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Weight loss after head and neck cancer: A dynamic relationship with depressive symptoms

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Abstract

Background—Weight loss (WL) and depressive symptoms are critical head and neck cancer (HNC) outcomes, yet their relation over the illness course is unclear.

Methods—Associations between self-reported depressive symptoms and objective WL across the year following HNC diagnosis were examined using growth curve modeling techniques (N=564).

Results—A reciprocal covariation pattern emerged—changes in depressive symptoms over time were associated with same-month changes in WL, $t(1148) = 2.05$, $p = .041$, and changes in WL were associated with same-month changes in depressive symptoms, $t(556) = 2.43$, $p = .015$. To the extent that depressive symptoms increased, patients lost incrementally more weight than was lost due to the passage of time, and vice versa. Results also suggested that pain and eating-related quality of life might explain the reciprocal association between depressive symptoms and WL.

Conclusions—In HNC, a transactional interplay between depressive symptoms and WL unfolds over time.

Keywords

depressive symptoms; weight loss; head and neck cancer; nutrition

Introduction

Head and neck cancer (HNC) is frequently accompanied by functional impairments and psychological distress. Structural and functional changes reduce nutritional intake, making weight loss (WL) and nutritional compromise primary concerns for HNC patients^(1, 2). Symptoms of depression are also prevalent and have important implications for illness

adjustment and recovery. A small body of research suggests that depressive symptoms and WL are related in HNC patients, yet longitudinal research designs are necessary to clarify the nature of these associations. In the present study, we implemented a longitudinal design and growth curve modeling techniques to clarify whether one variable (depressive symptoms or WL) is a driving force in the developmental course of the other variable, or whether a dynamic, reciprocal relation better characterizes their association following HNC diagnosis. Consequently, we were able to examine whether depressive symptoms contribute to a maladaptive cycle, perpetuating the escalation in WL often observed during the course of HNC diagnosis and treatment.

Weight Loss

Compared with other cancer patients, patients with HNC have the second highest malnutrition prevalence—20–67% are malnourished or at high risk of becoming malnourished at diagnosis^(3–6). In the absence of a recognized gold standard for malnutrition determination⁽⁷⁾, WL has optimal sensitivity and specificity for detecting nutritional depletion in patients with HNC^(4, 8), with 5–10% WL having superior prognostic value for post-operative complications and survival⁽⁹⁾. The *pattern* of weight change also has survival implications; patients who experience changes in weight (a gain or loss > 5%) by three months post-diagnosis have lower five-year survival rates than patients with stable weight⁽¹⁰⁾.

Significant WL is common before HNC diagnosis⁽¹¹⁾, during treatment⁽¹²⁾, and after treatment^(11–13), and occurs for up to a year following treatment⁽¹⁴⁾. Predictors of greater WL include tumor site (pharynx, larynx, and oral cavity)^(15–17); treatment type (radiation or a combination of radiation and chemotherapy)^(4, 11, 12, 15, 18); presence of dysphagia, xerostomia, thick saliva, difficulty chewing, and mouth pain^(13, 19); and higher initial weight and body mass index (BMI)⁽²⁰⁾. It appears that age, race, sex, history of tobacco and alcohol use, and radiation dose do not independently predict severe weight loss^(12, 15, 18, 20), and evidence is mixed regarding the predictive ability of cancer stage^(4, 8, 10, 11, 20, 21) and prediagnosis weight loss⁽¹⁵⁾.

Depressive Symptoms

The functional (e.g., changes in eating, swallowing, breathing, and speech), attitudinal (e.g., psychological distress, self-blame, body image/disfigurement), and social (e.g., perceived stigma, social/role disruption) impact of HNC and its treatment suggest why this type of cancer has been described as one of the most psychologically distressing to experience^(22, 23). In a comparative analysis of cancer patients, depression prevalence estimates were among the highest in patients with HNC^(24, 25). Prospective longitudinal analyses typically suggest a significant increase in average depressive symptoms during or soon after treatment^(26–28), followed by decline between six months and one year following diagnosis^(29, 30). On average, 20–60% of patients endorse some degree of depressive symptomatology two to three months post-diagnosis^(23, 26–28), compared with 17–24% between six months and one year post-diagnosis^(28–30). Pretreatment depressive symptoms and shorter time duration since diagnosis consistently predict posttreatment depressive

symptoms,^(26, 28, 29, 31, 32) and evidence conflicts regarding the predictive nature of age, sex, marital status, and disease stage^(26, 28, 31, 32).

