Associations Between Cytokine Levels and Long-Term Symptom Development in Head and Neck Cancer Patients

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Abstract

Cytokines have been associated with the development of cancer cachexia. Cytokine dysregulation is thought to cause cachexia and its associated symptoms by negatively affecting physiological homeostasis. Cytokines that have been associated with cachexia are thought to be associated with symptom development. Despite this increased association, there is mixed data regarding the development of symptoms, such as pain, anorexia, and lethargy. The purpose of this retrospective study was to examine the association of cytokine and C-reactive protein levels over time to determine if levels were associated with symptom development.

In addition to targeting cancer as a disease process in the hopes of driving remission, the advanced practice provider must contend with a myriad of symptoms that patients often endure during their illness, such as weight loss, depression, and fatigue. Currently, there is no way of deciphering which patients will develop mild to severe symptoms during the course of their illness. A potential tool for understanding which patients will develop negative symptoms during their illness may lie within our increasing understanding of the role of cytokines in cancer.

Cytokines have been associated with the development of cancer cachexia. Estimates indicate that up to 80% of all cancer patients experience cachexia (Walz, 2010). Cancer cachexia is a complex metabolic condition that is characterized by loss of skeletal muscle with or without loss of adipose tissue (Dodson et al., 2011; Fearon, Arends, & Baracos, 2013). About 20% to 30% of all United States cancer deaths are due to the debilitating effects of cachexia (Caro, Laviano, Pichard, & Candela, 2007; von Haehling & Anker, 2010).

Cachexia has a significant impact on patient morbidity and mortality, treatment tolerance, outcomes, and is a source of extraordinary psychological distress for patients and their families (Hopkinson, 2010;

Huhmann & Cunningham, 2005). Higher levels of depression, pain, decreased physical energy, performance, and fatigue have been reported in patients with cachexia compared with those who do not have cachexia (Giannousi et al., 2012; Laird et al., 2011; Oz, Theilla, & Singer, 2008; Roberts, Frye, Ahn, Ferreira, & Judge, 2013; Wallengren, Lundholm, & Bosaeus, 2013). Cytokine dysregulation is thought to cause cachexia and its associated symptoms by negatively affecting physiological homeostasis.

Three physiological processes are affected by cytokines in the development of cachexia: (1) Cytokines promote catabolism, specifically of muscle. The body responds to cancer, mediated by cytokines, by slowing the rate at which new muscle is produced; (2) Adipose breakdown is promoted through various pathways. This lipolytic degradation promotes the breakdown of triacylglycerols into glycerol and nonessential fatty acids. Glycerol stimulates liver gluconeogenesis. The tumor subsequently uses this additional fuel for growth and production of further cytokines, enhancing the effects of cytokines; (3) Altered metabolic processes caused by muscle and adipose breakdown work in concert to continue the production of "feeding" tumors through glucose and nonessential fatty acids, which continues to stress the body through increasing energy consumption. The body, therefore, responds to the tumor by increasing cytokine production, which also contributes to further altered metabolic processes experienced in cancer. Currently, the exact feedback mechanisms for the multiple processes that enhance cachexia are not entirely understood.

In addition to the initiation of cachexia, cytokines that have been associated with cachexia are thought to be associated with symptom development. Recent scientific research suggests that some of the most common symptoms reported by oncology patients are associated with changes in the levels of pro- and anti-inflammatory cytokines (Cleeland et al., 2003; Gupta et al., 2011; Imayama et al., 2013; Yakovenko, Cameron, & Trevino, 2018). Despite this increased association, there is mixed data regarding the development of symptoms, such as pain, anorexia, and lethargy. This is partially because of a lag between an elevation of cytokines and symptom development (Lucia, Esposito, Fanelli, & Muscaritoli, 2012). Also, there is an indication that symptoms can be present, such as pain, lethargy, and depression, prior to muscle and adipose wasting (Laird et al., 2011).

The purpose of this study was to examine the association of cytokine and C-reactive protein (CRP) levels over time and determine if levels were associated with symptom development.

METHODS

This study was a secondary analysis of data from a 4-year prospective, longitudinal, descriptive study. The aim was to determine if long-term associations between baseline cytokines and symptom progression could be better understood. To examine these assumptions, this secondary analysis examined cytokines, red blood cells (RBCs), albumin, and changes in symptoms and weight over a 12-month period posttreatment. The target population for the parent study consisted of patients with carcinoma of the head and neck. Eligibility criteria included (a) newly diagnosed, histologically proven carcinoma involving the head and neck; (b) stage 2 or greater; (c) age 21 or over; (d) willing and able to undergo baseline and follow-up assessment; and (e) able to speak English. Patients were excluded if (a) they had medical record documentation of cognitive impairment that would preclude the capacity to provide informed consent; (b) were unwilling to undergo routine follow-up; or (c) had recurrent cancer. No restriction was placed on the type of treatment. Only persons completing the 48-week assessment were included in this analysis. The data from the parent study were obtained through institutional review board–approved procedures. All participants gave informed consent.

Interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12p70, tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), matrix metalloproteinase (MMP)-2A, and MMP9A were measured using a sensitive flow cytometric bead array (CBA; Becton Dickinson) assay that allows multiple cytokine analyses of a single sample. The Vanderbilt Head and Neck Symptom Survey (VHNSS) version 2.0 is a 50-item patient-reported outcome measure with a Cronbach's α of > 0.89 that identifies and quantitates acute and late symptom burden and functional deficits experienced by head and neck can-

cer (HNC) patients. The VHNSS has 13 domains, including nutrition, swallowing, xerostomia, mucositis, excess mucus, speech, hearing, taste change, smell, and dental health. Items are scored on a Likert scale rating the severity of the symptom from 0 (none) to 10 (severe). The Center for Epidemiological Studies Depression Scale (CES-D; depressive symptomatology) is a 20-item self-reported measure that assesses the presence and severity of depressive symptoms occurring over the past week from the patient's perspective with a Cronbach's α of 0.89 (Ridner & Dietrich, 2008).

