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Research Article

Health Behaviors Predict Higher Interleukin-6 Levels among Patients Newly Diagnosed with Head and Neck Squamous Cell Carcinoma

Sonia A. Duffy[1,2,4], Theodoros Teknos[7], Jeremy M.G. Taylor[5], Karen E. Fowler[4], Mozaffarul Islam[7], Gregory T. Wolf[2], Scott McLean[3], Tamer A. Ghanem[6], and Jeffrey E. Terrell[2]

Abstract

Background: Health behaviors have been shown to be associated with recurrence risk and survival rates in patients with cancer and are also associated with interleukin-6 (IL-6) levels, but few epidemiologic studies have investigated the relationship of health behaviors and IL-6 among cancer populations. The purpose of the study is to look at the relationship between five health behaviors, viz.: smoking, alcohol problems, body mass index (BMI; a marker of nutritional status), physical activity, and sleep and pretreatment IL-6 levels in persons with head and neck cancer.

Methods: Patients ($N = 409$) were recruited in otolaryngology clinic waiting rooms and invited to complete written surveys. A medical record audit was also conducted. Descriptive statistics and multivariate analyses were conducted to determine which health behaviors were associated with higher IL-6 levels controlling for demographic and clinical variables among patients with newly diagnosed head and neck cancer.

Results: While smoking, alcohol problems, BMI, physical activity, and sleep were associated with IL-6 levels in bivariate analysis, only smoking (current and former) and decreased sleep were independent predictors of higher IL-6 levels in multivariate regression analysis. Covariates associated with higher IL-6 levels were age and higher tumor stage, whereas comorbidities were marginally significant.

Conclusion: Health behaviors, particularly smoking and sleep disturbances, are associated with higher IL-6 levels among patients with head and neck cancer.

Impact: Treating health behavior problems, especially smoking and sleep disturbances, may be beneficial to decreasing IL-6 levels, which could have a beneficial effect on overall cancer treatment outcomes. *Cancer Epidemiol Biomarkers Prev; 22(3); 374–81. ©2012 AACR.*

Introduction

Interleukin-6 (IL-6) is a cytokine that can be produced by a variety of cells (neutrophages, macrophages, fibroblasts, endothelial cells, damaged muscle cells, adipose cells, and cancer cells themselves; ref. 1) and has been shown to regulate immune defense mechanisms and hematopoiesis (2). High levels of IL-6 have been linked to higher cancer stage (3–6), faster tumor progression (7), and poorer prognosis of cancer in general (4, 5, 8, 9), and also in head and neck cancer (10–12); specifically, head and neck cancer cells have been shown to express high levels of IL-6 as are endothelial cells in the tumor microenvironment, which can facilitate tumor invasion and metastasis in an environment rich in this cytokine (7, 8). In a large study, our prior work identified IL-6 as a valuable biomarker for predicting recurrence and overall survival among patients with head and neck cancer (13).

Tobacco and alcohol use are well-known primary risk factors for developing head and neck cancer. Smoking and problem drinking have been associated with decreased quality of life scores (14, 15) and decreased survival (16–18). This may be due to the more advanced stage of disease in smokers and problem drinkers, the immunosuppressive effects of smoking and problem drinking, impaired absorption of nutrients, poor compliance with treatment, or increased rate of death due to other smoking and alcohol-related diseases (17, 19). The effects of smoking and excessive alcohol intake on IL-6 levels are well known and have been studied in different populations including patients with arthritis (20), peridontitis (21), cardiovascular risk (22), and in healthy populations (23, 24).

Authors' Affiliations: [1]School of Nursing, University of Michigan; Departments of [2]Otolaryngology—Head and Neck Surgery and [3]Otorhinolaryngology, University of Michigan Medical School; [4]Ann Arbor Veterans Affairs (VA) Center for Clinical Management Research; [5]Biostatistics Core, University of Michigan Comprehensive Cancer Center; [6]Department of Otolaryngology—Head and Neck Surgery, Henry Ford Health System, Detroit, MI; and [7]Department of Otolaryngology—Head and Neck Surgery, Ohio State Medical School, Columbus, Ohio

Corresponding Author: Sonia A. Duffy, University of Michigan, School of Nursing, 400 North Ingalls Building, Room 3178, Ann Arbor, MI 48109-5482; Phone: 734-395-0613; Fax: 734-647-0351; E-mail: bump@umich.edu

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Exercise in patients with head and neck cancer improves quality of life (25), which in turn improves survival rates (26). Regular mild exercise, such as walking has beneficial effects on IL-6 regulation (27), and on morbidity and mortality in patients with cancer (28). While the acute response to exercise may actually increase IL-6 levels, perhaps due to stress to the muscles, the long-term effects of exercise is lower IL-6 levels perhaps due to increased muscle mass and decreased adipose tissue, which secretes IL-6 (29–31).

