,630 new cases of larynx cancer and 3,610 new deaths were reported for 2014 [55]. For oral cavity cancer, more men were diagnosed and died than women in 2014 [55]. This trend of men being more likely to be diagnosed and die compared to women was also true for laryngeal cancer in 2014 [55]. Among men, diagnoses of oral cavity and pharynx cancer accounted for four percent of all incident cancer diagnoses in the United States ranking it as the eighth most diagnosed cancer in 2014 [55]. Historically, the median age of diagnosis occurs in the 6^{th} decade of life, with males diagnosed more frequently than females [56]. The average ratio of male to female diagnosis of oral cavity cancer was approximately 3:1 to 2:1 between 1975 and 2003 [34].

A slow but steady decline in overall head and neck cancer incidence has been documented over the past two decades and has been attributed to declines in smoking [34]. Concomitantly, incidence rates of a subgroup of head and neck cancer, namely those of the base of the tongue and tonsillar regions, have risen recently [57], particularly in young adults in Europe and the United States and is thought to be due to Human papillomavirus [58, 59]. Also thought to be due to HPV is a steady increase in oral cavity HNSCC incidence among individuals younger than 40 years of age as well among women who do not conform to the traditional risk factor profile characterized by tobacco use and alcohol consumption. [60–62].

With respect to race, Black men have traditionally had a higher HNSCC incidence rate compared to White men [35]; however, recently, it has been documented that incidence of HNSCC between Blacks and Whites is becoming more comparable [63]. Though the overall HNSCC incidence rate among Blacks is now comparable to Whites, Blacks continue to have a higher larynx cancer incidence rate compared to Whites. (Figure 1-4)

1.2.2.2 Survival and mortality

Although cancer is the primary cause of death, those afflicted with locoregionally advanced primary HNSCC have lifetime increased risk of dying from cardiac and respiratory illnesses as well as of being diagnosed with a second primary tumor [64].The estimated annual probability of second primary tumor occurrence in the aerodigestive tract among individuals with head and neck cancer, expressed as a percentage, has been estimated to be three to five percent [65–67]and is closely related to smoking [64, 67]. Those who continue to smoke after first diagnosis of a primary tumor are six times more likely to develop a second primary tumor relative to those who stop smoking after an initial diagnosis. [68–70]. It is estimated that between 34% and 57% of patients continue to use alcohol and tobacco products after being

diagnosed with HNSCC. This continued use of alcohol and tobacco increases the risks of surgical complications, increases the likelihood of cancer recurrences, and reduces disease-specific survival [65, 71]. Thus, cessation strategies for alcohol and tobacco use are a key therapeutic aim following initial diagnosis [9, 72].

The overall five-year survival percentage for HNSCC has been reported to range between 50 and 60 percent for the oral cavity, oropharynx, and larynx HNSCC anatomic subtypes [73]. In another investigation, the five-year relative survival rate, computed as the ratio of the observed five-year survival probability to the age-, sex-, and country-specific expected five-year survival probability, was 0.41, 0.30, and 0.63 among men for the oral cavity, oropharynx, and larynx HNSCC anatomic subtypes, respectively; while, for women, five-year relative survival probabilities were 0.53, 0.55, and 0.65, respectively [74]. Estimates from the Surveillance Epidemiology and End Results (SEER) data suggest the overall 5-year survival percentage for HNSCC is approximately sixty percent and worse for certain anatomic subsites like the hypopharynx [34]. Early-stage tumors (T1 or T2) are associated with a 5-year survival probability of 60 to 80 percent [75–77]; while advanced stage tumors fare worse as neck metastases have been reported to reduce the 5-year survival probabilities by 50 percent [76, Table 1-2].

Race seems to affect survival as Blacks tend to have lower HNSCC survival probabilities than their White counterparts [34, 55]. The 5-year survival probability for Blacks diagnosed with larynx cancers in the years 1975 to 1977 was 0.58 compared to 0.67 for Whites diagnosed with larynx cancers in those same years. This difference in Black and White 5-year survival probabilities persisted for larynx cancers diagnosed in the years 2003 to 2009 as well with Blacks having a 5-year survival probability of 0.52 compared to 0.64 for Whites.

These racial differences in survival also exist for oral cavity cancer. For oral cavity cancers diagnosed in the years 1975 to 1977, the 5-year survival probability for Blacks was 0.36 compared to 0.54 for Whites. Although both races have shown improvements in survival since 1977 for oral cavity cancer, the racial disparity in 5-year survival between Blacks and Whites persisted as oral cavity cancers diagnosed in the years 2003 to 2009 had 5-year survival probabilities of 46% and 67% for Blacks and Whites, respectively [55]. Additionally, Black males have higher mortality rates than their White counterparts for both oral cavity-pharynx HNSCC and larynx HNSCC. (Figure 1-3, Figure 1-5)

It should be noted that HPV-related HNSCC, the majority of which occur at the oropharynx [78], has been reported to have a better prognosis than HPV-negative cancers, possibly because HPV-positive HNSCC seems to better respond to radiation therapy and chemotherapy. HPV-positive HNSCC's susceptibility to immune surveillance of tumor-specific antigens is also thought to enhance its prognostic profile. [79].Head and neck cancer pathogenesis

1.2.3 Molecular biology of HNSCC Pathogenesis

Several somatic genetic-molecular events resulting in the inactivation of key tumor suppressor genes or the activation of oncogenes, or a combination of these types of genetic events, are involved in the initiation and progression of HNSCC [79]. Molecular techniques applied to tissue samples isolated from various stages on the continuum of HNSCC tumor progression have identified genetic and epigenetic alterations that serve as the basis for a proposed progression model for HNSCC pathogenesis [80–82]. Figure 1-6 provides a schematic of key molecular events.

Biological mediators involved with cell cycle regulation are important components of HNSCC pathogenesis. Telomerase, which is involved in telomere maintenance and

immortalization, was reactivated in 90% of HNSCC and premalignant lesions. [83]. Approximately seventy to eighty percent of pre-invasive lesions [84, 85] as well as mature HNSCC [85–87] show a genetic aberration at 9p21 suggesting loss of function at this chromosomal locus is a key early event in the molecular pathogenesis of HNSCC. A cell cycle regulatory protein, p16 is encoded by the INK4a gene located at 9p21 [88–90]. The competition with cyclin D1 for binding cyclin dependent-kinases 4 and 6 by p16 plays an important role in the regulation of the tumor suppressor protein Retinoblastoma (Rb) [88–90]. Accordingly, inactivation of p16 (CDKN2A), which may occur by homozygous deletion, point mutations, or promoter hypermethylation of the INK4a gene at 9p21 underscores the importance of the loss of function at 9p21 as a key early event in HNSCC pathogenesis. Loss of function at 3p is also thought to be an important early occurrence in HNSCC pathogenesis [82, 91]. Additionally, aggressive HNSCC tumor behavior may be linked with upregulation of the 11q13 locus and overexpression of cyclin D1 [92, 93].

Loss of heterozygosity at 17p, associated with a mutation in the p53 tumor suppressor gene, is seen in approximately 50% of HNSCC cases and pre-malignant lesions [94], suggesting that inactivation of p53 tumor suppressor protein is an important event in HNSCC pathogenesis [94, 95]. In one investigation, tumor resection margins showed the presence of a p53-related gene mutation in 53% of cases and, of these, 38% were associated with local recurrence [96]. Further, TP53 gene point mutations have been associated with reduced survival [97–100].

Endothelial growth factor receptor (EGFR), which belongs to the tyrosine kinase growth factor receptor family [101], has also been implicated in HNSCC pathogenesis. EGFR, which, when activated by EGF binding or through molecular interactions with platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF) among others, triggers cell signaling

cascades that control cell proliferation, apoptosis, metastatic potential, and angiogenesis [102]. Overexpression of EGFR is estimated to occur in ninety percent of HNSCC [103]and is suggestive of poor treatment outcomes [102, 104]. Further, because angiogenesis is critical to tumor growth and metastasis, vascular-endothelial growth factor (VEGF) upregulation is common in HNSCC and has prognostic implications [105].

Human papillomavirus high-risk types 16 and 18 exert their oncogenic potential through the inactivation of the tumor suppressor proteins p53 and pRb by the binding action of their viral oncoproteins E6 and E7, respectively [106]. The HPV type-16 E6 oncoprotein joins with a co-protein to bind p53 creating a protein-complex that is rapidly degraded by a ubiquitin-dependent proteolytic mechanism [107]; however, the susceptibility of p53 to binding by HPV type-16 viral oncoprotein E6 is not uniform; variant p53 genotypes with higher binding affinity are associated more often with HPV-positivity [108]. The expression of the E6 and E7 viral oncoproteins in HPV-positive HNSCC tumors is associated with wild-type p53 expression and diminished cellular pRb levels with a concomitant overexpression of p16 [109]. Notably, the lack of mutations in the p53 gene is characteristic of HPV type 16-positive HNSCC with active E6 and E7 oncoprotein expression [109]. Some investigators speculate that HPV's ability to degrade the p53 protein without inducing a p53 gene mutation and allowing the p53 gene to retain its functionality may explain why HPV-positive HNSCC has a better prognosis than HPV-negative HNSCC [110].

1.3 Important risk factors for incident HNSCC

The International Head and Neck Cancer Epidemiology (INHANCE consortium was established in 2004 to enhance HNSCC researchers' ability to better understand HNSCC etiology. Comprised of 33 independent case-control studies that represent populations from various countries in Europe, North America, South America, Asia, and Africa, the INHANCE

consortium facilitates the pooling of data from these investigations and consequently the ability for researchers to investigate nuances in exposure and confounding variables with respect to HNSCC as well as subgroup analyses that would otherwise be impossible because of a lack of statistical power. [111] As well, publications generated from the IHANCE consortium summarize key risk factors for HNSCC and provide estimates of measures of association between risk factors and HNSCC that are among the most precise available in the epidemiological head and neck literature. In reviewing key risk factors for incident HNSCC, emphasis will be given to INHANCE publications because of their superior epidemiologic quality.

1.3.1 Demographic characteristics

Black race, male sex, lower socioeconomic status, and older age are positively associated with incident HNSCC [34, 79]. However, for a subset of HNSCC, namely HPV-positive HNSCC, younger age and relative affluence are considered risk factors [112].

1.3.2 Tobacco

1.3.2.1 Cigarette Smoking

Cigarette smoking is a well-established risk factor for HNSCC. Studies have consistency shown a dose-response gradient with increasing HNSCC incidence for greater duration and frequency of use. These patterns are also present among never-drinkers. Cumulative exposure of cigarette smoking as measured by pack-years also shows a similar dose-response pattern. (Table 1-3, Table 1-5) Time since quitting smoking is associated with reduced odds of HSNCC. The risk does not approach that of a never-smoking until about 20 years of smoking cessation. (Table 1-11) There does not appear to be in risk with the use of filtered, including menthol, cigarettes [113]. Multiple studies have suggested that “dark” (“black”) tobacco is associated with a higher risk than “light” or “blonde” tobacco. [114–119].

1.3.2.1.1 *Sex, race, and anatomic subtype*

Women have been shown to have relatively higher odds of incident HSNCC than men for similar levels of cigarette smoking exposure [120–122]. Results from the analysis of CHANCE data suggested that Blacks had higher relative odds of incident HNSCC than Whites for cigarette smoking frequency and duration [113].Studies have indicated that the pattern of risk for cigarette smoking is higher for larynx cancer than for oral cavity of pharynx cancer. (Table 1-3) Smoking cessation may have a strong impact for oral cavity cancer than other sites. (Table 1-11)

1.3.2.2 Other Tobacco Products

Some studies have reported that cigar- and pipe-smokers are at an increased risk of HSNCC. (Table 1-12, Table 1-13) Smokeless tobacco has been shown to increase risk in some studies, although the magnitude of the effect varies by type of smokeless tobacco [113, 123–125].

1.3.2.3 Involuntary Smoking

Some studies have found that the duration of exposure to household and workplace tobacco smoke may be associated with an elevated risk of HSNCC [126].

1.3.3 Alcohol

1.3.3.1 Frequency, duration, cumulative dose, and cessation

Increasing daily frequency of alcohol consumption, but not duration, was associated with increased relative odds of incident HNSCC in a positive dose-response trend. The point estimates for the odds ratios representing the associations between years duration of alcohol consumption and incident HNSCC, although all greater than the null value, declined with increasing years of duration of use. Also, of note is that generally, the magnitudes of the positive associations for alcohol consumption are noticeably lower than those for tobacco smoking (Table 1-3, Table 1-4).

Increasing cumulative alcohol exposure, measures in drink-years, was also associated with increasing HNSCC incidence, even among never users of tobacco (Table 1-6).

1.3.3.2 Type of alcohol

For the three main types of alcohol, beer, liquor, and wine, increasing frequency, duration of use, and cumulative exposure measured in drink-years were associated with a positive dose-response trend with incident HNSCC. The relative odds of incident HNSCC for wine consumption frequency remained just slightly above the null value for lower levels of daily alcohol consumption frequency until consumption frequency exceeded thirty wine drinks per day at which point the odds ratio markedly increased to an estimated 6.3 (Table 1-7).

1.3.3.3 Alcohol Cessation

Cessation of alcohol drinking for a period of twenty years or more is required before the relative odds of incident HNSCC return to the level of a never drinker. The oral cavity appears to show declines in relative odds of incident HNSCC that approximate that of a never drinker sooner than do other anatomic subtypes for increasing durations of alcohol consumption cessation (Table 1-11).

1.3.3.4 Sex, race, and anatomic subtype

Men had higher relative odds of incident HNSCC than did females for beer and liquor consumption, but not wine when comparing individuals who consumed greater than 15 ethanol-standardized drinks per day with those who consumed zero drinks per day. No discernable pattern was evident between males and females when comparing individual who consumed at most 15 ethanol-standardized drinks per day with those who consumed zero drinks per day. (Table 1-8, Table 1-9) Blacks appear to be more vulnerable to alcohol exposure than Whites, regardless of the type of alcohol consumed or if alcohol consumption exposure is captured by

daily drink frequency or duration in years of use. (Table 1-10) The oral cavity and pharynx appear to be more vulnerable to alcohol exposure than the larynx. (Table 1-8, Table 1-9)

1.3.4 Tobacco and alcohol joint exposure

Tobacco and alcohol exposure appear to interact synergistically such that the relative odds of incident HNSCC for joint exposure to tobacco and alcohol is greater than that which would be expected if the odds ratios representing the independent associations of tobacco use and alcohol consumption with incident HNSCC were combined in a multiplicative fashion [54]. Further, the synergistic association for joint tobacco-alcohol exposure is more pronounced in Blacks compared to Whites [120] and for the larynx compared to other HNSCC anatomic subtypes (Table 1-6).

1.3.5 Human papillomavirus

Human papillomavirus, in particular type 16, and to a lesser extent, type 18, has emerged a key risk factor for a subset of HNSCC [38]. It is estimated that approximately 25% of all HNSCC contain HPV genomic DNA [127] and that 30 to 40 percent of oropharyngeal tumors contain at least one type of HPV [128–132].

HPV-16 and HPV-18 have been found to be present in 22% and 14% of all oropharyngeal tumors, respectively [130, 133–136], and with advances in biotechnology, HPV-16 genomic DNA has been detected in 72% to 90% of HPV-positive OPC [38, 127]. Of note is that HPV has been found to be most prevalent in cancers of the tonsil, prevalent to a lesser degree at other regions of the oropharynx, and least prevalent in cancer of the oral cavity and larynx [112].

Individuals diagnosed with HPV-related HNSCC tend to be non-smokers, non-drinkers, younger in age relative to non-HPV-related HNSCC cases, and have a fully intact immune system, suggesting that the role of HPV-16 may be independent of tobacco and alcohol use, the

traditional HNSCC risk factors [137]. Furthermore, individuals with HPV-positive tumors tend to be male, belong to higher socioeconomic class, and not be associated with excessive tobacco use or alcohol consumption [138, 139]. Further, sexual practices involving oro-anal and/or oro-genital contact are thought to enhance the transmission of HPV to the oral cavity and have been noted as possible risk factors for HPV-positive OPC [38, 140, 141].

D'Souza and colleagues caution that assumptions about the HPV-status of HNSCC should not be based on either demographic characteristics, behavioral factors, or non-tumor HPV biomarkers as each of these predictors do not have sufficient predictive ability individually or when considered jointly to warrant use in HPV classification of HNSCC cases when tumor HPV detection is possible [142]. As such, detection of HPV DNA in a tumor does not signify that HPV is itself "causative."

1.3.6 Marijuana smoking

Berthiller and colleagues showed that neither frequency of marijuana smoking, duration of marijuana smoking, nor cumulative marijuana smoking exposure were associated with HNSCC incidence. These non-associations between marijuana smoking and incident HNSCC persisted when the analysis was restricted to never tobacco users as well as when the analysis was executed among individuals who reported never using tobacco or consuming alcoholic beverages [143].

1.3.7 Family history of cancer

Negri and colleagues made use of INHANCE data to show that probands with first-degree relatives with a history of HNSCC had increased relative odds of incident HNSCC, with the magnitude of the association being more pronounced for siblings than for parents. Moreover, tobacco and alcohol use appears to interact with family history as individuals who both used tobacco and alcohol and also had a family member with a history of HNSCC had higher relative

odds of incident HNSCC than the expected relative odds of HNSCC calculated by multiplying the relative odds of incident HNSCC among tobacco- and alcohol-ever users who did not have a family member with HNSCC diagnosis history with the relative odds of incident HNSCC among individuals who did have a family member with an HNSCC diagnosis, but who never used either alcohol or tobacco [144].

1.3.7.1 Anatomic subtype

The distal sites, the hypopharynx and larynx, appeared to be more susceptible to family history of HNSCC than the other HNSCC anatomic subtypes [144].

1.3.8 Body Mass Index

Using INHANCE consortium data, Gaudet and colleagues found that leanness, measured as having a BMI no greater than 18.5 kilograms per meter squared was associated with elevated relative odds of incident HNSCC compared to individuals classified as having normal weight, or a BMI ranging from more than 18.5 to 25 kilograms per meter squared, inclusive. This inverse trend between low BMI and elevated HNSCC incidence persisted independent of an individual's tobacco use- or alcohol consumption status [145].

Conversely, higher BMI, or a BMI greater than 25 kilograms per meter squared was associated with reduced odds of incident HNSCC overall relative to normal-weight individuals. In evaluating effect measure modification by tobacco and alcohol use, Gaudet and colleagues noted that the inverse association of higher BMI with incident HNSCC was only observed among tobacco users and alcohol consumers and not among non-users of either tobacco or alcohol. In interpreting their findings, the authors caution the possibility of reverse causation as disease progression may affect BMI status [145].

1.3.8.1 BMI by race

Petrick's investigation showed an important difference in how leanness affects HNSCC incidence by race. In figure 1 of Petrick's study, it is possible to see that lower BMI is associated with increased relative incidence for both Blacks and Whites relative to normal weight individuals. For increasing BMI, however, the relative HNSCC incidence falls, and then rises again among Whites, though never below the null value relative to normal weight individuals, whereas, among Blacks, increasing BMI appears to confer considerable protection against incident HNSCC relative to normal weight Blacks [146]

1.3.8.2 Anatomic subtype

Gaudet and colleagues observed that the magnitude of the inverse associations between lower BMI and HNSCC incidence were most pronounced for the oropharynx, followed by the hypopharynx, oral cavity, and larynx. (M. M. Gaudet et al., 2010) Lubin and colleagues investigated subtype-specific associations between BMI and HNSCC incidence and found that when comparing individuals with lower BMI with those with normal BMI, the oral cavity and pharynx had higher relative odds of incident HNSCC than did the larynx [147].

1.3.9 Lifetime sexual behavior

Heck and colleagues reported that lifetime sexual behavior is positively associated with increased incidence of the subtype of HNSCC that had been linked to HPV infections, namely HNSCC of the oropharynx. The authors note that the oropharyngeal sub-regions of the base of the tongue and tonsils are especially vulnerable. Participation in oral sex, increasing number of lifetime sexual partners, and decreasing age at sexual debut are all positively associated with elevated odds of incident oropharynx HNSCC [140].

1.3.9.1 Anatomic subtype

Although sexual behavior was positively associated with incident oropharynx HNSCC, no associations were evident for oral cavity or larynx HNSCC [140].

1.3.10 Physical Activity

In an analysis of INHANCE data, increasing physical activity was reported to reduce incident HNSCC [148]. Conversely, a prospective cohort study that identified over one thousand cases over follow-up concluded that physical activity is not associated with incident HNSCC [149].

1.3.10.1 Anatomic subtype

Generally, increasing amounts of recreational physical activity was negatively associated with incident oral cavity and pharynx HNSCC and positively associated with incident larynx HNSCC in the pooled INHANCE analysis [148]; however, Leitzmann's prospective cohort investigation identified no such associations [149].

1.3.11 General oral health, hygiene practices, dentition, and dental prosthetics

Divaris and colleagues found that self-reported tooth loss is associated with increased odds of incident HNSCC; however, this association failed to persist among never smokers suggesting the possibility of residual confounding by tobacco use [150]. Nevertheless, others have also reported that tooth loss and poor oral hygiene increased oral cavity and pharynx HNSCC incidence [151–153]. In Latin America, daily mouthwash use was associated with incident HNSCC, even after accounting for tobacco use and alcohol consumption [152].

1.3.11.1 Oral health and missing teeth by race

Tooth loss is also implicated as an independent risk factor of HNSCC [154, 155**].** Day and Blot found that increasing numbers of missing teeth conferred protection against incident oral cavity and pharynx cancer among Blacks but increased the odds of incident oral cavity and

pharynx cancers among Whites, relative to individuals who had no missing teeth [120]**.** In the same investigation, the use of dentures among Blacks lowered the odds of incident oral and pharyngeal head and neck cancer among Blacks but increased the odds of incident oral and pharyngeal head and neck cancer among Whites, when compared to people who did not use dentures [120].

Mouthwash use, especially mouthwash with high alcohol-content, was associated with increased odds of incident oral cavity and pharyngeal head and neck cancer among both Blacks and Whites relative to those who did not use mouthwash [120]. Although there appeared to be a harmful effect of mouthwash on increasing the odds of head and neck cancer among both Blacks and Whites, the harmful effect was more prominent among Blacks [120].

1.3.12 Other notable risk factors:

Occupational and environmental exposures [146, 156–158], liver cirrhosis, and history of syphilis infection [120] have been identified as other possible risk factors for incident HNSCC. Certain syndromic conditions such as hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, Fanconi's anemia, and ataxia telangiectasia are associated with increased HNSCC incidence [159, 160].

1.4 Important predictors of head and neck cancer survival

1.4.1 Patient Factors

1.4.1.1 Demographics

Generally, lower socioeconomic status and advanced age is associated with poorer HNSCC prognosis [161–163]. As mentioned, race is an important modifier of HNSCC mortality and survival.

1.4.1.2 Behavioral and lifestyle considerations

Individuals diagnosed with HNSCC that continued smoking after diagnosis experienced a less favorable response to radiotherapy and have a lower survival probability than those individuals with HNSCC that quit smoking [164–166]. Continued smoking after HNSCC diagnosis was associated with higher risk of cancer recurrence as well as the diagnosis of new primary cancers relative to those who quit smoking or were former smokers [167–170].

For larynx cancer, an investigation from Italy reported that smoking, but not alcohol drinking, was found to negatively affect prognosis [161]. However, for oral cavity and oropharynx cancer, higher levels of smoking and alcohol consumption appraised before HNSCC diagnosis as well as after diagnosis were both associated with lower survival probabilities [166].

Smoking and alcohol use have been studied with respect to the occurrence of second primary esophageal cancers among individuals with HNSCC. Initiating the consumption of alcohol prior to the age of 20 years, regularly drinking alcohol for a period exceeding 30 years, or routinely consuming greater than 600 grams of ethanol per week, were each separately associated with the occurrence of a second primary esophageal squamous cell carcinoma diagnosis among individuals initially diagnosed with HNSCC, while no such associations were evident for smoking behaviors [171].

1.4.1.3 Body mass index

In a literature review of the role BMI has on HNSCC survival, the authors summarized that higher BMI confers longer overall and cancer-specific survival than does a normal-weight BMI [172, 173].

1.4.2 Clinical Factors

1.4.2.1 Disease characteristics

As would be expected advanced disease is associated with worse HNSCC prognosis [170]. In particular, lymph node involvement has been considered a predictor of poor survival in larynx HNSCC [161]. For oral cancer, the typical late stage at presentation resulting from delays in seeking professional care for an average of three months following awareness of having any oral symptoms is thought to contribute to poorer prognosis [174]. The HPV-status of the tumor also appears to also affect survival where HPV-positive tumors tend to have better survival profiles than do HPV-negative tumors [79].

1.4.2.2 Treatment modalities and survival

While treatments are designed to benefit individuals with HNSCC, the toxicities associated with treatment, especially those from radiotherapy and chemotherapy, can be substantial enough to compromise survival [79].

In meta-analyses, HFRT consistently outperforms CRT in terms of locoregional control and overall survival while the promise of AFRT with respect to HNSCC is a bit more controversial [51, 175]. Chemoradiotherapy has been shown to confer better overall survival than CRT alone in clinical trials [176–178] and is generally accepted as a superior treatment modality for all HNSCC compared to single-therapy CRT [50, 175] . Chemotherapy delivered alongside radiotherapy is known as concomitant chemoradiotherapy and has been shown to be more effective in prolonging survival than either neo adjuvant or adjuvant chemoradiotherapy treatment approaches [52]

1.5 Impact of Head and neck cancer

HNSCC responds well to early detection and prevention; however, because early-stage disease is often asymptomatic and screening of HNSCC has thus far been shown to be

ineffective [179–183], advanced-stage disease is common at diagnosis [174, 184, 185]. Treatment of advanced-stage disease requires complex multi-faceted management strategies and is associated with substantial morbidity, poor patient outcomes [9], and reduced quality of life [186–191].

HNSCC's 5-year survival percentage has remained at approximately 50% for decades despite advances in diagnosis and treatment [192]. Moreover, HNSCC-related treatment costs totaled an estimated $3.6 billion dollars in 2012. [193]. In sum, the high costs to patients and their families in addition to the public necessitates the identification of new modifiable targets whose manipulation has the potential to reduce HNSCC incidence and enhance survival after diagnosis.

1.6 Previous epidemiologic literature that has explored the relation between dietary exposures and incident HNSCC

Investigations of the relation between dietary factors and head and neck incidence typically categorize dietary measures, whether dietary intakes or summary diet quality scores, into equal categories based on the distribution of the dietary measure in the entire study population. As such, categorizations of dietary measures into tertiles, quartiles, and quintiles are common in the literature and relative effect measures are presented as contrasts of the ratio of individuals categorized into the highest dietary measure category to individuals categorized into the lowest dietary measure category among HNSCC cases with the same ratio comparison of individuals by dietary measure category among controls. Unless otherwise specified, discussion of levels of dietary measures and their association with HNSCC will be in reference to this general representation of relative effect measures common in the epidemiologic nutrition-HNSCC literature.

Additionally, because tobacco use and alcohol consumption remain the key risk factors of incident HNSCC, all diet quality-HNSCC measures of association that follow are adjusted for tobacco use and/or alcohol consumption unless otherwise stated.

1.6.1 Individual dietary components nutrients

1.6.1.1 Macronutrients and individual food groups

1.6.1.1.1 *Fruits*

Higher consumption of fruits relative to lower consumption has been consistently shown to reduce the odds of incident HNSCC, and this inverse association persists within strata of race, sex, age, anatomic subtypes. Most investigations report reductions in relative odds of incident HNSCC of 50% or greater (Table 1-14).

1.6.1.1.2 *Vegetables*

Vegetable consumption has also been shown to reduce the relative odds of incident HNSCC, though the magnitude of the reduction is generally less than it is for fruit consumption. A meta-analysis of 16 case-control investigations reported that high vegetable consumption reduced the relative odds of incident oral cavity and oropharyngeal HNSCC by 50% relative to low vegetable consumption [194].

Likewise, a European cohort study reported that high vegetable consumption resulted in a reduction of 24% of the relative odds of HNSCC; however, this estimate included esophageal cancer and so this estimate may be biased [195]. Other cohort investigations of incident HNSCC have also reported reductions incident HNSCC due to high vegetable consumption [195–199].

The type of vegetable consumed has also been investigated. Green salad, lettuce, tomatoes, carrots, and broccoli all tend to result in risk reduction of HNSCC when consumed more frequently [200]. Further, several investigations suggest that green [115, 200], yellow

[115], and red and orange vegetables have been shown to reduce the odds of incident HNSCC [200, 201] .

Some evidence suggests that cruciferous vegetable intake reduce the odds of incident HNSCC while other data shows that increasing levels of cruciferous vegetable intake increases the relative odds of HNSCC incident [200, 202]. This conflicting evidence may be a consequence of differential effects of specific cruciferous vegetables as broccoli has been shown to reduce the odds of incident HNSCC while mustard greens have been shown to increase the relative odds of incident HNSCC [200]. Allium vegetables, typified by onions and garlic, were associated with reduced odds of incident HNSCC [200].

1.6.1.1.3 *Cereals and grains*

Higher levels of cereal and grain consumption are associated with reduced odds of incident HNSCC [200]. However, higher intakes of refined grains have been reported to increase the odds of incident HNSCC. Still, higher levels of whole grain cereal consumption were found to be inversely associated with incident HNSCC [203].

1.6.1.1.4 *Dietary fiber*

Dietary fiber appears to be associated with reduced HNSCC incidence. The inverse association of dietary fiber against incident HNSCC is especially strong for fiber derived from fruits and vegetables. (Table 1-14)

1.6.1.1.5 *Legumes and pulses*

The effect of legume consumption on HNSCC incidence remains controversial as some evidence suggests that higher legume and pulse consumption reduces the relative odds of incident HNSCC [200] while other data shows legume consumption is positively associated with HNSCC incidence [202, 204, 205].

1.6.1.1.6 *Meats and animal proteins*

De Stefani reported that salted meat consumption increased the relative odds of incident oropharynx HNSCC among Uruguayan men. Additionally, the consideration of the joint exposure of salted meat consumption with moderate tobacco use and alcohol consumption revealed a synergistic effect that further increased the odds of incident oropharynx HNSCC [206]

Processed meats were also found to increase the odds of incident HNSCC [200, 204, 207]. Younger individuals who were moderate alcohol consumers and never smokers had higher odds of incident HNSCC associated with higher processed meat consumption than older individuals who used alcohol and tobacco routinely. [208]

Red meat consumption, generally, and beef and pork consumption specifically, are associated with increased odds HNSCC, while white meats generally are generally associated with reduced HNSCC incidence [200]. For example, poultry has been shown to consistently reduce the odds of incident HNSCC [200, 207]. Fish consumption has generally been shown to reduce the relative odds of incident HNSCC as well, though some investigations reported no association [200, 207].

Overall, egg consumption appears to increase the relative odds of HNSCC incidence [200, 204].

1.6.1.1.7 *Milk, yogurt, and other dairy products*

In a case-control investigation from Japan comprised of 959 cases of UADT cancer and 2877 age- and sex-matched controls, increasing frequency of yogurt consumption, ranging from less than once per week to at least once per day was associated with lower relative odds of HNSCC when compared to the lowest frequency of yogurt consumption category. When considering HNSCC anatomic subtypes, the inverse association of increased yogurt consumption

frequency with reduced incidence of for oral cavity HNSCC and larynx HNSCC persisted; however, for oropharynx HNSCC, increased yogurt consumption frequency was associated with increased odds of incident oropharynx HNSCC [209].

1.6.1.1.8 *Coffee, tea, and herbal infusions*

A meta-analysis demonstrated that higher versus lower coffee consumption conferred a 36 percent reduction in the relative odds of incident oral cavity and oropharynx. The same meta-analysis also reported an imprecise elevated odds ratio for coffee consumption and larynx HNSCC [210]. Further, although including esophageal cancer in their analysis, the authors also reported that the reduced odds of incident HNSCC was more pronounced in Europe and in America than it was in Asia [210]

A Japanese prospective cohort study found that overall, drinking at least one cup of coffee per day reduced the odds of incident oral cavity and pharynx HNSCC relative to never coffee drinkers by 65%, regardless of other HNSCC risk factors including an individual's sex or tobacco or alcohol use history [211]. The inverse association of higher coffee consumption with oral cavity and oropharynx HNSCC incidence was also reported in Europe [212].

Japanese investigations found that relative to drinking less than one cup of green tea per day, increasing cups of green tea drunk per day corresponded to increasing reductions in relative odds of incident oral cavity cancer among women, but not men; no relation between green tea consumption and oral cavity incidence was identified among men [213]. An investigation from Europe in contrast, concluded that increased tea consumption did not confer a measurable effect on HNSCC incidence [212].

Maté is an herbal infusion that is commonly consumed in South America as well as in certain regions of the Middle East and is positively associated with HNSCC incidence [214] .

Consumption of maté was associated with increased relative odds of incident oral cavity HNSCC and larynx HNSCC in Brazil [215]. Maté is usually ingested at high temperatures and it is thought that this way of drinking maté, in part, contributes to its carcinogenic potential in the UADT [214].

1.6.1.1.9 *Cakes, snacks, desserts*

Cakes, desserts, sugars and candies were not associated with incident HNSCC when considering additional servings per day or when contrasting the highest quintile of intake with the lowest quintile of intake [204].

1.6.1.1.10 *Fats and oils*

Franceschi and colleagues demonstrated that increased servings of olive oil resulted in increasingly reduced relative odds of incident HNSCC. Additionally, specific- and mixed-seed oils also were shown to confer protection against HNSCC incidence [204]. Conversely, butter and margarine intake was shown have a positive association, though the odds ratios were marginally elevated [204].

1.6.1.2 Micronutrients that may reduce HNSCC incidence.

Several micronutrients have been studied with respect to HNSCC incidence. Some micronutrients have been consistently shown to reduce the risk of HNSCC while the effects of others are not as clear. Generally, higher intakes of micronutrients derived from fruits and vegetables tend to reduce the relative odds of HNSCC incidence [216].

1.6.1.2.1 *Vitamins*

Vitamins have also been investigated with respect to HNSCC. Higher intakes of vitamin C and vitamin E have been shown to reduce the odds of incident HNSCC relative to lower

intakes [120]. Others have found that increasing intakes of vitamins A, B, C, and E taken in the form of supplements are associated with lower odds of incident HNSCC [217].

1.6.1.2.2 *Tocopherols*

Higher serum levels of alpha-tocopherol have also been associated with reduced HNSCC incidence [218]. Some evidence suggests that higher serum levels of gamma-tocopherol increase the odds of incident HNSCC while other data suggests that higher levels of serum gamma-tocopherol protect against incident HNSCC [218, 219].

1.6.1.2.3 *Carotenoids*

Several investigations have shown that the higher intakes and serum levels of carotenoids, consisting of beta-carotene, alpha-carotene, lutein, cryptoxanthine, and lycopene reduce the relative odds of incident HNSCC [120, 201, 219, 220]. The beneficial effect of lycopene appeared to be more prominent for larynx HNSCC than it was for oral cavity and pharynx HNSCC [201].

1.6.1.2.4 *Other antioxidant compounds*

Glutathione intake generally appears to be associated with reduced HNSCC incidence as well [221]. Importantly, both concomitant intake of dietary fiber as well as the source of glutathione affects the inverse association of this micronutrient. Glutathione derived from raw fruits and vegetables appears to be associated with a greater reduction in incident HNSCC than does glutathione derived from meats or cooked vegetables [221].

1.6.1.3 Micronutrients that may increase HNSCC incidence.

While many micronutrients derived from diet appear to reduce the risk of incident HNSCC, some micronutrients have been shown to increase the odds of incident HNSCC. Higher levels of serum selenium, for example, were associated with increased odds of incident HNSCC

[218]. Retinol, a vitamin A derivative has also been associated with increasing levels of incident HNSCC. [216, 218].

1.6.2 Cooking practices

Gaudet and others found that individuals in North Carolina who consumed at least four servings of raw vegetables per week had 0.66 times the odds of incident HNSCC as those who consumed less than two servings of raw vegetables. Conversely, cooked vegetables and legumes had odds ratios of 2.5 and 2.5, respectively. The authors speculated that the common practice of cooking with fatback, bacon, or other pork-derived fats in North Carolina may have contributed to the increased relative odds of incident HNSCC. [205].

A study from Brazil suggested that cooking on a wood-stove increased oral cavity HNSCC incidence as did increasing consumption of charcoal-grilled meats. [222]

1.6.3 Variation of dietary components by other factors associated with HNSCC incidence.

1.6.3.1 Geographic location

Chuang's pooled analysis 22 case-control studies presented the effects of dietary factors on HNSCC incidence stratified by study design characteristics that are important to consider when investigating the diet quality-HNSCC relation. Specifically, Chuang presented effects of fruits, vegetables, red meats, white meats, and processed meats on HNSCC incidence grouped by the four world-wide geographic regions (North America, Europe, Latin America, Asia), by control-selection type, and by HNSCC anatomic subtype.

Overall, fruits and white meats were inversely associated with incident HNSCC in all geographic regions. Further, the inverse association between fruit and incident HNSCC was most pronounced in Asia, followed by Europe and North America. The magnitude of the inverse association between fruit and incident HNSCC was least pronounced in Latin America [200].

Vegetables were inversely associated with incident HNSCC in all geographic regions except in North America, where an imprecise estimate suggested that individuals categorized to the highest quartile of vegetables intake had higher odds of incident HNSCC than those categorized to the lowest quartile of vegetable intake [200].

In contrast to fruits, white meats, and vegetables, red and processed meats generally demonstrated increased relative odds of incident HNSCC. In North America, Europe, and Latin America, individuals categorized to the highest quartile of intake had higher relative odds of HNSCC for both red and processed meats when the lowest intake quartile of red and processed meat was the reference group. In Asia, however, the same intake quartile contrast for both red and processed meats suggested a lower relative odds of incident HNSCC (OR=0.46 (95% CI: 0.24,0.89). [200]

1.6.3.2 Head and neck anatomic subtype

In an analysis of pooled case-control study data the magnitude of association estimates varied by HNSCC anatomic subsite. [200]. The inverse association of fruits was most pronounced for oral cavity cancers, while vegetables conferred greatest protection against laryngeal cancers relative to the other anatomic sites. The inverse association of white meats was less evident for larynx HNSCC compared to oral cavity and pharynx HNSCC [200].

Tomato-based food intakes were more negatively associated with incident larynx HNSCC than with incident oral cavity and pharynx HNSCC. [201].

1.6.3.3 Race

Carotenoid intake has been shown to confer greater reductions in incident oral cavity and pharynx HNSCC among Blacks than among Whites; a similar trend was shown for vegetables. [120]. In contrast, a pooled international study showed that Whites and Asians had a greater

reduction in relative odds of incident HNSCC for higher vegetable consumption than U.S. Blacks, Hispanics, and Brazilians [200].

Fruits have been shown to be inversely associated with incident HNSCC among all races; however, the magnitude of the inverse association appears to differ between races [120, 200]. Day and Blot showed that higher fruit intake conferred more protection for Whites than for Blacks [120]. Similarly, Chuang and colleagues reported that Whites and Asians had odds ratios further below the null value than did U.S. Blacks, Hispanics, and Brazilians for the contrast of highest and lowest quartile of fruit intake [200].

Higher intake of red meat increased the relative odds of incident HNSCC among Whites, Hispanics, and Brazilians while lowering the relative odds of incident HNSCC among Asians. [200]. For white meat intake, the relative odds were lower for Whites, Blacks, Brazilians, Hispanics, and Asians; with the smallest ORs for Hispanics and successively larger ORs for Whites, Asians, and Blacks [200]. Processed meat consumption was associated with increased HNSCC incidence among Brazilians, Whites, Blacks, Hispanics, but not Asians. [200].

1.6.3.4 Age

In Chuang's pooled analysis of diet and HNSCC, age did not appear to modify the association between the various food groups investigated and the incidence of HNSCC. [200].

1.6.3.5 Sex

Sex does not appear to modify the relations between the various food groups and the incidence of HNSCC. [200].

1.6.3.6 Tobacco

The inverse association with higher consumption of fruits and vegetables was more pronounced among former and current smokers than it was for never smokers, whereas white

meats demonstrated inverse associations that were more pronounced among never smokers than for current or former smokers [200].

For red meats, the positive association was more pronounced for never smokers compared to current or former smokers; though, for processed meat consumption, the positive association was more pronounced among current and former smokers compared to never smokers [200].

1.6.3.7 Alcohol

Vegetable and fruit consumption were associated with reduced odds of incident HNSCC regardless of the frequency of alcohol consumption. Notably, the inverse association of vegetable consumption with incident HNSCC was more pronounced for those who consumed more than three alcoholic drinks per day than it was for those who either never consumed alcoholic drinks or for those who consumed at most three drinks per day. No such differential inverse associations with incident HNSCC by daily frequency of alcohol consumption were reported for fruit consumption [200].

For meats, comparisons of higher quartiles of intake with lower ones showed that red and processed meats increased HNSCC incidence while white meat consumption reduced HNSCC incidence, regardless of alcohol consumption frequency. Further, neither the positive associations of red and processed meats nor the inverse associations of white meats differed in magnitude by category of weekly alcohol consumption frequency [200].

1.6.3.8 Human papillomavirus

Colacino and colleagues reported that intakes vitamin A, vitamin B12, and folate measured prior to initiation of treatment of HNSCC were associated with the methylation of tumor suppressor genes among HNSCC cases. Generally, higher intakes of vitamin A, vitamin

B12, and folate resulted in lower composite tumor suppressor gene methylation scores among cases suggesting that these nutrients may help mitigate the molecular pathogenesis of HNSCC. Moreover, the profile of DNA methylation associated with nutrients and antioxidants involved in one-carbon metabolism was modified by the HPV-status of the tumor. Gene sets involved in immune function, including cytokine production and antigen processing and presentation were significantly enriched based on DNA methylation differences in HPV-positive tumors from individuals with high and low vitamin B12 intakes [223]. Arthur and colleagues also reported that certain dietary nutrients were associated with HPV tumor positivity. In their investigation, increasing dietary intakes of vitamin A, vitamin E, beta carotene, iron, and folate were associated with HPV-positivity [224].

A case-control study found that among individuals who were HPV type 16-negative, higher fruit consumption had a reduced odds ratio; however, among HPV type 16-positive individuals, higher fruit consumption was associated with an increased odds ratio suggesting that fruit intake interacts with HPV type-16 to increase the relative odds of incident HNSCC [225].

1.6.4 Measures of overall diet

The motivation to study associations between overall diet and disease is based on the idea that the interactions between individual nutrients and foods that constitute the total diet mask or dilute the individual effects of nutrients or foods on disease occurrence and therefore make it difficult to isolate and appreciate the effects on disease of individual nutrients or foods. An overall measure of diet is instead thought to account for the interactions of individual foods and nutrients and therefore better capture the effect of diet on disease outcomes. Broadly, there are two main strategies that are used to capture overall diet in nutritional epidemiological literature: *a priori* data-driven diet scores and *a posteriori* hypothesis-based diet scores [226].

1.6.4.1 Overview of a priori diet scores: measures of diet quality

A priori hypothesis-based diet summary scores compare observed dietary intakes with an evidence-based recommended standard, such that greater concordance with such recommendations would favor better health. As such, *a priori* diet scores are a measure of diet quality [227–229]. The rigidity of the evidence-based standard can be circumvented by the adaptation and modification of an *a priori* index to suit a particular study population or disease outcome. As well, *ad hoc a priori* diet quality indices can be created by authors for a specific investigation. Nevertheless, commonly used *a priori* diet score indices include the Healthy Eating Index (HEI) and its derivatives [230–236] , the Mediterranean Diet Score and related indices (MDS) [227, 237–241] , and simple summary scores like the diet diversity score (DDS) [242–245] and the recommended food score (RFS) [235] .

The HEI and its derivatives measure how well an observed diet conforms to standard dietary recommendations prescribed by the United States Department of Agriculture (USDA) The HEI was first defined in 1995 and consists of 10 dietary components. The first five of these components measure the degree to which an individual's diet conforms to the serving recommendations of the now-replaced USDA Food Guide Pyramid for five major food groups: Grains; Vegetables; Fruits; Milk; and Meat. Total fat consumption as a percentage of total food energy intake Saturated fat intake as a percentage of total food energy intake, Cholesterol intake, Sodium intake, and Dietary diversity are captured by components six through 10, respectively. Each component score ranges between a low score of zero and a high score of 10; and thus, total composite scores, calculated as the simple summation of each component score, ranges from zero to 100, with higher scores indicating superior diet quality [233].

With improving evidence and changing recommendations documented every five years in the US Federal Government's Dietary Guidelines for Americans reports, the HEI has been accordingly reconstituted to the HEI-2005 and subsequently the HEI-2010 [230–232, 246]; . The HEI-2005 improves upon the original HEI by emphasizing aspects of diet quality which, at the time of development, were considered to be novel. Some of these novel aspects of diet quality included distinguishing whole grains from other types of grains, emphasizing certain types of vegetables as well as distinguishing between vegetable types. Additionally, HEI-2005 introduced the concept of discretionary calories. Despite the differences with the original HEI, higher scores of the HEI-2005, like the original HEI, generally reflect better diet quality [230].

The HEI-2005 components are measured as densities of cup- or ounce-equivalents of nutrients per 1,000 calories and are divided broadly into those that measure adequacy and those that measure moderation. Generally, higher intakes of adequacy dietary components are related to higher scores, whereas higher intakes of moderation components lead to lower scores. The nine adequacy components for HEI-2005 with their corresponding maximum scores following in parentheses were Total fruit (5); Whole fruit (5); Total vegetables (5); Dark green and orange vegetables and legumes (5); Total grains (5); Whole grains (5); Milk (10); Meat and beans (10); and Oils (10); while, the moderation components and their corresponding maximum scores following in parentheses were Saturated fat (10); Sodium (10); and Calories from fats, alcoholic beverages, and added sugars (20). Although the maximum summary score for the HEI-2005 is 100 as is the case for the original HEI, the variation in maximum scores for the different components of the HEI-2005 serves as a weighting scheme to reflect those aspects of a healthy diet emphasized in the USDA's MyPyramid and Dietary Guidelines for Americans reports [230, 233, 246, 247].

The HEI-2010 is very similar to the HEI-2005 in that it consists of 12 components including nine adequacy and three moderation components. As well, HEI-2010 uses a density approach to set standards in which cup- or ounce-equivalents are evaluated per 1,000 calories of energy intake. Further, HEI-2010, like the HEI-2005, employs the concept of least-restrictive standards which signifies that the standard to achieve the maximum score for any component is that which is easiest to achieve among the recommendations for a given dietary component and energy intake-sex-age stratification category [231].

The HEI-2010 also retain many of the same HEI-2005 components including Total fruit; Whole fruit; Total vegetables; Whole grains; and Sodium. As well, Milk and Meat and beans were also carried forward from HEI-2005, but were renamed to Dairy and Total protein foods, respectively for consistency with the 2010 USDA Food Patterns report [231, 247].

Despite many similarities between HEI-2005 and HEI-2010, there are important distinctions between the two *a priori* scoring algorithms. The Greens and Beans component in HEI-2010 replaces the Dark Green and orange vegetables and legumes component in HEI-2005. Also, a Seafood and plant proteins component has been added to capture specific choices from the protein group. Moreover, the Fatty acids adequacy component in HEI-2010, defined as the ratio of polyunsaturated and monosaturated to saturated fatty acids, replaces the Oils and Saturated fat components of the HEI-2005 in an effort to acknowledge the recommendation to replace saturated fat with monosaturated and polyunsaturated fatty acids. Finally, the HEI-2010 moderation component, Refined grains, replaces the HEI-2005 adequacy component, Total Grains, to assess overconsumption [231].

With respect to scoring, the HEI-2010 applied variable scoring to the 12 components to emphasize those components which were considered more important in enhancing diet quality

detailed in the 2010 Dietary Guidelines for Americans [248]. Specifically, the maximum score of five was assigned to the HEI-2010 adequacy components Total Fruit; Whole fruit; Total Vegetables; Greens and Beans; Total Protein Foods; and Seafood and plant proteins; while a maximum score of 10 was applied to the adequacy components Whole grains and Dairy and to the moderation components Refined grains and Sodium. The moderation component Empty calories was assigned a score maximum score of 20 [231].

Other variations of the original HEI have also been developed by researchers independent of the US Federal government. McCullough and colleagues developed the Alternate Healthy Eating Index (AHEI) to better predict chronic disease outcomes after their previous evaluations of the HEI suggested that better adherence to the HEI only marginally reduced overall mortality and cardiovascular disease (CVD) incidence. The authors developed the AHEI which retained many of the components of the HEI, but also added other components that they felt could better predict chronic disease based on the literature that was available at the time that they developed the AHEI [235, 249].

The AHEI is composed of nine components, eight of which have scores that can range between zero and 10 and one of which can range from 2.5 and 7.5; and thus, a composite summary score can range from a low of 2.5 to a maximum of 87.5. The components of the AHEI and their corresponding score range following in parentheses are Vegetables (0-10); Fruit (0-10); Nuts and soy protein (0-10); Ratio of white to red meat (0-10); Cereal fiber (0-10); *Trans*-fat as a percentage of total energy (0-10); Ratio of polyunsaturated to saturated fatty acids (0-10); Duration of multivitamin use (2.5-7.5); and Alcohol use (0-10) As is the case with the HEI, HEI-2005, and HEI-2005, higher AHEI summary scores suggest better diet quality [230–236] .

While the HEI-type indices measure diet quality based on adherence to the US federal government nutritional policy, the MDS and related indices measure how well an observed diet adheres to the traditional Mediterranean diet [227, 237, 240, 241, 250, 251]. Trichopoulou described the Greek variant of the Mediterranean diet as one characterized by high intakes of fresh fruits and vegetables, whole grains and cereals, legumes, and fat intake that is a consequence of generous use of olive oil for food preparation and cooking. Concomitantly, the traditional Mediterranean diet limits intakes of meats and dairy products while allowing for moderate alcohol consumption, typically with meals [238]. This general characterization of the traditional Mediterranean diet serves as the basis for all MDS-type indices [239, 250].

Generally, *a priori* diet quality indices based on the traditional Mediterranean diet use the median energy-adjusted daily intakes of each dietary component in the study base, separately for males and females, as the standard for assigning scores to individuals in the study population. With the exception of alcohol, dietary components of the MDS-type indices are broadly categorized into high consumption and low consumption categories based on how they map to the traditional Mediterranean diet [239, 250]. For example, since high fruit consumption is characteristic of the traditional Mediterranean diet, a score of one is assigned to those individuals whose daily intake of fruit exceed the sex-specific energy-adjusted median value in the study base for fruits while individuals whose intake is at or below the sex-specific energy-adjusted median value for fruit intake in the study base are assigned a score of zero. Conversely, for food groups that are less-frequently consumed in the traditional Mediterranean diet like dairy products, individuals whose daily dairy intake exceeds the sex-specific energy-adjusted median value in the study base for dairy intake would be assigned a zero and a one otherwise. Finally, for alcohol, pre-specified sex-specific ranges of what is considered moderate daily alcoholic

intake ensures a score of one for individuals who fall within the range and a zero otherwise. Thus, a simple summation of the component scores creates a summary MDS score that ranges from a low value of zero to a maximum equal to the total number of components included in the score [239, 250].

Although HEI- and MDS-type indices are relatively simple in their construction, even more straightforward are the DDS [242–245] which counts the number of different food groups or foods consumed regularly and the RFS which simply tallies the reported consumption of foods recommended by current dietary guidelines [235] .

1.6.4.2 Application of a priori diet scores to investigations of chronic disease and other cancers

The HEI and its derivatives have been used in several investigations to study the effect of overall diet on mortality as well as the incidence of cardiovascular disease (CVD) and diabetes mellitus type 2 (DM2). As well, the HEI-type indices have also been applied to study the effect of diet quality on incidence of neoplastic disease including cancers of the breast, stomach, pancreas, and esophagus [252, 253]. MDS-type indices have been applied similarly though CVD outcomes and mortality have been the prime focus. Although there is variability in the performance of each index with respect to each outcome, generally, higher scores for both MDS- and HEI-type indices appear to reduce mortality or confer protection against CVD, DM2, and most cancers [237, 254, 255].

1.6.4.3 Application of a priori diet scores to investigations of head and neck cancer

Table 1-15 summarizes the literature that has applied *a priori* diet scores to understand associations between diet quality and HNSCC incidence. Of the five investigations summarized in the table, four were conducted in Europe and one was conducted in the United States. All of the investigations used at least one scoring index that represented the Mediterranean diet and, in

each investigation,, higher adherence to the Mediterranean diet appeared to be associated with reduced HNSCC incidence. The HEI-2005 was used in the sole investigation form the United States that investigated the *a priori* diet scores and HNSCC and higher scores corresponding to increased adherence to the Dietary Guidelines for Americans was also inversely associated with incident HNSCC among men and women, although the inverse association appeared to be more pronounced among women. (Table 1-15)

1.6.4.4 Overview of a posteriori diet scores.

In contrast to *a priori* diet scores, *a posteriori* empirical diet-scores are derived using statistical data-reduction methods to generate dietary patterns based on observed dietary intakes ranging across all food items constituting the entire diet. In general, latent dietary patterns are formulated as linear combinations of observed dietary intakes weighted by the factor's loadings estimated by a method of regression. Common statistical techniques used to isolate dietary patterns from observed dietary intakes include principal components analysis (PCA), cluster analysis, exploratory factor analysis (EFA) or confirmatory factor analysis (CFA), reduced rank regression (RRR), and partial least squares (PLS)regression. [226, 229, 256–259].

In considering the relative strengths and weaknesses of the various statistical approaches, it is important to recognize that each method is applied to data for distinct purposes in nutritional epidemiology. PCA, EFA, and CFA are typically used to construct uncorrelated linear functions from original correlated food intake data that maximize the explained variation in food intakes whereas cluster analysis is used to identify and classify groups of study participants who share similar dietary intake patterns. RRR is similar to PCA, EFA, and CFA, in that it identifies linear functions from food intake data; however, it is constrained to identify these linear functions in a manner that maximizes the explained variation in nutrient or biomarker variables that are thought

to *a priori* be associated with a specific disease outcome. Finally, PLS is thought to be an approach that balances PCA, EFA, and CFA with RRR in that it identifies dietary patterns that maximizes the explained variation in both food intake and nutrient intakes simultaneously. Taken together, each approach can be viewed as advantageous given the goals of the analysis.

Collectively, all of these approaches are limited by the reproducibility of dietary patterns derived as each set of data from various populations may produce different patterns, even if the same statistical approach is applied. Although the methods are inherently empirical in nature, there are still subjective choices that need be made during the application of each method such as the choice of factor rotation method, the minimal amount of variance that need be explained in order to retain factors, and the naming of dietary patterns. As such, these decisions that can be viewed as arbitrary in nature are considered a weakness of this methodology by some.

1.6.4.5 Application of a posteriori diet scores to investigations of chronic disease and other cancers.

A posteriori diet scores were derived from principal components analysis and factor analysis in several investigations to evaluate the relation between diet and several chronic diseases including metabolic syndrome, CHD, and DM2 [260–271]. As is standard practice when using *a posteriori* diet scores, the authors assigned labels to the identified dietary patterns that reflected the dietary components which loaded most heavily for the identified patterns. Examples of names that were assigned to identified dietary patterns in these investigations include “traditional dietary pattern,” “meat and fast-food pattern,” “eastern pattern,” “mixed pattern,” “western pattern,” “neotraditional pattern,” “modern pattern,” “prudent dietary pattern,” and “western dietary pattern.” [260–265, 268, 269]. To avoid the subjectivity associated with naming patterns, some authors elect to simply describe the patterns that were identified.