DATA ANALYSIS

Ninety-six individuals originally enrolled in the parent study. The inclusion criteria resulted in a sample size of 56 persons. Randomly missing responses to items within the self-reported assessment tools were handled via protocols specified by the instrument developers. Within this sample, randomly missing values occurred for baseline, 6 months, and 12 months posttreatment lab and self-reported measures, resulting in minimally differing sample sizes for specific analyses.

Data were analyzed using SPSS Version 25 (Chicago). Due to extreme skewness, which is common to symptom data, cytokine distributions, and outlying values, all of the continuous data were summarized using median, 25th to 75th interquartile range (IQR) percentiles, and minimum and maximum values. Distributions were rank transformed for use in parametric statistical methods.

Chi-square tests of independence (nominal, ordinal) and Mann-Whitney tests were used to test for differences between the samples of 56 individuals from the parent study who were included in this study and the remaining 40 individuals from the parent study who were not included. An α of 0.05 was used for each test. Multiple linear regressions were performed on the pretreatment cytokine values, and 1-year symptom measurements were obtained from the VHNSS. Each variable prior to analysis was ranked and transformed.

RESULTS

The demographic characteristics of all participants in the parent study (N = 96), the subsample included in this study (N = 56), and those not included (N = 40) are summarized in Table 1. There were no statistically significant differences in demographic characteristics between those who were included and not included in this study. The average age of patients in this study was 57.7 years. The minimum age was 29, and the maximum age was 80.

The disease and treatment characteristics of all participants in the parent study (N = 96), the subsample included in this study (N = 56), and those not included (N = 40) are summarized in Table 2. The most common type of cancer diagnosis in the current study sample was squamous cell carcinoma (N = 48, 84.9%). The predominant location of the cancer was in the oropharynx (N = 28, 50.0%). Additionally, most patients underwent chemotherapy (N = 54, 96.4%). There was a statistically significant difference in the rates of viral etiology within the set of patients in the current study and those not in this study (*p* = .038). This rate was higher in the study sample (N = 30 of 56, 53.8%) than it was in the sample not included (N = 15 of 40, 37.5%). There were no other statistically significant differences in disease and treatment characteristics between the groups.

Depressive Symptoms

Descriptions of the CES-D measured at baseline and changes over time are provided in Table 3. There was considerable variability in self-reported CES-D scores over the duration of this study. Associations of initial levels of cytokines with changes in levels of depression are presented in Table 4. Lower levels (relative to higher levels) of TGF-β2 prior to treatment were statistically significantly associated with greater increases in CES-D scores from prior to treatment to 12 months posttreatment (β = −0.41, *p* = .002). In addition, a positive association with pretreatment CRP levels was observed (β = 0.28, *p* = .035), indicating that patients with higher CRP levels pretreatment tended to have greater increases in depressive symptoms in the 12 months posttreatment (relative to their symptoms prior to treatment) than did patients with lower pretreatment CRP levels.

Nutrition-Related Symptoms

Descriptions of the VHNSS nutrition cluster scores at baseline and changes over time are presented in Table 5. The median baseline score was < 0.3 on a 0 to 10 scale. Associations of initial levels

Table 1. Demographic Characteristics			
	Parent study (N = 96), total (%)	Not in current study (N = 40), total (%)	In current study (N = 56), total (%)	p value
Gender				.698
Male	70 (72.9)	30 (75.0)	40 (71.4)	
Female	26 (27.1)	10 (25.0)	16 (28.6)	
Race				.314
White	86 (89.6)	35 (87.5)	51 (91.1)	
Black or African American	7 (7.3)	4 (10.0)	3 (5.4)	
Other	3 (3.1)	1(2.5)	2 (3.6)	
Marital status				.952
Single/widowed	21 (21.9)	9 (22.5)	12 (21.4)	
Married/partnered	72 (75.0)	30 (75.0)	42 (75.0)	
Other	3 (3.1)	1 (3.6)	2 (3.6)	
Employment				.492
Full and part time	42 (43.8)	15 (37.5)	27 (48.2)	
Unemployed/retired/homemaker/other	54 (56.2)	25 (62.5)	29 (51.8)	
Location of residence				.130
City	42 (43.8)	22 (55.0)	20 (35.7)	
Country	45 (46.9)	14 (35.0)	31 (55.4)	
Other	9 (9.4)	4 (10.0)	5 (8.9)	
Smoking (now or past use)				.448
Yes	68 (70.8)	30 (75.0)	38 (67.9)	
No	28 (29.2)	10 (25.0)	18 (32.1)	
Alcohol history (now or past use)				.972
Yes	55 (57.3)	23 (57.5)	32 (57.1)	
No	41 (42.7)	17 (42.5)	24 (42.9)	
Current alcohol intake				.309
Yes	27 (54.0)	12 (63.3)	15 (48.4)	
No	23 (46.0)	7 (36.8)	16 (51.6)	
Income per year				.496
< $50,000	51 (53.1)	24 (60.0)	27 (48.2)	
> 50,000	28 (29.2)	10 (25.0)	18 (32.1)	
Did not respond	17 (17.7)	6 (15.0)	11 (19.6)	
Education				.258
< High school	9 (9.4)	4 (10.0)	4 (7.1)	
> High school	85 (88.5)	30 (90.0)	52 (92.9)	

of cytokines and changes in the VHNSS nutrition cluster scores over time are presented in Table 6. Higher levels of IL-6, IL-10, and MMP2A at baseline were associated with worsening nutrition consumption at 6 months (IL-6: β = 0.35, p = .006; IL-10: β = 0.33, p = .008; MMP2A: β = 0.27, p = .035). Lower levels of TGF-β1 and IFNγ at baseline were associated with worsening nutrition symptoms