Associations Between Depressive Symptoms and Nutritional Impairment

Cross-sectional studies have noted an association between higher levels of depressive symptoms and poorer nutritional markers (including WL) among patients with lung⁽³³⁾, prostate⁽³⁴⁾, and colorectal cancer⁽³⁵⁾, chronic kidney disease^(36, 37), and inflammatory bowel disease⁽³⁸⁾, as well as with geriatric patients^(39–42). Importantly, depressive symptoms have remained associated with poor nutritional status after controlling for factors such as disease severity, age, and functional status in these non-HNC patient populations^(37, 42–44). Although a cross-sectional association between depressive symptoms and malnutrition in HNC was first suggested over 25 years ago, indicating that depressed patients were significantly more likely to be malnourished one year posttreatment⁽⁴⁵⁾, surprisingly little research has been conducted since. One prospective study found that depressive symptoms predicted reduced energy intake and greater weight loss 2.5 months after HNC treatment⁽¹³⁾. Another study reported a trend toward a higher cross-sectional prevalence of depression across time in patients with HNC who experienced significant WL⁽²¹⁾. The methodologically strongest study, a prospective analysis accounting for several nutritional risk factors, found that depression during the first week of radiation treatment independently predicted malnutrition four weeks posttreatment⁽¹⁶⁾. Depression was not only associated with subsequent nutritional decline in radiation-treated HNC patients, but was also a stronger predictor than several commonly accepted risk factors for malnutrition (i.e., tumor stage, radiation fractionation amount, feeding tube status, caregiver presence, and dietician-conducted clinical assessment). Appropriately, the authors called for expanded research investigating whether depression functions as a cause or an indicator of malnutrition.

Across patient populations, it has been difficult to establish a causal association between depressive symptoms and nutritional status, creating a need to further elucidate directionality^(44, 46). Depressive symptoms could be either the “cause or consequence” of impaired nutritional status⁽⁴⁴⁾ and a reciprocal/bidirectional relationship may exist, such that the two domains simultaneously influence each other^(44, 46). In contrast to emerging research on the impact of depressive symptoms on WL in patients with HNC, it is problematic that the reverse effect of WL on depressive symptoms has not been studied in this population. Furthermore, although the association between depressive symptoms and nutritional compromise in patients with HNC may be best conceptualized as a bidirectional relationship in which the two domains reciprocally influence each other in a complex interplay over time⁽¹⁶⁾, this dynamic, evolving association has yet to be examined^(1, 16, 47, 48).

Characteristics of depression that could influence WL include reduced appetite and nutritional intake, decline in self-care, presence of anhedonia, and decreased interest in social or eating-related activities. Patients who experience depressive symptoms may take poorer care of themselves; in the context of HNC, decreased self-care may manifest as reduced nutritional intake⁽¹⁶⁾ and/or reduced adherence to nutritional supplementation regimens, rehabilitative exercises (e.g., swallowing), and adapting food preparation methods. Furthermore, manifestations of depressive symptoms in patients with HNC can entail social

withdrawal and not wanting to eat in the presence of others, which could negatively impact nutritional intake⁽¹⁾. Alternatively, poor nutrition could affect depressive symptoms in various ways. Deficiencies in essential macro- and micro-nutrients, individually and collectively, have detrimental effects on mood⁽⁴⁹⁾. Moreover, patients who experience significant nutritional deterioration early in the course of their HNC could respond to such a rapid decline in physical health with an “existential crisis” characterized by depressed mood and hopelessness⁽¹⁴⁾. Patients may also have poorer body images in response to nutritional deterioration and early WL, and poorer body image following HNC is associated with higher depressive symptoms across time⁽⁵⁰⁾.

In addition, research aimed at explicating the association between depressive symptoms and WL should routinely consider treatment-related side effects and functional impairments, including pain and eating-related HRQOL. Patients with greater vulnerabilities for developing depressive symptoms may also be prone to subjectively experiencing higher levels of pain, which could contribute to weight loss through an association between pain and nausea, fatigue, or appetite loss. In patients with HNC, depressive symptoms have been associated with pain^(51, 52) and pain was a robust predictor of poorer HNC-specific HRQOL⁽⁵¹⁾. Moreover, the longitudinal courses of depressive symptoms and general and HNC-specific HRQOL tend to parallel one another⁽²²⁾. Eating-related HRQOL is both a functional (i.e., patient’s level of functioning) and attitudinal (i.e., patient’s satisfaction with level of functioning) construct capturing eating impairments. Cross-sectional associations between depressive symptoms and eating-related impairments have previously been reported⁽¹⁾. Patients with depressive symptoms may be more likely to evaluate their eating impairments more negatively, which could contribute to WL through changes in eating practices. Although symptom overlap between WL, depression, pain, and HRQOL make outlining a cohesive conceptual framework for these disease sequelae a challenging and unresolved issue for the field, it is important to attempt to account for these constructs as the longitudinal association between WL and depressive symptoms is examined.

The Present Study

The existing literature fails to provide meaningful conclusions regarding longitudinal associations between depressive symptoms and nutritional change that generalize to patients who have diverse HNC treatment experiences and treatment-related side effects. Because depressive symptoms are common and nutritional functioning is a critical outcome in patients with HNC, an enriched understanding of how these constructs may influence one another over time is particularly needed in this population. Thus, the overall objective of this study was to investigate longitudinal associations between depressive symptoms and WL, as secondary analyses of a parent study following a large cohort of patients with HNC. More specifically, we aimed to evaluate the nature of change in depressive symptoms and WL across the first year following diagnosis and test whether the longitudinal association between these variables is better characterized by temporal precedence (i.e., initial level of one variable predicting the subsequent trajectory of the other) or concurrent covariation (i.e., variables changing together dynamically over time). An additional study aim was to account for relevant disease- and treatment-related factors (e.g., pain and eating-related HRQOL) that might help to explain the association between depressive symptoms and WL.