1.6.4.6 Application of a posteriori diet scores to investigations of head and neck cancer.

Table 1-16 summarizes the literature that has explored associations between a posteriori diet scores and incident HNSCC. Of the twelve studies summarized in the table only one is from the United States. Although the names for the factors identified through factor analysis are arbitrarily assigned, generally, raw fruits, raw vegetables, white meat, and poultry tend to be associated with reduced HNSCC incidence; whereas red meats, processed meats, and patterns associated with alcohol are associated with increased HNSCC incidence. (Table 1-16).

1.7 Previous epidemiologic literature that has explored the relation between dietary exposures and survival of HNSCC

1.7.1 Pre-HNSCC-diagnosis dietary exposures

1.7.1.1 Individual nutrients and foods

A secondary analysis of data derived from a clinical trial evaluating the benefits of beta-carotene and vitamin E supplementation on individuals diagnosed with early stage HNSCC and who were scheduled to undergo curative radiotherapy suggested that higher pre-treatment dietary vitamin D intake did not confer an additional survival benefit relative to lower pre-treatment dietary vitamin D intake [272].

Fruit and vegetable intake prior to HNSCC diagnosis has also been investigated as a prognostic factor for HNSCC survival. As part of a larger HNSCC case-control investigation to better understand the role of HPV in HNSCC pathogenesis, Sandoval and colleagues cleverly used the pre-diagnosis dietary history and follow-up data to evaluate to understand the relation between fruit and vegetable intake and HNSCC survival. Sandoval and colleagues' analysis found that intakes of higher levels of fruit and vegetable consumption prolonged survival more so than did lower levels of fruit and vegetable consumption [166].

Crosignani's investigation considered effects of pre-diagnosis intakes of several nutrients and foods on survival among male laryngeal HNSCC patients in Europe. The authors argued that because higher intake tertiles of fruits, vegetables, orange juice, olive oils, and breads all reduced the hazard of mortality compared to the lowest intake tertile, this supported the notion that a "Mediterranean" style diet may enhance survival. However, higher intakes of meats, including beef, were also found to highly reduce mortality, which as the as the authors mention, conflicts with the idea it is indeed a Mediterranean-style diet that was responsible for the reduction in mortality [273]. It is possible that higher meat intake may have been an indicator of higher socioeconomic status or higher BMI, neither of which were adjusted for in the regression models.

Similarly, another investigation from Europe found that pre-diagnosis assessments of dietary intake revealed that higher levels of vegetable and vitamin C intake prolonged survival among individuals with larynx and hypopharynx HNSCC relative to those with lower levels of intake [274]. Not all investigations; however, were able to report associations between individual foods or nutrients and survival following a diagnosis of larynx HNSCC [161].

1.7.1.2 Overall Diet and dietary patterns

Arthur identified two pre-treatment dietary patterns using principal components analysis that differentially affected HNSCC prognosis. A post-diagnosis food frequency questionnaire was administered shortly after diagnosis and cases were asked to recall their usual diet during the previous year. The "whole-foods" dietary pattern was characterized by high intakes of vegetables, fruit, fish, poultry, and whole grains while the "Western" dietary pattern was exemplified by high intakes of red meats, processed meats, refined carbohydrates, potatoes, and French fries. In Arthur's analysis, individuals diagnosed with HNSCC who previously consumed

a diet that scored in the highest quintile of the "whole-foods" pattern had a 44% reduction in their hazard of death compared to those who scored in the lowest quintile [275]. Notably, Arthur and colleagues did not find an association between the "Western" diet pattern and HNSCC survival [275].

Serum albumin, an indicator of overall nutritional status, has been considered a prognostic factor for HNSCC [276]. Indeed, Liu and colleagues found that individuals with HNSCC who had a pre-treatment serum albumin level less than 4.15 g/dL had a lower survival probability than did those individuals with HNSCC who had a pre-treatment serum albumin level of at least 4.15 g/dL [173].

1.7.2 At- and Post-HNSCC-diagnosis dietary exposures

At-diagnosis dietary exposures refer to dietary habits or nutrient levels that occur or exist during the time period including and immediately following diagnosis through the date occurring one year after diagnosis. Post-diagnosis dietary exposures refer to dietary habits or nutrient levels that occur or exist during the time period at least one year past the diagnosis of HNSCC. These at- and post-diagnosis dietary exposures are also assessed following the diagnosis of HNSCC. For details regarding the actual timing of dietary assessment for the references discussed in sections 1.7.1.1 and 1.7.1.2, please refer to Table 1-17.

In contrast, pre-diagnosis dietary exposures as described in section 1.7.1 refer to dietary habits or nutrient intakes that occurred or existed during the time period prior to HNSCC diagnosis, even though they too may have been assessed post-diagnosis.

1.7.2.1 Individual nutrients and foods

Sakhi and colleagues found that higher intakes of certain dietary carotenoids, namely lutein, alpha-carotene, beta-carotene, and lycopene were associated with longer overall HNSCC survival following radiotherapy [277, 278]. A similar result was reported for dietary glutathione

[279]. The source of the micronutrients, whether acquired through the diet or supplementation, and tobacco smoking; however, appear to be important factors to consider when assessing the utility of antioxidant micronutrients like carotenoids. Clinical trial findings demonstrated increased mortality from synthetic vitamin E and beta-carotene supplementation among HNSCC patients undergoing curative radiotherapy among all study participants, though the negative impact of supplementation was more pronounced among smokers [280, 281]. Tobacco smoking also appeared to interact with dietary carotenoids as well as Mayne and colleagues reported that increasing intakes of dietary carotenoids among smokers previously diagnosed with HNSCC increased mortality while simultaneously reducing mortality among individuals diagnosed with HNSCC who were non-smokers [277].

Fruit and vegetable intake following HNSCC diagnosis has also been investigated. In Sandoval's investigation from Spain, individuals still alive one year after HNSCC diagnosis were given an assessment of fruit and vegetable intake. Using this valuation of post-diagnosis fruit and vegetable intake, Sandoval and colleagues showed that individuals whose fruit and vegetable consumption fell into the highest consumption category had a lower hazard of death than those whose consumption was fell into the lowest consumption category [166].

1.8 Diet and head and neck cancer incidence and survival in animal models

1.8.1 Incidence

Isothiocyanates and indoles, which are prevalent compounds contained in cruciferous vegetables, as well as black raspberries, have been shown to be associated with reduced head and neck tumor formation in animal models [282–284].

1.8.2 Survival

Tanaka was able to show that indole-3-carbinol could reduce tongue neoplasm formation using a rat carcinogenesis model even after the initiation of carcinogenesis had begun suggesting a possible role of indoles in cancer survival [284].

1.9 Diet and head and neck cancer incidence and survival in *in vitro* investigations

Pathogenesis

The mechanisms by which diet is able to exert a reduction in HNSCC risk and prolong survivorship have been brought to light through laboratory investigations of plant-based phytochemicals and their actions on HNSCC cancer cell lines. These in vitro investigations suggest that the bioactive phytonutrients and vitamins which are rich in fruits and vegetables are able to allay HNSCC risk and prolong survivorship by preventing DNA damage through the scavenging of reactive oxygen species (ROS), inducing apoptosis, inhibiting DNA repair enzymes in HNSCC cancer cells, obstructing tumorigenic signaling cascades, and by limiting the actions of matrix metalloproteinases, enzymes that are critical in the development of metastatic HNSCC [285–296] .

1.10 Conclusions

Head and neck cancer incidence has declined in recent years, yet survival from head and neck cancer has not improved despite advances in treatment and diagnosis. Further, head and neck cancer remains a considerable economic burden for the public as well as a strain for HNSCC patients and their families. As such understanding how modifiable risk factors other than the major HNSCC risk factors of tobacco use and alcohol consumption might be associated with HNSCC is imperative to reducing the hardships associated with this cancer. Diet is one such risk factor which merits further investigation.

The initial investigations of dietary factors and HNSCC focused on individual nutrients and food groups. These investigations were valuable as they demonstrated consistently that higher relative fruit, vegetable, vitamin C, and beta-carotene intake was associated with reduced HNSCC incidence. Nevertheless, other food groups like dairy, meat, legumes, and grains showed inconsistent results as studies reported the range of possible associations including inverse, positive, and null associations. Because of these inconsistent results for some nutrients, investigators postulated that the interactions among nutrients may be confounding the results and therefore proposed that investigating the diet holistically as it related to HNSCC incidence may be more informative.

Measures of overall diet are thought to capture the interplay between individual nutrients and food that constitute an individual's diet when used to understand relations between the overall diet and chronic disease. Traditionally, investigations of the associations between overall diet and chronic illness apply either an *a posteriori* data-driven- or an *a priori* hypothesis-driven approach. Both approaches have been used in studies of cancer including HNSCC.

For investigations of incident HNSCC, the *a posteriori* approach to study overall diet has been used in 12 investigations: four from Uruguay, two from Italy, two from Brazil, and one each from Malaysia, Indonesia, the United States, and the INHANCE consortium. (Table 1-16) Because all 12 of these investigations were based case-control designs, investigators captured temporally relevant dietary exposures occurring prior to diagnosis by administering a food frequency questionnaire shortly after diagnosis and asking cases to recall his or her usual dietary patterns and intakes as they might have occurred during a time period prior to diagnosis and asking controls to report dietary patterns and intakes as they might have occurred during a time prior to the FFQ interview. Further, of these twelve *a posteriori* studies, only Edefonti's

INHANCE investigation [297] and Bradshaw's US investigation [298] included oral cavity, pharynx, and larynx anatomic subtypes and at least one thousand cases of HNSCC in their analyses. In all investigations, patterns that were higher in fruits, vegetables, lean meats, and less processed foods were associated with reduced HNSCC incidence; whereas patterns loading on foods that were processed or had high animal content were generally associated with increased HNSCC incidence.

The *a priori* approach to study overall diet and incident HNSCC has been investigated five times: four studies from Europe and one from the United States. (Table 1-15) The four European investigations were all case-control studies and applied variations of the Mediterranean diet score while the United States study was a cohort study that made use of both a derivative of the Mediterranean diet score and a measure of the US government's dietary recommendations, the Healthy Eating Index-2005. Like other case-control investigations of diet and incident HNSCC, investigators for the four case-control studies from Europe captured temporally relevant dietary exposures occurring prior to diagnosis by administering a food frequency questionnaire shortly after diagnosis and asking cases to recall his or her usual dietary patterns and intakes as they might have occurred during a time period prior to diagnosis and controls to report dietary patterns and intakes as they might have occurred during a time prior to the FFQ interview. The cohort study from the United States captured dietary exposures at baseline among those initially free of HNSCC and therefore captured dietary intakes that occurred prior to diagnosis. Although the US study included 1,868 cases in its analysis, the cohort was comprised almost exclusively of White individuals and those older than 60 years of age limiting the ability of the investigators to evaluate modification of associations by age and race. Nevertheless, all investigations

demonstrated that greater adherence to the prescribed diets resulted in reduction in HNSCC incidence.

Finally, the study of overall diet and HNSCC survival has been limited. Most investigations evaluate diet at the time of treatment, either before, or after surgery and or radiation therapy. Only two studies have evaluated pre-diagnosis diet and, of these, only one investigated the role of overall diet prior to diagnosis on long-term survival. In the overall diet investigation of long-term survival following HNSCC diagnosis, HNSCC cases were administered an FFQ and asked to recall his or her usual diet during the year prior to his or her diagnosis. This overall diet investigation made use of a cohort study design and the *a posteriori* approach to estimate diet scores from which the authors concluded that the pattern they named as "Whole foods" prolonged HNSCC survival, whereas the "Western" pattern appeared to shorten survival. Notably, the foods that loaded on the "Whole foods" pattern were those that pertain to the "traditional" Mediterranean diet.

The review of the diet quality-HNSCC literature reveals that investigations of overall diet and HNSCC incidence in the United States are limited to Bradshaw's use of *a posteriori* diet scores in a large racially- and age-diverse case-control investigation and Li's application of the *a priori* approach in the setting of a large cohort study composed of greater than 90 percent White individuals. Further, only the *a posteriori* approach has been used to understand whether HNSCC cases' usual diet before diagnosis, as captured by an FFQ assessed after having been-diagnosed in which cases recalled their usual past diet, is associated with long-term HNSCC survival in a study cohort of which over 90 percent were White individuals.

This dissertation will make use of the relatively large, racially- and age-diverse case-control dataset closely resembling that used by Bradshaw [298] to understand how adherence to

prescribed diets using the *a priori* approach may be associated with HNSCC incidence and survival. In an effort to facilitate comparisons with previous investigations, the *a priori* indices used will include the HEI-2005 and derivatives of the MDS. This investigation will be the first to make use of pre-diagnosis *a priori* diet scores to understand the association between overall diet quality and long-term HNSCC survival. Furthermore, Bradshaw's investigation will provide a unique opportunity to compare the performance of an *a priori* approach with that of the *a posteriori* approach as there are currently no investigations which have made use of both approaches within the same study population. As well, the availability of data on race, BMI, tobacco and alcohol use, anatomic subtypes, and Tumor HPV-positivity in the dataset will allow for the possibility of evaluating associations between overall diet quality and HNSCC as sub-aims through sub-group analysis which previously has not been possible in the United States because of the uniformity of study populations used in other studies of overall diet and HNSCC. Finally, the application of both the HEI-2005 as well as the MDS through an *a priori* approach may yield findings that inform the US government's decisions regarding dietary recommendations in the future.

1.11 Specific Research Aims

1.11.1 Specific Aim 1

To estimate the association between diet quality and incident HNSCC using an *a priori* hypothesis-driven approach to characterize overall diet quality. The *a priori* indices that will be used include the HEI-2005, the MDS, and derivatives of the MDS constructed based on previous literature.

1.11.1.1 Subaim 1 of specific aim 1

To evaluate associations between *a priori* hypothesis-driven diet quality scores and incident HNSCC by race.

*1.11.1.2 **Subaim 2 of specific aim 1***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and incident HNSCC by BMI

*1.11.1.3 **Subaim 3 of specific aim 1***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and incident HNSCC by tobacco use individually, alcohol consumption individually, and by tobacco and alcohol use jointly.

*1.11.1.4 **Subaim 4 of specific aim 1***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and incident HNSCC by tumor HPV-positivity.

*1.11.1.5 **Subaim 5 of specific aim 1***

To evaluate associations between *a priori* hypothesis-driven diet scores and incident HNSCC by anatomic subtypes including oral cavity, pharynx, and larynx.

1.11.2 Specific Aim 2

To estimate the association between diet quality and long-term survival following HNSCC diagnosis using an *a priori* hypothesis-driven approach to characterize overall diet quality. The *a priori* indices that will be used will be the MDS. For this aim, and subsequent subaims, "survival," implies both overall survival, and cancer-specific survival.

*1.11.2.1 **Subaim 1 of specific aim 2***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and HNSCC survival by race.

*1.11.2.2 **Subaim 2 of specific aim 2***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and HNSCC survival by BMI

*1.11.2.3 **Subaim 3 of specific aim 2***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and HNSCC survival by tobacco use individually, alcohol consumption individually, and by tobacco and alcohol use jointly.

*1.11.2.4 **Subaim 4 of specific aim 2***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and HNSCC survival by tumor HPV-positivity.

*1.11.2.5 **Subaim 5 of specific aim 2***

To evaluate associations between *a priori* hypothesis-driven diet quality scores and HNSCC survival by anatomic subtypes including oral cavity, pharynx, and larynx.

Table 1-1: Age-standardized incidence and mortality rates for oral cavity, pharynx, and larynx cancer per 100,000 persons by race and sex for the years 2008 to 2012: SEER18

	Oral Cavity and Pharynx				Larynx			
	Males		Females		Males		Females	
	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites
Incidence	14.6	17.1	5.2	6.4	8.8	5.8	1.7	1.2
Mortality	5.0	3.7	1.3	1.3	3.6	1.8	0.6	0.4

Rates are age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130). Trends are based on rates age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130).
The SEER 9 areas are San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta.; The SEER 13 areas comprise the SEER 9 areas plus San Jose-Monterey, Los Angeles, the Alaska Native Registry, and Rural Georgia.; The SEER 18 areas comprise the SEER 13 areas plus California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, and Georgia excluding ATL/RG.
US Mortality Files, National Center for Health Statistics, CDC.

Table 1-2:Estimated relative 5-year survival probabilities of head and neck cancer by subtype, stage, race and sex for the years 2005 to 2011 using SEER18 data.

Stage	Oral Cavity and Pharynx				Larynx			
	Males		Females		Males		Females	
	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites
Localized	0.72	0.82	0.82	0.84	0.74	0.77	0.73	0.71
Regional	0.41	0.65	0.46	0.58	0.40	0.44	0.43	0.49
Distant	0.24	0.39	0.29	0.38	0.30	0.37	0.31	0.35
All stages	0.41	0.65	0.53	0.66	0.54	0.63	0.51	0.57

SEER 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG). Based on follow-up of patients into 2012.
Stage at diagnosis is classified using SEER Summary Stage 2000 [299]

Table 1-3: Cigarette smoking as a risk factor for incident HNSCC among never drinkers of alcohol for all HNSCC and by HNSCC subtype: INHANCE, adapted from Hashibe et al.,2007 [300]

Risk Factor	Risk category	OR (95% CI)*				
		All	OCSCC	OPC/HPC	OC/PC-NOS	LC
Cigarette smoking‡						
Ever use						
	Yes	2.13 (1.52,2.98)	1.35 (0.90,2.01)	2.02 (1.34,3.05)	1.07 (0.50,2.28)	6.84 (4.25,11.01)
Frequency						
	1-10	1.82 (1.28,2.59)	1.38 (0.80,2.38)	2.55 (1.59,4.10)	1.55 (0.86,2.79)	5.72 (3.41, 9.60)
	11-20	2.36 (1.60, 3.47)	1.43 (0.85,2.38)	2.15 (1.38,3.34)	1.08 (0.39,2.99	8.36 (5.18,13.51)
	21-30	3.58 (2.09, 6.16)	1.61 (0.31,8.47)	3.86 (1.80,8.25)	2.68 (1.25,5.78)	14.38 (8.47,24.43)
	>31-40	4.46 (2.54, 7.83)	2.92 (0.91,9.44)	4.82 (2.42,9.60)	5.46 (0.92,33.47)	18.38 (7.14,47.31)
	>40	2.69 (1.21, 5.98)	1.40 (0.30,6.61)	3.10 (1.43,6.69)	6.00 (1.48,24.29)	11.02 (4.92,24.72)
Duration						
	1-10	1.45 (1.04, 2.03)	1.37 (0.84,2.23)	1.69 (1.00,2.88)	1.71 (0.62,4.74)	4.33 (1.13,16.62)
	11-20	1.10 (0.75, 1.61)	1.16 (0.64,2.10)	1.18 (0.61,2.28)	2.35 (0.69,7.96)	3.48 (1.61,7.50)
	21-30	1.79 (1.20, 2.67)	1.32(0.92,1.91)	1.47 (0.94,2.31)	2.14 (0.94,4.86)	5.75 (2.94,11.23)
	31-40	3.61 (2.26, 5.75)	2.28 (1.19,4.37)	3.74 (2.61,5.38)	2.07 (0.88,4.84)	9.30 (5.40,16.02)
	>40	4.83 (3.18, 7.33)	3.23 (1.54,6.77)	4.84 (2.22,10.54)	2.56 (1.29,5.07)	16.32 (9.58,27.79)

*Reference category for all ORs is never smoking; All ORs adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking (continuous), and years of pipe smoking (continuous).

†Abbreviations: OR: Odds ratio; CI: Confidence interval; OCSCC: Oral cavity squamous cell carcinoma; OPC: oropharyngeal cancer; HPC: hypopharyngeal cancer; OC/PC-NOS: oral cavity/pharynx cancer-not otherwise specified; LC: larynx cancer.

‡The definitions of ever cigarette smoking were 1) smoked 100 or more cigarettes in a lifetime (Central Europe, Los Angeles, North Carolina, Puerto Rico, Seattle, and Houston studies), 2) smoked one cigarette/day for 1 or more years (International Multicenter, Tampa, South America, Milan, Aviano, Italy Multicenter, and Switzerland studies), 3) smoked one-half pack per week for 1 or more years (Iowa study), and 4) smoked" regularly" (France study). The definitions of ever cigar and pipe smoking were smoked cigars or pipes for 6 or more months (Seattle, North Carolina, and Puerto Rico studies), smoked one cigar or one pipeful of tobacco per month for 6 or more months (Los Angeles study), smoked one cigar or pipe/day for 1 or more years (Milan, Aviano, Italy, Switzerland, and South America studies), smoked cigars or pipes "regularly" (France and Central Europe studies), ever used cigars or pipes (Houston study), one cigar or one pipeful of tobacco a week for 1 or more years (Iowa), smoked daily for 1 or more years (International Multicenter study), and smoked a cigar or pipe once a day for 1 or more years (Tampa study). The definitions of ever chewing and ever use of snuff differed across studies (i.e., ever use of snuff or chew for ≥ 6 months [Seattle, North Carolina, and Puerto Rico studies], one small can of snuff or one pouch of chewing tobacco per week for ≥ 1 year [Iowa study], use chew or snuff once per day for ≥ 1 year [Tampa study], chewed daily tobacco, betel quid, areca nut, or pan masala or snuffed tobacco daily for ≥ 1 year [International Multicenter studies], one plug of tobacco or one pinch of snuff of tobacco per month for ≥ 6 months [Los Angeles study], and ever use of snuff or chew [Houston study]). Frequency was defined as number of cigarettes smoked per day; Duration was defined as years of smoking in years.

Define ever use, frequency and duration for tobacco and alcohol use, respectively

Table 1-4: Alcohol consumption as a risk factor for incident HNSCC among never users of tobacco for all HNSCC and by HNSCC subtype: INHANCE, Adapted from Hashibe et al., 2007 [300]

Risk Factor	Risk category	OR (95% CI)*				
		All	OCSCC	OPC/HPC	OC/PC-NOS	LC
Alcohol consumption‡						
Ever						
	Yes	1.18 (0.93,1.50)	1.17 (0.92, 1.48)	1.38 (0.99,1.94)	1.09 (0.77,1.54)	1.21 (0.82,1.79)
Frequency						
	<1	1.04 (0.79,1.38)	1.14 (0.8,1.63)	1.39 (0.99,1.96)	1.08 (0.67,1.75)	0.92 (0.5,1.69)
	1-2	1.30 (0.94,1.80)	1.64 (1.19,2.25)	1.66 (1.18,2.34)	1.24 (0.77,1.99)	1.26 (0.77,2.07)
	3-4	1.82 (1.10,2.99)	1.11 (0.57,2.15)	2.33(1.37,3.98)	2.32 (1.24,4.34)	1.24 (0.62,2.45)
	>=5	2.81 (1.49,5.27)	1.23 (0.59, 2.57)	5.50 (2.26,13.36)	0.77 (0.27,2.18)	2.98 (1.72,5.17)
Duration						
	1-10	1.56 (1.11,2.19)	2.36 (1.43,3.88)	1.76 (0.99,3.14)	2.59 (1.38,4.86)	2.61 (1.14,5.98)
	11-20	1.22 (0.87, 1.71)	1.09 (0.65,1.85)	1.34 (0.81,2.11)	1.09 (0.56,2.11)	1.63 (0.78,3.43)
	21-30	1.27 (0.87, 1.87)	0.81 (0.49,1.33)	1.95 (1.37,2.77)	1.26 (0.73,2.17)	1.40 (0.79,2.48)
	31-40	1.17 (0.84, 1.62)	1.29 (0.88,1.9)	1.44(0.78,2.66)	0.86 (0.47,1.57)	1.10 (0.64,1.89)
	>40	1.05 (0.65, 1.68)	1.15 (0.77,1.73)	1.51(0.68,3.37)	0.92 (0.49,1.71)	1.00 (0.58,1.73)

*Reference category for all ORs is never smoking; All ORs adjusted for age, sex, race/ethnicity, education level, and study center.

†Abbreviations: OR: Odds ratio; CI: Confidence interval; OCSCC: Oral cavity squamous cell carcinoma; OPC: oropharyngeal cancer; HPC: hypopharyngeal cancer; OC/PC-NOS: oral cavity/pharynx cancer-not otherwise specified; LC: larynx cancer.

‡The definitions of ever alcohol drinking were 1) ever consumed alcohol (France, Central Europe, Aviano, Milan, Italy Multicenter, and Switzerland studies), 2) more than four drinks in a year (Seattle study), 3) one or more drinks per month for 6 or more months in a lifetime (Los Angeles study), 4) 12 or more drinks of any kind of alcohol in a lifetime (Puerto Rico study), 5) one or more times per month (Multicenter, South America studies), 6) average of one or more drinks per week for 1 or more years (Iowa study), 7) one or more times per week for 1 or more years (Tampa and Houston studies), and 8) four or more times per month of beer, wine, or liquor (North Carolina study). Frequency was defined as number of alcoholic drinkers consumed per day; Duration was defined as years of alcohol consumption in years.

Table 1-5: Cumulative tobacco use exposure among never alcohol consumers and cumulative exposure of alcohol consumption among never users of tobacco and incident HNSCC: INHANCE, Adapted from Hashibe et al.,2007 [300]

	OR (95% CI)*	
Cumulative dose†	Tobacco use among never consumers of alcohol	Alcohol consumption among never users of tobacco
1-10	1.58 (1.13,2.22)	1.07 (0.82,1.39)
11-20	1.85 (1.08,3.16)	1.31 (0.86,1.98)
21-30	2.75 (1.71,4.43)	1.33 (0.73,2.42)
31-40	4.06 (2.33,7.09)	1.31 (0.86,2.01)
41-50	3.46 (1.97,6.09)	1.15 (0.70,1.90)
>50	5.40 (3.06,9.53)	1.87 (1.27,2.75)

*Reference category for tobacco use is never users; for alcohol consumption is never drinkers.; ORs for tobacco exposure are adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking (continuous), and years of pipe smoking (continuous); ORs for alcohol exposures adjusted for age, sex, race/ethnicity, education level, and study center. ORs for tobacco exposure are adjusted for age, sex, race/ethnicity, education level, study center, years of cigar smoking (continuous), and years of pipe smoking (continuous); ORs for alcohol exposures adjusted for age, sex, race/ethnicity, education level, and study center; Interpretation of OR for cumulative alcohol exposure of >50 drink-years: Among never users of tobacco, the study period odds or incident HNSCC for those exposed to greater than 50 drink-years of alcohol consumption was 1.87 times the odds of incident HNSCC for those who never consumed alcohol, having accounted for confounding

†Cumulative dose units for tobacco use was measured as pack-years; cumulative dose units for alcohol consumption was measured in drink-years

Table 1-6: Ever tobacco and ever alcohol associations independently and jointly with incident HNSCC by anatomic subtype, sex, and age categories: INHANCE. Adapted from Hashibe et al.,2009. [54]

Sub-group	OR (95% CI)*		
	Alcohol alone†	Tobacco alone‡	Tobacco and Alcohol jointly
All HNSCC	1.06 (0.88,1.28)	2.37 (1.66,3.39)	5.73 (3.62,9.06)
Anatomic subtype			
Oral cavity	0.79 (0.60,1.04)	1.74 (1.10,2.76)	4.78 (2.59,8.81)
Pharynx	1.28 (0.91,1.80)	1.91 (1.39,2.62)	5.42 (3.21,9.16)
Larynx	1.21 (0.77,1.92)	6.76 (4.58,9.96)	14.22 (8.28,24.46)
Sex			
Male	1.07 (0.80,1.44)	2.06 (1.34,3.18)	5.19 (3.11,8.65)
Females	0.93 (0.73,1.19)	2.83 (1.97,4.06)	6.66 (3.89,11.41)
Age category			
<45 years	0.71 (0.46,1.09)	1.01 (0.56,1.82)	2.17 (1.22,3.86)
45-60 years	1.22 (0.88,1.69)	2.7 (1.71,4.25)	6.65 (3.63,12.16)
>60 years	0.98 (0.75,1.30)	2.68 (1.94,3.70)	6.02 (3.94,9.22)

*ORs adjusted for age, sex, education, race/ethnicity, and study center; ORs reflect relative odds of all incident HNSCC, except for the "Anatomic subtype" Sub-group, where ORs represent relative odds of incident HNSCC for each specific anatomic subtype.

†Reflects the association between alcohol consumption and incident HNSCC among never tobacco users.

‡ Reflects the association between tobacco use and incident HNSCC among never consumers of alcohol.

§Detailed definitions of alcohol and tobacco exposure as well as data standardization and harmonization methodology can be found in original publication upon which this table is based

Table 1-7: Associations between alcohol type and incident HNSCC by frequency, duration, and cumulative exposure: INHANCE. Adapted from Purdue et al., 2009 [301]

	OR (95% CI)*		
Type of alcohol	Beer	Liquor	Wine
Frequency†			
<=5	1.6 (1.3,2.1)	1.6 (1.0,2.6)	1.1 (0.8,1.6)
6-15	1.9 (1.4,2.7)	1.5 (1.0,2.4)	1.2 (0.8,1.9)
16-30	2.2 (1.3,3.5)	2.3 (1.4,4.0)	1.9 (0.9,3.9)
>30	5.4 (3.1,9.2)	3.6 (2.2,5.8)	6.3 (2.2,18.6)
Duration‡			
<=10	1.8 (1.2,2.6)	1.5 (0.8,2.7)	1.5 (0.9,2.5)
11-20	1.5 (1.0,2.1)	1.5 (0.8,2.6)	1.6 (0.8,3.2)
21-40	2.5 (1.7,3.6)	2.1 (1.3,3.5)	1.9 (1.2,3.0)
>40	2.2 (1.6,3.0)	2.6 (1.6,4.3)	1.7 (0.9,3.2)
Cumulative exposure§			
<=10	1.8 (1.4,2.3)	1.3 (0.8,1.9)	1.0 (0.7,1.4)
11-20	1.6 (1.1,2.4)	1.5 (0.8,2.6)	1.6 (1.0,2.8)
21-40	2.1 (1.5,3.0)	1.7(1.0,2.8)	1.1 (0.7,1.8)
41-80	1.9 (1.3,2.7)	3.6 (1.9,6.9)	1.4(0.7,2.9)
>80	4.0 (2.5,6.6)	2.9 (1.8,4.7)	4.0 (1.8,9.0)

*Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.; Reference category for all ORs is never consumers of alcohol; ORs represent adjusted relative odds of incident HNSCC for exclusive use of each alcohol type relative to the reference category.

†Frequency is defined as the number of standardized ethanol drinks consumed per day.

‡ Duration is defined as the number of years of alcohol consumption, regardless of frequency.

§Cumulative exposure measured as drink-years.

Table 1-8: Associations between exclusive consumption of at most 15 ethanol-standardized drinks per day of beer, liquor, or wine and incident HNSCC by anatomic subtype, sex, and age relative to never-drinkers: INHANCE, Adapted from Purdue et al., 2009 [301]

	OR (95% CI)*		
Subgroup	Beer	Liquor	Wine
Anatomic subtype			
Oral Cavity	2.0 (1.4,2.8)	1.7 (0.9,3.3)	1.3 (0.7,2.2)
Pharynx	2.3 (1.7,3.1)	2.0 (0.9,4.6)	1.4 (0.9,2.2)
Larynx	1.6 (1.1,2.2)	1.6 (0.8,3.1)	1.2 (0.6,2.3)
Sex			
Males	1.7 (1.3,2.2)	1.8 (1.2,2.8)	1.1 (0.7,1.9)
Females	2.1 (1.4,3.1)	1.1 (0.6,2.0)	1.2 (0.7,1.9)
Age			
<55	1.9 (1.4,2.7)	1.0 (0.3,2.7)	1.5 (1.0,2.2)
>=55	1.7 (1.3,2.2)	1.8 (1.2,2.6)	1.2 (0.7,2.0)

*Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.; Reference category for all ORs is never consumers of alcohol; ORs represent adjusted relative odds of incident HNSCC for exclusive use of each alcohol type relative to the reference category.

Table 1-9: Associations between exclusive consumption of greater than 15 ethanol-standardized drinks per day of beer, liquor, or wine and incident HNSCC by anatomic subtype, sex, and age relative to never drinkers: INHANCE. Adapted from Purdue et al., 2009 [301]

	OR (95% CI)*		
Subgroup	Beer	Liquor	Wine
Anatomic subtype			
Oral Cavity	6.4 (3.9,10.3)	3.2 (1.6,6.4)	5.9 (2.3,15.4)
Pharynx	4.3 (2.7,6.8)	3.6 (2.0,6.3)	4.4 (2.0,9.6)
Larynx	2.7 (1.7,4.4)	1.9 (0.9,3.9)	3.9 (1.2,13.0)
Sex			
Males	3.6 (2.4,5.4)	3.0 (1.8,5.7)	3.6 (1.4,8.8)
Females	2.1 (0.3,13.5)	2.2 (0.9,5.2)	3.6 (1.9,6.8)
Age			
<55	3.6 (2.1,6.0)	2.7 (1.0,7.1)	2.8 (1.3,5.8)
>=55	3.5 (2.3, 5.2)	3.0(2.0,4.7)	3.6 (1.4,8.9)

*Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.; Reference category for all ORs is never consumers of alcohol; ORs represent adjusted relative odds of incident HNSCC for exclusive use of each alcohol type relative to the reference category.

Table 1-10: Associations between frequency and duration of alcohol consumption and HNSCC incidence stratified by type of alcohol and race, CHANCE: 2002-2006. Adapted from Stingone et al., 2013 [113]

	OR (95% CI)*					
	Beer		Liquor		Wine	
	Blacks	Whites	Blacks	Whites	Blacks	Whites
Frequency†						
<1	0.67 (0.28,1.61)	0.98 (0.67,1.43)	0.67 (0.28,1.60)	1.3 (0.94,1.80)	0.36 (0.18,0.74)	0.65 (0.49,0.86)
1-4	1.78 (0.90,3.51)	1.02 (0.72,1.44)	1.57 (0.78,3.15)	1.25 (0.90,1.74)	1.06 (0.61,1.84)	0.53 (0.39,0.72)
5-14	1.66 (0.91,3.04)	1.32 (0.92,1.88)	3.22 (1.64,6.34)	1.26 (0.87,1.840	1.57 (0.79,3.10)	0.88 (0.59,1.29)
15-29	2.69 (1.29,5.62)	2.02 (1.29,3.18)	3.42 (1.60,7.34)	2.13 (1.35,3.34)	1.31(0.55,3.15)	0.67 (0.30,1.52)
>=30	4.42 (2.08,9.40)	2.5 (1.64,3.81)	5.75 (2.83,11.7)	2.93 (1.82,4.71)	4.58 (1.92,11.0)	2.36 (0.67,8.24)
Duration‡						
<10	0.81 (0.34,1.96)	0.79 (0.48,1.28)	1.35 (0.58,3.17)	0.91 (0.60,1.37)	1.1 (0.56,2.13)	0.43 (0.30,0.62)
10-19	1.51(0.73,3.15)	0.85 (0.56,1.30)	2.18 (1.08,4.42)	1.36 (0.93,2.00)	1.45 (0.75,2.80)	0.9 (0.62,1.32)
>=20	2.26(1.30,3.95)	1.55 (1.15,2.10)	2.88 (1.61,5.14)	1.67 (1.25,2.24)	1.12 (0.70,1.78)	0.68 (0.42,0.89)

*OR=odds ratio for HNSCC incidence; CI=confidence interval; All ORs adjusted for matching factors (age, race, sex), their interactions, education, fruit and vegetable consumption, duration of cigarette smoking, ever use of other tobacco products and use of other alcohol types.

†Frequency is defined as the number of alcoholic drinks per week.

‡Duration refers to years of consumption.

Table 1-11: Associations between the cessation of tobacco smoking and alcohol drinking with incident HNSCC by anatomic subtype: INHANCE. Adapted from Marron et al., 2010 [302]

Risk Factor	OR (95% CI)*			
	All	OCSCC	OPC/HPC	LC
Tobacco smoking status‡				
Current smoker	1.00	1.00	1.00	1.00
Former smoker	0.39 (0.33,0.46)	0.30 (0.26,0.34)	0.41 (0.32,0.53)	0.38 (0.31,0.47)
Never smoker	0.25 (0.17,0.36)	0.20 (0.14,0.29)	0.26 (0.16,0.44)	0.12 (0.08,0.16)
Years of tobacco smoking cessation				
0 – Current smoker	1.00	1.00	1.00	1.00
>1-4	0.70 (0.61,0.81)	0.65 (0.52,0.80)	0.72 (0.52,1.00)	0.70 (0.56,0.87)
5-9	0.48 (0.40,0.58)	0.43 (0.32,0.58)	0.51 (0.38,0.67)	0.57 (0.46,0.71)
10-19	0.34 (0.28,0.40)	0.25 (0.21,0.31)	0.36 (0.27,0.49)	0.36 (0.27,0.47)
>=20	0.23 (0.18,0.31)	0.19 (0.15,0.24)	0.29 (0.19,0.43)	0.19 (0.15,0.25)
Never smoker	0.23 (0.16,0.34)	0.19 (0.14,0.27)	0.25 (0.15,0.42)	0.11 (0.08,0.16)
Alcohol drinking status				
Current drinker	1.00	1.00	1.00	1.00
Former drinker	0.85 (0.63,1.14)	0.60 (0.43,0.84)	0.98 (0.69,1.39)	0.79 (0.57,1.08)
Never drinker	0.73 (0.51,1.06)	0.64 (0.36,1.15)	0.64 (0.41,1.00)	0.67 (0.42,1.07)
Years of alcohol drinking cessation				
0 – Current drinker	1.00	1.00	1.00	1.00
>1-4	0.99 (0.69,1.43)	0.81 (0.61,1.07)	1.04 (0.73,1.48)	1.16 (0.82,1.63)
5-9	0.90 (0.62,1.30)	0.77 (0.52,1.15)	0.95 (0.61,1.49)	0.88 (0.65,1.19)
10-19	0.94 (0.75,1.18)	0.66 (0.47,0.92)	1.15 (0.92,1.43)	0.93 (0.64,1.36)
>=20	0.60 (0.40,0.89)	0.45 (0.26,0.78)	0.74 (0.50,1.09)	0.69 (0.52,0.91)
Never drinker	0.74 (0.51,1.06)	0.65 (0.36,1.16)	0.65(0.43,1.02)	0.69 (0.43,1.09)

*ORs adjusted for age, sex, race/ethnicity, study center, education level, tobacco pack-years and drinking frequency.
Abbreviations: OR: Odds ratio; CI: Confidence interval; OCSCC: Oral cavity squamous cell carcinoma; OPC: oropharyngeal cancer; HPC: hypopharyngeal cancer; LC: larynx cancer; ORs for tobacco smoking cessation relative to current smokers; ORs for alcohol cessation are relative to current drinkers.
†Some ORs exclude data from individual INHANCE investigations. Please see original report for details (Marron et al., 2010)

Table 1-12: Associations between types of smoking and incident HNSCC by frequency, duration, and cumulative dose: INHANCE: Adapted from Wyss et al., 2013 [303]

	OR (95% CI)*		
Type of smoking	Cigarette	Cigar	Pipe
Frequency‡			
Never	1.0	1.0	1.0
1-10	1.88 (1.72,2.05)	1.99 (1.47.2.71)	2.11 (1.53,2.90)
11-20, >10	3.87 (3.59,4.17)	10.13 (4.96,20.67)	2.19 (0.89,5.40)
21-30	5.30 (4.81,5.85)	--	--
31-40	5.37 (4.85,5.95)	--	--
>40	4.02 (3.54,4.58)	--	--
Duration§			
Never	1.0	1.0	1.0
1-10	1.04 (0.90,1.19)	0.91 (0.51,1.62)	1.27 (0.76,2.14)
11-20	1.37 (1.23,1.53)	2.42 (1.18,4.95)	1.52 (0.71,3.23)
21-30	2.95 (2.71,3.22)	1.92 (0.95,3.85)	0.82 (0.32,2.13)
31-40	5.02 (4.62,5.45)	3.78 (2.18,6.55)	2.34 (1.11,4.91)
>40	6.55 (6.01,7.15)	5.62 (3.29,9.60)	5.81 (3.15,10.70)
Cumulative exposure#			
Never	1.0	1.0	1.0
1-10	1.29 (1.16,1.43)	0.96 (0.52,1.77)	1.31 (0.72,2.40)
11-20	2.20 (1.99,2.42)	1.15 (0.63,2.11)	0.89 (0.47,1.69)
21-30, >20	3.53 (3.21,3.88)	4.87 (3.36,7.06)	3.76 (2.45,5.76)
31-40	4.93 (4.48,5.42)	--	--
41-50	5.85 (5.26,6.50)	--	--
>50	6.81 (6.24,7.44)	--	--

*All ORs adjusted for age, race, sex, education level, frequency of alcohol use (milliliters per day); reference group for all ORs were never smokers of product of interest (cigarettes, cigars, tobacco pipes); cigar ORs estimated among never cigarette users; further adjusted for duration of pipe smoking; pipe smoking ORs estimated among never cigarette users; further adjusted for duration of cigar smoking.

†Interpretation of incident HNSCC OR for >40 years duration of exclusive ever cigar smoking, among never cigarette smokers: The odds of incident HNSCC among exclusive ever cigar smokers who smoked cigars exclusively for greater than 40 years was 5.62 times the odds of incident HNSCC among never cigar smokers, during the study period, adjusted for age, race, sex, educational level, frequency of alcohol use, and duration of pipe smoking.

‡Frequency defined as the number of times per day the product of interest (cigarettes, cigars, tobacco pipes) were smoked.

§Duration defined as the number of years the product of interest (cigarettes, cigars, tobacco pipes) were smoked

#Cumulative exposure defined as pack-years for cigarettes, cigar-years for cigars, and tobacco-pipe-years for tobacco pipe smoking; note one pack was defined as 20 cigarettes.

Table 1-13: Associations between types of smoking and incident HNSCC by anatomic subtype, sex, and age category: INHANCE: Adapted from Wyss et al., 2013 [303]

Sub-group	OR (95% CI)*		
	Cigarette smoking	Cigar smoking	Pipe Smoking
Anatomic subtype			
Oral cavity	2.87 (2.60,3.18)	2.83 (1.91,4.17)	2.51 (1.68,3.75)
Oropharynx	3.01 (2.71,3.35)	2.31 (1.54,3.45)	1.65 (1.04,2.60)
Pharynx	3.35 (3.03,3.70)	2.34 (1.59,3.42)	1.84 (1.20,2.82)
Hypopharynx	6.48 (4.94,8.51)	2.51 (0.90,6.97)	3.90 (1.39,10.92)
Larynx	8.33 (7.07,9.81)	6.31 (3.09,12.92)	3.53 (1.48,8.37)
Sex			
Male	3.45 (3.17,3.75)	2.44 (1.82,3.26)	1.90 (1.37,2.64)
Females	3.53 (3.14,3.98)	21.98 (4.11, 117.52)	7.15 (2.58,19.78)
Age category			
<45 years	2.00 (1.67,2.40)	1.78 (0.51,6.20)	0.50 (0.09,2.68)
>=45 years	3.80 (3.54,4.09)	2.90 (2.18, 3.86)	2.48 (1.82,3.38)

*All ORs adjusted for age, race, sex, education level, frequency of alcohol use (milliliters per day); reference group for all ORs were never smokers of product of interest (cigarettes, cigars, tobacco pipes); cigar ORs estimated among never cigarette users; further adjusted for duration of pipe smoking; pipe smoking ORs estimated among never cigarette users; further adjusted for duration of cigar smoking.

†Interpretation of cigar OR for larynx HNSCC: Among never cigarette smokers, exclusive ever cigar smokers had 6.31 times the odds of incident larynx HNSCC as never cigar smokers, during the study period, adjusted for age, race, sex, educational level, frequency of alcohol use, and duration of pipe smoking.

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Table 1-14: Summary of Epidemiological investigations and reviews characterizing associations between individual foods and nutrients and HNSCC incidence

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
de Stefani 1988 [115]	Case-control/ Uruguay	OC/PC	108 male cases, 286 controls	Maté	Maté consumption increased OC/PC incidence in a positive dose-response fashion. (OR 1-<2 units vs. <1 unit=2.5, 95% CI: 1.1,5.7); (OR >2 units vs. <1 unit=5.2, 95% CI: 2.1,13.1);
Goldenberg 2003 [214]	Review	All UADT	--	Maté	Authors conclude that Maté increases UADT incidence based on review of literature
Pintos 1994 [215]	Case-control/ Southern Brazil	OC, PC, LC	378 cases; 756 controls	Maté, Coffee, Tea	Maté consumption increases HNSCC incidence for all UADT (OR ever vs. never=1.6, 95% CI: 1.2,2.2); OC (OR ever vs. never=1.9, 95% CI: 1.1, 3.3); LC (OR ever vs. never=2.2, 95% CI: 1.1,4.5) Coffee and tea consumption was not associated with HNSCC incidence
Tavani [212] 2003	Case-control/ Italy, Switzerland	OC-PC	749 cases; 1772 controls	Coffee, Decaffeinated coffee; Tea	Coffee consumption reduces HNSCC incidence (OR: >3 cups/day vs. <=1 cup/day=0.6, 95% CI: 0.5,0.9) Decaffeinated coffee and tea consumption not associated with HNSCC incidence.
Ide [213] 2007	Cohort/ Japan	OC	37 cases among 20,550 men and 29,671 women with mean follow-up time = 10.3 years	Green tea	Green tea consumption reduces OC incidence among women (OR 1-2 cups/day vs. <1 cup/day = 0.51, 95% CI: 0.10, 2.68); (OR 3-4 cups/day vs. <1 cup/day = 0.60, 95% CI: 0.17, 2.10); (OR >5 cups/day vs. <1 cup/day = 0.31, 95% CI: 0.09, 1.07) Great tea consumption was not associated with HNSCC incidence among men
Naganuma 2008 [211]	Cohort/ Japan	OC, PC, EC	157 cases among 38,679 persons with mean follow-up time = 13.6 years	Coffee	Coffee consumption protects against HNSCC incidence for all cancer sites and regardless of sex (HR >=1 cup/day vs. 0 cups=0.51, 95% CI: 0.33, 0.77)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Turati 2011 [210]	Meta-analysis	OC-PC, LC, EC, EAC	2633 cases from 8 case-control and 1 cohort study of OC	Coffee	Coffee consumption reduces OC-PC incidence (OR HvL consumption category = 0.64, 95% CI: 0.51,0.80) Coffee consumption not associated with LC incidence
Galeone [304] 2010	Case-control/ International	OC, PC, OPC, HPC LC	5,139 cases, 9,028 controls	Coffee, Tea	Caffeinated coffee intake was associated with reduced OC-PC incidence. ORs were 0.96 (95% CI, 0.94,0.98) for an increment of 1 cup per day and 0.61 (95% CI, 0.47,0.80) in drinkers of >4 cups per day versus nondrinkers. This latter estimate was consistent for different anatomic sites: (OR, 0.46; 95% CI, 0.30,0.71 for OC; OR, 0.58; 95% CI, 0.41,0.82 for OPC/HPC and OR, 0.61; 95% CI, 0.37,1.01 for OC-PC NOS) and across strata of selected covariates. No association of caffeinated coffee drinking was found with LC incidence (OR, 0.96; 95% CI, 0.64–1.45 in drinkers of >4 cups per day versus nondrinkers). Tea intake was not associated with HNSCC incidence (OR, 0.99; 95% CI, 0.89–1.11 for drinkers versus nondrinkers).
Kawakita 2012 [209]	Case-control/ Japan	OC, PC, HPC;LC, EC	959 cases, 2877 controls	Dairy	Yogurt intake reduces UADT incidence (OR <1 time/week vs no intake=0.70, 95% CI: 0.54,0.91); (OR >=1 time/week and < 1 time/day vs. no intake=0.67, 95% CI: 0.54,0.84); (OR >=1 time/day vs. no intake=0.73, 95% CI: 0.55,0.95); Yogurt reduced incidence of hypopharyngeal cancer, laryngeal cancer; and esophageal cancer. No association between milk or butter and UADT incidence.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Soler 2001 [305]	Case-control/ Italy	OC, PC	271 OC, 327 PC, 304 EC; 1950 controls	Dietary fiber	Dietary fiber intake reduced OC-PC-EC incidence. (ORs HvL quintile of intake of total fiber, soluble fiber, cellulose-type fiber, insoluble non-cellulose polysaccharide fiber, total insoluble fiber, and lignin-type fiber were 0.40, 0.37, 0.52, 0.48, 0.33, and 0.38, respectively.) The inverse relations were similar for vegetable fiber (OR HvL intake quintile= 0.51), fruit fiber (OR HvL intake quintile=0.60) and grain fiber (OR HvL intake quintile=.56), and were somewhat stronger for OC-PC than for EC.
Pelucchi 2003 [306]	Case-control/ Italy; Switzerland	LC	527 cases, 1297 controls	Dietary fiber	Dietary fiber intake was associated with reduced LC incidence. ORs for HvL intake quintiles for total fiber, soluble non-cellulose polysaccharide fiber, total insoluble fiber including cellulose, insoluble non-cellulose polysaccharide fiber, vegetable-derived fiber, fruit-derived fiber, and grain-derived fiber were 0.3 (95% CI: 0.2,0.4), 0.3 (95% CI: 0.2,0.5), 0.3 (95% CI: 0.2,0.4), 0.4 (95% CI: 0.3,0.7), 0.2 (95% CI: 0.1,0.4), 0.5 (95% CI: 0.3, 0.7), and 1.1 (95% CI: 0.6,1.9)
Lam 2011 [307]	Cohort/ United States	OC, OPC, HPC, LC,	1867 cases among 494,991 persons with mean follow-up time =11 years	Dietary fiber and grain consumption	Total fiber and total grains consumption reduced HNSCC incidence among women (HR total fiber per 10 grams/day=0.77, 95% CI: 0.64,0.93); (HR total grains per serving/1000 kcal = 0.89, 95% CI: 0.80,0.99). The authors concluded that total fiber and grain intake was not associated with HNSCC incidence among men.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Franceschi 1999 [204]	Case-control/ Italy	OC, PC	598 cases, 1491 controls	Food groups, Oils, butter	Increasing intakes of soups, eggs, processed meats, cakes and desserts, and butter were associated with increased HNSCC incidence. Coffee and tea, white bread, poultry, fish, raw and cooked vegetables, citrus fruit, and olive oil intake was associated with reduced HNSCC incidence (Incidence was approximately halved in the highest compared to the lowest intake quintile)
Toporcov 2004 [308]	Case-control/ Brazil	OC	70 cases, 70 controls	Habitual fatty food intake in the context of the Brazilian diet	Intake of foods rich in animal and saturated fat such as pork meat, soup, cheese, bacon, and fried food were associated with increased OC incidence. Non-cooked butter and margarine were shown to reduce OC incidence.
Galeone [309] 2005	Case-control/ Italy, Switzerland	OC-PC	749 cases OC-PC/1772 controls	Fried foods	Increasing portions of weekly fried food intake were associated with increased OC-PC incidence (OR for each additional portion of fried food intake per week=1.11, 95% CI: 1.05,1.17).
Winn [310] 1984	Case-control/ United States	OC, PC	227 OC/PC female cases, 405 controls	Food groups	Fruit and vegetable intake reduced the OC/PC incidence (OR moderate vs. infrequent=0.65); (OR high vs. infrequent = 0.52) Breads and cereals lowered OC/PC incidence generally, but increased OC/PC incidence among women who were lower in height-adjusted weight. Meat and fish increased OC/PC incidence. Dairy and egg consumption was unrelated to OC/PC incidence

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Franco [222] 1989	Case-control/ Brazil	OC	232 cases, 464 controls	Maté, Coffee, Tea, Fruits, Vegetables, Cooking practices	Consumption of Chimarrão, a type of maté, and coffee increased OC incidence in a positive dose-response fashion Charcoal-grilled meat consumption increased OC incidence Consumption of carotene-rich vegetables and citrus fruits reduced OC incidence; however, green vegetables were not associated with OC incidence.
Franceschi 1991 [311]	Case-control/ Italy	OC/PC	302 cases, 609 controls	Pasta or rice, polenta, cheese, eggs, pulses, carrots, fresh tomatoes, green peppers, meal consumption frequency	More frequent consumption of pasta or rice, polenta, cheese, eggs, and pulses increased OC-PC incidence. (ORs HvL intake tertile for pasta or rice, polenta, cheese, eggs, and pulses were 1.6, 2.1, 1.9, and 1.9, respectively). More frequent consumption of carrots, fresh tomatoes, and green peppers reduced OC-PC incidence. (ORs HvL intake tertile for carrots, fresh tomatoes, and green peppers were 0.6, 0.5, and 0.5 respectively). Higher daily meal consumption frequency was associated with increased OC-PC incidence (OR >-4 meals/day vs. <=2 meals/day=1.7)
Oreggia 1991 [312]	Case-control/ Uruguay	OC (tongue)	57 male cases, 353 controls	Vegetables	Infrequent consumption of vegetables was associated with higher OC incidence (OR=<1 time/week vs. >=5/week = 5.3, 95% CI:1.5,19.4)
Zheng 1992 [313]	Case-control/ China	OC-PC	204 cases, 414 controls	Fruits, vegetables, salt preserved meats and fish	Increasing fruit consumption, especially of oranges and tangerines, was associated with reduced OC-PC incidence Increasing vegetable consumption, especially of dark yellow vegetables and Chinese white radish, was associated with reduced OC-PC incidence Increasing frequency of salt-preserved meat and fish consumption was associated with increased OC-PC incidence.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Day 1993 [120]	Case-control/ United States	OC-PC	1065 cases, 1182 controls	Fruits, vegetables, Carotene, Vitamin C	Increasing consumption frequency of fruits reduced OC-PC incidence. (OR HvL intake quartile = 0.3); Increasing consumption frequency of carotene reduced OC-PC incidence. (OR HvL intake quartile = 0.6); Increasing consumption frequency of micronutrients reduced OC-PC incidence. (OR HvL intake quartile = 0.4);
Kune 1993 [314]	Cases-control/ Australia	OC-PC	41 male OC-PC cases, 398 male controls	Fruits, vegetables, Dietary Vitamin C, Dietary Vitamin A	Increasing consumption of dietary vitamin C, dietary beta carotene, fruits, and vegetables reduced OC-PC incidence. ORs for HvL intake tertile for dietary vitamin C, dietary beta-carotene, and fruits were 0.23 (95% CI: 0.1,0.5), 0.36 (95% CI: 0.1,0.9), 0.10 (95% CI: 0.0,0.3), respectively.
Levi 1998 [315]	Case-control/ Switzerland	OC-PC	156 cases, 284 controls	Eggs, red meat, Pork and processed meat, milk, fish, raw vegetables, cooked vegetables, citrus fruits, other fruits	After allowance for education, alcohol, tobacco and total energy intake, significant trends of increasing OC-PC incidence with more frequent intake emerged for eggs (OR HvL tertile = 2.3), red meat (OR HvL tertile = 2.1), and pork and processed meat (OR HvL tertile= 3.2). Reduced OC-PC incidence was observed for increasing consumption frequency of milk (OR HvL tertile= 0.4), fish (OR HvL tertile= 0.5), raw vegetables (OR HvL tertile= 0.3), cooked vegetables (OR HvL tertile= 0.1), citrus fruit (OR HvL tertile= 0.4) and other fruits (OR HvL tertile = 0.2).