Diets high in fruits and vegetables and low in high-fat foods such as red meat are protective against most cancers of the head and neck (32, 33), can affect the occurrence of second primary cancers (34), and are associated with reduced cancer mortality (17, 35). Diets low in fat and high in fruit, vegetables, whole grains, fish, and poultry are associated with lower IL-6 levels compared with higher fat diets (36, 37). Cancer occurring in the head and neck region coupled with curative or palliative surgery, radiation, and chemotherapy can change a patient's ability to speak, chew, salivate, swallow, smell, taste, and/or see and in consequence impair their nutritional situation and induce weight loss. IL-6 levels are higher among malnourished patients with cancer compared with normally nourished patients (38). IL-6 levels have also been shown to be higher among those with obesity and obstructive sleep apnea (OSA).

In the general population, OSA is often associated with obesity and large neck circumference (39), but these conditions may be conspicuously absent in patients with head and neck cancer, who generally have lower body mass index (BMI) than the general population.(40). Airway obstruction in these patients can instead be caused by the tumor physically blocking or compressing the airway (41, 42), stenosis of the upper aerodigestive tract resulting from tumor resection, or reconstruction of a surgical defect (40). Radiotherapy to treat head and neck tumors can also create edema, fibrosis, or alterations in physiology leading to airway obstruction (43). Receiving radiation in the head and neck can also cause severe xerostomia, which can keep people awake at night in and of itself, or lead to nocturnal polyuria, which also disturbs the patient's sleep.

Our prior work has shown that sleep problems are common among patients with head and neck cancer (44). Although there is no evidence of causality, associations have been drawn between sleep and mortality, with patients sleeping either 8 hours or more or 6 hours or less having a significantly higher risk of mortality than those who slept 7 hours per night (45). The association between sleep deprivation and compromised immune response as shown by elevated IL-6 levels has been well documented (46–50).

While the relationship between individual health behaviors and IL-6 have been well documented in specific populations, no studies have looked at the combined effects of these health behaviors on patients with head and neck cancer, who are at risk for poor health behaviors and among whom IL-6 has been shown to be a significant prognostic marker. Hence, the specific aim of this study was to determine the association between health behaviors and serum IL-6 levels among patients with newly diagnosed head and neck cancer, controlling for clinical and demographic characteristics.

Materials and Methods

This was a cross-sectional examination from a prospective, cohort study of patients enrolled in the University of Michigan Head and Neck Cancer (Ann Arbor, MI), Specialized Programs of Research Excellence (SPORE). The primary explanatory variables were smoking, problem drinking, physical activity, BMI, and sleep. The outcome variable was pretreatment serum IL-6 levels. Control variables were cancer site and stage, comorbidities, and demographic variables.

Study population/setting/place

The study population consisted of 869 newly diagnosed patients with head and neck squamous cell carcinoma. Exclusion criteria were: (i) less than 18 years of age; (ii) pregnant; (iii) non-English speaking; (iv) psychiatrically or mentally unstable (such as suicidal ideation, acute psychosis, or dementia); and (v) nonupper aerodigestive tract cancer (such as thyroid or skin cancer). Of those approached, 636 (73%) were eligible and agreed to participate. For this analysis, those with recurrent disease or previously treated head and neck cancer were also excluded ($n = 42$). An additional 144 subjects did not have a pretreatment serum sample available, and another 43 were missing other data, which left a sample size of 407. Human subjects' approval was received from 3 study sites: the University of Michigan Medical Center (Ann Arbor, MI), Veterans Affairs (VA) Ann Arbor Healthcare System (Ann Arbor, MI), and Henry Ford Health System (Detroit, MI). Subjects were recruited into this study between January 2003 and June 2006.

Procedures

Research assistants recruited patients to the study in the waiting rooms of otolaryngology clinics. They obtained signed, informed consent and provided a written survey that had questions on demographics and health behaviors. A medical record audit was also conducted. Pretreatment blood was drawn into coded sterile red-top vacuum tubes.