Table 2. Description of Disease and Treatment

	Parent study (N = 96), total (%)	Not in current study (N = 40), total (%)	In current study (N = 56), total (%)	*p* value
Type of cancer				.517
Squamous cell carcinoma	81 (84.4)	33 (82.5)	48 (84.9)	
Other	15 (15.6)	7 (17.5)	8 (14.3)	
Location of cancer				.427
Oral cavity	20 (20.8)	9 (22.5)	11 (19.6)	
Oropharynx	41 (42.7)	13 (32.5)	28 (50.0)	
Larynx	13 (13.5)	8 (20.0)	5 (8.9)	
Other	22 (22.9)	10 (25.0)	9 (16.1)	
Known viral etiology				.039
None	51 (53.1)	25 (62.5)	26 (46.4)	
HPV	28 (29.2)	5 (12.5)	23 (41.1)	
Other	17 (17.7)	10 (25.0)	7 (12.5)	
Surgery				.422
Yes	41 (42.7)	19 (47.5)	22 (39.4)	
No	55 (57.3)	21 (52.5)	34 (60.7)	
Chemotherapy				.227
Yes	94 (97.9)	40 (100)	54 (96.4)	
No	2 (2.1)	0 (0)	2 (3.6)	
Type of surgery	(N = 41)	(N = 19)	(N = 22)	.764
RND	2 (4.9)	1 (5.3)	1 (4.6)	
Modified ND	25 (61.0)	10 (52.6)	15 (68.2)	
Total/Partial laryngectomy	4 (9.8)	3 (15.8)	1 (4.6)	
Other	10 (24.4)	5 (26.3)	5 (22.7)	
Concurrent radiation				.239
Yes	94 (97.9)	38 (100)	54 (96.4)	
No	2 (2.1)	0 (0)	2 (3.6)	
PEG				.078
Yes	49 (52.1)	24 (63.2)	25 (44.6)	
No	45 (47.9)	14 (36.8)	31 (55.4)	
Type of treatment				.380
Chemo XRT	15 (16.0)	7 (18.4)	8 (14.3)	
Induction + chemo XRT	42 (44.7)	14 (36.8)	28 (50.0)	
Surgery + chemo XRT	25 (26.6)	11 (28.9)	14 (25.0)	
Surgery + radiotherapy	2 (2.1)	0 (0)	2 (2.1)	
Induction + chemo XRT + surgery	10 (10.6)	6 (15.8)	4 (7.1)	

Note. HPV = human papillomavirus; PEG = percutaneous endoscopic gastrostomy; RND = radical neck dissection; ND = neck dissection; XRT = radiation.

Table 2. Description of Disease and Treatment (cont.)

	Parent study (N = 96), total (%)	Not in current study (N = 40), total (%)	In current study (N = 56), total (%)	p value
Distant metastasis				.445
Yes	5 (5.2)	3 (7.5)	2 (3.6)	
No	91 (94.8)	37 (92.5)	54 (96.4)	
Tumor TNM stage				.317
Stage 0–3	45 (46.9)	20 (50.0)	25 (44.6)	
Stage 2a, 2b, 2c, 3b	51 (53.1)	20 (50.0)	31 (55.4)	
Stage of tumor				.849
Stage 1–3	26 (27.1)	11 (27.5)	15 (26.8)	
Stage 4a and 4b	70 (72.9)	29 (72.5)	41 (73.2)	
Size of tumor				.259
3 or less	67 (68.8)	23 (57.5)	44 (76.8)	
4	12 (12.5)	9 (22.5)	3 (5.4)	
4a/b	11 (11.4)	5 (12.5)	6 (10.7)	
X	6 (6.3)	3 (7.5)	3 (5.4)	

Note. HPV = human papillomavirus; PEG = percutaneous endoscopic gastrostomy; RND = radical neck dissection; ND = neck dissection; XRT = radiation.

at 6 months (TGF-β1: β = –0.31, *p* = .014; IFNγ: β = –0.25, *p* = 0.048). IL-6 was the only biomarker with short-term effects that remained at a statistically significant level over the longer 12-month posttreatment period (β = 0.21, *p* = 0.041).

Swallowing

Descriptions of patients' self-reported difficulties with swallowing solids as assessed by the VHNSS swallowing solids cluster score at baseline and changes over time are presented in Table 7. Associations of initial levels of cytokines with changes over time are presented in Table 8. Higher initial levels of IL-6, IL-10, and TNFα were associated with an increase in difficulty swallowing solids from baseline to 6 and 12 months posttreatment (IL-6 at 6 months: β = 0.34, *p* = .009, at 12 months: β = 0.36, *p* = .006; IL-10 at 6 months: β = 0.31, *p* = .023, at 12 months: β = 0.39, *p* = .003; and TNFα at 6 months: β = 0.31, *p* = 0.019). Lower levels of albumin pretreatment were both associated with increased difficulty swallowing solids 1 year later (β = –0.27, *p* = .048).

Taste-Smell

Descriptions of the VHNSS taste/smell cluster scores at baseline and changes over time are pre-sented in Table 9. The median baseline score was 0 on a 0 to 10 scale and did not change more than a point over the course of the study. There was moderate variability in self-reported taste/smell scores throughout the duration of the study. As shown in Table 10, higher baseline levels of IL-1β and IL-6 were associated with worsening taste/smell symptoms at 6 and 12 months posttreatment (all βs > 0.30, *p* < .05).