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Brown 2001 [316]	Case-control/ Puerto Rico	OC-PC	342 cases, 521 controls	Raw fruit and vegetables	Infrequent weekly consumption of raw fruits and vegetables increased OC-PC incidence, especially among those study participants reporting a family history of UADT cancer. (OR lowest intake quartile of weekly serving consumption + no UADT family history vs. highest intake quartile of weekly serving consumption + no UADT family history = 2,0, 95% CI: 1,0,3.9) (OR lowest intake quartile of weekly serving consumption + UADT family history vs. highest intake quartile of weekly serving consumption + no UADT family history = 6.8, 95% CI: 2.0,22.7)
Fernandez-Garrote 2001 [151]	Case-control Cuba	OC-PC	200 cases, 200 controls	Maize, meat, ham and salami, fruits	Higher relative to lower intakes of maize, meat, and ham and salami was associated with increased OC-PC incidence. (ORs for HvL intake tertile for maize, meat, and ham and salami= 1.9, 2.2, and 2.0, respectively) Higher relative to lower intakes of fruits was associated with reduced OC-PC incidence. (OR for HvL intake tertile for fruit=0.4)
Tavani 2001[317]	Case-control/ Italy	OC-PC	132 cases, 148 controls	Green vegetables, Green salad, total fruit, apples	Higher consumption of total green vegetables was associated with reduced OC-PC incidence (OR HvL intake tertile = 0.37, 95% CI: 0.16,0.88) Higher consumption of green salad was associated with reduced OC-PC incidence (OR HvL intake tertile = 0.33, 95% CI: 0.16,0.69) Higher consumption of total fruit was associated with reduced OC-PC incidence (OR HvL intake tertile = 0.34, 95% CI: 0.13,0.87) Higher consumption of apples was associated with reduced OC-PC incidence (OR HvL intake tertile = 0.27, 95% CI: 0.11,0.62)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Lissowska 2003 [153]	Case-control/ Poland	OC, PC	122 cases, 124 controls	Fresh fruits, juices	High fruit intake was associated with reduced OC-PC incidence (OR HvL tertile of intake=0.4, 95% CI: 0.17,0.95)
Freedman 2008 [318]	Cohort/ United States	OC, OPC, PC, HPC, LC	787 cases identified among 490,802 persons over 2,193,751 person-years of follow-up	Fruits, vegetables	Every additional calorie-adjusted daily serving of total fruit and vegetable intake combined was associated with reduced hazards of incident HNSCC (HR=0.94, 95% CI: 0.89,0.99). Increased vegetable consumption (HR for HvL quintile of vegetable intake=0.65, 95% CI: 0.50,0.85), and increased fruit consumption (HR for HvL quintile of fruit intake=0.87, 95% CI: 0.68, 1.11)
Rajkumar 2003 [319]	Case-control/ India	OC	591 cases, 582 controls	Fruits, vegetables	Higher consumption of fruits was associated with reduced OC incidence (OR >=4 vs. <=2 servings/wk=0.55, 95% CI: 0.38,0.81). High consumption of vegetables was associated with reduced OC incidence (OR >=14 vs. <7 servings/wk=0.44, 95% CI: 0.28,0.69)
Llewellyn 2004 [320]	Case-control/ England	OC	116 cases, 207 controls	Fruits, vegetables	Vegetarian diets were associated with lower OC incidence (OR vegetarian vs. non-vegetarian diet=0.6, 95% CI: 0.3,1.4). Higher consumption of fresh fruits and vegetables during childhood as well as 10 years prior to diagnosis was associated with lower HNSCC incidence (OR childhood consumption of >=3 portions/day vs. <=2 portions/day=0.5, 95% CI: 03,0.9); (OR consumption 10 years prior to diagnosis of >=3 portions/day vs. <=2 portions/day=0.5, 95% CI: 03,0.8)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Gaudet 2004 [205]	Case-control/ United States	OC, PC, LC	149 cases, 180 controls	Fruits, vegetables	Increased consumption of all fruits, fruit juices, and citrus fruits was associated with reduced HNSCC incidence. (OR all fruits >=14 vs. <7 servings/wk. = 0.60, 95% CI: 0.28,1.3); (OR fruit juices >=7 vs. 0 servings/wk=0.60, 95% CI: 0.27,1.3); (OR citrus fruits >=7 vs. <2 servings/wk. = 0.77, 95% CI 0.39,1.5) Raw vegetable intake was associated with reduced HNSCC incidence (OR >=4 vs <2 servings/wk = 0.66, 95% CI: 0.3,1.3); Increased consumption of cooked vegetables, cruciferous vegetables, and legumes was associated with increased HNSCC incidence. (OR cooked vegetables >=14 vs. <7 servings/wk. = 2.5, 95% CI: 1.1,6.0); (OR cruciferous vegetables >=3 vs. 0 servings/wk=1.4, 95% CI: 0.47,4.4); (OR legumes >=2 vs 0 servings/wk. = 2.5, 95% CI 1.2,5.2)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
de Stefani 2005 [321]	Case-control/ Uruguay	OC-PC	230 male cases, 460 male controls	Food groups	Increasing consumption of the following food groups were associated with increased OC-PC incidence for the contrast of HvL quartile of intakes: Red meat (OR=1.5, 95% CI: 0.9,2.8); Preserved meat (OR=1.5, 95% CI: 0.9,2.6); Total meat (OR=1.6, 95% CI: 0.9,2.7); Stew (OR=3.9, 95% CI: 2.1,7.4); Dairy foods (OR=1.1, 95% CI: 0.6,1.9); Eggs (OR=1.5, 95% CI:0.9,2.5); Desserts (OR=1.4, 95% CI: 0.8,2.5); Fatty foods (OR=2.3, 95% CI: 1.3,4.1); Cereals (OR=1.3, 95% CI; 0.7,2.2); All tubers (OR=1.6, 95% CI: 0.9,2.8) Increasing consumption of the following food groups were associated with reduced OC-PC incidence for the contrast of HvL quartile of intakes: Raw vegetables (OR=0.4, 95% CI: 0.2,0.7); Cooked vegetables (OR=0.9, 95% CI: 0.5,1.7); Total vegetables (OR=0.6, 95% CI: 0.3,1.0); Citrus fruits (OR=0.3, 95% CI: 0.2,0.7); Other fruits (OR=0.8, 95% CI: 0.5,1.4); Total fruits (OR=0.7, 95% CI: 0.4,1.3); Total vegetables and fruits (OR= 0.5, 95% CI: 0.3,0.9); Legumes (OR=0.4, 95% CI: 0.2,0.8)
Zheng 1993 [218]	Case-control/ China	OC	404 cases, 404 controls	Food groups, macronutrients, micronutrients	When contrasting the HvL tertile of intakes, the following dietary components were associated with increased OC incidence: carbohydrates, millet, and cornbread. When contrasting the HvL tertile of intakes, the following dietary components were associated with reduced OC incidence: protein, fat, total carotene, vegetable-derived carotene, fruit-derived carotene, total vitamin C, vegetable-derived vitamin C, fruit-derived vitamin C, vegetable-derived dietary fiber, fruit-derived dietary fiber, fresh meat, fresh chicken, fresh liver, carp, hairtail, shrimp, lobster, rice, grapes, bananas, oranges, tangerines, peaches, and pears.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
McLaughlin 1988 [202]	Case-control/ United States	OC, PC	871 cases, 979 controls	Food groups, micronutrients	Higher intakes of fruits were associated with reduced OC-PC incidence.
Gridley 1990 [322]	Case-control/ United States	OC, PC	248 Black cases, 262 Black controls	Food groups, micronutrients	Higher intakes of fruits, vitamin C, and fiber were associated with reduced OC-PC incidence for both sexes. Among men, higher intake of carotene and vitamin E were associated with reduced OC-PC incidence; whereas higher intakes of nitrite-containing meats were associated with increased OC-PC incidence.
de Stefani [323] 1999(a)	Case-control/ Uruguay	OC, PC, EC, LC	33 OC-PC cases, 34 LC cases, 66 EC cases, 393 controls	Food groups	Red meat intake was associated with increased UADT incidence (OR Red meat for HvL intake tertile=2.4, 95% CI: 1.2,4.8); (OR salted meat for HvL intake tertile=1.7, 95% CI: 0.8,3.3) Fruit, vegetable, and legume intake were associated with reduced UADT incidence (OR fruits for HvL intake tertile=0.3, 95% CI: 0.2,0.6); (OR vegetables for HvL intake tertile=0.5, 95% CI: 0.3,0.9); (OR raw vegetables for HvL intake tertile=0.4, 95% CI: 0.2,0.8); (OR legumes for HvL intake tertile=0.4, 95% CI: 0.3,0.8)
de Stefani 1999 (b) [324]	Case-control/ Uruguay	OC, PC, EC, LC	33 OC-PC cases, 34 LC cases, 66 EC cases, 393 controls	Macronutrients, Micronutrients	Protein intake was associated with increased UADT incidence (OR protein HvL intake tertile=2.5, 95% CI: 1.5,4.4); whereas carbohydrates were associated with reduced UADT incidence. The following micronutrients were associated with reduced UADT incidence: vitamin C, vitamin E, alpha-carotene, lycopene, beta-cryptoxanthine, and flavanoids

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Franceschi 1999 [204]	Case-control/ Italy, Switzerland	OC, PC	754 cases, 1,775 controls	Macronutrients, energy intake	Cases reported higher total energy intake, due to higher intake of alcohol energy; whereas non-alcohol energy intake was lower in cases than controls. Protein intake (OR for an addition of 100 kcal/day = 0.8) and monounsaturated fatty acids (OR = 0.8) were associated with reduced OC-PC incidence. Saturated fatty acids intake (OR = 1.4) was associated with increased OC-PC incidence. Vegetable intake, which was positively correlated with oil intake, was lower in cases than controls, but accounted only partly for the observed difference in fat intake pattern.
Uzcudun 2002 [325]	Case-control/ Spain	PC, OPC, HPC	232 cases, 232 controls	Food groups	Lower intakes relative to higher intakes of fruits, fruit juices, uncooked vegetables, fiber, fish, and dairy products were associated with increased PC-OPC-HPC incidence. Higher intakes relative to lower intakes of meat and fried foods were associated with increased PC-OPC-HPC incidence

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Pisa 2002 [326]	Case-control/ Italy	OC, PC, LC, LungCa	58 OC-PC cases, 43 LC cases, 111 LungCa cases, 247 controls	Food groups	Increasing weekly consumption frequency of fruits and vegetable intake was associated with reduced OC-PC and LC incidence; whereas, increasing weekly consumption frequency of meat and processed meat was associated with increased OC-PC and LC incidence. ORs: Green salad for >=7 vs. <=1 serving per week=0.3 (95% CI:=0.1,0.7) for OC-PC incidence and 0.9 (95% CI: 0.3,3.0) for LC; Apples for >=7 vs. <=1 serving per week=0.3 (95% CI:=0.2,0.8) for OC-PC and 0.4 (95% CI: 0.2,1.1) for LC; Tomatoes >=7 vs. <=1 serving per week=0.4 (95% CI:=0.1,1.0) for OC-PC and 0.7 (95% CI: 0.2, 1.7) for LC; Citrus fruits for >=7 vs. <=1 serving per week=0.4 (95% CI:=0.1,1.1) for OC-PC and 0.4 (95% CI: 0.1,1.2) for LC; Carrots for >=4 vs. <=1 serving per week=0.6 (95% CI:=0.2,1.5) for OC-PC and 0.7 (95% CI: 0.2,1.9) for LC; Meats for >=4 vs. <=1 serving per week=2.0 (95% CI:=0.8,5.1) for OC-PC and 1.4 (95% CI: 0.5, 4.4) for LC; Processed meats for >=4 vs. <=1 serving per week=2.1 (95% CI:=0.7,6.6) for OC-PC and 1.4 (95% CI: 0.4,4.5) for LC;
Sapkota 2008 [327]	Case-control/ Eastern Europe	OC, Pc, LC, EC	948 cases, 1,228 controls	Food groups	Dairy product intake was associated with reduced LC incidence (OR HvL intake tertile=0.73 (95% CI: 0.48,1.13) for OC-PC and 0.38 (95% CI: 0.23,0.62) for LC) Yellow/orange vegetables were associated with reduced OC-PC and LC incidence (OR HvL intake tertile=0.53 (95% CI: 0.35,0.81) for OC-PC and 0.62 (95% CI: 0.38,1.00) for LC Preserved (pickled) vegetables were associated with increased OC-PC and LC incidence. (OR HvL intake=1.92 (95% CI: 1.23,2.99) for OC-PC and 1.78 (95% CI: 1.08, 2.95) for LC

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Lagiou 2009 [328]	Case-control/ Europe	OC, PC, LC, EC	1,360 OC-PC cases, 702 LC cases, 235 EC cases, 7 NOS cases, 2,227 controls	Food groups	Consumption of red meat (OR per increasing tertile=1.14, 95% CI: 1.05–1.25) was associated with increased UADT Consumption of fruits (OR per increasing tertile=0.68, 95% CI: 0.62–0.75) and vegetables (OR per increasing tertile=0.73, 95% CI: 0.66–0.81) as well as of olive oil (OR for above versus below median =0.78, 95% CI 0.67–0.90) and tea (OR for above versus below median=0.83, 95% CI 0.69–0.98) were significantly associated with reduced UADT incidence
Chuang 2012 [200]	Case-control/ International	OC, PC, OPC, HPC, LC	14,520 cases, 22,737 controls	Food groups	Higher fruit and vegetable intake was associated with reduced HNSCC incidence. (ORs HvL intake quartile were 0.52, 95% CI: 0.43,0.62 for fruits and 0.66, 95% CI: 0.49,0.90 for vegetables. Higher intake of red meat (OR HvL intake quartile = 1.40, 95% CI: 1.13,1.74) and processed meat (OR HvL intake quartile=1.37, 95% CI: 1.14,1.65) were associated with increased HNSCC incidence. Higher dietary pattern scores, reflecting high fruit/vegetable and low red meat intake, were associated with reduced HNSCC incidence (per score increment OR= 0.90, 95% CI:0.84,0.97).
Notani 1987 [329]	Case-control/ India	OC, PC, EC, LC	Cases all male: 278 OC, 225 PC, 236 EC, 80 LC 215 hospital controls, 177 population controls	Vegetables, Fish, Pulses with buttermilk, Red chili powder, Tea	Daily vegetable consumption, higher weekly fish consumption, and pulses consumed with buttermilk were associated with reduced UADT incidence, Red chili power consumption was associated with increased UADT incidence. Tea consumption was associated with increased PC incidence.
Jafarey 1977 [330]	Case-control/ Pakistan	OC, OPC	1192 cases, 3562 controls	Fruits, vegetables, cereals, meats, fish, dairy products	The authors reported that fruits, vegetables, and meats were associated with reduced OC, OPC incidence; whereas, cereal consumption was associated with increased OC, OPC incidence.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
La Vecchia 1991 [331]	Case-control/ Italy	OC, PC	106 cases, 1169 controls	Milk, meat, cheese, carrots, green vegetables, fruit	When contrasting HvL intake tertiles, the authors reported that the following food groups were associated with reduced OC-PC incidence: Milk (OR=0.3, 95% CI: 0.2,0.7), meat (OR=0.4, 95% CI: 0.2,0.7), cheese (OR=0.6, 95% CI: 0.4,0.9), carrots (OR=0.4, 95% CI: 0.2,0.7), green vegetables (OR=0.4, 95% CI: 0.2,0.8), and fruit (OR=0.1, 95% CI: 0.1,0.2)
Chyou 1995 [196]	Cohort/ United States (Japanese ancestry)	UADT	92 cases among 7,995 Japanese-American men with mean follow-up time=24 years	Candy, Jelly, soda pop, fruit	Increasing weekly consumption of candy, jelly, soda pop, and fruit were associated with reduced UADT incidence.
Takezaki 1996 [332]	Case-control/ Japan	OC, OPC, HPC	266 cases, 36,527 controls	Fruits, vegetables,	Frequent intake of fruits and vegetables were associated with reduced HNSCC incidence.(OR fruits HvL intake tertile=0.5, 95% CI: 0.4,0.7); (OR vegetables HvL intake tertile=0.5, 95% CI: 0.4,0.7);
Petridou 2002 [333]	Case-control/ Greece	OC	106 cases, 106 controls	Cereals, fruits, dairy products, added lipids, micronutrients	Increasing consumption of cereals, fruits, dairy products, olive oil, and intake of the micronutrients riboflavin, magnesium, and iron were associated with reduced OC incidence.
Sánchez 2003 [334]	Case-control/ Spain	OC, OPC	375 cases, 375 controls	Fruits, vegetables	Increasing consumption of weekly total fruit intake was associated with reduced OC-OPC incidence (OR HvL weekly intake tertile=0.52, 95% CI: 0.34,0.79); Increasing consumption of weekly vegetable intake was associated with reduced OC-OPC incidence (OR HvL weekly intake tertile=0.54, 95% CI: 0.34,0.87);
Boeing 2006 [195]	Cohort/ Europe	OC, PC, LC, EC	352 cases among 345,904 persons who collectively experienced 2,182,560 person-years of follow-up	Fruits, vegetables	Total fruits and vegetables intake was associated with reduced UADT incidence (OR HvL quintile of predicted fruit and vegetable intake=0.60, 95% CI: 0.37,0.99) ORs for HvL quintile of predicted intake for total fruits and total vegetables were (0.60, 95% CI: 0.38,0.97) and (0.80, 95% CI: 0.49,1.31), respectively.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Pavia 2006 [194]	Meta-analysis	OC, PC, HPC	15 case-control studies; 1 cohort study	Fruits, vegetables	Every additional portion of fruits and vegetable consumption was associated with reduced HNSCC incidence. (OR fruit for every additional portion=0.51, 95% CI: 0.40,0.65); (OR vegetables for every additional portion=0.50, 95% CI: 0.38, 0.65)
Franceschi 1990 [335]	Case-control/ Italy	OC, PC, EC	107 OC, 107 PC, 68 EC, 505 controls	Maize	Increasing intake of maize was associated with increased HNSCC incidence (OR OC for >=3 vs. 1-2 servings/wk=3.3, 95% CI: 2.0,5.4); (OR PC for >=3 vs. 1-2 servings/wk=3.2, 95% CI: 2.0,5.3)
de Stefani 2000 [201]	Case-control/ Uruguay	OC, PC, LC, EC	238 cases, 491 controls	Tomatoes, tomato products, lycopene	Tomatoes, foods enriched with tomato sauce, tomato-based foods, and lycopene intake were all associated with reduced UADT incidence. ORs for OC-PC incidence for contrast of HvL servings/year categories for exposures to tomatoes, foods enriched with tomato sauce, and tomato-based foods were 0.45 (95% CI: 0.21,0.95); 0.69 (95% CI: 0.31,1.53); and 0.43 (95% CI: 0.19,0.97), respectively. ORs for LC incidence for same contrast and exposure were 0.42 (95% CI: 0.22,0.83); 0.33 (95% CI: 0.16,0.71); and 0.23 (95% CI: 0.11, 0.49), respectively. ORs for HvL weekly lycopene intake categories for OC-PC and LC incidence were 0.42 (95% CI: 0.19,0.91); and 0.21 (95% CI: 0.10,0.43), respectively.
de Stefani 1994 [206]	Case-control/ Uruguay	OPC	246 male cases, 253 controls	Salted meat	Current consumption of salted meat was associated with increased OPC incidence (OR current vs. never consumers of salted meat=2.3, 95% CI: 1.1,5.2)
Levi 2004 [208]	Case-control/ Switzerland	OC, PC, EC, LC, CRC	316 OC-PC cases, 138 EC cases, 91 LC cases, 323 CRC cases, 1271 controls	Processed meat	Processed meat consumption was associated with increased OC-PC and LC incidence. (OR OC-PC incidence for HvL intake quartiles=4.68, 95% CI: 2.54,8.62); (OR LC incidence for HvL intake quartiles=3.42, 95% CI: 1.38,8.46)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Steffen 2012 [207]	Cohort/ Europe	UADT (OC, OPC, HPC, EC, LC)	682 cases among 348,738 persons with mean follow-up time = 11.8 years	Total meat, red meat, poultry, processed meat, fish, Heme iron	Processed meat was associated with increased UADT incidence (OR HvL intake quintile=1.41, 95% CI: 1.41,1.03). This association was more evident among smokers. Red meat, poultry, processed meat, fish, heme iron were not consistently associated with UADT overall or by UADT subtype.
Gridley 1992 [217]	Case-control/ United States	OC, PC	1114 OC-PC cases; 1268 controls	Vitamin, mineral supplements	Vitamin E supplements were associated with reduced OC-PC incidence (OR ever vs. never regular users=0.5, 95% CI: 0.4,0.6).
Zheng 1993 [218]	Case-control/ United States	OC, PC	28 cases, 112 controls	Serum nutrient levels	Increasing serum levels of carotenoids and alpha-tocopherol were associated with reduced OP-PC incidence, whereas increasing serum levels of retinol, gamma-tocopherol and selenium were associated with increased OP-PC incidence. ORs for HvL intake tertiles for total carotenoids, beta-carotene, alpha-carotene, cryptoxanthine, lutein, lycopene, alpha-tocopherol, retinol, gamma-tocopherol, and selenium were 0.33, 0.50, 0.37, 0.33, 0.61, 0.65, 0.31, 2.51, 4.04, and 4.30, respectively.
Rogers 1995 [336]	Case-control/ United States	OC-PC, LC, EC	351 OC-PC, 125 EC, 169 LC, 458 controls	N-nitroso compounds (NDMA, nitrites, nitrates)	Increasing dietary nitrate intake was associated with reduced OC-PC and LC incidence (ORs for >226 vs <134 mg of daily dietary nitrate intake for OC-PC and LC were 0.46 (95% CI: 0.28,0.76) and 0.42 (95% CI: 0.22,0.80), respectively. Increasing dietary NDMA intake was associated with increased HNSCC incidence (ORs for >0.179 vs <0.06 micrograms of daily dietary intake for OC-PC and LC were 1.82 (95% CI: 1.10,3.00) and 1.70 (95% CI: 0.91,3.18), respectively.
Nomura 1997 [219]	Case-control/ United States	OPC, EC, LC	16 OPC, 28 EC, 23 LC, 138 controls	Serum nutrient levels	Serum carotenoids, especially beta- and alpha-carotene were associated with reduced UADT overall, and for all subsites.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary component	Key Findings (adjusted for tobacco, and alcohol intake)
Lawal 2012 [337]	Case-control/ Nigeria	OC	30 OC cases, 33 controls	Serum nutrient levels	Vitamin E was associated with reduced OC incidence.
Negri 2000 [216]	Case-control/ Italy; Switzerland	OC, PC	344 OC, 410 PC, 1,775 controls	Micronutrients	Increased vitamin C, vitamin E, and carotenoids were associated with reduced OC-PC incidence.
Pelucchi 2003 [306]	Case-control/ Italy; Switzerland	OC, PC	749 cases, 1772 controls	Dietary folate	Increased dietary folate intake was associated with reduced OC-PC incidence (OR HvL tertile dietary folate intake=0.53, 95% CI: 0.40,0.69)
Galeone 2015 [338]	Case-control/ International	OPC	5,127 cases, 13,249 controls	Dietary folate	Increased total dietary folate intake was associated with reduced OPC incidence (OR HvL intake quintile=0.65, 95% CI: 0.43,0.99), and especially so for OC incidence (OR HvL intake quintile=0.57, 95% CI: 0.43,0.75).
Suzuki 2006 [339]	Case-control/ Japan	OC, PC, LC	193 OC, 132 PC, 60 LC cases, 1,925 controls	Dietary antioxidants	Increased dietary antioxidant intake, especially of carotene, vitamin C, and vitamin E, were associated with reduced HNSCC incidence overall, and for all anatomic subtypes.
Zheng 1995 [220]	Cohort/ United States	UADT (OC, PC, EC, GC)	59 female cases (33 OC-PC-EC; 26 GC) identified among 34,691 persons with mean follow-up time-7 years	Dietary antioxidants	Higher intake of carotene, vitamin C, and vitamin E were associated with reduced OC-PC-EC incidence. ORs for HvL tertiles of intakes of carotene, vitamin C, and vitamin E were 0.7 (95% CI: 0.3,1.8), 0.7 (95% CI: 0.3,1.7), and 0.8 (95% CI: 0.3,2.0), respectively.
Garavello 2007 [340]	Case-control/ Italy	LC	460 cases, 1088 controls	Flavanoids	Increased intakes of dietary flavonoids were associated with reduced LC incidence.
Rossi 2007 [341]	Case-control/ Italy	OC, PC	805 cases, 2,081 controls	Flavanoids	Increased intakes of dietary flavonoids were associated with reduced OC-PC incidence.

Table abbreviations: OC: oral cavity, PC: pharynx cancer; LC: larynx cancer; OPC: oropharynx cancer; EC: esophageal cancer, EAC: esophageal adenocarcinoma; HPC: hypopharyngeal cancer; LungCa: Lung Cancer; CRC: colorectal cancer; GC: gastric cancer; NOS: not otherwise specified; NDMA: nitroso dimethylamine; OR: odds ratio; 95% CI: 95 percent confidence interval; HvL: highest vs. lowest

Table 1-15: Summary of epidemiological investigations that have characterized associations between *a priori* diet indices and HNSCC incidence.

Reference	Study design/ Location	HNSCC subtypes	Sample size	A Priori Diet Index	Key Finding (adjusted for tobacco and alcohol intake)
Li 2014 [342]	Cohort/ United States	OC, PC, OPC, HPC, LC	1868 cases identified among 494,967 persons over 4,803,358 person-years of follow-up	1. Healthy Eating Index-2005 (HEI-2005) 2. Alternate Mediterranean Diet Score (aMED)	Higher HEI-2005 and higher aMED scores were both associated with reduced HNSCC incidence. The inverse associations for both indices were stronger among women than among men and did not vary by anatomic subtype. ORs for HEI-2005 for HvL score quintile were 0.74 (95% CI: 0.61,0.89) among men and 0.48 (95% CI: 0.33,0.70) among women. ORs for aMED for HvL score quintile were 0.80 (95% CI: 0.64,1.01) among men and 0.42 (95% CI: 0.24,0.74) among women
Bosetti 2003 [343]	Case-control/ Italy	OC, PC, LC, EC	598 OC-PC cases, 1,491 controls; 460 LC cases, 1,088 controls	1. Mediterranean Diet Score (MDS)	Higher adherence to the MDS was associated with reduced HNSCC incidence. ORs for adhering to >=6 vs. <3 MDS characteristics were 0.40 (95% CI: 0.26,0.62) for OC-PC and 0.23 (95% CI: 0.13,0.40) for LC.

Reference	Study design/ Location	HNSCC subtypes	Sample size	A Priori Diet Index	Key Finding (adjusted for tobacco and alcohol intake)
Samoli 2010 [344]	Case-control/ Greece	OC, PC, LC, EC	239 cases, 194 controls	1. Mediterranean Diet Score (MDS)	Every two units of increasing adherence to the Mediterranean diet as approximated by the MDS were associated with a 30% reduction in the relative odds of UADT. Notably, mutually-adjusted components of the MDS were not individually associated with UADT incidence.
Filomeno 2014 [345]	Case-control/ Italy, Switzerland	OC, PC	768 OC-PC cases, 2,078 controls	1. Mediterranean Diet Score (MDS) 2. Mediterranean Dietary Pattern Adherence Index (MDP) 3. Mediterranean Adequacy Index (MAI)	Higher MDS, MDP, and MAI scores, relative to lower scores, were all associated with reduced OC-PC incidence. OR for adherence to >=6 vs <=2 MDS characteristics was 0.20 (95%CI: 0.14,0.28); OR for HvL quintile of MDP was 0.20 (95% CI: 0.14,0.28); OR for HvL quintile MAI was 0.48 (95% CI: 0.33,0.69)
Giraldi 2016 [346]	Case-control/ Italy	OC, PC, LC	500 cases, 433 controls	1. Mediterranean Diet Score	Every unit increase in MDS scores resulted in a 36 percent decrease in the relative odds of incident HNSCC; this relative reduction in incidence was evident across OC-PC and LC subtypes as well.

Table abbreviations: OC: oral cavity, PC: pharynx cancer; LC: larynx cancer; OPC: oropharynx cancer; EC: esophageal cancer, EAC: esophageal adenocarcinoma; HPC: hypopharyngeal cancer; LungCa: Lung Cancer; OR: odds ratio; 95% CI: 95 percent confidence interval; HvL: highest vs. lowest

Table 1-16: Summary of epidemiological investigations that have characterized associations between *a posteriori* diet scores and HNSCC incidence.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
de Stefani 2005 [321]	Case-control/ Uruguay	OC-PC	230 male cases, 460 male controls	1. "Stew": boiled meat, cooked vegetables, potato, sweet potato 2. "Vegetables and fruits": raw vegetables, citrus fruits, other fruits, liver, fish, desserts	"Stew" pattern was associated with increased OC-PC incidence (OR HvL quartile of factor score=3.75, 95% CI: 1.99,7.06) "Vegetables and fruit pattern" was associated with reduced OC-PC incidence (OR HvL quartile of factor score=0.34, 95% CI: 0.18,0.64)
Marchioni 2005 [347]	Case-control/ Brazil	OC	260 cases, 257 controls	1. "Prudent": vegetable, fruit, meats 2. "Traditional": cereals (rice), pulses (beans) 3. "Snacks": dairy products, processed meats, sweets	Associations between identified dietary patterns and HNSCC incidence were not estimated.
de Stefani 2007 [348]	Case-control/ Uruguay	LC	290 male cases, 290 controls	1. "Pattern 1 (traditional)": boiled meat, cooked vegetables, all tubers, 2. "Pattern 2 (healthy)": fish, raw vegetables, total fruits, tea 3. "Pattern 3 (high-fat): cheese, butter, mayonnaise, custard, tea 4. "Pattern 4 (substituter)": processed meat, whole milk, soft drinks 5. "Pattern 5 (drinker)": beer, wine, hard liquor 6. "Pattern 6 (western)": fried meat, barbecued meat	Patterns 1, 5, and 6 were associated with increased LC incidence; whereas pattern 2 was associated with reduced LC incidence. ORs for HvL quartile of factor scores for patterns 1, 5, 6, and 2 were 2.00 (95% CI: 0.96,4.15), 3.80 (95% CI: 1.93,7.48), 3.16 (95% CI: 1.60,6.25), and 0.64 (95% CI: 0.24, 1.18), respectively.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
Amtha 2009 [349]	Case-control/ Indonesia	OC	81 cases, 162 controls	1. "Preferred": fast food, fermented food, canned food, snacks high in fat and sugar, cooked and raw vegetables, seafood. 2. "Combination": dairy products, red meat, white meat, fruits 3. "Chemical-related": processed foods, monosodium glutamate 4. "Traditional": drinks, grains	"Preferred", "Chemical-related", and "Traditional" patterns were associated with increased OC incidence. ORs for HvL tertiles of factor scores for "Preferred," Chemical-related" and "Traditional" patterns were 2.17 (95% CI: 1.05,4.50) , 2.56 (95% CI: 1.18,5.54), and 2.04 (95% CI: 1.10,4.41), respectively. "Combination" pattern was associated with reduced OC incidence. (OR HvL tertile of factor score=0.50, 95% CI: 0.24,1.00)
de Stefani 2009 [350]	Case-control/ Uruguay	OC, PC, LC, EC,	283 OC-PC cases, 281 LC cases, 234 EC cases, 2532 controls	1. "Prudent": raw vegetables, total fruits 2. "Drinker": alcohol drinking 3. "Traditional": cooked vegetables 4. "Western": red meat	"Prudent" pattern was associated with reduced OC-PC and LC incidence (OR HvL factor score tertile=0.46, 95% CI: 0.31,0.67 for OC-PC and 0.45, 95% CI: 0.31,0.65 for LC "Drinker" pattern was associated with increased OC-PC and LC incidence (OR HvL factor score tertile=2.27, 95% CI: 1.53,3.37 for OC-PC and 1.67, 95% CI: 1.17,2.41 for LC "Traditional" pattern was associated with increased OC-PC and LC incidence (OR HvL factor score tertile=1.55, 95% CI: 0.99,2.43 for OC-PC and 1.47, 95% CI: 0.94,2.29 for LC "Western" pattern was associated with increased OC-PC and LC incidence (OR HvL factor score tertile=1.36, 95% CI: 0.96,1.92 for OC-PC and 1.80, 95% CI: 1.25,2.59 for LC

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
Edefonti 2010 [351]	Case-control/ Italy	OC, PC	804 cases, 2080 controls	1. "Animal products": animal protein, animal fat, cholesterol, saturated fatty acids, calcium, phosphorus, riboflavin (vitamin B2), 2. "Starch-rich": vegetable protein, starch, sodium, 3. "Vitamins and fiber": soluble carbohydrates, vitamin C, beta-carotene equivalents, total fiber 4. "Unsaturated fats": vegetable fat, monosaturated fatty acids, polyunsaturated fatty acids, vitamin E 5. "Retinol and niacin": niacin, retinol	"Animal products" pattern was associated with increased OC-PC incidence (OR HvL quintile of factor score=1.56, 95% CI: 1.13,2.15) "Starch-rich", "Vitamins and fiber", and "Unsaturated fats" patterns were associated with reduced OC-PC incidence. ORs for HvL factor score intakes for "Starch-rich", "Vitamins and fiber", and "Unsaturated fats" were 0.71 (95% CI: 0.50,0.99), 0.47 (95% CI: 0.34,0.65), and 0.63 (95% CI: 0.45,0.86), respectively.

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
Edefonti 2010 [352]	Case-control/ Italy	LC	460 cases, 1,088 controls	1. "Animal products": animal protein, cholesterol, saturated fatty acids, calcium, phosphorus, zinc, riboflavin (vitamin B2) 2. "Starch-rich": vegetable protein, starch, sodium 3. "Vitamins and fiber": total folate, vitamin C, beta-carotene equivalents, total fiber 4. "Vegetable unsaturated fatty acids": linoleic acid, linolenic acid, vitamin E 5. "Animal unsaturated fatty acids": other polyunsaturated fatty acids, vitamin D	"Animal products", "Starch-rich" and "Animal unsaturated fatty acids" patterns were associated with increased LC incidence. ORs for HvL quartile of factor scores for "Animal products", "Starch-rich" and "Animal unsaturated fatty acids" patterns were 2.34 (95% CI: 1.59,3.45), 1.43 (95% CI: 0.97,2.10), and 2.07 (1.42,3.01), respectively. "Vitamins and fiber" and "Vegetable unsaturated fatty acid" patterns were associated with reduced LC incidence. ORs for HvL quartile of factor scores for "Vitamins and fiber" and "Vegetable unsaturated fatty acid" patterns were 0.35 (95% CI: 0.24,0.52) and 0.83 (95% CI: 0.57,1.22), respectively.
Bradshaw 2012 [298]	Case-control/ United States	OC, PC, LC	1,176 cases, 1,317 controls	1. "Factor 1 (Fruits, Vegetables, and Lean Protein)" 2. "Factor 2 (Fried foods, High-fat and Processed meats, and Sweets)	"Factor 1 (Fruits, Vegetables, and Lean Protein)" was associated with reduced OC-PC and LC incidence (ORs for HvL quartile of factor score=0.45 (95% CI: 0.32,0.63) for OC-PC and 0.73 (95% CI: 0.48,1.10) for LC "Factor 2 (Fried foods, High-fat and Processed meats, and Sweets) was associated with increased LC incidence. (OR for HvL quartile of factor score=2.12 (95% CI: 1.21,3.72) for LC

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
Toledo 2010 [353]	Case-control/ Brazil	OC	210 cases, 251 controls	1. "Prudent": vegetables, raw vegetables, fruit, dairy products, potato, fish, yogurt 2. "Snacks": bread, butter, cheese, pork, sandwich meat, egg, sweets and dessert; inversely associated with fruits, poultry, carrots, citrus fruits, brassica 3. "Traditional": rice, beans, pulses, beef, potatoes	ORs for HvL factor score tertiles for "Prudent", "Snacks", and "Traditional" patterns were 0.44 (95% CI: 0.25,0.75), 1.25 (95% CI: 0.73,2.15), and 0.53 (95% CI: 0.30,0.93), respectively. "Snacks" pattern was associated with increased OC incidence; whereas "Prudent" and "Traditional" patterns were associated with reduced OC incidence.
Edefonti 2012 [297]	Case-control/ International	OC, PC, LC	2,452 cases, 5,013 controls	1. "Animal products and cereals": 2. "Antioxidant vitamins and fiber" 3. "Fats"	"Antioxidant vitamins and fiber" pattern was associated with reduced OC-PC incidence. (OR HvL factor score quintile=0.57, 95% CI: 0.43,0.76) "Animal products and cereals" pattern was associated with increased LC incidence (OR HvL factor score quintile=1.54, 95% CI: 1.12,2.11) "Fats" pattern was associated with reduced OC-PC incidence (OR HvL factor score quintile = 0.78, 95% CI: 0.63,0.97); however, it was associated with increased LC incidence (OR HvL factor score quintile=1.69, 95% CI: 1.22,2.34)

Reference	Study design/ Location	HNSCC subtypes	Sample size	Dietary Patterns identified from factor analysis	Key Findings (adjusted for tobacco and alcohol intake)
Helen-Ng 2012 [354]	Case-control/ Malaysia	OC	153 cases, 153 controls	1. "Modern": processed foods, snacks 2. "Prudent": fruits and vegetables 3. "Traditional": beverages and starches 4. "Combination": dairy, fermented/salted meat, meat/by-products	"Combination" and "Traditional" patterns were associated with increased OC incidence. (OR HvL factor score tertile=2.986, 95% CI: 1.551,5.746 and 2.078, 95% CI: 1.088,3.970) for "Combination" and "Traditional" patterns, respectively. "Prudent" pattern was associated with reduced OC incidence (OR HvL factor score tertile=0.574 (95% CI: 0.295,1.117)
de Stefani 2013 [355]	Case-control/ Uruguay	OC, PC, LC	563 male cases (103 OC, 185 PC, 275 LC), 1099 male controls	1. "Prudent": poultry, fish, desserts, raw vegetables, other fruits 2. "Starchy plants": potato, sweet potato, winter squash 3. "Western": beef, processed meat, boiled eggs, fried eggs, total grains, 4. "Drinker": beer, wine, hard liquor	"Prudent" pattern was associated with reduced OC-PC and LC incidence; whereas, "Starchy plants", "Western", and "Drinker" patterns were all associated with increased OC-PC and LC incidence.

Table abbreviations: OC: oral cavity, PC: pharynx cancer; LC: larynx cancer; OPC: oropharynx cancer; EC: esophageal cancer, EAC: esophageal adenocarcinoma; HPC: hypopharyngeal cancer; LungCa: Lung Cancer; OR: odds ratio; 95% CI: 95 percent confidence interval; HvL: highest vs. lowest

Table 1-17: Summary of epidemiological investigations characterizing associations between dietary factors and HNSCC survival.

References	Study design/ Location	HNSCC Subtypes	Sample size	Dietary Component	Key Findings (adjusted for tobacco and alcohol intake)
Crosignani 1996 [273]	Cohort/ France, Spain, Switzerland	LC	213 cases	Pre-diagnosis food group intake	The consumption of vegetables, citrus fruits, olive oil, and orange juice was associated with better prognosis; conversely, butter and milk consumption was associated with a poorer prognosis. The authors suggested that adherence to a "Mediterranean diet" was associated with a 36% advantage in survival.
Mayne 2004 [277]	Cohort/ United States	OC, PC, OPC, HPC, LC	264 surgery and/or radiation treated cases of stage I or II HNSCC	Baseline dietary information recorded during trial recruitment. Eligible patients completed treatment with curative intent for stage I or II HNSCC. Post-operative serum nutrient levels following beta-carotene supplementation obtained at in-person visits. Two blood samples were taken before the intervention (before and after the placebo run-in), then samples were obtained at three months, 1 year, 2 years, and yearly thereafter for 5 years.	Plasma carotenoid concentration was associated with survival; higher carotenoid concentration was associated with higher survival probabilities. Smoking appears to modify the association between serum carotenoid levels and survival following HNSCC diagnosis.

References	Study design/ Location	HNSCC Subtypes	Sample size	Dietary Component	Key Findings (adjusted for tobacco and alcohol intake)
Bairati 2006 [280]	Clinical trial/ United States	OC, PC, LC	540 radiation-treated cases of stage I or II HNSCC	Patients were randomly assigned to receive daily supplementation consisting of vitamin E and beta-carotene or placebos during radiation therapy and for three years after radiation therapy ended. Peri- and post-operative beta-carotene and vitamin E supplementation information was obtained every six months during the three years following the end of radiation therapy and then once per year until the end of the study.	Vitamin E supplementation was associated with increased cause-specific and all-cause mortality rates. All-cause mortality hazard ratio for supplement arm vs. placebo= 1.38 (95% CI: 1.03,1.85)
Bohn 2006 [279]	Clinical trial/ Finland	OC, PC, OPC, HPC, LC. ELC	29 radiation-treated cases of HNSCC	HNSCC patients receiving external beam radiation and/or brachytherapy were included in the study. Post-radiation serum levels of glutathione were collected at two time points: post-radiotherapy (immediately after the end of radiotherapy) and 6 weeks following the end of radiotherapy.	Higher relative to lower pre- and post-radiation serum glutathione levels were associated with longer survival among HNSCC cases.
Liu 2006 [173]	Cohort/ Taiwan	OC	1010 OC cases	Pre-operative serum albumin levels captured from retrospective chart review. (Serum albumin assessed following HNSCC diagnosis, but prior to surgery). Exact time following diagnosis of serum albumin level not given.	Higher relative to lower pre-radiation serum albumin levels were associated with longer survival among HNSCC cases

References	Study design/ Location	HNSCC Subtypes	Sample size	Dietary Component	Key Findings (adjusted for tobacco and alcohol intake)
Meyer 2008 [281]	Clinical trial/ Canada	OC, PC, LC	540 radiation-treated cases of stage I or II HNSCC	Stage I or II HNSCC cases treated with radiation therapy were eligible for chemoprevention trial of alpha tocopherol, beta-carotene, or placebo. Peri- and post-operative beta-carotene and vitamin E supplementation information was collected at baseline before randomization, immediately after radiation therapy, one month after radiation therapy, every six months during the three years following the end of radiation therapy, and then once per year.	The hazard for death and complications among those HNSCC cases who were classified as smokers during radiation therapy was higher among the those receiving antioxidant supplementation relative to placebo.
Sandoval 2009 [166]	Cohort/ Spain	OC, OPC	146 OC cases	Pre- and At-diagnosis fruit and vegetable consumption. Initial questionnaire asked cases of HNSCC to recall "dietary habits with a focus on fruit and fresh vegetable intake before diagnosis." One year after diagnosis, patients who survived completed a second follow-up questionnaire that elicited information on behavioral and lifestyle factors.	Higher pre- and At-diagnosis weekly vegetable consumption was associated with reduced incidence or recurrence, mortality, and cancer mortality among OC-OPC patients.

References	Study design/ Location	HNSCC Subtypes	Sample size	Dietary Component	Key Findings (adjusted for tobacco and alcohol intake)
Sakhi 2010 [278]	Clinical trial/ Finland	OC, PC, OPC, HPC, LC. ELC	29 radiation-treated cases of HNSCC	Post-radiation serum levels of carotenoids and tocopherols collected at two time points: postradiotherapy (immediately after the end of radiotherapy period) and six weeks following the end of the radiotherapy. At the end of radiotherapy, food intake was registered using a 24-h dietary recall method in the form of an interview.	Higher vs. lower post-radiotherapy serum levels of select carotenoids (lutein, alpha-carotene, beta-carotene) among HNSCC cases were associated with longer progression-free survival.
Meyer 2011 [272]	Clinical trial/ Canada	OC, PC, LC	540 radiation-treated cases of stage I or II HNSCC	Stage I or II HNSCC patients were eligible for participation in a chemoprevention trial of alpha-tocopherol vs. beta-carotene vs. placebo. Baseline data and biospecimen collection were completed before the randomization and the initiation of radiation therapy. Questionnaires included data on dietary intake, vitamin, and mineral supplement use. Average daily dietary intake over the year preceding randomization was assessed by an 840item semi-quantitative FFQ. Total vitamin D intake was calculated by summing up dietary and supplement sources. Blood samples were collected at the time of randomization from all participants.	Neither pre-radiation serum levels nor dietary intake of Vitamin D were associated with survival among cases of HNSCC.

References	Study design/ Location	HNSCC Subtypes	Sample size	Dietary Component	Key Findings (adjusted for tobacco and alcohol intake)
Arthur 2013 [275]	Cohort/ United States	OC, PC, LC	542 cases (118 OC, 305 PC, 119 LC)	At-diagnosis assessment in which cases recalled usual diet during the previous year: Dietary patterns identified through factor analysis: 1. "Whole foods: vegetables, fruit, legumes, fish, poultry, whole grains, fruit juice, olive oil, nuts, garlic 2. "Western": red meat, processed meat, refined grains, french fries, potatoes, condiments, high-fat dairy products, margarine, butter, eggs, coffee, desserts, snacks, mayonnaise, regular beverages	Higher pre-treatment "Whole foods" pattern scores were associated with longer survival among HNSCC patients (Hazard ratio HvL score quintile for survival=0.56, 95% CI: 0.34,0.92)
Fu 2016 [356]	Cohort/ China	LC	975 cases of LC who had undergone curative laryngectomy	Pinato Nutritional Index (PNI) score calculated based on pre-operative serum albumin level and lymphocyte count	Higher vs. lower categories of PNI score were associated with higher cancer-specific and overall survival among LC patients.
Miles 2016 [357]	Cohort/ United States	UADT (OC, PC, LC, EC), LungCa	601 UADT, 611 LungCa	Pre-diagnosis red meat, processed meat consumption	Higher pre-diagnosis red and processed meat consumption was associated with higher mortality among UADT patients. Hazard ratios for HvL daily intake quartile=1.64 (95% CI: 1.04,2.57), 1.30 (95% CI: 0.85,1.98), 1.39 (95% CI: 0.90,2.14), and 1.76 (95% CI: 1.10,2.82) for red meat, processed red meat, processed fried meat, and red processed fried meat, respectively.

Table abbreviations: OC: oral cavity, PC: pharynx cancer; LC: larynx cancer; OPC: oropharynx cancer; EC: esophageal cancer, EAC: esophageal adenocarcinoma; HPC: hypopharyngeal cancer; LungCa: Lung Cancer; ELC: epilarynx cancer OR: odds ratio; 95% CI: 95 percent confidence interval; HR: hazard ratio; HvL: highest vs. lowest

Figure 1-1: Schematic of head and neck anatomy

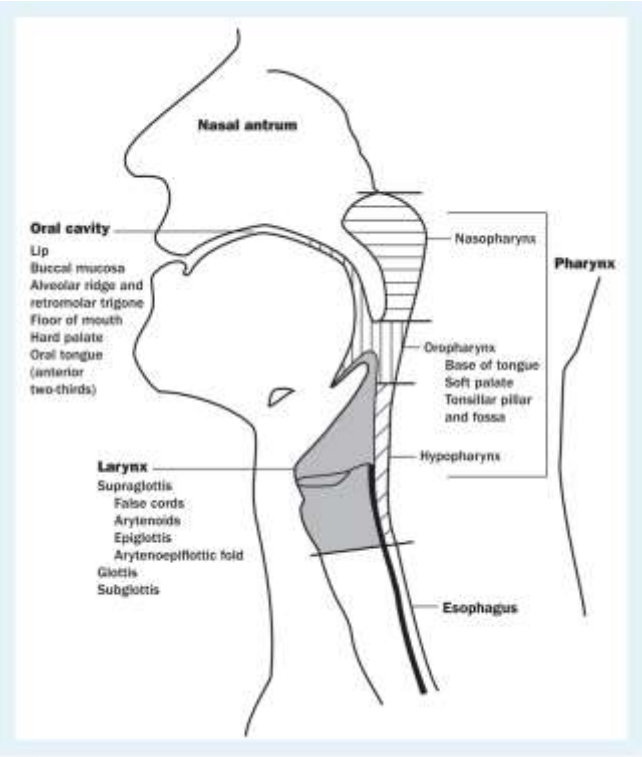
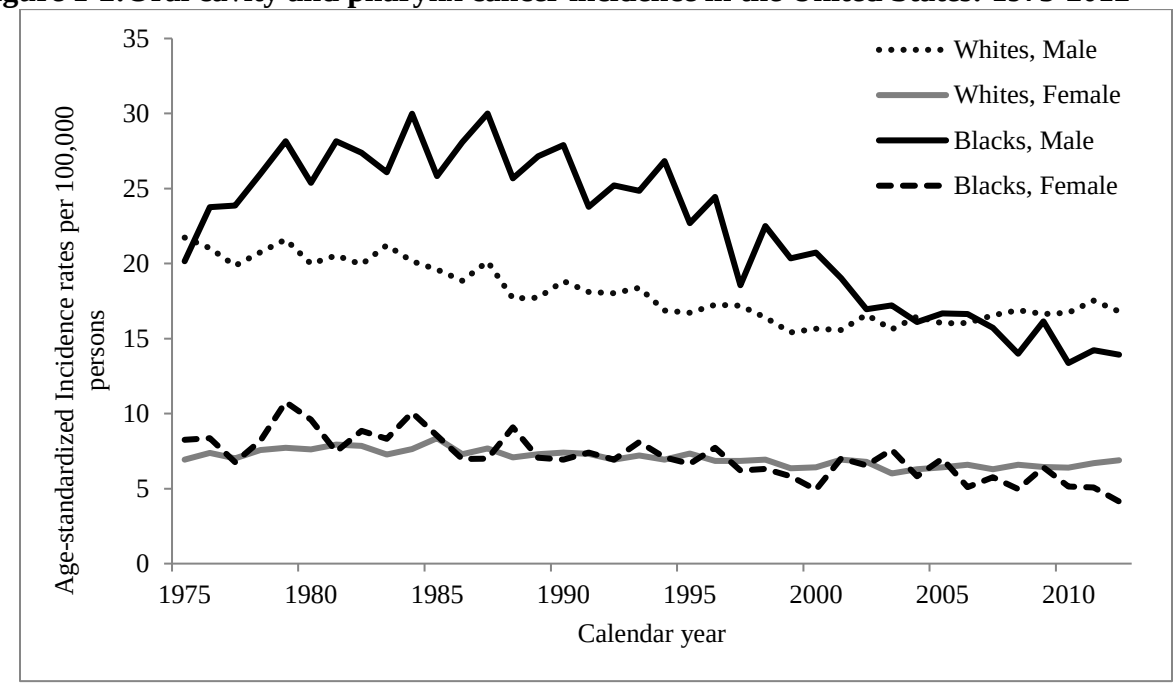


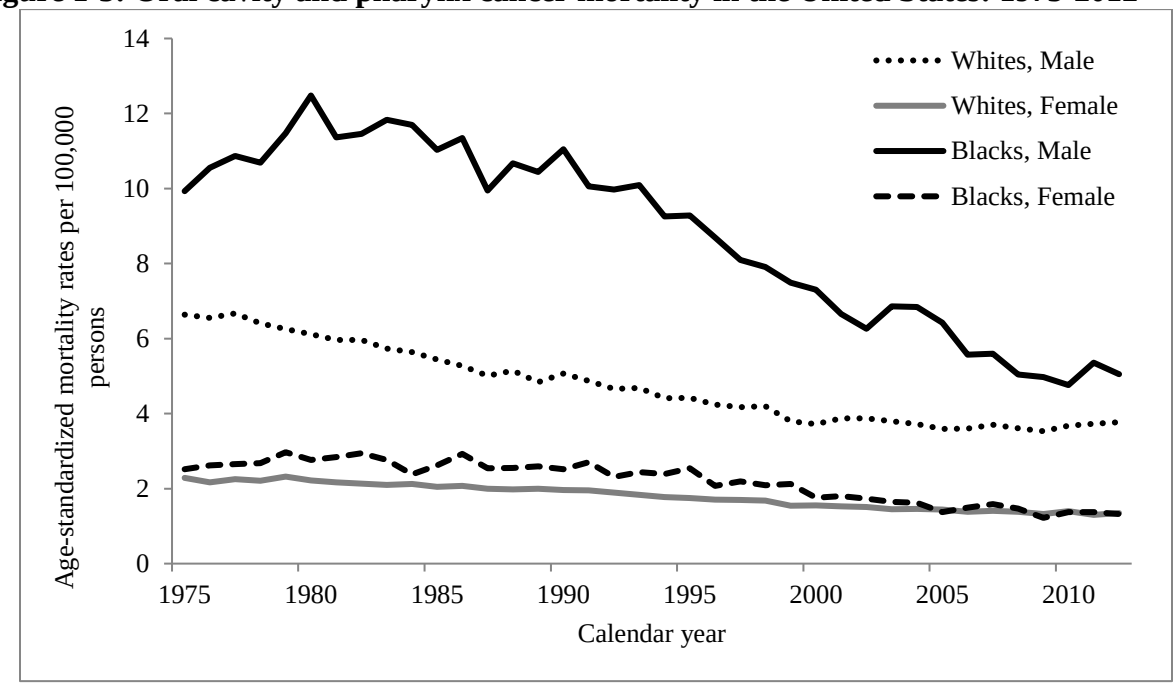
Figure 1: Schematic of Head and Neck Anatomy. Image from National Comprehensive Cancer Network Website and used per permission guidelines: http://www.nccn.org/about/permissions/academic.aspx

Figure 1-2:Oral cavity and pharynx cancer incidence in the United States: 1975-2012



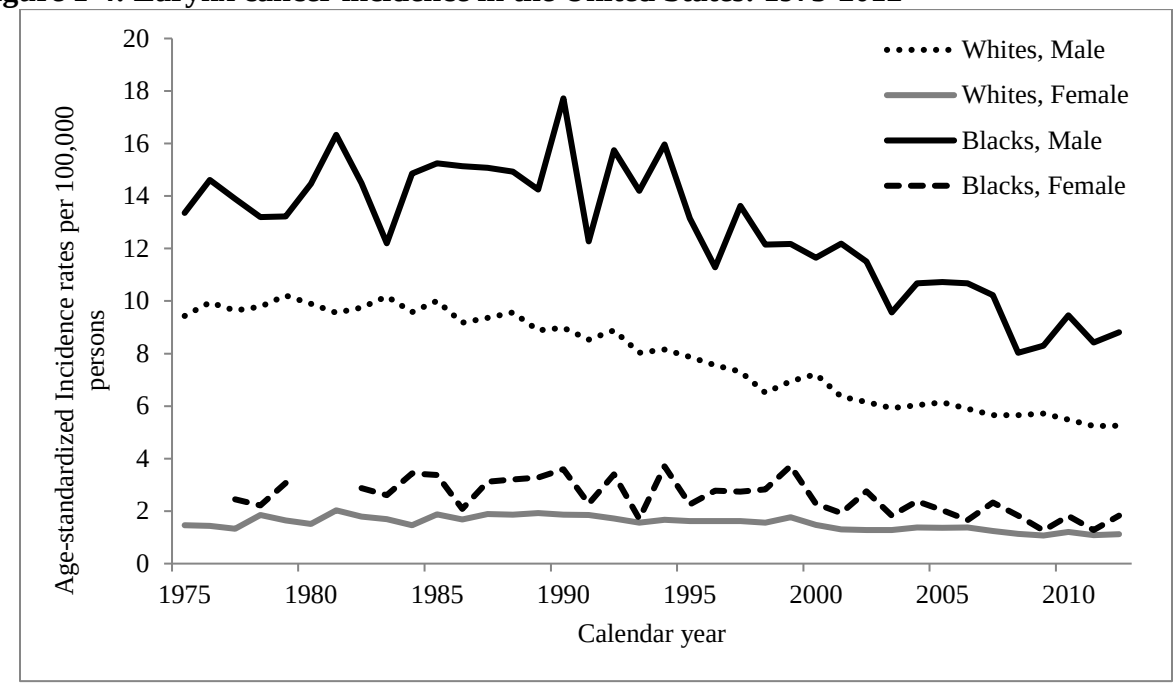
Rates standardized to the age distribution of the United States in calendar year 2000. Based on data from SEER18.