Materials and Methods

Participants and Procedures

The present report includes secondary data analysis of an ongoing longitudinal study of HNC outcomes conducted at a large academic medical center in the Midwestern United States. All study procedures were approved by the university's Institutional Review Board. Participants were adults diagnosed with upper aerodigestive tract carcinomas (oral cavity, lip, oropharynx, hypopharynx, and larynx). Patients with primary or recurrent cases were eligible, regardless of stage or performance status. At time of diagnosis, patients were offered participation in a longitudinal study of cancer-related outcomes and consented in writing if interested. Across the enrollment duration of the parent study (February 1998–October 2013), 76.0% of eligible patients enrolled, 5.5% refused participation, and 18.5% were missed (i.e., not approached). Through September 2013, the cohort had 2,377 enrolled patients, with observed all-cause survival rates of 91.8% at 9-month follow-up and 88.0% at 12-month follow-up. Because measurement of depressive symptoms was not included in the survey battery for patients enrolled between December 1999 and November 2001, patients who initially enrolled in the parent study during this time were not eligible for inclusion in the present secondary analyses ($n = 194$), thereby reducing the overall eligible sample for the present secondary analyses to 2,183 patients. Actual enrollment dates for patients included in the present secondary analyses were March 1998–October 1999 and November 2001–July 2013. Of these 2,183 patients, 140 actively withdrew from study participation at some point during the course of the study.

A combination of patient- and provider-reported data, as well as information extracted from patients' medical charts, were collected at enrollment (i.e., at time of diagnosis and before initiation of oncologic treatment; "baseline") and at the clinic's routine follow-up visits every three months thereafter (i.e., 3, 6, 9, and 12 months after diagnosis). One of the advantages of the data analytic approach employed in the present report (described below) is that patients could be retained in primary analyses as long as they had a minimum of one score across the repeated measures. However, because weight loss scores were computed as percentage weight loss *since baseline*, the sample for the present study consisted of participants who completed assessments of weight and depressive symptoms *at baseline and* at a minimum of one additional time point (3-, 6-, 9-, or 12-month follow-up). Thus, all included patients had data at a minimum of two time points, with the sample size for weight data ranging from 325 to 434 across time points and for depressive symptom data ranging from 311 to 564. Of the 2,183 eligible patients in the parent cohort, 564 met these inclusion criteria and were evaluated in the present secondary analyses. For clinical and demographic characteristics of the sample, see Table 1.

Using the 2,183 patients from the parent study, chi-square and independent sample t tests were conducted to compare patients who did and did not meet inclusion criteria for the present secondary analyses ($n=564$ and $n=1,619$, respectively). The groups did not significantly differ in terms of age, race, marital status, cancer stage, recurrence status at diagnosis, alcohol use or abuse at diagnosis, use of a gastric tube at diagnosis, or depressive symptoms at diagnosis. Significant group differences were found, however, for sex ($\chi^2(1) =$

7.95, $p = .005$), cancer site ($\chi^2(5) = 26.63$, $p < .001$), tobacco use at diagnosis ($\chi^2(2) = 30.26$, $p < .001$), and weight at diagnosis ($t(2009) = 2.28$, $p < .05$). Among patients who met inclusion criteria for the present analyses, significantly more than expected were female ($z = 2.0$, $p < .01$), had oral cavity cancer ($z = 3.2$, $p < .01$), and had never used tobacco ($z = 2.5$, $p < .05$), and significantly fewer than expected had laryngeal cancer ($z = -2.6$, $p < .01$) and were using tobacco at diagnosis ($z = -3.7$, $p < .001$). On average, included patients weighed more ($M = 179.33$ pounds, $SD = 46.76$) than excluded patients ($M = 174.26$ pounds, $SD = 45.34$).

Measures

Weight loss—Weight in pounds was measured by clinic staff at baseline and reassessed at each time point. Because net change in weight affects individuals to varying degrees on the basis of their body compositions, proportion of body weight lost is a more accurate way to compare weight loss across individuals. Thus, we conceptualized WL as overall percentage change in weight relative to baseline. The following formula was used to calculate each patient's total percentage of weight lost at each time point:

$$\frac{(\text{weight at baseline}) - (\text{weight at time point})}{(\text{weight at baseline})} \times 100$$

Beck Depression Inventory (BDI)⁽⁵³⁾—Symptoms of depression were measured using the BDI, a widely used self-report assessment of depressive symptomatology that has been well-validated in psychiatric and non-psychiatric samples⁽⁵⁴⁾. In patients with HNC, the BDI is highly accurate in identifying depression compared to a diagnostic clinical interview (area under the curve > 0.96)⁽²³⁾. Given the overlap between depressive symptoms and the study's outcome of weight loss, BDI questions regarding change in appetite and change in weight were not included in the total BDI score used in analyses. Thus, the modified BDI measure consisted of 19 items measured on a 0–3 ordinal response scale (possible score range: 0–57), with higher scores indicating higher level of depressive symptoms.