DISCUSSION

A primary goal of this study was to assess how initial baseline cytokines and CRP correlated with long-term symptom development in patients posttreatment for HNC. Many patients within this study had advanced cancer at the time of diagnosis (stage 3 or greater); therefore, the inflammatory mediators responsible for the development of cachexia and symptoms were already promoting metabolic derangements at the time of enrollment. Additionally, there was no statistical difference in cytokines according to cancer stage and intensity of treatments. Due to the fact that cytokines have variable half-lives ranging from seconds to a few minutes, examining how these biomarkers influence long-term symptom development was important so that fu-

Table 3. Description of Depressive Symptoms as Measured by CES-D at Baseline and Changes From Baseline at 6 and 12 Months

	Baseline	6-month change	12-month change
N	56	54	54
Median	12.00	–3.50	–4.00
IQR	7.00, 21.75	–10.00, 1.00	–10.00, 1.00
Min, max	0.0, 39.00	–34.00, 16.00	–34.00, 15.00

Note. CES-D = Center for Epidemiologic Studies Depression Scale; IQR = interquartile range.

ture research can target modalities that may interfere with cytokines that appear to promote worse symptoms. The caveat to understanding cytokines is that the ability to understand the development of cytokines in human cancer patients during early stages is limited, because cancers are generally not detected at the onset of the disease. Thus, determining the progression of cytokine initiation from the tumor is difficult to elucidate.

Depression

Within this study, two significant associations with increased levels of depression were lower baseline levels of TGF-β2 and higher initial levels of CRP. No similar associations of TGF-β2 have been found in regards to depression in previous research. However, TGF-β levels have been associated with higher levels of depression in some recent non-cancer studies (Davami et al., 2016). TGF has been associated with increased fatigue during cancer in some cancer studies (Breitbart et al., 2014). Regarding CRP, an association with increased CRP levels and increased levels of depressive symptoms has previously been described in the literature (Archer, Buxton, & Sheffield, 2015). Depression is a common symptom that is associated with cancer

Table 4. Initial Biomarker Levels and Changes in Depression From Baseline at 6 and 12 Months

Biomarker	6-month change		12-month change	
	β	*p* value	β	*p* value
IL-β1	< 0.01	0.987	–0.01	0.957
IL-6	0.22	0.079	0.04	0.750
IL-8	0.17	0.184	0.20	0.139
IL-10	0.08	0.543	–0.13	0.347
IL-12p70	–0.08	0.511	0.12	0.362
MMP2A	–0.08	0.545	–0.15	0.255
MMP9A	–0.19	0.129	–0.10	0.445
TGF-β1	–0.21	0.099	0.07	0.584
TGF-β2	–0.21	0.119	–0.41	0.002[a]
TGF-β3[b]	0.12	0.443	–0.02	0.902
TNFα	0.16	0.207	–0.07	0.599
IFNγ	0.14	0.270	0.20	0.125
CRP	0.17	0.168	0.28	0.035[a]
RBC	–0.20	0.112	0.01	0.966
Albumin	0.01	0.941	–0.03	0.857

Note. IL = interleukin; MMP = matrix metalloproteinase; TGF = transforming growth factor; TNF = tumor necrosis factor; IFN = interferon; CRP = C-reactive protein; RBC = red blood cell.
[a]Statistically significant. [b]N = ~25 with data for TGF-β3 pretreatment, 6 and 12 months posttreatment.

Table 5. Reported Difficulties With Consuming Nutrition at Baseline and Changes From Baseline at 6 and 12 Months

	Baseline	6-month change	12-month change
N	56	54	54
Median	0.25	0.00	0.00
IQR	0.00, 1.50	–0.50, 0.75	–1.00, 0.25
Min, max	0.00, 7.00	–5.25, 7.75	–7.00, 3.75

Note. IQR = interquartile range.

(Archer, Hutchison, Dorudi, Stansfeld, & Korszun, 2012; Kamath, 2012; Moubayed et al., 2014). Several studies indicate an association between cytokines and the development of depression in cancer patients. With the exception of CRP (which is not a cytokine), no other cytokine correlated with worsening symptoms of depression. TGF is considered inflammatory in nature, and this inflammation may associate with the development of depression.

Although it is possible the finding is spurious, further studies examining this association will need to be conducted. This study indicates that a biomarker for depression prediction is not sophisticated enough to be employed by providers to help understand depression trajectory. C-reactive protein is a generic marker of inflammation within the body and has been linked with not only depressive symptoms, but that of fatigue and pain in cancer patients (Myers, 2008). Most studies report a negative association with outcomes and cancer when CRP levels are elevated (Chung & Chang, 2003; Wallengren et al., 2013).

Nutrition Consumption

Head and neck cancer patients are prone to developing difficulties obtaining adequate nutritional

Table 6. Initial Biomarker Levels and Changes in Nutrition-Related Symptoms From Baseline at 6 and 12 Months

Biomarker	6-month change		12-month change	
	β	*p* value	β	*p* value
IL-β1	0.06	0.660	0.06	0.592
IL-6	0.35	0.006	0.21	0.041[a]
IL-8	–0.06	0.641	0.06	0.568
IL-10	0.33	0.008[a]	0.12	0.237
IL-12p70	–0.06	0.631	–0.03	0.764
MMP2A	0.27	0.035[a]	0.11	0.297
MMP9A	–0.17	0.202	0.03	0.765
TGF-β1	–0.31	0.014[a]	–0.06	0.600
TGF-β2	0.12	0.359	–0.14	0.201
TGF-β3[b]	–0.04	0.854	–0.36	0.096
TNFα	0.18	0.155	0.17	0.112
IFNγ	–0.25	0.048[a]	–0.03	0.807
CRP	–0.24	0.064	–0.03	0.789
RBC	–0.13	0.321	–0.04	0.727
Albumin	–0.01	0.930	–0.10	0.369

Note. IL = interleukin; MMP = matrix metalloproteinase; TGF = transforming growth factor; TNF = tumor necrosis factor; IFN = interferon; CRP = C-reactive protein; RBC = red blood cell.
[a]Statistically significant. [b]N = ~25 with data for TGF-β3 pretreatment, 6 and 12 months posttreatment.

