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Psychological Aspects of Head and Neck Cancer

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PSYCHOLOGICAL ASPECTS OF HEAD AND NECK CANCER

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

HNC	Head and neck cancer
US	United States
NPC	Nasopharyngeal Carcinoma
EBV	Epstein Barr Virus
HPV	Human Papillomavirus
PAF	Population Attributable Fraction
NCDB	National Cancer Database
CT	Computed Tomography
PET	Positron Emission Tomography
AJCC	The American Joint Commission on Cancer
PTSD	Posttraumatic Stress Disorder
DNA	Deoxyribonucleic Acid
SEER	Surveillance, Epidemiology, and End Results
ICD-O3	International Classification of Disease for Oncology, Version 3
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
CCI	Charlson Comorbidity Index
HMO	Health Maintenance Organization
OR	Odds Ratio
95% CI	95% Confidence Interval
HR	Hazard Ratio
PHQ	Patient Health Questionnaire

ABSTRACT

Patients with head and neck cancer may be at increased risk for depression diagnosis when compared to other cancer sites, both before and after their cancer diagnosis. Behavioral risk factors for head and neck cancers, including tobacco and alcohol use, may be indicative of depression before cancer diagnosis. Further, head and neck cancers and their treatments can cause serious morbidity among patients, including physical disfigurement and loss of function. Additionally, these cancers are often accompanied by social stigma, personal shame, and guilt. While there is a significant body of research examining depression in this cancer population, there are still several gaps in the existing literature.

This dissertation explores the relationship between depression and head and neck cancer. Utilizing SEER-Medicare data, this research examines the rates of depression in the elderly adult head and neck cancer population, the influence that depression has on stage and survival, and the associations between radiation treatment side-effects and depression diagnosis. The results of the studies included in this dissertation may assist in guiding interventions for depression prevention and management in this population, and in improving cancer outcomes and quality of life for head and neck cancer patients.

CHAPTER I

OVERVIEW OF HEAD AND NECK CANCER

What Is Head and Neck Cancer?

Head and neck cancers (HNC) are malignancies of the upper aerodigestive tract and include areas of the body such as oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx (1; 2). According to a recent GLOBOCAN report by the International Agency for Research on Cancer, in 2008 HNC was the seventh most common cancer in the world (1; 3). Though often grouped together, HNCs are a relatively heterogeneous group of cancers, affecting different parts of the body and physical function.

HNCs can have significant effects on morbidity and mortality of patients, as well as their quality of life and well-being. In this dissertation, we will first examine this disease and its treatments in order to better understand how HNC can affect those diagnosed. HNCs can be grouped into sub-categories based on location in the body as well as specific cancer type. In the subsequent sections, we will describe the following groups of HNCs in more detail: Oral cavity and oropharyngeal cancers, nasopharyngeal cancers, and laryngeal and hypopharyngeal cancers.

Oral cavity and oropharyngeal cancers. The oral cavity includes the mucosal lining of the lips, buccal mucosa, retromolar trigone, alveolar ridges, the anterior tongue, floor of the mouth, and the hard palate (4). The oropharynx includes the posterior third of the tongue, the soft palate and uvula, tonsils, and the upper part of the posterior pharyngeal wall (4). The oral cavity and oropharynx help in breathing, talking, eating, chewing, and swallowing, while salivary glands produce saliva that aids in food digestion (5).

Different cancers can develop from the various cells in the oral cavity and oropharynx. Squamous cell carcinomas make up around 90% of cancer in these areas of the body (4).

However, other types, including lymphomas, adenocarcinoma of the salivary glands, and malignant melanomas can also occur (4). Based on national estimates, approximately 1.1% of males and females in the United States (US) will receive a diagnosis of oral or pharynx cancer during their lifetime (6). In 2015 alone, it is estimated that there were over 45, 000 new cases of oral cavity and pharynx cancer nationally (7).

Nasopharyngeal cancer. The nasopharynx is the portion of the pharynx located behind the nasal cavities located behind the nose, just above the oropharynx (8). The nasopharynx serves as a passage for air into the body (9).

Nasopharyngeal carcinomas (NPC) are the most common malignancies of the nasopharynx, and arise in the epithelial cells and include squamous cell carcinomas, non-keratinizing carcinomas, and undifferentiated carcinomas (10; 11). Other types of cancers that can occur in the nasopharynx include lymphomas and adenocarcinoma and adenoid cystic carcinomas (12).

NPC is much more commonly found in certain parts of Asia and Africa, and tends to afflict men more than women (10). In the US, NPC is relatively uncommon, representing an estimated 1 in every 100,000 cases of cancer, compared to 25 in every 100,000 cases in parts of China (13).

Laryngeal and hypopharyngeal cancer. The larynx, or voice box, is the opening into the trachea from the pharynx and functions in respiration, swallowing, and speech (14). The hypopharynx, which makes up the lower region of the pharynx, is located just above the larynx and helps in respiration (15). As with other cancers of the head and neck, the majority of laryngeal and hypopharyngeal cancers are squamous cell carcinomas (16; 17). However, other types, such as adenocarcinomas, may also occur (17).

In 2015, there is estimated to be over 13,500 new cases of laryngeal cancer in the United States, and that there will be approximately 3,400 new cases of pharynx cancer that will start in the hypopharynx (7; 18). The rates of laryngeal cancer have been declining in recent years due to the reduction of smoking in the US population (19).

Epidemiology of Head and Neck Cancer

Worldwide, there is variation in the rates of the disease between populations. For men in developed countries, the age standardized rates for oral cavity, pharynx, and larynx cancers range from 5.1-7.9 in more developed regions, compared to 3.4-5.7 in less developed regions (20). For females in more developed regions, the age standardized rates of these cancers ranges from 0.7-2.4, compared to 0.6-3.5 in less developed regions (20).

Though relatively rare in the US, the burden of HNC is still significant. It is estimated that there will be nearly 60,000 new cancer cases of oral cavity, pharynx, and larynx cancers combined, with over 43,000 of these new cases in males and nearly 16,000 in females (7). Combined, these cancers will be associated with over 12,000 deaths (7). Further, HNC carries a significant financial burden, with the estimated direct medical costs in the US for HNC patients was over $3.6 billion in 2010, with nearly equal indirect costs associated with factors such as work loss in these patients (21).

In the US, the rates of certain HNCs have been on the decline in recent years, while other HNCs have remained steady or are on the rise. For instance, cancer of the larynx has been declining by 2.4% annually over the last decade (22), likely due to decreases in tobacco use. However, oropharyngeal cancers have shown increases in recent decades, which is thought to be associated with human papillomavirus (HPV) in the population (23; 24). Though improvement in HNC survival has been seen in recent years (25), the survival of HNC remains low, with five-year

survival estimates around 60% (26). Five year relative survival for larynx cancer ranges from 35.2%-75.9% depending on stage of cancer, while five year relative survival for cancers of the oral cavity and pharynx ranges from 37.7%-83.0% (26).

The incidence and associated mortality of HNC in the US have, overall, shown downward trends. However, within certain subpopulations and cancer sites, these trends are not consistent. For example, Kingsley et al (2008) found that the incidence of oral cavity cancer in Black females from 2000–2004 increased by over 3% (20; 27). Further, Gayar et al. found increases in the incidence of oropharyngeal carcinoma among white men from 1973-2009, but a decrease in incidence during this same time period among Black men (24). These examples may be indicative of the changes in risk factors and behaviors associated with the diagnosis of HNC based on sociodemographic differences.

Risk Factors for Head and Neck Cancer

HNCs as a group have been associated with a number of risk factors for their development. There are two major risk factors associated with HNC diagnosis: substance abuse (alcohol and tobacco) and HPV (1). Though these risk factors tend to be discussed most frequently in the literature, other risk factors that have also been linked to HNC as described more in details in the following sections.

Tobacco and alcohol use. Substance use, specifically alcohol and tobacco use, is a major risk factor for HNC (2). The risk for developing HNC has been shown to be as high as 25 fold higher for in those who smoke cigarettes than nonsmokers (28; 29). Further, alcohol consumption has been associated with a twofold higher risk of HNC development compared to those who do not consume alcohol (2). While both tobacco and alcohol use alone have been shown to be independent risk factors, the attributable risk of HNC for the combination of use has been shown

to be approximately 75-80% in past literature, indicating there is a synergistic effect (2; 29). As risky lifestyle behaviors, such as smoking, have declined in the United States, so have their associated cancers, including some forms of HNC. However, new risk factors are being identified in relation to HNC incidence.

Infections. Certain viral infections have been found to be associated with HNC development. Epstein Barr Virus (EBV) has been shown to be associated with different cancers in humans, including NPC. NPC is more common in areas where the incidence of EBV is high, including some African and Asian countries, especially Southern China (30).

HPV has also been found to be associated with several types of HNC, including oral cavity, laryngeal, and hypopharyngeal cancers, but the relationship is inconsistent and not clearly related to causation. HPV, particularly subtypes 16 and 18, is most frequently associated with oropharyngeal cancers (2). Recent studies on HPV, specifically subtype 16, have suggested that this virus may be an independent risk factor for oropharyngeal carcinoma arising in the palatine and lingual tonsil tissue (31). Further, HPV-associated HNCs are distinct from non-HPV associated HNCs in terms of presentation and prognosis (2).

The impact of infection on cancer incidence varies by both cancer site, as well as geographic location. The global estimated population attributable fraction (PAF) of EBV infection for NPC is 85.5%, with a greater number of attributable infections in less developed regions. For oropharyngeal cancer, the PAF of HPV infection is 25.6%, but there are a greater number of attributable infections in more developed regions (32). These variations are largely due to the prevalence of HPV infection in these areas, and may change in response to increasing rates of HPV in the future.

Age, gender, and race. There are differences in HNC incidence across age and gender. While there are differences based on specific location and subtype, like many other cancers,

HNCs are more likely to be diagnosed in individuals aged 50 and older (33; 34). Based on data from the National Cancer Database (NCDB), in the US, nearly 70% of all HNCs occur in individuals over the age of 50 (34). However, data from the NCDB also showed that a decline in the proportion of squamous cell cancers among older adults, and a greater proportion of HNC cases in individuals aged 40-49 years of age (34), which likely is a manifestation of increasing HPV-associated cancers of the oropharynx and a decline in tobacco-associated cancers.

There are also notable gender and racial differences in HNC incidence. In general, the male-to-female ratio for HNC is 2:1 to 5:1 (35). However, in recent years, the gap between the genders has started to narrow slightly, with declines in HNC incidence being more dramatic in males compared to females (36), likely due to declining rates of substance use (37). Further, there are racial differences in HNC incidence and mortality in the US, with Blacks bearing a greater burden compared to Non-Hispanic Whites (38).

Other risk factors. Many other factors have been associated with an increased risk of HNC. Certain genetic factors have been associated with greater risk of HNC, including polymorphisms in genes involved in tobacco and alcohol metabolism (2). Further, studies have found that individuals with a family history of HNC are at increased risk for HNC diagnosis (39). Certain environmental and occupational exposures such as asbestos and cement, as well as certain heavy metals such as nickel and chromium, have been identified as potential risk factors for HNCs (40; 41).

Other factors have also been associated with HNC diagnosis. Lower body mass index has also been associated with increased risk of HNC, even after controlling for tobacco and alcohol use (42). Similarly, diet has been found to be associated with HNC, with higher consumption of red or processed meats associated with a greater risk of HNC, and higher consumption of fruits and vegetables associated with a lower risk of HNC (43). Additionally, due to the association

between HPV and HNC, sexual history and number of sexual partners has also been found to be associated with increased risk for HNC (44).

Diagnosis of Head and Neck Cancer

Depending on stage and site, HNC can sometimes be difficult to identify because of vague symptoms and location. Symptoms of oral cancers often include non-healing sores in the oral cavity, while those of the pharyngeal cancers include symptoms such as sore throat, trouble swallowing, or pain in the ear (28; 35).

The diagnosis of HNC may vary by specific site of cancer within the HNC group. However, in general, diagnosis begins with a general physical examination, with a health care provider examining all areas of the oral cavity, as well as the nose, ears, scalp, and lymph nodes (2; 28). Endoscopy may then be performed for examination of areas such as the nasal cavities, base of the tongue, larynx, and pharynx (2; 28). Biopsies may be taken from any abnormal areas for further confirmation (2; 28).

Once cancer is confirmed, there are several tests which can be used to examine the extent, or stage, of the disease. Computed tomography (CT) is often performed for this purpose, as well as positron emission tomography (PET) (28). Other tests may also be performed, including x-ray to examine potential spread to the bone, chest imaging for those at risk for distant metastases and molecular and HPV testing of the tumor to guide treatment (2; 28; 45).

Staging and Treatment of Head and Neck Cancer

The American Joint Commission on Cancer (AJCC) TNM staging system is often used for HNC staging (28). This system utilizes information on tumor size and location, information on lymph node spread, and cancer metastasis to stage cancer. Though differences in classification

may occur based on specific cancer site, in general, the "T" classifications range from T1 to T4 depending on size and location of the tumor, with T1 representing the least advanced stage and T4 representing the most advanced stage. For this classification, T4 describes advanced stages of the disease where the tumor has invaded adjacent structures. The "N" classifications range from N0 to N3, with N3 describing metastasis in a lymph node > 6 cm in greatest dimension. Finally, the "M" classifications range from M0 to M1, where M1 indicates the presence distant metastasis and M0 indicates none (28; 45). Together, these cancer characteristics are used in helping to determine the stage of HNC.

The specific treatment of HNC depends on the site and stage of cancer, side-effects of treatments, and patient demographics and preferences (28; 45). Treatment for HNC can involve surgery, radiation, chemotherapy, or some combination of these (28; 45). Single-modality therapy is the goal when possible. Generally, cancers in the early stages are treated with surgery or radiation (28). For more advanced stages, HNC is often treated with surgery, if possible, followed by radiation with or without chemotherapy, or with concurrent chemoradiation when tumor resections not advisable (28).

The diagnosis and treatment of HNC is a very complex and multifaceted process. As with other cancer, treatment for HNC often involves a multidimensional team approach, utilizing the knowledge and skills of different healthcare professionals. Those involved in the treatment of HNC may include oncologists, radiologists, and surgical oncologists for the eradication of cancer; plastic surgeons, prosthodontists, and physical and speech therapists for physical construction and rehabilitation; and psychologists and social workers for the psychological and emotional health of patients (45).

DEPRESSION IN HEAD AND NECK CANCER

Cancer and Depression

Cancer diagnosis and treatment often cause psychological distress for patients. As a result, there is a significant body of literature on the relationship between cancer and mental health disorders, including anxiety, adjustment disorders, and posttraumatic stress disorder (PTSD) (46; 47). However, depression, both diagnosis and symptomology, has received the most attention of any psychological illness in previous oncology literature (48).

Depression is common among cancer patients. In a recent meta-analysis, the prevalence of depression in cancer patients ranges from 8% to as high as 27% (49). Further, it has been estimated that the occurrence of major depressive episodes among cancer patients is approximately two to three times higher than in the general population (50). Overall estimates show that the prevalence of major depression in cancer patients range from 3% to as high as 38% and that depressive spectrum syndromes among cancer patients may be as high as 52% (51). The prevalence of depression varies by several factors including patient characteristics (such as gender and age) depression assessment features (such as time of administration and type of measurement), as well as clinical factors of cancer diagnosis (49; 52).

Not surprisingly, clinical features, including stage and specific site of cancer, have also been shown to impact estimates of the prevalence of depression in cancer patients. Certain types of cancer have been found to have a greater association with depression than others in previous literature. HNCs, along with those of the brain, pancreas, breast, and digestive tract, have been associated with higher rates of depression (49; 51). At the time of diagnosis, depression rates in HNC have been estimated to be as high as 40%, and depression has been shown to afflict nearly 30% of HNC patients even three years after diagnosis (51; 53). The diagnosis and treatment of

HNC have been associated with high morbidity in patients, including physical disfigurement, loss of function, and reduced quality of life (51; 54; 55), all of which may help explain the increased risk of depression among HNC patients. Further, lifestyle factors preceding cancer, such as excessive tobacco and alcohol use, may be indicative of preexisting depression.

Depression Preceding Cancer

The relationship between depression and chronic illnesses, such as diabetes and coronary artery disease, is thought to be reciprocal in that one may increase the risk of the other (56). There are a number of factors associated with both depression and HNC, including excessive alcohol and tobacco use and other poor lifestyle choices (57), which may put this particular cancer patient population at higher risk for experiencing depression during cancer diagnosis and recovery. However, these factors may also be signs of preexisting depression, indicating that preexisting depression may put individuals at risk for developing cancers such as HNC. Because depression can affect behavioral risk factors for cancer, there has been speculation as to whether depression may influence the incidence of certain cancers (58).

Depression has been theorized to influence cancer development in one of several ways. One theory is that depression may weaken the immune system causing the individual to be at greater risk for disease development (59). Another is that chronic stressors associated with depression may cause a decrease in deoxyribonucleic acid (DNA) repair enzymes and natural killer cells important in apoptosis, therefore allowing malignant cells to grow (59). Others include shared genes relating to both diseases, as well as shared behavioral risk factors (59). These theories indicate the potential influence of depression on cancer development and suggest potential areas of intervention to improve HNC outcomes.

While the reciprocal relationship between depression and other chronic diseases has been shown (56) there is still significant debate about the reciprocity of depression and cancer, and previous research on the topic has led to mixed results. In an examination of patients hospitalized for depression in Denmark, the authors found that brain cancers and tobacco-related cancers, such as lung cancer, were higher than expected in depressed patients, but that overall cancer incidence in depressed patients was not significantly different from national cancer incidence rates (58). The authors suggest the results may highlight the negative effect that depression and other mental illness may have on health behaviors (58). Further, in a sample of 3,177 individuals in the United States followed for 24 years, Gross et al. (2010) found an increased incidence of overall cancer and hormonally-mediated cancers, including prostate and breast, among individuals with a history of depression (59). However, the authors found no association between depression and other cancers including colon, lung, and skin. Because there is still significant debate surrounding the influence of depression on cancer development, additional larger, longitudinal studies are needed to help understand the relationship between depression and cancer development.

Depression and Cancer Diagnosis

Understandably, the diagnosis of cancer can cause significant physical and psychological distress. Cancer patients must cope with the physical changes, medical care and financial costs of treatment, and time away from family and work. HNC patients may face a number of challenges during diagnosis and treatment that may put them at increased risk of depression (54). The diagnosis of HNC often carries significant stigma, as these cancers may be seen as self-inflicted due to lifestyle choices (60). Further, individuals with depression may present with later stages of cancer at the time of diagnosis, resulting in more intensive treatments, higher morbidity, and poorer survival outcomes (61). Patients with HNC may be at increased risk of depression because many diagnostic and treatment procedures of HNC lead to obvious physical disfigurement, loss of

basic functions such as eating and speaking, and other negative side-effects of treatments (53). In particular, radiation treatment may result in various side-effects that can impact the psychological health of HNC patients.