Head and Neck Cancer Inventory (HNCI)⁽⁵⁵⁾—To assess for eating impairments as a potential confound, eating-related HRQOL was measured using the 10-item eating subscale of the HNCI, a self-report measure of HNC-specific HRQOL. Functional items assess eating speed, difficulty chewing solid food, food restrictions, difficulty chewing due to loss of teeth, swallowing, and changes in food preparation. Attitudinal items assess the extent to which patients are bothered by changes in eating habits, teeth, and mouth dryness. Adequate reliability and validity of this measure have previously been reported⁽⁵⁵⁾. Higher scores represent higher (i.e., better) HRQOL.

Short Michigan Alcohol Screening Test (SMAST)⁽⁵⁶⁾—The SMAST is a 13-item self-report screening measure for possible alcohol abuse. Its reliability and validity are adequate and comparable to the original, 25-item measure^(56, 57). Patients respond “yes” or “no” to items assessing drinking behavior and consequences of drinking. Scores range from 0–13, with each “yes” representing one point. Scores of three or higher suggest probable alcohol abuse^(56, 57). In the present study, SMAST scores were used to classify patients as

problematic drinkers (score of three or higher) or not problematic drinkers (score below three) at time of HNC diagnosis.

Data Analytic Strategy

Comprehensive analyses were conducted using growth curve modeling (GCM) techniques⁽⁵⁸⁾ with the HLM 7 software⁽⁵⁹⁾. GCM estimates within-person change or growth curve trajectories for a variable (e.g., depressive symptoms), based upon two parameters: intercept (e.g., level of depressive symptoms at a certain point in time) and slope (e.g., rate of change in depressive symptoms over time). Time was measured in months and, based on theoretical rationale regarding the longitudinal course of the primary variables, the 6-month follow-up was chosen as the intercept. That is, time in the GCM analyses was modeled as months since the 6-month assessment, although data collection occurred every three months. Rather than assume universal assessment completion precisely on the date of each quarterly follow-up interval, each patient's unique dates of assessment were calculated to account for any variability in timing of follow-up assessments. Thus, the intercept represents scores at each participant's unique "6-month" assessment, accounting for some variability in the timing of that assessment.

GCM analyzes whether, on average, intercepts and slopes differ significantly from zero, whether there is significant variability in parameter estimates across participants (e.g., whether patients vary in their degree or rates of change over time), and whether specific participant characteristics or experiences predict individual variation in the parameter estimates. In GCM, the coefficients represent the degree of association between two variables and are functionally comparable to unstandardized regression coefficients. There are multiple advantages of using GCM to analyze longitudinal data. Unlike alternative methods, time points are nested within participants and interdependence among repeated measures (within subjects) is taken into account. As such, within-subject change across time (individual trajectories or growth curves) can be modeled, between-subject differences in these individual trajectories can be examined, and predictors of growth curve variability can be identified⁽⁶⁰⁾. Additionally, participants missing some of the repeated assessments—a common occurrence in the context of longitudinal research, especially with high-risk patient samples—can be retained. Whereas missing data is allowable at the within-subjects (repeated measures) level given the use of restricted maximum likelihood estimation methods in HLM, missing data at the between-subjects level is addressed via pairwise deletion.

Results

For descriptive information regarding average percentage weight loss and depressive symptoms at each repeated assessment, see Table 2. Average percentage weight loss peaked at the 9-month follow-up visit ($M = 6.41$, $SD = 9.81$). Given the variability in previously reported trajectories of weight loss following HNC, the timing of this peak is consistent with some reports and somewhat later than others^(4, 11, 18). Although the sample's average weight loss at the 9-month follow-up was 6.41%, it is notable that 39.3% of patients with weight data at this time point had lost at least 10% of their body weight since diagnosis. An

additional 13.4% lost 5–9.9% and 20.4% lost weight totaling less than 5% of baseline body weight, totaling 73% of patients having lost some percentage of weight since diagnosis. Average depressive symptoms remained fairly consistent across time, with the highest level observed at the 6-month follow-up visit ($M = 7.31$, $SD = 7.27$). After the 6-month assessment, patients' depression symptom scores declined to below baseline levels, on average. This relative stability across time is somewhat inconsistent with other literature depicting an increase in depressive symptoms during or soon after treatment^(26–28) followed by a decline in symptoms six months to one year after diagnosis^(29, 30). Given that the suggested clinical cutoff score for the full BDI is 13 in HNC patients^(22, 23), patients' average depression symptom levels appear to be in the low-severity range. However, interpretation of the severity of scores in the present study is not straightforward due the exclusion of two BDI items (which could add up to six points to scores).

Trajectories of Change

First, baseline models of change were tested to evaluate whether percentage weight loss or depressive symptoms demonstrated significant systematic monthly change and to identify the nature of that change (e.g., linear versus curvilinear). Percentage weight loss followed a negative curvilinear pattern (inverted U-shape), $t(562) = -4.12$, $p < .001$, across the first year after HNC diagnosis, on average (see Figure 1). Additionally, there was significant between-subject variability in monthly rates of curvilinear change, $\chi^2(320) = 569.57$, $p < .001$. On average, depressive symptoms were relatively stable across the first year after HNC diagnosis, $t(562) = -1.35$, $p = .18$ (see Figure 2). However, consistent with predictions, there was significant between-subject variability in monthly rates of (linear) change in depressive symptoms across time, $\chi^2(561) = 791.24$, $p < .001$. Thus, although depressive symptoms were relatively stable on average for the sample, they did change at different rates (increasing or decreasing on a monthly basis over time) for some patients.