Table 7. Reported Difficulties With Swallowing Solids From Baseline and Changes From Baseline at 6 and 12 Months

	Baseline	6-month change	12-month change
N	56	54	54
Median	0.63	0.63	0.38
IQR	0.03, 2.63	−0.38, 2.91	−0.38, 1.16
Min, max	0.00, 8.00	−3.50, 5.63	−4.63, 6.13

Note. IQR = interquartile range.

intake due to the location of their tumor. Furthermore, there is a direct link between lack of caloric intake and increased mortality (Jager-Wittenaar et al., 2011; O'Neill & Shaha, 2011) and decreased quality of life (Caro et al., 2007). The role of cytokines and their mediation of caloric intake by influencing the brain, specifically the hypothalamus, have become increasingly researched. Increased inducible nitric oxide synthase production in the hypothalamus leads to severe anorexia, which is a possible pathway through which proinflammatory cytokines lead to anorexia (Morley & Farr, 2008). Various cytokines influence several neuropeptides

that directly affect the desire to eat (Patra & Arora, 2012). This study did not demonstrate any association between cytokines and weight loss.

Individuals with higher levels of IL-6, IL-10, MMP2A, TGF-β1, and IFNγ at baseline were prone to reporting greater difficulties obtaining nutrition. The precise role of cytokines on the progression of anorexia and cachexia is not fully understood, but there are two hypotheses: (1) Cytokines influence neuropeptide interaction through the blood-brain barrier, promoting early satiety and anorexia (Banks, 2001); and (2) IL-6 specifically alters the JAK/STAT pathway, promoting

Table 8. Initial Biomarker Levels and Changes in Swallowing Solids From Baseline at 6 and 12 Months

Biomarker	6-month change		12-month change	
	β	*p* value	β	*p* value
IL-β1	0.26	0.057	0.25	0.060
IL-6	0.34	0.009	0.36	0.006[a]
IL-8	0.22	0.107	0.21	0.116
IL-10	0.31	0.023	0.39	0.003[a]
IL-12p70	−0.04	0.770	−0.11	0.394
MMP2A	0.03	0.828	0.16	0.233
MMP9A	0.16	0.262	0.11	0.416
TGF-β1	−0.17	0.223	−0.11	0.445
TGF-β2	−0.12	0.399	−0.14	0.303
TGF-β3[b]	−0.17	0.448	−0.10	0.628
TNFα	0.31	0.019[a]	0.23	0.091
IFNγ	−0.07	0.625	−0.05	0.711
CRP	−0.09	0.509	−0.15	0.253
RBC	0.18	0.198	0.24	0.085
Albumin	−0.15	0.292	−0.27	0.048[a]

Note. IL = interleukin; MMP = matrix metalloproteinase; TGF = transforming growth factor; TNF = tumor necrosis factor; IFN = interferon; CRP = C-reactive protein; RBC = red blood cell.
[a]Statistically significant. [b]N = ~25 with data for TGF-β3 pretreatment, 6 and 12 months posttreatment.

Table 9. Reported Changes in Taste/Smell From Baseline and Changes From Baseline at 6 and 12 Months

	Baseline	6-month change	12-month change
N	56	53	54
Median	0.00	0.67	0.00
IQR	0.00, 1.33	0.00, 2.33	−0.42, 1.00
Min, max	0.00, 8.00	−5.50, 7.00	−5.17, 6.50

Note. IQR = interquartile range.

muscle catabolism and decreases muscle production by promoting an increase in circulating levels of myostatin, which inhibits muscle regeneration.

The role of IL-10 and MMP2 on cachexia is less clear than that of IL-6. In a large study of 203 patients examining multiple cytokine polymorphisms, only IL-10-1082 polymorphism was linked to the development of cachexia in gastric cancer (Deans et al., 2009). Increased IL-10 serum expression was significantly associated with worse survival in early-stage oral squamous cell carcinoma (Chen et al., 2013). Another recent study indicates that certain IL-10 genotypes in-

crease the susceptibility of oral cancer (Tsai et al., 2014).

MMP2 has generally been correlated with tumor promotion and progression, as its role in the healthy individual is tissue repair and regulation of vascularization. Currently, an association with MMP2 and cachexia remains unclear. However, MMP2 may play a role in the vascularization of tumors, which help them grow and subsequently enhances the release of cachexia-inducing cytokines.

The TGF-β superfamily cytokine MIC-1/GDF15 circulates in all humans and leads to anorexia/cachexia when overproduced in cancer by

Table 10. Initial Biomarker Levels and Changes in Taste/Smell Symptoms From Baseline at 6 and 12 months

Biomarker	6-month change		12-month change	
	β	*p* value	β	*p* value
IL-β1	0.37	0.005	0.32	0.003[a]
IL-6	0.31	0.022	0.36	0.001[a]
IL-8	0.02	0.897	0.16	0.148
IL-10	0.26	0.055	0.16	0.154
IL-12p70	0.02	0.867	0.05	0.680
MMP2A	0.14	0.312	0.04	0.719
MMP9A	0.04	0.749	0.16	0.148
TGF-β1	−0.24	0.079	−0.06	0.563
TGF-β2	0.19	0.169	−0.02	0.870
TGF-β3[b]	−0.02	0.946	0.30	0.149
TNFα	0.20	0.150	0.19	0.088
IFNγ	−0.27	0.050	−0.14	0.217
CRP	−0.17	0.209	0.01	0.904
RBC	−0.03	0.811	−0.07	0.512
Albumin	0.17	0.221	−0.05	0.685

Note. IL = interleukin; MMP = matrix metalloproteinase; TGF = transforming growth factor; TNF = tumor necrosis factor; IFN = interferon; CRP = C-reactive protein; RBC = red blood cell.
[a]Statistically significant. [b]N = ~25 with data for TGF-β3 pretreatment, 6 and 12 months posttreatment.

direct action on brain-feeding centers, specifically the hypothalamus. However, within this study, lower levels of TGF-β1 were associated with worsening nutrition symptoms. This finding was only statistically significant at the 6-month mark and is likely spurious. It is possible that an unknown feedback mechanism between these cytokines as well as the multiple pathways a cytokine was acting upon in head and neck cancer patients was occurring. Further studies examining this association will need to be performed to determine if this is indeed the case. Both higher levels of IFNγ and TGF-β1 have been associated with worsening cachexia (Argilés, Busquets, Felipe, & López-Soriano, 2005; Bing, 2011; Blum et al., 2011; Cahlin et al., 2000; Donohoe, Ryan, & Reynolds, 2011; Patra & Arora, 2012).