Radiation Treatment and Depression

Radiation therapy, either alone or in combination with surgery, is the typical treatment for HNC (62). Though these therapies have been proven to help decrease mortality in HNC patients, radiation treatments are frequently associated with several side-effects unique to or more severe in this patient population. There are a number of radiation side-effects that can impact the daily lives and functioning of HNC patients.

Oral or dental related diagnoses have been reported in previous studies and may be particularly pertinent to the HNC population (63). HNC patients undergoing radiation may have oral and dental issues related to cancer itself, but also due to the radiation they receive. Patients who receive radiation have been shown to have increased trouble producing saliva and swallowing, concerns about social eating due to loss of functioning, dry mouth, increased risk of dental caries, and oral infection (63; 64). Further, xerostomia, or dry mouth, has been shown to significantly affect functioning and quality of life (65; 66). In fact, in a systematic review by So et al. (2012), two of the three most commonly reported side-effects related to quality of life in HNC patients were xerostomia and sticky saliva (66).

Weight loss, loss of appetite, and malnutrition have also been reported side-effects of radiation treatment in HNC patients (67; 68). The HNC population has been shown to be at increased risk for these side-effects compared to other cancer sites due to both the physical obstructions and limitations that may be involved in HNC, as well as potential toxicities from treatment (67; 68). Other common side-effects reported in HNC patients include fatigue, pain,

and dermatitis (66; 69; 70). These can all negatively affect the psychological health of HNC patients and, ultimately, patient outcomes.

Radiation has also been found to be associated with depression. In a randomized trial of the antidepressant escitalopram for the prevention of depression in HNC patients, it was observed that the development of depression was more likely to occur in those patients who received radiation (71). Furthermore, recent evidence shows suicide risk is also substantially higher in HNC patients who receive radiation as part of their treatment (72).

Depression and Survival Outcomes among Head and Neck Patients

Depression in HNC and other cancer patients can have a significant and lasting impact on these individuals, and this impact can be seen both before and after cancer diagnosis. In general, mental illness, such as depression, may lead to less frequent screening for cancer and therefore later stage at diagnosis (73; 74). The diagnosis of cancer at later stages can result in more invasive treatments and poorer survival probability for patients. In fact, previous research has shown that depression in cancer patients results in lower quality of life and may affect survival outcomes (48; 75). Specific to the HNC population, studies have shown that individuals with HNC have a substantially higher risk for completed suicide when compared to other cancers and the general population (72; 76; 77).

Limitations of Previous Research

Previous literature looking at depression in HNC has estimated the proportion of depressed patients in this cancer population to vary widely. This may be due to the differences between these earlier studies, as well as the limitations of each. Many previous studies have used smaller sample sizes, or single-site hospital-based samples for their research, which may not

allow for representative estimates of depression of this population. However, the most significant differences among many of these studies were the variation in how depression has been measured.

Depression in previous literature among HNC patients has been assessed by a number of different methods. In a systematic review done in 2009, the authors identified over ten different inventories, scales, or symptom checklists used to assess depression in HNC patients in over 50 studies (53). Within each of these studies, even those that used the same inventory utilized different cut-off scores for their definition of depression. Further, the type of assessment differed amongst many of these studies and included self-report measures, symptom frequency checklists administer by a third party, and diagnostic codes found in administrative data. The differences among these studies make it difficult, not only to make comparisons among these, but also make it difficult to compare the rates of depression between HNC patients and other cancer groups.

In addition to gaps in the literature regarding depression incidence or prevalence estimates in HNC patients, there is also limited information on the prevalence of depression prior to cancer diagnosis in this population. Further, there is scarce research examining the influence that preexisting depression may have on the stage of cancer at the time of diagnosis in the HNC population. A large population-based clinical/administrative database, such as the SEER-Medicare linked data, offers a unique opportunity to examine depression diagnosis in cancer patients in the US, both before and after cancer diagnosis, and help to understand the potential reciprocal relationship between depression and HNC throughout the course of cancer.

SEER-Medicare Linked Database as a Unique Source of Depression Research

The Surveillance, Epidemiology and End Results (SEER) database is a surveillance system designed to track cancer incidence and survival in the US (78). Data collection for this

system began in 1973 and it has continued to routinely collect high quality data on cancer incidence and mortality over the last four decades. The SEER data cover over 20 geographic areas in the United States with 98% completeness, and is considered to be highly valid and representative of the US population (79). While SEER data offers much valuable information on cancer incidence and outcomes, by itself, it is not able to offer information on risk factors, comorbidities, and certain treatments received by the cancer population.

Starting in 1991, SEER data began being linked to Medicare data in order to fill some of the gaps in cancer research. Medicare is a form of public insurance offered to individuals 65 and older in the United States, and is the primary insurer for approximately 97% of this population (79). Medicare data offer demographic and clinical information on Medicare patients for things such as inpatient and outpatient visits, hospice and home health care, and prescription medication use (79). The SEER-Medicare data files are linked using a series of algorithms matching individuals in the data using identifying information such as name, date of birth, and social security number, and approximately 93% of those in the SEER data are successfully linked to Medicare files (78).

SEER-Medicare linked data offer the benefit of having population-based cancer data as well as longitudinal information on risk factors and comorbidities found in medical record files. Because SEER-Medicare data offer information on medical diagnoses other than cancer, this linked dataset has been used in previous studies in order to examine the associations between depression and various cancer sites, including breast, prostate, and pancreatic cancers (61; 80; 81), and therefore may provide an opportunity to compare depression rates in HNC patients to those of other cancer sites.

Specific Aims

HNCs are a distressing group of cancers, both physically and emotionally. While there is a significant amount of literature examining the relationship between cancer and emotional and psychological health, this existing body of literature has not yet fully examined the influence of depression on stage at diagnosis, the influence that treatment side-effects may have on depression development in these patients, or the role of depression in the survival of HNC.

The purpose of this dissertation is to examine the psychological aspects of HNC in order to fill these gaps in the literature. The first study of this dissertation (Chapter 2) examines the existing literature concerning depression in cancer patients and aims to develop a conceptual model to better understand the pathways to depression in the HNC population. Utilizing the SEER-Medicare linked data, the aims of the second study of this dissertation (Chapter 3) are to: (1) estimate the prevalence of depression two years before cancer diagnosis, (2) estimate the incidence of emergent depression one year after diagnosis of HNC, and (3) compare stage of HNC diagnosis by depression status. The third study (Chapter 4) aims to investigate the 5-year survival of HNC patients by depression status, and the final study (Chapter 5) aims to examine the association between radiation treatment side-effects and depression outcomes in HNC patients.

Together, these studies will help to reexamine the existing assumptions of the relationship between depression and HNC diagnosis, and provide population-level information on the associations between depression and cancer outcomes. The results of these studies may help to establish policies for screening for depression in HNC patients at the time of cancer diagnosis, but also help in influencing cancer treatment choices based on the risk of depression development and standards for continued screening for depression during cancer treatment and recovery.

CHAPTER II

CONCEPTUAL MODEL DEVELOPMENT TO UNDERSTAND THE PATHWAY TO DEPRESSION AMONG HEAD AND NECK CANCER PATIENTS

Abstract

This paper proposes a conceptual model to understand the development of depression in head and neck cancer patients. We conducted literature reviews of existing conceptual models of depression among chronic disease patients and risk factors of depression in cancer patients. The resulting model shows that both individual and contextual level factors can directly and indirectly affect depression outcomes. Additionally, depression diagnosis may also impact treatment decisions and lead to poor survival outcomes. The resulting model can help guide future research in this and other cancer populations, and be used to develop targeted interventions for depression in cancer patients.

Background

While cancer patients in general have been shown to be at risk for depression, head and neck cancer (HNC) patients experience a number of risk factors for mental illness that are unique to this group of cancers (82). Patient lifestyle preceding cancer often includes a history of substance use and other high-risk behaviors (57). These behaviors may put individuals at increased risk not only for cancer development, but also at increased risk for mental illness both before and after cancer diagnosis. Upon cancer diagnosis, HNC patients may be forced to contend with feelings of guilt knowing that their past behaviors may have predisposed them to cancer, and may experience shame and stigma associated with an HNC diagnosis (83). During treatment and

recovery, HNC patients are often left with functional impairment and physical disfigurement as a result of their treatments (57; 84; 85), as well as the struggle associated with withdrawal and abstinence from tobacco and alcohol use (86). Though cancer diagnosis has been associated with a variety of mental illnesses, including anxiety and post-traumatic stress disorder (46; 47), depression may be one of the most prevalent comorbidities in the cancer population (48).

Previous research has shown that depression may affect anywhere from 9-54% of HNC patients during the course of cancer and recovery (53). Preexisting depression has been linked to a lower survival, worse nutrition and lower quality of life in HNC patients (87) . In a prospective depression prevention trial, emergent depression was strongly associated with radiation therapy (88). Further, the rate of suicide in HNC patients has been estimated to exceed most other cancer sites, with rates estimated at 53.1 and 46.8 per 100,000 person-years for oral cavity/pharynx and larynx cancers compared to 32.4 for all cancers sites combined (72; 77). Suicide appears to be especially high in patients that receive radiation therapy (72). Based on existing literature, there is an apparent connection between depression and HNC, both before and after cancer diagnosis. However, although contributing factors in this population have been identified, the pathway to how these factors influence depression development is not well understood and the need for a more methodical understanding is acute.

In health research, conceptual models help to provide a way of unifying and organizing ideas to help structure the design and interpretation of studies (89). Additionally, conceptual models can aid in research design and offer clinical utility in understanding disease development and prognosis. While several conceptual models have been proposed to understand the association between depression and cancer, very few have focused specifically on the HNC population.

In their article on depression in HNC patients, Archer et al. developed a conceptual model to understand the pathways linking depression and oral cancer, focusing heavily on the

biological components of the disease. After a review of the literature, the authors concluded that preexisting depression had no effect on cancer incidence. However, the authors developed a model to explain the possible effects of stress-hormone activity and increased cytokine levels that may lead to increased risk of mortality in cancer patients with depression (82). Emphasizing more of psychosocial aspects of disease, Frampton described a conceptual model centering on factors relating to psychological distress in relation to the diagnosis of treatment of HNC (90). In this model, the author included factors such as body image, social stress, and history of psychiatric illness in the development of psychological distress in HNC patients. Additionally, Llewellyn et al. used the common sense model framework to describe how HNC patient beliefs about their illness influence outcomes such as depression of quality of life (91). While each of these models offers insights into the relationships between HNC and depression, they concentrate mostly on depression after cancer diagnosis and, therefore, do not fully explain the relationship between HNC and depression.

The purpose of this paper was to develop a conceptual model examining the associations between depression and HNC at various time points, both before and after cancer diagnosis. Using the current literature of depression development in cancer and other chronic diseases, as well as the existing body of knowledge of factors contributing to depression in HNC, we have developed a conceptual model to understand the development of depression in HNC patients and its influence on cancer outcomes in this population.

Methods

A literature search was conducted to identify existing conceptual models of depression among chronic disease patients and risk factors of depression in cancer patients. Articles were identified by literature database searches of MEDLINE and EMBASE from January 2000-May 2015. Keywords that were searched included the following: conceptual model, conceptual

framework, cancer, depression, and head and neck cancer. In order to incorporate known factors associated with depression in HNC patients, a second literature search was conducted utilizing MEDLINE and EMBASE databases from January 2000-May 2015using the keywords depression and head and neck cancer. The searches were limited to humans and articles in English.

Relevant articles were reviewed and variables associated with depression in chronic disease patients were extracted from the literature. From these variables, those relevant to the HNC population were incorporated into the model. Articles utilizing conceptual models or theoretical frameworks were reviewed and relevant aspects were incorporated into the proposed conceptual model at various time points over the course of cancer diagnosis and treatment. Using previous models as a framework and previous literature identifying factors associated with psychological health in HNC patients, we developed a conceptual model of depression in HNC focusing on both the effects of depression prior to cancer diagnosis, as well as the development of depression following cancer diagnosis. Factors that were related to HNC patients were included in the model

Results

Our search for conceptual models for depression and cancer or HNC resulted in a total of 203 unduplicated articles between the searched databases. All abstracts were reviewed for relevance, and citations of relevant publications were examined to identify any articles missed in the search. This resulted in a total of 47 articles that utilized or developed conceptual or theoretical models concerning cancer patients and other chronic diseases with some incorporation of the psychological aspects of the disease. The search for depression and HNC resulted in 426 unduplicated articles across the databases. Of these, 85 articles were identified which examined risk factors for depression development in HNC or identified implications of depression in HNC patients. Table1 gives a listing of the various factors influencing depression in HNC patents

before and after cancer diagnosis, and Figure 1 shows the proposed conceptual model based on our synthesis of the literature. As can be seen from the model, we included factors influencing depression prior to cancer diagnosis as well as the influence that cancer diagnosis may have depression development. The proposed model incorporates a number of variables found in previously proposed models for depression in cancer patients, as well as risk factors that have been identified in previous literature.

Previous models. Our literature search resulted in a number of articles that utilized conceptual models or theoretical frameworks which incorporated psychological aspects of cancer and other chronic diseases. While several models and frameworks were utilized, the majority of these incorporated aspects of transactional theory related to stress, appraisal, and coping. In this, psychological symptoms are the response to the relationship between the individual and environment, where the person sees the environment as taxing if there is a discrepancy between situational demands and personal resources (92; 93). Theories focusing on unpleasant symptoms and symptom management were also used as the theoretical framework for several publications aimed at understanding performance outcomes in relation to the side-effects of HNC and other cancers (94; 95). Additionally, applicable to the HNC population, Cataldo et al. developed a conceptual framework surrounding the stigma associated with lung cancer, which incorporates both the perception of attitudes toward smoking and smoking-related cancers, as well as personal knowledge of the patient (96).

Factors influencing preexisting depression. A history of depression or depressive symptoms has been associated with greater risk of depression at later time points over the course of cancer diagnosis and treatment (97-100). In order to focus on the association between HNC and depression prior to cancer diagnosis, factors associated with depression in HNC patients were applied to the model showing depression development prior to cancer diagnosis. The left side of

the model in Figure 1 shows the potential pathways for the individual and environmental variables that may be risk factors for the development of depression prior to cancer diagnosis. As can be seen in the model, individual differences such as family history of mental illness and heredity (82), certain demographic factors such as gender, age, marital and employment status, income (53; 101-103) religiosity or spirituality (104), and early childhood experiences (105) can all affect the personality, coping style, and worldview of these individuals (106-110). Environmental factors, such as family and social environment and patients' social networks, can also affect personality and worldview of an individual (86; 99; 111; 112). Together and separately, these can affect depression development prior to cancer diagnosis, as well as exposure to potential risk factors, such as smoking and alcohol consumption, which have been associated with depression in HNC patients (113).

Factors such as having a positive social environment and social support, and higher education may reduce the likelihood of risky behaviors associated with depression and the development of HNC (e.g. smoking and alcohol consumption) (104) or having fewer comorbidities and greater overall self-care (53; 114). As can be seen in the model, these not only impact the personality and world view of the individual, but may also affect the diagnosis of preexisting depression and HNC. For example, improved social support may lead to a lack of addiction to tobacco and alcohol that may, in turn, continue to improve this level of social support and improve mental and physical health.

Factors influencing depression after cancer diagnosis. After cancer development and diagnosis, individual and environmental factors continue to influence the risk of depression development in HNC patients. Factors listed on the left-hand side of the model can continue to influence depression status after cancer diagnosis. Additionally, individual factors, such as fear or shame concerning the diagnosis (115; 116), as well as clinical factors, such as the specific site and stage of cancer, may influence patients' mental health and coping (86; 117-119). Medical

comorbidities and functional status of patients may also influence psychological health (120-124; 85).

Likewise, other environmental factors may affect depression status of patients after cancer diagnosis. Emotional and social support continue to play a role in depression in HNC patients (107; 112; 124-126), as well as experiencing social stigma related to the disease (60). Previous literature has also shown that satisfaction with information provided by healthcare workers may be associated with better depression outcomes in this patient population (107; 127). Because of this, patients' relationship with healthcare providers was included in the model as part of the environmental factors impacting depression outcomes.

Treatment side-effects appear to play a significant role in depression development in HNC patients. Side-effects of treatment such as pain, fatigue, and sleeping difficulties (128- 135) speech difficulties (123; 136-138) xerostomia, dysphagia or other swallowing difficulties (134; 138-142) and trouble eating, loss of appetite, and malnutrition (123; 134; 143-145) have all been shown to be associated with the psychological health of HNC patients. Further, surgery and disfigurement have also been associated with depression development in HNC patients, in part in relation to the loss of function, as well as concerns about body image (146-148). Finally, increases in symptoms, as well as receipt of radiation and the associated side-effects of this treatment, have been associated with greater risk of depression (62; 149).

In the proposed conceptual model in Figure 1, individuals may experience side-effects associated with treatments, which may vary by cancer site. Patients who are unable physically manage these side-effects or emotionally cope with them may be affected by individual and environmental factors, such as personal shame and social support, but this relationship can be seen as bidirectional, as their inability to cope can also affect these factors. As an example, a patient who experiences a side-effect of trouble with saliva production may feel uncomfortable in social eating situations, causing personal shame (139; 140; 144). This may lead to the patient

removing themselves from social situations, which limits their social supports and may lead to depression.

Factors influencing HNC outcomes. In terms of depression status and HNC outcomes, as is shown in the model, these can be affected by the individual and environmental factors of earlier parts of the model (such as cancer stage, medical comorbidities, or economic factors), as well as treatments received. The individual and environmental factors presented earlier in the model may influence patients' ability to cope with the side-effects of treatments that may also be associated with overall better self-care. For example, greater education, supportive family environments, and greater resources such as income and insurance may be associated with improved self-care in these patients and, therefore, better treatment adherence. Additionally, these may be associated with reduced likelihood of returning to prior risky behaviors, such as tobacco and alcohol use (150-152), therefore, improving outcomes.

Depression has been shown to affect treatment decisions of cancer patients (81), which can affect mortality rates of these patients. Further, psychological morbidity has also been shown to be associated with a greater fear of recurrence in HNC patients (116). Finally, several studies have shown that HNC patients who are depressed may have overall lower quality of life (124; 135; 153; 154), are at greater risk for suicide (72; 76), and have overall worse survival (75; 155). Because of the influence that depression may have on quality of life and survival of HNC patients, identifying and treating depression in this patient population may be important for improving current survival treads of HNCs.

Discussion

HNC is especially distressing for patients diagnosed with these cancers. Patients with HNC may struggle not only with the physical effects of the disease and its treatments, such as

functional impairment and physical disfigurement, but the psychological effects as well. In addition to the influence of any cancer diagnosis, this particular cancer population may be at increased risk for psychological illnesses, such as depression, because of the shared risk factors for these diseases. Additionally, depression diagnosis prior to cancer may leave these individuals at an increased risk for depression recurrence after cancer diagnosis. Further, survival has been shown to be lower in patients with preexisting depression (87). Understanding the complex relationship between depression and HNC is crucial for future studies in this field.