Temporal Precedence Models

To clarify whether the initial level of one variable (depressive symptoms or WL) is a driving force in longitudinal trajectories of the other, we included baseline scores of one variable as predictors of intercept and slope parameters of the other variable. Baseline depressive symptoms did not differentiate the level of severity of percentage weight loss at 6 months, $t(561) = -1.50$, $p = .13$, or rates of monthly change in percentage weight loss over time, $t(561) = 1.38$, $p = .17$. Similarly, degree of early percentage weight loss (from baseline to 3-month follow-up) did not differentiate the level of severity of depressive symptoms at 6 months, $t(432) = 0.24$, $p = .81$, or monthly rates of change in depressive symptoms over time, $t(432) = 1.31$, $p = .19$. (Of note, early percentage WL was conceptualized as WL from diagnosis to the first follow-up assessment (i.e., 3-month visit). Because 130 patients did not have weight data specifically at the 3-month assessment, which is needed for the predictor in this particular model, they were dropped from this particular analysis. These 130 patients were retained in all other analyses.)

Reciprocal Models

To evaluate a reciprocal association, time-varying covariation models were tested to examine the extent to which depressive symptoms and percentage WL changed in concert over time.

These covariation analyses used GCM to evaluate whether monthly change in one variable predicted same-month change in the dependent variable, above and beyond change in the dependent variable occurring as a function of the passage of time. Each variable was entered as a time-varying predictor of the other variable. Significance of both models would suggest a reciprocal/bidirectional relation in which monthly change in either variable influenced immediate (i.e., same-month) change in the other.

Monthly changes in depressive symptoms were associated with same-month deviations from average trajectories of percentage weight loss, $t(1148) = 2.05$, $p = .041$ (see Table 3 for detailed model results). To the extent that depressive symptoms increased on a monthly basis, patients lost incrementally more weight during that month than could be attributed to the passage of time. Similarly, monthly changes in percentage weight loss were associated with same-month deviations from average trajectories of depressive symptoms, $t(556) = 2.44$, $p = .015$ (see Table 3 for detailed model results). To the extent that percentage weight loss increased on a monthly basis, patients experienced a greater increase in depressive symptoms than could be attributed to the passage of time.

Time invariant covariates—To examine whether the reciprocal relation between depressive symptoms and percentage WL persisted when accounting for potential patient-, disease-, and treatment-related factors, we reviewed two sets of bivariate Pearson correlations. Two sets of correlations were required because one set of control variables reflected demographic factors (e.g., sex) that were measured once at baseline, whereas a second set of control variables reflected fluctuating, post-treatment sequelae that were measured repeatedly at follow-up assessments. To account for the influence of potential covariates on depressive symptoms and percentage WL at a time of particular importance in the disease trajectory—6 months after diagnosis, when weight loss was expected to be most severe—both sets of correlations used modified BDI scores and percentage WL at 6 months. Moreover, because the largest correlations between variables are often observed within the same time points, it was important to account for possible covariates at 6 months given that the intercept was centered at 6 months in the growth curve analyses. Categorical variables were dichotomized (e.g., whether there were differences in patients with *early* versus *advanced* stage cancer).

First, we examined the correlations among demographic and clinical variables at baseline with percentage WL and modified BDI scores (at 6 months). The following variables were evaluated with baseline data: sex, age, BMI, cancer site, cancer stage (*advanced* [stage III-IV] or *early* [stage I-II]), cancer status at diagnosis (*recurrence* or *no recurrence*), treatment modality (three separate direct comparisons: *single-* or *multi-modality treatment*, *radiation* or *non-radiation*, *radiation and chemotherapy* or *other*), years of tobacco use, previous tobacco use (*never* or *ever*), years of alcohol use, and alcohol abuse status (*problematic drinking* or *not problematic drinking*).

Second, we examined the correlations among the following clinical variables at the 6-month follow-up visit with percentage WL and modified BDI (at 6 months): BMI, weight gain (*did* or *did not gain* 5% of initial body weight), current use of a gastric feeding tube (*yes* or *no*), current dietary status (*NPO* or *not-NPO*), current tobacco use (*yes* or *no*), current pain level

(continuous measurement, 0=“No pain” to 10=“Worst Possible Pain”), and current eating-related HRQOL (HNCI-eating subscale, continuous measurement). These variables provided the best indication of potential treatment-related toxicities and impairments from available data. If data on these between-subject, time-invariant control variables were missing, pairwise deletion was utilized in accordance with GCM requirements.