Figure 1-3: Oral cavity and pharynx cancer mortality in the United States: 1975-2012



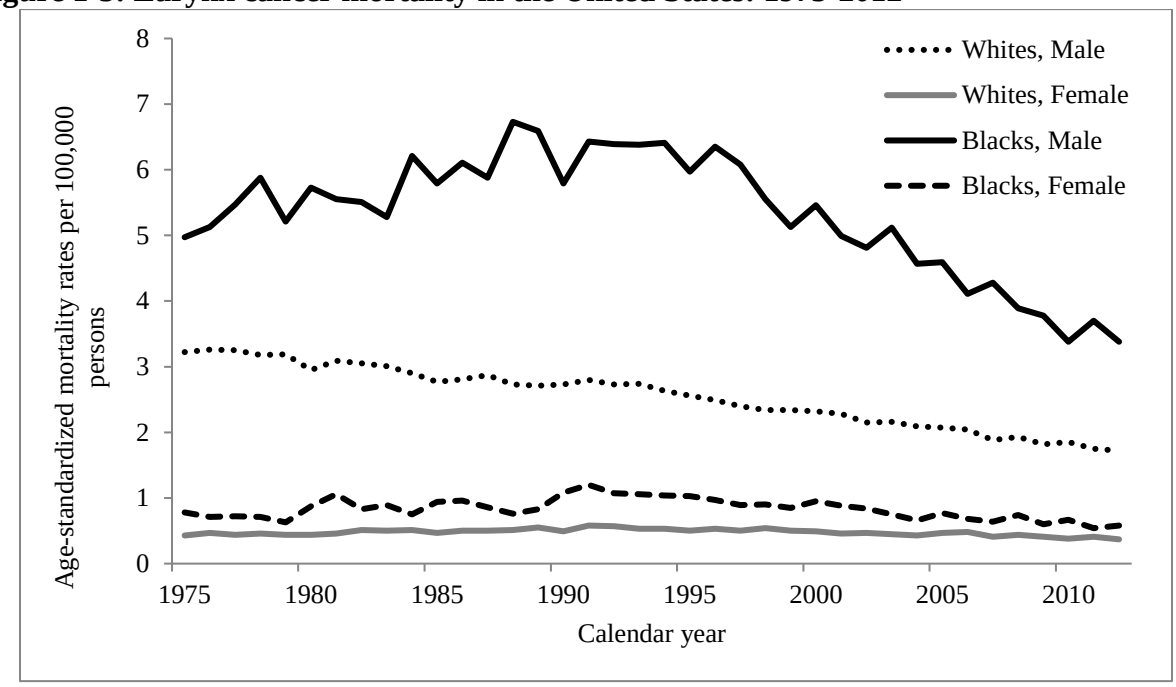
Rates standardized to the age distribution of the United States in calendar year 2000. Based on data from SEER18.

Figure 1-4: Larynx cancer incidence in the United States: 1975-2012



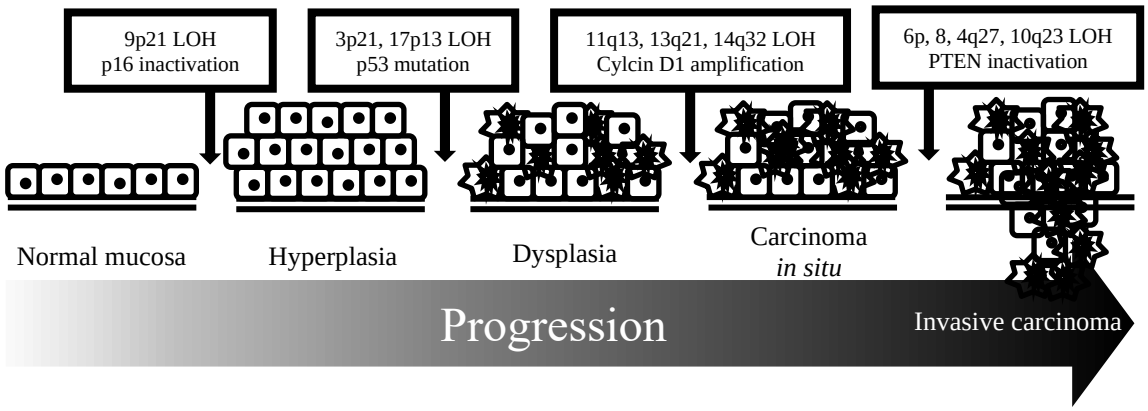
Rates standardized to the age distribution of the United States in calendar year 2000. Based on data from SEER18.

Figure 1-5: Larynx cancer mortality in the United States: 1975-2012



Rates standardized to the age distribution of the United States in calendar year 2000. Based on data from SEER18.

Figure 1-6: Molecular and histological progression schematic for head and neck cancer



Progression schematic for head and neck cancer adapted from Califano et al. 1996 [80] and Pai and Westra 2009 [78]. Candidate tumor suppressor genes include p16 (9p21), p53 (17p), and Retinoblastoma (Rb)(13q) and proto-oncogene include cyclin D1 (11q13). LOH: Loss of heterozygosity; PTEN (Phosphatase and tensin homolog.)

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CHAPTER 2: METHODS (RESEARCH STRATEGY)

2.1 Carolina head and neck cancer epidemiology study

Carolina Head and Neck Cancer Epidemiology (CHANCE) is a population-based case-control study in which eligible cases were all individuals diagnosed with primary head and neck squamous cell carcinoma between January 1, 2002 and February 28, 2006, at least 18 years of age, and residents of one of 46 counties in Eastern or Central North Carolina. Specifically included were cancers of the oral cavity, including lip (mucosa), pharynx, and larynx. Excluded were tumors of the salivary glands, nasopharynx, nasal cavity, nasal sinuses, and any tumor with a histological profile distinct from squamous cell carcinoma.

2.1.1 Case identification

Cases were identified by the North Carolina Central Cancer Registry (CCR) using a rapid case ascertainment system in which CCR staff contacted cancer registrars at 54 hospitals on a monthly basis. Upon identifying an eligible case, a pathology report was provided to the CCR within four weeks. CCR staff recorded the age, pathology, tumor site, and physician name from each report and forwarded this information to the study office at University of North Carolina at Chapel Hill, USA.

2.1.2 Case recruitment

Prior to recruiting eligible cases for study enrollment, the physicians of eligible cases were contacted by mail and given the opportunity to either allow or refuse CHANCE staff to contact their patient. After physician permission to recruit cases was obtained, brochures with frequently asked questions about the study and a letter from CCR describing the purpose of CCR

and its mission to work with researchers to improve the health of North Carolinians. The letter also explained the study purpose, the questionnaire, and biologic specimen collection (whole blood and/or mouth rinse). Further, the letter indicated that participation was completely voluntary, that participants would be paid $50 for completing the questionnaire, and that a nurse would contact the patient by telephone to answer questions and schedule an appointment. Nurse-interviewers then verified case eligibility and scheduled an in-person interview at the participant's residence or other convenient locale. Prior to conducting the interview, informed consent of the interview, the collection of biologic specimens, and medical records of the case were obtained. The medical records were used to confirm the histological diagnoses and obtain information regarding tumor stage and treatment modality.

2.1.3 Control identification and recruitment

Potentially eligible controls were identified through the North Carolina Department of Motor Vehicles (DMV) records and considered for enrollment if they resided within the same 46-county region of NC from which the case series was derived. Controls were frequency-matched to cases on age categories of 20-49, 50-45, 55-59, 60-64, 65-69, 70-74, and 75-80 years; race categories of White, Black, other; and sex categories of male and female to improve adjustment for these factors.

2.1.4 HPV status

The International Agency for Research on Cancer (IARC) performed the p16 immunocytochemistry evaluation according to the protocol provided with the CINtec Histology p16INK4a Kit (9511, mtmlabs) for the qualitative detection of the p16 expression pattern on slides prepared from formalin-fixed, paraffin-embedded tumor samples. The percentage of stained cells (0%=0, 1‑10%=1, 11‑50%=2, 51‑80%=3, 81‑100%=4) and the intensity of the

nuclear or cytoplasmic staining (none=0, weak=1, moderate=2, strong=3) were multiplied to yield a composite score ranging from zero to 12. Scores equal to or greater than 4 were considered positive for p16 expression. Since p16 is the most commonly used clinical marker, tumors with p16 protein expression were considered HPV-positive. HPV infection was also determined through DNA extraction and genotyping by Luminex-based multiplex PCR for the following genotypes: HPV6, HPV8, HPV11 HPV16, HPV18, HPV26, HPV31, HPV33,HPV35, HPV39, HPV58, and HPV59. All cases of oropharyngeal cancer (N = 248) and a random sample of non-oropharyngeal cancers (N = 244) were selected for the evaluation of the p16 protein.

2.2 Exposure

2.2.1 Measurement of diet in CHANCE

A structured questionnaire was administered by trained interviewers during the in-home visit to assess information on demographic, lifestyle, and dietary behaviors. Questionnaires collected information on established risk factors for HNSCC, including cigarette smoking, alcohol use, anthropometric measures (self-reported), and education. Dietary intakes were collected through a modification of the National Cancer Institute's Diet History Questionnaire (DHQ) [1], a food frequency questionnaire (FFQ) designed to assess usual intakes in servings per day, week, or month of various foods consumed in the year prior to diagnosis for cases and the year prior to the interview for controls. The 77-item CHANCE FFQ was designed to account for the dietary and cooking practices in North Carolina [2]. Data from the modified DHQ were processed by Nutrition Epidemiology Core of the University of North Carolina Clinical Nutrition Research Center using the Diet*Calc analysis program [3] to estimate daily intake of total energy, nutrients, and individual food items.

The use of *a priori* dietary indices to characterize overall diet quality improves upon the limitations of nutritional epidemiological studies in which single nutrients or foods were

evaluated separately with respect to HNSCC incidence [4, 5] . Specifically, *a priori* hypothesis-driven dietary patterns account for the complex interplay of foods captured in whole diets that is not possible with assessments of single dietary components and also generate findings that are plausible biologically and easier to interpret and implement in to public health programs. Two *a priori* diet quality indices will be used because they will optimize our ability to accomplish our study aims. These indices are the Healthy Eating Index-2005 (HEI-2005) and Mediterranean Diet Score (MDS) and its derivatives.

Table 2-1 and Table 2-2 specify each *a priori* diet quality index and how scores for each index are derived.

2.2.2 Healthy Eating Index-2005

The Healthy Eating Index-2005 will be used to assess adherence to the dietary recommendations of the US government based on its formulation as reviewed by Guenther and colleagues [6] . The HEI-2005 will be used for three main reasons. First, the HEI-2005 is a prescribed diet that can be used to accomplish both of our primary research aims. Second, the HEI-2005, which if adhered to as recommended by experts, would lead to a reduction in HNSCC incidence because an individual who complies with such a diet would eat more fruits and vegetables, which have been shown to reduce HNSCC risk and eat less red meat and saturated fat, which are positively associated with HNSCC. Finally, the HEI-2005 is standardized and would therefore enhance comparability with other HNSCC studies in which the HEI-2005 is employed as well as with other studies of relations between the HEI-2005 and other health outcomes. The diet data available in the CHANCE will allow for the calculation of this score without modification.

Healthy Eating Index-2005 ranges in score from a minimum of zero to a maximum of 100. In Li's investigation of the HEI-2005 and incident HNSCC using an American study cohort,

the median score for the median quintile (quintile 3) for the HEI-2005 was 67 among men and 71 among women[7] . The Calculation of the score is based the criteria detailed in Table 2-1.

2.2.3 Mediterranean Diet Score

The MDS is another measure of diet quality that is selected for this dissertation work because foods that result in a higher MDS scores are those that have shown to be associated with lower HNSCC incidence and longer HNSCC survival. Unlike the HEI-2005, the MDS is not a standard prescribed diet. Rather, it can be modified to accommodate a particular region or outcome of interest while still satisfying *a priori* hypotheses regarding biological disease pathogenesis between diet and HNSCC. This feature of the MDS is particularly important for this proposal because North Carolinian cooking practices and food preparation techniques in which pork products and saturated animal fats are added to cooked vegetables has led to positive associations between vegetable intake and the incident HNSCC.[2] Because CHANCE has collected data on food preparation techniques, it may be possible to modify the traditional MDS to account for the addition of fats to foods in North Carolina. Taken together, the modifiability of the MDS as well as its prescription of a diet that has been associated with reduced HNSCC incidence and prolonged HNSCC survival makes this *a priori* diet quality index ideal for this proposed work.

The Mediterranean diet score typically ranges in value from a minimum of zero to a maximum of nine. In Li's investigation of the Alternate Mediterranean diet score and incident HNSCC using an American study cohort, the median score for the median score category ("Score 4") for the alternate MDS was 4 among both men and women. [7] Calculation of the score is detailed in Table 2-2.

2.2.4 Exposure variable construction and specification

Because the Mediterranean diet score can be formulated based on specific population or outcomes, a new MDS index will be formulated that will predict lower HNSCC incidence and longer survival from HNSCC with increasing adherence to the new MDS index. The new MDS index, MDS-HNC, is based on the diet quality-HNSCC literature and will not require validation because it is exploratory in nature. Rather, this investigation itself will serve as a preliminary validation study for an MDS-HNC index that may inform future investigations of HNSCC and diet quality.

The derivation of a new score will be derived using the following approach: First, a table will be constructed of studies that have evaluated associations between the MDS and health outcomes, have reviewed the Mediterranean diet and its components, or have used the Mediterranean diet to construct a questionnaire or index. These studies will then be used to identify the scoring items most frequently used to construct an MDS (Table 2-3). After an MDS scoring item list has been identified, the papers listed in Table 1-15 or diet papers from INHANCE will be evaluated to a generate secondary list of scoring items (Table 2-4, Table 2-5, Table 2-6) that will be reconciled with the set of scoring items summarized in Table 2-3 in an effort to identify scoring list items which appear to be most influential with respect to HNSCC. This collection of scoring items will then be used to construct the new MDS-HNC score (Table 2-7, Table 2-8). A final table will be constructed to operationalize the identified scoring items based on the data and FFQ questions available in CHANCE. This final table will make explicit which questions, data sources, and food items will be included in the final score (Table 2-7).

To review, the identified traditional MDS scoring items include the following components: monounsaturated to saturated fatty acid ratio, high legume intake, high cereal/grain intake, high fruit intake, high vegetable intake, high olive oil intake, high fish intake, moderate

alcohol consumption, moderate wine consumption, moderate or low milk and dairy intake, low meat intake, low saturated fatty acid intake as a percent of total energy, and low cholesterol intake (Table 2-3). The reconciliation of these items with those used in the four investigation of MDS- incident HNSCC associations (Table 2-4) as well as those food items identified through an evaluation of INHANCE data (Table 2-5, Table 2-6) will serve as the basis of the MDS-HNC index. Thus, the MDS-HNC index will include the following items: High legume intake, high fruit intake, high vegetable intake (excluding potatoes), high fish intake, moderate alcohol intake, low red meat (beef, pork) intake, low processed meat intake (sausage, bacon, salami, hot dogs, sandwich meat, meat preserved through salting, curing, or smoking), high poultry intake, low egg intake, low potato intake, and high caffeinated coffee intake. Cornbread intake will be analyzed separately because although it appears to be associated with incident HNSCC in INHANCE, there is currently no biologic plausibility for this association. Additionally, single food items, like corn bread, are typically not included in MDS derivatives. Notwithstanding that this dissertation work is focused on overall diet, evaluating cornbread separately in CHANCE data may provide insight into a possible mechanism for its association with HNSCC. Table 2-7 describes how the MDS indices will be operationalized using the CHANCE FFQ and nutrition data dictionary.

The scoring of the MDS-HNC is calculated in exactly the same manner as is the MDS. That is for each component, a comparison is made between a standardized value of the study participant's intake or practice with the sex-specific median value for the reference population. The reference population will be controls and cases for specific aims one and two, respectively. If the study participant's intake satisfied the pre-determined criterion, then the study participant will be assigned a score of one for that component. For example, in the MDS-HNC, an

individual whose non-potato vegetable consumption is greater than the median sex-specific energy-adjusted non-potato vegetable intake in the reference population will attain the maximum score of one. After all components are evaluated, the summary score is tabulated as the simple summation of the scores for each component. The various components of the traditional MDS and that of the proposed MDS-HNC are presented in Table 2-8

2.3 Outcome

2.3.1 Specific aim 1: Case status

Detailed in sections 2.1.1 and 2.1.2.

2.3.2 Specific aim 2: Survivorship of cases

In May 2011, CHANCE staff utilized the National Death Index (NDI), a national archive of identified death record information compiled through data submitted by state vital statistics offices, to determine the mortality status of study participants by through 2011. If death was determined to have occurred for a study participant, the time and cause of death was recorded. The NDI contains information on mortality that is useful for research purposes. This information is also reliable as the discrepancy rate between causes of death found in the index and those verified by a specialist have been reported to be only four percent [7].

CHANCE study collected rich demographic information, which included social security numbers (SSNs) that facilitated the matching of study participants to the NDI. In fact, 75% of linkages between study participants and the NDI were perfect/very close matches on SSN, date of birth, and sex. Partial matches were examined on a case-by-case basis in order to make a final determination of linkage. Using NDI mortality data up to and including December 31, 2011, the follow-up time on CHANCE participants ranged from 2.8 to 9 years.

2.4 Covariates

Generally, all factors that are associated with HNSCC incidence and/or survival or are involved with the design of the CHANCE data will be considered for inclusion in regression models. This section focuses on how these covariates may be associated with our main exposure, the usual pre-diagnosis diet of study participants. A review of the epidemiologic relations between each covariate and HNSCC incidence and HNSCC survival can be found in sections 1.3 and 1.4, respectively. In addition, the CHANCE data used to construct only those covariates that will be included in the data analysis phase will be detailed.

2.4.1 Consideration of covariates for inclusion in regression models for both research aims.

2.4.1.1 For both Specific Aims

2.4.1.1.1 *Age, Race, Sex*

Controls were frequency-matched to cases according to cross-classifications of age-race-sex. The details of the cross-classifications are noted in Section 2.1.3. Because matching artificially changes the distribution of matching factors in the reference population and thus induces a bias, these variables will have to be included in all regression models to counteract this bias, even though each factor may or may not be associated with both overall diet quality and HNSCC.

2.4.1.1.2 *Tobacco use*

Tobaccos use is associated with diet quality because tobacco users have been shown to have lower serum antioxidant levels and have generally poorer dietary choices [8]. .

2.4.1.1.3 *Alcohol consumption*

Alcohol consumption is associated with diet quality because some alcohol consumers choose to consume alcohol because they may seek the benefits of moderate alcohol consumption. These “health-conscientious” consumers of alcohol may also choose to make healthier dietary

choices. Conversely, individuals who attain much of their daily caloric intake from alcohol are also less likely to attain their calories from more nutrient-dense sources and foods [9, 10].

2.4.1.1.4 *Human papillomavirus*

Tumor HPV-status appears to modify the association between diet and a subset of HNSCC, namely oropharyngeal squamous cell carcinoma [11–13] and will therefore be considered further in sub-group analyses for both research aims.

2.4.1.1.5 *Socioeconomic status*

Lower socioeconomic status is associated with lower-quality diets as individuals classified as belonging to lower SES communities may not have access to nutritious foods due to the non-existence of or the inability of low-SES individuals to afford such foods [14].

2.4.1.1.6 *Body mass index*

BMI is associated with diet because individuals of lower BMI may consumer fewer calories than an individual with higher BMIs. As well, an individual's diet contributes to his or her BMI [15].

2.4.1.1.7 *Physical Activity*

Energy expenditure is associated with energy intake, though the relationship appears to be weak [16]. Furthermore, individuals who eat poor diets have been reported to be less health-conscientious and therefore be less likely to be physically active [17]. Taken together, physical activity and diet are likely to be associated; however, because the relation between physical activity and HNSCC incidence and survival is equivocal, it will not be considered further.

2.4.1.1.8 *Energy Intake:*

As is customary in nutritional epidemiology, all models will be adjusted for energy intake. According to Willett, adjustment for total energy intake is usually appropriate in

epidemiologic studies to control for confounding, reduce extraneous variation, and predict the effect of dietary interventions [18]. Although Willett argues that energy intake confounds diet-disease relations, one may alternatively contend that energy intake lies on diet-disease associational pathways as a mediator and therefore should not be included in multivariable models. Nevertheless, the potential benefit in terms of measurement error reduction in conjunction with best practice principles typically results in the adjustment of total energy intake in nutritional epidemiological investigations.

2.4.1.1.8.1 *Nutrient density model*

In nutrient density model, nutrient intakes are divided by total energy intake and entered into the model. The advantage of this method is that these densities can be calculated directly and easily for each study participant, it is intuitive, and intakes per energy intake are units used in national dietary guidelines. The main limitation occurs if energy intake is associated with disease. In such a circumstance, the nutrient density ratio may actually induce confounding, possibly in the opposite direction [18].

2.4.1.1.8.2 *Standard multivariate model*

In a standard multivariate model, confounding control by total energy is attempted by including total energy intake in multi-variate risk model along with the nutrient of interest. In this approach, the coefficient for the nutrient is supposed to represent a one-unit increase in nutrient intake while holding total energy intake constant. A major disadvantage of this model is that is does not provide an indication of the actual variation in the nutrient intake with total energy intake held constant; and thus, a measure of risk may be given for an increment in nutrient intake that is unrealistic. [18]

2.4.1.1.8.3 *Nutrient residual (energy-adjusted) model*

In the nutrient-residual modeling approach, the nutrient intakes of the individuals in a group are regressed on their total energy intakes. The residuals from the regression represent the differences between each individual's actual intake and the intake predicted by their total energy intake. The nutrient residual is uncorrelated with total energy intake and this allows the variation due to nutrient composition of the diet to be studied directly. The major advantage of this method is that the nutrient residual component of the model represents nutrient composition, and the total energy component represents total energy [18].

2.4.1.1.8.4 *Energy-partition (decomposition) model*

In energy-partition modeling, energy from the primary nutrient is included as one term and energy from other nutrients is included as a second term. The coefficient for the primary nutrient can be interpreted as the difference in disease-risk associated with a difference of 1 unit in nutrient intake while other sources of energy are held constant [18] It is important to note that micronutrients do not contribute energy, though foods that contain micronutrients do carry energy.

2.4.1.1.8.5 *Multivariate nutrient density model*

This is the same as nutrient density model except that a term for total energy is also added. The addition of the total energy term is thought to address the major problem with the standard nutrient density approach by adjusting for the confounding influence of total energy intake. Willett and colleagues advocate for its greater use because of its potential to be translated directly into public health policy [18].

This dissertation work will make use of the multivariate nutrient density model because of its potential for public health translation.

2.4.1.1.8.6 *Energy adjustment debate*

Several authors have expressed differing opinions and views of Willett and colleagues' assertions regarding energy adjustment in nutritional epidemiology. Generally, much of the debate centers around interpretation of coefficients from the various models [19–26].

*2.4.1.2 **For specific aim 1 only***

2.4.1.2.1 *Oral health*

Poor oral health is positively associated with HNSCC incidence [27]. As well, individuals who are missing teeth, or who wear dentures are unable to eat certain foods that may be higher in nutritional value [28] and thus, oral health is associated with an individual's diet.

2.4.1.2.2 *Sexual behavior*

Although sexual behavior is associated with oropharyngeal HNSCC incidence [29], its relation with diet quality has not been examined in the literature; and as such, a link between sexual behavior and diet cannot be determined at this time. Since sexual behavior cannot be deemed a prior cause to dietary choice, sexual behavior will not be considered further for analysis.

2.4.1.2.3 *Family history*

Although family history, which represents both genetic and environmental factors, is associated with dietary choice [30], its association with HNSCC is equivocal at best. As such, family history will not be considered further for inclusion in our analysis.

*2.4.1.3 **For specific aim 2 only***

2.4.1.3.1 *Tumor stage at diagnosis*

Tumor stage at diagnosis is an important predictor of survival, but it cannot be a prior cause of an individual's "pre-diagnosis usual diet"; and therefore, cannot confound the pre-

diagnosis diet quality-HNSCC survival association. Tumor stage may still be associated with diet and survival as a mediator between diet and mortality. Because tumor stage is a mediator of the associational pathway, it should not be included in regression models for confounding adjustment. Nevertheless, because tumor stage is routinely included in epidemiological investigations of cancer survival, its influence on the diet quality-HNSCC survival association will be assessed primarily within the context of a sensitivity analysis.

2.4.1.3.2 *HNSCC treatment modality*

The treatment modality used to treat HNSCC cannot precede pre-diagnosis usual diet. However, like tumor stage, it also may be associated with diet and survival as a mediator between diet and mortality. Because treatment modality is a mediator of the associational pathway between pre-diagnosis diet and HNSCC survival, it should not be included in regression models for confounding adjustment. Nevertheless, because the treatment modality variable is routinely included in epidemiological investigations of cancer survival, its influence on the diet quality-HNSCC survival association will be assessed primarily within the context of a sensitivity analysis.

2.4.2 Covariate selection for inclusion in regression models

Substantive subject matter knowledge was the primary basis for covariate selection.

2.4.2.1 Specific Aim 1: Associations between adherence to prescribed diets and HNSCC incidence.

2.4.2.1.1 *Final adjustment set for specific aim 1.*

Covariates selected to adjust for confounding of the total association between overall diet quality and HNSCC incidence: age, race, sex, body mass index, oral health, socioeconomic status, alcohol consumption, and tobacco use, and energy intake.

2.4.2.2 Specific Aim 2: Associations between adherence to prescribed diets and HNSCC survival.

2.4.2.2.1 *Final adjustment set for specific aim 2.*

Covariates selected to adjust for confounding of the total association between overall diet quality and HNSCC survival: age, race, sex, body mass index, socioeconomic status, alcohol consumption, and tobacco use, and summary stage.

2.4.3 Covariate construction and specification for confounding adjustment

In general, and to aide in comparisons with previous literature, variable specifications used in previous literature will be adopted for this proposed research. Priority will be given to all investigations conducted using CHANCE data followed by investigations which made use of INHANCE data. Table 2-10 summarizes the construction and specification of the covariates that will be used in regression models to adjust for confounding.

2.5 Heterogeneity of associations

Heterogeneity of associations will be broadly classified into effect measure modification and sub-group analyses. Covariates that may be examined for effect measure modification are those that contain values that could be shared by both cases and controls, whereas variables that may apply to only cases such as tumor anatomic subtype or tumor HPV-status will be limited to sub-group analyses. Section 2.5.1 and Section 2.5.3 describe effect measure modification and subgroup analyses, respectively.

2.5.1 General principles regarding effect measure modification

Generally, likelihood ratio tests will be used to compare models with and without multiplicative product terms in order to appreciate possible differences in diet-HNSCC associations by potential effect measure modifiers for both HNSCC incidence and HNSCC survival. Interactions will be presented as stratum-specific and single-referent estimates as

recommended by Knol and VanderWeele [31]. This general approach will apply to both specific research aims.

2.5.2 Covariates to consider for Effect measure modification.

2.5.2.1 Race

As described in section 1.2.2, Blacks are differentially affected with respect to HNSCC incidence and survival compared to Whites. Thus, associations between adherence to prescribed diets and HNSCC incidence and survival within strata of race will be explored to better understand these racial differences in HNSCC incidence and survival.

2.5.2.2 BMI

Because BMI has been associated with HNSCC incidence and survival, diet quality-HNSCC associations within strata of BMI will be explored to better understand associations between BMI and HNSCC.

2.5.2.3 Tobacco use, Alcohol consumption, Joint exposure of tobacco and alcohol

Tobacco use and alcohol consumption are major risk factors for HNSCC incidence and have also been associated with HNSCC survival. As such diet quality-HNSCC associations will be explored within strata of tobacco use, alcohol consumption, and joint tobacco-alcohol use cross-classifications.

2.5.3 General principles regarding sub-group analyses

For specific aim one, polytomous logistic regression will be used to assess possible differences in diet-HNSCC incidence by characteristics that apply only to cases, such as anatomic subtype, or tumor HPV-status. For specific aim two, however, multiplicative product terms will be entered into Cox proportional hazards models to appreciate possible differences in diet-HNSCC related hazards of death by tumor anatomic subtype or tumor HPV-status.

2.5.4 Covariates to be considered for sub-group analyses.

2.5.4.1 Anatomic Subtype

HNSCC incidence and survival appears to vary by anatomic subtype and therefore exploring diet quality-HNSCC associations by anatomic subtype will be evaluated in sub-group analyses.

2.5.4.2 Tumor HPV-status

As HPV has been documented as an important risk factor for cancers of the base of the tongue, lingual tonsil, oropharynx, and Waldeyer's ring [32, 33] we will explore associations between diet quality and Tumor HPV-status to understand whether diet quality-HNSCC associations vary by tumor HPV-status.

2.5.5 Variable construction to explore effect measure modification.

Analyses across strata of race, age, BMI, tobacco use, and alcohol consumption variables will be explored to understand possible heterogeneity of diet quality-HNSCC associations between strata for each of the variables listed above. Details regarding the model-based exploration of effect measure modification are reported in section 2.5.1.

2.5.5.1 Race

Observations for individuals self-reporting a race other than "Black" or "White" will be excluded to facilitate an understanding of potential differences in diet-quality-HNSCC associations between Blacks and Whites.

2.5.5.2 BMI

BMI strata will be specified as detailed in Table 2-10.

2.5.5.3 Tobacco use, Alcohol consumption, Joint exposure of tobacco and alcohol

Two-level categorizations each for tobacco use and alcohol consumptions will be created based on ever- versus never-use of each item. Joint exposure will then result in four cross-

classifications for doubly exposed, singly exposed to tobacco use, singly exposed to alcohol consumption, or doubly unexposed to tobacco use or alcohol consumption. Diet quality-HNSCC associations will then be explored in each cross-classification.

2.5.6 Variable construction for sub-group analyses

Strata of anatomic subtypes and tumor HPV-status will be explored in sub-group analyses. General principles regarding the model-based exploration of sub-group analyses are reported in section 2.5.3.

2.5.6.1 Anatomic subtype

Associations between diet quality and HNSCC incidence as well as HNSCC survival will be examined for oral cavity-pharynx and larynx anatomic subtypes. For specific aim one, oral cavity-pharynx HNSCC vs. controls and larynx HNSCC vs. controls will be modeled simultaneously using polytomous logistic regression. For specific aim two, diet-quality - anatomic subtype multiplicative interaction terms will be specified in a survival time model.

2.5.6.2 Tumor HPV-status

Associations between diet quality and HNSCC incidence as well as HNSCC survival will be examined for HPV-positive and HPV-negative tumors. For specific aim one, HPV-positive tumors vs. controls and HPV-negative tumors vs. controls will be modeled simultaneously using polytomous logistic regression. For specific aim two, diet-quality –HPV-tumor-type multiplicative interaction terms will be specified in a survival time model.

2.6 Analysis Plan

2.6.1 Considerations for all analyses

2.6.1.1 Data cleaning and variable exploration

Prior to using statistical methods to evaluate specific aims, data analysis will begin by examining the univariate distributions of exposures, outcomes, and covariates using graphical

and tabular methods. Continuous variables will be examined graphically and categorical variables using tables. During this stage of the analysis, each variable will be scrutinized by summarizing minima, maxima, extreme observations, quintiles, measures of central tendency (means, medians), spread (standard deviations, ranges), overall shape of distributions (skewness), and patterns of missing data.

2.6.1.2 Exploration of bivariate associations

After cleaning the data for implausible values, bivariate evaluations of distributions of selected covariates for HNSCC cases and controls will be explored using simple linear regression methods for continuous variables and logistic regression models for our categorical variables. A key modeling assumption of linearity of outcome with estimated coefficients of explanatory variables will be examined by testing model fit for several parameterizations of each explanatory variable (linear, quadratic, cubic, spline, restricted quadratic splines). These analyses will inform choices to model continuous variables using linear terms, ordinal categories, or reference cell coding. Results from these evaluations will be considered for all subsequent models of increasing complexity.

2.6.1.3 Missing Data

The underlying assumption that is assumed when complete case analysis is performed is that data are missing completely at random (MCAR). MCAR implies that the missingness of any variable does not depend on the variable itself or on the values of any observed variable. MCAR may still hold if the missingness of one variable is related to the missingness of another variable [34–36]. MCAR is a very strong assumption, though at times, even if it is violated, complete case analysis may still return reasonable results in terms of bias and variance estimates, e.g., if the proportion of missing data is low.

Nevertheless, if MCAR is violated, then the data are assumed to be at least missing at random (MAR) or not missing at random (NMAR). For MAR, if there are two random variables Y and X, and Y is sometimes observed, but X is always observed, then one can say that data are MAR if the probability of missing data on Y is conditional on X alone. In other words, the missingness of Y does not depend on its own values but may depend on the values of another fully observed variable, in this case, X [34]. When data are MAR, as stated above, complete case analysis may still perform well, but methods like multiple imputation, expectation maximization, maximum likelihood estimation [34], or multiple imputation using chained equations [37] may be employed to evaluate the robustness of the results obtained from complete case analysis.

For the purposes of this dissertation work, data will be explored for violations of MCAR by comparing descriptive statistics for each covariate according to its probability of being missing. If MCAR appears not to be violated, then data will be analyzed using complete case analysis. Otherwise, multiple imputation will be considered to account for missing data.

2.6.1.4 Formal statistical tests

Unless otherwise specified, the a priori type I error rate will be set to 0.05 for all formal statistical tests. For likelihood ratio tests of interaction, alpha will be set to 0.10. Whenever possible, formal statistical tests to evaluate heterogeneity of associations across sub-groups and effect measure modifiers will be employed. Further, formal statistical tests for linear trend will be performed. Tests for linear trend for diet scores will be performed by including dietary index scores as continuous variables in regression models for both aims.

For specific aim one, multinomial logistic regression will be used to estimate effects across tumor types (OC/PC vs. controls and LC vs. control). As well, HPV-positivity will be evaluated in a similar way (HPV-positive tumors vs. controls and HPV-negative tumors vs.

controls). Homogeneity of effect across tumor sites and HPV-positivity will be evaluated by testing equality of corresponding coefficients on diet score variables for the two equations in the model with a likelihood ratio test that compares the model allowing the effects to vary across tumor sites and tumor HPV-status with the model in which the effects are constrained to be the same across tumor site and tumor HPV-status.

For specific aim two, heterogeneity of survival by tumor subtype, and tumor-HPV status will be evaluated by likelihood ratio tests between models with and without multiplicative interaction terms.

2.6.1.5 Underreporting of nutrient intake

As was done in Bradshaw's investigation using CHANCE data [38] , study participants who reported energy intakes below the 2.5^{th} percentile or above the 97.5^{th} percentile of the entire study population will be excluded to minimize the influence of implausible energy intakes.

2.6.1.6 Sensitivity analyses

2.6.1.6.1 ***Residual confounding by tobacco use and alcohol consumption.***

Because tobacco use and alcohol consumption remain major risk factors for HNSCC, attempts will be made to account for residual confounding by these variables. Restricting analyses to non-smokers and non-drinkers will be considered; however, sample size limitations may compromise this approach. Another strategy to mitigate residual confounding by tobacco use and alcohol consumption will by varying the parameterizations of the tobacco and alcohol variables.

2.6.1.6.2 ***Alcohol as a covariate and as an MDS score component***

Because alcohol is included as part of the MDS scores (MDS and MDS-HNC), adjustment for the alcohol covariate will be alternately added to all models. That is, models will

be executed for the MDS score with alcohol as a covariate and with it removed. Additionally, the alcohol covariate will be included in models as a product term with the MDS score to identify possible interaction between the alcohol covariate and the MDS scores.

2.6.1.6.3 ***Energy adjustment considerations***

All food groups used to construct diet quality scores will be energy-starndardized using the density approach. As discussed in section 2.4.1.1.8, the multivariate nutrient density model will be used to adjust for total energy. Although energy adjustment reduces measurement error, it may also induce collider stratification bias or over-adjustment, though a previous investigation using diet quality scores and colon cancer has suggested that this bias is negligible. [39] Nevertheless, total energy intake will alternately be included and excluded in models to evaluate potential differences in study results.

2.6.1.6.4 ***Tumor stage, HNSCC treatment covariates***

Survival models will be run with and without tumor stage and HNSCC treatment covariates to determine how these covariates might affect study results.

2.6.1.6.5 ***Energy intake included and excluded in models.***

Nutrients and food components used to derive diet quality scores will be energy-adjusted using the density method. Total energy intake will be adjusted for using the multivariate nutrient density model as described in section 2.4.1.1.8.5. Although adjusting for energy intake reduces measurement error and standardizes nutrient and food intakes across different total energy intake levels between individual diets, adjusting for total energy intake may also induce collider stratification bias or over-adjustment. The concern regarding the inducement of collider stratification bias and over-adjustment resulting from the adjustment of total energy intake was evaluated in an investigation of diet quality indices and colorectal cancer. In that investigation of

diet quality and colorectal cancer, the authors concluded that the inclusion of total energy intake in the models did not appreciably alter estimates of the measures of association of interest, suggesting that the collider stratification- or over-adjustment bias induced by including total energy intake in regression models is small [39]. Nevertheless, a sensitivity analysis will be executed in which models will both include and exclude total energy intake to evaluate the robustness of study results.

2.6.1.6.6 *Missing data*

Complete case analysis assumes missing data are MCAR; however, complete case analysis may still be valid even if MCAR is violated. Nevertheless, if missing data happen to be MAR at best, multiple imputation methods will be considered to test the robustness of our results from complete case analysis.

2.6.2 Analytic considerations unique to specific aim 1

Unconditional logistic regression will be used to estimate odds ratios and 95% confidence intervals [40] to characterize associations between *a priori* hypothesis-driven dietary indices and incident HNSCC. Logistic regression models will be adjusted for covariates as detailed in Table 2-10 and discussed in section 2.4.2. To estimate associations for each anatomic subtype, polytomous logistic regression will be used to estimate associations between incident oral cavity-pharynx HNSCC, incident larynx HNSCC, and HPV-associated subtypes relative to controls. Effect measure modification will be evaluated through multiplicative interaction terms to ascertain possible differences in associations between adherence to prescribed diets and incident HNSCC by race, BMI, and tobacco and alcohol use.

2.6.3 Analytic considerations unique to specific aim 2

2.6.3.1 Semi-parametric approach

Cox proportional hazards models will be used to evaluate the relation between diet quality and HNSCC survival, while adjusting for covariates as detailed in Table 2-10 and discussed in section 2.4.2. Effect measure modification will be assessed on the multiplicative scale by including a multiplicative interaction term to assess heterogeneity of diet quality-HNSCC associations by categories of race, BMI, tobacco and alcohol exposure, as well as by anatomic subtypes, and tumor HPV positivity. The specification of these sub-groups is detailed in sections 2.5.5 and 2.5.6. Interaction will be presented as described in Section 2.5.1.

2.6.3.2 Events and censoring

Follow-up for ascertainment of death began at the date of HNC diagnosis and ended five years after diagnosis. Individuals were censored if they were still alive at five years following diagnosis. Follow-up time for our analysis was calculated as the time between the HNC diagnosis and the date of censoring or death, whichever came first.

2.6.3.3 Proportionality assumption of the Cox model and model fit.

The proportional hazards assumption was evaluated by using the Supremum Test for Proportional Hazards through which the cumulative sums of martingale-based residuals for the main exposure and all covariates were assessed [41].

2.7 Study Power

Study power for both specific aims was calculated assuming the sample size presented in Bradshaw's investigation [38] of *a posteriori* diet scores and HNSCC incidence using CHANCE data. In Bradshaw's investigation, the study sample included 1,176 cases and 1,317 controls. Because analyses will be conducted comparing highest and lowest index score percentile categories between cases and controls, exposure proportions would be 0.2 and 0.33 for quintile

and tertile index score categorizations, respectively among controls in specific research aim one and events for specific research aim two. As such, exposure proportions were varied from 0.10 to 0.40 in increments of 0.10 and sample size was reduced based on contrasts between highest and lowest percentile categorization. For example, for tertile, quartile, and quintile categorizations, sample sizes were reduced by 33% (N=784 cases, 878 controls), 50% (N=588 cases, 658 controls), and 60% (N=470 cases, 526 controls), respectively. The expected range as well as an estimate of the median value for the HEI-2005 and a derivative of the MDS is discussed in sections 2.2.2 and 2.2.3, respectively.

2.7.1 Power calculation for Specific Aim 1

Desired odds ratios were set to reflect modest inverse and positive associations. For this power analysis, minimum detectable inverse effect estimates were represented by odds ratios equal to 0.60 and 0.70; whereas 1.5 and 1.6 were odds ratios that represented minimum detectable positive associations. By convention, the type I error rate was set to five percent.

Previous investigations which have used *a priori* hypothesis-driven diet scores to estimate associations between adherence to prescribed diets and incident HNSCC have compared highest and lowest tertile scores. This type of comparison assumes an exposure prevalence of 0.33 by design. Power calculations summarized in Table 28 demonstrate that study power will be well above 0.80 for exposure prevalence exceeding 0.30 and even for modest size of the measure of association. Further, previous literature (Table 1-15, Table 1-16, Table 1-17) suggests that magnitudes of the inverse associations that are likely in this proposed investigation will be much more prominent than those presented in Table 2-11.

2.8 Power calculations for specific aim 2

The assumption for the proportion of cases expected to die over the follow-up period was based on Hakenewerth's work on polymorphisms of genes involved in alcohol metabolism and

HNSCC survival which also used CHANCE data. In Hakenewerth's survival analysis data, 39.4 percent of the cases died with the median survival time equal to 46 months [42]. Assumptions for exposure proportions and relative measures of association were like those exacted for specific research aim one power calculations. The type one error rate was set to five percent.

Although *a priori* diet scores have not been used previously for the investigation of pre-diagnosis usual diet and HNSCC survival, Arthur's 2013 study [43] of *a posteriori*- diet scores and HNSCC survival in a US cohort demonstrated large reductions in the relative hazard for death were associated with the dietary pattern that aligned with the Mediterranean diet. As such reductions in the relative hazards of magnitudes that are more prominent than the modest desired detectable HRs presented in Table 2-12 are expected, suggesting that statistical power will be sufficient for specific research aim two.

2.8.1 Study power for sub-group analysis

Because sub-group analysis will reduce sample size, statistical power to detect meaningful associations outlined in the subaims of each specific research aim will be reduced relative to main effects models. Further discussion of this issue is presented in section 2.9.

2.9 Strengths and Limitations:

2.9.1 Strengths

To date, there are five investigations that have made use of *a priori* diet indices to study diet quality and HNSCC incidence, of which, only one was conducted in the United States. Further, there have been no studies that have used the *a priori* approach to study pre-diagnosis overall diet quality and long-term HNSCC survival. This investigation will be the first to make use of *a priori* hypothesis-driven diet indices to study overall diet and HNSCC survival and the first to use such indices in a large, racially- and age- diverse dataset to study overall diet quality and HNSCC incidence.

In addition, the use of *a priori* dietary indices to inform diet quality improves upon the limitations of evaluating dietary exposure using single nutrients or foods. Hypothesis-driven indices are designed to measure overall diet quality and can be used to capture the complexities of the human diet that are missed in single-nutrient and single-food approaches to studying dietary exposures and health outcomes. Furthermore, findings from this dissertation work will be readily comparable with other investigations that have made use of the same or similar diet quality indices. The ability to compare the findings from this work with similar investigations will be crucial for informing dietary guidelines as they relate to head and neck cancer [2, 44].

A key strength of this proposed research is the ability to adjust for total energy intake derived from FFQ data. Because energy intake is related to body size, metabolic efficiency, and physical activity, adjusting for energy intake is thought to reduce the confounding influence of these energy-related factors on diet quality-HNSCC associations as well as reduce measurement error inherent in dietary data [18].

2.9.2 Limitations

While some investigations have shown that FFQs introduce biases that can be substantial enough to change the interpretation of epidemiological measures of association [45], others have suggested that FFQs perform reasonably well as a measure of dietary intake when compared to standards for dietary intake like a 7-day food record or a series of 24-hour dietary recall surveys [46–51]. .

Despite its inherent limitations, the FFQ is best suited for assessing the role of past diet on cancer incidence because it can capture relative dietary intakes during a period time that is temporally relevant for the incidence of HNSCC. Still, to make inferences regarding whether the FFQ dietary intake data captured in CHANCE is associated with HNSCC, an assumption must be made that the recalled "usual diet" from the year prior to the diagnosis date for cases and the

year prior to the interview date for controls adequately represents the dietary intakes for study participants during the induction period occurring several years if not decades prior to an observed or counterfactual HNSCC diagnosis.

Research regarding the reliability of recalled past diet's ability to agree with actual past dietary intake suggests that an individual's current diet influences his or her ability to accurately recall past diet, though the relative categorization of individuals based on food habits changes little over time [46, 49, 52]. Some have characterized retrospectively collected dietary data as having "some meaningfulness" [53], while others have found that recalled past diet agrees more closely with previously recorded intakes than do current diets [46, 49]. Further, some investigators have argued that current diet may be unduly and differentially influenced by diagnosis, further suggesting that recalled past diet may be a less-biased surrogate for past diet exposure [54, 55]. Thus, CHANCE dietary data, while not providing the most reliable estimate of study participants' actual past intake, provides a reasonable representation of dietary intakes during a temporally relevant period prior to a potential HNSCC diagnosis.

Additionally, the use of proxy interviews to capture exposure and covariate information for those cases who could not participate in an interview, could introduce a bias if proxy interviewees misclassify information relative to the information that would have been recorded had the case him- or herself provided the information. Since the 69 observations for which proxy interviews were used accounted for less than 3% of the study population, and because proxy interviews have been shown to provide reasonable representations of self-report dietary intake, these observations will be retained as the bias due to proxy interview would be quite small. Nevertheless, a sensitivity analysis will be conducted by excluding proxy responses to test the robustness of study results.

As with any recall methodology, recall bias is a possibility. That is, even if the FFQ can capture temporally relevant past intake, recall bias may be present as cases may differentially recall their dietary intakes compared to controls as the diagnosis of HNSCC may have served as a stimulus for cases to be overly sensitive to past exposures. Furthermore, the sensitization of cases to previous exposures may also result in the differential misclassification of information captured for other lifestyle-related covariates like tobacco use and alcohol consumption history.

Although misclassification is likely to some degree, CHANCE employed several quality control measures to ensure that the dietary data was of the highest quality. These measures included training, calibrating, and periodically re-calibrating nurse-interviewers to make that questions are asked in a standardized manner. Additionally, dietary data were input directly into computer systems during the interview to obviate the clerical errors that result from data entry from paper records.

Another limitation of this investigation is the possibility of selection bias resulting from differential study participation proportion by cases status overall and by race among controls. Because response percentage of cases was appreciably higher than that of controls (76% versus 46%, respectively), and because a greater percentage of eligible White controls chose to participate than did eligible Black controls (50% versus 35%, respectively), a self-selection bias may occur if the distribution of exposures and covariates among controls who chose to participate differs from the distribution of covariates and exposures in the study base from which the cases arose. That is, if controls that participated have a covariate distribution that differs from the population from which the cases were derived, then bias will be present. Further, if the Black controls that participated differ with Blacks who chose not to participate with respect to covariate distributions that are related to both diet quality and HNSCC, then bias again may be present. In

Stingone's CHANCE investigation of racial disparities of HNSCC incidence by tobacco and alcohol use, covariate distributions among control participants were compared with those of the NC general population using the 2002-2005 Behavioral Risk Factor Surveillance System (BRFSS) surveys for NC. From this evaluation, Stingone [56] concluded that controls who participated in CHANCE were more likely to be male ever-smokers than the general population in NC and that this pattern of control participation would have likely resulted in associations biased toward the null. In addition, this research proposal excludes enrolled cases that die without completing the questionnaire which eliminates the most aggressive HNSCC cases and highest-grade tumors from study. This is a form of selection bias which may impact the results of this proposed research.

Finally, although subaims to explore heterogeneity of diet quality-HNSCC associations by race, BMI, tobacco and alcohol use, HNSCC anatomic subtype, and tumor HPV-positivity have been specified in this proposed research, the ability to accomplish these subaims will be limited somewhat due to insufficient statistical power. Nevertheless, the identification of general trends of variation by these subgroups that could be used to inform future investigations of HNSCC epidemiology may still be possible.

2.10 Conclusions

Although rare, head and neck cancer continue to represent a substantial public health problem in the United States in terms of quality of life for patients and their caregivers and with respect to the fiscal burden on the American healthcare infrastructure. This proposed research aims to 1) determine if diet quality using an *a priori* hypothesis-driven approach is associated with HNSCC incidence and 2) HNSCC survival. Further, the results of the sub-group analyses based on categorizations of race, BMI, tobacco and alcohol use, anatomic subtypes, and tumor

HPV positivity may have the potential to be used to prevent this cancer, inform future HNSCC investigations, and facilitate targeted interventions.

In sum, this proposed investigation is conceptualized to generate three important areas of new information. First, the use of hypothesis-driven *a priori* diet quality indices will allow for study findings to be more readily translatable and understood by the general public, comparable across other studies that may use the same standardized dietary indices, and implementable into public health policy and interventions. Second, the use of a large, extant, population-based case-control study with complimentary survival data will allow for an efficient opportunity to investigate whether pre-diagnosis overall diet quality is associated with HNSCC incidence and survival. Additionally, findings related to whether diet quality, as measured by adherence to a traditional Mediterranean diet, its derivative, or the dietary recommendation of the US government, may be associated with HNSCC incidence and survival has the potential to inform future dietary guidelines in the United States.

The investigation of a modifiable risk factor, namely an individual's overall diet quality and whether it associated with the incidence and survival of a debilitating cancer will deliver key information that can be used to prevent HNSCC, enhance survival, inform public health interventions, and allay unnecessary health care expenditures.

Table 2-1: Score enumeration for the Healthy Eating Index 2005. [57]

Component	Standard for maximum score	Standard for minimum score of zero	Maximum points*
Adequacy			
Total fruit†	>= 0.8 cup equivalent per 1,000 kcal	No fruit	5
Whole fruit‡	>= 0.4 cup equivalent per 1,000 kcal	No whole fruit	5
Total vegetables§	>= 1.1 cup equivalents	No vegetables	5
Dark green and orange vegetables and legumes§	>= 0.4 cup equivalent per 1,000 kcal	No Dark green or orange vegetables or legumes	5
Total grains	>= 3.0-ounce equivalents per 1,000 kcal	No grains	5
Whole grains	>=1.5-ounce equivalents per 1,000 kcal	No Whole grains	5
Milk#	>=1.3 cup equivalents per 1,000 kcal	No Milk	10
Meat and beans**	>=2.5-ounce equivalents per 1,000 kcal	No Meat or beans	10
Oils††	>=12 grams per 1,000 kcal	No oil	10
Moderation			
Saturated fats‡‡	<= 7% of energy	>=15% of energy	10
Sodium‡‡	<= 0.7 grams per 1,000 kcal	>= 2.0 grams per 1,000 kcal	10
Calories from SoFAAS§§	<= 20% of energy	>= 50% of energy	20
Total	--	--	100

*Intakes between the minimum and maximum standards are scored proportionately, except for Saturated Fat and Sodium (see footnote l).
†Includes fruit juice.
‡Includes all forms except juice.
§Includes any beans and peas (legumes) not counted as Total Protein Foods (Meat and Beans).
#Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages.
**Beans and peas are included here (and not with vegetables) when the Total Protein Foods (Meat and Beans) standard is otherwise not met.
††Includes nonhydrogenated vegetable oils and oils in fish, nuts, and seeds.
‡‡Saturated Fat and Sodium get a score of 8 for the intake levels that reflect the 2005 Dietary Guidelines, 10% of calories from Saturated Fat and 1.1 g of Sodium/1,000 kcal, respectively. Intakes between the standards for scores of 0 and 8 and between 8 and 10 are scored proportionately.
§§Calories from solid fats, alcoholic beverages, and added sugars.

Table 2-2: Score enumeration for the Mediterranean diet Score [58–60]

Component	Higher*	Lower†	Component score range
Fruits	x		0,1
Vegetables	x		0,1
Cereals/grains	x		0,1
Legumes	x		0,1
Fish	x		0,1
MUFA:SFA§	x		0,1
Dairy		X	0,1
Meat		X	0,1
Moderate alcohol#		X	0,1
Total	--	--	0,9

*Implies that a study participant's energy-adjusted intake must be higher than his or her corresponding median sex-specific energy-adjusted intake in the reference population to attain the maximum score of 1 for a given component.
†Implies that a study participant's energy-adjusted intake must be lower than his or her corresponding median sex-specific energy-adjusted intake in the reference population to attain the maximum score of 1 for a given component.
‡the location of the "x" for a given component of the Mediterranean diet score suggests which criterion must be satisfied for a study participant to attain the maximum score. For example, for fruits, the "x" is located under the column labeled "Higher" which suggests that study participants with energy-adjusted fruit intake above his or her corresponding median sex-specific energy-adjusted fruit intake for the reference population would be assigned a score of 1, and 0 otherwise.
§MUFA:SFA is the ratio of monosaturated fatty acids to saturated fatty acids
#Moderate alcohol intake is evaluated differently than the other components. A value of 1 is assigned to men who consume between 10 and 50 grams of ethanol per day and to women who consume between 5 and 25 grams of ethanol per day, otherwise, a score of 0 will be assigned.
Energy adjusted intake implies Intakes will be calculated as servings or grams per 1000 kcals of energy intake

Table 2-3: Summary of MDS scoring items identified through appraisal of reviews, and other investigations that have used Mediterranean diet to explore health outcomes.