As can be seen in the proposed model, there are many individual and environmental factors that can influence the diagnosis of depression in the HNC population. Factors such as demographics of the patient, social support and network, and clinical variables related to cancer may all play a role in the development of depression in HNC patients. In the model proposed in this paper, depression can be seen as both a risk factor for and the result of the diagnosis of HNC, and therefore, may be helpful in understanding the full relationship between depression and HNC.

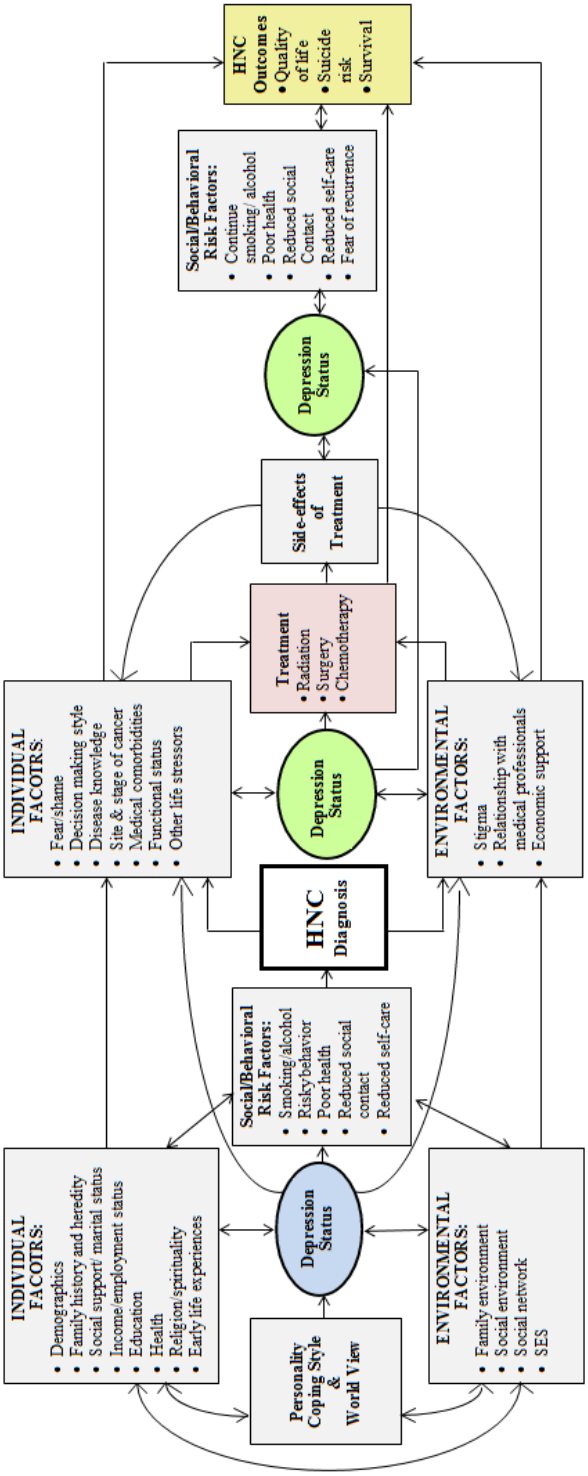
Previous literature indicates that cancer patients may not be forthcoming about their emotional wellbeing during consultations with their physicians (156). Moreover, physicians may only briefly discuss psychological or emotional issues with patients, even when patients voice concerns (157). The proposed conceptual model may help physicians and other healthcare workers to not only identify HNC patients who may be at increased risk for depression development, but also to help them understand the effect that depression can have on cancer outcomes of their patients.

Depression has been associated with worse treatment outcomes and poorer quality of life in HNC patients. Identifying the pathways by which depression may develop and influence patient outcomes is an essential step toward prevention. The model proposed can help guide future research in this and other cancer populations, and be used to develop targeted interventions for depression in cancer patients.

Table 1. Factors influencing depression development in HNC patients

	Factors influencing Preexisting Depression	**Factors influencing Depression after Cancer Diagnosis and HNC Outcomes**
Individual- Level Factors	Demographics Family history and heredity Social support/ marital status Income/employment status Education Health Religion/spirituality Early life experiences	Fear/shame Decision making style Disease knowledge Site & stage of cancer Medical comorbidities Functional status Other life stressors Treatment received/receipt of radiation
Environmental-Level Factors	Family environment Social environment Social network SES	Stigma Relationship with medical professionals Economic support
Social/Behavioral Risk Factors	Smoking/alcohol Risky behavior Poor health Reduced social contact Reduced self-care	Continue smoking/ alcohol Poor health Reduced social Contact Reduced self-care Fear of recurrence

Figure 1. Proposed conceptual model of the pathway to depression among HNC patients



CHAPTER III

POPULATION-BASED RETROSPECTIVE STUDY TO INVESTIGATE PREEXISTING AND NEW DEPRESSION DIAGNOSIS AMONG HEAD AND NECK CANCER PATIENTS

Publication Acknowledgement:

Rieke K, Boilesen E, Lydiatt W, Schmid KK, Houfek J, Watanabe-Galloway S. Population-based retrospective study to investigate preexisting and new depression diagnosis among head and neck cancer patients (In Press, *Cancer Epidemiology*; DOI:10.1016/j.canep.2016.06.008).

Abstract

This study aimed to estimate the pre-cancer prevalence and post-cancer incidence of depression in older adult head and neck cancer patients. Using SEER-Medicare files, cancer was identified from SEER data and depression diagnosis was identified using Medicare claims. Of 3,533 head and neck cancer patients, 10.6% were diagnosed with depression during the two years prior to cancer diagnosis, and an additional 8.9% developed depression in the year following cancer diagnosis. This study supports the critical need of screening for depression throughout cancer diagnosis and treatment, as well as a preventative approach in depression development in the older head and neck cancer patient population.

Introduction

Head and neck cancers (HNC) have been said to be more emotionally traumatic than other types of cancers (57; 158). There are a number of factors shared between depression and

HNC, including substance use and other poor lifestyle behaviors, which put this particular cancer population at risk for experiencing depression (57). Additionally, HNCs can be especially distressing because they can affect patients' communication and functioning, and may cause severe disfigurement (51; 53). Treatment options for HNC, such as radiation therapy, have also been associated with increased emotional distress in HNC patients, potentially as a result of the side-effects of treatment (62). Recent data demonstrates a higher incidence of depression in patients receiving radiation as the primary modality compared with surgery in a randomized trial (71). These findings suggest that the long-standing view of disfigurement as the primary cause of emergent depression may need to be reconsidered in order to understand how psychiatric illnesses impacts patient quality of life and survival.

The effects of depression in HNC patients can be severe. Studies have shown that HNC patients are at higher risk for suicide compared to other cancers and the general population (76), and may have poorer quality of life and survival (48; 75). Further, research on other cancer sites has shown that poor mental health may lead to less frequent screening and later stage at (73; 74). However, even with the shared associations of substance use and high emotional cost, there are still knowledge gaps in the literature surrounding depression and HNC.

Though HNC patients may be at increased risk for depression, currently there is no precise estimate of depression in this population. Previous studies, which have been mostly small-scale, have reported the prevalence to range from 9-54% (53). This wide range may be due to differences between these studies such as sociodemographic characteristics, cancer site and staging, and the time at which depression was measured. Additionally, many have used self-reported depression from various inventories with different cut-offs for the definition of depression, making it difficult to make cross-study comparisons. There is limited information on the effect that preexisting depression may have on cancer stage at the time of HNC diagnosis.

Further, lack of longitudinal research has resulted in a limited understanding of depression development and outcomes among HNC patients.

There is a clear need to explore the role of depression in HNC outcomes. To our knowledge, there are no population-based studies that have examined rates of depression in HNC patients at multiple time-points or the implications of preexisting depression on cancer stage at diagnosis. The specific aims of the study were to: (1) estimate the prevalence of depression two years before cancer diagnosis in an older adult head and neck cancer population using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data, (2) estimate the incidence of depression one year after cancer diagnosis, and (3) compare stage of HNC by depression status.

Materials and Methods

Study Sample. The sample consisted of individuals diagnosed with HNC from 2004-2005 who were linked to Medicare data. HNC was identified by International Classification of Disease for Oncology, Version 3 (ICD-O3) codes: 000-009 (lip), 021-023, 030-031, 039-041, 048-050, 058-062, 068-069 (oral cavity), 019-020,024, 028-029, 051-052, 090-091, 098-103, 108-109, 140, 142, 148 (oropharynx); 110-113, 118-119 (nasopharynx), 129-132, 138-139 (hypopharynx), and 320-323, 328-329 (larynx). Individuals had to have HNC as their only cancer diagnosis and be 67 years of age or older at diagnosis in order to ensure a minimum of two years of Medicare enrolment prior to cancer diagnosis. Individuals had to be continuously enrolled in Medicare Parts A and B for 24 months prior to HNC diagnosis until December of 2010 or their death, and could not be enrolled in a health maintenance organization (HMO) during this same time period to avoid incomplete claims records (74; 81).

Depression Identification and Statistical Analysis. From this group, diagnosis of depression was identified using ICD-9-CM codes from Medicare claims data. ICD-9-CM codes for depression included the following: 300.4 (dysthymic disorder); 296.2-296.24, 296.3-296.34 (major depression single or recurrent episode); 309.0, 309.1(adjustment disorder with depressive symptoms or prolonged depressive reaction); 311 (depressive disorder not otherwise classified); 296.5-296.54 (bipolar I disorder, most recent episode or current depressed); 298.0 (depressive type psychosis); 301.10 (affective personality disorder, unspecified); 301.12 (chronic depressive personality disorder); and 301.13 (cyclothymic disorder). To be included in the preexisting depression group, subjects had to have at least one inpatient, outpatient, or carrier claim diagnosis of depression within the 24 months prior to HNC diagnosis. To be considered part of the post-HNC depression group, participants could not have been diagnosed with depression before cancer diagnosis and had to have a depression diagnosis within the year following cancer diagnosis. Individuals diagnosed with cancer at death or autopsy were excluded from all analysis of post-HNC depression because there was no possibility of depression development.

All sociodemographic information was taken from SEER data, with education and income based on census tract. Receipt of radiation as part of the initial course of treatment was included as a dichotomous variable. Medical comorbidity was measured using an adaptation of the Charlson Comorbidity Index (CCI) developed for Medicare data, utilizing diagnostic codes based on the Deyo method (159-161). Diagnostic codes from inpatient, outpatient, and carrier claims during the 12 months prior to cancer diagnosis were used to calculate the index score. Stage of cancer diagnosis was taken from the derived SEER Summary Stage.

Chi-square and t-tests were carried out to examine demographic differences between those with and without depression, both before and after cancer diagnosis. Forward selection was used to fit the multivariable logistic regression model to examine factors associated with

depression at both time points. All data were analyzed using SAS version 9.3. This study was approved by the University of Nebraska Medical Center Institution Review Board.

Results

From 2004-2005, 12,175 individuals were diagnosed with HNC. Of these, 2,951 individuals were excluded because HNC was not their only cancer diagnosis, and 4,315 were excluded for being under the age of 67 at the time of HNC diagnosis. Another 151 individuals were removed for not being continuously enrolled in Medicare Parts A and B during the study period, and 1,225 were removed for being enrolled in an HMO at some point during the study period. This left 3,533 individuals in the final sample.

Prevalence and Incidence of Depression. In total, 375 (10.6%) individuals were diagnosed with depression during the two years prior to HNC diagnosis. Table 1 shows the characteristics of the sample by preexisting depression status. The groups differed significantly by gender, with a higher percentage of females in the depressed group (45.9% vs. 32.5%). The groups also differed by race, with 89.9% of the depressed group being Non-Hispanic White, compared to 83.5% of the non-depressed group. Additionally, the groups differed by marital status, with 40.5% of depressed subjects being married vs. 52.0% of non-depressed subjects. Conversely, 34.1% of depressed patients were widowed compared to 24.5% of the non-depressed group. Finally, in the pre-HNC depression group, 20.3% of individuals had a CCI score of one or more, compared to 6.3% of the non-depressed group.

To examine incident depression, we eliminated individuals with pre-existing depression and those diagnosed with HNC at death or autopsy, leaving 3,157 individuals. Of these, 281(8.9%) had a depression diagnosis within the year following HNC diagnosis. Table 2 shows the characteristics of subjects by post-HNC depression status. Again, there were significant

differences in gender, with 40.6% of the depressed group being female vs. 31.7% of the non-depressed group. The groups also differed by age, with 35.2% of the depressed group being 70-74 years old compared to 27.8% of the non-depressed group. There were differences in receipt of radiation, with 69.8% of the depressed group receiving radiation compared to 45.7% of the non-depressed group. Finally, there were differences in stage of cancer at diagnosis, with 19.2% of the depressed group diagnosed with distant stage vs. 13.3% of the non-depressed group.

Multivariable Analysis. Table 3 shows the multivariable logistic regression examining factors associated with depression prior to cancer diagnosis. The odds of having depression prior to cancer diagnosis differed significantly by gender, with females having 1.59 (95% CI=1.26, 2.02) times the odds of pre-HNC depression compared to men after adjustment for other variables in the model. Race was also associated with pre-HNC depression, with non-White patients having lower odds of depression (OR=0.50; 95% CI=0.35, 0.72). Marital status of patients was also significant, with those who were divorced/separated (OR=1.52; 95% CI=1.05, 2.21) or widowed (OR=1.46; 95% CI= 1.11, 1.92) having greater odds of depression compared to those who were married. CCI was associated with pre-HNC depression, with a score of one or more having 4.08 (95% CI= 3.02, 5.50) times the odds of depression compared to a score of zero. Finally, cancer stage was associated with preexisting depression, with distant stage having 1.61 (95%CI=1.17, 2.22) times the odds of depression compared to local and or regional disease.

Table 4 shows the multivariable results examining factors associated with developing depression within the year following HNC diagnosis. Age was significantly associated with the development of depression after HNC, with those aged 70-74 (OR= 1.53; 95% CI=1.07, 2.18) and 80-84 (OR= 1.53; 95%CI=1.01, 2.31) having greater odds of developing depression compared to those aged 67-69. In terms of gender, women had 1.57 (95% CI= 1.21, 2.03) times the odds of developing depression compared to men. Receiving radiation was associated with 1.86 (95% CI= 1.40, 2.46) times the odds of developing depression compared to those who did

not receive this form of treatment. Finally, in terms of cancer stage, those with distant stage had 1.72 (95%CI=1.20, 2.47) times the odds of developing depression compared to the non-metastatic group. Potential interactions of gender with race and marital status were examined with no significant associations found.

Discussion

The results of this study show that the prevalence of depression diagnosis during the two years prior to HNC diagnosis in older adults was approximately 10.6%. This is slightly higher than the prevalence found in SEER-Medicare studies focusing on other cancer sites older adult head and neck cancer population. Boyd et al. (2012) (61) found that approximately 7.9% of pancreatic adenocarcinoma patients had a depression diagnosis during the 3-27 months preceding cancer, while Goodwin et al. (2004) (80) found that approximately 7.5% of breast cancer patients had a pre-existing diagnosis of depression during the two years prior to cancer, and Prasad et al. (2014) (81) found that approximately 5% of prostate cancer patient had a depression diagnosis during this time period. Though the methodologies of these studies were not identical, it appears that individuals with HNC may have a modestly higher prevalence of depression before cancer diagnosis. Additionally, the present study found that the incidence of depression was 8.9%, indicating that almost 9% of individuals without a depression diagnosis prior to HNC were diagnosed with depression within one year of cancer diagnosis. This is likely a conservative estimate of depression after HNC diagnosis, since this estimate does not include those who were part of the preexisting depression group, which may be at risk for continued or recurrent depression. Together, the results of this study show the burden of depression in the HNC population, both at the time of cancer diagnosis as well as during treatment and recovery.

This study also showed differences in depression based on gender and race. Gender was significantly associated with diagnosis of depression before and after cancer diagnosis, with

females having higher odds of depression. This is consistent with previous literature indicating that women may be more likely to experience depressive symptoms, or at least are more likely to express them to their physician, especially in relation to cancer (74). Similarly, in the multivariable analysis, being Non-Hispanic White was shown to be significantly associated with depression diagnosis prior to cancer. These results may help in the identification of individuals who may be at increased risk for depression.

The results of this study also indicated that individuals who were divorced/separated or widowed at the time of cancer diagnosis had greater odds of experiencing depression prior to HNC compared to those who were married. This may be indicative of a lack of social support, which has been previously shown to be associated with increased emotional distress in HNC patients (162). Additionally, higher medical comorbidities were associated with depression prior to cancer diagnoses. While the interaction of marital status and comorbidity score was not shown to be significant in the present study, social support may be a common thread among these variables in their association with depression.

The data showed that individuals receiving radiation as part of their first course of treatment had significantly greater odds of developing depression within one year of cancer diagnosis. Previous studies have found that radiation treatment may cause a number of side-effects including trouble swallowing, dental issues, and trouble hearing (63; 107; 163; 164). It is possible that these side-effects may impact patients' emotional well-being, putting them at risk for depression. Additional factors that may be at play include systemic Il-6 elevation or chronic unremitting stress during and after radiation therapy (165).

Age at the time of cancer diagnosis was also shown to be associated with depression development. While the overall association was not shown to be significant, the 70-74 and 80-84 age groups differed significantly from the 67-69 age group. However, the estimates associated with each age group were inconsistent in the direction of their association. While, in general,

younger age has been associated with depression in HNC patients (57) it is possible that the restricted age range of this study (age 67+) did not allow linear comparison by the assigned age groups.

Finally, highly advanced stage at diagnosis was shown to be significantly related to depression, both before and after cancer diagnosis. The implications of this finding are that having preexisting depression may lead to poorer self-care and therefore less frequent physician visits, leading to later stage at diagnosis. After cancer diagnosis, stage may be indicative of severity of cancer and its side-effects, as well as fear of associated mortality, and therefore lead to depression.

Targeted approaches to diagnose or prevent depression are urgently needed in patients undergoing therapy for cancer, and HNC patients are at particular risk. This data supports earlier literature of the profile of patients at high risk to develop depression, and thus, trends towards the divorced/separated or widowed, white female with comorbidities and later stage of diagnosis who will receive radiation therapy as a primary treatment modality. However this is not to say that others are not at risk.

In terms of study limitations, SEER- Medicare files only offer diagnostic codes to identify depression. Though we found that nearly 19% of this population was diagnosed with depression during the study period, previous studies have found that as high as 54% of the HNC population may have some form of depression (53). Utilizing diagnostic codes to identify depression may not capture all cases of depression, such as those with subclinical symptoms or those who never received a recorded diagnosis, which may underestimate the rates of depression in this cancer population. Similarly, SEER-Medicare files only offer diagnostic codes for variables concerning substance abuse. While previous literature has shown that diagnostic codes for substance abuse disorders are reliable for psychiatric patients (166), patients with mental illness may be more likely to receive substance abuse diagnoses than the general population,

regardless of substance usage. Because of this, we chose not to examine substance abuse in relation to depression outcomes. Additionally, Singer et al. found that HNC patients may experience greater emotional distress compared to other cancer sites, but that this relationship may be confounded by the level of perceived social support (162). Because SEER-Medicare data does not offer any information on this construct, the effects of social support were not examined in this study. Finally, restricting the age at diagnosis to 67 years and older eliminated more than half of all HNC patients, so the study results cannot be generalized to younger HNC patients.