Measures

Dependent variable—serum IL-6 analysis. Serum samples were kept frozen at −80°C and then thawed shortly before determination of IL-6 levels. Quantitation of serum IL-6 levels was conducted using an ELISA conducted in duplicate using a commercially available ELISA kit (Quantikine Human IL-6 Immunoassay, R&D Systems). Briefly, serum samples from all patients were incubated for 2 hours at room temperature in duplicate (100 μL) on microtiter plates coated with a monoclonal antibody specific for IL-6. Any unbound substances were washed away and an enzyme-linked polyclonal antibody specific for IL-6 was introduced. This was incubated for 2 hours at room temperature and the plates were washed to remove unbound antibody. A substrate solution was added and color development was stopped after 25 minutes at room temperature. A microplate reader was then used to determine colorimetric densities at 570 and 450 nm for each sample. The optical density for each sample was determined by subtracting the readings at 570 nm from the reading at 450 nm. Results were calculated from a standard curve generated by a parametric logistic curve fit and expressed in pg/mL of serum. The test sensitivity as determined by the manufacturer is less than 9.0 pg/mL.

Predictor variables. Smoking status was classified into never smokers, former smokers, and those who were currently smoking (smoked in the last month). Alcohol use was measured with the Alcohol Use Disorders Identification Test (AUDIT); a score of 8 or more on the AUDIT indicates problem drinking (51). The validated Physical Activity Scale for the Elderly (PASE) was used to measure activity (18). Height and weight were used to determine BMI (weight in kilograms divided by the square of height in meters), which was used as a measure of nutritional status. Sleep was assessed using the well-validated, 12-item Medical Outcomes Study (MOS) Sleep Scale; scores ranged from 0 to 100 with lower scores indicating more sleep problems (52–54). The MOS Sleep Scale measures global sleep by asking about the following concepts: time falling asleep, hours of sleep, feel sleep was quiet, feel rested, short of breath, drowsy, trouble falling asleep, awaken during sleep, trouble staying awake, snoring, take naps, and get enough sleep.

Covariates. Tumor sites were classified into 3 groups: (i) larynx; (ii) oro-, hypo, nasopharynx, or unknown primary; and (iii) oral cavity or sinus. Tumor stages were measured using the American Joint Committee on Cancer (AJCC) staging classification system (55) and grouped into stage 0, I, and II versus stage III and IV. Comorbidities were measured using the Adult Comorbidity Evaluation-27 (ACE-27) and grouped into none or mild comorbidities versus moderate or severe comorbidities (56, 57). Standard questions on demographics were asked including age, sex, race, educational level, and marital status. Median household income for the census tract of each subject was found using American Fact Finder data for the 2000 U.S. census, found on the www.census.gov website.

Statistical analysis

Means and frequency distributions were examined for all variables. Similar to other studies that have looked at IL-6 levels (27, 50), as the data was not normally distributed, values for IL-6 were log transformed [$\ln(\text{IL-6} + 2)$] to make the IL-6 variable better meet the assumptions of linear regression. Bivariate associations between IL-6 and the 5 health behavior variables (smoking, problem drinking, physical activity, BMI, and sleep), clinical covariates (cancer site and stage and comorbidities), and demographic variables (age, sex, race marital status, education, and income) were assessed using Student t tests and ANOVA. To determine multivariate associations, smoking, alcohol, physical activity, BMI, sleep, tumor site and stage, comorbidities, and demographics were included in multiple linear regression analysis.

Results

Description of the sample

The description of the sample can be seen in Table 1. About 28% were current smokers and about 57% were former smokers. About 25% screened positive for problem drinking. The mean score for physical activity was 113. About 23% were obese, 36% were overweight, 36% were normal, and only 5% had low BMI. The mean Sleep score was about 66%.

About 22% had cancer of the oral cavity, 52% had cancer of the pharynx, and 26% had cancer of the larynx. Most (64%) had stage IV cancer. About two thirds had none or mild comorbidities. The mean age was 59 years (SD = 11), most were males, White, married, and educated at the high school or lower level. The median household income was $43,078. The median IL-6 level was 13 pg/mL (range, 0–453).

Bivariate predictors of IL-6

Bivariate analyses is shown in Table 2. Current and former smokers were more likely to have higher IL-6 levels than nonsmokers ($P < 0.001$). Persons with problem drinking had significantly higher IL-6 levels than those without ($P < 0.05$). Those with lower physical activity scores had significantly higher IL-6 levels than those with higher scores ($P < 0.001$). A low BMI was significantly associated with higher IL-6 levels ($P < 0.01$). Lower Sleep scores were associated with higher IL-6 levels ($P < 0.001$).