Variables that were correlated with both outcomes of interest—depressive symptoms and WL—at the intercept time point (6 months) at a significance level of $p < .10$ were examined as time invariant control variables, including: cancer stage ($n=557$), treatment modality (*single* or *multimodal* comparison; $n=507$), weight gain at 6 months ($n=531$), pain level at 6 months ($n=323$), and eating-related HRQOL at 6 months ($n=338$). The effect of changes in depressive symptoms on changes in percentage weight loss was no longer significant when controlling for pain levels at 6 months, $t(665) = 0.42$, $p = 0.67$, or eating-related HRQOL at 6 months, $t(690) = -0.38$, $p = 0.71$. Likewise, the effect of changes in percentage weight loss on changes in depressive symptoms was no longer significant when controlling for pain, $t(322) = 0.97$, $p = 0.33$, or eating-related HRQOL, $t(337) = -0.67$, $p = 0.51$. For all other control variables, the covariation models remained significant despite their inclusion in the models (ts ranged from 1.68 to 2.92 and $ps < .05$).

In sum, results indicate that the reciprocal association between depressive symptoms and percentage weight loss may be explained by the shared associations between these variables and both pain and eating-related HRQOL. That is, patients experiencing greater depressive symptoms and WL during the year following diagnosis also reported greater pain and more eating-related impairments, which may play a pivotal role in the observed association between depressive symptoms and WL.

Discussion

This investigation provided information regarding the nature of the longitudinal association between depressive symptoms and WL in patients with HNC. Neither temporal precedence model was supported—baseline depressive symptoms did not predict the severity of WL at 6 months or the monthly course of WL over a year, and early WL did not predict the severity of depressive symptoms at 6 months or the monthly course of depressive symptoms over a year. Instead, the data supported a dynamic reciprocal association between these variables. Across time, changes in either variable were associated with concurrent, same-month changes in the other variable, reflecting a deviation from its average longitudinal trajectory. Patients experiencing greater monthly increases in depressive symptoms experienced incrementally more same-month WL than would have occurred solely due to the passage of time. That is, escalating depressive symptoms explained, in part, the increase in WL that is often observed following diagnosis of HNC. Additionally, patients experiencing monthly increases in WL experienced greater same-month increases in depressive symptoms than were attributable to the passage of time. Taken together, these results suggest an ongoing transactional interplay between depressive symptoms and WL over the first year after HNC diagnosis. Notably, the reciprocal association was consistent across patients and did not differ in strength or direction across the sample, despite inclusion of patients from various

HNC sites, disease stages, and treatment modalities. The robust nature of this association suggests generalizability of the results to a diverse set of patients with HNC.

Several patient, disease, and treatment characteristics that could theoretically be associated with both depressive symptoms and WL were evaluated. These analyses were included to identify potential variables explaining the association between depressive symptoms and WL. For the most part, the inclusion of those variables as covariates did not impact the association between depressive symptoms and percentage WL. This finding is particularly noteworthy for disease stage, cancer site, and treatment modality, factors that have been linked to both depressive symptoms and WL outcomes.

Nonetheless, the reciprocal, dynamic association between depressive symptoms and WL was no longer significant when accounting for pain and eating-related HRQOL (reported 6 months after diagnosis). Patients reporting greater pain at 6 months experienced higher levels of depressive symptoms and percentage WL at 6 months, as well as greater monthly changes in WL over time. Likewise, patients reporting poorer eating-related HRQOL at 6 months (i.e., those experiencing greater functional impairments in eating, chewing, and swallowing, greater adjustments in meal preparation and eating techniques, and greater concern regarding changes in eating, teeth, and mouth dryness) experienced higher levels of depressive symptoms and percentage WL at 6 months, as well as greater monthly changes in WL over time.

Thus, it appears that pain and eating-related HRQOL represent key constructs for explaining the link between depressive symptoms and WL in HNC patients. One possible explanation for this pattern of findings is that depressive symptoms and WL do not influence one another and that the observed association between these two variables is an artifact of their shared associations with pain and eating-related HRQOL. However, another equally plausible explanation is that pain and eating-related HRQOL represent *mechanisms* through which depressive symptoms and WL affect one another across the first year after HNC diagnosis. For example, perhaps depressive symptoms exacerbate one's experience of pain and diminish one's eating-related HRQOL which, in turn, leads to greater WL. Taken together, our results suggest that researchers should consider pain and eating-related HRQOL when examining the association between depressive symptoms and WL in HNC patients. Further, a next step in this line of research is to formally investigate these factors as mechanisms linking depressive symptoms to subsequent WL, and vice versa, within the context of robust mediation designs (e.g., longitudinal panel models).

Clinical Implications

A unique contribution of the present study is the examination of a dynamic rather than a static risk factor for WL. Results indicate that escalation in depressive symptoms over time may contribute to the increase in WL that is often observed during the months following a diagnosis of HNC, and that persistent WL, in turn, may contribute to greater depressive symptoms. This maladaptive cycle that appears to unfold over time suggests that ongoing assessment and treatment for both depressive symptoms and WL throughout the course of the first year after HNC diagnosis is likely important. Given that most risk factors for nutritional decline are related to non-modifiable aspects of the HNC tumor (e.g., stage, site)

and its treatment, it is noteworthy that depressive symptoms are treatable and that a brief, self-report instrument assessing depressive symptoms may assist with early identification of nutritionally at-risk patients. Although these results suggest the possibility that interventions that reduce depressive symptoms may also reduce WL and that patients who regain weight may experience a reduction in depressive symptoms, the study was purely observational. Future research should directly examine these crossover effects within an intervention context, as successful treatment for either symptom presentation may be associated with improvements in both psychological and nutritional health.