Conclusions

This study found that the prevalence of depression diagnosis in older adults prior to cancer was 10.6%; modestly higher than in previous studies examining depression in other cancer sites using SEER-Medicare data. Additionally, we found that approximately 9% of older adult HNC patients had newly diagnosed depression within one year of cancer diagnosis. These results support the need for depression screening within this population. It also adds credence to the concept of a prevention approach in HNC patients. Given the significant associations of receipt of radiation and depression outcomes in this study, there is a need to understand how this treatment and its side-effects may affect depression development. Additionally future research of depression in HNC patients should focus on the impact that depression has on survival and quality of life, as well as identify interventions to prevent post-HNC depression in this patient group.

Table 1. Demographics by pre-HNC depression diagnosis

			Yes (N=375)		No (N=3,158)
Variable	Number	%	Number	%	p-value
Age					0.043
67-69	61	16.3%	671	21.2%	
70-74	108	28.8%	899	28.5%	
75-79	75	20.0%	696	22.0%	
80-84	70	18.7%	484	15.3%	
85+	61	16.3%	408	12.9%	
Gender					<0.001
Male	203	54.1%	2,133	67.5%	
Female	172	45.9%	1,025	32.5%	
Race					0.001
Non-Hispanic white	337	89.9%	2,637	83.5%	
Other	38	10.1%	521	16.5%	
% of census tract with 4 year college degree					0.185
0-33%	254	67.7%	2,260	71.6%	
34+%	93	24.8%	723	22.9%	
Unknown	28	7.5%	175	5.5%	
Marital status					<0.001
Married/Living as	152	40.5%	1,642	52.0%	
Separated/Divorced	43	11.5%	284	9.0%	
Single	32	8.5%	274	8.7%	
Widowed	128	34.1%	775	24.5%	
Unknown	20	5.3%	183	5.8%	
Median census tract income					0.934
< $35, 000 or Missing	124	33.1%	1,005	31.8%	
$35, 000- $44,999	87	23.2%	723	22.9%	
$45, 000- $59,999	80	21.3%	714	22.6%	
$60, 000+	84	22.4%	716	22.7%	
Cancer site					0.179
Lip	26	6.9%	248	7.9%	
Oral Cavity	105	28.0%	731	23.1%	
Oropharynx	101	26.9%	841	26.6%	
Nasopharynx/Hypopharynx	36	9.6%	283	9.0%	
Larynx	107	28.5%	1,055	33.4%	
SEER region					0.363
Pacific/West	156	41.6%	1,201	38.0%	
Northeast	64	17.1%	637	20.2%	
Midwest	47	12.5%	435	13.8%	
South	108	28.8%	885	28.0%	
CCI					<0.001
0	299	79.7%	2,960	93.7%	
1+	76	20.3%	198	6.3%	
Stage					0.057
Unstaged	51	13.6%	363	11.5%	
In Situ/Localized	149	39.7%	1376	43.6%	
Regional	107	28.5%	983	31.1%	
Distant	68	18.1%	436	13.8%	

CCI= Charlson Comorbidity Index score

Table 2. Demographics by post-HNC depression diagnosis

	Yes (N=281)		No (N=2,876)		
Variable	**Number**	**%**	**Number**	**%**	**p-value**
Age					0.011
67-69	52	18.5%	619	21.5%	
70-74	99	35.2%	800	27.8%	
75-79	52	18.5%	644	22.4%	
80-84	52	18.5%	432	15.0%	
85+	26	9.3%	381	13.2%	
Gender					0.002
Male	167	59.4%	1,965	68.3%	
Female	114	40.6%	911	31.7%	
Race					0.366
Non-Hispanic white	240	85.4%	2,396	83.3%	
Other	41	14.6%	480	16.7%	
% of census tract with 4 year college degree					0.370
0-33%	197	70.1%	2,062	71.7%	
34+%	72	25.6%	651	22.6%	
Unknown	12	4.3%	163	5.7%	
Marital status					0.190
Married/Living as	131	46.6%	1,510	52.5%	
Separated/Divorced	23	8.2%	261	9.1%	
Single	29	10.3%	245	8.5%	
Widowed	83	29.5%	692	24.1%	
Unknown	15	5.3%	168	5.8%	
Median census tract income					0.818
< $35, 000 or Missing	84	29.9%	921	32.0%	
$35, 000- $44,999	63	22.4%	659	22.9%	
$45, 000- $59,999	69	24.6%	645	22.4%	
$60, 000+	65	23.1%	651	22.6%	
Cancer site					0.859
Lip	18	6.4%	230	8.0%	
Oral Cavity	66	23.5%	665	23.1%	
Oropharynx	80	28.5%	760	26.4%	
Nasopharynx/Hypopharynx	24	8.5%	259	9.0%	
Larynx	93	33.1%	962	33.4%	
SEER region					0.068
Pacific/West	98	34.9%	1,103	38.4%	
Northeast	73	26.0%	563	19.6%	
Midwest	40	14.2%	395	13.7%	
South	70	24.9%	815	28.3%	
CCI					0.923
0	263	93.6%	2,696	93.7%	
1+	18	6.4%	180	6.3%	
Radiation received					<0.001
Yes	196	69.8%	1,563	54.3%	
No	85	30.2%	1,313	45.7%	
Stage					0.002
Unstaged	27	9.6%	335	11.6%	
In Situ/Localized	98	34.9%	1278	44.4%	
Regional	102	36.3%	881	30.6%	
Distant	54	19.2%	382	13.3%	

CCI= Charlson Comorbidity Index score

Table 3. Multivariable logistic regression of depression two years before HNC diagnosis

	OR	95% CI		p-value
Gender				<0.001
Males	1.00	-	-	
Female	1.59	1.26	2.02	
Race				<0.001
Non-Hispanic white	1.00	-	-	
Other	0.50	0.35	0.72	
Marital status				0.052
Married/Living as	1.00	-	-	
Single	1.19	0.78	1.80	
Widowed	1.46	1.11	1.92	
Divorced/Separated	1.52	1.05	2.21	
Unknown	1.11	0.67	1.84	
CCI				<0.001
0	1.00	-	-	
1+	4.08	3.02	5.50	
SEER region				0.055
Pacific/West	1.00	-	-	
Midwest	0.74	0.52	1.06	
Northeast	0.66	0.47	0.91	
South	0.86	0.66	1.12	
Stage				0.013
In Situ/Localized	1.00	-	-	
Unstaged	1.38	0.96	1.98	
Regional	1.04	0.79	1.36	
Distant	1.61	1.17	2.22	

CCI= Charlson Comorbidity Index score

Table 4. Multivariable logistic regression of depression one year after HNC diagnosis

	OR	95% CI		p-value
Age				0.012
Ages 67-69	1.00	-	-	
Ages 70-74	1.53	1.07	2.18	
Ages 75-79	1.00	0.67	1.50	
Ages 80-84	1.53	1.01	2.31	
Ages 85+	0.88	0.53	1.45	
Gender				<0.001
Males (REF)	1.00	-	-	
Female	1.57	1.21	2.03	
Race				0.141
Non-Hispanic white	1.00	-	-	
Other	0.77	0.54	1.09	
Stage				0.032
In Situ/Localized	1.00	-	-	
Unstaged	1.12	0.71	1.75	
Regional	1.29	0.95	1.74	
Distant	1.72	1.20	2.47	
Radiation received				<0.001
No	1.00	-	-	
Yes	1.86	1.40	2.46	

CCI= Charlson Comorbidity Index score

CHAPTER IV

DEPRESSION AND SURVIVAL IN HEAD AND NECK CANCER PATIENTS

Abstract

Objective. Though depression often afflicts head and neck cancer (HNC) patients, few studies have examined the association between depression and survival in this particular cancer population. The objective of this study is to investigate the five-year survival of HNC patients by depression status.

Materials and Methods. This study used SEER-Medicare data from 2002-2010 and identified depression diagnosis two years before and one year after cancer diagnosis. HNC patients were identified using ICD-O3 codes and depression was identified using ICD-9-CM codes from Medicare claims.

Results. Of the 3,466 patients included in the study, 642 (18.5%) were diagnosed with depression during the study period. Compared to those who received no depression diagnosis, those diagnosed with depression prior to cancer or after cancer diagnosis were more likely to die of cancer (HR= 1.49; 95% CI=1.27, 1.76 and HR=1.38; 95% CI=1.16, 1.65, respectively). Similarly, when looking at death from any cause, those diagnosed with depression prior to cancer diagnosis and those who received a diagnosis of depression after cancer were more likely to (die from any death compared to those without depression (HR= 1.55; 95% CI=1.36, 1.76 and HR=1.40; 95% CI=1.21, 1.62, respectively).

Conclusions. The results emphasize the need for early identification and treatment of depression in HNC patients, as well as the establishment of policies to routinely screen these patients throughout the cancer treatment process. Early detection and treatment of depression in these patients may help to improve survival.

Introduction

Lower survival and poorer outcomes have been demonstrated in cancer patients with depression (81; 167; 168). Previous studies examining depression in cancer populations have found higher cancer recurrence and lower quality of life in cancer patients with clinical depression or depressive symptomology (167; 169). Depression has also been associated with increased mortality in patients with cancer, with mortality rates up to 25% higher in cancer patients who experience depression (48; 170). Though previous studies have examined the effect that depression may have on cancer mortality rates, there are few large-scale studies that have examined the association between depression and survival in patients with head and neck cancers (HNC).

HNC patients face unique psychological challenges compared to many other cancer sites. HNCs and their treatments can cause severe physical and functional impairments, which have been associated with depression development in HNC patients (51; 53; 106; 146). Further, radiation therapy has been shown to be significantly associated with depression (102). Moreover, patients with HNC may experience permanent facial disfigurement from treatments (106), and unlike other cancer sites, patients may be left with visible scars or deformities that cannot be concealed, which may cause issues with personal shame and self-consciousness, and ultimately lead to depression (54; 83; 171).

Because of the associations between HNC and depression, as well as the psychological impact that these cancers and their treatments may have on patients, we previously examined depression rates in HNC patients both before and after cancer diagnosis utilizing two linked national datasets. The results of this study showed not only that depression diagnosis in HNC patients was moderately higher than estimates from other cancer sites, but also that depression was associated with advanced stage at diagnosis. However the question still remains as to the effect that depression has on the survival of HNC patients. Therefore, the objective of the present study is to investigate the five-year survival of HNC patients by depression status.

Materials and Methods

We utilized the Surveillance Epidemiology and End Results (SEER)-Medicare linked data from 2002-2010. We identified all individuals diagnosed with HNC from 2004-2005 based on International Classification of Disease for Oncology, Version 3 (ICD-O3) codes who were linked to Medicare data. Individuals had to have HNC as their only cancer diagnosis and be 67 years of age or older at the time of diagnosis in order to ensure a minimum of two years of Medicare enrolment prior to cancer diagnosis. Individuals had to be continuously enrolled in Medicare Parts A and B for 24 months prior to their HNC diagnosis until December of 2010 or their death, and could not be enrolled in a health maintenance organization (HMO) during this same time period due to the possibility of incomplete claims records (74; 81).

From this group, diagnosis of depression two years prior to cancer diagnosis was identified using ICD-9-CM codes from Medicare claims data. To be included in the preexisting depression group, subjects had to have at least one claim diagnosis of depression within the 24 months prior to HNC diagnosis. To be considered part of the post-HNC depression group, participants could not have been diagnosed with depression before cancer diagnosis and had to have at least one inpatient, outpatient, or carrier claim diagnosis of depression within one year

after diagnosis of HNC. Individuals whose reporting source indicated they were diagnosed with cancer at the time of death or autopsy were excluded from all analyses for the present study.

Five-year survival of all patients was examined, with censoring time being December 2010 (the end of the study period). The survival of patients was identified using the number of years and months of survival provided in SEER data. For this variable, survival time was calculated using the date of diagnosis and either the date of death, date last known to be alive, or December of 2010 for the study data. Survival outcomes of interest included all-cause and cancer-specific death based on SEER data reporting. For all-cause mortality, vital status at the end of the study period (December 2010) was used. For cancer specific survival, deaths attributed to HNC were treated as events and deaths from other causes were treated as censored observation (78).

Statistical analysis. Kaplan-Meier curves were used to examine basic survival estimates by depression status of patients. Cox regression models were used to control for potential confounding variables. Covariates included in the models were determined using forward selection and clinical importance. Candidate covariates included sociodemographic information taken from SEER data, with education and income based on census tract. Because survival outcomes may differ by treatment received, radiation as part of the initial course of treatment (dichotomous variable) was included as a potential covariate. Additionally, because survival may differ by time of onset of depression, depression based on time of diagnosis was examined as a potential covariate in the model. Medical comorbidity was measured using an adaptation of the Charlson Comorbidity Index (CCI) developed for Medicare data (159-161). All analyses were performed using SAS 9.4, with the default method used to handle ties within the data (Breslow method). For the multivariable models, time-dependent variables were entered into the models to test the proportional hazards assumption of each variable. Forward selection was used to fit the

models, with significant time-dependent variables left in the model as the interaction of each of these time-dependent variables with survival time.

Results

Bivariate analysis. Based on the inclusion and exclusion criteria listed above, there were 3,533 individuals eligible for inclusion in the analyses. From these, an additional 67 individuals were excluded for being diagnosed with cancer at the time of death or autopsy, leaving a total of 3,466 individuals in the study sample (Appendix A). Table 1 shows the demographic and clinical characteristics of the study sample by depression status over the course of cancer. Of the study sample, 361 individuals (10.4%) had a diagnosis of depression prior to HNC diagnosis, an additional 281 individuals (8.1%) developed depression after cancer diagnosis, and 2,824 individuals (81.5%) were not diagnosed with depression at any point during the study period. As can be seen from Table 1, there were significant differences between the groups in terms of survival for both cancer–specific and all-cause mortality. For cancer-specific deaths, there were over 35% more deaths from cancer in those who were diagnosed with depression prior to cancer compared to those who were never diagnosed with depression (48.8% vs. 36.0%, respectively). Similarly, there were over 41% more deaths from cancer in those who were diagnosed with depression after their cancer diagnosis compared to those where never diagnosed with depression (50.9% vs. 36.0%, respectively). Other significant differences between groups included age, gender, ethnicity, marital status, stage, medical comorbidity, and receipt of radiation. When looking at all-cause mortality, there were over 35% more deaths in the group diagnosed with depression prior to cancer diagnosis compared to those who were never diagnosed with depression (77.6% vs. 57.4%, respectively). Similarly, when looking at those who developed depression after cancer diagnosis compared to those who were never diagnosed with depression,

there were nearly 30% more deaths in the group that developed depression after cancer (74.4% compared to 57.4%, respectively).

The Kaplan-Meier survival curves for cancer-specific death by depression status showed those without a diagnosis of depression during the specific time period had better survival compared to those who received a depression diagnosis, either before or after cancer (Log Rank chi square =63.03, p=<0.0001). Those who received a diagnosis of depression prior to cancer had a median survival time of 37 months, compared to 29 months for those who received a diagnosis of depression after cancer diagnosis. The median survival time could not be computed for those who received no diagnosis of depression as median survival exceeded the 60 month follow-up period.

Similarly, for all-cause mortality, individuals without a depression diagnosis had better survival outcomes compared to those who received a depression diagnosis, either before or after cancer diagnosis (Log Rank chi square = 99.56, p=<0.0001). Those who received a diagnosis of depression prior to cancer had a median survival time of 17 months, compared to 18 months for those who received a diagnosis of depression after cancer diagnosis, and 46 months for those who received no diagnosis of depression.

Multivariable Analysis. Table 2 shows the multivariable analysis results for the outcome of cancer-specific death. As can be seen from the table, depression diagnosis was significantly associated with cancer death in the multivariable model after controlling for all other covariates. Compared to those who received no depression diagnosis, those who were diagnosed with depression prior to cancer diagnosis had nearly 1.5 times the hazard of cancer death, while those who were diagnosed with depression after cancer diagnosis had nearly 1.4 times the hazard of cancer death. Other significant variables associated with cancer death included age, marital status,

income, specific cancer site, stage at diagnosis, medical comorbidity, receipt of radiation and the interaction of receipt of radiation over time.

The multivariable results for all-cause mortality are show in Table 3. Again, depression was found to be significantly associated with the outcome after controlling for demographic and clinical variables. Those who were diagnosed with depression prior to cancer diagnosis had 1.55 times the hazard of any death compared to those who received no depression diagnosis. Similarly, those who received a diagnosis of depression after had 1.40 times the hazard of any death. Other variables that were found to be significantly associated with all-cause mortality included age, marital status, gender, race, income, specific cancer site, stage at diagnosis, medical comorbidity, receipt of radiation, and the interaction of time with age, marital status, race, and receipt of radiation.

Discussion

This study showed that HNC patients with a diagnosis of depression had significantly greater risk for death from cancer and death from any cause. Even after controlling for potential confounding variables, including stage of cancer at the time of diagnosis, individuals with a diagnosis of depression had 38% and 49% greater hazard of cancer-specific mortality and 40% and 55% greater hazard of all-cause mortality compared to those patients who never received a depression diagnosis.

The results of our study support those of several previous studies which have examined the association of depression on the survival of various types of cancer. Patients with cancers such as those of the breast (80; 168; 172), prostate (81), and lung (173) who also struggle with depression or depressive symptoms have been shown to have decreased survival compared to their non-depressed counterparts. Several previous studies of smaller scale have also examined

the association of depression on survival of individuals with cancers of the head and neck. In a prospective study of 241 patients, Kim et al. found that HNC patients with pre-treatment depression had decreased 3-year survival compared to their non-depressed counterparts (87). In a clinical trial of prophylactic depression treatment of HNC patients, Lazure et al. found that patients with depression had significantly greater mortality and disease recurrence compared to those who were not depressed (75). Similarly, Shinn et al. found that, of 130 patients with oropharynx cancer, self-reported depression was associated with a 3.6 greater hazard of death and 3.8 greater hazard of disease recurrence (167). Further, Kam et al. found that individuals with HNC have 3 times greater incidence of suicide compared the general population in the United States (72). They also found an association with radiation and depression which is again confirmed in this study. Previous work by our group has also shown a higher risk of emergent depression in patients that undergo radiation as part of their primary treatment for HNC (71). Together with the present study, these studies underline the importance of patient psychological health during the diagnostic and treatment process of HNC, as well as the need for the recognition of past and current depressive symptoms by clinicians especially in those undergoing radiation as part of their treatment.