Those with stage III and stage IV cancers had higher levels of IL-6 than those with stage 0, I, or II cancers ($P < 0.01$). Those with moderate/severe comorbidities had significantly higher IL-6 levels than those with no or mild comorbidities ($P < 0.01$). Older persons were more likely to have higher IL-6 levels than younger persons ($P < 0.05$). Those who were not married had higher IL-6 levels than those who were married ($P < 0.05$). Persons with high school or less education had higher levels of IL-6 ($P < 0.01$) than those with some college or more. Persons with lower incomes had higher IL-6 levels and persons with higher incomes ($P < 0.05$). There were no significant associations between IL-6 and cancer site, sex, and race (see Table 2).

Multivariate analysis

Table 3 shows the results of the multivariate regression analysis. Sex was omitted from the multivariate analysis as there were no differences in IL-6 levels in the bivariate analysis. Current ($P < 0.01$) and former tobacco use ($P < 0.01$) and lower Sleep scores ($P < 0.01$) continued to be significantly associated with IL-6 levels, whereas problem drinking, physical activity, and BMI were no longer

Table 1. Baseline demographics and health characteristics of patients with newly diagnosed head and neck cancer ($N = 407$)

	Mean (SD)/ median	Range
Age	58.8 y (10.7)	25–88 y
PASE (103 population norm)	113 (81)	0–473
BMI (28 population norm)	26.7 (5.8)	15.2–55.0
Sleep (72 population norm)	65.8 (21.3)	0–100
Median household income ($41,994 population median per 2000 Census)	$43,078	$15,969–$137,720
Median serum IL-6 Levels	13 pg/mL	0–453
	N	Percentage
Smoking (cigarette, cigar, pipe)		
Current (21% US population)	113	27.8
Former	233	57.2
Never	61	15.0
Alcohol Problem (4%–17% population norm)	102	25.1
BMI		
Obese (BMI > 30; 30.2% Michigan)	95	23.4
Overweight (BMI 25–29; 35.2% Michigan)	145	35.6
Normal (BMI 18.5–24)	145	35.6
Low (BMI < 18.5)	22	5.4
Tumor site		
Oral cavity/sinus	91	22.4
Pharynx (oro, hypo, naso, unknown primary)	209	51.3
Larynx	107	26.3
Tumor stage		
0–I	38	9.3
II	45	11.1
III	64	15.7
IV	260	63.9
ACE-27 comorbidity score		
None	106	26.0
Mild	161	39.6
Moderate	95	23.3
Severe	45	11.1
Sex		
Male	320	78.6
Female	87	21.4
Hispanic or Latino	9	2.2
Race		
White	363	89.2
African American	33	8.1
American Indian/other	11	2.7
Marital status		
Married	250	61.4
Not married	157	38.6
Educational level		
High school or less	209	51.3
Less than 4 years of college	130	32.0
Bachelors degree or more	68	16.7

(Continued on the following column)

Table 1. Baseline demographics and health characteristics of patients with newly diagnosed head and neck cancer ($N = 407$) (Cont'd)

significant. Being older ($P < 0.05$) and higher tumor stage ($P < 0.001$) predicted higher IL-6 levels. The association of comorbidities with IL-6 scores was marginally significant in the expected direction ($P = 0.052$). Cancer site, race, education, and income were not significantly associated with IL-6 levels.

Discussion

This is the first study that we know of that has shown the potential contribution of 5 health behaviors to elevated IL-6 levels among patients with head and neck cancer. As has been shown in other studies, smoking was highly predictive of increased IL-6 levels and about 28% of the sample was current smokers compared with about 19% in the Michigan population (58). Even former smokers had increased IL-6 levels and some inflammatory mediators have been shown to be present 10 to 20 years after quitting (59). Intensive smoking cessation interventions are needed among the current smokers. Effective pharmaceutical interventions are available to assist in treating smokers including nicotine replacement therapy, bupropion, and varenicline. Behavioral interventions, which have been shown to be beneficial (60, 61) are also available including referral to 1-800-QUIT-NOW state supported quit support phone lines offered in 48 states.

Decreased sleep was also a significant predictor of high IL-6 levels in the multivariate analysis and Sleep scores were 6 points lower than population means (score, 0–100). A published study by our team showed that sleep disorders are common among patients with head and neck cancer (62). Both behavioral and pharmacologic interventions are available to treat sleep disorders (63, 64). However, before initiating pharmacologic therapy, the underlying causes of the sleep disturbance need to be evaluated. Pain, xerostomia, and depression as well as smoking and problem drinking have been associated with decreased sleep among patients with head and neck cancer (44). Sleep apnea related to obesity or airway obstruction resulting from complications of head and neck cancer should also be evaluated (40–42).