Limitations

As in previous research investigating WL in cancer patients, the present study was inherently limited by an inability to incorporate prediagnosis WL. It does not capture the full amount of WL that patients experience and more closely illustrates WL associated with or exacerbated by treatment and treatment-induced impairments. Although average weight at diagnosis was slightly higher in patients who met inclusion criteria for the present secondary analyses than in patients from the parent study who did not meet criteria, we note that our use of *intra-individual percentage WL* relative to baseline minimized the potential that this difference reduced the generalizability of the findings.

The study also did not assess the level of prediagnosis depressive symptoms or lifetime history of depression and does not account for whether patients received any depression treatment during the study time period. Receipt of pharmacological or psychological treatment for depression could have influenced the degree and course of depression symptomatology and weight change. Although interpretation of the severity of depressive symptoms was constrained by use of a modified BDI measure, patients appeared to report mild severity symptoms. This modification limits the generalizability of the findings and warrants replication of the results in a sample of patients with more moderate-to-severe depressive symptoms. Despite the relatively low levels of depressive symptoms observed in this sample, it is notable that significant associations with weight loss were nevertheless detected.

Conclusions are limited by incomplete baseline data (e.g., disease site and stage, treatment, and substance use) and a high level of missing control variable data at the 6-month follow-up (e.g., feeding tube use, dietary intake, pain, eating-related HRQOL). Although all patients were assessed at routine follow-up time points (i.e., baseline/diagnosis, and 3, 6, 9, and 12 months post-diagnosis), it is also important to note that patients may have been at different points along the trajectory of care at these times, depending on the nature of their individualized treatment plan. As a set of secondary analyses, the present study was restricted to inclusion of data collected in the parent study. Unfortunately, the parent study lacked detailed information regarding education, type/extent of surgery, and type of radiotherapy, which could have influenced depressive symptoms and/or weight loss. Given the number of analyses conducted, there was also an elevated risk of Type 1 error.

A final consideration for generalizability of the results is the nature of the sample. A sizeable number of patients from the overarching longitudinal cohort were not eligible for these secondary analyses due to attrition from the parent study, which resulted in a lack of

requisite repeated measures data. Compared with patients who were enrolled in the parent study but did not meet inclusion criteria for the present analyses, included patients were more likely to be female, have oral cavity cancer, and have never used tobacco, and less likely to have laryngeal cancer. Moreover, the racial homogeneity of the sample is important to account for when extrapolating the results.

Conclusion

By depicting an ongoing transactional interplay between depressive symptoms and WL over the first year after HNC diagnosis, and identifying variables that might explain this association (i.e., pain and eating-related HRQOL), this study expanded our understanding of the course of these important HNC outcomes. Given the broad inclusion criteria and robustness of the findings across the sample, the present results are expected to generalize to a clinically diverse group of HNC patients. By lengthening the range of the study time period to one year post-diagnosis, the present study better reflects long-term associations between depressive symptoms and WL than previous investigations.

Through use of statistical methods that modeled population-level patterns of change while accounting for individual-level differences (i.e., within- and between-subject variability in individual trajectories), this investigation produced novel conclusions. We were unable to identify any published analyses of such a dynamic, reciprocal association between depressive symptoms and WL, and believe these results point to important areas for future research. Ultimately, an improved conceptual understanding of the relation between these variables could contribute to early interventions for nutritional and mental health outcomes that may extend patient survival without compromising quality of life.

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Figure 1.

Estimated average curvilinear pattern of change in percentage weight loss (trajectory, accounting for within- and between-subject change) across the first 12 months following head and neck cancer diagnosis. Note: Graph does not depict observed average values for the sample.

Trajectory of BDI Scores

Figure 2.

Estimated average linear pattern of change in depressive symptoms (trajectory, accounting for within- and between-subject change) over the first 12 months following head and neck cancer diagnosis. Possible score range: 0–57. Note: Graph does not depict observed average values for the sample.

Abbreviations. BDI=Beck Depression Inventory.