The present study adds to the existing literature of the effects of depression on survival of HNC in several ways. By utilizing a large, population-based sample, this study provides information on the relationship between depression and survival which may be more representative of the elderly HNC population than previous smaller-scale studies. Further, by examining the diagnoses of depression both before and after cancer diagnosis, the results offer a unique look at the influence that pre-existing depression may have on cancer outcomes, in addition to incident depression after cancer diagnosis. Based on our findings, future studies examining outcomes of HNC and other cancer patients should consider both current and historical psychological health of patients.

In terms of study limitations, we identified depression based on ICD-9-CM codes, thereby limiting our findings to only those individuals with diagnosed depression. Because of this, we are not able to capture the influence that sub-clinical or underdiagnosed depression may have on survival outcomes of this population. Additionally, our study did not include information on depression treatments received, which may have additional influence on survival. Further, Medicare only includes data in individual 65 and older, and the present study included only individuals 67 years of age and older in order to be able to examine depression diagnosis prior to cancer. The age limitation of both the data and our selection criteria do not allow for the examination of the effect of depression on younger patients. Another limitation of the present study is the lack of information on human papillomavirus (HPV) status of the study subjects. Previous research on oropharyngeal cancer has shown that HPV-positive patients may have better survival than those without the virus (174). Unfortunately, because there is no information on HPV status within SEER-Medicare files, we were unable to examine or control for this relationship in our study. However, this may only affect survival of patients with specific forms of HNC, and the current study can still be used to estimate the effect of depression on survival of HNCs as a group. Strengths of the present study include a large sample size as well as diagnostically confirmed cancer and depression in the selected sample.

Conclusion

In our study, depression diagnosis was associated with decreased survival in HNC patients. These results emphasize the need for strategies designed to prevent depression, early identification and treatment of depression in HNC patients, as well as the establishment of policies to routinely screen these patients throughout the cancer treatment process. Identifying and treating depression in these patients may not only help to improve quality of life during cancer treatment and recovery, but may also help to improve survival in these patients.

Table 1. Profile of the study sample by depression status

	Pre-Cancer Depression (N=361)		Post-Cancer Depression (N=281)		No Depression (N=2,824)		p-value
Variable	N	%	N	%	N	%	
Age							0.0061
67-69	60	16.6%	52	18.5%	615	21.8%	
70-74	106	29.4%	99	35.2%	788	27.9%	
75-79	73	20.2%	52	18.5%	635	22.5%	
80-84	68	18.8%	52	18.5%	418	14.8%	
85+	54	15.0%	26	9.3%	368	13.0%	
Gender							<0.0001
Male	196	54.3%	167	59.4%	1931	68.4%	
Female	165	45.7%	114	40.6%	893	31.6%	
Ethnicity							0.0059
Non-Hispanic white	324	89.8%	240	85.4%	2353	83.3%	
Other	37	10.2%	41	14.6%	471	16.7%	
% With 4 year college degree							0.3212
0-33%	245	67.9%	197	70.1%	2025	71.7%	
34+%	90	24.9%	72	25.6%	644	22.8%	
Missing	26	7.2%	12	4.3%	155	5.5%	
Marital status							0.0002
Married/Living as Married	148	41.0%	131	46.6%	1499	53.1%	
Separated/Divorced	39	10.8%	23	8.2%	249	8.8%	
Single	31	8.6%	29	10.3%	239	8.5%	
Widowed	124	34.3%	83	29.5%	671	23.8%	
Unknown	19	5.3%	15	5.3%	166	5.9%	
Median Income Census Tract							0.9547
< $35, 000 or Missing	118	32.7%	84	29.9%	897	31.8%	
$35, 000- $44,999	86	23.8%	63	22.4%	649	23.0%	
$45, 000- $59,999	75	20.8%	69	24.6%	633	22.4%	
$60, 000+	82	22.7%	65	23.1%	645	22.8%	
Cancer Site							0.3433
Lip	26	7.2%	18	6.4%	228	8.1%	
Oral Cavity	103	28.5%	66	23.5%	654	23.2%	
Oropharynx	96	26.6%	80	28.5%	736	26.1%	
Nasopharynx/Hypopharynx	35	9.7%	24	8.5%	255	9.0%	
Larynx	101	28.0%	93	33.1%	951	33.7%	
SEER Region							0.0572
Pacific/West	155	42.9%	98	34.9%	1085	38.4%	
Northeast	57	15.8%	73	26.0%	558	19.8%	
Midwest	47	13.0%	40	14.2%	391	13.8%	
South	102	28.3%	70	24.9%	790	28.0%	
Stage							0.0021
Unstaged	37	10.2%	27	9.6%	285	10.1%	
InSitu/Localized	149	41.3%	98	34.9%	1278	45.3%	
Regional	107	29.6%	102	36.3%	881	31.2%	
Distant	68	18.8%	54	19.2%	380	13.5%	
Charlson Comorbidity							<0.0001
0	290	80.3%	263	93.6%	2650	93.8%	
1+	71	19.7%	18	6.4%	174	6.2%	
Radiation Received							<0.0001
No	186	51.5%	85	30.2%	1261	44.7%	
Yes	175	48.5%	196	69.8%	1563	55.3%	
Any Death							<0.0001
No	81	22.4%	72	25.6%	1204	42.6%	
Yes	280	77.6%	209	74.4%	1620	57.4%	
Cancer Death							<0.0001
No	185	51.2%	138	49.1%	1808	64.0%	
Yes	176	48.8%	143	50.9%	1016	36.0%	

Table 2. Multivariable results for cancer-specific mortality

Variable	HR	95% CI		p-value	Type 3 p-value
Depression Status					<0.001
No Depression Diagnosis	REF	-	-		
Pre-HNC Depression	1.49	1.27	1.76	<0.001	
Post-HNC Depression	1.38	1.16	1.65	<0.001	
Age					<0.001
67-69	REF	-	-		
70-74	1.15	0.98	1.36	0.098	
75-79	1.55	1.30	1.84	<0.001	
80-84	1.83	1.52	2.20	<0.001	
85+	2.32	1.90	2.82	<0.001	
Marital Status					<0.001
Married/Living as Married	REF	-	-		
Single	1.30	1.07	1.57	0.008	
Widowed	1.41	1.24	1.06	<0.001	
Divorced/ Separated	1.44	1.19	1.74	<0.001	
Unknown	1.06	0.80	1.39	0.702	
Median Income Census Tract					<0.001
< $35, 000 or Missing	REF	-	-		
$35, 000- $44,999	0.77	0.66	0.89	<0.001	
$45, 000- $59,999	0.72	0.61	0.84	<0.001	
$60, 000+	0.71	0.61	0.82	<0.001	
Cancer Site					<0.001
Lip	REF	-	-		
Larynx	3.54	2.38	5.24	<0.001	
Nasopharynx/Hypopharynx	5.52	3.64	8.35	<0.001	
Oral Cavity	3.47	2.34	5.15	<0.001	
Oropharynx	3.71	2.49	5.52	<0.001	
Stage					<0.001
In Situ/Localized	REF	-	-		
Regional	3.30	2.83	3.86	<0.001	
Distant	4.93	4.17	5.83	<0.001	
Unstaged	2.68	2.20	3.28	<0.001	
Charlson Comorbidity					<0.001
0	REF	-	-		
1+	1.47	1.21	1.80	<0.001	
Radiation Received					<0.001
No	REF	-	-		
Yes	0.48	0.41	0.57	<0.001	
Radiation*TIME	1.03	1.02	1.04	<0.001	<0.001

Table 3. Multivariable results for all-cause mortality

Variable	HR	95% CI		p-value	Type 3 p-value
Depression Status					<0.001
No Depression Diagnosis	REF	-	-		
Pre-HNC Depression	1.55	1.36	1.76	<0.001	
Post-HNC Depression	1.40	1.21	1.62	<0.001	
Age					<0.001
67-69	REF	-	-		
70-74	1.15	1.00	1.33	0.052	
75-79	1.47	1.26	1.73	<0.001	
80-84	1.67	1.39	2.02	<0.001	
85+	2.40	1.96	2.95	<0.001	
Age*TIME	1.00	1.00	1.01	<0.001	<0.001
Marital Status					<0.001
Married/Living as Married	REF	-	-		
Single	1.38	1.16	1.63	<0.001	
Widowed	1.62	1.40	1.88	<0.001	
Divorced/ Separated	1.52	1.29	1.78	<0.001	
Unknown	1.31	1.03	1.67	0.028	
Marital*TIME	1.00	1.00	1.00	0.015	0.015
Gender					<0.001
Male	REF	-	-		
Female	0.84	0.76	0.93	<0.001	
Race					0.003
Non-Hispanic white	REF	-	-		
Other	1.28	1.09	1.51	0.003	
Race*TIME	0.99	0.99	1.00	<0.001	<0.001
Median Income Census Tract					<0.001
< $35, 000 or Missing	REF	-	-		
$35, 000- $44,999	0.82	0.73	0.92	<0.001	
$45, 000- $59,999	0.75	0.66	0.84	<0.001	
$60, 000+	0.73	0.64	0.82	<0.001	
Cancer Site					<0.001
Lip	REF	-	-		
Larynx	1.66	1.35	2.05	<0.001	
Nasopharynx/Hypopharynx	2.46	1.93	3.13	<0.001	
Oral Cavity	1.61	1.30	1.99	<0.001	
Oropharynx	1.74	1.40	2.16	<0.001	
Stage					<0.001
In Situ/Localized	REF	-	-		
Regional	2.34	2.08	2.63	<0.001	
Distant	3.27	2.86	3.73	<0.001	
Unstaged	2.08	1.79	2.43	<0.001	
Charlson Comorbidity					<0.001
0	REF	-	-		
1+	1.86	1.61	2.15	<0.001	
Radiation Received					<0.001
No	REF	-	-		
Yes	1.64	1.44	1.88	<0.001	
Radiation*TIME	1.01	1.01	1.02	<0.001	<0.001

CHAPTER V

RADIATION SIDE-EFFECTS AND DEPRESSION IN HEAD AND NECK CANCER PATIENTS

Abstract

Background. The influence of radiation side-effects on psychological distress of head and neck cancer (HNC) patients is not well understood. The objective of this study was to examine the association between radiation treatment side-effects and depression outcomes in HNC patients.

Methods. SEER-Medicare data was examined for 1,759 HNC patients who received radiation as part of their initial course of treatment. Radiation side-effects in Medicare data were identified and examined in their association with one year post-cancer depression diagnosis.

Results. Nearly 85% of those in the depressed group were diagnosed with at least one radiation side-effect, compared to 59% of the non-depressed group. A diagnosis of at least one radiation side-effect was associated with 3.70 (95% CI= 2.47, 5.55) times the odds of being diagnosed with depression.

Conclusions. It appears that potential side-effects of radiation are associated with the emotional well-being of HNC patients during the first year following cancer diagnosis.

Introduction

Radiation therapy is a well-established treatment for head and neck cancers (HNC), with half or more of all HNC patients receiving some form of radiation as part of their cancer treatment (34; 175). Unfortunately, this treatment has also been associated with a number of side-effects and toxicities which can be detrimental to HNC patients (55; 62; 176). Common side-effects of radiation treatment in HNC patients include xerostomia (dry mouth) and other salivary problems, oral health issues, malnutrition, and extreme fatigue (63-68). These side-effects can not only cause physical impairment in HNC patients, they may also affect the emotional well-being of these individuals (62; 176).

HNC patients in particular may be at risk for depression development due to the physical disfigurement and functional impairment that accompany the treatment of these cancers (53; 54). Previous literature has shown that individuals who receive radiation treatment have poorer quality of life and may have increased mental health issues or mental distress (67; 71). Further, patients who received radiation therapy have been shown to have an increased risk of depression development as treatment persists (62). While this treatment modality may be beneficial for survival, there is a dearth of research examining the influence that radiation side-effects may have on the psychological health of this group of patients already at risk for depression.

Though previous studies have suggested that radiation side-effects may influence psychological health (62; 102; 134; 176), few studies that have specifically examined the influence of treatment side-effects on depression development in HNC patients, even though the risk in this population may particularly high. Because of the frequency of radiation treatment and increased risk for psychological illness or distress in this population, and the treatment options available for depression, there is a clear need to explore the associations between the side-effect of this treatment and depression diagnosis in HNC patients. The objective of the present study

was to examine the association between radiation treatment side-effects and depression outcomes in HNC patients.

Methods

The methods for sample selection have been previously reported (177). Briefly, utilizing Surveillance Epidemiology and End Results (SEER)-Medicare linked data from 2002-2010, we identified all individuals diagnosed with HNC from 2004-2005. From this group, diagnosis of depression was identified using ICD-9-CM codes from Medicare inpatient, outpatient, or carrier claim claims data. Individuals whose reporting source indicated they were first diagnosed with cancer at the time of death or autopsy were excluded from all analysis. For the present study, we excluded individuals who had a diagnosis of depression during the two years prior to their cancer diagnosis in order to be able to capture incident depression cases. The study sample was also limited to those individuals who received radiation as part of their initial course of treatment, either alone or in addition to other treatments.

ICD-9-CM codes for potential side-effects of radiation treatment were identified from previous literature and clinical judgment. Side-effect diagnostic codes included: Xerostomia (527.7); Dysphagia (787.2, 787.21-787.24, 787.29); Aspiration (507.0, 508.9); Malnutrition (260, 261, 262, 263, 263.1, 263.8-263.9, 799.4); Fatigue or Malaise (780.7, 780.79); Radiation sickness (366.46, 692.82, 990, 909.2); Speech disturbances (784.59, V40.1, V57.3); and Dental caries (521, 521.01-521.04, 521.06-521.09; 525.13; 526.89). Patients had to have at least one inpatient, outpatient, or carrier claim diagnosis of a given side-effect within one year of cancer diagnosis to be included within a given side-effect group.

Bivariate analyses were carried out to examine basic differences in side-effects between those with and without a depression diagnosis. Multivariable logistic regression was used to

examine the association between side-effects and depression outcomes while controlling for potential confounding factors. All two-way interactions were investigated between the following variables: race, income, age, sex, cancer stage and site. Forward selection was used to fit the multivariable logistic regression model with the p-value$\leq$0.15 for entry and data were analyzed using SAS version 9.4.

Results

Bivariate Analysis. The final sample included 1,759 patients who were diagnosed with HNC between 2004-2005 and met all inclusion criteria for the study. Table 1 shows the demographic and clinical characteristics of the study sample by depression status. The only significant differences in group characteristics were gender and marital status. A greater proportion of those in the non-depressed group were male (72.9% versus 58.7%), and a greater proportion of those in the non-depressed group were married or living as married at the time of diagnoses when compared to the depressed group (57.6% versus 49.5%, respectively).

Table 2 shows the radiation side-effects in the study sample by depression status. Overall, there were significant differences in diagnosed side-effects by depression status for all side-effects examined (dysphagia, aspiration, malnutrition, and fatigue or malaise), other than xerostomia. Other than the xerostomia, over three quarters of the depressed group had a diagnosis of each side-effect, compared to less than half in of the non-depressed group. Though the difference was not statistically significant, a greater proportion of the depressed group received a diagnosis of xerostomia compared to the non-depressed group (10.2% versus 6.8%, respectively). When looking at all side-effects combined, nearly 85% of the depressed group had at least one side-effect diagnosis in the year following cancer diagnosis, compared to only 59% in the non-depressed group.

Multivariable Analysis. Table 3 shows the multivariable results of the factors associated with depression diagnosis in HNC patients. As in the bivariate analysis, females had greater odds of receiving a diagnosis of depression following HNC when compared to males (OR= 1.78; 95% CI= 1.30, 2.44). As can be seen from the table, gender and side-effect diagnosis were significantly associated with depression diagnosis. Having diagnosis of at least one radiation side-effect was associated with 3.70 (95% CI= 2.47, 5.55) times the odds of being diagnosed with depression compared to those with no radiation side-effect diagnoses.

Discussion

In this study, over half of the patient sample received a diagnosis of dysphagia, aspiration, malnutrition, or fatigue or malaise during the year following cancer diagnosis. Further, nearly 62% of the HNC patient sample had at least one potential radiation side-effect diagnosis within the first year of cancer diagnosis. Specific to the influence of side-effects on psychological health of patients, nearly 85% of those with a depression diagnosis were also diagnosed with at least one radiation side-effect, compared to only 59% of the non-depressed population. Even after controlling for age, gender and ethnicity, HNC patients who had received a diagnosis of at least one of the proposed radiation side-effects had nearly four times the odds of depression compared to those with no side-effect diagnoses. Based on the results of this study, it appears that potential side-effects of radiation are associated with the emotional well-being of HNC patients during the first year following cancer diagnosis.

The results of the present study add to and are supported by the existing literature examining the association of radiation and depression in the HNC population. Chen at al. (2010) found that symptom severity related to oral cancer was significantly associated with both depression and radiation dose in a sample of 76 oral cavity cancer patients receiving radiation (134). Additionally, Nguyen et al. (2010) found that severity of dysphagia was associated with

risk of depression in HNC patients (178). Previous work by Kelly at al. (2007), Rose at al. (2001), and Chen et al. (2009) found that patients receiving radiation treatment had increased level of depression as their radiation treatment progressed (62; 102; 176). Comparing radiation treatment with other cancer treatments, in a clinical trial of prophylactic antidepressant use in HNC patients, Lydiatt et al. (2013) found that individuals who received radiation as part of their initial course of treatment had greater mean depression rates compared to those who only received surgery (71). Additionally, Kam et al. (2015) found that HNC patients treated with radiation only or radiation with surgery had greater incidence of suicide compared to those treated with only surgery (72).

There are several limitations that should be taken into account when interpreting the results of this study. First, we identified depression in this patient population by diagnostic codes from Medicare data. Because of this, HNC patients with subclinical or undiagnosed depression were not included in the depression group in this study. Further, we eliminated those with pre-existing depression from inclusion in the study, a group which may be more likely to develop depression after cancer diagnosis. In spite of this, the significant results of this study are still relevant, since any subsequent misclassification would result in an underestimate of the influence that radiation side-effects have on depression diagnosis in the HNC population. Another limitation of this study is the lack of ability to identify a temporal relationship between depression development and radiation side-effects. Receipt of a diagnosis of both depression or side-effects of radiation would require a scheduled appoint with a healthcare provider and diagnostic date would, therefore, depend on appointment availability. Because of this, the analysis of this study only examined the association between side-effect diagnosis and depression diagnosis with the year following HNC diagnosis, without concern for which was diagnosed first. Further, this study focused on patients who received radiation with or without other treatments. It is possible that additional treatments, such as surgery or chemotherapy, may be indicative of severity of cancer or of other side-effects, such as physical disfigurement, and therefore be associated with depression

development. However, given the nature of the data, additional treatments would only be proxies for factors, and therefore were not included in the analyses. Finally, diagnostic codes for the side-effects of radiation were taken from previous literature and identified through medical records. It is possible that these side-effect diagnoses were unrelated to radiation treatments received by patients. However, the side-effects diagnostic codes used in this study were limited to those reported more commonly in the literature or that are specific to radiation treatments, giving credence to the results.