Swallowing-Related Symptoms

Difficulties swallowing are directly related to several factors such as the direct impact of the tumor, cancer resection, chemotherapy, and radiotherapy (Raber-Durlacher et al., 2012). What is not well described in the literature is the association between cytokines and swallowing dysfunction in the HNC patient over time. Interestingly, IL-6 and IL-10 also correlated with difficulties in regards to nutrition consumption. However, in this case, IL-6 and IL-10 were associated with difficulty swallowing at 12 months, but this was not the case when patients self-reported difficulties obtaining nutrition on the VHNSS. This perhaps indicates that some patients were able to adapt to their difficulty obtaining nutrition over the year by consuming different foods. Their perception of obtaining nutrition may have changed over the duration of their illness, but they still experienced "trouble" swallowing.

TNFα has been implicated in the development of cachexia in several studies (Tisdale, 2009). TNFα appears to be a stimulus for the production of other catabolic cytokines that subsequently cause the development of cachexia (Argilés, Busquets, Stemmler, & López-Soriano, 2014). Additionally, TNFα appears to affect the hypothalamus through proinflammatory signals that affect neurotransmitters and subsequent hunger signaling to patients, perpetuating the cycle of cachexia by inducing anorexia (Amaral et al., 2006). TNFα also promotes fat lipolysis and fat depletion (Tsoli & Robertson, 2013). TNFα has also been recently identified to regulate lipolysis through the G0/G1 switch gene 2 (GOS2). By inhibiting expression of GOS2, an increased level of lipolysis occurs (Yang, Zhang, Heckmann, Lu, & Liu, 2011). Presently, it appears that TNFα directly relates to adipose tissue loss, but not directly to the loss of muscle protein (van Hall, 2012). With limited effects on muscle loss, the association with decreased ability to swallow and increased TNFα levels in HNC is not clear. It is possible that the elevation of TNFα promoted the metabolic effects that promoted muscle degradation through the promotion of myostatin.

Taste Dysfunction

Higher levels of baseline IL-1β and IL-6 correlated with increased taste dysfunction at both 6 and 12 months. IL-1β is involved in olfactory abilities (Poretti et al., 2015). An examination of the influence of IL-1β on the influence of smell and taste in HNC patients has not been conducted. Increasing levels of IL-1β may inhibit the ability to smell, which is the predominant sense that humans utilize for taste. In a recent study, an injury to the tongue correlated with higher IL-1β levels approximately 2 days after an initial injury (Shi, He, Sarvepalli, & McCluskey, 2012). This same process could also be occurring in the HNC population both through tumor mediation as well as through the negative sequela of treatment.

CONCLUSION

The search for a biomarker to assist in understanding disease trajectories is ongoing. This is likely confounded by the multiple modalities that a cytokine can undertake in the human body. Based upon the evidence, IL-6 and CRP levels at the time of diagnosis may give insight into issues surrounding negative sequalae that patients will experience through their illness. Further studies examining these relationships will need to be conducted in prospective clinical trials. Specifically, studies of a much longer duration examining patients who remain disease free and their cytokine profiles should be conducted. Due to many cancers typically not being diagnosed until later stages, longer randomized controlled trials examining cytokine profiles and stages of cancer should be conducted to better understand the association of cytokines and long-term effects on symptoms and disease-free status. ●

Disclosure

The author has no conflicts of interest to disclose.

References

Amaral, M. E., Barbuio, R., Milanski, M., Romanatto, T., Barbosa, H. C., Nadruz, W., & Velloso, L. A. (2006). Tumor necrosis factor-alpha activates signal transduction in hypothalamus and modulates the expression of proinflammatory proteins and orexigenic/anorexigenic neurotransmitters. *Journal of Neurochemistry, 98*(1), 203–212. https://doi.org/10.1111/j.1471-4159.2006.03857.x

Archer, S., Buxton, S., & Sheffield, D. (2015). The effect of creative psychological interventions on psychological outcomes for adult cancer patients: A systematic review of randomized controlled trials. *Psychooncology, 24*(1), 1–10. https://doi.org/10.1002/pon.3607

Archer, J. A., Hutchison, I. L., Dorudi, S., Stansfeld, S. A., & Korszun, A. (2012). Interrelationship of depression, stress and inflammation in cancer patients: A preliminary study. *Journal of Affective Disorders, 143*(1–3), 39–46. https://doi.org/10.1016/j.jad.2012.05.023

Argilés, J. M., Busquets, S., Felipe, A., & López-Soriano, F. J. (2005). Molecular mechanisms involved in muscle wasting in cancer and ageing: Cachexia versus sarcopenia. *International Journal of Biochemical Cell Biology, 37*(5), 1084–1104. https://doi.org/10.1016/j.biocel.2004.10.003

Argilés, J. M., Busquets, S., Stemmler, B., & López-Soriano, F. J. (2014). Cancer cachexia: Understanding the molecular basis. *Nature Reviews Cancer, 14*(11), 754–762. https://doi.org/10.1038/nrc3829

Banks, W. A. (2001). Anorectic effects of circulating cytokines: Role of the vascular blood-brain barrier. *Nutrition, 17*(5), 434–437. https://doi.org/10.1016/S0899-9007(01)00507-X

Bing, C. (2011). Lipid mobilization in cachexia: mechanisms and mediators. *Current Opinion in Supportive Palliative Care, 5*(4), 356–360. https://doi.org/10.1097/SPC.0b013e32834bde0e

Blum, D., Omlin, A., Baracos, V. E., Solheim, T. S., Tan, B. H., Stone, P., Strasser, F. (2011). Cancer cachexia: A systematic literature review of items and domains associated with involuntary weight loss in cancer. *Critical Reviews in Oncology/Hematology, 80*(1), 114–144. https://doi.org/10.1016/j.critrevonc.2010.10.004

Breitbart, W., Rosenfeld, B., Tobias, K., Pessin, H., Ku, G. Y., Yuan, J.,...Wolchok, J. (2014). Depression, cytokines, and pancreatic cancer. *Psychooncology, 23*(3), 339–345. https://doi.org/10.1002/pon.3422

Cahlin, C., Körner, A., Axelsson, H., Wang, W., Lundholm, K., & Svanberg, E. (2000). Experimental cancer cachexia: The role of host-derived cytokines interleukin (IL)-6, IL-12, interferon-gamma, and tumor necrosis factor alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia. *Cancer Research, 60*(19), 5488–5493.