Reference	Study goal/health outcome with respect to Mediterranean Diet	MDS Scoring Items	Specification of scoring items, comments
Trichopoulou 1997 [61]	Review	8-items: (1) high monounsaturated/saturated fat ratio, (2) moderate ethanol consumption, (3) high consumption of legumes, (4) high consumption of grains and cereals, including bread, (5) high consumption of fruits, (6) high consumption of vegetables, (7) low consumption of meat and meat products (8) moderate consumption of milk and dairy products	"In the traditional Greek diet, meals such as soups and salads include large quantities of whole-grain bread, olive oil, legumes, and vegetables. Intake of milk is moderate, but consumption of cheese and, to a lesser extent, yogurt is high; feta cheese is regularly added to most salads and vegetable stews. Meat was once expensive and rarely consumed, but fish consumption was a function of proximity to the sea."
Lasheras 2000 [62]	Mortality among elderly	8-items: (1) monounsaturated fat to saturated fat ratio, (2) ethanol, (3) legumes, (4) cereals, (5) fruit, (6) vegetables, (7) meat, meat products, (8) milk and dairy products	(4) [including bread and potatoes];higher scores for intakes greater than age- and sex-specific median intake values for each age- and sex-group (1)-(6); higher scores for less than age- and sex-specific median intake values for each age-sex group (7), and (8)
Scali 2001[63]	Development of Mediterranean diet quality index	7-items: (1) olive oil, (2) meat,(3) fish, (4) cereals, (5) vegetables + fruits, (6) saturated fatty acids (%energy), (7) cholesterol,	(2) [processed, fresh-cut beef, veal, mutton, lamb, pork], (3) [white, fatty fish], (4)[all bread (wheat, barley, plain, whole-grain), pasta (plain and whole-grain), rice (plain and whole-grain)]
Martinez-González 2002 [64]	Myocardial infarction	(1) olive oil, (2) fiber, (3) fruits, (4) vegetables, (5) fish, (6) alcohol, (7) meat/meat products, (8) high-glycemic load food items	(8) [white bread, pasta]; higher scores for higher intakes of(1)-(6) and lower intakes of (7), and (8)
Martinez-González 2004 [65]	Development of cardioprotective dietary intake questionnaire	9-itmes: (1) olive oil, (2) fruit, (3) vegetables or salad, (4) fruit and vegetables, (5) legumes, (6) fish, (7) wine, (8) meat, (9) [white bread and rice] or whole-grain bread	olive oil (>= 1 spoon/day); fruit (>= 1 serving/day); vegetables or salad (>= 1 serving/day); fruit (>=1 serving/day) and vegetables (>= 1 serving/day); legumes (>=2 servings/day); fish (>=3 servings) day; wine (>=1) glass/day; meat (<1 serving/day); [white bread (<1 serving/day) and rice (<1/week)] or whole-grain bread (>5/week)
Schroder 2004 [66]	Obesity	9-item: (1) vegetables, (2) fruits, (3) pulses, (4) nuts, (5) fish, (6) cereals, (7) meat, (8) high-fat dairy products, (9) wine	higher scores for higher consumption of (1)-(6) and lower consumption of (7) and (8); higher score for greater than 0 g, but less than 20 grams per day of wine consumption

Reference	Study goal/health outcome with respect to Mediterranean Diet	MDS Scoring Items	Specification of scoring items, comments
Trichopoulou 2005 [67]	Body Mass Index, Waist-to-hip ratio	9-item: (1) vegetables, (2), legumes, (3) fruits and nuts, (4) cereals, (5) fish, (6) meat and meat products, (7) dairy products, (8) monounsaturated to saturated lipid ratio (9) ethanol	Higher scores for higher than median sex-specific intake for (1)-(5), and (8); and lower than median sex-specific intake of (6) and (7). (9) consumption of10-50 g/day for men; 5-25 g/day for women constituted higher score
Sánchez-Villegas 2006 [68]	Weight gain	10-item: (1) vegetables, (2) fruits, (3) cereals, (4) nuts, (5) pulses, (6) fish, (7) olive oil, (8) moderate red wine consumption, (9) meat/meat products, (10) whole-fat dairy products	(1)-(8) positively weighted for higher intakes; (9), (10) inversely weighted for higher intakes; (8) variable transformation centered at 20 g/day for men; 10 g/day for women
Mendez 2006 [69]	3-year obesity incidence	9-items:(1) Fish, (2) vegetables, (3) fruit, (4) legumes, (5) cereals, (6) monounsaturated to saturated fatty acid ratio, (7) meat, (8) dairy products, (9) nuts	(2) [excluding potatoes]; (4) [chickpeas, lentils]; (5)[bread, rice, pasta]; (8)[milk, yogurt, but excluding desserts such as ice cream], intakes as grams/ 1000 kilojoules; (8) [considered beneficial and detrimental and alternatively omitted]; (9) included with fruit previously, but analyzed separately
Panagiotakos 2006 [70]	Obesity	(1) non-refined cereals and products, (2) fruits, (3) vegetables, (4) olive oil, (5) non-fat/low-fat dairy products, (6) fish, poultry, potatoes, olives, pulses, nuts (7) eggs, sweets (8) red meat, meat products, (9) wine (10)high monounsaturated to saturated fat ratio	(1) [whole grain bread, pasta, 4-6 servings/day]; (2)[4-6 servings/day];(3)[2-3 servings/day]; (4)[as main added lipid]; (5)[1 or 2 servings/day]; (6)[4-6 servings/week]; (7) [1-3 servings/week.]; (8)[4-5 servings/month] (9)[1-2 wine glass/day]; (10)[>=2]
Mitrou 2007 [71]	Mortality	9-items: (1) vegetables, (2) legumes, (3) fruits, (4) nuts, (5) whole grains, (6) fish, (7) monounsaturated fat-saturated fat ratio, (8) alcohol, (9) meat/dairy	(1) [excludes potatoes]; higher scores for intakes greater than sex-specific median intakes for (1)-(7); and less than sex-specific median intake for (9); higher score for (8) daily grams of consumption 5-25 g for women; 10-50 grams for men
Fung [72] 2009	Coronary Heart disease	9-items (1) alcohol, (2) red/processed meat, (3) fish, (4) whole grains, (5) legumes, (6) nuts, (7) fruits, (8) vegetables, (9) monounsaturated to saturated fat ratio	(8) [excludes potatoes]; higher score for greater than median intake for (3)-(9); and lower than median intake for (2); (1)[intake between 5-15 g/d received high score, 0 otherwise]

Table 2-4: Summary of results of four investigations [73–76] of MDS and HNC incidence relative to scoring items detailed in Table 2-3

MDS Scoring Item	Bosetti 2003	Samoli 2010	Filomeno 2014	Giraldi 2016	Conclusion?
High Mono-unsaturated to saturated FA ratio	OC/PC:0.72 (0.56,0.93); LC:0.97 (0.73, 1.28)	0.99 (0.61,1.61)	0.66 (0.51,0.84)	--	Inconclusive
High Legumes, pulses	OC/PC:1.09 (0.87,1.38) LC: 0.75 (0.58, 0.98)	0.64 (0.40,1.01)	--	0.06 (0.01,0.23)	Generally inversely associated
High grains, cereals, non-refined cereals	OC/PC: 0.77 (0.59,1.00); LC: 0.92 (0.68, 1.24)	1.18 (0.72,1.92)	--	--	Inconclusive
High Cereals, potatoes	--	--	0.90 (0.68,1.18)	--	Inconclusive
High Fiber	--	--	--	--	--
High fruits	OC: 1.06 (0.83,1.35); LC: 0.82 (0.62, 1.07)	--	0.68 (0.53,0.87)	0.10 (0.04,0.22)	Generally inversely associated
High nuts	--	--	--	--	--

MDS Scoring Item	Bosetti 2003	Samoli 2010	Filomeno 2014	Giraldi 2016	Conclusion?
High fruits/nuts	--	0.84 (0.52,1.35)	--	--	Inconclusive
High vegetables	OC/PC: 0.79 (0.62,1.01); LC: 0.51 (0.39,0.67)	--	0.47 (0.37,0.60)	0.06 (0.03, 0.15)	Generally inversely associated
High vegetables, excluding potatoes	--	--	--	--	--
High Olive oil	--	--	--	--	--
High Fish	--	0.73 (0.46,1.15)	1.01 (0.80,1.26)	0.52 (0.22,1.23)	Generally inversely associated
Moderate wine	--	1.06 (0.66,1.71)	--	--	Inconclusive
Moderate vs. non/light drinking	--	1.25 (0.75,2.08)	--	--	Inconclusive

MDS Scoring Item	Bosetti 2003	Samoli 2010	Filomeno 2014	Giraldi 2016	Conclusion?
Heavy vs. non/light drinking	--	2.08 (0.91, 4.78)	--	--	Generally positively associated
No/Heavy vs. moderate alcohol	OC/PC: 4.26 (3.11,5.83); LC: 2.77 (2.01,3.83)	--	--	--	Generally positively associated
Moderate vs. No/Heavy alcohol	--	--	0.23 (0.18,0.29)	0.29 (0.19,0.45)	Generally inversely associated
Moderate red wine consumption	--	--	--	--	--
Moderate Ethanol consumption	--	--	--	--	--
Moderate non-fat, low-fat dairy	--	--	--	--	--
High milk, dairy products	OC/PC: 1.09 (0.86,1.40); LC: 1.07 (0.81, 1.42)	1.30 (0.80,2.10)	--	--	Inconclusive

MDS Scoring Item	Bosetti 2003	Samoli 2010	Filomeno 2014	Giraldi 2016	Conclusion?
Low milk, dairy products	--	--	1.03 (0.81,1.31)	--	Inconclusive
Moderate/low milk, dairy products	--	--	--	--	--
Low high-fat dairy	--	--	--	--	--
High meat, meat products	OC/PC: 1.42 (1.11, 1.81); LC: 1.53 (1.15, 2.04)	1.13 (0.70, 1.83)	--	--	Generally positively associated
Low Meat, meat products	--	--	0.81 (0.64,1.04)	0.65 (0.39,1.10)	Generally Inversely
Low Saturated fatty acids (% of Energy)	--	--	--	--	--
Low Cholesterol	--	--	--	--	--

MDS Scoring Item	Bosetti 2003	Samoli 2010	Filomeno 2014	Giraldi 2016	Conclusion?
Low High-glycemic load food items	--	--	--	--	--
Low eggs	--	--	--	--	--
Low sweets	--	--	--	--	--

Table 2-5: INHANCE data [77] for food items returning 95% confidence intervals excluding null values when contrasting highest and lowest intake quartiles.

Group	Food item	Cases/controls in lowest quartile of intake	Cases/controls in highest quartile of intake	OR 95% CI (4^{th} vs. 1^{st} quartile of intake)	No. of Studies
Cereals/grains	Corn bread*	2535/3833	1218/1305	1.27 (1.03,1.55)	9
Eggs	Eggs	2145/4172	3172/4068	1.44 (1.12,1.86)	20
Fruits	Bananas	3393/3939	1832/2555	0.76 (0.59,0.97)	14
Fruits	Citrus fruits	4098/4365	1790/3729	0.66 (0.56,0.77)	16
Fruits	All fruits combined	4962/4889	2108/5119	0.61 (0.52,0.73)	15
Vegetables	Potatoes	1707/2450	2330/2649	1.24 (1.05,1.46)	12
Vegetables	Non-starchy vegetables	4508/5052	2209/4708	0.68 (0.51,0.90)	20
Vegetables	Non-potato vegetables	4558/5039	2465/5659	0.66 (0.49,0.90)	22
Vegetables	Allium vegetables	1263/2073	576/1026	0.66 (0.54,0.81)	8
Vegetables	Green vegetables	4439/4574	2043/4285	0.65 (0.53,0.81)	18
Vegetables	Carrots	4567/4998	1771/3912	0.64 (0.57,0.72)	18
Meat	Pork	1795/3185	2003/1789	1.48 (1.19,1.83)	11
Meat	Red meat	1926/3852	2858/3081	1.4 (1.13,1.74)	15
Meat	Processed meat	2758/5038	3763/5057	1.37 (1.14,1.65)	21
Meat	Beef	1750/2733	2951/3106	1.37 (1.16,1.61)	12
Meat	Seafood	3054/4135	2294/3883	0.83 (0.74,0.94)	19
Meat	White	4442/5158	1909/4843	0.68 (0.55,0.84)	20

*Lack of literature supporting biologic plausibility of cornbread being associated with HNSCC incidence. Cornbread will be analyzed separately in sensitivity analysis.

White meat includes poultry, fish, shellfish; Seafood includes fish and shellfish, Red meat includes beef and pork. All ORs adjusted for age, tobacco use, alcohol consumption, sex, race/ethnicity, study center, education level, and weight.

Table 2-6: INHANCE data [77, 78] for food items returning 95% confidence intervals excluding null values when contrasting highest and lowest consumption frequency categories with respect to HNSCC incidence.

Group	Food item	Cases/controls in lowest consumption frequency category	Cases/controls in highest consumption frequency category	OR 95% CI (highest vs. lowest consumption frequency	No. of Studies
Eggs	Eggs	2443/4534	1304/1578	1.48 (1.2,1.82)	20
Fruit	Apples and pears	4081/3560	1679/3482	0.61 (0.44,0.86)	12
Fruit	Citrus fruit	3349/3512	1310/2520	0.51 (0.41,0.64)	9
Vegetables	Fried potatoes	1147/2816	42/36	2.97 (1.40,6.32)	6
Vegetables	Fresh tomatoes	1842/1734	1401/1722	0.77 (0.64,0.92)	9
Vegetables	Green salad	2010/1521	1897/3080	0.6 (0.36,0.76)	12
Vegetables	Lettuce	650/533	277/528	0.52 (0.36,0.76)	4
Meat	Pork	4970/7611	106/59	1.81 (1.15,2.84)	11
Meat	Beef	860/870	960/658	1.55 (1.07,2.23)	4
Coffee/tea	Caffeinated coffee	542/1435	525/830	0.61 (0.47,0.80)	7

Coffee OR for oral cavity/pharynx cancers; highest and lowest consumption frequency categories for coffee/tea and other food groups were [>4 cups/day vs. non-drinkers] and [>=7 servings/week vs. <1 serving/week], respectively. ORs adjusted for age, tobacco use, alcohol consumption, sex, race/ethnicity, study center, education level, and weight.

Table 2-7: Operationalization of MDS and MDS-HNC indices using CHANCE data.

	Index	Foods included	CHANCE questionnaire	CHANCE data dictionary variables
High Cereals and grains intake	MDS	All whole-grain food items, rice, pasta	Q37 (macaroni), Q36 (rice), Q38 (pasta), Q39 (cold cereal), Q40 (oatmeal),	Vars to consider: TOTAL_NUMBER_OF_GRAIN_SERVINGS NUMBER_OF_WHOLE_GRAIN_SERVINGS NUMBER_OF_NON_WHOLE_GRAIN_SERVIN
High MUFA:SFA ratio	MDS	Monounsaturated FA intake; Saturated FA intake	--	MONOUNSATURATED_FAT___G SATURATED_FAT___G
High legume intake	MDS, MDS-HNC	Peas, lentils, beans	Q26, Q42	NUMBER_OF_DRY_BEAN_AND_PEA_SERVI
High fruit intake	MDS, MDS-HNC	All fruits, excluding juices	Q13, Q18(citrus fruit), Q15 (apples/pears), Q17(bananas)	TOTAL_NUMBER_OF_FRUIT_SERVINGS
High non-potato vegetable intake	MDS, MDS-HNC	All non-potato vegetables, exclude vegetable soups	Q9, Q20 (raw tomatoes), Q21 (broccoli, cauliflower), Q23 (spinach, greens, collards) Q22 (carrots), Q27 (raw green salad), Q31 (vegetable soups), Q33 other vegetables	Sum of VARS: NUMBER_OF_DARK_GREEN_VEGETABLE_S NUMBER_OF_DEEP_YELLOW_VEGETABLE_ NUMBER_OTHER_STARCHY_VEGETABLE_S NUMBER_OF_TOMATO_SERVINGS NUMBER_OF_OTHER_VEGETABLE_SERVIN
High fish intake	MDS, MDS-HNC	All fatty fish, white fish, shellfish, seafood, fish sticks	Q55	OZ_LEAN_MEAT_FROM_FISH_OTHER_SEA
High poultry intake	MDS-HNC	Chicken, fowl	Q53,	OZ_LEAN_MEAT_FROM_MEAT_POULTRY_F
High caffeinated coffee intake.	MDS-HNC	Caffeinated coffee, tea excluded, decaf excluded	Q2	--M2

	Index	Foods included	CHANCE questionnaire	CHANCE data dictionary variables
Low milk, dairy products intake	MDS	All dairy milks, ice cream, frozen yogurt, cheeses; exclude soy, rice, other milks, milk added to cereal	Q3(milk), Q39 (milk to cereal); Q62	TOTAL_NUMBER_OF_DAIRY_SERVINGS NUMBER_OF_MILK_SERVINGS NUMBER_OF_YOGURT_SERVINGS NUMBER_OF_CHEESE_SERVINGS
Low total meat intake	MDS	All meats combined (beef, pork, white, seafood, organ, processed)	Q43	OZ_LEAN_MEAT_FROM_MEAT_POULTRY_F OZ_LEAN_MEAT_FROM_BEEF_PORK_LAMB OZ_LEAN_MEAT_FROM_ORGAN_MEATS OZ_LEAN_MEAT_FROM_FRANKS_LUNCHEO OZ_LEAN_MEAT_FROM_POULTRY OZ_LEAN_MEAT_FROM_FISH_OTHER_SEA
Low red meat (beef, pork) intake	MDS-HNC	Beef, pork, organ meats	Q43(all meat), Q46, Q47, Q49,	OZ_LEAN_MEAT_FROM_BEEF_PORK_LAMB OZ_LEAN_MEAT_FROM_ORGAN_MEATS
Low processed meat	MDS-HNC	Hotdogs, bacon, salami, cured, salted,	Q48, Q50, Q51, Q52	OZ_LEAN_MEAT_FROM_FRANKS_LUNCHEO
Low corn bread intake	MDS-HNC	Cornbread	Q35 (corn bread)	--M35
Low egg intake	MDS-HNC	Eggs	Q54	OZ_LEAN_MEAT_EQUIVALENT_FROM_EGG
Low potato intake	MDS-HNC	Potatoes, sweet potatoes	Q28 (French fries), Q29 (sweet potato), Q30,	NUMBER_OF_WHITE_POTATO_SERVINGS
Moderate alcohol intake	MDS, MDS-HNC	Alcohol	Q6, Q7,Q8	TOTAL_DRINKS_OF_ALCOHOL
Discretionary fat added to cooked vegetables	MDS-HNC	Discretionary fat	Q10(vegetable cooking), Q11(vegetables at table) Q42 (beans)	GRAMS_OF_DISCRETIONARY_FAT

Table 2-8: Comparison of traditional MDS scoring index with proposed MDS-HNC index

"Traditional" MDS		"Proposed" MDS-HNC	
Fruits	H	Fruits	H
Vegetables	H	Vegetables	H
Cereals/grains	H	Caffeinated coffee	H
Legumes	H	Legumes	H
Fish	H	Fish	H
MUFA:SFA§	H	Poultry	H
Dairy	L	Red meat	L
Meat	L	Processed meat	L
Alcohol	M	Eggs	L
		Potatoes	L
		Discretionary fat	L
		Alcohol	M

Table notes and abbreviations: H: Higher; L: lower, M: Moderate; Higher implies that a study participant's energy-adjusted intake must be higher than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.; Lower implies that a study participant's energy-adjusted intake must be lower than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component. Moderate alcohol intake: A value of 1 is assigned to men who consume between 10 and 50 grams of ethanol per day and to women who consume between 5 and 25 grams of ethanol per day, otherwise, a score of 0 will be assigned. Intakes will be calculated as servings or grams per 1000 kcals of energy intake.

Table 2-9: Matrix of covariates that will be considered for inclusion in regression models for specific research aims.

Covariate	Main exposure: Associated with Pre-diagnosis usual diet?	Outcome for Aim 1: Associated with HNSCC incidence?	Outcome for Aim 2: Associated with HNSCC survival?	Design variable	Will be included in Directed acyclic graph for further consideration
Age		x	x	x	x
Race	x	x	x	x	x
Sex	x	x	x	x	x
Tobacco Use	x	x	x		x
Alcohol consumption	x	x	x		x
HPV	x	x	x		x
Sexual behavior		x			
BMI	x	x	x		x
Physical activity	x				
Energy intake	x			x	x
Oral health	x	x			x
Family history	x				
Tumor stage	x		x		x
HNSCC treatment strategy	x		x		x

Notes: HPV, Tumor stage, and HNSCC treatment strategy are associated with the main exposure through other variables. See DAGs for each research aim for details. Design variable implies that the study design mandates adjustment for these variables, regardless of relations with exposure and outcome.

Table 2-10: Construction of covariates and how they will be specified in regression models.

Covariate	Aim relevance	CHANCE data used to construct covariate	Specifications that will be used in regression models	CHANCE reference
Age	1,2	Self-reported age at time of interview	1. Indicator variables for age categories used in matching in years: 20-49 (referent), 50-45, 55-59, 60-64, 65-69, 70-74, 75-80	Petrick 2013 [79]
Race	1,2	Self-reported race at time of interview	Indicator coding for three categories of race: Whites (referent), Blacks, other race	Divaris 2010[80]
Sex	1.2	Self-reported sex at time of interview	Indicator coding for two sex categories male and female (referent)	Petrick 2013 [79]
Energy intake	1,2	UNC cores estimated total energy intake from food frequency questionnaire data	For HEI-2005, MDS, MDS-HNC, nutrient scores will be based on grams/1000 kcal; total energy intake will be added to the model as a continuous variable.	Bradshaw 2012 [38]
Body mass index	1,2	Self-reported height in meters reported at time of interview and self-reported weight in kilograms at time one year prior to interview	1. BMI: weight in kilograms divided by the square of the height in meters. 2. Three-category indicator variable: "Leanness" (<18.5 kilograms per square meter); "Normal weight" (18.5-<25 kilograms per square meter); also, the reference category: "Overweight" (25-30 kilograms per square meter); "Obese" (>30 kilograms per square meter);	Petrick 2013 [79]
Oral health	1	Self-reported number of natural teeth lost excluding third molars and teeth extracted due to orthodontic reasons (range = 0–28); history of self-reported tooth mobility, or ''teeth loose in their socket due to disease''; self-reported history of regular mouthwash use; or self-reported one or more routine (non-emergency) dental visits during the decade prior to HNSCC diagnosis	1. Tooth loss will be coded as a three-level indicator variable, with 0–5 lost teeth as the referent category, and 6–15 and 16–28 lost teeth as the moderate and severe tooth loss groups, respectively. 2. History of self-reported tooth mobility, self-reported mouthwash use, or routine dental visits will be dichotomized variables with "no" as the reference category.	Divaris 2010 [80]
Socio-economic status	1,2	Self-reported education level	3-level categorical variable: less than college (referent), college, and more than college education.	Divaris 2010 [80]

Covariate	Aim relevance	CHANCE data used to construct covariate	Specifications that will be used in regression models	CHANCE reference
Alcohol consumption	1,2	Self-reported alcohol consumption history	Three-level indicator coding: Never consumers (referent), former consumers, current consumers 1. Cumulative dose continuous specification: total lifetime ethanol consumed in grams. 2. Cumulative dose quartile specification of total ethanol with cut points based on distribution among the controls	Petrick 2013, Divaris 2010 [79, 80]
Tobacco use	1,2	Self-reported smoking history; Ever users were those reporting having ever used cigarettes, cigars, pipes, chewing tobacco, or snuff or those who reported having smoked at least 100 cigarettes or 5 packs of cigarettes during his or her entire life.	Three-level indicator coding: Never users (referent), former users, current users Intensity/frequency: three-category indicator variable: never smoker (referent), those having smoked 1-19 cigarettes per day; those having smoked >19 cigarettes per day. Duration in years; 5-category indicator variable: never smoker (referent), those having smoked 1-<20 years, 20-<40 years, 40-<50 years >=50 years	Stingone 2013 [56]
HPV Tumor-status	1,2	HPV-typing of tumors	Two-level indicator: HPV-positive, HPV-negative	--
Tumor Stage	2	Summary stage from medical records	Four-level indicator: Stage I, II, III, IV	--
Treatment modality	2	Treatment modalities derived from medical records: Surgery (S), Chemotherapy (C), Radiation (R)	Binary Indicators for each of Surgery: Yes/No; Chemotherapy: Yes/No; Radiation: Yes/No	--

Table Notes: Aim relevance can take values of 1,2, or both. "1" implies variable will be used for the analysis constructed for aim 1; "2" implies the variable will be used for the analysis constructed for specific research aim 2.

Table 2-11: Summary of power calculations for specific aim 1

Exposure prevalence*	Desired OR detection	Study power†		
		Tertile	Quartile	Quintile
0.10	0.60	0.79	0.67	0.57
	0.70	0.52	0.40	0.33
	1.5	0.76	0.63	0.54
	1.6	0.88	0.78	0.68
0.20	0.60	0.97	0.91	0.84
	0.70	0.78	0.65	0.56
	1.5	0.93	0.85	0.77
	1.6	0.98	0.94	0.88
0.30	0.60	0.99	0.97	0.93
	0.70	0.89	0.79	0.69
	1.5	0.97	0.92	0.86
	1.6	>0.99	0.98	0.94
0.40	0.60	>0.99	0.99	0.97
	0.70	0.93	0.85	0.76
	1.5	0.98	0.94	0.89
	1.6	>0.99	0.98	0.96

*Prevalence within control population that is classified into the highest tertile score of the HEI-2005, MDS, or MDS-HNC. Sample size based on Bradshaw 2012 [38]: N=1,176 cases; 1,317 controls. Power calculations based on reductions of Bradshaw's sample size by 33% (N=784 cases, 878 controls), 50% (N=588 cases, 658 controls), and 60% (N=470 cases, 526 controls) for tertile, quartile, and quintile categorizations, respectively; control: case ratio=1.1; alpha=0.05; Calculations executed in Episheet.xls. [81]

†Tertile, Quartile, and Quintile represent study power for highest versus lowest percentile categorization contrasts for tertile, quartile, and quintile categorizations, respectively.

Table 2-12: Summary of power calculations for specific aim 2.

Exposure prevalence*	Desired HR detection	Study power†		
		Tertile	Quartile	Quintile
0.10	0.50	0.95	0.89	0.81
	0.60	0.77	0.65	0.55
	1.5	0.57	0.46	0.38
	1.55	0.64	0.52	0.43
0.20	0.50	0.99	0.99	0.97
	0.60	0.94	0.87	0.79
	1.5	0.81	0.69	0.59
	1.55	0.86	0.76	0.66
0.30	0.50	>0.99	>0.99	0.99
	0.60	0.98	0.95	0.89
	1.5	0.90	0.81	0.72
	1.55	0.94	0.86	0.78
0.40	0.50	>0.99	>0.99	>0.99
	0.60	0.99	0.97	0.93
	1.5	0.94	0.86	0.77
	1.55	>0.97	0.90	0.83

PowerSurvEpi package in R [82] (arguments: Total number of subjects, N=1,176. Power calculations based on a reduction of cases by 33% (N=784 cases), 50% (N=588 cases), and 60% (N=470 cases) for tertile, quartile, and quintile percentile categorizations, respectively; desired HR detected, hr=; Proportion exposed, p= *Prevalence within control population that is classified into the highest tertile score of the HEI-2005, MDS, or MDS-HNC; Proportion of N who get event, psi=483/1227=0.394 from [42]Hakenewerth 2013 ; correlation between exposure and covariates, rho2=0 (implies no covariates); alpha level, alpha=0.05

†Tertile, Quartile, and Quintile represent study power for highest versus lowest percentile categorization contrasts for tertile, quartile, and quintile categorizations, respectively.

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CHAPTER 3: MANUSCRIPT #1: "THE ASSOCIATOIN BETWEEN DIET QUALITY AND CANCER INCIDENCE OF THE HEAD AND NECK"

3.1 Manuscript #1 Summary

The association between diet quality and head and neck squamous cell carcinoma (HNSCC) was explored using a population-based case-control study of 1170 HNSCC cases and 1303 age-, race-, and sex-matched controls from the United States.

Diet quality was assessed with three diet quality scores (DQS): a) Healthy Eating Index 2005 (HEI-2005), b) Mediterranean Diet Score (MDS), and c) HNSCC-specific Mediterranean Diet Score (MDS-HNC), a modified MDS that we developed to be more applicable to HNSCC.

Logistic regression models estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) representing diet quality-incident HNSCC associations. We examined effect measure modification (EMM) by body mass index (BMI), race, cigarette smoking, and alcohol consumption and associational heterogeneity by HPV positivity and tumor site.

A one standard deviation summary DQS decrement suggested a consistent inverse association (ORs (CIs)) for the HEI-2005, MDS, and MDS-HNC: 1.35 (1.21, 1.50), 1.13 (1.02, 1.25), and 1.17 (1.06, 1.31), respectively. This association did not vary by tumor site or tumor HPV status, though additive EMM by alcohol use and by BMI was observed.

Our findings suggest the Mediterranean diet can be used to study HNSCC in American populations, and that poor diet quality elevates HNSCC incidence, particularly among alcohol users.

3.2 Introduction

Head and neck squamous cell carcinoma (HNSCC) includes cancer of the oral cavity, pharynx, and larynx. In the United States of America (USA), it is projected in 2019 that there will be 65,410 new HNSCC diagnoses and 14,620 HNSCC deaths. [1]. Generally, men have had higher incidence than women and Blacks have had higher incidence than Whites [2, 3]. Tobacco use and alcohol consumption are well established risk factors for HNSCC [4–15], while more recent studies show that the human papillomavirus (HPV) is an important risk factor for HNSCC of the oropharynx [16–24].

A pooled analysis of 22 case-control studies (14,520 cases, 22,737 controls) of diet and HNSCC risk by the International Head and Neck Cancer Consortium (INHANCE) found that fruit and vegetable consumption reduced HNSCC risk, while red and processed meats increased risk [25]. INHANCE also observed that a dietary pattern of increased antioxidant vitamin and fiber consumption was inversely associated with HNSCC risk, while higher consumption of animal products, cereals, and fats was positively associated [26].

The INHANCE results suggest the importance of not only specific foods, but of the overall diet in HNSCC incidence. Indeed, comprehensive measures of diet may better reflect dietary exposure by accounting for synergy among dietary components, which may be missed when investigating nutrient components or food items individually. In addition, analysis of dietary patterns may yield greater statistical precision [27], as diet scores incorporate multiple potentially etiologically relevant individual exposures.

Previous investigations of the overall diet and HNSCC risk have characterized diet using either an *a posteriori,* data-driven approach [28] or, an *a priori,* hypothesis-driven approach [29–33]. The *a posteriori* study identified a dietary pattern characterized by fruits, vegetables, and lean protein that reduced HNSCC risk and a high-fat, processed meats, and sweet pattern that

was positively associated with laryngeal cancer risk [28]. The *a priori* studies from Europe all relied on a version of the Mediterranean Diet Score (MDS), whereas the *a priori* study from the US used both an MDS derivative as well as the Healthy Eating Index 2005 (HEI-2005). These *a priori* studies all found that diet quality was inversely associated with HNSCC risk.

Previous studies that have used an *a priori* approach to study associations between diet quality and HNSCC risk have not explored heterogeneity by tumor HPV status, nor have they explored effect measure modification (EMM) by race, BMI, smoking, and alcohol, despite differential HNSCC risk associated with varying levels of these factors. To address these gaps, we investigated the association between diet quality and HNSCC incidence using *a priori* diet quality score (DQS)s using data from a large, population-based case-control study of HNSCC. Bradshaw and colleagues used these same data for their study of *a posteriori* diet patterns, allowing a direct comparison of diet defined by an *a priori* approaches with an *a posteriori* approach. We additionally evaluated whether these associations were similar across tumor sites and by tumor HPV status, and whether they differed by BMI, race, tobacco use, and alcohol consumption, and between DQSs.

3.3 Materials and methods.

The Carolina Head and Neck Cancer Epidemiology (CHANCE) study is a population-based case-control study of HNSCC conducted in North Carolina, USA. The CHANCE study protocol was approved by the institutional review boards of all participating institutions [34] and this investigation was approved by the UNC Institutional Review Board (UNC IRBIS: 16-2503).

3.3.1 Study Population.

Cases ranged in age from 20 to 80 years at diagnosis, resided within a 46-country region in central and eastern North Carolina, and were diagnosed with a new first primary invasive squamous cell carcinoma of the oral cavity, pharynx, or larynx between January 1, 2002 and

February 28, 2006. A rapid case ascertainment system was utilized through the North Carolina Cancer Registry and included monthly contact with the cancer registrars of 54 hospitals within the study area to identify eligible cases. Potential controls who resided in the same counties were identified through North Carolina Department of Motor Vehicles records and were frequency-matched with cases on age group (20–49; 50–54; 55–59; 60–64; 65–69; 70–74; 75-80 years), race (Black; White, other), and sex (male; female) [34]. Study participants who self-reported a race other than Black or White were excluded (n=68) as were people with missing dietary data (n=136).

3.3.2 Dietary Intake Assessment.

A structured questionnaire was administered by trained interviewers during the in-home visit to assess information on demographic, lifestyle, and dietary behaviors. Questionnaires collected information on established risk factors for HNSCC, including cigarette smoking, alcohol use, anthropometric measures (self-reported), and education. Dietary intakes were collected through a modification of the National Cancer Institute's Diet History Questionnaire (DHQ) [35], a food frequency questionnaire (FFQ) designed to assess usual intakes in servings per day, week, or month of various foods consumed in the year prior to diagnosis for cases and the year prior to the interview for controls. The DHQ was modified to account for the dietary and cooking practices in North Carolina [36]. Data from the modified DHQ were processed with the Diet*Calc analysis program [37] to estimate daily intake of total energy, nutrients, and individual food items. To minimize outlier influence, we excluded subjects (n=130) for whom total energy intake was below the 2.5^{th} percentile (934.9 kilocalories per day) or above the 97.5^{th} percentile (4325.1 kilocalories per day) of the distribution for all subjects.

The Healthy Eating Index 2005 (HEI-2005) measures diet quality based on the United States Department of Agriculture (USDA)'s Dietary Guidelines for Americans [38, 39]. We

specified the HEI-2005 as described by Guenther and colleagues [38]. The HEI-2005 is composed of twelve components: for nine components, higher consumption contributed positively to the HEI-2005 score (total fruit (including juice); whole fruit; total vegetables; dark green and orange vegetables and legumes; total grains; whole grains; milk; meat and beans/legumes; and oils (vegetable, fish, nut, and seed)) and for three components, higher consumption contributed negatively to the score (saturated fats; sodium; and calories from solid fats, alcoholic beverages, and added sugars). Full specification of the HEI-2005 is detailed in Supplemental Table 3-1. Daily intakes for each component were standardized for energy by dividing each study participant's daily component intake by his or her total daily energy intake in kilocalories and multiplying by 1000 prior to applying the HEI-2005 scoring algorithm. Each of the twelve components of the HEI-2005 had a minimum score of zero and a maximum score ranging from 5 to 20 that reflected a pre-established level of intake (Supplemental Table 3-1). The summary HEI-2005 score was calculated by summation of each component score, ranging from a theoretical minimum of zero to a maximum of 100. Lower scores indicate poorer diet quality.

The Mediterranean diet score (MDS) reflects adherence to the traditional Mediterranean diet, a diet associated with reduced mortality and lower chronic disease incidence [40–44, 44, 45] The MDS score was originally developed by Trichopoulou et al. [46], and was later revised to include fish intake, [47]. The MDS was calculated as the sum of nine dietary components: 6 components were scored positively (fruit, vegetables, cereals/grains, legumes, fish, MUFA: SFA) and 2 components were scored negatively (dairy, meat); moderate alcohol consumption was scored positively, lower or higher alcohol consumption was scored negatively (Supplemental Table 3-2). For all MDS components other than alcohol, daily intakes were

adjusted for energy by dividing a participant's daily component intake by his or her daily energy intake in kilocalories and multiplying by 1000 prior to applying the MDS scoring algorithm. For each non-alcohol component, participants were scored 0 or 1 based on whether his or her consumption was higher (scored 1 for positive components, 0 for negative components) or lower (scored 1 for negative components, 0 for positive components) than the median sex-specific energy-adjusted intake among controls. For alcohol, males who consumed between 10 and 50 grams per day and females who consumed between 5 and 25 grams per day were assigned a one. All other alcohol intakes were scored a zero. This specification for the alcohol intake component was the same specification used in the original enumeration of the MDS [47]. The summary MDS score was calculated by simple summation; thus, the score ranged from a theoretical minimum of zero to a maximum of nine. As with the HEI-2005, lower scores implied poorer diet quality.

The MDS, which was originally developed to study cardiovascular disease, has a history of being modified based on new evidence [48]. Thus, we incorporated the findings from the INHANCE studies of diet and HNSCC [25, 49] to inform a modified MDS, the "MDS-HNC." This MDS-HNC focused on food groups identified in the INHANCE investigations to be most strongly associated (both positively and negatively) with HNSCC risk. For the MDS-HNC, summation of scores (0 or 1, as with the MDS) from the beneficial components (fruits, vegetables, coffee, legumes, fish, poultry), non-beneficial components (red meat, processed meat, eggs, potatoes, discretionary fat), and a component for moderate alcohol consumption defined exactly as it was for the MDS. Supplemental Table 3-3 illustrates how the MDS and MDS-HNC are different and similar to one another. The MDS-HNC has a theoretical range from 0 to 12, with lower scores reflecting poorer diet quality.

3.3.3 Laboratory Assays.

All case participants with oropharyngeal tumors (n =339) and a random sample of case participants with non-oropharyngeal tumors (n=94) were analyzed for the presence of HPV by p16 immunohistochemistry (IHC) and polymerase chain reaction (PCR) (total n = 433). Cases with hypopharynx cancers, cases for whom the hospital would not release tumor blocks, and cases for whom interviews were completed by a proxy were excluded from laboratory assays [50]. To assess tumor HPV status, the International Agency for Research on Cancer performed a pathologic examination of formalin-fixed paraffin embedded tumor tissues to confirm the presence of tumor and semi-quantitative measurement of the presence of HPV by IHC with p16 ^{IKN4a} antibody, according to the protocol provided with the CINtec Histology p16- INK4a kit (9511; MTm Laboratories Inc., Westborough, Mass). The expression of p16 was measured by applying a combined score based on both the intensity (0 to 3) and the percentage (0 to 4) of positivity. A combined score ≥ 4 was considered overexpression. DNA extraction and genotyping using Luminex-based multiplex (PCR) (TS-E7-MPG, IARC, Lyon, France) identified HPV type 6 (HPV6), HPV8, HPV11 HPV16, HPV18, HPV26, HPV31, HPV33, HPV35, HPV39, HPV58, and HPV59 [51]. Cases were designated HPV-positive (HPV+) if they were positive for HPV16 DNA (deoxyribonucleic acid) and overexpressed p16 and HPV-negative (HPV-) otherwise. Cases were designated protein16 (p16+) if they overexpressed p16, protein16-negative (p16-) otherwise.

3.3.4 Statistical Analyses.

Pearson correlation coefficients were estimated between individual components within each DQS and between each summary DQS. Chi-square tests were used to evaluate univariate associations between categorical variables and summary DQS quartiles separately for case and control participants and generalized linear models were used to evaluate univariate associations

between continuous variables and summary DQS quartiles separately for case and control study participants.

Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between each of the three DQSs and incident HNSCC. Associations with individual DQS components were evaluated using two modeling strategies: 1) all DQS components were included in the same model and adjusted for potential confounders and 2) each component was examined in separate models while still adjusting for potential confounders used for the full model adjustment. For MDS and MDS-HNC individual components scores, relative odds for the individual component score analyses was based on "non-adherence" with prevailing dietary recommendations. For example, eating less versus more fruits and eating more versus less processed meat as prescribed in the MDS-HNC was considered non-adherence for the fruit and processed meats components, respectively.

The confounders used for full model adjustment included all matching factors (age in years (20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (White; Black), sex (male; female)) and covariates identified based on the diet and HNSCC literature (BMI, in kilogram per square meter [52] (≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth [34] (yes; no), educational attainment [34, 52] (high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes [2, 15] (0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams [5, 7, 8, 53] (≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day [28, 54] (>0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5)).

Multinomial logistic regression was used to estimate relative odds of HNSCC according to 1) tumor site (oral cavity, pharynx, or larynx) and 2) tumor HPV-status (HPV-positive or

HPV-negative). Controls were the referent group in each analysis. Heterogeneity of effect across tumor sites and tumor HPV-status was evaluated by testing equality of corresponding DQS coefficients with the likelihood ratio test, which compared the model allowing the effects to vary across the outcome categories with the model in which the effects were constrained to be the same across the outcome categories.

BMI, race, tobacco use, and alcohol consumption were explored as potential EMMs. EMM was assessed on the multiplicative scale by the likelihood ratio test (LRT) comparing models with and without product terms. Additive EMM was assessed using the Relative Excess Risk due to Interaction (RERI) estimator [55]. For the purposes of evaluating EMM, dichotomous categorizations of the summary DQS (≤ median summary DQS among controls (poor diet quality) and > median summary DQS among controls (better diet quality)), race (Black, White), BMI (≥ 25 kg/m^2 (high BMI) and < 25 kg/m^2 (low BMI); smoking (never smoker, ever smoker), and alcohol use (never drinker; ever drinker) were used to reduce the imprecision caused by small strata.

3.3.5 Sensitivity Analyses.

Because tobacco use and alcohol consumption are key risk factors for HNSCC, the impact of residual confounding in these risk factors was assessed by restricting models to never smokers and to never drinkers. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The type I error rate was set to 0.05 for all statistical tests.

3.4 Results

A higher proportion of cases compared to controls had a low BMI, history of loose teeth, low educational attainment, history of smoking, high lifetime intake of alcohol, and high daily energy intake. (Table 3-1). Over half of cases in the study sample had tumors of the oral cavity. Among the 423 cases evaluated for tumor HPV-status, 142 were classified as HPV-positive and

189 were classified as p16-positive (Table 3-1). Overall, there was no more than 5.5% missing data among cases and 3% missing data among controls (Table 3-1). Controls had higher mean summary DQSs than did cases for all three DQSs. (Table 3-1, Supplemental Figure 3-1, Supplemental Figure 3-2, Supplemental Figure 3-3).

Pearson correlations between individual components of the HEI-2005 where generally more highly correlated with one another than were individual components of the MDS or the MDS-HNC (Supplemental Table 3-4, Supplemental Table 3-5, Supplemental Table 3-6) As expected, the MDS and MDS-HNC summary scores correlated positively with one another. With respect to the HEI-2005, the MDS-HNC summary score was more highly positively correlated with the HEI-2005 than was the MDS summary score (Supplemental Table 3-7). Univariate associations between demographic variables and summary DQS quartiles and between dietary variables and summary DQS quartiles were observed for all three DQSs. Each summary DQS was found to be positively associated with the summary DQS quartiles of the other two DQSs (Supplemental Table 3-8, Supplemental Table 3-9, Supplemental Table 3-10)

Supplemental Table 3-11, Supplemental Table 3-12, and Supplemental Table 3-13 display associations between incident HNSCC and summary and individual component DQSs. The ORs (CI) represent a unit decrease in the summary DQS of interest. In general, a pattern of elevated ORs for incident HNSCC were associated with decreasing DQSs. For HEI-2005 the OR (CI) was 1.04 (1.02, 1.05). The OR for individual HEI-2005 component scores for whole fruit intake, whole grain intake, fat-derived energy intake, and SoFAAS were 1.11 (1.01, 1.21), 1.12 (1.01, 1.24), 1.07 (1.03, 1.10), and 0.91 (0.85, 0.98), respectively (Supplemental Table 3-11). For summary DQS for MDS, the OR was 1.08 (1.01, 1.14). For individual MDS component scores for fruit intake, and cereals/grain intake the ORs were 1.35 (1.08, 1.68) and 1.22 (1.00,

1.49), respectively (Supplemental Table 3-12). The OR for MDS-HNC summary DQS was 1.08 (1.02, 1.13). The OR (CI) individual MDS-HNC component scores for fruit intake was 1.30 (1.04, 1.62) (Supplemental Table 3-13). When summary DQSs were rescaled to reflect a decrease of one standard deviation in the DQS, the HEI-2005 was associated with 35% greater odds of HSNCC (OR: 1.35 (1.21, 1.50)). Likewise, MDS was associated with 13% greater odds of HSNCC (OR: 1.13 (1.02, 1.25)), and MDS-HNC was associated with 17% greater odds of HSNCC (OR: 1.17 (1.06, 1.31)) (Table 3-2).

For all three DQSs the inverse association between DQS and incident HNSCC persisted across all tumor sites (Table 3-2) and regardless of tumor HPV positivity (Table 3-3). For tumor sites, the test for heterogeneity suggested that the inverse association did not differ significantly by tumor site (Table 3-2). Similarly, tests for heterogeneity also suggested that associations between DQS scores and HNSCC incidence did not differ by HPV tumor status, regardless of how tumor status was specified (p16+/- or HPV +/-) (Table 3-3).

We observed multiplicative EMM of the diet quality-incident HNSCC association by BMI (LRT p-value < .05), but only for the HEI-2005 (Supplemental Figure 4). For individuals with BMI ≥ 25, having a summary HEI-2005 DQS ≤ 51 resulted in incident HNSCC odds 1.74 times those of individuals with a summary HEI-2005 DQS > 51 (OR (CI): 1.74 (1.36, 2.23)). This same summary HEI-2005 DQS contrast among those with a BMI < 25 was 2.64 (1.92, 3.65). Graphical representations of the exploration of multiplicative EMM are presented in Supplemental Figures 4-6. We did not observe EMM on the multiplicative scale by race, smoking, or alcohol use for any of the DQSs (LRT p-values > 0.05) (Supplemental Figure 3-4, Supplemental Figure 3-5, Supplemental Figure 3-6).

Supplemental Figure 3-7, Supplemental Figure 3-8, Supplemental Figure 3-9, and Supplemental Figure 3-10 illustrate that, on the additive scale, BMI modified the association between diet quality and HNSCC risk and did so for all three DQSs. The RERI (CI) between BMI and the HEI-2005, BMI and the MDS, and BMI and the MDS-HNC were (RERI: 0.87 (0.27, 1.48)), (RERI: 0.53 (0.06, 1.00)), and (RERI: 0.57 (0.04, 1.10)), respectively (Supplemental Figure 3-7). Alcohol use also modified the association between diet quality and HNSCC on the additive scale, but only for the HEI-2005 and MDS-HNC. The alcohol use RERI (CIs) estimates for the HEI-2005 and MDS-HNC were 1.61 (0.65, 2.56) and 1.33 (0.61, 2.05), respectively (Supplemental Figure 3-10).

Supplemental Table 3-14, Supplemental Table 3-15, Supplemental Table 3-16display results from the exploration of residual confounding by smoking and alcohol consumption using restriction methods. For all three DQSs, models restricted to never-smokers and never-users of alcohol resulted in diet quality-HNSCC risk associations further from the null than corresponding associations observed in models in which smokers and alcohol users were included. For example, the odds ratio for the diet-quality-HNSCC risk association for a one standard-deviation decrease in the HEI-2005 summary DQS that was estimated from the model which was restricted to never-smokers and never-drinkers was 1.70 (95% CI: 1.09, 2.64) ("Model4", Supplemental Table 3-14). In contrast, the model which included both never- and ever-smokers as well as never- and ever-drinkers resulted in a diet quality-HNSCC risk odds ratio of 1.35 (95% CI: 1.21, 1.50) ("Model1", Supplemental Table 3-14). Similar patterns were observed between corresponding models for the MDS (Supplemental Table 3-15) and MDS-HNC (Supplemental Table 3-16).

3.5 Discussion

Our finding that diet quality was inversely associated with HNSCC incidence agrees with the other studies of overall diet and HNSCC incidence, regardless of whether the studies [29–33] used *a priori* diet quality scores as we did, or an *a posteriori* characterization of dietary patterns as was previously done using CHANCE data [28]. The pooled analysis of 22 case-control studies of diet and head and neck cancer conducted by the INHANCE consortium identified inverse associations with HNSCC incidence for fruit and vegetable intake and positive associations with HNSCC incidence for red and processed meat intake [25]. Our findings agree with this pooled analysis as increased intakes of fruits and vegetables and decreased intakes of red and processed meats resulted in higher summary scores for all the DQSs we studied.

Dietary micronutrients, especially antioxidants found in fruits and vegetables can neutralize many of the carcinogenic tobacco and alcohol by-products [9, 10, 56–62]. It follows that fruit and vegetable intakes would be inversely associated with smoking- and alcohol-related HNSCC. Indeed, we observed additive EMM by alcohol use suggesting that poor diet and alcohol use amplify the risk of HNSCC in a super-additive fashion.

Meyer observed an inverse association with total fruit and citrus fruit consumption among HPV-seronegative individuals, but positively associated among HPV-seropositive individuals [63]. Arthur reported that dietary micronutrients are associated with HPV-positivity and suggested that some micronutrients may increase susceptibility to HPV infection [64]. We did not observe difference in the diet quality-HNSCC risk association by tumor HPV-status. This inconsistency may be explained in part by the fact that we had a larger number of HPV-positive cases and that we explored overall diet as opposed to individual nutrients and food groups.

Previous studies which have explored BMI and HNSCC have suggested that BMI may simply be a consequence of the disease process as pathophysiological changes may induce

weight loss [65, 66]. In addition, physical changes in the head and neck region may inhibit consumption of certain foods and calories and consequently result in weight loss [65]. Further, residual confounding by smoking has also been suggested as an explanation for the inverse BMI-HNSCC association as smokers tend to have lower BMIs than non-smokers and smoking is a major risk factor for HNSCC [52]. Taken together, these previous findings regarding BMI and HNSCC suggest that the EMM of the diet-HNSCC association by BMI observed in our data may be spurious.

The strengths of this study include the use of data from a large racially diverse population-based case-control study, the ability to explore heterogeneity by HPV-status and other factors, a validated diet assessment instrument, and the utilization of the *a priori*-approach to characterize diet quality. The high degree of correlation among individual components for all three DQSs as well as the associations between demographic and dietary variables with each DQS further support our choice to study overall diet. Our study was limited by inherent challenges of capturing comprehensive and high-quality data on usual diet through an FFQ administered after diagnosis.

Our findings further support using Mediterranean-style measures of diet quality to study health outcomes. In this American study population, the magnitude of the diet quality-HNSCC risk association for both the MDS and MDS-HNC mapped closely to the HEI-2005, the DQS designed for the American population in mind. This mapping was particularly good for the MDS-HNC. Thus, it appears that the MDS and its derivatives can be used to study diet quality and health outcomes in American study populations, and that the MDS-HNC, in particular, may be especially appropriate for studies of HNSCC in the American population.

A key takeaway from this work is that public health interventions aimed at improving diet quality, particularly those targeting alcohol consumers, have the potential to reduce the incidence of HNSCC.

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

3.6 Tables

Table 3-1. Distribution of Select Variables Among Cases With Head and Neck Squamous Cell Carcinoma and Controls, CHANCE Study, North Carolina, USA, 2002-2006

	Cases		Controls	
Variable	N	%	N	%
CHANCE participants				
Total	1170	100.0	1303	100.0
Age group, years				
20-49	228	19.5	145	11.1
50-54	182	15.6	151	11.6
55-59	191	16.3	200	15.3
60-64	203	17.4	197	15.1
65-69	160	13.7	232	17.8
70-74	131	11.2	220	16.9
75-80	75	6.4	158	12.1
Missing	--	--	--	--
Race				
White	896	76.6	1055	81.0
Black	274	23.4	248	19.0
Missing	--	--	--	--
Sex				
Male	899	76.8	904	69.4
Female	271	23.2	399	30.6
Missing	--	--	--	--
Body Mass Index (kg/m^2)				
≥0, <18.5	37	3.2	11	0.8
≥18.5, <25	478	40.9	438	33.6
≥25, <30	370	31.6	498	38.2
≥30	285	24.4	354	27.2
Missing	0	0.0	2	0.2
History of loose teeth				
Yes	425	36.3	299	22.9
No	742	63.4	1002	76.9
Missing	3	0.3	2	0.2

Education				
High school or less	707	60.4	514	39.4
Some college	288	24.6	385	29.5
College graduation or more	175	15.0	404	31.0
Missing	--	--	--	--
Years smoking cigarettes				
0	157	13.4	498	38.2
1-19	110	9.4	280	21.5
20-39	446	38.1	314	24.1
40+	455	38.9	208	16.0
Missing	2	0.2	3	0.2
Lifetime number of standard alcoholic drinks [a]				
0	111	9.5	274	21.0
>0, ≤416	14	1.2	44	3.4
>416, ≤4,394	126	10.8	314	24.1
>4,394, ≤21,216	239	20.4	317	24.3
>21,216	616	52.6	315	24.2
Missing	64	5.5	39	3.0
Quartile of lifetime alcohol intake, grams				
≥0, ≤5,824	125	10.7	318	24.4
>5,824, ≤61,516	126	10.8	314	24.1
>61,516, ≤297,024	239	20.4	317	24.3
>297,024	616	52.6	315	24.2
Missing	64	5.5	39	3.0
Quartile of energy intake, kcal/day				
>0, ≤1,517.8	142	12.1	326	25.0
>1,517.8, ≤1,909.5	178	15.2	326	25.0
>1,909.5, ≤2,359.5	260	22.2	326	25.0
>2,359.5	590	50.4	325	24.9
Missing	--	--	--	--
Cancer site				
Oral cavity	638	54.5	N/A	N/A
Pharynx	120	10.3	N/A	N/A
Larynx	412	35.2	N/A	N/A

Missing	--	--	N/A	N/A
Tumor HPV-status [b]				
HPV-	291	24.9	N/A	N/A
HPV+	142	12.1	N/A	N/A
Missing	737	63.0	N/A	N/A
Tumor p16-status [c]				
p16-	244	20.9	N/A	N/A
p16+	189	16.2	N/A	N/A
Missing	737	63.0	N/A	N/A

Abbreviations, symbols: CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; N, Counts; %, Percentage; kg/m^2, kilogram per square meter; kcal, kilocalorie; HPV, Human papillomavirus; p16, protein16; N/A, Not applicable; +, positive; -, negative.

[a] Standard alcoholic drinks include 12 fluid ounces (355 milliliters) of beer, 5 fluid ounces (148 milliliters) of wine, or 1.5 fluid ounces (44 milliliters) of distilled spirits.

[b] Cases were designated HPV+ if they were positive for both HPV16 DNA (deoxyribonucleic acid) and p16 expression, and HPV-, otherwise.

[c] Cases were designated p16+ if they were overexpressing p16 protein by immunohistochemistry, and p16-, otherwise.

Notes: To minimize bias from implausible energy intake, study participants with energy intake values less than the 2.5^{th} percentile of energy intake (934.87 kcal/day, N=65) among all study participants and study participants with energy intake values greater than the 97.5^{th} percentile of energy intake (4325.12 kcal/day, N=65) among all study participants were excluded. Study participants reporting a race other than Black or White were excluded (N=46). An additional 136 Study participants were excluded for missing dietary questionnaire data.

Table 3-2. Associations between HNC and HEI-2005, MDS, and MDS-HNC Summary Scores: Overall and Stratified by Site, CHANCE Study, North Carolina, USA, 2002-2006

	Overall		Oral Cavity		Pharynx		Larynx		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	*P* [a]
HEI-2005									
1 SD-unit change (SD=8.0)	1.35	1.21, 1.50	1.26	1.11, 1.42	1.47	1.14, 1.91	1.53	1.30, 1.79	0.0552
MDS									
1 SD-unit change (SD=1.7)	1.13	1.02, 1.25	1.14	1.01, 1.28	1.08	0.86, 1.36	1.14	0.99, 1.32	0.8933
MDS-HNC									
1 SD-unit change (SD=2.2)	1.17	1.06, 1.31	1.16	1.03, 1.31	1.40	1.09, 1.79	1.15	0.99, 1.34	0.3126

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; HEI, Healthy Eating Index; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck Cancer-specific MDS; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; OR, Odds ratio; 95% CI, 95% Confidence interval; SD, standard deviation.