The study has several implications on both clinical practice and future research. First, for patients who will be undergoing radiation treatment, prevention measures should be taken prior to treatment initiation in order to help reduce side-effect symptomology. As outlined in a review by Andrews and Griffiths (2001), there are a number of prevention and management efforts that can be made in order to reduce dental complications associated with radiation therapy including pre-treatment assessments and potential extractions. Use of agents such as oral lubricants or fluoridation methods in irradiated patients may help reduce oral and dental complications (179). Further, monitoring of side-effects and treatment of side-effects in patients may be necessary in order to improve psychological health and quality of the in these patients. Follow up support during treatment, such as nutritional counselling, may be beneficial in helping to each side-effects of radiation. In practice, healthcare providers should monitor and screen patients undergoing radiation treatment for depression on a regular basis, especially those who develop treatment side-effects. In terms of implications on research, future studies examining psychological well-being in the HNC population should include information about treatments received and the side-effects associated with these treatments. Additionally, future prospective studies should also include information on physical disfigurement and functional impairment that may be caused by additional treatment received, such as surgery. Finally, the present study was unable to show temporality in the relationship between side-effect diagnoses and depression, and therefore unable

to determine a causal relationship. Future research should try to identify whether side-effects precede depression, or whether depression precedes side-effects in order to potentially improve depression screening or side-effect outcomes in the HNC population.

Conclusions

The results of this study suggest that not only are side-effects of radiation common in HNC patients receiving radiation therapy, but that these side-effects may be associated with depression development in this patient population. Care needs to be taken in order to mitigate radiation side-effects and to screen for depression in HNC patients undergoing radiation therapy, especially those at increased risk for depression development.

Table 1. Profile of the study sample by depression status

	No Depression N=1563		Depression N=196		p-value
	N	%	N	%	
Age					0.053
67-69	399	25.5%	43	21.9%	
70-74	461	29.5%	71	36.2%	
75-79	352	22.5%	33	16.8%	
80-84	209	13.4%	35	17.9%	
85+	142	9.1%	14	7.1%	
Gender					<0.001
Male	1139	72.9%	115	58.7%	
Female	424	27.1%	81	41.3%	
Ethnicity					0.153
Non-Hispanic white	1266	81.0%	167	85.2%	
Other	297	19.0%	29	14.8%	
Marital vs. Not					0.030
Not Married/Living as Married	662	42.4%	99	50.5%	
Married/Living as Married	901	57.6%	97	49.5%	
Median Income Census Tract					0.874
< $35, 000 or Missing	502	32.1%	63	32.1%	
$35, 000- $44,999	357	22.8%	43	21.9%	
$45, 000- $59,999	345	22.1%	48	24.5%	
$60, 000+	359	23.0%	42	21.4%	
Cancer Site					0.536
Oral Cavity and lip	263	16.8%	38	19.4%	
Oropharynx	466	29.8%	64	32.7%	
Nasopharynx/Hypopharynx	175	11.2%	21	10.7%	
Larynx	659	42.2%	73	37.2%	
SEER Region					0.123
Pacific/West	601	38.5%	67	34.2%	
Northeast	329	21.0%	53	27.0%	
Midwest	199	12.7%	30	15.3%	
South	434	27.8%	46	23.5%	
Charlson Comorbidity					0.952
0	1469	94.0%	184	93.9%	
1+	94	6.0%	12	6.1%	
Stage					0.097
Missing/Unstaged	103	6.6%	16	8.2%	
In Situ/Localized	576	36.9%	55	28.1%	
Regional	630	40.3%	86	43.9%	
Distant	254	16.3%	39	19.9%	

Table 2. Potential radiation side-effects in the study sample by depression status

	No Depression N=1563		Depression N=196		p-value
	N	%	N	%	
Side-Effects					
Xerostomia					0.799
No	1457	93.2%	176	89.8%	
Yes	106	6.8%	20	10.2%	
Dysphagia					<0.001
No	799	51.1%	41	20.9%	
Yes	764	48.9%	155	79.1%	
Aspiration					<0.001
No	830	53.1%	44	22.4%	
Yes	733	46.9%	152	77.6%	
Dental Caries					<0.001
No	857	54.8%	47	24.0%	
Yes	706	45.2%	149	76.0%	
Malnutrition					<0.001
No	792	50.7%	40	20.4%	
Yes	771	49.3%	156	79.6%	
Fatigue or Malaise					<0.001
No	789	50.5%	41	20.9%	
Yes	774	49.5%	155	79.1%	
Speech Disturbances					<0.001
No	851	54.4%	46	23.5%	
Yes	712	45.6%	150	76.5%	
Radiation Sickness/Dermatitis					<0.001
No	847	54.2%	45	23.0%	
Yes	716	45.8%	151	77.0%	
Osteoradionecrosis of Jaw					<0.001
No	858	54.9%	47	24.0%	
Yes	705	45.1%	149	76.0%	
Any Side-Effect					<0.001
No	642	41.1%	30	15.3%	
Yes	921	58.9%	166	84.7%	

Table 3. Multivariable analysis of depression diagnosis in HNC patients

	OR	95% CI		p-value
Age				
Ages 67-69	REF			
Ages 70-74	1.29	0.86	1.94	0.077
Ages 75-79	0.78	0.48	1.27	0.118
Ages 80-84	1.37	0.84	2.24	0.077
Ages 85+	0.78	0.41	1.50	0.277
Gender				
Male	REF			
Female	1.78	1.30	2.44	<0.001
Ethnicity				
Non-Hispanic White	REF			
Other	0.70	0.46	1.07	0.097
Any Side-Effect				
No	REF			
Yes	3.70	2.47	5.55	<0.001

CHAPTER VI

DISCUSSION AND CONCLUSIONS

Summary of Current Research

HNCs are a group of cancers that, although somewhat rare in the United States, appear to be highly associated with the psychological health of patients. Individuals with HNC have to deal with not only the physical effects of the disease and its treatments, but social, financial, and emotional effects of the disease as well (53; 55). Because of the unique ways HNC can affect human life, this group of patients may be at increased risk for depression development when compared to other cancer sites (49; 51). While previous studies have been conducted to examine the psychological effects of HNC more closely, there are still significant gaps in the literature regarding the understanding how often HNC patients are afflicted with depression, as well as the consequences of this on outcomes. This dissertation sought to help narrow some of the existing gaps in the literature and to bring attention to the salient biopsychosocial factors that affect patients during HNC development, diagnosis, and treatment. .

The SEER-Medicare linked database provided an opportunity to explore the relationship between depression and HNC in a national, representative sample of older adults diagnosed with HNC. This linked databased allowed us to utilize a standard method of identifying both HNC and depression diagnoses through diagnostic codes in exiting medical record data. Further, a secondary analysis of SEER-Medicare data afforded us the ability to study a large number of patients with HNC, which is a relatively rare disease. This data also allowed us to include several potential confounding variables that have been identified in the existing literature when examining the relationship between cancer diagnosis and depression.

Chapter 2 of this dissertation utilized existing literature in order to better understand the potential ways in which depression may develop in patients with cancers of the head and neck. Previous studies have identified both individual and contextual-level factors that can influence the development of depression after cancer diagnosis. Further, based on our review and synthesis, there are also individual and contextual factors that can influence depression diagnosis before cancer, which may leave individuals at increased risk for HNC. From the resulting conceptual model, it can be seen that there are a number of factors that can influence depression in HNC patients at all stages. However, most previous literature was based on smaller-scale studies, which may not have been representative of the HNC population as a whole.

Utilizing SEER-Medicare data, Chapter 3 of this dissertation examined the frequency at which individuals with HNC are diagnosed with depression. This data allowed the examination of over 3,500 individuals from more than 20 locations in the U.S. Based on the study results, some form of depression is diagnosed in nearly 19% of HNC patients. Of this group, nearly 11% are diagnosed with depression before HNC and an additional 9% develop depression within the first year of cancer diagnosis. Additionally, the multivariable analyses showed that those with depression had greater odds of being diagnosed with distant stage HNC and those who developed depression were diagnosed with later stage of cancer at the time of diagnosis. Chapter 4 further studied one segment of the sample from Chapter 3 and examined the potential effect that depression diagnosis may have on the survival of HNC patients. The results of Chapter 4 clearly showed that individuals diagnosed with depression had significantly poorer survival when compared to individuals who received no diagnosis of depression during the study period.

The final study of this dissertation focused on a sub-group of the patient sample from Chapter 4. In this chapter, the potential side-effects of radiation in HNC patients were examined in relation to depression development within the first year of cancer diagnosis among those without pre-existing depression. The results of the Chapter 5 study indicate that HNC patients

experiencing side-effects of their radiation treatments may be a greater risk for depression diagnosis than those who do not experience side-effects. Together, the studies from these chapters offer new insight into the relationship between depression and HNC.

Implications of Current Research

The findings of this dissertation have extensive clinical implications. The results of all studies from this dissertation emphasize the notion that HNC is both a physically and emotionally traumatic diagnosis, and that healthcare workers, family members, and patients need to be watchful of the potential signs of depression. Recent guideline adaptations released by the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend that all patients who receive a diagnosis of cancer be screened for depression and anxiety at their first visit, and at other times during the course of cancer that could result in changes in emotional well-being, such as at the beginning of treatment (180; 181). Also applicable to the current study population, the US Preventive Services Task Force recommends regular depression screening for older adults, utilizing tools such as the Patient Health Questionnaire (PHQ) (182).

Along with screening for depression, Stout et al. discussed the idea of making emotional well-being a part of the patient's model of care and helping them think of emotional health as a targeted outcome of their cancer recovery (183). The authors also suggested that educating patients about their disease and treatments may be beneficial in reducing unnecessary stress and including family and friends in some of the skill building strategies for coping may give added support (183). The results of this dissertation show just how common diagnosable depression may be in this cancer population. Identifying those who may be at risk for, or dealing with, depression is the first step in helping these individual improve their psychological health.

In addition to identifying existing depression in the HNC and other cancer population, emphasis should also be placed on preventing depression in those individuals without depressive symptoms. As has been discussed in this dissertation, depression can afflict patients throughout the diagnosis and treatment of cancer. Lydiatt et al. (2013) found that prophylactic use of antidepressants can help prevent depression development in HNC patients (71). Healthcare workers and patients should consider preventative measures, such as psycho pharmaceutical or psychotherapeutic interventions for the prevention of depression, both during and after cancer.

In addition to prevention and early detection of depression in newly diagnosed cancer patients, the results of Chapter 3 also support the notion of HNC screening in those with depression. The results of the study indicated that individuals with preexisting depression may be at increased risk for later stage HNC at diagnosis. It is possible that these individuals have higher risk factors and lower self-care and, therefore, may not seek medical attention during the early stages of HNC. Based on these results, it may be beneficial to screen individuals who have been diagnosed with depression for HNC, specifically if they engage in other risky behavior related to the disease such as alcohol or tobacco use. Screening this higher risk population may help to detect HNC at earlier stages, leading to better prognoses and less invasive or extensive treatment.

Chapter 4 of this dissertation found that survival among HNC patients with depression was significantly worse when compared to those without depression. These results give support to not only the notion of depression screening but also the need for depression treatment in the HNC population. Depression treatments can include psychosocial or pharmacological treatments, and both have shown to be effective in cancer populations (180; 184). Further, a study by Lydiatt et al. found that prophylactic use of antidepressants may reduce depression development in the HNC population (71). Identifying and treating HNC patients experiencing depression, or preventing depression development, may improve survival outcomes in this patient population.

The results of Chapter 5 of this dissertation found a significant association between potential side-effects of radiation treatment and depression, indicating that individuals experiencing radiation side-effects may be at greater risk of depression. While a causative relationship cannot be assumed given the study methods, healthcare providers may consider taking preventative measures before radiation treatment aimed at reducing the risk of side-effect development in the HNC population. Additionally, providers should be vigilant of side-effects in patients' treatments with radiation, and screen these patients periodically during treatments in order to identify and treat depression, as well as mitigate side-effect symptoms.

Suggested Future Research

The work in this dissertation adds to the existing literature on the relationship between HNC and psychological health. However, there are still many gaps in the literature on which future research in this area should focus. Based on the results of this dissertation, several future directions are suggested.

The second chapter of this dissertation focused on the development of a conceptual model for understanding the relationship between depression and HNC, which was based on previous peer-reviewed literature. This model, which may help in guiding future research, included individual and environmental factors that may influence this relationship between depression and cancer in the HNC population. However, many of these same factors may apply to other cancer sites in terms of depression diagnosis, especially for other substance abuse-related cancers, such as lung or esophageal. To continue to understand the influence depression may have on health throughout the life course, future research should include developing conceptual models of the relationship between depression and cancer diagnosis, focusing on depression before and after cancer diagnosis.

The current research found that the prevalence of preexisting depression was relatively high in this population, though few studies have examined the potential increased risk of HNC based on preexisting depression. Moreover, the results of the study done in Chapter 3 showed that individuals with preexisting depression may present with later stage of cancer at the time of diagnosis when compared to those without depression. Future research should further examine the relationship between preexisting depression and cancer development as a potential avenue for prevention of HNC by depression mitigation or early detection of HNC through screening in individuals experiencing depression. Experimental studies should focus on implementation and evaluation of interventions concentrated on increased awareness of early signs of HNC in high-risk populations. Future longitudinal cohort studies should further examine the potential risks that subclinical and clinical depression may have on stage of HNC diagnosis.

The results of this dissertation work showed that individuals who received a diagnosis of depression had worse survival when compared to those who were never depressed. This may be due to a lack of self-care and social support, or the result of an underlying biological mechanism related to depression. Unfortunately, given our use of secondary data, we were unable to determine the reason for this difference. Future studies should attempt to identify the reason for this disparity in survival. Further, while depression may be present in the HNC population, and appears to influence survival outcomes, there is minimal literature on the preferred or recommended treatments for depression in this cancer group. Future observational or experimental studies should aim to identify the most beneficial treatments for depression in HNC patients. Given the influence that depression may have on survival in these patients, finding appropriate depression treatments in the HCN population may help to improve not only quality of life, but also survival outcomes.

Radiation side-effects in HNC patients were found to be associated with depression development. However, given the nature of the data used, a temporal relationship between side-

effects and depression could not be identified. Further, side-effects were based on diagnoses from administrative data and selected based on previous literature. Therefore, these do not fully depict the potential consequences of radiation treatments received by these patients. Future studies should further examine the temporal relationships between radiation side-effect and depression diagnosis in order to explain this relationship. Additionally, future observational studies should utilize primary data collection and qualitative methods to better understand the potential effects of radiation treatment on the physical and psychological health of HNC patients. By collecting data prospectively, future observational studies could also identify potential implications that pre-existing depression might have on patients' treatment decisions. In addition to observational studies, future experimental studies should try to identify prophylactic measure that can be taken in order to ease these side-effects in the HNC population and improve patient quality of life during and after cancer treatments, which may help to reduce the incidence of depression during treatment.

Limitations

This dissertation is a secondary analysis of existing administrative and registry data. There are several limitations associated with the use of secondary data for this dissertation research. In each study conducted in this dissertation, both depression and cancer diagnoses were identified using diagnostic codes from the data. This method of identifying depression does not allow for a full understanding of specific criteria that were met for depression diagnosis, and also does not give us any indication of the severity of the diagnosis. Additionally, there may be misclassification when utilizing administrative data, specifically in the exposure groups of these dissertation studies. Future studies should work to utilize alternative methods for identifying subclinical and clinical depression in the HNC population.

In addition to the limitations presented by the identification of diagnoses, the data used for this dissertation offers minimal information on any social support or social aspects of the lives of these individuals. Because the nature of this dissertation research focuses on the psychological aspects of HNC, the social lives of these patients, the support they receive, and the individuals with which they may interact can significantly influence the study design and results. Each of the studies conducted as part of this dissertation would benefit from having additional information about the social aspects of these patients' lives. Future research should strive to collect more detailed information on received and perceived social support in these patients, as well as information on their social networks.

In addition to the lack of information on severity of depression and social aspects of patients' lives, there is also a dearth of information in data concerning depression treatments for these individuals. While SEER-Medicare does offer access to Part D files, thereby giving some information about psychopharmaceutical treatments received by these patients, these files were not available for all years of our study and therefore could not be explored in full. Further, SEER-Medicare offers minimal information on use of other psychological treatments such as behavioral therapy. As a result, the effectiveness of treatments received by these patients could not be examined. Future observational and experimental studies should attempt to identify treatments received by these individuals as well as the effectiveness of these in the HNC population.

Conclusions

Based on the results of this dissertation, approximately one in five HNC patients will also be diagnosed with depression, which can affect the quality of life and outcomes of this cancer population. Screening for depression throughout the course of cancer, mitigation of treatment side-effects, and identifying appropriate depression treatments are all crucial to improving the psychological health and survival of the HNC population.

Bibliography

1. Rettig E, D'Souza G. Epidemiology of head and neck cancer. *Surgical Oncology Clinics Of North America* 2015;24(3):379-396.
2. Mehanna H, Paleri V, West C, Nutting C. Head and neck cancer--Part 1: Epidemiology, presentation, and prevention. *BMJ (Clinical Research Ed.)* 2010;341:c4684.
3. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal Of Cancer* 2010;127(12):2893-2917.
4. Lambert R, Sauvaget C, de Camargo Cancela M, Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. *European Journal Of Gastroenterology & Hepatology* 2011;23(8):633-641.
5. Matsuo, K and Palmer, JB. Oral phase preparation and propulsion: Anatomy, physiology, rheology, mastication, and transport. Principles of Deglutition. New York : Springer, 2013, pp. 117-131.
6. National Cancre Institute (NCI). SEER Cancer Statistics Factsheets: Oral Cavity and Pharynx Cancer. [Online] 2015. http://seer.cancer.gov/statfacts/html/oralcav.html.
7. Siegel R, Miller K, Jemal A. Cancer statistics, 2015. *CA: A Cancer Journal For Clinicians* 2015;65(1):5-29.
8. Gleeson, MJ and Clarke, RC, [ed.]. Scott-Brown's Otorhinolaryngology: Head and Neck Surgery. s.l. : CRC Press, 2008.
9. Maqbool, M and Maqbool, S. Textbook of Ear, Nose and Throat Diseases. s.l. : JP Medical Ltd, 2013.
10. Jemal A, Bray F, Center M, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: A Cancer Journal For Clinicians* 2011;61(2):69-90.
11. Brennan B. Nasopharyngeal carcinoma. *Orphanet Journal Of Rare Diseases* 2006;1:23.