Caro, M. M., Laviano, A., Pichard, C., & Candela, C. G. (2007). Relationship between nutritional intervention and quality of life in cancer patients. *Nutrition Hospital, 22*(3), 337–350.

Chen, C. J., Sung, W. W., Su, T. C., Chen, M. K., Wu, P. R., Yeh, K. T.,...Lee, H. (2013). High expression of interleukin 10 might predict poor prognosis in early stage oral squamous cell carcinoma patients. *Clinica Chimica Acta, 415*, 25–30. https://doi.org/10.1016/j.cca.2012.09.009

Chung, Y. C., & Chang, Y. F. (2003). Serum C-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. *European Journal of Gastroenterology and Hepatology, 15*(4), 369–373. https://doi.org/10.1097/00042737-200304000-00006

Cleeland, C. S., Bennett, G. J., Dantzer, R., Dougherty, P. M., Dunn, A. J., Meyers, C. A.,...Lee, B. N. (2003). Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer, 97*(11), 2919–2925. https://doi.org/10.1002/cncr.11382

Davami, M. H., Baharlou, R., Vasmehjani, A. A., Ghanizadeh, A., Keshtkar, M., Dezhkam, I., & Atashzar, M. R. (2016). Elevated IL-17 and TGF-β serum levels: A positive correlation between T-helper 17 cell-related proinflammatory responses with major depressive disorder. *Basic Clinical Neurosciences, 7(2),* 137–142. https://doi.org/10.15412/J.BCN.03070207

Deans, D. A., Tan, B. H., Ross, J. A., Rose-Zerilli, M., Wigmore, S. J., Howell, W. M.,...Fearon, K. C. (2009). Cancer cachexia is associated with the IL10 -1082 gene promoter polymorphism in patients with gastroesophageal malignancy. *American Journal of Clinical Nutrition, 89*(4), 1164–1172. https://doi.org/10.3945/ajcn.2008.27025

Dodson, S., Baracos, V. E., Jatoi, A., Evans, W. J., Cella, D., Dalton, J. T., & Steiner, M. S. (2011). Muscle wasting in cancer cachexia: Clinical implications, diagnosis, and emerging treatment strategies. *Annual Review of Medicine, 62,* 265–279. https://doi.org/10.1146/annurev-med-061509-11248

Donohoe, C. L., Ryan, A. M., & Reynolds, J. V. (2011). Cancer cachexia: Mechanisms and clinical implications. Gastroenterology *Research and Practice, 2011.* https://doi.org/10.1155/2011/601434

Fearon, K., Arends, J., & Baracos, V. (2013). Understanding the mechanisms and treatment options in cancer cachexia. *Nature Reviews in Clinical Oncology, 10*(2), 90–99. https://doi.org/10.1038/nrclinonc.2012.209

Giannousi, Z., Gioulbasanis, I., Pallis, A. G., Xyrafas, A., Dalliani, D., Kalbakis, K.,...Papandreou, C. N. (2012). Nutritional status, acute phase response and depression in metastatic lung cancer patients: Associations and association prognosis. *Supportive Care in Cancer, 20*(8), 1823–1829. https://doi.org/10.1007/s00520-011-1282-x

Gupta, S. C., Kim, J. H., Kannappan, R., Reuter, S., Dougherty, P. M., & Aggarwal, B. B. (2011). Role of nuclear factor-κB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. *Experimental Biological Medicine, 236*(6), 658–671. https://doi.org/10.1258/ebm.2011.011028

Hopkinson, J. (2010). The emotional aspects of cancer anorexia. *Current Opinion in Supportive and Palliative Care, 4*(4), 254–258. https://doi.org/10.1097/SPC.0b013e32833ef813

Huhmann, M. B., & Cunningham, R. S. (2005). Importance of nutritional screening in treatment of cancer-related weight loss. *Lancet Oncology, 6*(5), 334–343. https://doi.org/10.1016/S1470-2045(05)70170-4

Imayama, I., Alfano, C. M., Neuhouser, M. L., George, S. M., Smith, A. W., Baumgartner, R. N.,...McTiernan, A. (2013). Weight, inflammation, cancer-related symptoms and health-related quality of life among breast cancer survivors. *Breast Cancer Research and Treatment, 140*(1), 159–176. https://doi.org/10.1007/s10549-013-2594-y

Jager-Wittenaar, H., Dijkstra, P. U., Vissink, A., Langendijk, J. A., van der Laan, B. F., Pruim, J., & Roodenburg, J. L. (2011). Changes in nutritional status and dietary intake during and after head and neck cancer treatment. *Head & Neck, 33*(6), 863–870. https://doi.org/10.1002/hed.21546

Kamath, J. (2012). Cancer-related fatigue, inflammation and thyrotropin-releasing hormone. *Current Aging Science, 5*(3), 195–202. https://doi.org/10.2174/1874609811205030005

Laird, B. J., Scott, A. C., Colvin, L. A., McKeon, A. L., Murray, G. D., Fearon, K. C., & Fallon, M. T. (2011). Pain, depression, and fatigue as a symptom cluster in advanced cancer. *Journal of Pain Symptom Management, 42*(1), 1–11. https://doi.org/10.1016/j.jpainsymman.2010.10.261