OR represents relative odds of HNC for 1-SD unit decrease in diet quality summary score.

[a] Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across the three tumor sites are equal.

All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

Table 3-3. Associations between HNC and HEI-2005, MDS, and MDS-HNC Summary Scores: Overall and Stratified by Tumor HPV-status and Tumor p16-status, CHANCE Study, North Carolina, USA, 2002-2006

	Overall		HPV-		HPV+			p16-		p16+		
	OR	95% CI	OR	95% CI	OR	95% CI	*P* [a]	OR	95% CI	OR	95% CI	*P* [b]
HEI-2005												
1 SD-unit change (SD=8.0)	1.35	1.21, 1.50	1.43	1.18, 1.72	1.30	1.04, 1.64	0.5147	1.41	1.15, 1.72	1.34	1.09, 1.64	0.7127
MDS												
1 SD-unit change (SD=1.7)	1.13	1.02, 1.25	1.13	0.95, 1.34	1.04	0.84, 1.28	0.5137	1.11	0.93, 1.33	1.08	0.90, 1.31	0.8440
MDS-HNC												
1 SD-unit change (SD=2.2)	1.17	1.06, 1.31	1.25	1.05, 1.49	1.13	0.91, 1.41	0.4564	1.18	0.98, 1.43	1.23	1.01, 1.50	0.7216

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; HEI, Healthy Eating Index; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck Cancer-specific MDS; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HPV, Human papillomavirus; p16, protein-16; +, positive; -, negative; OR, Odds ratio; 95% CI, 95% Confidence interval; SD, standard deviation.

OR represents relative odds of HNC for 1-SD unit decrease in diet quality summary score.

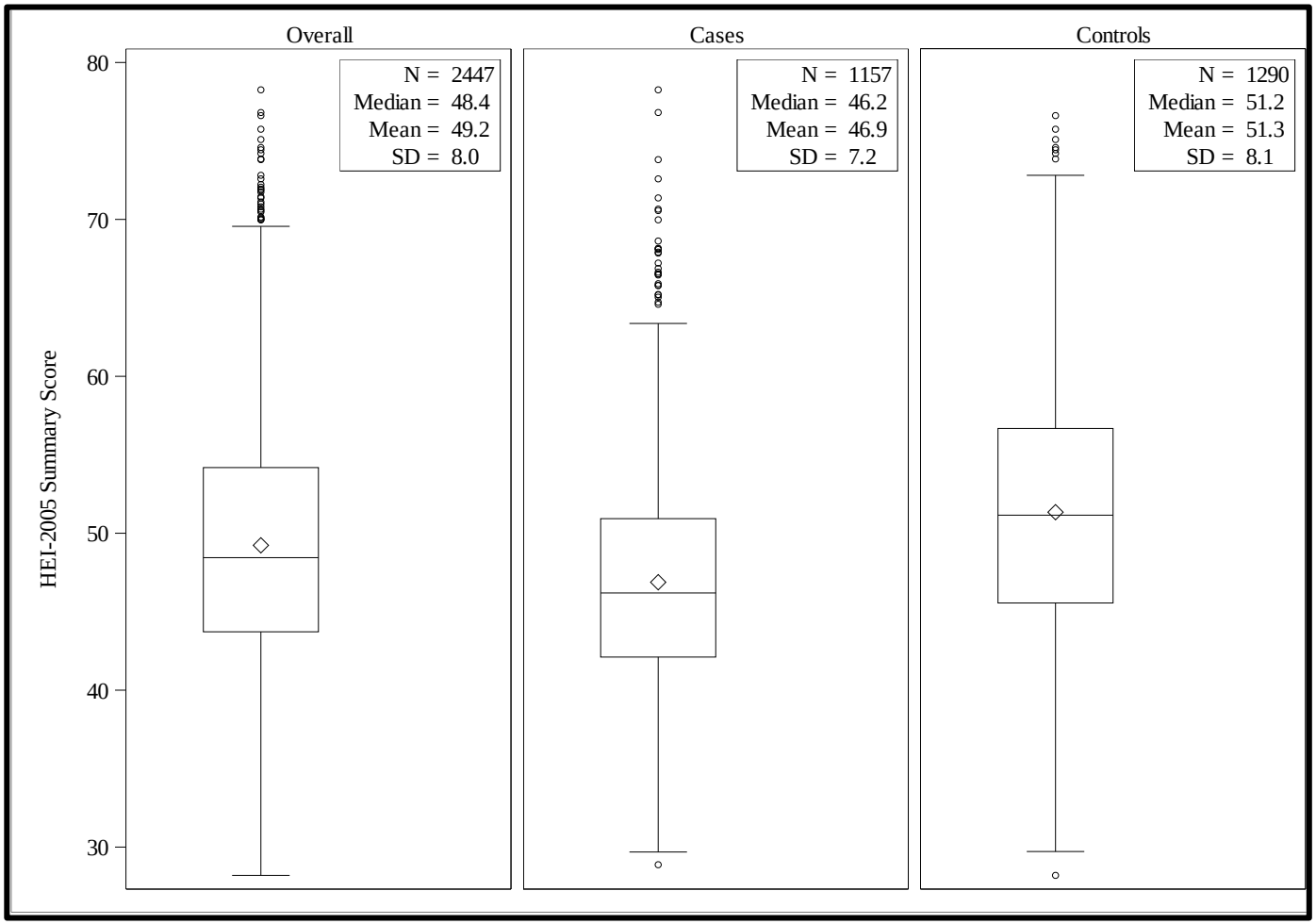
[a] Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across HPV- and HPV+ tumors are equal.

[b] Represents the probability of observing a test statistic as extreme or more extreme than that which was observed given a test of the null hypothesis that estimates for the relative odds of incident HNC across p16- and p16+ tumors are equal.

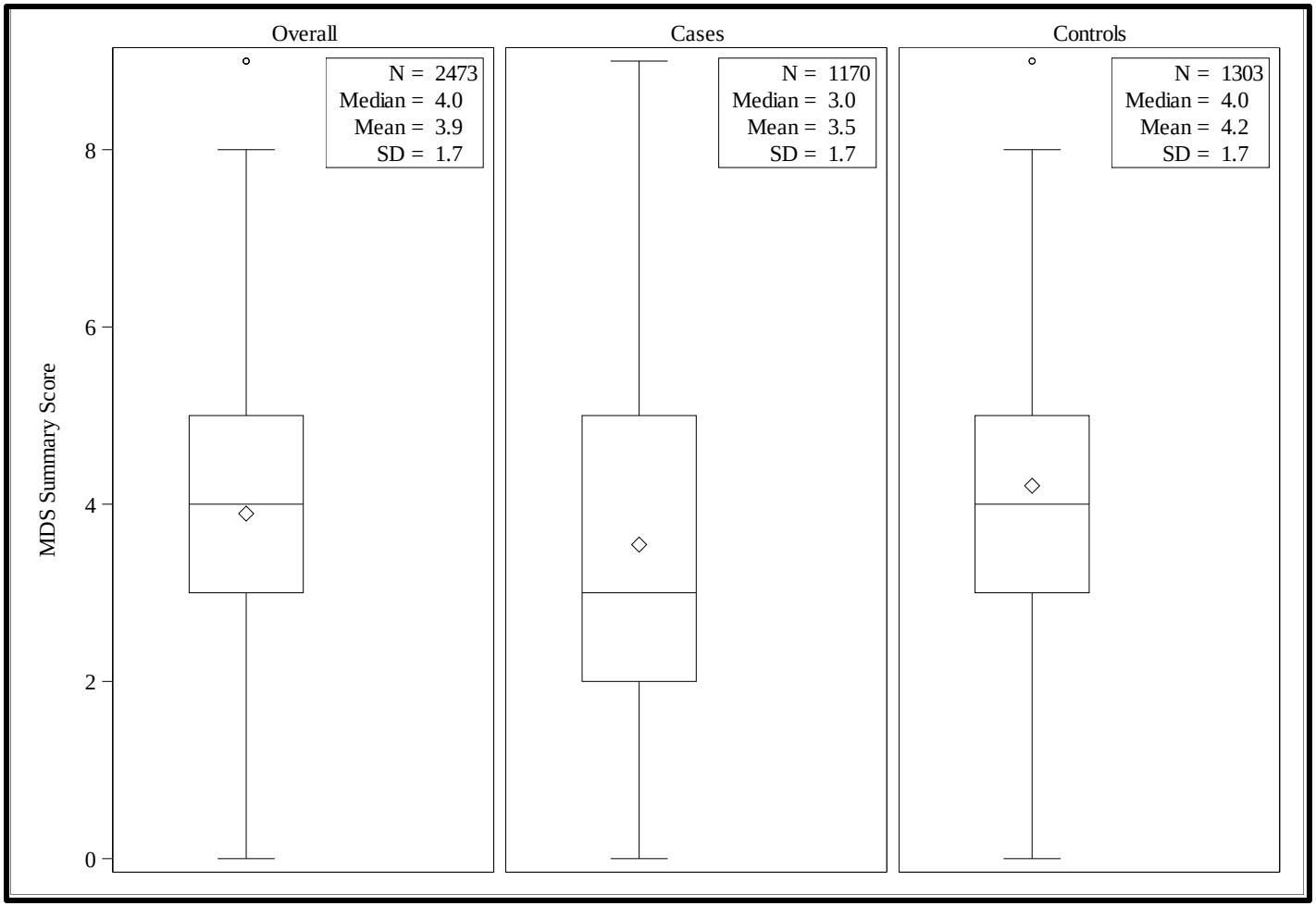
All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

3.7 Supplemental Materials

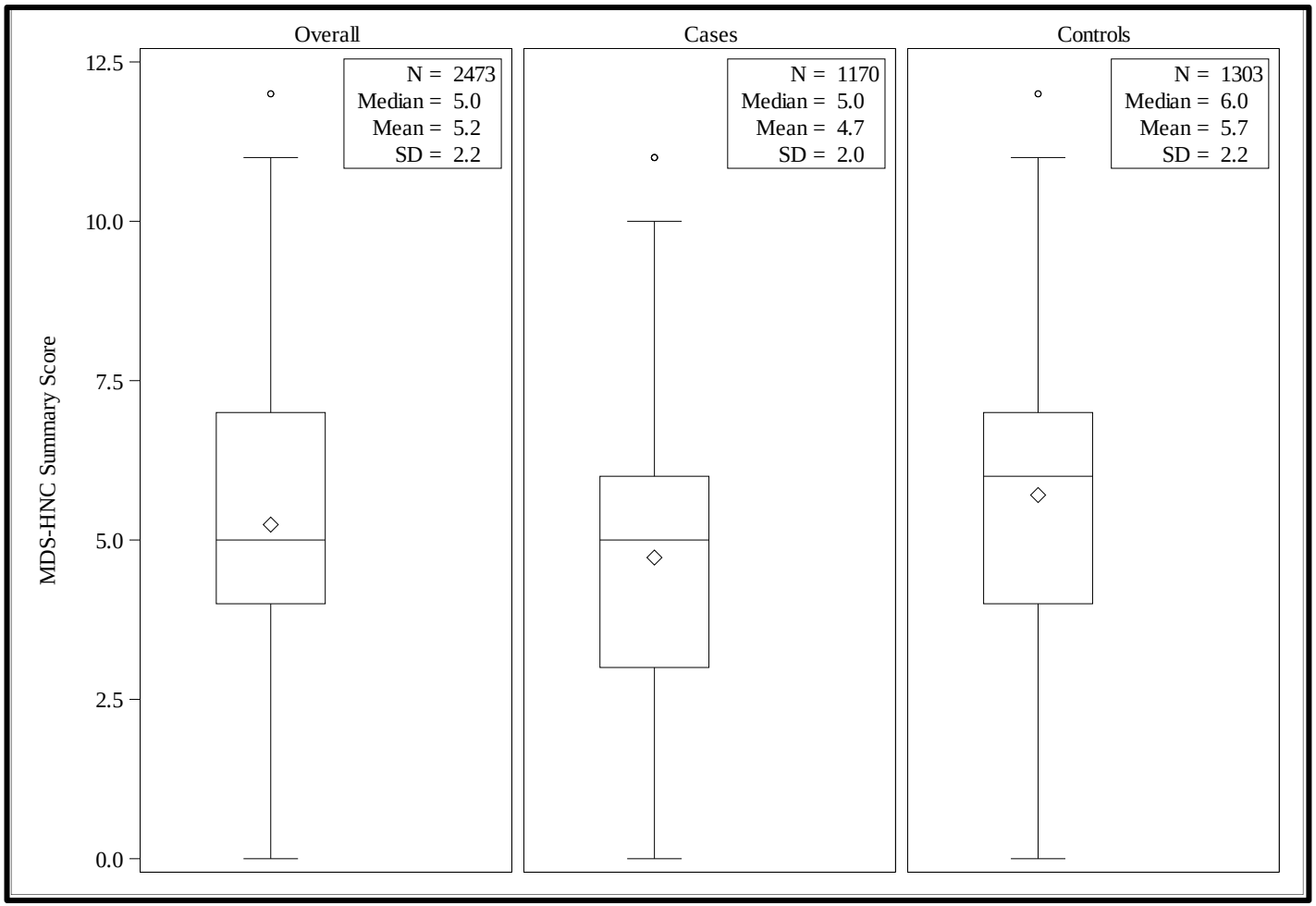
Supplemental Figure 3-1. HEI-2005 Summary Score Distributions: Overall and for Cases and Control, CHANCE, 2002-2006.



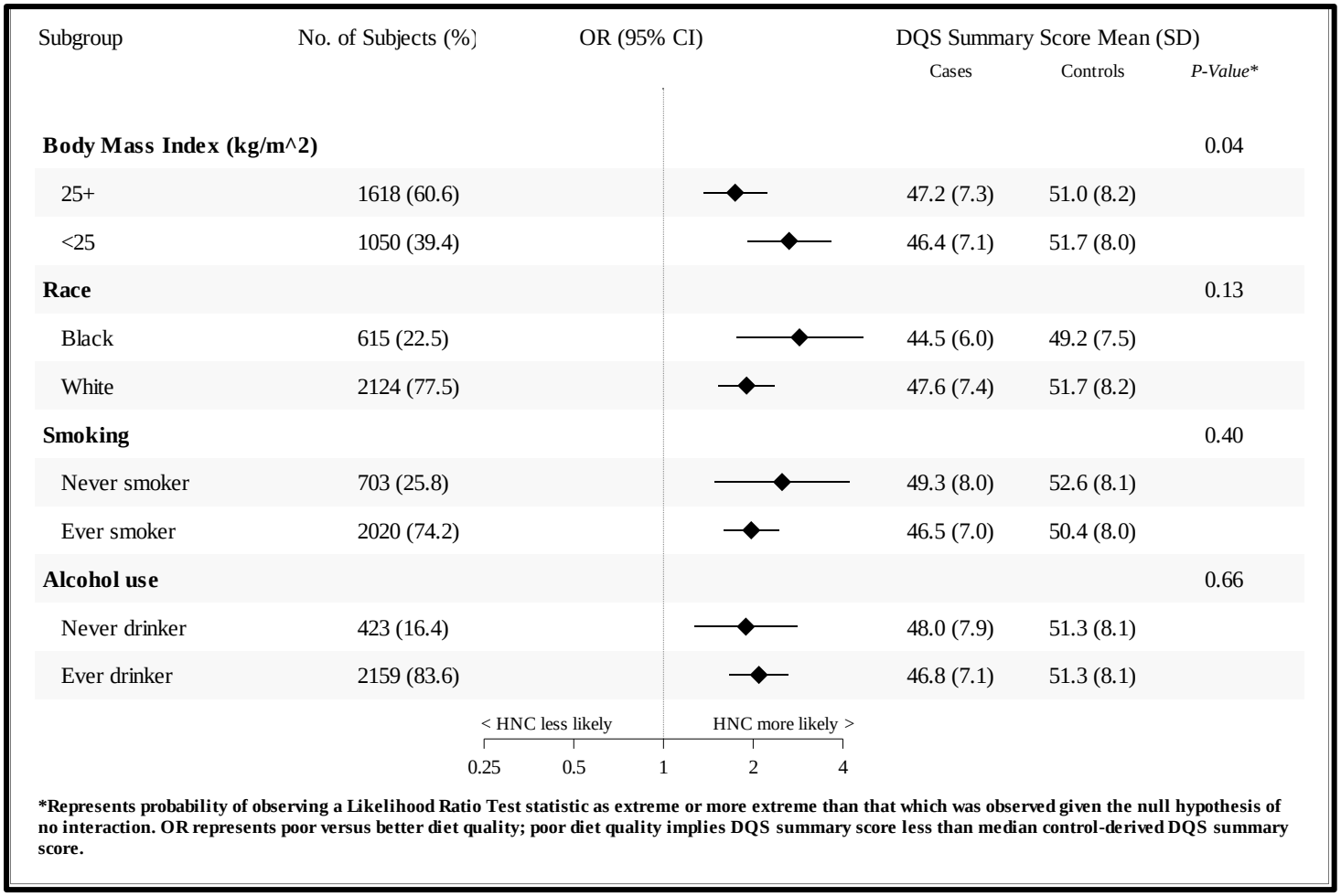
Supplemental Figure 3-2. MDS Summary Score Distributions: Overall and for Cases and Control, CHANCE, 2002-2006.



Supplemental Figure 3-3: MDS-HNC Summary Score Distributions: Overall and for Cases and Control, CHANCE, 2002-2006.



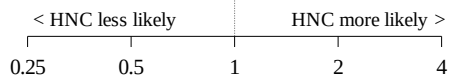
Supplemental Figure 3-4: Graphical Display of the Exploration of Multiplicative EMM by BMI, Race, Smoking, and Alcohol Use for HEI-2005



***Represents probability of observing a Likelihood Ratio Test statistic as extreme or more extreme than that which was observed given the null hypothesis of no interaction. OR represents poor versus better diet quality; poor diet quality implies DQS summary score less than median control-derived DQS summary score.**

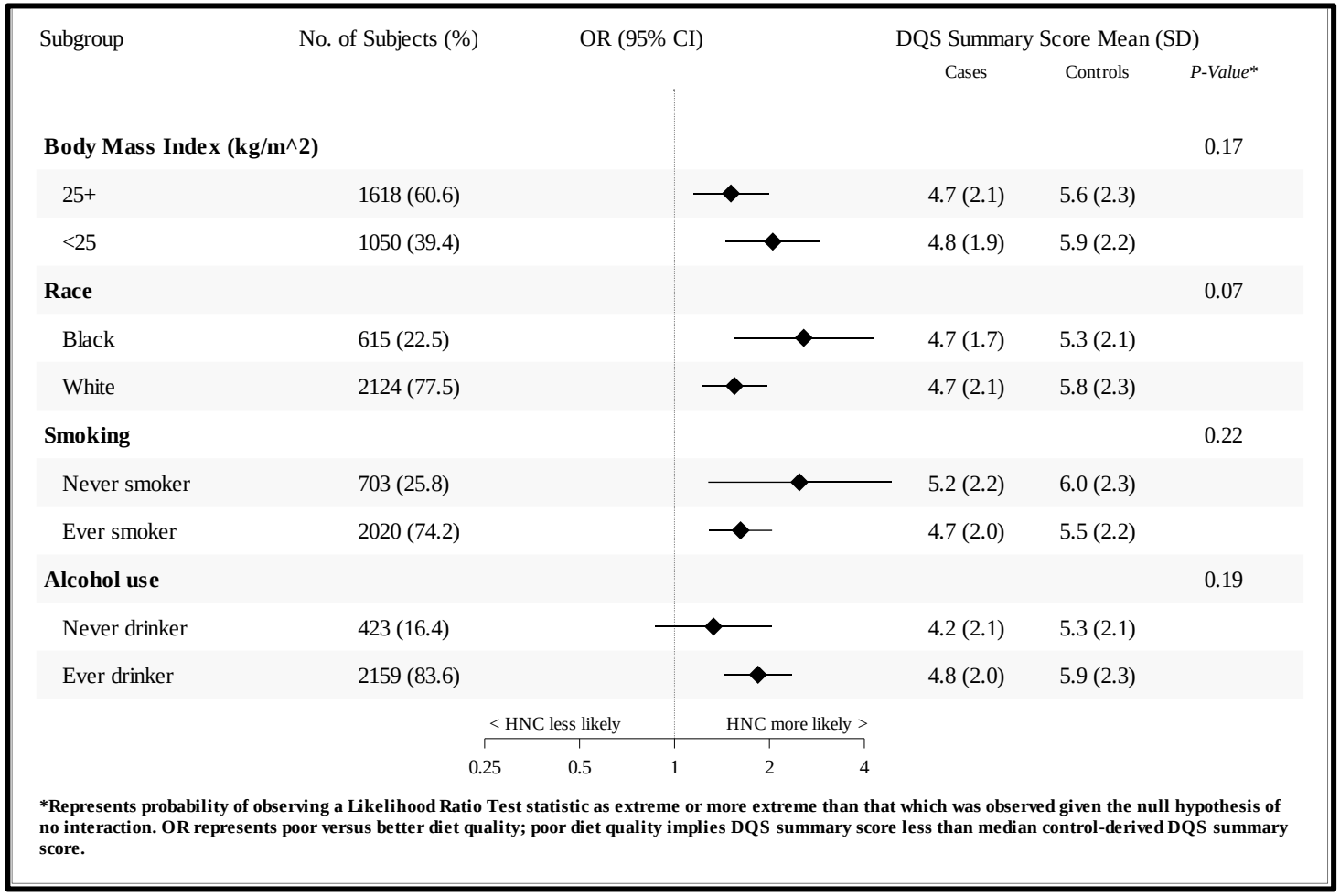
Supplemental Figure 3-5. Graphical Display of the Exploration of Multiplicative EMM by BMI, Race, Smoking, and Alcohol Use for MDS

Subgroup	No. of Subjects (%)	DQS Summary Score Mean (SD) Cases	Controls	*P-Value**
Body Mass Index (kg/m^2)				0.10
25+	1618 (60.6)	3.6 (1.7)	4.1 (1.7)	
<25	1050 (39.4)	3.4 (1.6)	4.4 (1.6)	
Race				0.11
Black	615 (22.5)	3.6 (1.6)	4.2 (1.6)	
White	2124 (77.5)	3.5 (1.7)	4.2 (1.7)	
Smoking				0.17
Never smoker	703 (25.8)	3.8 (1.9)	4.4 (1.7)	
Ever smoker	2020 (74.2)	3.5 (1.6)	4.1 (1.6)	
Alcohol use				0.65
Never drinker	423 (16.4)	3.4 (1.7)	4.1 (1.6)	
Ever drinker	2159 (83.6)	3.5 (1.6)	4.2 (1.7)	



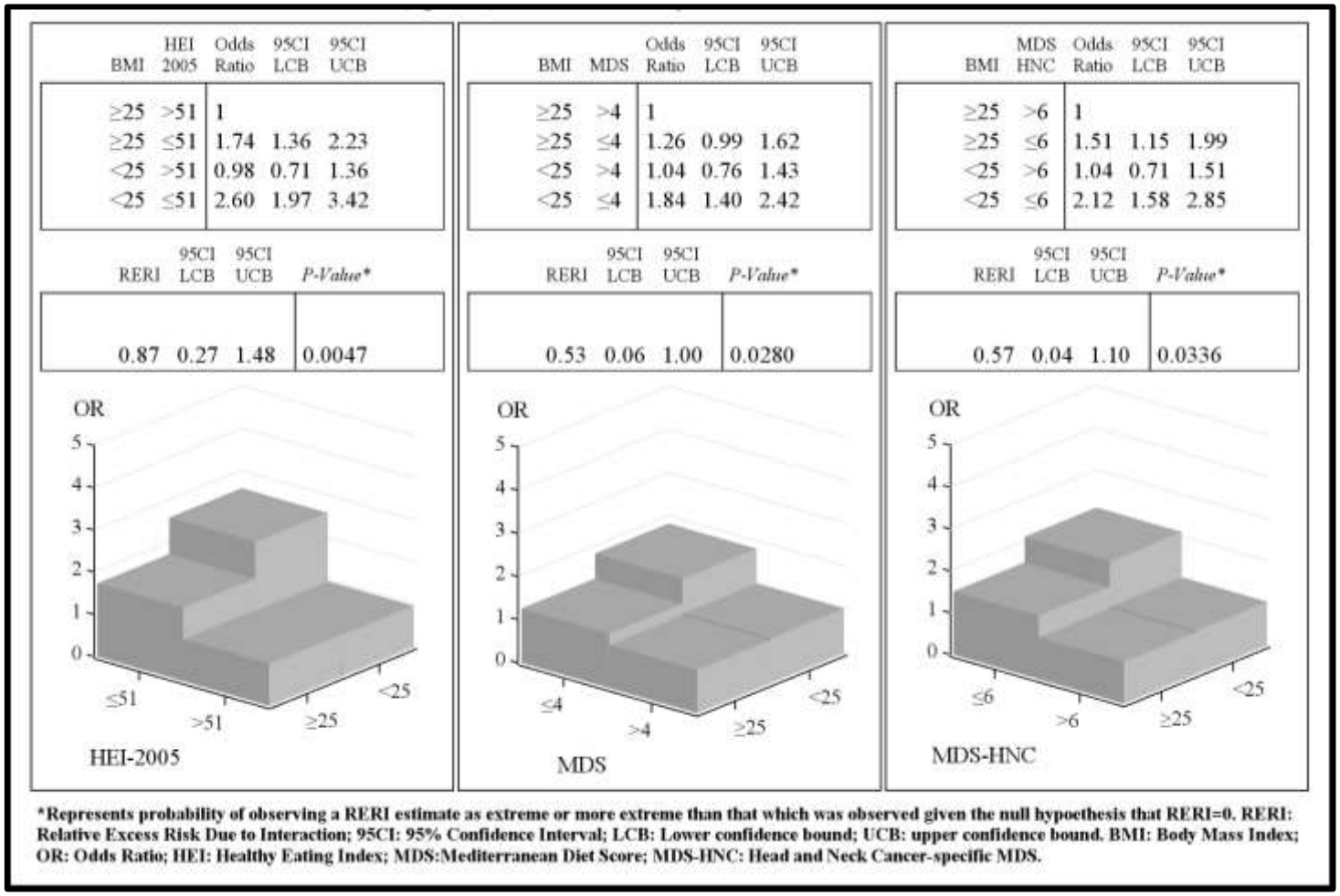
***Represents probability of observing a Likelihood Ratio Test statistic as extreme or more extreme than that which was observed given the null hypothesis of no interaction. OR represents poor versus better diet quality; poor diet quality implies DQS summary score less than median control-derived DQS summary score.**

Supplemental Figure 3-6. Graphical Display of the Exploration of Multiplicative EMM by BMI, Race, Smoking, and Alcohol Use for MDS-HNC



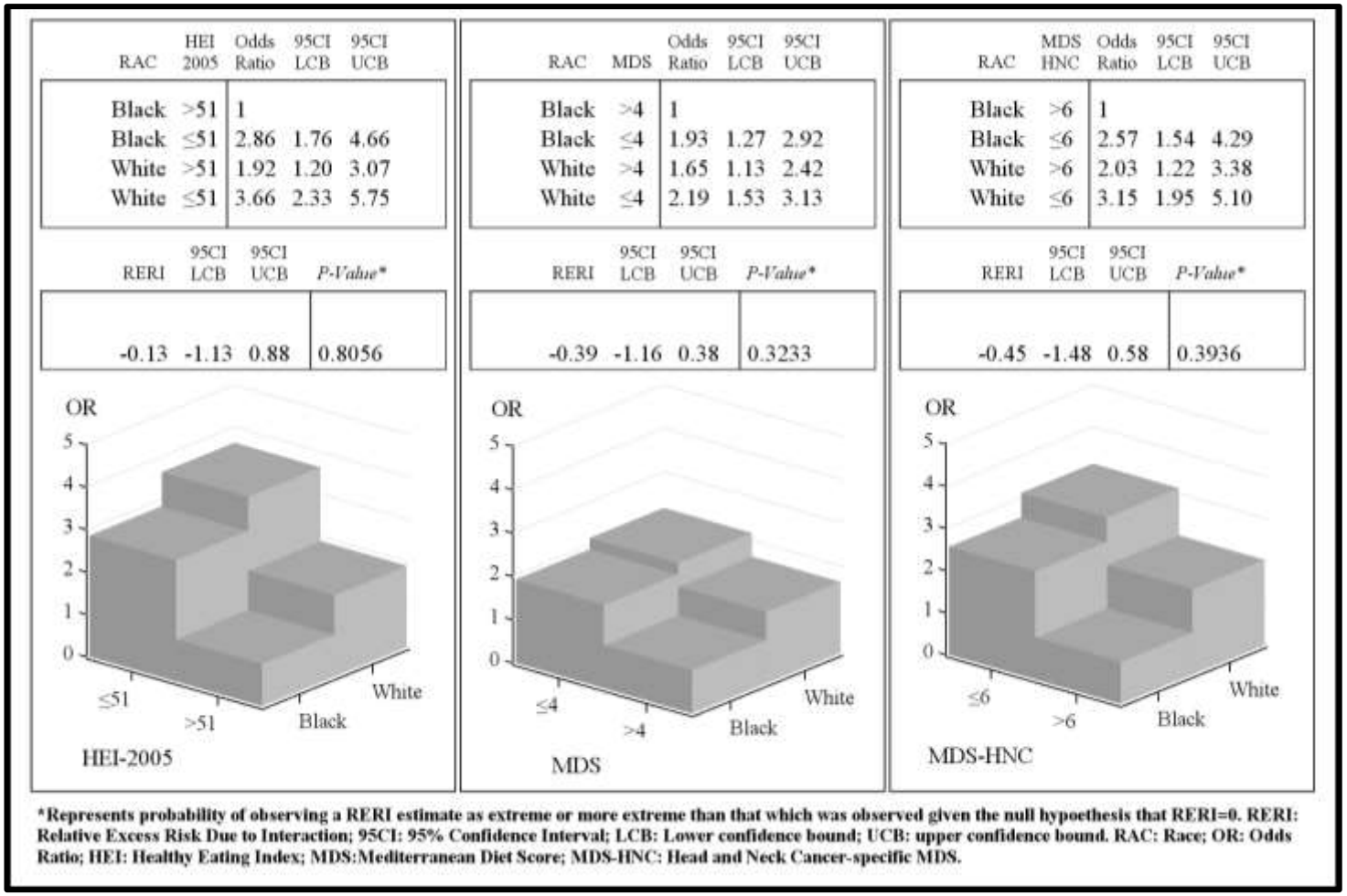
***Represents probability of observing a Likelihood Ratio Test statistic as extreme or more extreme than that which was observed given the null hypothesis of no interaction. OR represents poor versus better diet quality; poor diet quality implies DQS summary score less than median control-derived DQS summary score.**

Supplemental Figure 3-7. Graphical Display of the Exploration of Additive EMM by BMI (kg/m^2), CHANCE Study, NC, USA, 2002-2006.



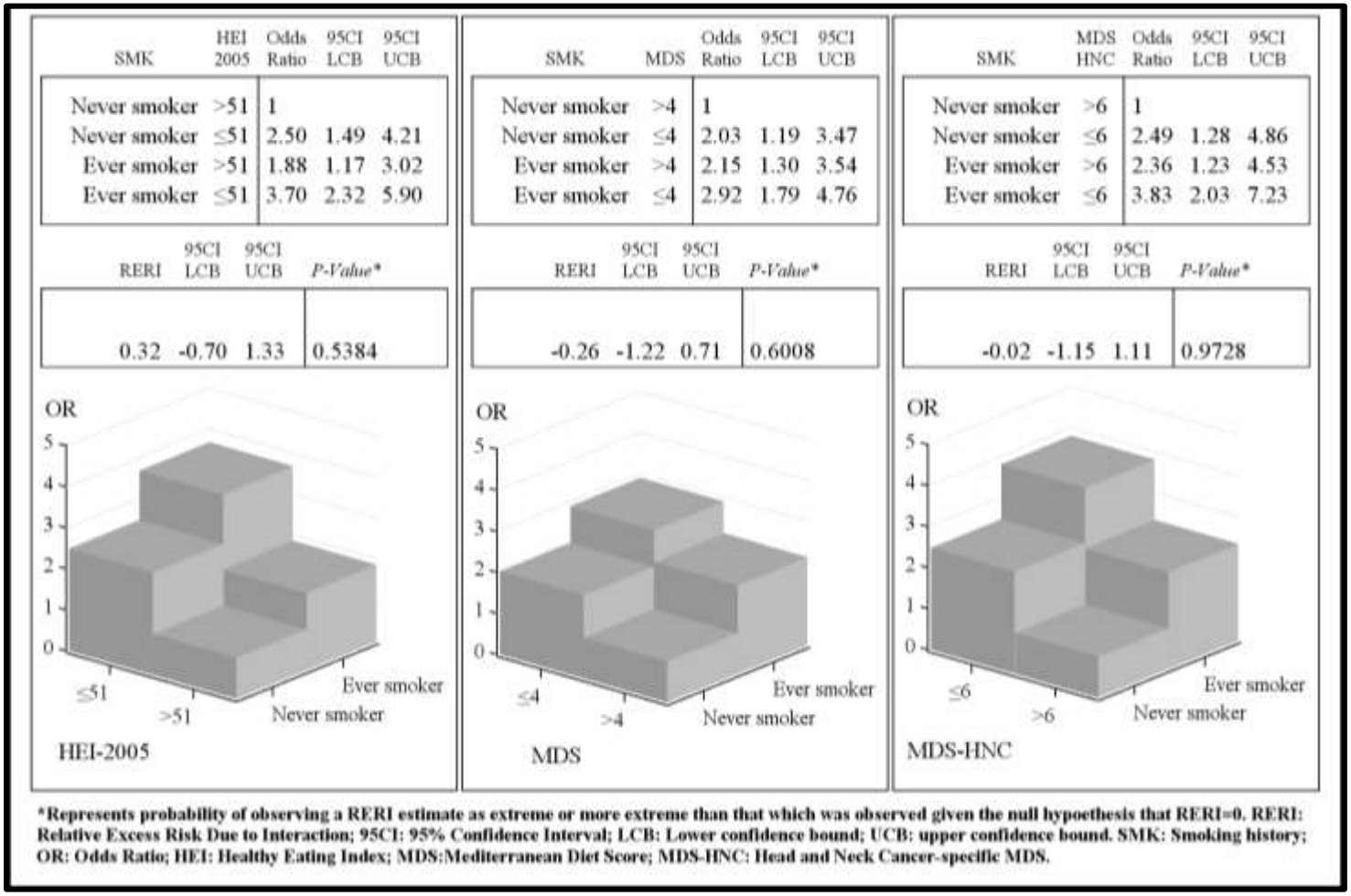
*Represents probability of observing a RERI estimate as extreme or more extreme than that which was observed given the null hypoethesis that RERI=0. RERI: Relative Excess Risk Due to Interaction; 95CI: 95% Confidence Interval; LCB: Lower confidence bound; UCB: upper confidence bound. BMI: Body Mass Index; OR: Odds Ratio; HEI: Healthy Eating Index; MDS:Mediterranean Diet Score; MDS-HNC: Head and Neck Cancer-specific MDS.

Supplemental Figure 3-8. Graphical Display of the Exploration of Additive EMM by Race, CHANCE Study, NC, USA, 2002-2006.



*Represents probability of observing a RERI estimate as extreme or more extreme than that which was observed given the null hypoethesis that RERI=0. RERI: Relative Excess Risk Due to Interaction; 95CI: 95% Confidence Interval; LCB: Lower confidence bound; UCB: upper confidence bound. RAC: Race; OR: Odds Ratio; HEI: Healthy Eating Index; MDS:Mediterranean Diet Score; MDS-HNC: Head and Neck Cancer-specific MDS.

Supplemental Figure 3-9. Graphical Display of the Exploration of Additive EMM by Smoking, CHANCE Study, NC, USA, 2002-2006.

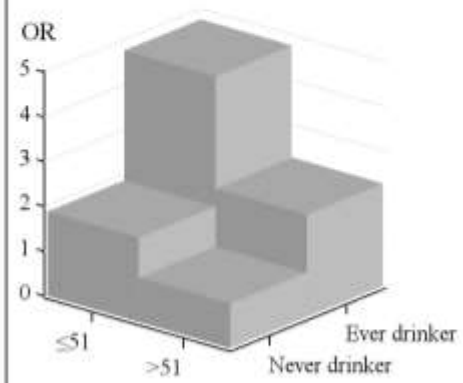


***Represents probability of observing a RERI estimate as extreme or more extreme than that which was observed given the null hypoethesis that RERI=0. RERI: Relative Excess Risk Due to Interaction; 95CI: 95% Confidence Interval; LCB: Lower confidence bound; UCB: upper confidence bound. SMK: Smoking history; OR: Odds Ratio; HEI: Healthy Eating Index; MDS:Mediterranean Diet Score; MDS-HNC: Head and Neck Cancer-specific MDS.**

Supplemental Figure 3-10. Graphical Display of the Exploration of Additive EMM by Alcohol Use, CHANCE Study, NC, USA, 2002-2006.

ALC	HEI 2005	Odds Ratio	95CI LCB	95CI UCB
Never drinker	>51	1		
Never drinker	≤51	1.89	1.27	2.81
Ever drinker	>51	2.29	1.60	3.28
Ever drinker	≤51	4.79	3.41	6.72

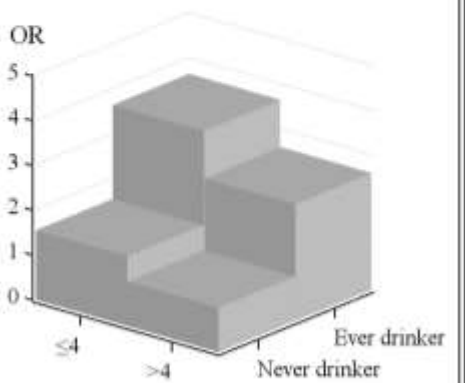
RERI	95CI LCB	95CI UCB	*P-Value**
1.61	0.65	2.56	0.0010



HEI-2005

ALC	MDS	Odds Ratio	95CI LCB	95CI UCB
Never drinker	>4	1		
Never drinker	≤4	1.56	1.04	2.32
Ever drinker	>4	2.61	1.81	3.77
Ever drinker	≤4	3.66	2.59	5.17

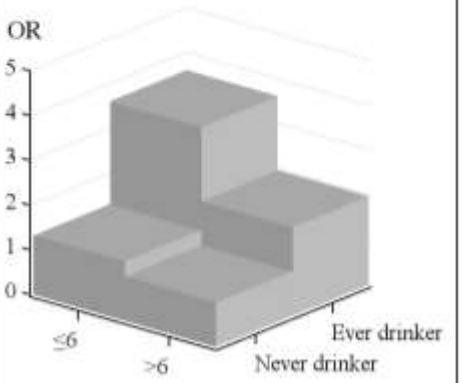
RERI	95CI LCB	95CI UCB	*P-Value**
0.49	-0.30	1.28	0.2217



MDS

ALC	MDS HNC	Odds Ratio	95CI LCB	95CI UCB
Never drinker	>6	1		
Never drinker	≤6	1.33	0.87	2.03
Ever drinker	>6	1.98	1.31	2.97
Ever drinker	≤6	3.63	2.49	5.30

RERI	95CI LCB	95CI UCB	*P-Value**
1.33	0.61	2.05	0.0003



MDS-HNC

***Represents probability of observing a RERI estimate as extreme or more extreme than that which was observed given the null hypoethesis that RERI=0. RERI: Relative Excess Risk Due to Interaction; 95CI: 95% Confidence Interval; LCB: Lower confidence bound; UCB: upper confidence bound. ALC: Alcohol Use history; OR: Odds Ratio; HEI: Healthy Eating Index; MDS:Mediterranean Diet Score; MDS-HNC: Head and Neck Cancer-specific MDS.**

Supplemental Table 3-1. Score Enumeration for HEI-2005

Component	Standard for Maximum Score	Standard for Minimum Score	Maximum Points [i]
Adequacy			
Total fruit [a]	≥0.8 cup equivalent per 1,000 kcal	No fruit	5
Whole fruit [b]	≥0.4 cup equivalent per 1,000 kcal	No whole fruit	5
Total vegetables [c]	≥1.1 cup equivalents	No vegetables	5
Dark green and orange vegetables and legumes [c]	≥0.4 cup equivalent per 1,000 kcal	No Dark green or orange vegetables or legumes	5
Total grains	≥3.0-ounce equivalents per 1,000 kcal	No grains	5
Whole grains	≥1.5-ounce equivalents per 1,000 kcal	No Whole grains	5
Milk [d]	≥1.3 cup equivalents per 1,000 kcal	No Milk	10
Meat and beans [e]	≥2.5-ounce equivalents per 1,000 kcal	No Meat or beans	10
Oils [f]	≥12 grams per 1,000 kcal	No oil	10
Moderation			
Saturated fats [g]	≤7% of energy	≥15% of energy	10
Sodium [g]	≤0.7 grams per 1,000 kcal	≥2.0 grams per 1,000 kcal	10
Calories from SoFAAS [h]	≤20% of energy	≥50% of energy	20
Total	--	--	100

Abbreviations: HEI-2005, Healthy Eating Index 2005; kcal, kilocalorie.;

[a] Includes fruit juice.

[b] Includes all forms except juice.

[c] Includes any beans and peas (legumes) not counted as Total Protein Foods (Meat and Beans)

[d] Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages

[e] Beans and peas are included here (and not with vegetables) when the Total Protein Foods (Meat and Beans) standard is otherwise not met.

[f] Includes non-hydrogenated vegetable oils and oils in fish, nuts, and seeds.

[g] Saturated Fat and Sodium get a score of 8 for the intake levels that reflect the 2005 Dietary Guidelines: 10% of calories from Saturated Fat and 1.1 grams of Sodium per 1,000 kcal, respectively. Intakes between the standards for scores of 0 and 8 and between 8 and 10 are scored proportionately.

[h] Calories from solid fats, alcoholic beverages, and added sugars.

[i] Intakes between the minimum and maximum standards are scored proportionately, except for Saturated Fat and Sodium.

Supplemental Table 3-2. Score Enumeration for Traditional Mediterranean Diet Score (MDS)

Component	Higher [a]	Lower [b]	Range
Fruits	x		0,1
Vegetables	x		0,1
Cereals/grains	x		0,1
Legumes	x		0,1
Fish	x		0,1
MUFA : SFA [c]	x		0,1
Dairy		x	0,1
Meat		x	0,1
Moderate alcohol [d]		x	0,1
Total	--	--	0,9

Abbreviations: MDS, Mediterranean Diet Score; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

[a] Implies that a study participant's energy-adjusted intake must be higher than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.

[b] Implies that a study participant's energy-adjusted intake must be lower than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.

[c] Is the ratio of monosaturated fatty acid intake to saturated fatty acid intake.

[d] Moderate alcohol intake is evaluated differently than the other components. A value of 1 is assigned to men who consume between 10 and 50 grams of ethanol per day and to women who consume between 5 and 25 grams of ethanol per day, otherwise, a score of 0 will be assigned.

Notes: The location of the "x" for a given component of the Mediterranean diet score suggests which criterion must be satisfied for a study participant to attain the maximum score. For example, for fruits, the "x" is located under the column labeled "Higher" which suggests that study participants with energy-adjusted fruit intake above his or her corresponding median sex-specific energy-adjusted fruit intake for the reference population would be assigned a score of 1, and 0 otherwise. Energy adjusted intake implies Intakes will be calculated as servings or grams per 1000 kcals of energy intake.

Supplemental Table 3-3.Comparison between Traditional Mediterranean Diet Score (MDS) and Proposed HNC-specific Mediterranean Diet Score (MDS-HNC)

Traditional MDS		Proposed HNC-specific MDS	
Component	Criterion for Adherence	Component	Criterion for Adherence
Fruits	H	Fruits	H
Vegetables	H	Vegetables	H
Cereals/grains	H	Caffeinated coffee	H
Legumes	H	Legumes	H
Fish	H	Fish	H
MUFA : SFA	H	Poultry	H
Dairy	L	Red meat	L
Meat	L	Processed meat	L
Alcohol	M	Eggs	L
		Potatoes	L
		Discretionary fat	L
		Alcohol	M

Abbreviations: HNC, Head and Neck Cancer; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; H, Higher; L, lower; M, Moderate; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

Notes: Higher implies that a study participant's energy-adjusted intake must be higher than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.; Lower implies that a study participant's energy-adjusted intake must be lower than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component. Moderate alcohol intake: A value of 1 is assigned to men who consume between 10 and 50 grams of ethanol per day and to women who consume between 5 and 25 grams of ethanol per day, otherwise, a score of 0 will be assigned. Intakes will be calculated as servings or grams per 1000 kcals of energy intake

Supplemental Table 3-4. Pearson Correlation Coefficients Among Individual Components of the HEI-2005 Diet Quality Score, CHANCE Study, North Carolina, USA, 2002-2006

HEI-2005 Individual Component	TF	WF	TV	CV	TG	WG	MK	MB	OL	EF	NA	SF
Total Fruit (TF)												
Whole Fruit (WF)	0.81											
Total Vegetables (TV)	0.32	0.23										
Colored Vegetables (CV)	0.31	0.32	0.56									
Total Grains (TG)	0.07	0.10	0.11	0.11								
Whole Grains (WG)	0.24	0.26	0.16	0.25	0.53							
Milk Products (MK)	0.07	0.08	-0.06	0.00	-0.05	0.01						
Meat, Beans, Legumes (MB)	-0.11	-0.10	0.14	0.09	0.03	-0.05	-0.15					
Oils (OL)	-0.01	-0.01	0.14	0.06	0.15	0.05	0.01	0.26				
Energy from Fat (EF)	0.24	0.18	0.02	0.09	0.07	0.17	-0.11	-0.18	-0.11			
Sodium (NA)	-0.18	-0.14	-0.44	-0.38	-0.44	-0.30	0.01	-0.29	-0.16	0.22		
SoFAAS (SF)	0.35	0.34	0.24	0.35	0.26	0.37	0.17	-0.07	-0.02	0.29	-0.33	

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; SoFAAS, calories from solid fats, alcohol, and added sugars.

Supplemental Table 3-5. Pearson Correlation Coefficients Among Individual Components of The MDS Diet Quality Score, CHANCE Study, North Carolina, USA, 2002-2006

MDS Individual Component	FR	VE	CE	LE	FI	MS	DA	ME	AL
Fruits (FR)									
Vegetables (VE)	0.42								
Cereals/grains (CE)	0.03	0.02							
Legumes (LE)	-0.01	0.09	0.04						
Fish (FI)	0.17	0.23	0.01	0.08					
MUFA:SFA Ratio (MS)	0.05	0.05	0.08	0.07	0.06				
Dairy (DA)	-0.02	-0.02	0.03	0.02	0.02	0.21			
Meat Intake (ME)	0.07	-0.03	0.06	0.02	-0.09	0.00	-0.11		
Alcohol (AL)	-0.00	0.03	-0.10	-0.03	0.10	-0.03	-0.02	-0.02	

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; MDS, Mediterranean Diet Score; MUFA:SFA, monounsaturated fatty acid to saturated fatty acid ratio.

Supplemental Table 3-6. Pearson Correlation Coefficients Among Individual Components of the MDS-HNC Diet Quality Score, CHANCE Study, North Carolina, USA, 2002-2006

MDS-HNC Individual Component	FR	VE	CO	LE	FI	PL	RM	PM	EG	PT	DF	AL
Fruits (FR)												
Vegetables (VE)	0.42											
Coffee (CO)	0.09	0.10										
Legumes (LE)	-0.01	0.09	-0.02									
Fish (FI)	0.17	0.23	0.06	0.08								
Poultry (PL)	0.10	0.18	0.07	-0.04	0.20							
Red Meat (RM)	0.09	-0.01	-0.06	0.03	-0.04	-0.23						
Processed Meat (PM)	0.14	0.05	-0.03	0.02	0.01	-0.15	0.47					
Eggs (EG)	0.05	0.02	0.05	-0.02	-0.02	0.02	-0.00	0.15				
Potatoes (PT)	0.11	0.00	0.02	-0.02	0.04	0.03	0.10	0.06	0.01			
Discretionary Fat (DF)	0.26	0.18	0.06	-0.04	0.07	0.07	0.10	0.22	0.22	0.09		
Alcohol (AL)	-0.00	0.03	0.04	-0.03	0.10	0.02	-0.02	0.02	0.03	0.02	0.05	

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; USA, United States of America.

Supplemental Table 3-7. Pearson Correlation Coefficients Between the HEI-2005, MDS, and MDS-HNC Summary Scores, CHANCE Study, North Carolina, USA, 2002-2006

Diet Quality Score	HEI-2005	MDS	MDS-HNC
HEI-2005			
MDS	0.45		
MDS-HNC	0.60	0.65	

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score.

Supplemental Table 3-8. Distribution of Demographic and Dietary Variables Stratified by HEI-2005 Summary Score quartile, CHANCE Study, North Carolina, USA, 2002-2006

	Cases					Controls				
	Q1	Q2	Q3	Q4	*P* [a]	Q1	Q2	Q3	Q4	*P* [b]
Counts, (N)	533	343	175	106		322	323	322	323	
Categorical variables, N (%)										
Age category (years)										
> 60	207 (36.4)	162 (44.6)	95 (50.8)	75 (67.6)		177 (51.9)	182 (54.2)	210 (63.1)	225 (67.8)	
≤ 60	362 (63.6)	201 (55.4)	92 (49.2)	36 (32.4)	<.0001	164 (48.1)	154 (45.8)	123 (36.9)	107 (32.2)	<.0001
Race										
White	406 (71.4)	268 (73.8)	153 (81.8)	106 (95.5)		260 (76.2)	259 (77.1)	272 (81.7)	294 (88.6)	
Black	163 (28.6)	95 (26.2)	34 (18.2)	5 (4.5)	<.0001	81 (23.8)	77 (22.9)	61 (18.3)	38 (11.4)	0.0001
Sex										
Male	460 (80.8)	267 (73.6)	140 (74.9)	72 (64.9)		246 (72.1)	246 (73.2)	235 (70.6)	203 (61.1)	
Female	109 (19.2)	96 (26.4)	47 (25.1)	39 (35.1)	0.0010	95 (27.9)	90 (26.8)	98 (29.4)	129 (38.9)	0.0025
Educational attainment										
High school or less	396 (69.6)	223 (61.4)	95 (50.8)	42 (37.8)		177 (51.9)	142 (42.3)	118 (35.4)	96 (28.9)	
Some graduation or more	109 (19.2)	93 (25.6)	55 (29.4)	40 (36.0)		85 (24.9)	101 (30.1)	104 (31.2)	111 (33.4)	
College graduation or more	64 (11.2)	47 (12.9)	37 (19.8)	29 (26.1)	<.0001	79 (23.2)	93 (27.7)	111 (33.3)	125 (37.7)	<.0001
History of loose teeth										

Yes	225 (39.5)	132 (36.4)	65 (34.8)	26 (23.4)		96 (28.2)	89 (26.5)	59 (17.7)	62 (18.7)	
No	343 (60.3)	231 (63.6)	121 (64.7)	85 (76.6)		245 (71.8)	245 (72.9)	274 (82.3)	270 (81.3)	
Missing	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0.0407	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0.0010
Smoking history										
Ever smoker	512 (90.0)	320 (88.2)	148 (79.1)	84 (75.7)		240 (70.4)	215 (64.0)	200 (60.1)	171 (51.5)	
Never smoker	57 (10.0)	43 (11.8)	38 (20.3)	26 (23.4)		99 (29.0)	121 (36.0)	132 (39.6)	161 (48.5)	
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.9)	<.0001	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	<.0001
Alcohol use history										
Ever drinker	495 (87.0)	307 (84.6)	159 (85.0)	91 (82.0)		252 (73.9)	262 (78.0)	249 (74.8)	253 (76.2)	
Never drinker	47 (8.3)	37 (10.2)	19 (10.2)	14 (12.6)		74 (21.7)	65 (19.3)	71 (21.3)	75 (22.6)	
Missing	27 (4.7)	19 (5.2)	9 (4.8)	6 (5.4)	0.8299	15 (4.4)	9 (2.7)	13 (3.9)	4 (1.2)	0.2389
Continuous variables, mean (SD)										
Diet Quality Summary Score										
HEI-2005	41.0 (3.5)	48.0 (1.6)	53.6 (1.6)	61.7 (4.6)	<.0001	41.3 (3.5)	48.4 (1.6)	53.7 (1.5)	61.9 (4.3)	<.0001
MDS	3.0 (1.4)	3.5 (1.5)	4.2 (1.8)	5.1 (1.7)	<.0001	3.2 (1.4)	4.0 (1.6)	4.6 (1.6)	5.1 (1.5)	<.0001
MDS-HNC	3.9 (1.6)	4.8 (1.7)	5.9 (1.8)	7.2 (1.9)	<.0001	4.0 (1.8)	5.1 (1.8)	6.2 (1.9)	7.5 (1.8)	<.0001
Fruit										
Total (servings/day)	1.3 (1.0)	2.3 (1.5)	3.3 (2.0)	4.1 (1.6)	<.0001	1.3 (0.9)	2.2 (1.4)	2.9 (1.6)	3.8 (1.7)	<.0001

Citrus (servings/day)	0.5 (0.4)	0.8 (0.6)	1.0 (0.6)	1.2 (0.6)	<.0001	0.5 (0.4)	0.8 (0.5)	1.0 (0.6)	1.2 (0.6)	<.0001
Vegetables										
Total (servings/day)	2.3 (1.2)	2.5 (1.2)	2.7 (1.7)	2.6 (1.0)	0.0001	1.9 (1.0)	2.2 (1.0)	2.2 (0.9)	2.2 (0.9)	<.0001
Green (servings/day)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	<.0001	0.1 (0.1)	0.1 (0.2)	0.2 (0.2)	0.3 (0.2)	<.0001
Yellow (servings/day)	0.1 (0.1)	0.2 (0.1)	0.2 (0.3)	0.3 (0.2)	<.0001	0.1 (0.1)	0.2 (0.1)	0.2 (0.2)	0.3 (0.2)	<.0001
Starchy (servings/day)	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.0397	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0457
Tomatoes (servings/day)	0.3 (0.3)	0.5 (0.4)	0.6 (0.5)	0.7 (0.3)	<.0001	0.3 (0.3)	0.4 (0.3)	0.5 (0.3)	0.6 (0.3)	<.0001
Potatoes (servings/day)	0.9 (0.7)	0.8 (0.6)	0.8 (0.7)	0.6 (0.4)	<.0001	0.7 (0.6)	0.7 (0.5)	0.6 (0.4)	0.4 (0.3)	<.0001
Pulses										
Legumes [c] (servings/day)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.2 (0.2)	0.5313	0.1 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.0070
Coffee										
Coffee (servings/day)	1.5 (1.7)	1.5 (1.5)	1.4 (1.4)	1.7 (1.4)	0.3357	1.2 (1.4)	1.2 (1.3)	1.2 (1.1)	1.3 (1.3)	0.9228
Caffeine (g/day)	0.2 (0.2)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.5556	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.7720
Grains										
Total (servings/day)	4.9 (2.3)	5.2 (2.2)	4.8 (2.1)	4.7 (2.1)	0.1289	4.2 (2.2)	4.6 (2.0)	4.3 (1.9)	4.4 (1.7)	0.0378
Whole (servings/day)	0.6 (0.6)	0.9 (0.7)	1.0 (0.8)	1.4 (0.9)	<.0001	0.7 (0.6)	0.9 (0.7)	1.0 (0.7)	1.4 (0.8)	<.0001
Cornbread (servings/day)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.0767	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.2308

Dairy										
Total (servings/day)	0.8 (0.9)	0.9 (0.9)	1.1 (1.1)	1.1 (1.0)	<.0001	0.5 (0.6)	0.7 (0.8)	0.7 (0.8)	0.9 (0.9)	<.0001
Cheese (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0004	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0 (0.0)	<.0001
Milk [d] (servings/day)	0.7 (0.9)	0.8 (0.9)	1.0 (1.1)	1.0 (1.0)	<.0001	0.5 (0.5)	0.6 (0.8)	0.6 (0.8)	0.8 (0.9)	<.0001
Meat										
Total (servings/day)	5.6 (2.5)	5.0 (2.2)	4.6 (2.1)	3.7 (1.6)	<.0001	5.3 (2.5)	4.5 (2.0)	4.1 (2.0)	3.6 (1.5)	<.0001
Red (servings/day)	2.8 (1.4)	2.5 (1.3)	2.2 (1.2)	1.8 (0.9)	<.0001	2.6 (1.5)	2.2 (1.2)	2.0 (1.2)	1.6 (0.8)	<.0001
Organ (servings/day)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001
Processed (servings/day)	1.5 (0.8)	1.3 (0.6)	1.2 (0.7)	0.7 (0.4)	<.0001	1.4 (0.7)	1.1 (0.6)	0.9 (0.5)	0.7 (0.4)	<.0001
Fish (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2319	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)	0.2 (0.1)	0.0780
Poultry (servings/day)	1.1 (0.7)	1.1 (0.7)	1.1 (0.6)	1.0 (0.6)	0.4836	1.1 (0.8)	1.1 (0.6)	1.1 (0.7)	1.2 (0.7)	0.6792
Eggs (servings/day)	0.6 (0.4)	0.5 (0.4)	0.4 (0.4)	0.3 (0.3)	<.0001	0.4 (0.3)	0.4 (0.3)	0.3 (0.3)	0.3 (0.2)	<.0001
Fat										
Total (g/day)	117.5 (45.7)	104.4 (41.2)	93.5 (42.6)	69.6 (29.5)	<.0001	96.0 (38.5)	90.0 (36.0)	78.2 (29.8)	61.9 (22.4)	<.0001
Monounsaturated (g/day)	47.2 (18.7)	41.6 (16.8)	37.0 (17.8)	27.3 (12.4)	<.0001	38.7 (16.2)	36.1 (14.9)	31.7 (13.1)	24.7 (10.3)	<.0001
Polyunsaturated (g/day)	22.5 (10.6)	21.0 (9.3)	19.2 (9.3)	15.1 (7.4)	<.0001	18.5 (8.3)	18.6 (8.6)	16.3 (7.0)	13.1 (5.3)	<.0001
Saturated (g/day	38.5 (15.4)	33.2 (13.8)	29.3 (14.0)	20.9 (8.5)	<.0001	30.8 (12.8)	27.7 (11.4)	23.3 (9.2)	18.3 (6.8)	<.0001

Sodium, Sugar, Alcohol, Energy										
Sodium (g/day)	3.8 (1.4)	3.7 (1.3)	3.6 (1.6)	3.1 (1.0)	<.0001	3.2 (1.2)	3.2 (1.2)	3.0 (1.0)	2.8 (0.8)	<.0001
Added sugar (teaspoons/day)	22.1 (15.3)	24.5 (15.6)	21.0 (14.5)	14.7 (11.0)	<.0001	16.5 (12.9)	19.6 (14.1)	16.8 (11.4)	12.8 (8.2)	<.0001
Total energy (100-kcal/day)	26.3 (9.7)	26.5 (9.8)	24.9 (11.6)	19.9 (7.1)	<.0001	20.2 (7.9)	21.2 (7.7)	19.8 (6.7)	17.6 (5.0)	<.0001
Alcohol (g/day)	24.7 (47.6)	28.1 (49.7)	24.5 (45.2)	10.4 (21.0)	0.0058	6.6 (14.5)	7.4 (15.6)	10.2 (18.0)	7.5 (13.8)	0.0170

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; g, grams; kcal, kilocalorie; SD, standard deviation.