12. Dubrulle F, Souillard R, Hermans R. Extension patterns of nasopharyngeal carcinoma. *European Radiology* 2007;17(10):2622-2630.
13. Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. *Cancer Epidemiology* 2013;37(6):793-802.
14. Thibodeau, GA and Patton, KT. Anatomy & physiolog, 4th edition. s.l. : St. Louis ; London : Mosby,1999.
15. Pierce R, Worsnop C. Upper airway function and dysfunction in respiration. *Clinical And Experimental Pharmacology & Physiology* 1999;26(1):1-10.
16. Merquiol F, Montelimard A, Nourissat A, Molliex S, Zufferey P. Cervical epidural anesthesia is associated with increased cancer-free survival in laryngeal and hypopharyngeal cancer surgery: a retrospective propensity-matched analysis. *Regional Anesthesia And Pain Medicine* 2013;38(5):398-402.
17. Popescu C, Bertesteanu S, Mirea D, Grigore R, lonescu D, Popescu B. The epidemiology of hypopharynx and cervical esophagus cancer. *Journal Of Medicine And Life* 2010;3(4):396-401.
18. American Cancer Society (ACS). Laryngeal and Hypopharyngeal Cancers. [Online] 2015. http://www.cancer.org/acs/groups/cid/documents/webcontent/003108-pdf.pdf.
19. Sturgis E, Cinciripini P. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers?. *Cancer* 2007;110(7):1429-1435.
20. Curado M, Hashibe M. Recent changes in the epidemiology of head and neck cancer. *Current Opinion In Oncology* 2009;21(3):194-200.
21. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos C. The economic burden of head and neck cancer: a systematic literature review. *Pharmacoeconomics* 2014;32(9):865-882.

22. National Cancer Institute (NCI). SEER Stat Fact Sheets: Larynx Cancer. [Online] 2015. http://seer.cancer.gov/statfacts/html/laryn.html.
23. Simard E, Ward E, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA: A Cancer Journal For Clinicians* 2012;62(2):118-128.
24. Gayar OH, Ruterbusch JJ, Elshaikh M, Cote M, Ghanem T, Hall F, Siddiqui F. Oropharyngeal carcinoma in young adults: an alarming national trend. *Otolaryngology--Head And Neck Surgery: Official Journal Of American Academy Of Otolaryngology-Head And Neck Surgery* 2014;150(4):594-601.
25. Davies L, Welch H. Epidemiology of head and neck cancer in the United States. *Otolaryngology--Head And Neck Surgery: Official Journal Of American Academy Of Otolaryngology-Head And Neck Surgery* 2006;135(3):451-457.
26. Howlander N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF. SEER Cancer Statistics Review, 1975–2012. National Cancer Institute: Bethesda, MD, USA, 2015.
27. Kingsley K, O'Malley S, Ditmyer M, Chino M. Analysis of oral cancer epidemiology in the US reveals state-specific trends: implications for oral cancer prevention. *BMC Public Health* 2008;8:87.
28. Marur S, Forastiere A. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clinic Proceedings* 2008;83(4):489-501.
29. Kim L, King T, Agulnik M. Head and neck cancer: changing epidemiology and public health implications. *Oncology (Williston Park, N.Y.)* 2010;24(10):915-919.
30. Polesel, J, Franceschi, S, Talamini, R, Negri, E, Barzan, L, Montella, M, Libra, M, Vaccher, E, Franchin, G, La Vecchia, C, Serraino, D. Tobacco smoking, alcohol drinking, and the risk of different histological types of nasopharyngeal cancer in a low-risk population. *Oral Oncology* 2011;47(6):541-545.

31. Syrjänen S. The role of human papillomavirus infection in head and neck cancers. *Annals Of Oncology: Official Journal Of The European Society For Medical Oncology / ESMO* 2010;21 Suppl 7:vii243-vii245.
32. de Martel, C, Ferlay, J, Franceschi, S, Vignat, J, Bray, F, Forman, D, Plummer, M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *The Lancet. Oncology* 2012;13(6):607-615.
33. National Cancer Institute (NCI). Head and Neck Cancers. [Online] 2013. http://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet#q6.
34. Cooper, J, Porter, K, Mallin, K, Hoffman, H, Weber, R, Ang, K, Gay, E, Langer, C. National Cancer Database report on cancer of the head and neck: 10-year update. *Head & Neck* 2009;31(6):748-758.
35. Van Waes, C, Haglund, KE and Conley, BA. Head and Neck. [ed.] J Abraham, JL Gulley and CJ Allegra. Bethesda Handbook of Clinical Oncology. Phildelphia : Lippincott Williams & Wilkins, 2014.
36. Ragin C, Modugno F, Gollin S. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. *Journal Of Dental Research* 2007;86(2):104-114.
37. Brown L, Check D, Devesa S. Oral cavity and pharynx cancer incidence trends by subsite in the United States: changing gender patterns. *Journal Of Oncology* 2012;2012:649498.
38. Goodwin, W, Thomas, G, Parker, D, Joseph, D, Levis, S, Franzmann, E, Anello, C, Hu, J. Unequal burden of head and neck cancer in the United States. *Head & Neck* 2008;30(3):358-371.
39. Conway, D, Hashibe, M, Boffetta, P, Wunsch-Filho, V, Muscat, J, La Vecchia, C, Winn, D. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. *Oral Oncology* 2009;45(9):743-746.

40. Purdue M, Järvholm B, Bergdahl I, Hayes R, Baris D. Occupational exposures and head and neck cancers among Swedish construction workers. *Scandinavian Journal Of Work, Environment & Health* 2006;32(4):270-275.
41. Khlifi R, Hamza-Chaffai A. Head and neck cancer due to heavy metal exposure via tobacco smoking and professional exposure: a review. *Toxicology And Applied Pharmacology* 2010;248(2):71-88.
42. Gaudet M, Olshan A, Hashibe M, et al. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. *International Journal Of Epidemiology* 2010;39(4):1091-1102.
43. Chuang S, Jenab M, Hashibe M, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes & Control: CCC* 2012;23(1):69-88.
44. Heck J, Berthiller J, Hashibe M, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. *International Journal Of Epidemiology* 2010;39(1):166-181.
45. The American Society of Clinical Oncology (ASCO). Head and Neck Cancer. [Online] 2015. Retrieved from http://www.cancer.net/cancer-types/head-and-neck-cancer.
46. Mitchell, A, Chan, M, Bhatti, H, Halton, M, Grassi, L, Johansen, C, Meader, N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *The Lancet. Oncology* 2011;12(2):160-174.
47. Akechi T, Okuyama T, Sugawara Y, Nakano T, Shima Y, Uchitomi Y. Major depression, adjustment disorders, and post-traumatic stress disorder in terminally ill cancer patients: associated and predictive factors. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2004;22(10):1957-1965.

48. Satin J, Linden W, Phillips M. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer* 2009;115(22):5349-5361.
49. Krebber, A, Buffart, L, Kleijn, G, Riepma, I, de Bree, R, Leemans, C, Becker, A, Brug, J, van Straten, A, Cuijpers, P, Verdonck-de Leeuw, I. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psycho-Oncology* 2014;23(2):121-130.
50. Dauchy S, Dolbeault S, Reich M. Depression in cancer patients. *EJC Supplements: EJC: Official Journal Of EORTC, European Organization For Research And Treatment Of Cancer ... [Et Al.]*2013;11(2):205-215.
51. Massie MJ, Lloyd-Williams M, Irving G, Miller K. The prevalence of depression in people with cancer. Depression and Cancer. Oxford: Willey-Blackwell. 2011:1-36.
52. Pasquini M, Biondi M. Depression in cancer patients: a critical review. *Clinical Practice And Epidemiology In Mental Health: Clinical Practice and Epidemiology in Mental Health*2007;3:2.
53. Haisfield-Wolfe M, McGuire D, Soeken K, Geiger-Brown J, De Forge B. Prevalence and correlates of depression among patients with head and neck cancer: a systematic review of implications for research. *Oncology Nursing Forum* 2009;36(3):E107-E125.
54. Lydiatt W, Moran J, Burke W. A review of depression in the head and neck cancer patient. *Clinical Advances In Hematology & Oncology: H&O* 2009;7(6):397-403.
55. Panwar A, Cheung V, Lydiatt W. Supportive Care and Survivorship Strategies in Management of Squamous Cell Carcinoma of the Head and Neck. *Hematology/Oncology Clinics Of North America* 2015;29(6):1159-1168.
56. Snyderman D, Wynn D. Depression in cancer patients. *Primary Care* 2009;36(4):703-719.

57. Semple C, Sullivan K, Dunwoody L, Kernohan W. Psychosocial interventions for patients with head and neck cancer: past, present, and future. *Cancer Nursing* 2004;27(6):434-441.

58. Dalton S, Mellemkjaer L, Olsen J, Mortensen P, Johansen C. Depression and cancer risk: a register-based study of patients hospitalized with affective disorders, Denmark, 1969-1993. *American Journal Of Epidemiology* 2002;155(12):1088-1095.

59. Gross A, Gallo J, Eaton W. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. *Cancer Causes & Control: CCC* 2010;21(2):191-199.

60. Lebel S, Castonguay M, Mackness G, Irish J, Bezjak A, Devins G. The psychosocial impact of stigma in people with head and neck or lung cancer. *Psycho-Oncology* 2013;22(1):140-152.

61. Boyd C, Benarroch-Gampel J, Sheffield K, Han Y, Kuo Y, Riall T. The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma. *Surgery* 2012;152(3):403-413.

62. Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. *Otolaryngology--Head And Neck Surgery: Official Journal Of American Academy Of Otolaryngology-Head And Neck Surgery* 2007;136(1):108-111.

63. Hancock P, Epstein J, Sadler G. Oral and dental management related to radiation therapy for head and neck cancer. *Journal (Canadian Dental Association)* 2003;69(9):585-590.

64. Epstein J, Robertson M, Emerton S, Phillips N, Stevenson-Moore P. Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. *Head & Neck* 2001;23(5):389-398.

65. Jellema A, Slotman B, Doornaert P, Leemans C, Langendijk J. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with

head and neck cancer. *International Journal Of Radiation Oncology, Biology, Physics* 2007;69(3):751-760.

66. So, W, Chan, R, Chan, D, Hughes, B, Chair, S, Choi, K, Chan, C. Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. *European Journal Of Cancer (Oxford, England: 1990)* 2012;48(15):2391-2408.
67. Ravasco P, Monteiro-Grillo I, Camilo M. Does nutrition influence quality of life in cancer patients undergoing radiotherapy?. *Radiotherapy And Oncology: Journal Of The European Society For Therapeutic Radiology And Oncology* 2003;67(2):213-220.
68. Couch, M, Lai, V, Cannon, T, Guttridge, D, Zanation, A, George, J, Hayes, D, Zeisel, S, Shores, C. Cancer cachexia syndrome in head and neck cancer patients: part I. Diagnosis, impact on quality of life and survival, and treatment. *Head & Neck* 2007;29(4):401-411.
69. Giro, C, Berger, B, Bölke, E, Ciernik, I, Duprez, F, Locati, L, Maillard, S, Ozsahin, M, Pfeffer, R, Robertson, A, Langendijk, J, Budach, W. High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: results of a survey in EORTC institutes. *Radiotherapy And Oncology: Journal Of The European Society For Therapeutic Radiology And Oncology* 2009;90(2):166-171.
70. Elliott, E, Wright, J, Swann, R, Nguyen-Tân, F, Takita, C, Bucci, M, Garden, A, Kim, H, Hug, E, Ryu, J, Greenberg, M, Saxton, J, Ang, K, Berk, L. Phase III Trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2006;24(13):2092-2097.
71. Lydiatt W, Bessette D, Schmid K, Sayles H, Burke W. Prevention of depression with escitalopram in patients undergoing treatment for head and neck cancer: randomized, double-blind, placebo-controlled clinical trial. *JAMA Otolaryngology-- Head & Neck Surgery* 2013;139(7):678-686.

72. Kam, D, Salib, A, Gorgy, G, Patel, T, Carniol, E, Eloy, J, Baredes, S, Park, R. Incidence of Suicide in Patients With Head and Neck Cancer. *JAMA Otolaryngology-- Head & Neck Surgery* 2015;141(12):1075-1081.
73. Kaida A, Colman I, Janssen P. Recent Pap tests among Canadian women: is depression a barrier to cervical cancer screening?. *Journal Of Women's Health (2002)* 2008;17(7):1175-1181.
74. Baillargeon J, Kuo Y, Lin Y, Raji M, Singh A, Goodwin J. Effect of mental disorders on diagnosis, treatment, and survival of older adults with colon cancer. *Journal Of The American Geriatrics Society* 2011;59(7):1268-1273.
75. Lazure K, Lydiatt W, Denman D, Burke W. Association between depression and survival or disease recurrence in patients with head and neck cancer enrolled in a depression prevention trial. *Head & Neck* 2009;31(7):888-892.
76. Zeller J. High suicide risk found for patients with head and neck cancer. *Jama* 2006;296(14):1716-1717.
77. Misono S, Weiss N, Fann J, Redman M, Yueh B. Incidence of suicide in persons with cancer. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2008;26(29):4731-4738.
78. National Cancer Institute (NCI). SEER-Medicare: SEER Program & Data. [Online] 2015. http://healthcaredelivery.cancer.gov/seermedicare/.
79. Warren J, Klabunde C, Schrag D, Bach P, Riley G. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Medical Care* 2002;40(8 Suppl):IV-3-18.
80. Goodwin J, Zhang D, Ostir G. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. *Journal Of The American Geriatrics Society* 2004;52(1):106-111.

81. Prasad S, Eggener S, Lipsitz S, Irwin M, Ganz P, Hu J. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2014;32(23):2471-2478.
82. Archer J, Hutchison I, Korszun A. Mood and malignancy: head and neck cancer and depression. *Journal Of Oral Pathology & Medicine: Official Publication Of The International Association Of Oral Pathologists And The American Academy Of Oral Pathology* 2008;37(5):255-270.
83. Kissane, D, Patel, S, Baser, R, Bell, R, Farberov, M, Ostroff, J, Li, Y, Singh, B, Kraus, D, Shah, J. Preliminary evaluation of the reliability and validity of the Shame and Stigma Scale in head and neck cancer. *Head & Neck* 2013;35(2):172-183.
84. Hagedoorn M, Molleman E. Facial disfigurement in patients with head and neck cancer: the role of social self-efficacy. *Health Psychology: Official Journal Of The Division Of Health Psychology, American Psychological Association* 2006;25(5):643-647.
85. Hassanein K, Musgrove B, Bradbury E. Functional status of patients with oral cancer and its relation to style of coping, social support and psychological status. *The British Journal Of Oral & Maxillofacial Surgery* 2001;39(5):340-345.
86. Kugaya, A, Akechi, T, Okuyama, T, Nakano, T, Mikami, I, Okamura, H, Uchitomi, Y. Prevalence, predictive factors, and screening for psychologic distress in patients with newly diagnosed head and neck cancer. *Cancer* 2000;88(12):2817-2823.
87. Kim, S, Roh, J, Lee, S, Lee, S, Kim, S, Choi, S, Nam, S, Kim, S. Pretreatment depression as a prognostic indicator of survival and nutritional status in patients with head and neck cancer. *Cancer* 2016;122(1):131-140.
88. Lydiatt W, Denman D, McNeilly D, Puumula S, Burke W. A randomized, placebo-controlled trial of citalopram for the prevention of major depression during treatment for

head and neck cancer. *Archives Of Otolaryngology--Head & Neck Surgery* 2008;134(5):528-535.

89. Mock, V, St Ours, C, Hall, S, Bositis, A, Tillery, M, Belcher, A, Krumm, S, McCorkle, R. Using a conceptual model in nursing research--mitigating fatigue in cancer patients. *Journal Of Advanced Nursing* 2007;58(5):503-512.
90. Frampton M. Psychological distress in patients with head and neck cancer: review. *The British Journal Of Oral & Maxillofacial Surgery* 2001;39(1):67-70.
91. Llewellyn C, McGurk M, Weinman J. Illness and treatment beliefs in head and neck cancer: is Leventhal's common sense model a useful framework for determining changes in outcomes over time?. *Journal Of Psychosomatic Research* 2007;63(1):17-26.
92. Maeda T, Kurihara H, Morishima I, Munakata T. The effect of psychological intervention on personality change, coping, and psychological distress of Japanese primary breast cancer patients. *Cancer Nursing* 2008;31(4):E27-E35.
93. Matthieu MM, Ivanoff A. Using stress, appraisal, and coping theories in clinical practice: Assessments of coping strategies after disasters. *Brief Treatment and Crisis Intervention* 2006;6(4):337.
94. Merriman, J, Dodd, M, Lee, K, Paul, S, Cooper, B, Aouizerat, B, Swift, P, Wara, W, Dunn, L, Miaskowski, C. Differences in self-reported attentional fatigue between patients with breast and prostate cancer at the initiation of radiation therapy. *Cancer Nursing* 2011;34(5):345-353.
95. Dirksen S, Belyea M, Epstein D. Fatigue-based subgroups of breast cancer survivors with insomnia. *Cancer Nursing* 2009;32(5):404-411.
96. Cataldo J, Slaughter R, Jahan T, Pongquan V, Hwang W. Measuring stigma in people with lung cancer: psychometric testing of the cataldo lung cancer stigma scale. *Oncology Nursing Forum* 2011;38(1):E46-E54.

97. Buchmann L, Conlee J, Hunt J, Agarwal J, White S. Psychosocial distress is prevalent in head and neck cancer patients. *The Laryngoscope* 2013;123(6):1424-1429.

98. Karnell L, Funk G, Christensen A, Rosenthal E, Magnuson J. Persistent posttreatment depressive symptoms in patients with head and neck cancer. *Head & Neck* 2006;28(5):453-461.

99. Adachi, Y, Kimura, H, Sato, N, Nagashima, W, Nakamura, K, Aleksic, B, Yoshida, K, Fujimoto, Y, Nakashima, T, Ozaki, N. Preoperative level of depression is a predictor of postoperative levels of depression in patients with head and neck cancer. *Japanese Journal Of Clinical Oncology* 2014;44(4):311-317.

100. de Graeff A, de Leeuw J, Ros W, Hordijk G, Blijham G, Winnubst J. Pretreatment factors predicting quality of life after treatment for head and neck cancer. *Head & Neck* 2000;22(4):398-407.

101. Hutton J, Williams M. An investigation of psychological distress in patients who have been treated for head and neck cancer. *The British Journal Of Oral & Maxillofacial Surgery* 2001;39(5):333-339.

102. Chen, A, Jennelle, R, Grady, V, Tovar, A, Bowen, K, Simonin, P, Tracy, J, McCrudden, D, Stella, J, Vijayakumar, S. Prospective study of psychosocial distress among patients undergoing radiotherapy for head and neck cancer. *International Journal Of Radiation Oncology, Biology, Physics* 2009;73(1):187-193.

103. Reisine, S, Morse, D, Psoter, W, Eisenberg, E, Cohen, D, Cleveland, D, Mohit-Tabatabai, M. Sociodemographic risk indicators for depressive symptoms among persons with oral cancer or oral epithelial dysplasia. *Journal Of Oral And Maxillofacial Surgery: Official Journal Of The American Association Of Oral And Maxillofacial Surgeons* 2005;63(4):513-520.

104. Chen S, Huang B, Lin C. Depression and predictors in Taiwanese survivors with oral cancer. *Asian Pacific Journal Of Cancer Prevention: APJCP* 2013;14(8):4571-4576.