Lucia, S., Esposito, M., Fanelli, F. R., & Muscaritoli, M. (2012). Cancer cachexia: From molecular mechanisms to patient's care. *Critical Reviews in Oncogenesis, 17*(3). https://doi.org/10.1615/CritRevOncog.v17.i3.90

Morley, J. E., & Farr, S. A. (2008). Cachexia and neuropeptide Y. *Nutrition, 24*(9), 815–819. https://doi.org/10.1016/j.nut.2008.06.020

Moubayed, S. P., Sampalis, J. S., Ayad, T., Guertin, L., Bissada, E., Gologan, O. E.,...Christopoulos, A. (2014). Predicting depression and quality of life among long-term head and neck cancer survivors. *Otolaryngology—Head and Neck Surgery, 152*(1), 91–97. https://doi.org/10.1177/0194599814557772

Myers, J. S. (2008). Proinflammatory cytokines and sickness behavior: Implications for depression and cancer-related symptoms. *Oncology Nursing Forum, 35*(5), 802–807. https://doi.org/10.1188/08.ONF.802-807

O'Neill, J. P., & Shaha, A. R. (2011). Nutrition management of patients with malignancies of the head and neck. *Surgical Clinics of North America, 91*(3), 631–639. https://doi.org/10.1016/j.suc.2011.02.005

Oz, V., Theilla, M., & Singer, P. (2008). Eating habits and quality of life of patients receiving home parenteral nutrition in Israel. *Clinical Nutrition, 27*(1), 95–99. https://doi.org/10.1016/j.clnu.2007.06.016

Patra, S. K., & Arora, S. (2012). Integrative role of neuropeptides and cytokines in cancer anorexia-cachexia syndrome. *Clinica Chimica Acta, 413*(13–14), 1025–1034. https://doi.org/10.1016/j.cca.2011.12.008

Poretti, M. B., Rask-Andersen, M., Kumar, P., Rubiales de Barioglio, S., Fiol de Cuneo, M., Schiöth, H. B., & Carlini, V. P. (2015). Ghrelin effects expression of several genes associated with depression-like behavior. *Progress in Neuro-psychopharmacology and Biological Psychiatry, 56*, 227–234. https://doi.org/10.1016/j.pnpbp.2014.09.012

Raber-Durlacher, J. E., Brennan, M. T., Verdonck-de Leeuw, I. M., Gibson, R. J., Eilers, J. G., Waltimo, T.,...Spijkervet, F. K. L. (2012). Swallowing dysfunction in cancer patients. *Supportive Care in Cancer, 20*(3), 433–443. https://doi.org/10.1007/s00520-011-1342-2

Ridner, S. H., & Dietrich, M. S. (2008). Self-reported comorbid conditions and medication usage in breast cancer survivors with and without lymphedema. *Oncology Nursing Forum, 35*(1), 57–63. https://doi.org/10.1188/08.ONF.57-63

Roberts, B. M., Frye, G. S., Ahn, B., Ferreira, L. F., & Judge, A. R. (2013). Cancer cachexia decreases specific force and accelerates fatigue in limb muscle. *Biochemical and Biophysical Research Communications, 435*(3), 488–492. https://doi.org/10.1016/j.bbrc.2013.05.018

Shi, L., He, L., Sarvepalli, P., & McCluskey, L. P (2012). Functional role for the interleukin-1 in the injured peripheral taste system. *Journal of Neuroscience Research, 90*(4), 816–830. https://doi.org/10.1002/jnr.22798

Tisdale, M. J. (2009). Mechanisms of cancer cachexia. *Physiological Reviews, 89*(2), 381–410. https://doi.org/10.1152/physrev.00016.2008

Tsai, C. W., Chang, W. S., Lin, K. C., Shih, L. C., Hsiao, C. L., Yang, M. D.,...Bau, D. T. (2014). Significant association of interleukin-10 genotypes and oral cancer susceptibility in Taiwan. *Anticancer Research, 34*(7), 3731–3737.

Tsoli, M., & Robertson, G. (2013). Cancer cachexia: Malignant inflammation, tumorkines, and metabolic mayhem. *Trends in Endocrinology and Metabolism, 24*(4), 174–183. https://doi.org/10.1016/j.tem.2012.10.006

van Hall, G. (2012). Cytokines: Muscle protein and amino acid metabolism. *Current Opinion in Clinical Nutrition and Metabolic Care, 15*(1), 85–91. https://doi.org/10.1097/MCO.0b013e32834e6ea2

von Haehling, S., & Anker, S. D. (2010). Cachexia as a major underestimated and unmet medical need: Facts and numbers. *Journal of Cachexia Sarcopenia and Muscle, 1*(1), 1–5. https://doi.org/10.1007/s13539-010-0002-6

Wallengren, O., Lundholm, K., & Bosaeus, I. (2013). Diagnostic criteria of cancer cachexia: Relation to quality of life, exercise capacity and survival in unselected palliative care patients. *Supportive Care in Cancer, 21*(6), 1569–1577. https://doi.org/10.1007/s00520-012-1697-z

Walz, D. A. (2010). Cancer-related anorexia-cachexia syndrome. *Clinical Journal of Oncology Nursing, 14*(3), 283–287. https://doi.org/10.1188/10.CJON.283-287

Yakovenko, A., Cameron, M., & Trevino, J. G. (2018). Molecular therapeutic strategies targeting pancreatic cancer induced cachexia. *World Journal of Gastroenterology Surgery, 10*(9), 95–106. https://doi.org/10.4240/wjgs.v10.i9.95

Yang, X., Zhang, X., Heckmann, B. L., Lu, X., & Liu, J. (2011). Relative contribution of adipose triglyceride lipase and hormone-sensitive lipase to tumor necrosis factor-alpha (TNF-α)-induced lipolysis in adipocytes. *Journal of Biological Chemistry, 286*(47), 40477–40485. https://doi.org/10.1074/jbc.M111.257923