[a] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and HEI-2005 quartile among case participants.

[b] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and HEI-2005 quartile among control participants

[c] Includes dried beans.

[d] Includes soy milk.

Quartiles of HEI-2005 summary score estimated among control participants.

Associations tested using generalized linear models for continuous variables and Chi-square tests for categorical variables.

Supplemental Table 3-9. Distribution of Demographic and Dietary Variables Stratified by MDS Summary Score quartile, CHANCE Study, North Carolina, USA, 2002-2006

	Cases					Controls				
	Q1	Q2	Q3	Q4	*P* [a]	Q1	Q2	Q3	Q4	*P* [b]
Counts, (N)	598	257	166	149		466	263	273	301	
Categorical variables, N (%)										
Age category (years)										
> 60	244 (37.8)	109 (40.4)	94 (53.4)	99 (63.5)		239 (48.9)	168 (61.3)	176 (62.6)	221 (70.8)	
≤ 60	401 (62.2)	161 (59.6)	82 (46.6)	57 (36.5)	<.0001	250 (51.1)	106 (38.7)	105 (37.4)	91 (29.2)	<.0001
Race										
White	505 (78.3)	184 (68.1)	136 (77.3)	120 (76.9)		394 (80.6)	229 (83.6)	230 (81.9)	244 (78.2)	
Black	140 (21.7)	86 (31.9)	40 (22.7)	36 (23.1)	0.0111	95 (19.4)	45 (16.4)	51 (18.1)	68 (21.8)	0.4018
Sex										
Male	483 (74.9)	202 (74.8)	146 (83.0)	122 (78.2)		323 (66.1)	203 (74.1)	198 (70.5)	216 (69.2)	
Female	162 (25.1)	68 (25.2)	30 (17.0)	34 (21.8)	0.1284	166 (33.9)	71 (25.9)	83 (29.5)	96 (30.8)	0.1353
Educational attainment										
High school or less	419 (65.0)	180 (66.7)	90 (51.1)	77 (49.4)		226 (46.2)	118 (43.1)	91 (32.4)	101 (32.4)	
Some graduation or more	147 (22.8)	53 (19.6)	60 (34.1)	41 (26.3)		136 (27.8)	85 (31.0)	87 (31.0)	98 (31.4)	
College graduation or more	79 (12.2)	37 (13.7)	26 (14.8)	38 (24.4)	<.0001	127 (26.0)	71 (25.9)	103 (36.7)	113 (36.2)	0.0001
History of loose teeth										

Yes	253 (39.2)	97 (35.9)	63 (35.8)	45 (28.8)		112 (22.9)	63 (23.0)	68 (24.2)	66 (21.2)	
No	391 (60.6)	172 (63.7)	113 (64.2)	110 (70.5)		377 (77.1)	209 (76.3)	213 (75.8)	246 (78.8)	
Missing	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.6)	0.2602	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0.1896
Smoking history										
Ever smoker	562 (87.1)	243 (90.0)	154 (87.5)	119 (76.3)		323 (66.1)	183 (66.8)	154 (54.8)	175 (56.1)	
Never smoker	82 (12.7)	27 (10.0)	22 (12.5)	36 (23.1)		166 (33.9)	89 (32.5)	126 (44.8)	137 (43.9)	
Missing	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.6)	0.0044	0 (0.0)	2 (0.7)	1 (0.4)	0 (0.0)	0.0011
Alcohol use history										
Ever drinker	543 (84.2)	236 (87.4)	149 (84.7)	136 (87.2)		370 (75.7)	196 (71.5)	208 (74.0)	252 (80.8)	
Never drinker	68 (10.5)	21 (7.8)	15 (8.5)	13 (8.3)		102 (20.9)	66 (24.1)	63 (22.4)	57 (18.3)	
Missing	34 (5.3)	13 (4.8)	12 (6.8)	7 (4.5)	0.7602	17 (3.5)	12 (4.4)	10 (3.6)	3 (1.0)	0.0940
Continuous variables, mean (SD)										
Diet Quality Summary Score										
HEI-2005	44.7 (6.0)	46.7 (7.3)	48.8 (6.8)	53.6 (7.3)	<.0001	47.1 (7.1)	51.0 (8.0)	53.2 (7.3)	56.2 (6.8)	<.0001
MDS	2.2 (0.8)	4.0 (0.0)	5.0 (0.0)	6.5 (0.7)	<.0001	2.4 (0.8)	4.0 (0.0)	5.0 (0.0)	6.5 (0.7)	<.0001
MDS-HNC	3.8 (1.6)	5.0 (1.7)	5.6 (1.7)	7.2 (1.9)	<.0001	4.1 (1.7)	5.5 (1.8)	6.7 (1.8)	7.6 (1.8)	<.0001
Fruit										

Total (servings/day)	1.7 (1.4)	2.2 (1.7)	2.6 (2.1)	3.3 (1.6)	<.0001	2.0 (1.5)	2.4 (1.7)	2.8 (1.6)	3.4 (1.8)	<.0001
Citrus (servings/day)	0.6 (0.5)	0.7 (0.6)	0.8 (0.7)	1.0 (0.6)	<.0001	0.7 (0.5)	0.8 (0.6)	0.9 (0.6)	1.1 (0.6)	<.0001
Vegetables										
Total (servings/day)	2.2 (1.1)	2.5 (1.2)	2.8 (1.8)	2.8 (1.3)	<.0001	2.0 (1.0)	2.0 (0.9)	2.2 (0.9)	2.3 (1.0)	<.0001
Green (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)	0.2 (0.2)	<.0001	0.1 (0.2)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	<.0001
Yellow (servings/day)	0.1 (0.1)	0.2 (0.1)	0.2 (0.3)	0.3 (0.2)	<.0001	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	<.0001
Starchy (servings/day)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	<.0001	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.0022
Tomatoes (servings/day)	0.4 (0.3)	0.4 (0.3)	0.6 (0.6)	0.6 (0.4)	<.0001	0.4 (0.3)	0.4 (0.3)	0.5 (0.3)	0.6 (0.3)	<.0001
Potatoes (servings/day)	0.9 (0.7)	0.8 (0.6)	0.9 (0.8)	0.7 (0.6)	0.0122	0.7 (0.6)	0.6 (0.4)	0.5 (0.4)	0.5 (0.4)	<.0001
Pulses										
Legumes [c] (servings/day)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)	0.3 (0.2)	<.0001	0.1 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	<.0001
Coffee										
Coffee (servings/day)	1.6 (1.7)	1.4 (1.5)	1.5 (1.6)	1.2 (1.1)	0.0538	1.3 (1.5)	1.1 (1.2)	1.3 (1.2)	1.2 (1.2)	0.1625
Caffeine (g/day)	0.2 (0.2)	0.2 (0.1)	0.2 (0.2)	0.1 (0.1)	0.0002	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0029
Grains										
Total (servings/day)	4.7 (2.2)	5.1 (2.5)	5.1 (2.3)	5.2 (2.0)	0.0272	4.3 (2.1)	4.2 (1.8)	4.4 (1.8)	4.6 (1.8)	0.1625
Whole (servings/day)	0.7 (0.7)	0.9 (0.8)	0.9 (0.8)	1.1 (0.9)	<.0001	0.8 (0.7)	0.9 (0.8)	1.1 (0.8)	1.3 (0.8)	<.0001

Cornbread (servings/day)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.2 (0.3)	0.0152	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.1473
Dairy										
Total (servings/day)	1.1 (1.1)	0.7 (0.7)	0.6 (0.6)	0.5 (0.6)	<.0001	0.9 (0.9)	0.7 (0.7)	0.6 (0.6)	0.4 (0.5)	<.0001
Cheese (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.3152	0.1 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	0.0001
Milk [d] (servings/day)	1.0 (1.1)	0.6 (0.7)	0.5 (0.6)	0.4 (0.6)	<.0001	0.9 (0.9)	0.6 (0.7)	0.5 (0.6)	0.4 (0.5)	<.0001
Meat										
Total (servings/day)	5.5 (2.4)	4.9 (2.1)	5.0 (2.5)	4.0 (2.0)	<.0001	5.2 (2.3)	4.3 (1.8)	4.2 (1.9)	3.4 (1.8)	<.0001
Red (servings/day)	2.8 (1.4)	2.4 (1.2)	2.5 (1.4)	1.8 (1.0)	<.0001	2.6 (1.4)	2.0 (1.0)	1.9 (1.0)	1.5 (0.9)	<.0001
Organ (servings/day)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001
Processed (servings/day)	1.4 (0.8)	1.3 (0.7)	1.2 (0.8)	1.0 (0.6)	<.0001	1.2 (0.7)	1.0 (0.5)	0.9 (0.5)	0.7 (0.5)	<.0001
Fish (servings/day)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.1)	<.0001	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.2)	<.0001
Poultry (servings/day)	1.1 (0.7)	1.1 (0.6)	1.0 (0.7)	1.0 (0.6)	0.1893	1.2 (0.8)	1.1 (0.7)	1.2 (0.7)	1.0 (0.6)	0.0002
Eggs (servings/day)	0.5 (0.4)	0.5 (0.4)	0.5 (0.3)	0.4 (0.3)	0.0045	0.4 (0.3)	0.4 (0.3)	0.3 (0.3)	0.3 (0.3)	0.0082
Fat										
Total (g/day)	110.6 (45.7)	104.3 (44.0)	103.3 (47.5)	87.1 (37.6)	<.0001	90.8 (38.4)	79.0 (31.3)	78.2 (31.2)	72.8 (31.7)	<.0001
Monounsaturated (g/day)	43.9 (18.7)	41.7 (18.3)	41.7 (19.2)	35.1 (16.0)	<.0001	36.3 (16.0)	31.7 (13.3)	31.6 (13.4)	29.7 (14.1)	<.0001
Polyunsaturated (g/day)	21.0 (10.1)	21.3 (10.9)	21.3 (9.9)	19.0 (8.3)	0.0954	17.5 (8.2)	16.3 (7.3)	16.3 (7.6)	15.9 (7.4)	0.0238

Saturated (g/day	37.0 (15.6)	32.7 (13.5)	31.4 (15.6)	25.3 (11.7)	<.0001	29.5 (12.8)	24.2 (9.6)	23.4 (9.4)	20.4 (9.3)	<.0001
Sodium, Sugar, Alcohol, Energy										
Sodium (g/day)	3.7 (1.4)	3.6 (1.3)	3.8 (1.8)	3.5 (1.3)	0.3980	3.2 (1.2)	3.0 (1.0)	3.1 (1.0)	3.0 (1.0)	0.0024
Added sugar (teaspoons/day)	25.0 (15.9)	20.6 (14.4)	19.5 (14.8)	14.5 (8.8)	<.0001	19.5 (13.5)	17.3 (13.1)	14.9 (10.1)	12.1 (8.3)	<.0001
Total energy (100-kcal/day)	27.0 (10.1)	25.0 (9.5)	24.5 (11.7)	21.6 (7.4)	<.0001	21.1 (8.1)	19.2 (6.5)	19.3 (6.1)	18.3 (6.1)	<.0001
Alcohol (g/day)	30.1 (53.6)	23.8 (45.8)	16.5 (34.6)	12.8 (17.0)	<.0001	7.1 (17.7)	6.8 (13.4)	9.0 (15.3)	9.2 (13.6)	0.1026

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; g, grams; kcal, kilocalorie; SD, standard deviation.

[a] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and MDS quartile among case participants.

[b] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and MDS quartile among control participants.

[c] Includes dried beans.

[d] Includes soy milk.

Quartiles of MDS summary score estimated among control participants.

Associations tested using generalized linear models for continuous variables and Chi-square tests for categorical variables.

Supplemental Table 3-10. Distribution of Demographic and Dietary Variables Stratified by MDS-HNC Summary Score quartile, CHANCE Study, North Carolina, USA, 2002-2006

	Cases					Controls				
	Q1	Q2	Q3	Q4	*P* [a]	Q1	Q2	Q3	Q4	*P* [b]
Counts, (N)	555	405	102	108		397	427	193	286	
Categorical variables, N (%)										
Age category (years)										
> 60	233 (39.8)	199 (45.6)	49 (44.5)	65 (56.0)		208 (50.1)	275 (62.1)	125 (62.8)	196 (65.6)	
≤ 60	352 (60.2)	237 (54.4)	61 (55.5)	51 (44.0)	0.0096	207 (49.9)	168 (37.9)	74 (37.2)	103 (34.4)	<.0001
Race										
White	447 (76.4)	309 (70.9)	87 (79.1)	102 (87.9)		323 (77.8)	351 (79.2)	164 (82.4)	259 (86.6)	
Black	138 (23.6)	127 (29.1)	23 (20.9)	14 (12.1)	0.0012	92 (22.2)	92 (20.8)	35 (17.6)	40 (13.4)	0.0189
Sex										
Male	452 (77.3)	329 (75.5)	81 (73.6)	91 (78.4)		278 (67.0)	309 (69.8)	141 (70.9)	212 (70.9)	
Female	133 (22.7)	107 (24.5)	29 (26.4)	25 (21.6)	0.7546	137 (33.0)	134 (30.2)	58 (29.1)	87 (29.1)	0.6430
Educational attainment										
High school or less	400 (68.4)	277 (63.5)	49 (44.5)	40 (34.5)		221 (53.3)	176 (39.7)	72 (36.2)	67 (22.4)	
Some graduation or more	122 (20.9)	110 (25.2)	36 (32.7)	33 (28.4)		118 (28.4)	132 (29.8)	51 (25.6)	105 (35.1)	
College graduation or more	63 (10.8)	49 (11.2)	25 (22.7)	43 (37.1)	<.0001	76 (18.3)	135 (30.5)	76 (38.2)	127 (42.5)	<.0001
History of loose teeth										

Yes	218 (37.3)	173 (39.7)	39 (35.5)	28 (24.1)		110 (26.5)	109 (24.6)	48 (24.1)	42 (14.0)	
No	366 (62.6)	261 (59.9)	71 (64.5)	88 (75.9)		304 (73.3)	334 (75.4)	150 (75.4)	257 (86.0)	
Missing	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0.0756	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0.0023
Smoking history										
Ever smoker	512 (87.5)	391 (89.7)	94 (85.5)	81 (69.8)		277 (66.7)	264 (59.6)	126 (63.3)	168 (56.2)	
Never smoker	72 (12.3)	45 (10.3)	16 (14.5)	34 (29.3)		138 (33.3)	176 (39.7)	73 (36.7)	131 (43.8)	
Missing	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.9)	<.0001	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0.0181
Alcohol use history										
Ever drinker	483 (82.6)	384 (88.1)	94 (85.5)	103 (88.8)		287 (69.2)	334 (75.4)	156 (78.4)	249 (83.3)	
Never drinker	71 (12.1)	29 (6.7)	8 (7.3)	9 (7.8)		110 (26.5)	95 (21.4)	38 (19.1)	45 (15.1)	
Missing	31 (5.3)	23 (5.3)	8 (7.3)	4 (3.4)	0.0696	18 (4.3)	14 (3.2)	5 (2.5)	5 (1.7)	0.0024
Continuous variables, mean (SD)										
Diet Quality Summary Score										
HEI-2005	44.0 (5.6)	47.2 (6.4)	50.6 (7.0)	56.6 (7.0)	<.0001	45.8 (5.9)	50.3 (7.0)	54.7 (6.9)	57.9 (7.1)	<.0001
MDS	2.7 (1.3)	3.7 (1.4)	4.7 (1.4)	5.8 (1.3)	<.0001	2.9 (1.3)	4.0 (1.4)	4.9 (1.2)	5.7 (1.3)	<.0001
MDS-HNC	3.0 (1.0)	5.4 (0.5)	7.0 (0.0)	8.7 (0.9)	<.0001	3.1 (1.0)	5.5 (0.5)	7.0 (0.0)	8.8 (0.9)	<.0001
Fruit										

Total (servings/day)	1.7 (1.3)	2.2 (1.8)	2.7 (1.9)	3.6 (1.8)	<.0001	1.8 (1.4)	2.5 (1.6)	3.0 (1.6)	3.4 (1.8)	<.0001
Citrus (servings/day)	0.6 (0.4)	0.8 (0.6)	0.9 (0.7)	1.1 (0.7)	<.0001	0.6 (0.5)	0.8 (0.6)	1.0 (0.6)	1.1 (0.6)	<.0001
Vegetables										
Total (servings/day)	2.4 (1.2)	2.4 (1.5)	2.3 (1.2)	2.6 (1.3)	0.5279	2.1 (1.0)	2.1 (1.0)	2.2 (1.0)	2.2 (0.8)	0.3458
Green (servings/day)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	<.0001	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	<.0001
Yellow (servings/day)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)	<.0001	0.1 (0.1)	0.2 (0.1)	0.2 (0.2)	0.3 (0.2)	<.0001
Starchy (servings/day)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.0057	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2131
Tomatoes (servings/day)	0.4 (0.3)	0.5 (0.4)	0.6 (0.5)	0.7 (0.5)	<.0001	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	<.0001
Potatoes (servings/day)	1.0 (0.7)	0.7 (0.7)	0.6 (0.4)	0.5 (0.4)	<.0001	0.8 (0.6)	0.6 (0.4)	0.5 (0.4)	0.3 (0.3)	<.0001
Pulses										
Legumes [c] (servings/day)	0.2 (0.2)	0.3 (0.3)	0.2 (0.2)	0.2 (0.3)	0.0214	0.1 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.0192
Coffee										
Coffee (servings/day)	1.3 (1.5)	1.7 (1.6)	1.4 (1.3)	1.7 (1.4)	0.0026	1.0 (1.3)	1.3 (1.3)	1.3 (1.3)	1.5 (1.3)	<.0001
Caffeine (g/day)	0.2 (0.2)	0.2 (0.2)	0.1 (0.1)	0.2 (0.1)	0.0316	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.0307
Grains										
Total (servings/day)	5.4 (2.2)	4.7 (2.3)	4.2 (2.0)	4.2 (2.1)	<.0001	4.7 (2.1)	4.5 (1.9)	4.1 (1.8)	3.9 (1.7)	<.0001
Whole (servings/day)	0.8 (0.7)	0.8 (0.7)	0.8 (0.6)	1.1 (0.8)	0.0039	0.9 (0.8)	1.0 (0.8)	1.0 (0.8)	1.1 (0.8)	0.0001

Cornbread (servings/day)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1370	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.4632
Dairy										
Total (servings/day)	0.9 (1.0)	0.9 (1.0)	0.7 (0.9)	0.9 (0.8)	0.2509	0.7 (0.8)	0.7 (0.8)	0.7 (0.8)	0.7 (0.6)	0.6422
Cheese (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0003	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)	0.0 (0.0)	<.0001
Milk [d] (servings/day)	0.8 (1.0)	0.8 (1.0)	0.6 (0.9)	0.8 (0.8)	0.2931	0.7 (0.8)	0.6 (0.8)	0.6 (0.8)	0.6 (0.6)	0.8688
Meat										
Total (servings/day)	5.9 (2.3)	4.7 (2.2)	3.9 (2.2)	3.9 (2.2)	<.0001	5.4 (2.2)	4.4 (2.1)	3.9 (1.8)	3.3 (1.5)	<.0001
Red (servings/day)	3.0 (1.3)	2.3 (1.2)	1.9 (1.2)	1.8 (1.2)	<.0001	2.8 (1.4)	2.1 (1.1)	1.7 (0.9)	1.4 (0.8)	<.0001
Organ (servings/day)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<.0001
Processed (servings/day)	1.6 (0.7)	1.1 (0.7)	0.9 (0.6)	0.8 (0.6)	<.0001	1.4 (0.6)	1.0 (0.6)	0.8 (0.4)	0.6 (0.4)	<.0001
Fish (servings/day)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	<.0001	0.1 (0.1)	0.1 (0.2)	0.2 (0.1)	0.2 (0.2)	<.0001
Poultry (servings/day)	1.1 (0.6)	1.1 (0.8)	1.0 (0.7)	1.1 (0.6)	0.6432	1.1 (0.7)	1.1 (0.7)	1.2 (0.8)	1.1 (0.7)	0.8918
Eggs (servings/day)	0.6 (0.4)	0.4 (0.4)	0.3 (0.3)	0.3 (0.3)	<.0001	0.5 (0.3)	0.4 (0.3)	0.3 (0.3)	0.2 (0.2)	<.0001
Fat										
Total (g/day)	119.6 (41.9)	100.9 (43.8)	80.1 (40.8)	73.2 (41.1)	<.0001	97.6 (37.6)	83.6 (32.7)	72.7 (29.0)	62.8 (24.9)	<.0001
Monounsaturated (g/day)	47.9 (17.1)	40.3 (18.2)	31.3 (16.4)	28.7 (16.7)	<.0001	39.6 (15.8)	33.6 (13.8)	29.2 (12.7)	24.9 (11.0)	<.0001
Polyunsaturated (g/day)	23.7 (10.0)	19.8 (9.8)	15.9 (8.6)	15.2 (8.1)	<.0001	19.3 (8.3)	17.2 (7.7)	15.0 (6.5)	13.2 (6.0)	<.0001

Saturated (g/day	38.6 (14.2)	32.5 (14.6)	25.9 (13.6)	22.5 (13.8)	<.0001	30.6 (12.5)	25.6 (10.3)	21.8 (9.2)	18.7 (7.8)	<.0001
Sodium, Sugar, Alcohol, Energy										
Sodium (g/day)	4.0 (1.3)	3.5 (1.5)	3.1 (1.3)	3.2 (1.6)	<.0001	3.4 (1.2)	3.1 (1.1)	2.9 (1.0)	2.7 (0.8)	<.0001
Added sugar (teaspoons/day)	24.1 (15.5)	22.3 (15.4)	16.7 (13.0)	14.7 (10.3)	<.0001	19.9 (14.2)	16.2 (11.7)	15.7 (11.4)	12.2 (7.8)	<.0001
Total energy (100-kcal/day)	27.2 (9.1)	25.9 (10.8)	20.9 (8.6)	20.3 (10.2)	<.0001	21.7 (8.1)	19.9 (6.9)	18.9 (6.1)	17.3 (5.2)	<.0001
Alcohol (g/day)	19.7 (39.8)	34.4 (58.7)	21.5 (32.6)	16.3 (31.6)	<.0001	4.2 (11.2)	8.2 (18.1)	10.1 (18.0)	11.2 (13.7)	<.0001

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; MDS, Mediterranean Diet Score; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; g, grams; kcal, kilocalorie; SD, standard deviation.

[a] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and MDS-HNC quartile among case participants.

[b] Represents the probability of observing associations as extreme or more extreme than those observed, assuming the null that there is no association between the variables and MDS-HNC quartile among control participants.

[c] Includes dried beans.

[d] Includes soy milk.

Quartiles of MDS-HNC summary score estimated among control participants.

Associations tested using generalized linear models for continuous variables and Chi-square tests for categorical variables

Supplemental Table 3-11. Associations between HNC and HEI-2005: Summary and Individual Component Scores, CHANCE Study, North Carolina, USA, 2002-2006

	Diet Quality Scores: Summary or Individual Component			Model 1				Model 2			
	Cases	Controls	Overall	Counts		OR	95% CI	Counts		OR	95% CI
	Mean (SD)	Mean (SD)	Mean (SD)	N1	N0	PE	L95, U95	N1	N0	PE	L95, U95
HEI-2005											
Summary score	46.9 (7.2)	51.3 (8.1)	49.2 (8.0)	1157	1290	1.07	1.06, 1.08	1094	1246	1.04	1.02, 1.05
Total fruit	2.2 (1.7)	3.2 (1.7)	2.7 (1.8)	1103	1259	1.13	1.07, 1.20	1094	1246	1.02	0.93, 1.13
Whole fruit	2.3 (1.8)	3.3 (1.8)	2.8 (1.9)	1094	1246	1.14	1.08, 1.20	1094	1246	1.11	1.01, 1.21
Total vegetables	3.9 (1.1)	4.3 (0.9)	4.1 (1.1)	1103	1259	1.05	0.96, 1.16	1094	1246	0.98	0.86, 1.11
Colored vegetables	2.2 (1.4)	2.8 (1.5)	2.5 (1.5)	1103	1259	1.08	1.01, 1.15	1094	1246	1.04	0.95, 1.14
Total grains	3.3 (1.1)	3.6 (1.0)	3.4 (1.1)	1103	1259	1.15	1.05, 1.26	1094	1246	1.08	0.95, 1.22
Whole grains	1.2 (1.1)	1.7 (1.3)	1.5 (1.2)	1103	1259	1.19	1.09, 1.29	1094	1246	1.12	1.01, 1.24
Milk products	2.5 (2.4)	2.6 (2.3)	2.6 (2.3)	1103	1259	1.01	0.96, 1.05	1094	1246	1.03	0.98, 1.07
Meat, Beans, Legumes	9.5 (1.6)	9.4 (1.6)	9.5 (1.6)	1103	1259	1.00	0.94, 1.07	1094	1246	1.02	0.95, 1.09
Oils	10.0 (0.5)	10.0 (0.1)	10.0 (0.3)	1103	1259	1.12	0.64, 1.95	1094	1246	1.10	0.62, 1.95
Energy from fat	4.8 (3.3)	5.6 (3.1)	5.2 (3.2)	1103	1259	1.06	1.03, 1.09	1094	1246	1.07	1.03, 1.10

Sodium	4.6 (2.3)	3.8 (2.1)	4.2 (2.3)	1103	1259	0.97	0.93, 1.02	1094	1246	0.97	0.91, 1.04
SoFAAS	0.4 (1.3)	1.0 (2.1)	0.7 (1.8)	1103	1259	1.03	0.97, 1.09	1094	1246	0.91	0.85, 0.98

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; HEI, Healthy Eating Index; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; OR, Odds ratio; 95% CI, 95% Confidence interval; N1, Number of cases; N0, Number of controls; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation; SoFAAS, calories from solid fats, alcohol, and added sugars. OR represents relative odds of incident HNC for 1 unit decrease in HEI-2005 summary or individual component scores.

Counts between models vary due to missing data

For the summary score model, "Model 1" was adjusted for matching factors only (age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), and sex (categorical indicator: male; female)). "Model 2" for the summary score model and both "Model 1" and "Model 2" for individual diet quality score component models were adjusted for all variables that were included in "Model 1" of the summary score model and further adjusted for body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

"Model 1" for individual diet quality score component models included only the individual diet quality component for which associations were estimated and did not include other individual components diet quality score components.

"Model 2" for individual diet quality score component models included all individual diet quality score components in the same model.

Supplemental Table 3-12. Associations between HNC and MDS: Summary and Individual Component Scores, CHANCE Study, North Carolina, USA, 2002-2006

	Diet Quality Scores: Summary or Individual Component			Model 1				Model 2			
	Cases	Controls	Overall	Counts		OR	95% CI	Counts		OR	95% CI
	Mean (SD)	Mean (SD)	Mean (SD)	N1	N0	PE	L95, U95	N1	N0	PE	L95, U95
MDS											
Summary score	3.5 (1.7)	4.2 (1.7)	3.9 (1.7)	1170	1303	1.24	1.18, 1.30	1103	1259	1.08	1.01, 1.14
Fruits	0.3 (0.4)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.39	1.13, 1.70	1103	1259	1.35	1.08, 1.68
Vegetables	0.3 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.21	0.98, 1.48	1103	1259	1.11	0.88, 1.38
Cereals/grains	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.20	0.99, 1.46	1103	1259	1.22	1.00, 1.49
Legumes	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.92	0.76, 1.12	1103	1259	0.89	0.73, 1.08
Fish	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.13	0.92, 1.38	1103	1259	1.09	0.89, 1.34
MUFA:SFA ratio	0.4 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	1.18	0.97, 1.44	1103	1259	1.20	0.98, 1.46
Dairy	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.96	0.79, 1.17	1103	1259	0.93	0.76, 1.13
Meat intake	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.98	0.81, 1.20	1103	1259	0.94	0.77, 1.15
Alcohol	0.3 (0.4)	0.2 (0.4)	0.2 (0.4)	1103	1259	0.97	0.76, 1.24	1103	1259	0.97	0.76, 1.25

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; HEI, Healthy Eating Index; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; OR, Odds ratio; 95% CI, 95% Confidence interval; N1, Number of cases; N0, Number of controls; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation.

OR represents relative odds of incident HNC for 1 unit decrease in MDS summary or individual component scores.

Counts between models vary due to missing data.

For the summary score model, “Model 1” was adjusted for matching factors only (age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), and sex (categorical indicator: male; female)). “Model 2” for the summary score model and both “Model 1” and “Model 2” for individual diet quality score component models were adjusted for all variables that were included in “Model 1” of the summary score model and further adjusted for body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

“Model 1” for individual diet quality score component models included only the individual diet quality component for which associations were estimated and did not include other individual components diet quality score components.

“Model 2” for individual diet quality score component models included all individual diet quality score components in the same model.

Supplemental Table 3-13. Associations between HNC and MDS-HNC: Summary and Individual Component Scores, CHANCE Study, North Carolina, USA, 2002-2006

	Diet Quality Scores: Summary or Individual Component			Model 1				Model 2			
	Cases	Controls	Overall	Counts		OR	95% CI	Counts		OR	95% CI
	Mean (SD)	Mean (SD)	Mean (SD)	N1	N0	PE	L95, U95	N1	N0	PE	L95, U95
MDS-HNC											
Summary score	4.7 (2.0)	5.7 (2.2)	5.2 (2.2)	1170	1303	1.21	1.17, 1.26	1103	1259	1.08	1.02, 1.13
Fruits	0.3 (0.4)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.39	1.13, 1.70	1103	1259	1.30	1.04, 1.62
Vegetables	0.3 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.21	0.98, 1.48	1103	1259	1.07	0.86, 1.35
Coffee	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.88	0.71, 1.08	1103	1259	0.87	0.70, 1.07
Legumes	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.92	0.76, 1.12	1103	1259	0.91	0.75, 1.11
Fish	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.13	0.92, 1.38	1103	1259	1.09	0.88, 1.34
Poultry	0.3 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.22	0.99, 1.49	1103	1259	1.21	0.98, 1.49
Red meat	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	0.99	0.81, 1.20	1103	1259	0.91	0.73, 1.14
Processed meat	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	1.18	0.97, 1.43	1103	1259	1.15	0.92, 1.44
Eggs	0.4 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	1.20	0.99, 1.45	1103	1259	1.16	0.95, 1.42
Potatoes	0.4 (0.5)	0.5 (0.5)	0.5 (0.5)	1103	1259	1.09	0.90, 1.33	1103	1259	1.07	0.88, 1.31

Discretionary fat	0.4 (0.5)	0.5 (0.5)	0.4 (0.5)	1103	1259	1.26	1.03, 1.53	1103	1259	1.11	0.90, 1.37
Alcohol	0.3 (0.4)	0.2 (0.4)	0.2 (0.4)	1103	1259	0.97	0.76, 1.24	1103	1259	0.96	0.75, 1.22

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; HEI, Healthy Eating Index; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; OR, Odds ratio; 95% CI, 95% Confidence interval; N1, Number of cases; N0, Number of controls; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation

OR represents relative odds of incident HNC for 1 unit decrease in MDS-HNC summary or individual component scores

Counts between models vary due to missing data

For the summary score model, "Model 1" was adjusted for matching factors only (age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), and sex (categorical indicator: male; female)). "Model 2" for the summary score model and both "Model 1" and "Model 2" for individual diet quality score component models were adjusted for all variables that were included in "Model 1" of the summary score model and further adjusted for body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

"Model 1" for individual diet quality score component models included only the individual diet quality component for which associations were estimated and did not include other individual components diet quality score components

"Model 2" for individual diet quality score component models included all individual diet quality score components in the same model.

Supplemental Table 3-14. Exploration of Residual Confounding of the Association between HNC and HEI-2005 Diet Quality Summary Score by Traditional HNC Risk Factors: Smoking and Alcohol Drinking Using Restriction, CHANCE Study, North Carolina, USA, 2002-2006

	Counts		OR	95% CI
	N1	N0	Point Estimate	L95, U95
HEI-2005 Summary Score (mean=49.2, SD=8.0)				
Model1: Smokers (+, -), Drinkers (+, -)	1094	1246	1.35	1.21, 1.50
Model2: Smokers (-), Drinkers (+, -)	149	482	1.53	1.22, 1.92
Model3: Smokers (+, -), Drinkers (-)	111	270	1.52	1.12, 2.06
Model4: Smokers (-), Drinkers (-)	44	187	1.70	1.09, 2.64

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HEI-2005, Healthy Eating Index 2005; OR, Odds ratio; 95% CI, 95% Confidence Interval; N1, Number of Cases; N0, Number of Controls; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation.

OR represents relative odds of incident HNC for 1-SD unit decrease in HEI-2005 summary score

'Smokers (+, -)' implies model included both ever- and never-smokers.

'Drinkers (+, -)' implies model included both ever- and never-drinkers

'Smokers (-)' implies model included only never smokers

'Drinkers (-)' implies model included only never drinkers

Model1 (no restrictions) was adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5)

Smoking was accounted for either by restricting model to never smokers (Models 2, 4) or by adjusting for lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40) for models that included ever smokers (Models 1, 3). Similarly, alcohol was accounted for either by restricting model to never drinkers (Models 3, 4) or by adjusting for quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024) for models that included ever drinkers (Models 1, 2).

Supplemental Table 3-15. Exploration of Residual Confounding of the Association between HNC and MDS Diet Quality Summary Score by Traditional HNC Risk Factors: Smoking and Alcohol Drinking Using Restriction, CHANCE Study, North Carolina, USA, 2002-2006

	Counts		OR	95% CI
	N1	N0	Point Estimate	L95, U95
MDS Summary Score (mean=3.9, SD=1.7)				
Model1: Smokers (+, -), Drinkers (+, -)	1103	1259	1.13	1.02, 1.25
Model2: Smokers (-), Drinkers (+, -)	152	487	1.29	1.04, 1.59
Model3: Smokers (+, -), Drinkers (-)	111	273	1.46	1.09, 1.96
Model4: Smokers (-), Drinkers (-)	44	188	1.25	0.85, 1.85

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; MDS, Mediterranean Diet Score; OR, Odds ratio; 95% CI, 95% Confidence Interval; N1, Number of Cases; N0, Number of Controls; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation

OR represents relative odds of incident HNC for 1-SD unit decrease in MDS summary score.

'Smokers (+, -)' implies model included both ever- and never-smokers.

'Drinkers (+, -)' implies model included both ever- and never-drinkers.

'Smokers (-)' implies model included only never smokers.

'Drinkers (-)' implies model included only never drinkers.

Model1 (no restrictions) was adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

Smoking was accounted for either by restricting model to never smokers (Models 2, 4) or by adjusting for lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40) for models that included ever smokers (Models 1, 3). Similarly, alcohol was accounted for either by restricting model to never drinkers (Models 3, 4) or by adjusting for quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024) for models that included ever drinkers (Models 1, 2).

Supplemental Table 3-16. Exploration of Residual Confounding of the Association between HNC and MDS-HNC Diet Quality Summary Score by Traditional HNC Risk Factors: Smoking and Alcohol Drinking Using Restriction, CHANCE Study, North Carolina, USA, 2002-2006

	Counts		OR	95% CI
	N1	N0	Point Estimate	L95, U95
MDS-HNC Summary Score (mean=5.2, SD=2.2)				
Model1: Smokers (+, -), Drinkers (+, -)	1103	1259	1.17	1.06, 1.31
Model2: Smokers (-), Drinkers (+, -)	152	487	1.50	1.19, 1.88
Model3: Smokers (+, -), Drinkers (-)	111	273	1.41	1.04, 1.90
Model4: Smokers (-), Drinkers (-)	44	188	1.47	0.94, 2.30

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; MDS-HNC, Head and Neck cancer-specific Mediterranean Diet Score; OR, Odds ratio; 95% CI, 95% Confidence Interval; N1, Number of Cases; N0, Number of Controls; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation

OR represents relative odds of incident HNC for 1-SD unit decrease in MDS-HNC summary score.

'Smokers (+, -)' implies model included both ever- and never-smokers.

'Drinkers (+, -)' implies model included both ever- and never-drinkers.

'Smokers (-)' implies model included only never smokers.

'Drinkers (-)' implies model included only never drinkers.

Model1 (no restrictions) was adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), history of loose teeth (categorical indicator: yes; no), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024), and quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5).

Smoking was accounted for either by restricting model to never smokers (Models 2, 4) or by adjusting for lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40) for models that included ever smokers (Models 1, 3). Similarly, alcohol was accounted for either by restricting model to never drinkers (Models 3, 4) or by adjusting for quartile of lifetime intake of alcohol in grams (categorical indicator: ≥0, ≤ 5,824; >5,824, ≤ 61,516; >61,516, ≤ 297,024; >297,024) for models that included ever drinkers (Models 1, 2).

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CHAPTER 4: MANUSCRIPT #2: "THE ASSOCIATION BETWEEN DIET QUALITY AND DEATH FROM CANCER OF THE HEAD AND NECK"

4.1 Manuscript #2 Summary

The association between diet quality, captured by the Mediterranean Diet Score (MDS), and mortality was studied among 1,184 individuals diagnosed with head and neck cancer (HNSCC) who reflected on the year preceding diagnosis about their usual diet using a food frequency questionnaire. Intakes of nine dietary components were scored and summed to construct the MDS (sample: median=4; range=(0-9); lower MDS reflects poorer diet quality; 5-year survival probability=0.62;). Cox regression estimated 5-year hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality and for HNSCC-specific death per unit MDS decrement. Effect measure modification (EMM) by tumor features (human papillomavirus (HPV)-positivity; anatomic site) and sociodemographic-behavioral factors (race, body mass index (BMI), smoking, alcohol consumption) was explored.

Unit MDS decrements associated with higher (HR: 95% CI) all-cause- (1.05: 0.99, 1.12) and HNSCC-specific mortality (1.06: 0.97, 1.16). For HNSCC-specific death, MDS decrements were more strongly associated with HPV+: (1.33: 0.97,1.83), p16+ (1.17: 0.90, 1.53), and oral cavity cancer (1.15: 1.02, 1.30). Poor diet quality (MDS $\leq$ 4) in combination with lower BMI (< 25) or in combination with ever-drinking alcohol resulted in all-cause- and HNSCC-specific HRs greater than expected assuming additive effects. Poor diet quality prior to HNSCC diagnosis may accelerate post-diagnosis death.

4.2 Introduction

Head and neck cancer (HNSCC) includes cancer of the oral cavity, pharynx, and larynx. The approximately 67,000 HNSCC cases diagnosed annually makes HNSCC the 5th most frequently occurring cancer in the United States (US) [1, 2]. Despite Blacks' increases in overall 5-year survival over time, Blacks continue to have a lower survival than Whites. [3, 4]. Higher tobacco and alcohol consumption are associated with lower survival probabilities while HPV-positive tumors have been associated with more favorable prognoses than HPV-negative tumors [5, 6].

Although poor diet has been shown to be associated with an increased HNSCC risk [7, 8], few studies have evaluated associations between pre-diagnosis dietary patterns and HNSCC survival. Moreover, past studies have only examined the role of individual nutrients and food groups [9–13]. Comprehensive measures of diet quality may better reflect dietary exposure by accounting for synergy among dietary components, which may be missed when investigating nutrient components or food items individually. In addition, analysis of dietary patterns may yield greater statistical precision, as diet scores incorporate multiple potentially etiologically relevant individual exposures. The one investigation that examined the role of the overall pre-diagnosis diet pattern on HNSCC survival used principal components analysis, a data-driven *a posteriori* approach to characterize overall diet [14]. This study suggested that a "whole-foods" pattern characterized by high intakes of vegetables, fruit, fish, poultry, and whole grains, was associated with a reduced hazard of death [14]. This dietary pattern, identified by Arthur and colleagues, maps closely to a Mediterranean-style diet [15].

Thus, to build upon this prior work, we sought to investigate the association between overall HNSCC survival and diet quality characterized *a priori* using the Mediterranean Diet Score (MDS). We used data from HNSCC cases in the Carolina Head and Neck Epidemiology

(CHANCE) Study, a population-based case-control study conducted in eastern and central North Carolina from 2002-2006. In addition, we further characterized potential heterogeneity of the association between the MDS and HNSCC survival according to body mass index (BMI), race, cigarette smoking, alcohol consumption, anatomic tumor site, and tumor HPV-status.

4.3 Materials and Methods

The Carolina Head and Neck Cancer Epidemiology (CHANCE) study is a population-based case-control study of HNSCC conducted in North Carolina, USA. The CHANCE study protocol was approved by the UNC Institutional Review Board (UNC IRBIS: 16-2503).

4.3.1 Study Population.

The study population comprised individuals aged 20 to 80 years, who resided within a 46-county region in central and eastern North Carolina, and who were diagnosed with a new first primary invasive squamous cell carcinoma of the oral cavity, pharynx, or larynx between January 1, 2002 and February 28, 2006. A rapid case ascertainment system was utilized through the North Carolina Cancer Registry and included monthly contact with the cancer registrars of 54 hospitals within the study area to identify eligible cases [16]. Study participants who self-reported a race other than Black or White were excluded (n=28) as were people with missing dietary data (n=114).

4.3.2 Survival.

Individuals with HNSCC from CHANCE were linked to the National Death Index (NDI) [17] based on name, social security number, date of birth, sex, race, and state of residence to identify deaths through December 31, 2013, at which time individuals were assumed to be alive if no NDI match was determined. 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 online newspaper obituaries [18]. Topography codes from the International Classification of Diseases for Oncology, Third Revision (C0.00–C14.8 for oral cavity or pharynx cancer and C32.0–C32.9 for larynx cancer) listed as an underlying cause of death were considered cancer-specific deaths.

4.3.3 Survival Time.

Follow-up for ascertainment of death began at the date of HNSCC diagnosis and ended five years after diagnosis. Individuals were censored if they were still alive at five years following diagnosis. Follow-up time for our analysis was calculated as the time between the HNSCC diagnosis and the date of censoring or death, whichever came first.

4.3.4 Dietary Intake Assessment, Sociodemographic and, Lifestyle data.

A structured questionnaire was administered by trained interviewers during the in-home study visit to assess information on demographic, lifestyle, and dietary behaviors. Questionnaires collected self-reported information on established risk factors for HNSCC, including cigarette smoking, alcohol use, anthropometric measures, and education.

Dietary intakes were assessed using a modification of the National Cancer Institute's Diet History Questionnaire (DHQ) [19], a food frequency questionnaire designed to assess past-year consumption. The DHQ was modified to account for the dietary and cooking practices in North Carolina, as previously described [20]. Data from the modified DHQ were processed with the Diet*Calc analysis program [21] to estimate daily intake of total energy, nutrients, and individual food items. To minimize bias from implausible energy intake, study participants with energy intake values less than the 2.5^{th} percentile of energy intake (1017.95 kcal/day, N=31) or greater than the 97.5^{th} percentile of energy intake (4768.19 kcal/day, N=32) among all study participants were excluded.

The Mediterranean Diet Score (MDS) reflects adherence to the traditional Mediterranean diet, a diet associated with reduced mortality and lower chronic disease incidence [22–26, 26, 27] The MDS was originally developed by Trichopoulou et al. [28] and was later revised to include fish intake [29]. The MDS was calculated as the sum of nine dietary components: 6 components [fruit(all fruit; including fruit juices)], vegetables[non-potato starchy vegetables; green-colored; yellow-colored; tomatoes], cereals/grains[rice; pasta; cereals; whole-grains], legumes[peas; lentils; beans], fish[all fatty fish, white fish, shellfish, seafood], monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA) ratio) for which increased consumption is traditionally Mediterranean, and hence contributes to the summary score. Two additional components include [dairy (milk, cheese, yogurt, excludes (soy milk, rice milk, milk added to cereal)], meat[beef, pork, lamb, poultry, organ meats, lunch meats]) for which decreased consumption is traditionally Mediterranean, and hence contributes to the summary score. Finally, 1 additional component, alcohol consumption, contributed to the summary score if an individual's consumption was considered 'moderate' based on pre-defined sex-specific ranges. (Supplemental Table 4-1). For all MDS components other than alcohol, daily intakes were standardized for energy by dividing a participant's daily component intake by his or her daily energy intake in kilocalories and multiplying by 1000 prior to applying the MDS scoring algorithm. For each non-alcohol component, participants were scored 0 or 1 based on whether his or her consumption was higher (scored 1 for positive components, 0 for negative components) or lower (scored 1 for negative components, 0 for positive components) than the median sex-specific energy-adjusted intake among all participants. For alcohol, moderate intake was defined as consuming between 10 and 50 grams per day for males and between 5 and 25 grams per day for females. All other alcohol intakes were scored a zero. This specification for

the alcohol intake component was the same specification used in the original enumeration of the MDS [29]. The summary MDS was calculated by the sum of the component scores; thus, the score ranged from a theoretical minimum of zero to a maximum of nine. Lower scores reflect poorer quality Mediterranean-style diet.

4.3.5 HPV Laboratory Assays.

To assess tumor HPV status, all participants with oropharyngeal tumors (n =339) were analyzed for the presence of HPV by p16 immunohistochemistry (IHC) and polymerase chain reaction (PCR) (total n = 433). Individuals with hypopharynx cancers, those for whom the hospital would not release tumor blocks, and those for whom interviews were completed by a proxy were excluded from laboratory assays [6]. To assess tumor HPV status, the International Agency for Research on Cancer performed a pathologic examination of formalin-fixed paraffin embedded tumor tissues to confirm the presence of tumor and semi-quantitative measurement of the presence of HPV by IHC with p16 IKN4a antibody, according to the protocol provided with the CINtec Histology p16- INK4a kit (9511; MTm Laboratories Inc., Westborough, Mass). The expression of p16 was measured by applying a combined score based on both the intensity (0 to 3) and the percentage (0 to 4) of positivity. A combined score ≥ 4 was considered overexpression. DNA extraction and genotyping using Luminex-based multiplex (PCR) (TS-E7-MPG, IARC, Lyon, France) identified HPV type 6 (HPV6), HPV8, HPV11 HPV16, HPV18, HPV26, HPV31, HPV33, HPV35, HPV39, HPV58, and HPV59 [30]. Cases were designated HPV-positive (HPV+) if they were positive for HPV16 DNA (deoxyribonucleic acid) and overexpressed p16 and HPV-negative (HPV-) for other HPV types. Cases were designated protein16 (p16+) if they overexpressed p16, protein16-negative (p16-) otherwise [8].

4.3.6 Statistical Analyses.

Distributions of covariates were explored among quartiles of the summary MDS, where the values used to distinguish summary MDS quartiles were based on the distribution of summary MDS among all study participants. Similarly, the median summary MDS value used to produce sub-groups for Kaplan-Meier curves was derived from the distribution of the summary MDS among all study participants. Kaplan-Meier curves were plotted for all-cause mortality through five years of follow-up to compare study participants above and below this summary MDS median value. The median summary MDS was chosen to allow for easier interpretation of the generated curves. Spearman rank correlation coefficients were evaluated to better understand dependencies between individual MDS components.

Cox proportional hazards regression [31] was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (95CI) for the association between unit decreases in the summary MDS and the 5-year hazard of death from any cause and from head and neck cancer. The 5-year hazard of death was chosen as the measure of association of interest for this study because it was thought that any influence pre-diagnosis dietary habits might have on survival from HNSCC would be realized not more than five years following diagnosis. The proportional hazards assumption was evaluated by using the Supremum Test for Proportional Hazards through which the cumulative sums of martingale-based residuals for the main exposure and all covariates were assessed [32]. Associations with individual MDS components and 5-year hazards of death from any cause and from head and neck cancer were evaluated using two modeling strategies: 1) all MDS components were included in the same model and adjusted for potential confounders and 2) each of the nine MDS component scores was examined in separate models while adjusting for the same potential confounders used for the full model adjustment.

For the MDS component models, the estimated measure of association represented the five-year relative hazard of death for poorer (i.e., non-traditional Mediterranean) consumption.

The confounders used for full model adjustment were based on prior literature and included age in years (20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (White; Black), sex (male; female), body mass index (BMI) in kilogram per square meter (≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), educational attainment (high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (≥0, ≤ 84,448; >84,448, ≤ 435,344; >435,344, ≤ 1,306,032; >1,306,032), quartile of energy intake in kilocalories per day (>0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), and summary stage (I, II, III, IV).

Clinical effect measure modifier (EMM) candidates, HPV-positivity (HPV-positive or HPV-negative) and anatomic site (oral cavity, pharynx, or larynx), were evaluated on the multiplicative scale by including product terms between the summary MDS score and the clinical parameters of interest.

Because of the potential for public health impact, heterogeneity of effect by socio-demographic or behavioral factors like race, BMI, alcohol consumption, and cigarette smoking, were also evaluated on both the multiplicative and additive scales. For the risk factors that would be evaluated on both the additive and multiplicative scales, dichotomous categorizations of the summary MDS and modifying factors were used to reduce the imprecision caused by small strata. The categories for the summary MDS were based on the median summary MDS among all study participants: (‘Low MDS’: ≤ median summary MDS (poorer diet quality), ‘High MDS’: > median summary MDS (better diet quality)). The potential modifying factors and their respective categories were specified as follows: Race (Black, White); BMI (‘High BMI’: ≥ 25

kg/m^2, 'Low BMI': < 25 kg/m^2); smoking (never smoker, ever smoker); and alcohol use (never drinker; ever drinker). Additive interaction was assessed using the Relative Excess Risk due to Interaction (RERI) estimator [33, 34]. Single referent hazard ratios were estimated in which case the reference group was always the group thought to have the lowest relative 5-year hazard of death from any cause or from head and neck cancer. For example, because individuals with higher BMIs have better survival than individuals with lower BMIs [35], and because individuals who consume diets of higher quality are thought to have higher 5-year survival than individuals who consume lower diet quality [14], the reference category for 'Single referent' hazard ratios included those individuals with 'High BMI' and 'High MDS.' These 5-year 'Single referent' hazard ratios were the basis for the RERI estimator.

Multiplicative EMM was assessed using likelihood ratio tests by comparing models with and without product terms between the dichotomized summary MDS variable and the potential modifying variable. The 5-year 'modifier stratified' hazard ratios were estimated in which case the contrast between 'Low MDS' (index) and 'High MDS' (referent) were estimated within each category of the potential modifying factor. The ratios of these "within modifier" hazard ratios (RHR) were also estimated in which case the modifier-summary MDS combination thought to be associated with the highest relative 5-year hazard served as the index level and the modifier-summary MDS combination thought to be associated with the lowest 5-year hazard served as the reference category. For all evaluations of EMM, the type I error rate was set to 0.10 because the statistical power to detect associations in the consideration of sub-group analyses is diminished. Unless otherwise stated, the significance level for all other statistical tests was set to 0.05. The SAS system (SAS v9.4, SAS Institute, Cary, NC, USA) was used to execute analyses and generate tables and graphics.