105. Archer J, Hutchison I, Dorudi S, Stansfeld S, Korszun A. Interrelationship of depression, stress and inflammation in cancer patients: a preliminary study. *Journal Of Affective Disorders* 2012;143(1-3):39-46.

106. Hassanein K, Musgrove B, Bradbury E. Psychological outcome of patients following treatment of oral cancer and its relation with functional status and coping mechanisms. *Journal Of Cranio-Maxillo-Facial Surgery: Official Publication Of The European Association For Cranio-Maxillo-Facial Surgery* 2005;33(6):404-409.

107. Llewellyn C, McGurk M, Weinman J. Are psycho-social and behavioural factors related to health related-quality of life in patients with head and neck cancer? A systematic review. *Oral Oncology* 2005;41(5):440-454.

108. Horney, D, Smith, H, McGurk, M, Weinman, J, Herold, J, Altman, K, Llewellyn, C. Associations between quality of life, coping styles, optimism, and anxiety and depression in pretreatment patients with head and neck cancer. *Head & Neck* 2011;33(1):65-71.

109. Kobayashi M, Sugimoto T, Matsuda A, Matsushima E, Kishimoto S. Association between self-esteem and depression among patients with head and neck cancer: a pilot study. *Head & Neck* 2008;30(10):1303-1309.

110. Aarstad A, Lode K, Larsen J, Bru E, Aarstad H. Choice of psychological coping in laryngectomized, head and neck squamous cell carcinoma patients versus multiple sclerosis patients. *European Archives Of Oto-Rhino-Laryngology: Official Journal Of The European Federation Of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated With The German Society For Oto-Rhino-Laryngology - Head And Neck Surgery* 2011;268(6):907-915.

111. de Leeuw J, de Graeff A, Ros W, Blijham G, Hordijk G, Winnubst J. Prediction of depression 6 months to 3 years after treatment of head and neck cancer. *Head & Neck* 2001;23(10):892-898.

112. de Leeuw J, de Graeff A, Ros W, Blijham G, Hordijk G, Winnubst J. Prediction of depressive symptomatology after treatment of head and neck cancer: the influence of pre-treatment physical and depressive symptoms, coping, and social support. *Head & Neck* 2000;22(8):799-807.

113. Morse, D, Psoter, W, Baek, L, Eisenberg, E, Cohen, D, Cleveland, D, Mohit-Tabatabai, M, Reisine, S. Smoking and drinking in relation to depressive symptoms among persons with oral cancer or oral epithelial dysplasia. *Head & Neck* 2010;32(5):578-587.

114. Reiter P, Wee A, Lehman A, Paskett E. Oral cancer screening and dental care use among women from Ohio Appalachia. *Rural And Remote Health* 2012;12:2184.

115. Elani H, Allison P. Coping and psychological distress among head and neck cancer patients. *Supportive Care In Cancer: Official Journal Of The Multinational Association Of Supportive Care In Cancer* 2011;19(11):1735-1741.

116. Humphris G, Rogers S, McNally D, Lee-Jones C, Brown J, Vaughan D. Fear of recurrence and possible cases of anxiety and depression in orofacial cancer patients. *International Journal Of Oral And Maxillofacial Surgery* 2003;32(5):486-491.

117. Neilson, K, Pollard, A, Boonzaier, A, Corry, J, Castle, D, Smith, D, Trauer, T, Couper, J. A longitudinal study of distress (depression and anxiety) up to 18 months after radiotherapy for head and neck cancer. *Psycho-Oncology* 2013;22(8):1843-1848.

118. Aarstad A, Beisland E, Aarstad H. Personality, choice of coping and T stage predict level of distress in head and neck cancer patients during follow-up. *European Archives Of Oto-Rhino-Laryngology: Official Journal Of The European Federation Of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated With The German Society For Oto-Rhino-Laryngology - Head And Neck Surgery* 2012;269(9):2121-2128.

119. Aarstad H, Aarstad A, Heimdal J, Olofsson J. Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life. *Acta Oto-Laryngologica* 2005;125(5):557-565.

120. Hammerlid E, Silander E, Hörnestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer--a longitudinal study. *Head & Neck* 2001;23(2):113-125.

121. Chang, W, Huang, J, Klahan, S, Su, P, Kuo, C, Yu, H, Chang, W, Huang, M. Association between oral cavity cancer and depression: a population-based study in Taiwan. *Oral Oncology* 2014;50(4):e21-e22.

122. Chiou, W, Lee, M, Ho, H, Hung, S, Lin, H, Su, Y, Lee, C. Prognosticators and the relationship of depression and quality of life in head and neck cancer. *Indian Journal Of Cancer* 2013;50(1):14-20.

123. Irish, J, Sandhu, N, Simpson, C, Wood, R, Gilbert, R, Gullane, P, Brown, D, Goldstein, D, Devins, G, Barker, E. Quality of life in patients with maxillectomy prostheses. *Head & Neck* 2009;31(6):813-821.

124. Lue B, Huang T, Chen H. Physical distress, emotional status, and quality of life in patients with nasopharyngeal cancer complicated by post-radiotherapy endocrinopathy. *International Journal Of Radiation Oncology, Biology, Physics* 2008;70(1):28-34.

125. De Leeuw J, De Graeff A, Ros W, Hordijk G, Blijham G, Winnubst J. Negative and positive influences of social support on depression in patients with head and neck cancer: a prospective study. *Psycho-Oncology* 2000;9(1):20-28.

126. Karnell L, Christensen A, Rosenthal E, Magnuson J, Funk G. Influence of social support on health-related quality of life outcomes in head and neck cancer. *Head & Neck* 2007;29(2):143-146.

127. Llewellyn C, McGurk M, Weinman J. How satisfied are head and neck cancer (HNC) patients with the information they receive pre-treatment? Results from the satisfaction with cancer information profile (SCIP). *Oral Oncology* 2006;42(7):726-734.

128. Moye J, June A, Martin L, Gosian J, Herman L, Naik A. Pain is prevalent and persisting in cancer survivors: differential factors across age groups. *Journal Of Geriatric Oncology* 2014;5(2):190-196.

129. Rogers, L, Courneya, K, Robbins, K, Rao, K, Malone, J, Seiz, A, Reminger, S, Markwell, S, Burra, V. Factors associated with fatigue, sleep, and cognitive function among patients with head and neck cancer. *Head & Neck* 2008;30(10):1310-1317.

130. Shuman, A, Duffy, S, Ronis, D, Garetz, S, McLean, S, Fowler, K, Terrell, J. Predictors of poor sleep quality among head and neck cancer patients. *The Laryngoscope* 2010;120(6):1166-1172.

131. Tesch R, Denardin O, Baptista C, Dias F. Depression levels in chronic orofacial pain patients: a pilot study. *Journal Of Oral Rehabilitation* 2004;31(10):926-932.

132. Chen M, Chang H. Physical symptom profiles of depressed and nondepressed patients with cancer. *Palliative Medicine* 2004;18(8):712-718.

133. Chen S, Liao C, Chang J. Orofacial pain and predictors in oral squamous cell carcinoma patients receiving treatment. *Oral Oncology* 2011;47(2):131-135.

134. Chen S, Lai Y, Liao C, Lin C, Chang J. Changes of symptoms and depression in oral cavity cancer patients receiving radiation therapy. *Oral Oncology* 2010;46(7):509-513.

135. Duffy, S, Ronis, D, Valenstein, M, Fowler, K, Lambert, M, Bishop, C, Terrell, J. Depressive symptoms, smoking, drinking, and quality of life among head and neck cancer patients. *Psychosomatics* 2007;48(2):142-148.

136. Chan J, Lua L, Starmer H, Sun D, Rosenblatt E, Gourin C. The relationship between depressive symptoms and initial quality of life and function in head and neck cancer. *The Laryngoscope* 2011;121(6):1212-1218.

137. Danker H, Wollbrück D, Singer S, Fuchs M, Brähler E, Meyer A. Social withdrawal after laryngectomy. *European Archives Of Oto-Rhino-Laryngology: Official Journal Of The European Federation Of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated*

With The German Society For Oto-Rhino-Laryngology - Head And Neck Surgery 2010;267(4):593-600.

138. Nguyen N, Sallah S, Karlsson U, Antoine J. Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. *Cancer* 2002;94(4):1131-1141.

139. Verdonck-de Leeuw I, van Bleek W, Leemans C, de Bree R. Employment and return to work in head and neck cancer survivors. *Oral Oncology* 2010;46(1):56-60.

140. Zwahlen, R, Dannemann, C, Grätz, K, Studer, G, Zwahlen, D, Moergeli, H, Drabe, N, Büchi, S, Jenewein, J. Quality of life and psychiatric morbidity in patients successfully treated for oral cavity squamous cell cancer and their wives. *Journal Of Oral And Maxillofacial Surgery: Official Journal Of The American Association Of Oral And Maxillofacial Surgeons* 2008;66(6):1125-1132.

141. Airoldi, M, Garzaro, M, Raimondo, L, Pecorari, G, Giordano, C, Varetto, A, Caldera, P, Torta, R. Functional and psychological evaluation after flap reconstruction plus radiotherapy in oral cancer. *Head & Neck* 2011;33(4):458-468.

142. Dirix P, Nuyts S, Vander Poorten V, Delaere P, Van den Bogaert W. The influence of xerostomia after radiotherapy on quality of life: results of a questionnaire in head and neck cancer. *Supportive Care In Cancer: Official Journal Of The Multinational Association Of Supportive Care In Cancer* 2008;16(2):171-179.

143. Trzcieniecka-Green A, Bargiel-Matusiewicz K, Borczyk J. Quality of life of patients after laryngectomy. *Journal Of Physiology And Pharmacology: An Official Journal Of The Polish Physiological Society* 2007;58 Suppl 5(Pt 2):699-704.

144. Verdonck-de Leeuw, I, de Bree, R, Keizer, A, Houffelaar, T, Cuijpers, P, van der Linden, M, Leemans, C. Computerized prospective screening for high levels of emotional distress in head and neck cancer patients and referral rate to psychosocial care. *Oral Oncology* 2009;45(10):e129-e133.

145. Britton, B, Clover, K, Bateman, L, Odelli, C, Wenham, K, Zeman, A, Carter, G. Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. *Supportive Care In Cancer: Official Journal Of The Multinational Association Of Supportive Care In Cancer* 2012;20(2):335-342.

146. Katz M, Irish J, Devins G, Rodin G, Gullane P. Psychosocial adjustment in head and neck cancer: the impact of disfigurement, gender and social support. *Head & Neck* 2003;25(2):103-112.

147. Fingeret M, Vidrine D, Reece G, Gillenwater A, Gritz E. Multidimensional analysis of body image concerns among newly diagnosed patients with oral cavity cancer. *Head & Neck* 2010;32(3):301-309.

148. Mochizuki Y, Matsushima E, Omura K. Perioperative assessment of psychological state and quality of life of head and neck cancer patients undergoing surgery. *International Journal Of Oral And Maxillofacial Surgery* 2009;38(2):151-159.

149. Lee, P, Kwan, T, Kwong, D, Sham, J, Pow, E, McMillan, A, Au, G. A prospective study of the impact of nasopharyngeal cancer and radiotherapy on the psychosocial condition of Chinese patients. *Cancer* 2007;109(7):1344-1354.

150. Humphris G, Rogers S. The association of cigarette smoking and anxiety, depression and fears of recurrence in patients following treatment of oral and oropharyngeal malignancy. *European Journal Of Cancer Care* 2004;13(4):328-335.

151. Potash A, Karnell L, Christensen A, Vander Weg M, Funk G. Continued alcohol use in patients with head and neck cancer. *Head & Neck* 2010;32(7):905-912.

152. Berg, C, Thomas, A, Mertens, A, Schauer, G, Pinsker, E, Ahluwalia, J, Khuri, F. Correlates of continued smoking versus cessation among survivors of smoking-related cancers. *Psycho-Oncology* 2013;22(4):799-806.

153. Hassel A, Danner D, Freier K, Hofele C, Becker-Bikowski K, Engel M. Oral health-related quality of life and depression/anxiety in long-term recurrence-free patients after

treatment for advanced oral squamous cell cancer. *Journal Of Cranio-Maxillo-Facial Surgery: Official Publication Of The European Association For Cranio-Maxillo-Facial Surgery* 2012;40(4):e99-e102.

154. Lin B, Starmer H, Gourin C. The relationship between depressive symptoms, quality of life, and swallowing function in head and neck cancer patients 1 year after definitive therapy. *The Laryngoscope* 2012;122(7):1518-1525.

155. Suthahar, A, Gurpreet, K, Ambigga, D, Dhachayani, S, Fuad, I, Maniam, T, Osman, C, Ainsah, O. Psychological distress, quality of life and coping in cancer patients: a prospective study. *The Medical Journal Of Malaysia* 2008;63(5):362-368.

156. Heyn L, Finset A, Ruland C. Talking about feelings and worries in cancer consultations: the effects of an interactive tailored symptom assessment on source, explicitness, and timing of emotional cues and concerns. *Cancer Nursing* 2013;36(2):E20-E30.

157. Marvel K, Major G, Jones K, Pfaffly C. Dialogues in the exam room: medical interviewing by resident family physicians. *Family Medicine* 2000;32(9):628-632.

158. Koster ME, Bergsma J. Problems and coping behaviour of facial cancer patients. *Social Science & Medicine* 1990;30(5):569-78.

159. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal Of Chronic Diseases* 1987;40(5):373-383.

160. Klabunde C, Potosky A, Legler J, Warren J. Development of a comorbidity index using physician claims data. *Journal Of Clinical Epidemiology* 2000;53(12):1258-1267.

161. Deyo R, Cherkin D, Ciol M. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal Of Clinical Epidemiology* 1992;45(6):613-619.

162. Singer, S, Krauss, O, Keszte, J, Siegl, G, Papsdorf, K, Severi, E, Hauss, J, Briest, S, Dietz, A, Brähler, E, Kortmann, R. Predictors of emotional distress in patients with head and neck cancer. *Head & Neck* 2012;34(2):180-187.

163. Schultz C, Goffi-Gomez M, Pecora Liberman P, Pellizzon A, Carvalho A. Hearing loss and complaint in patients with head and neck cancer treated with radiotherapy. *Archives Of Otolaryngology--Head & Neck Surgery* 2010;136(11):1065-1069.

164. Mujica-Mota M, Waissbluth S, Daniel S. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head & Neck* 2013;35(11):1662-1668.

165. Hughes, S, Jaremka, L, Alfano, C, Glaser, R, Povoski, S, Lipari, A, Agnese, D, Farrar, W, Yee, L, Carson, W, Malarkey, W, Kiecolt-Glaser, J. Social support predicts inflammation, pain, and depressive symptoms: longitudinal relationships among breast cancer survivors. *Psychoneuroendocrinology* 2014;42:38-44.

166. Walkup J, Boyer C, Kellermann S. Reliability of Medicaid claims files for use in psychiatric diagnoses and service delivery. *Administration And Policy In Mental Health* 2000;27(3):129-139.

167. Shinn, E, Valentine, A, Jethanandani, A, Basen-Engquist, K, Fellman, B, Urbauer, D, Atkinson, E, Yusuf, S, Lenihan, D, Woods, M, Kies, M, Sood, A, Carmack, C, Morrison, W, Gillenwater, A, Sturgis, E, Garden, A. Depression and Oropharynx Cancer Outcome. *Psychosomatic Medicine* 2016;78(1):38-48.

168. Vodermaier, A, Linden, W, Rnic, K, Young, S, Ng, A, Ditsch, N, Olson, R. Prospective associations of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer. *Breast Cancer Research And Treatment* 2014;143(2):373-384.

169. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ (Clinical Research Ed.)* 2005;330(7493):702.

170. Pinquart M, Duberstein P. Depression and cancer mortality: a meta-analysis. *Psychological Medicine* 2010;40(11):1797-1810.

171. Howren M, Christensen A, Karnell L, Funk G. Psychological factors associated with head and neck cancer treatment and survivorship: evidence and opportunities for behavioral medicine. *Journal Of Consulting And Clinical Psychology* 2013;81(2):299-317.

172. Giese-Davis J, Collie K, Rancourt K, Neri E, Kraemer H, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2011;29(4):413-420.

173. Arrieta, O, Angulo, L, Núñez-Valencia, C, Dorantes-Gallareta, Y, Macedo, E, Martínez-López, D, Alvarado, S, Corona-Cruz, J, Oñate-Ocaña, L. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Annals Of Surgical Oncology* 2013;20(6):1941-1948.

174. Marur S, D'Souza G, Westra W, Forastiere A. HPV-associated head and neck cancer: a virus-related cancer epidemic. *The Lancet. Oncology* 2010;11(8):781-789.

175. Chen M, Roman S, Yarbrough W, Burtness B, Sosa J, Judson B. Trends and variations in the use of adjuvant therapy for patients with head and neck cancer. *Cancer* 2014;120(21):3353-3360.

176. Rose P, Yates P. Quality of life experienced by patients receiving radiation treatment for cancers of the head and neck. *Cancer Nursing* 2001;24(4):255-263.

177. Rieke K, Boilesen E, Lydiatt W, Schmid KK, Houfek J, Watanabe-Galloway S. Population-based retrospective study to investigate preexisting and new depression diagnosis among head and neck cancer patients (In Press, *Cancer Epidemiology;* DOI:10.1016/j.canep.2016.06.008).

178. Nguyen, N, Frank, C, Moltz, C, Vos, P, Smith, H, Karlsson, U, Dutta, S, Midyett, A, Barloon, J, Sallah, S. Impact of dysphagia on quality of life after treatment of head-and-

neck cancer. *International Journal Of Radiation Oncology, Biology, Physics* 2005;61(3):772-778.

179. Andrews N, Griffiths C. Dental complications of head and neck radiotherapy: Part 2. *Australian Dental Journal* 2001;46(3):174-182.

180. Andersen, B, DeRubeis, R, Berman, B, Gruman, J, Champion, V, Massie, M, Holland, J, Partridge, A, Bak, K, Somerfield, M, Rowland, J. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology* 2014;32(15):1605-1619.

181. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Distress Management Version 1.2014. [Online] 2014. http://williams.medicine.wisc.edu/distress.pdf .

182. Siu, A, Bibbins-Domingo, K, Grossman, D, Baumann, L, Davidson, K, Ebell, M, García, F, Gillman, M, Herzstein, J, Kemper, A, Krist, A, Kurth, A, Owens, D, Phillips, W, Phipps, M, Pignone, M. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *Jama* 2016;315(4):380-387.

183. Stout RA, Beckman NJ, Shelby SR, Labott SM. Psychological Issues in Head and Neck Cancer. *Head & Neck Cancer: Current Perspectives, Advances, and Challenges.* Springer Netherlands 2013;751-800.

184. Laoutidis Z, Mathiak K. Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. *BMC Psychiatry* 2013;13:140.

185. Duffy, S, Khan, M, Ronis, D, Fowler, K, Gruber, S, Wolf, G, Terrell, J. Health behaviors of head and neck cancer patients the first year after diagnosis. *Head & Neck* 2008;30(1):93-102.

Appendix A. Flow chart of the selection of the study sample