Table 1

Demographic and Clinical Variables

Variable	Mean (SD)	Range
Age	60.47 (12.3)	25–93
BMI	27.45 (6.36)	12.85–69.23
Variable	No. of patients (%)	
Male	356 (63.1)	
Married	367 (65.1)	
Caucasian	528 (96.7)	
Employed (full- or part-time)	230 (40.7)	
Cancer Site:		
Oral cavity	233 (41.3)	
Oropharynx	120 (21.3)	
Hypopharynx	24 (4.3)	
Larynx	101 (17.9)	
Other	65 (11.5)	
Unknown	21 (3.7)	
Disease Stage ^a :		
Early (0-II)	212 (37.6)	
Advanced (III- IV)	312 (55.3)	
Not stageable	13 (2.3)	
Unknown	27 (4.8)	
Treatment Modality:		
Surgery only	206 (36.5)	
Radiation or chemotherapy only	57 (10.1)	
Surgery & Radiation	146 (25.9)	
Radiation & Chemotherapy	72 (12.8)	
Surgery & Chemotherapy	2 (0.4)	
Surgery, Radiation, & Chemotherapy	31 (5.5)	
None	2 (0.4)	
Unknown	48 (8.5)	
Recurrence Status at Diagnosis ^b :		
Primary cancer	469 (83.2)	
Recurrent cancer	62 (11.0)	
Persistent cancer	12 (2.1)	
Unknown	21 (3.7)	
Tobacco Use at Diagnosis:		
Current	153 (27.1)	
Previous	265 (47.0)	
Never	137 (24.3)	
Unknown	9 (1.6)	

Variable	Mean (SD)	Range
Alcohol Use Status at Diagnosis (SMAST):		
Problem drinker	98 (17.4)	
Possible alcoholic	47 (8.3)	
Nonalcoholic	312 (55.3)	
Unknown	107 (19.0)	
Comorbidity Score (Kaplan-Feinstein Index):		
None	83 (14.7)	
Mild	156 (27.7)	
Moderate	60 (10.6)	
Severe	24 (4.3)	
Unknown	241 (42.7)	
Feeding Tube Use at 6 Months:		
Using	23 (4.1)	
Not using	93 (16.5)	
Unknown	448 (79.4)	
Dietary Intake Status at 6 Months:		
NPO	29 (5.1)	
Other (not-NPO)	345 (61.2)	
Unknown	190 (33.7)	
Variable	Mean (SD)	Range
Pain at 6 Months	1.73 (2.67)	0–10
Eating HRQOL at 6 Months	53.58 (28.51)	0–100

Note. All variables are collected at baseline (i.e., diagnosis), unless otherwise noted. *Abbreviations.* *SD*=standard deviation. *N*=number of subjects. *BMI*=body mass index. *SMAST*=Short Michigan Alcohol Screening Test.^(56, 57) *NPO*=Nothing by mouth. *HRQOL*=health-related quality of life.

^aRepresents pathological stage; if unavailable, represents clinical stage.

^bRecurrence refers to presentation for treatment and initial enrollment in study with recurrence of a previously treated primary tumor. Persistent cancer refers to patients who presented at our clinic after being diagnosed and treated elsewhere for a primary/secondary tumor, but never considered disease-free.

Table 2

Descriptive Statistics for Percentage Weight Loss and Depressive Symptoms

Variable	Mean (SD)	No. of patients
Percentage Weight Loss ^a :		
3 months	4.74 (6.93)	434
6 months	6.09 (9.81)	366
9 months	6.41 (10.64)	325
12 months	5.44 (11.81)	364
Depressive Symptoms ^b :		
Baseline	7.14 (6.41)	564
3 months	6.92 (6.34)	372
6 months	7.31 (7.27)	357
9 months	6.37 (6.52)	311
12 months	6.31 (6.88)	367

Note. Table reflects actual observed average values for the sample, rather than growth curve estimates of the longitudinal pattern of change.

Abbreviations. *SD*=standard deviation.

^aPercentage relative to baseline, calculated for each patient using the following formula:

^bFull scale Beck Depression Inventory minus two weight-related items (possible score range: 0–57).

Table 3

Reciprocal Growth Curve Analyses

Change in Depressive Symptoms Predicting Change in Percentage Weight Loss					
	Coefficient	SE	t	df	p
β_{0j} (Intercept)	5.86	0.42	14.06	556	<.001
β_{1j} (Depressive Symptoms)	0.07	0.03	2.05	1148	.041
β_{2j} (Time)	0.22	0.06	3.49	556	<.001
β_{3j} (Time ²)	−0.04	0.01	−3.76	556	<.001
<i>Pair^a Included as Covariate</i>					
β_{1j} (Depressive Symptoms)	0.02	0.04	0.42	665	0.673
<i>Eating HRQOL^a Included as Covariate</i>					
β_{1j} (Depressive Symptoms)	−0.02	0.04	−0.38	690	0.707
Change in Percentage Weight Loss Predicting Change in Depressive Symptoms					
	Coefficient	SE	t	df	p
β_{0j} (Intercept)	6.95	0.26	26.43	556	<.001
β_{1j} (Percentage Weight Loss)	0.06	0.02	2.44	556	.015
β_{2j} (Time)	−0.09	0.03	−3.15	556	.002
<i>Pair^a Included as Covariate</i>					
β_{1j} (Percentage Weight Loss)	0.03	0.03	0.97	322	.334
<i>Eating HRQOL^a Included as Covariate</i>					
β_{1j} (Percentage Weight Loss)	−0.02	0.03	−0.67	337	.506

Note. Time was modeled in months since the 6-month assessment (intercept time-point). Each patient's unique dates of assessment were calculated to account for any variability in follow-up assessment timing.

Abbreviations. SE=standard error. t=t-statistic. df=degrees of freedom. p=p-value. HRQOL=health-related quality of life.

^aMeasured at the 6-month assessment.