4.4 Results

This study included a cohort of 1,184 individuals diagnosed with HNSCC, among whom 46% were aged between 55 and 69 years, inclusive. Just over 41% of the cohort had tumors classified as summary stage IV, and approximately 24% had tumors classified as summary stage I. Approximately three quarters of the study's participants self-reported White race, over 55% of the cohort had a BMI greater than 25, and almost 80% of the cohort reported having smoked cigarettes for at least 20 years. Among those whose dietary intake was classified as belonging to the highest quartile of summary MDS, approximately 16% reported lifetime alcohol consumption that was classified into the highest quartile of lifetime alcohol consumption (Table 4-1). The distribution of the MDS appears to be symmetric (Supplemental Figure 4-1).

With respect to Spearman correlation coefficients with absolute values greater than 0.10, the Fruit component was correlated positively with the Vegetables component (0.41), and the Fish component (0.18); the Vegetables component was additionally positively correlated with Legumes (0.12), and Fish (0.22); the Cereals/grains component was positively correlated with the MUFA:SFA Ratio component (0.14); the Legumes component was positively correlated with the Fish component (.10). Finally, the Meat component was negatively inversely correlated with Dairy (-0.14) and Fish component (-0.10). (Supplemental Table 4-2).

Visual examination of unadjusted Kaplan-Meier plots showed that 'High MDS' study participants had higher survival probabilities than 'Low MDS' study participants over the first 5 years of follow-up. (Figure 4-1). The 1-, 3-, and 5-year survival probabilities for the cohort were 0.921, 0.722, and 0.618, respectively. The median survival time among those who died over the 5-year follow-up period was 1.96 years.

We observed no evidence for violation of the proportional hazards assumption (Supremum Test: p-value for death from any cause model: 0.641; p-value for death from

HNSCC: 0.319) Table 4-2 and. Table 4-3 show the adjusted associations between summary MDS and 5-year relative hazards of death from any cause and death from HNSCC. The 5-year hazard of death for a unit decrease in summary MDS (poorer diet) for death from any cause and from HNSCC was 1.05 (0.99, 1.12) ("Model 2",Table 4-2) and 1.06 (0.97, 1.16) ("Model 2",Table 4-3), respectively. Individuals with a fish intake below the median fish intake value had an increase in the relative 5-year hazard of death from any cause: 1.24 (1.01, 1.52) ("Model 2",Table 4-2) and for death from HNSCC: 1.45 (1.07, 1.97)) ("Model 2",Table 4-3). The 5-year HR for unit decrement in the cereals/grains component score for death from any cause was 1.24 (1.00, 1.52) (Table 4-2) and for death from HNSCC was 1.51 (1.10, 2.06) ("Model 2", Table 4-3). Unit decrements in the vegetable component score were related to a lower hazard for death from any cause [0.96 (0.77, 1.20); "Model 2", Table 2] and death from HNSCC [0.65 (0.47, 0.90); "Model 2", Table 4-3].

For analyses of heterogeneity of the association by tumor HPV-status and by anatomic tumor site, the likelihood ratio tests did not reach statistical significance (all p-values >0.10). However, the 5-year hazard ratios for death from HNSCC for HPV-positive (HPV+ or p16+) tumors were notably greater in magnitude than their corresponding HPV-negative specifications (HPV-, or p16-). For example, the 5-year relative hazards for death from HNSCC for unit decrement in summary MDS for HPV+ and HPV- tumors were 1.33 (0.97, 1.83) and 1.01 (0.85, 1.20), respectively (Table 4-4). Similarly, the 5-year relative hazards for death from HNSCC for unit decrement in summary MDS for p16+ and p16- tumors were 1.17 (0.90, 1.53) and 1.04 (0.86, 1.26), respectively (Table 4-4). For tumor anatomic site, likelihood ratio tests for interaction between summary MDS and tumor anatomic site also did not reach statistical significance for death from any cause (p=0.382) but did reach statistical significance for death

from HNSCC (p=0.071 (Table 4-5)). The 5-year relative hazards for death from any cause for oral cavity, pharynx, and larynx cancer were 1.06 (0.98, 1.15), 0.93 (0.78, 1.11), and 1.07 (0.97, 1.18), respectively (Table 4-5) The corresponding 5-year relative hazards for death from HNSCC for oral cavity, pharynx, and larynx cancer were 1.15 (1.02, 1.30), 0.85 (0.63, 1.13), and 0.99 (0.86, 1.15), respectively (Table 4-5).

For both death from any cause and from HNSCC, we observed super-additive effect measure modification by BMI (RERI p-value for death from any cause: 0.071; RERI p-value for death from HNSCC: 0.003) and by alcohol consumption (RERI p-value for death from any cause: 0.096; RERI p-value for death from HNSCC: 0.074) (Table 4-6, Table 4-7). The pattern for both combinations (poor diet quality and 'Low BMI'; poor diet quality and 'Ever Drinking'), had an HR representing the combination of effects that was greater than an HR that would have been derived from the simple addition of the individual component effects of the combination. (Table 4-6, Table 4-7).

4.5 Discussion

In this investigation, we sought to understand the association between the MDS and mortality among individuals with HNSCC identified in the CHANCE study. Overall, lower diet quality as characterized by the MDS was associated with both 5-year all-cause and HNSCC-specific mortality. Of the individual MDS components, fish and cereal/grains intake were both observed to be inversely associated with 5-year HRs for death from any cause and death from HNSCC. Surprisingly, vegetable intake was positively associated with HNSCC-specific death. We observed multiplicative EMM by anatomic subtype for HNSCC-specific death, with poorer diet quality associated with increased 5-year relative hazards of death for individuals with oral cavity cancer. Though not statistically significant, we observed that poor diet quality appeared to be related to greater relative 5-year hazards of HNSCC-specific death for HPV-positive and p16-

postive tumors compared to HPV-negative and p16-negative tumors, respectively. For both all-cause and HNSCC-specific death, we observed additive interaction by BMI and by alcohol consumption, such that poor diet quality in the presence of low BMI or in the presence of alcohol consumption, resulted in a greater 5-year relative hazards of both all-cause and cancer-specific death beyond the expectation of the simple summation of the effects of each factor (low BMI, alcohol consumption) and poor diet quality alone.

We were able to locate only one publication that examined pre-diagnosis dietary patterns and HNSCC survival. Arthur and colleagues previously reported that a "whole foods" pattern (derived by principal components analysis) characterized by vegetables, fruit, fish, poultry, and whole grains was associated with reduced hazards of death among cases head and neck cancer [14]. Comparing the highest quintile (higher diet quality) to the lowest quintile of the "whole foods" pattern, Arthur and colleagues reported a multivariable adjusted HR (95CI) of 0.56 (0.34, 0.92) [14]. Our finding of an inverse association between summary MDS and survival following an HNSCC diagnosis agrees with those observed in this previous work, as increased intakes of the food items comprising the "whole foods" pattern would result in a higher summary MDS. To further evaluate the degree of congruence between our findings and those of Arthur and colleagues, we modeled the summary MDS as a categorical indicator variable and observed a nearly identical hazard ratio for death from any cause for the contrast of the highest (best diet quality) versus lowest (worst diet quality) quintile of the summary MDS using our data (HR: 0.52 (95CI: 0.34, 0.81)).

Our observation that lower intake of fish results in higher relative hazards of death also agrees with the results presented by Arthur. Further, an investigation among individuals with breast cancer has also showed a positive association between fish intake and survival [36]. It is

not certain why fish intake is positively associated with cancer survival; however, it is possible that anti-tumor [37, 38] and anti-inflammatory properties [39, 40] of omega-3 fatty acids, of which, fish are a rich source [41], play a role. As Supplemental Table 2 shows, the Spearman correlation coefficient between fish intake and meat intake were inversely correlated suggesting that not only may individuals who eat fish at higher levels benefit from the nutritional gains related to increased fish consumption itself, but also from the concomitant decreased consumption in red and processed meat which have traditionally been associated with increased HNSCC risk. Additionally, socioeconomic status (SES) may confound the association between fish intake and mortality as individuals who belong to higher SES may consume fish at higher levels because they can afford to do so whereas individuals from lower SES backgrounds may not have the same capability [42]. As well, higher SES also affects mortality and thus satisfies the conditions necessary for being classified as a confounder of the association between fish intake and mortality. Although we adjusted for SES by including levels of completed education in our models, residual confounding by SES may persist.

That we observed cereals/grain intake was inversely associated with the 5-year hazard ratios for death from any cause and for death from HNSCC aligns with in vitro and in vivo studies that suggest grains contain antioxidant and phytochemicals that have anti-tumor properties [43–45]. Surprisingly, lower vegetable intake in our study was associated with a reduced 5-year relative hazard of HNSCC-specific mortality. However, this may in part be attributed to cooking practices in North Carolina, namely vegetables that are prepared with animal fat and meat products, as has been documented previously [20]. Still, the positive correlation of the Vegetables Component with the Fish and Fruits components would suggest that the Vegetables component would also be inversely associated with the relative 5-year hazard

of HNSCC-specific death. Additionally, if indeed other components or food items like animal fats and meat products were interacting with the Vegetables component to influence its observed association with the relative 5-year hazard of HNSCC-specific death, then 'Model 2' in Table 3, which is mutually adjusted for the other MDS components, would not have resulted in the strengthening of the association as we observed. The challenges of sorting out the individual effects of interacting dietary components lends further support to studying diet holistically as we have done with the summary MDS.

For the clinical tumor characteristics, poor diet quality was associated with an increased 5-year hazard ratio for HNSCC-specific death among those with cancers of the oral cavity. Because oral cavity cases accounted for the vast majority in the cohort under study, we may have only identified statistically significant findings for oral cavity cancer and not for pharynx or larynx cancer simply because of the larger sample size of oral cavity tumors compares to pharynx and larynx tumors. Still, we note that pharynx and larynx HRs were below one. The findings for HPV-positivity, whether specified as HPV+ or p16+, suggested that poor diet quality increased the 5-year HNSCC-specific HR for death for HPV-positive tumors than it did for HPV-negative tumors. The literature regarding diet and HPV-positivity is mixed. One study exploring the role diet plays in HNSCC incidence found that citrus fruit consumption to be positively associated with HPV-seropositivity [46]. Higher citrus fruit consumption would result in higher diet quality based on the MDS scoring algorithm, and thus, our findings, although not focusing on risk, but rather on survival, appear to conflict with those of Meyer.

We also noted additive and multiplicative interaction of the association between summary MDS and the 5-year relative hazard of death from any cause and death from HNSCC by BMI and separately by alcohol consumption. The subgroup of cases with the combination of

‘Low MDS’ and ‘Low BMI’ or ‘Low MDS’ and ‘Ever Drinker’ had higher relative 5-year hazards of death from head and neck cancer than did subgroups of individuals with the combination of ‘High MDS’ and ‘High BMI’ or ‘High MDS’ and ‘Ever Drinker,’ respectively. This finding regarding BMI agrees with those reported in the review by den Hollander and colleagues [35] who suggested that nutritional reserves may be more available to people with high BMI, thus increasing their survival. In alignment with this suggestion, the combination of poor diet quality and poor nutritional reserves resulting from low BMI would result in lower survival probabilities. Of course, it is also quite plausible that the use of tobacco products as well as the disease process itself may have resulted in underweight status. With respect to alcohol consumption, dietary micronutrients and bioactive compounds found in many traditional-Mediterranean components can neutralize many of the carcinogenic byproducts of alcohol, and tobacco as well. [47–52] through a variety of mechanisms including epigenetic regulation of gene expression [53, 54]. Thus, the observed amplification of the relative hazard of death in a super-additive fashion among drinkers who had consumed a poor-quality pre-diagnosis diet may have resulted because their diets had insufficient amounts of the micronutrients and anti-cancer compounds necessary to mitigate the alcohol-related processes that contribute to tumor growth and progression.

The strengths of this study include the large number of individuals with HNSCC from a population-based study as well as the rich set of covariate information available in from a population-based study. A limitation of this investigation is the possibility of recall bias to collect dietary data following diagnosis but also for all the other self-reported covariates under study. In addition, the timing of the assessment of our main exposure could be problematic as the symptoms or disease itself may have influence dietary intake and thus the dietary intakes

reported by study participants to reflect their ‘usual diet’ in the year prior to diagnosis may not actually reflect the ‘usual diet’ that our survey instrument intended to capture. In our discussion regarding the elevated relative 5-year hazard of death associated with less-than-optimal fish intake, we stated that residual confounding of this association could not be ruled out. Indeed, SES may more generally affect overall diet quality as those with resources will be ablet to purchase and consume more nutrient-dense foods consistently than might individuals who may be lacking in financial means to do the same.

To conclude, our investigation of the association between diet quality as captured by the Mediterranean Diet Score and survival following diagnosis among a cohort of individuals diagnosed with HNSCC revealed that diet quality was inversely associated with both death from any cause and death from HNSCC. In addition, we observed that poor diet quality in combination with being underweight or with having a history of alcohol use amplified the relative hazards of death. While individual components of the MDS were also inversely associated with HNSCC, the key finding of this investigation was that a higher quality, traditional Mediterranean diet composed of a variety of food items provides a combination of bioactive compounds and micronutrients that can prolong survival and reduce mortality.

4.6 Tables

Table 4-1 Distributions of Select Covariates Among Individuals with Head and Neck Cancer by summary MDS quartile, CHANCE Study, North Carolina, USA, 2002-2006

	Summary MDS									
	MDS Q1: 0-<4		MDS Q2: 4-<5		MDS Q3: 5-<6		MDS Q4: 6-9		Total Cohort	
	(n=382)		(n=276)		(n=253)		(n=273)		(n=1184)	
Variable	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cause of Death										
Censored	229	(59.95)	160	(57.97)	159	(62.85)	184	(67.40)	732	(61.82)
HNC Death	71	(18.59)	60	(21.74)	34	(13.44)	37	(13.55)	202	(17.06)
Non-HNC Death	82	(21.47)	56	(20.29)	60	(23.72)	52	(19.05)	250	(21.11)
Missing	0		0		0		0		0	
Age group, years										
20-49	95	(24.87)	60	(21.74)	48	(18.97)	24	(8.79)	227	(19.17)
50-54	74	(19.37)	37	(13.41)	36	(14.23)	35	(12.82)	182	(15.37)
55-59	64	(16.75)	49	(17.75)	43	(17.00)	42	(15.38)	198	(16.72)
60-64	60	(15.71)	45	(16.30)	42	(16.60)	59	(21.61)	206	(17.40)
65-69	46	(12.04)	32	(11.59)	40	(15.81)	46	(16.85)	164	(13.85)
70-74	30	(7.85)	30	(10.87)	31	(12.25)	42	(15.38)	133	(11.23)
75-80	13	(3.40)	23	(8.33)	13	(5.14)	25	(9.16)	74	(6.25)
Missing	0		0		0		0		0	
Race										
White	302	(79.06)	213	(77.17)	183	(72.33)	205	(75.09)	903	(76.27)
Black	80	(20.94)	63	(22.83)	70	(27.67)	68	(24.91)	281	(23.73)

Missing	0		0		0		0		0	
Sex										
Male	284	(74.35)	218	(78.99)	196	(77.47)	214	(78.39)	912	(77.03)
Female	98	(25.65)	58	(21.01)	57	(22.53)	59	(21.61)	272	(22.97)
Missing	0		0		0		0		0	
BMI										
<18.5	12	(3.14)	13	(4.71)	7	(2.77)	6	(2.20)	38	(3.21)
18.5-<25	165	(43.19)	110	(39.86)	105	(41.50)	103	(37.73)	483	(40.79)
25-<30	104	(27.23)	79	(28.62)	81	(32.02)	110	(40.29)	374	(31.59)
30+	101	(26.44)	74	(26.81)	60	(23.72)	54	(19.78)	289	(24.41)
Missing	0		0		0		0		0	
Education										
High school or less	245	(64.14)	190	(68.84)	142	(56.13)	146	(53.48)	723	(61.06)
Some graduation or more	90	(23.56)	62	(22.46)	64	(25.30)	73	(26.74)	289	(24.41)
College graduation or more	47	(12.30)	24	(8.70)	47	(18.58)	54	(19.78)	172	(14.53)
Missing	0		0		0		0		0	
Years smoking cigarettes										
Never smoker	44	(11.52)	30	(10.87)	39	(15.42)	41	(15.02)	154	(13.01)
1-19	29	(7.59)	27	(9.78)	23	(9.09)	31	(11.36)	110	(9.29)
20-39	162	(42.41)	104	(37.68)	96	(37.94)	91	(33.33)	453	(38.26)
40+	147	(38.48)	115	(41.67)	95	(37.55)	109	(39.93)	466	(39.36)
Missing	0		0		0		1		1	
Alcohol use (kg)										
Q1: ≥0, <84	89	(23.30)	64	(23.19)	64	(25.30)	63	(23.08)	280	(23.65)

Q2: ≥84, <435	70	(18.32)	70	(25.36)	57	(22.53)	84	(30.77)	281	(23.73)
Q3: ≥435, <1,306	89	(23.30)	73	(26.45)	59	(23.32)	60	(21.98)	281	(23.73)
Q4: ≥1,306	112	(29.32)	60	(21.74)	63	(24.90)	46	(16.85)	281	(23.73)
Missing	22		9		10		20		61	
Quartile of energy intake (kcal)										
Q1: ≥0, <1,884	81	(21.20)	69	(25.00)	70	(27.67)	76	(27.84)	296	(25.00)
Q2: ≥1,884, <2,419	79	(20.68)	72	(26.09)	64	(25.30)	83	(30.40)	298	(25.17)
Q3: ≥2,419, <3,038	91	(23.82)	75	(27.17)	60	(23.72)	68	(24.91)	294	(24.83)
Q4: ≥3,038	131	(34.29)	60	(21.74)	59	(23.32)	46	(16.85)	296	(25.00)
Missing	0		0		0		0		0	
Cancer site										
Oral cavity	207	(54.19)	153	(55.43)	136	(53.75)	149	(54.58)	645	(54.48)
Pharynx	39	(10.21)	23	(8.33)	32	(12.65)	23	(8.42)	117	(9.88)
Larynx	136	(35.60)	100	(36.23)	85	(33.60)	101	(37.00)	422	(35.64)
Missing	0		0		0		0		0	
Tumor HPV-status [a]										
HPV-	98	(25.65)	70	(25.36)	65	(25.69)	61	(22.34)	294	(24.83)
HPV+	51	(13.35)	30	(10.87)	22	(8.70)	38	(13.92)	141	(11.91)
Missing	233		176		166		174		749	
Tumor p16-status [b]										
p16-	77	(20.16)	62	(22.46)	57	(22.53)	50	(18.32)	246	(20.78)
p16+	72	(18.85)	38	(13.77)	30	(11.86)	49	(17.95)	189	(15.96)
Missing	233		176		166		174		749	
Summary stage										

I	85	(22.25)	64	(23.19)	60	(23.72)	78	(28.57)	287	(24.24)
II	88	(23.04)	51	(18.48)	42	(16.60)	40	(14.65)	221	(18.67)
III	56	(14.66)	47	(17.03)	48	(18.97)	39	(14.29)	190	(16.05)
IV	153	(40.05)	114	(41.30)	103	(40.71)	116	(42.49)	486	(41.05)
Missing	0		0		0		0		0	

Abbreviations, symbols: CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HNC, cancer of the head and neck; MDS, Mediterranean Diet Score; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; N, Counts; %, Percentage; kg/m^2, kilogram per square meter; kcal, kilocalorie; HPV, Human papillomavirus; p16, protein p16.

[a] Cases were designated HPV+ if they were positive for both HPV16 DNA (deoxyribonucleic acid) and protein p16 overexpression, and HPV-, otherwise.

[b] Cases were designated p16+ if they were positive for protein p16 overexpression, and p16-, otherwise.

Notes: MDS quartile cut-points based on distribution of summary MDS among individuals experiencing death from any cause within five years of diagnosis. To minimize bias from implausible energy intake, study participants with energy intake values less than the 2.5^{th} percentile of energy intake (1017.95 kcal/day, N=31) among all study participants and study participants with energy intake values greater than the 97.5^{th} percentile of energy intake (4768.19 kcal/day, N=32) among all study participants were excluded. Study participants reporting a race other than Black or White were excluded (N=28). An additional 114 Study participants were excluded for missing dietary questionnaire data.

Table 4-2. Associations between 5-year Hazard of Death from any cause following HNC diagnosis and unit decrease in MDS: Summary and Individual Component Scores, CHANCE Study, North Carolina, USA, 2002-2006

	Diet Quality Scores: Summary or Individual Component		Model 1				Model 2			
	Cases	Deaths	Counts		HR	95% CI	Counts		HR	95% CI
	Mean (SD)	Mean (SD)	Cases	Deaths	PE	L95, U95	Cases	Deaths	PE	L95, U95
MDS										
Summary score	4.3 (1.7)	4.2 (1.6)	1184	452	1.09	1.04, 1.16	1122	426	1.05	0.99, 1.12
Fruits	0.5 (0.5)	0.5 (0.5)	1122	426	0.98	0.80, 1.21	1122	426	0.96	0.77, 1.20
Vegetables	0.5 (0.5)	0.4 (0.5)	1122	426	0.97	0.79, 1.18	1122	426	0.93	0.75, 1.16
Cereals/grains	0.5 (0.5)	0.5 (0.5)	1122	426	1.19	0.97, 1.46	1122	426	1.24	1.00, 1.52
Legumes	0.5 (0.5)	0.5 (0.5)	1122	426	1.09	0.89, 1.32	1122	426	1.08	0.88, 1.33
Fish	0.5 (0.5)	0.5 (0.5)	1122	426	1.21	0.99, 1.48	1122	426	1.24	1.01, 1.52
MUFA:SFA ratio	0.5 (0.5)	0.5 (0.5)	1122	426	0.93	0.77, 1.13	1122	426	0.85	0.69, 1.05
Dairy	0.5 (0.5)	0.5 (0.5)	1122	426	1.08	0.89, 1.32	1122	426	1.15	0.93, 1.42
Meat intake	0.5 (0.5)	0.5 (0.5)	1122	426	1.14	0.94, 1.40	1122	426	1.20	0.98, 1.47
Alcohol	0.3 (0.4)	0.3 (0.4)	1122	426	0.98	0.78, 1.24	1122	426	1.02	0.80, 1.29

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HR, Hazard ratio; 95% CI, 95% Confidence interval; N, Number of cases; D, Number of deaths from any cause; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation.

HR represents relative instantaneous hazard of death at any given survival time, provided a subject is at risk for death at the given survival time, for 1 unit decrease in MDS summary or individual component scores.

For the summary score model, "Model 1" was adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), and sex (categorical indicator: male; female). "Model 2" for the summary score model and both "Model 1" and "Model 2" for individual diet quality score component models were adjusted for all variables that were included in "Model 1" of the summary score model and further adjusted for body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 84,448; >84,448, ≤ 435,344; >435,344, ≤ 1,306,032; >1,306,032), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), and summary stage (categorical indicator: I; II; III; IV).

"Model 1" for individual diet quality score component models included only the individual diet quality component for which associations were estimated and did not include other individual components diet quality score components.

"Model 2" for individual diet quality score component models included all individual diet quality score components in the same model.

Table 4-3. Associations between 5-year Hazard of Death from cancer following HNC diagnosis and unit decrease in MDS: Summary and Individual Component Scores, CHANCE Study, North Carolina, USA, 2002-2006

	Diet Quality Scores: Summary or Individual Component		Model 1				Model 2			
	Cases	Deaths	Counts		HR	95% CI	Counts		HR	95% CI
	Mean (SD)	Mean (SD)	Cases	Deaths	PE	L95, U95	Cases	Deaths	PE	L95, U95
MDS										
Summary score	4.3 (1.7)	4.1 (1.6)	1184	202	1.10	1.02, 1.20	1122	191	1.06	0.97, 1.16
Fruits	0.5 (0.5)	0.5 (0.5)	1122	191	1.00	0.74, 1.37	1122	191	1.05	0.76, 1.46
Vegetables	0.5 (0.5)	0.5 (0.5)	1122	191	0.74	0.55, 1.00	1122	191	0.65	0.47, 0.90
Cereals/grains	0.5 (0.5)	0.4 (0.5)	1122	191	1.41	1.04, 1.91	1122	191	1.51	1.10, 2.06
Legumes	0.5 (0.5)	0.5 (0.5)	1122	191	1.22	0.90, 1.64	1122	191	1.32	0.97, 1.79
Fish	0.5 (0.5)	0.4 (0.5)	1122	191	1.37	1.01, 1.84	1122	191	1.45	1.07, 1.97
MUFA:SFA ratio	0.5 (0.5)	0.5 (0.5)	1122	191	0.87	0.65, 1.17	1122	191	0.74	0.54, 1.01
Dairy	0.5 (0.5)	0.5 (0.5)	1122	191	1.10	0.82, 1.48	1122	191	1.16	0.84, 1.59
Meat intake	0.5 (0.5)	0.5 (0.5)	1122	191	1.09	0.81, 1.47	1122	191	1.18	0.87, 1.60
Alcohol	0.3 (0.4)	0.2 (0.4)	1122	191	1.05	0.74, 1.51	1122	191	1.13	0.79, 1.63

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; HR, Hazard ratio; 95% CI, 95% Confidence interval; N, Number of cases; D, Number of deaths from cancer; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation.

HR represents relative instantaneous hazard of death at any given survival time, provided a subject is at risk for death at the given survival time, for 1 unit decrease in MDS summary or individual component scores.

For the summary score model, "Model 1" was adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), and sex (categorical indicator: male; female). "Model 2" for the summary score model and both "Model 1" and "Model 2" for individual diet quality score component models were adjusted for all variables that were included in "Model 1" of the summary score model and further adjusted for body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 84,448; >84,448, ≤ 435,344; >435,344, ≤ 1,306,032; >1,306,032), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), and summary stage (categorical indicator: I; II; III; IV).

"Model 1" for individual diet quality score component models included only the individual diet quality component for which associations were estimated and did not include other individual components diet quality score components.

"Model 2" for individual diet quality score component models included all individual diet quality score components in the same model.

Table 4-4. Associations between MDS and 5-year hazard of death from any cause and specifically from head and neck cancer following HNC diagnosis: by tumor HPV-status and p16-status, for unit decrease in summary MDS, CHANCE Study, North Carolina, USA, 2002-2006

		All-Cause [a]					HNC-specific [b]				
	MDS Summary score	Counts		HR	95% CI		Counts		HR	95% CI	
	Mean (SD)	Cases	Deaths	PE	L95, U95	*P-value*	Cases	Deaths	PE	L95, U95	*P-value*
Stratum											
Overall	4.3 (1.7)	1122	235	1.05	0.99, 1.12	--	1122	191	1.06	0.97, 1.16	--
HPV-	4.2 (1.7)	277	71	1.05	0.94, 1.18	--	277	58	1.01	0.85, 1.20	--
HPV+	4.2 (1.9)	136	15	1.04	0.85, 1.27	0.910	136	13	1.33	0.97, 1.83	0.118
p16-	4.3 (1.7)	234	61	1.10	0.97, 1.24	--	234	53	1.04	0.86, 1.26	--
p16+	4.1 (1.9)	179	25	0.99	0.84, 1.17	0.342	179	18	1.17	0.90, 1.53	0.463

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; DQS, HR, Hazard ratio; 95% CI, 95% Confidence interval; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation; HPV, Human papillomavirus; p16, protein p16.

[a] Cox proportional hazards regression for death resulting from any cause.

[b] Cox proportional hazards regression for death resulting specifically from head and neck cancer.

Cases were designated HPV+ if they were positive for both HPV16 DNA (deoxyribonucleic acid) and protein p16 overexpression, and HPV-, otherwise.

Cases were designated p16+ if they were positive for protein p16 overexpression, and p16-, otherwise.

HR represents relative instantaneous hazard of death at any given point during follow-up, provided a subject is at risk for death at the given time point, for a 1 unit decrease in MDS summary score.

P-value for the Likelihood Ratio Test (LRT) test for interaction. In either p-value column while moving from top to bottom, the p-values are represented by values other than '--' where the first numerical value encountered represents the p-value for the LRT test for interaction between MDS summary score and tumor HPV-status and the second value represents the p-value for the LRT test for interaction between MDS summary score and tumor p16-status.

All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 84,448; >84,448, ≤ 435,344; >435,344, ≤ 1,306,032; >1,306,032), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), summary stage (categorical indicator: I; II; III; IV).

Table 4-5. Associations between MDS and 5-year hazard of death from any cause and specifically from head and neck cancer following HNC diagnosis: by tumor site, for unit decrease in summary MDS, CHANCE Study, North Carolina, USA, 2002-2006

		All-Cause [a]					HNC-specific [b]				
	MDS Summary score	Counts		HR	95% CI		Counts		HR	95% CI	
	Mean (SD)	Cases	Deaths	PE	L95, U95	*P-value*	Cases	Deaths	PE	L95, U95	*P-value*
Stratum											
Overall	4.3 (1.7)	1122	235	1.05	0.99, 1.12	--	1122	191	1.06	0.97, 1.16	--
Oral cavity	4.3 (1.7)	616	112	1.06	0.98, 1.15	--	616	104	1.15	1.02, 1.30	--
Pharynx	4.2 (1.6)	108	35	0.93	0.78, 1.11	--	108	21	0.85	0.63, 1.13	--
Larynx	4.3 (1.7)	398	88	1.07	0.97, 1.18	0.382	398	66	0.99	0.86, 1.15	0.071

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; DQS, HR, Hazard ratio; 95% CI, 95% Confidence interval; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; SD, standard deviation.

[a] Cox proportional hazards regression for death resulting from any cause.

[b] Cox proportional hazards regression for death resulting specifically from head and neck cancer.

HR represents relative instantaneous hazard of death at any given point during follow-up, provided a subject is at risk for death at the given time point, for a 1 unit decrease in MDS summary score.

P-value for the Likelihood Ratio Test (LRT) test for interaction. In either p-value column while moving from top to bottom, the p-values are represented by values other than '--' where the first numerical value encountered represents the p-value for the LRT test for interaction between MDS summary score and tumor site (oral cavity, pharynx, larynx).

All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: ≥0, <18.5; ≥18.5, <25; ≥25, <30; ≥30), educational attainment (categorical indicator: high school or less; some college; college graduation or more), lifetime number of years smoking cigarettes (categorical indicator: 0; 1-19; 20-39; ≥40), quartile of lifetime intake of alcohol in grams (categorical indictor: ≥0, ≤ 84,448; >84,448, ≤ 435,344; >435,344, ≤ 1,306,032; >1,306,032), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), summary stage (categorical indicator: I; II; III; IV).

Table 4-6. Effect measure modification of the association between MDS summary score and the 5-year hazard of death from any cause by body mass index, race, smoking, and alcohol use, CHANCE Study, North Carolina, USA, 2002-2006

	MDS	Counts		Single Referent		RERI			Modifier Stratified		RHR		
Modifier Category	Summary Score	N (%)	D (%)	HR	95% CI	PE	95% CI	*P* [a]	HR	95% CI	PE	95% CI	*P* [b]
Body Mass Index (kg/m^2)													
≥ 25	> 4	285 (25.4)	52 (22.1)	1					1				
	≤ 4	345 (30.7)	70 (29.8)	1.10	0.88, 1.38				1.10	0.88, 1.38			
< 25	> 4	210 (18.7)	52 (22.1)	1.14	0.89, 1.46				1				
	≤ 4	282 (25.1)	61 (26.0)	1.58	1.25, 1.98	0.34	-0.03, 0.70	0.071	1.38	1.10, 1.74	1.26	0.91, 1.73	0.164
Race													
Black	> 4	133 (11.9)	36 (15.3)	1					1				
	≤ 4	135 (12.0)	33 (14.0)	1.07	0.79, 1.44				1.07	0.79, 1.44			
White	> 4	362 (32.3)	68 (28.9)	0.79	0.60, 1.04				1				
	≤ 4	492 (43.9)	98 (41.7)	1.03	0.80, 1.32	0.18	-0.16, 0.51	0.298	1.31	1.07, 1.60	1.23	0.86, 1.76	0.262
Smoking													
Never smoker	> 4	76 (6.8)	10 (4.3)	1					1				
	≤ 4	73 (6.5)	5 (2.1)	1.26	0.69, 2.29				1.26	0.69, 2.29			

Ever smoker	> 4	419 (37.3)	94 (40.0)	1.42	0.83, 2.42				1				
	≤ 4	554 (49.4)	126 (53.6)	1.75	1.03, 2.96	0.07	-0.61, 0.74	0.851	1.23	1.04, 1.46	0.97	0.52, 1.81	0.936
Alcohol use													
Never drinker	> 4	41 (3.7)	6 (2.6)	1					1				
	≤ 4	70 (6.2)	9 (3.8)	0.94	0.53, 1.64				0.94	0.53, 1.64			
Ever drinker	> 4	454 (40.5)	98 (41.7)	1.43	0.94, 2.17				1				
	≤ 4	557 (49.6)	122 (51.9)	1.81	1.20, 2.73	0.44	-0.08, 0.96	0.096	1.26	1.06, 1.50	1.35	0.75, 2.42	0.314

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; N, Number of Cases; D, Number of Deaths from any cause; %, Percentage; HR, Hazard ratio; 95% CI, 95% Confidence interval; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; RERI, Relative Excess Risk Due to Interaction; RHR, Ratio of Hazard Ratios; kg, kilogram; m, meter.

HR represents relative hazard of death from any cause for a contrast between individuals with MDS summary scores below the control-derived median summary score value (index) with those above the control-derived median summary score (referent).

[a] p-value for test of additive interaction based on the RERI.

[b] p-value for Likelihood Ratio Test for multiplicative interaction.

All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: <25; ≥25), educational attainment (categorical indicator: high school or less; some college; college graduation or more), history of having smoked cigarettes (categorical indicator: yes; no), history of having drunk alcohol (categorical indictor: yes; no), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), summary stage (categorical indicator: I; II; III; IV).

Table 4-7. Effect measure modification of the association between MDS summary score and the 5-year hazard of death from head and neck cancer by body mass index, race, smoking, and alcohol use, CHANCE Study, North Carolina, USA, 2002-2006

	MDS	Counts		Single Referent		RERI			Modifier Stratified		RHR		
Modifier Category	Summary Score	N (%)	D (%)	HR	95% CI	PE	95% CI	*P* [a]	HR	95% CI	PE	95% CI	*P* [b]
Body Mass Index (kg/m^2)													
≥ 25	> 4	285 (25.4)	37 (19.4)	1					1				
	≤ 4	345 (30.7)	49 (25.7)	1.17	0.78, 1.75				1.17	0.78, 1.75			
< 25	> 4	210 (18.7)	29 (15.2)	0.92	0.57, 1.47				1				
	≤ 4	282 (25.1)	76 (39.8)	2.06	1.40, 3.03	0.98	0.34, 1.61	0.003	2.24	1.47, 3.42	1.92	1.08, 3.42	0.025
Race													
Black	> 4	133 (11.9)	24 (12.6)	1					1				
	≤ 4	135 (12.0)	25 (13.1)	1.28	0.75, 2.20				1.28	0.75, 2.20			
White	> 4	362 (32.3)	42 (22.0)	0.79	0.47, 1.31				1				
	≤ 4	492 (43.9)	100 (52.4)	1.40	0.90, 2.19	0.33	-0.31, 0.97	0.311	1.78	1.25, 2.53	1.39	0.73, 2.62	0.317
Smoking													
Never smoker	> 4	76 (6.8)	7 (3.7)	1					1				
	≤ 4	73 (6.5)	7 (3.7)	1.99	0.66, 6.00				1.99	0.66, 6.00			

Ever smoker	> 4	419 (37.3)	59 (30.9)	1.30	0.45, 3.70				1				
	≤ 4	554 (49.4)	118 (61.8)	2.07	0.73, 5.82	-0.22	-1.84, 1.41	0.793	1.59	1.17, 2.16	0.80	0.26, 2.52	0.701
Alcohol use													
Never drinker	> 4	41 (3.7)	3 (1.6)	1					1				
	≤ 4	70 (6.2)	13 (6.8)	1.07	0.42, 2.72				1.07	0.42, 2.72			
Ever drinker	> 4	454 (40.5)	63 (33.0)	1.27	0.61, 2.63				1				
	≤ 4	557 (49.6)	112 (58.6)	2.15	1.06, 4.35	0.81	-0.08, 1.69	0.074	1.69	1.24, 2.30	1.58	0.60, 4.20	0.360

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; MDS, Mediterranean Diet Score; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; N, Number of Cases; D, Number of Deaths from head and neck cancer; %, Percentage; HR, Hazard ratio; 95% CI, 95% Confidence interval; PE, point estimate; L95, lower bound of 95% CI; U95, upper bound of 95% CI; RERI, Relative Excess Risk Due to Interaction; RHR, Ratio of Hazard Ratios; kg, kilogram; m, meter.

HR represents relative hazard of death from head and neck cancer for a contrast between individuals with MDS summary scores below the control-derived median summary score value (index) with those above the control-derived median summary score (referent).

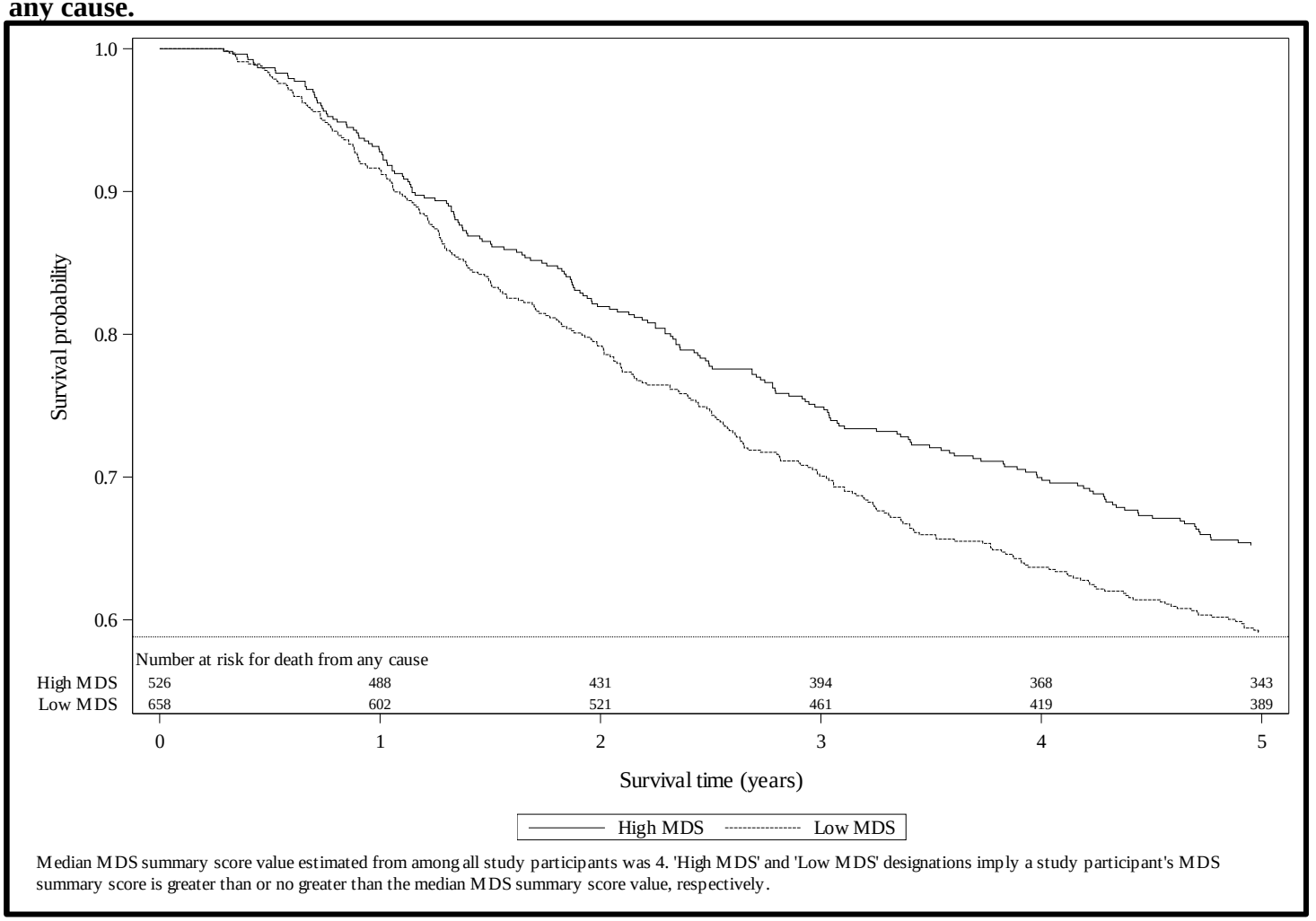
[a] p-value for test of additive interaction based on the RERI.

[b] p-value for Likelihood Ratio Test for multiplicative interaction.

All models were adjusted for age in years (categorical indicator: 20-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-80), race (categorical indicator: White; Black), sex (categorical indicator: male; female), body mass index in kilogram per square meter (categorical indicator: <25; ≥25), educational attainment (categorical indicator: high school or less; some college; college graduation or more), history of having smoked cigarettes (categorical indicator: yes; no), history of having drunk alcohol (categorical indictor: yes; no), quartile of energy intake in kilocalories per day (categorical indicator: >0, ≤ 1,517.8; >1,517.8, ≤ 1,909.5; >1,909.5, ≤ 2,359.5; >2,359.5), summary stage (categorical indicator: I; II; III; IV).

4.7 Figures

Figure 4-1. Product-Limit Survival Estimates for 'High' vs. 'Low' summary MDS for 5-year death from any cause.



Median MDS summary score value estimated from among all study participants was 4. 'High MDS' and 'Low MDS' designations imply a study participant's MDS summary score is greater than or no greater than the median MDS summary score value, respectively.

4.8 Supplemental Materials

Supplemental Table 4-1. Score Enumeration for Traditional Mediterranean Diet Score (MDS)

Component	Higher [a]	Lower [b]	Range
Fruits	x		0,1
Vegetables	x		0,1
Cereals/grains	x		0,1
Legumes	x		0,1
Fish	x		0,1
MUFA : SFA [c]	x		0,1
Dairy		x	0,1
Meat		x	0,1
Moderate alcohol [d]		x	0,1
Total	--	--	0,9

Abbreviations: MDS, Mediterranean Diet Score; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

[a] Implies that a study participant's energy-adjusted intake must be higher than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.

[b] Implies that a study participant's energy-adjusted intake must be lower than his or her corresponding median sex-specific energy-adjusted intake in the reference population in order to attain the maximum score of 1 for a given component.

[c] Is the ratio of monosaturated fatty acid intake to saturated fatty acid intake.

[d] Moderate alcohol intake is evaluated differently than the other components. A value of 1 is assigned to men who consume between 10 and 50 grams of ethanol per day and to women who consume between 5 and 25 grams of ethanol per day, otherwise, a score of 0 will be assigned.

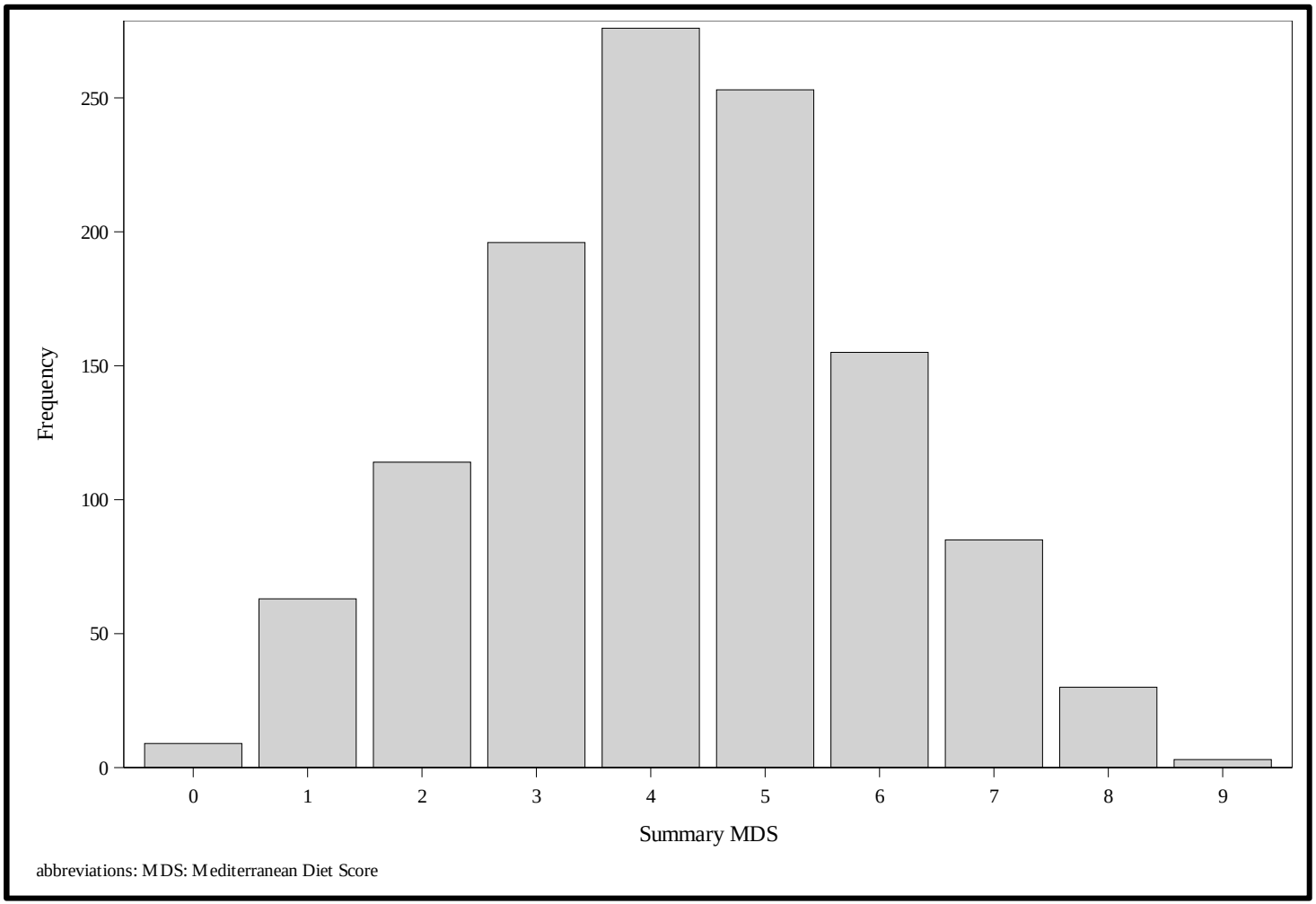
Notes: The location of the "x" for a given component of the Mediterranean diet score suggests which criterion must be satisfied for a study participant to attain the maximum score. For example, for fruits, the "x" is located under the column labeled "Higher" which suggests that study participants with energy-adjusted fruit intake above his or her corresponding median sex-specific energy-adjusted fruit intake for the reference population would be assigned a score of 1, and 0 otherwise. Energy adjusted intake implies Intakes will be calculated as servings or grams per 1000 kcals of energy intake.

Supplemental Table 4-2. Spearman Correlation Coefficients Among Individual Components of the MDS, CHANCE Study, North Carolina, USA, 2002-2006

MDS Individual Component	FR	VE	CE	LE	FI	MS	DA	ME	AL
Fruits (FR)									
Vegetables (VE)	0.41								
Cereals/grains (CE)	0.04	0.04							
Legumes (LE)	0.01	0.12	0.03						
Fish (FI)	0.18	0.22	0.05	0.10					
MUFA:SFA Ratio (MS)	0.05	0.06	0.14	0.09	0.04				
Dairy (DA)	-0.03	-0.01	0.00	0.04	0.06	0.22			
Meat Intake (ME)	0.06	-0.02	0.03	-0.00	-0.10	-0.02	-0.14		
Alcohol (AL)	-0.00	0.04	-0.08	-0.02	0.08	-0.02	-0.03	-0.07	

Abbreviations, symbols: HNC, Head and Neck Squamous Cell Carcinoma; CHANCE, Carolina Head and Neck Cancer Epidemiology Study; USA, United States of America; MDS, Mediterranean Diet Score; MUFA:SFA, monounsaturated fatty acid to saturated fatty acid ratio.

Supplemental Figure 4-1. Distribution of summary Mediterranean Diet Score, CHANCE, 2002-2006, NC, USA



abbreviations: MDS: Mediterranean Diet Score

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CHAPTER 5: DISCUSSION AND CONCLUDING THOUGHTS

5.1 Motivation

In 2021, there will be an estimated 67,000 new diagnoses of head and neck cancer (HNSCC) in the US. Because the aftermath of a head and neck cancer diagnosis is difficult to conceal from the public eye, it poses unique challenges for those who are afflicted with it. Treatment often requires surgical resection of large portions of the head and neck region. The resulting disfigurement and accompanying functional loss results in substantial declines in quality of life. HNSCC diagnosis is not only taxing for the individual experiencing the disease, but also for his or her family. Routine life experiences like being seen in public, enjoying a favorite food item, or even being close with a loved one are all severely impacted. Additionally, the management of HNSCC results in healthcare costs annually in the United States on the order of billions of dollars.

Smoking and alcohol use are established risk factors, and HPV has also emerged as a risk factor, in particular for oropharynx cancer. Because of the impact that HNSCC has on individuals and society, there is still a grave need to identify and study other potential targets that could prevent the occurrence of HNSCC, or if it does occur, to minimize the associated morbidity and prolong survival. Once such promising target is the diet.

In nutritional epidemiology, the original approach in which diet had been studied in relation to disease was to study the associations between individual nutrients and disease. In recent years, there has been a move to study diet holistically, to better appreciate the interplay

between individual nutrients and food groups on one another and how those interactions result in biological processes that affect the disease state.

The *a priori* and *a posteriori* approaches are used to characterize diet holistically. The former uses current knowledge on holistic diets and hypotheses and places them in context of real-world disease processes whereas the latter is data-driven and is hypothesis-generating.

Previously, studies have used *a posteriori* approaches to characterize the overall diet and explore its associations with head and neck cancer. For this dissertation work, the focus was to make use of *a priori* hypothesis-driven approaches to study how overall diet might be associated with HNSCC incidence and survival.

5.2 Aims and Key Findings:

This project made use of data from the Carolina Head and Neck Cancer Epidemiology (CHANCE) study, a population-based case-control study of HNSCC.

My first aim was to characterize the association between diet quality and cancer incidence of the head and neck. I also explored the association by anatomic site, HPV-positivity, race, BMI, alcohol consumption, and smoking.

For aim 1, we found that all three Diet Quality indices were inversely associated with HNSCC incidence with the HEI-2005 having the most prominent odds ratios for incident HNSCC, followed by the MDS-HNC and then the MDS. In terms of effect measure modification (EMM) we observed EMM by BMI and by alcohol use, both of which worked in a super-additive manner with poor diet quality to elevate the incidence OR. The key takeaway was that the MDS and its derivatives could be used in studies of HNSCC and also could be applied to an American population. Since all the indices mapped together consistently with respect to the diet quality-incident HNSCC association, we focused on just the MDS for the 2nd study aim. The goal of the second aim was to characterize the association between diet quality and head and

neck cancer survival and to also evaluate if anatomic site, HPV-positivity, race, BMI, alcohol use, and smoking modifies the association.

We observed a similar inverse association between diet quality and mortality; however, our findings were not as precise. We additionally observed EMM by BMI and alcohol use for both death from any cause and death from HNSCC.

5.3 Strengths and Limitations

As with observational studies in which exposure and covariate information is captured after disease state has been determined, recall bias is always a threat to the internal validity. This dissertation work is no different. Particularly aim 1, when both cases and controls provided self-reported responses to an array of questionnaire items, cases may respond to questions in a way that is distinct from that in which controls may respond. For example, an individual recently diagnosed with head and neck cancer may recall his/her smoking history much more accurately than might a control individual because he or she has heightened awareness of the links between smoking and head and neck cancer. Conversely, the same individual may instead underreport their social or behavioral history because of social desirability bias. Examples of items that individuals may be reluctant discuss include sexual practices or the degree to which they may use tobacco products or consume alcoholic beverages. There are forces and influences that cause cases and controls to differentially self-report information and this can bias the results of any investigation based on data that was collected from such a process. When cases are much more accurately recalling their exposure to cigarette smoking, for example, and controls are perhaps less so, the measure of association under study will likely be exaggerated.

The other major challenge for this study is that we are assuming that the diet that is recalled by our study participants is constant and reflects the diet that was relevant the many years prior when the initiating or progressing event for the study participant's cancer occurred.

Of course, with respect to survival, it is possible that events closer to diagnosis may have more influence. In cancer epidemiology, there is often a lengthy latent period between the initiation and eventual progression to the point of symptomatic disease. Because of this lengthy latent period, and because of the likely fluctuation of dietary practices over the life course, the dietary exposure that is captured by self-report to reflect the 'usual diet' in the year preceding the diagnosis or interview is likely misclassified to some degree which means that the resulting measures of association are biased towards the null.

Some strengths of this study include the population-based design, ability to study HPV, the fairly large sample size of cases and controls, and a rich set of covariate information that allowed us to adjust for confounding. The use of a validated FFQ to capture our exposure was also key. Additionally, the ability to explore racial differences, was important because of the long-lasting disparity in cancer outcomes between Blacks and White individuals in the United States. Although the data we used for our analysis was a racially diverse sample, the number of Black study participants was still too small to identify differences in the diet quality HNSCC associations by race.

We did observe EMM between BMI and alcohol consumption in both aims. In both cases, the finding with BMI is thought to be due to reverse causation. That is, the disease or their smoking history is more likely to have cause individuals to have low BMI as opposed to cases naturally being underweight. Additionally, we noted that folks who drink alcohol, do so at the expense of key nutrients that are necessary to counteract the carcinogenic compounds to which an individual is exposed when he or she consumes alcohol.

5.4 Future directions and public health impact

Diet is ubiquitous. And we observed in our work that diet quality is inversely associated with incident HNSCC and with delaying mortality following diagnosis. This finding is key, and

it suggests that efforts and interventions focused on improving diet quality, especially among underweight individuals, or among individuals who choose to drink alcohol, could have important implications with respect to the possible prevention of the occurrence of HNSCC and the possible ability to prolong life if adequate nutrition were practiced prior to diagnosis. Perhaps our results provide further justification for improving diet quality. That is, we may have position to convey that a high-quality diet allows one to not only avoid chronic diseases generally, but also that, as our findings suggest, on average, an individual who consumes a higher quality diet, compared to an exchangeable person who consumes a lower quality diet is more likely to avoid being diagnosed with head and neck cancer. And, if one is unfortunate to have been diagnosed with HNSCC, then he or she who consumed a higher quality diet prior to his or her diagnosis, is likely to delay experiencing death compared to a similar individual who had consumed a poorer quality diet.

Of course, it would be important for other investigators to replicate our findings and conduct other investigations that might be able to overcome the limitation of our study. If there were a way to capture an individual's dietary patterns more accurately over the life course and map these changes to an individuals' physiology and molecular profile over time, then we may very well have the data we need to fully understand the associations between diet quality and head and neck cancer. Right now, though, because HNSCC is so rare, the traditional case-control study in which a food frequency questionnaire is administered to capture dietary exposure data, even with its flaws, is still one of the most efficient ways of studying diet-cancer relations.

If another case-control study were to be designed, an effort should be made to recruit more Black study participants. As was the case in our analysis, there simply were not enough

Black study participants to power sub-group analyses, and so future studies should emphasize Black recruitment so that we may better understand the challenges that have led to the racial health disparities and create a society that will strive for more equitable healthcare access and better health outcomes for everyone.