While significant in bivariate analyses, problem drinking was no longer significantly associated with IL-6 on multivariate analysis. Other articles that showed an association between problem drinking and IL-6 were not

Table 2. Bivariate associations with log serum IL-6 ($N = 407$)

Variable	Mean IL-6	*P* value
Smoking		<**0.001**
Current	2.85	
Former	2.69	
Never	2.05	
Alcohol problem		**0.027**
Yes	2.85	
No	2.56	
PASE (10 points)[a]	−0.027	<**0.001**
Lowest quartile BMI (<22.9)		**0.002**
Yes	2.93	
No	2.53	
Sleep (10 points)[a]	−0.102	<**0.001**
Cancer site		0.374
Pharynx	2.56	
Oral/sinus	2.76	
Larynx	2.67	
Tumor stage		**0.013**
0	2.12	
I	2.17	
II	2.43	
III	2.50	
IV	2.77	
Comorbidity score		**0.009**
None	2.46	
Mild	2.53	
Moderate	2.83	
Severe	3.00	
Age (in decades)[a]	0.122	**0.020**
Sex		0.703
Male	2.62	
Female	2.68	
Race		**0.189**
White non-Hispanic	2.61	
Non-White/Hispanic	2.83	
Marital status		**0.048**
Married	2.55	
Not Married	2.78	
Education		**0.014**
High school or less	2.77	
Some college or more	2.49	
Income ($10,000)[a]	−0.063	**0.042**

NOTE: Bolded *p*-values indicate statistically significant values.
[a]ANOVA.

Table 3. Multivariate regressions health behavior and log serum IL-6 ($R^2 = 0.163$) $N = 407$

Variable	Parameter estimate	SE	*P* value
Current tobacco	0.497	0.188	**0.009**
Former tobacco	0.448	0.163	**0.006**
Alcohol problem	0.186	0.131	0.157
PASE	−0.007	0.007	0.357
Lowest quartile BMI	0.201	0.128	0.118
Sleep	−0.071	0.027	**0.010**
Larynx site	−0.141	0.159	0.374
Pharynx site	−0.247	0.146	0.093
Tumor stage	0.222	0.055	<**0.001**
ACE comorbidity score	0.117	0.060	0.052
Age in decades	0.118	0.056	**0.035**
Non-White	0.049	0.165	0.768
Married	−0.042	0.114	0.712
High school or less	0.096	0.111	0.386
Median household income ($10,000)	0.012	0.031	0.700

NOTE: Bolded *p*-values indicate statistically significant values.

necessarily conducted among patients with cancer and may not have controlled for all of the covariates included in this analysis (such as smoking, which is highly correlated with problem drinking; refs. 65, 66). Yet it is hard to dispute the impaired immune function among heavy drinkers (24). Problem drinking rates were higher than population norms (25% in our population compared with about 4.7% to 17.2% in other studies; refs. 67–69). Brief clinic interventions (60, 70), referral for inpatient treatment, and referral to Alcoholics Anonymous may be needed for problem drinkers.

Physical activity scores (113) were slightly higher than population norms (103; ref. 18). Moreover, mean BMI (26.7) and obesity rates (23.5%) were lower than population norms (28% and 30.2%, respectively; ref. 71). While both physical activity and BMI were significant in the bivariate analysis, they were also no longer significant in the multivariate analysis, suggesting that other predictors had a stronger influence on IL-6 levels. Nonetheless, the benefits of a diet high in fruits and vegetables and moderate exercise cannot be ignored.

While tumor site was not associated with IL-6 levels, similar to other studies (3–6), tumor stage was associated and tumor cells have been known to secrete IL-6 (1). A higher comorbidity score was marginally associated with IL-6 levels suggesting that comorbidities may influence the inflammatory process. As has been shown in other studies (72), age was associated with higher IL-6 levels. While significant in the bivariate analyses, educational level and income were no longer significant when controlling for other factors in the multivariate analyses.

The source of IL-6 in cancer patients' serum has been shown predominately to emanate from the tumor itself and tumor cells have been known to proliferate in an environment rich in IL-6 (7, 8). Importantly, we have recently shown that IL-6 production by normal endothelial cells in the tumor microenvironment is critical and essential for tumor invasion and stem cell proliferation (73). Furthermore, monocytes in patients with head and neck cancer have also been shown to secrete higher levels than monocytes from normal individuals (74). Smoking, problem drinking, sedentary life style, diets low in seeds, nuts, vegetables, fruits and whole grains, and poor sleep have all been shown to be related to an increase in monocytes (75–79) and may be responsible for the activation of monocytes among patients with head and neck cancer. It raises an interesting hypothesis that by changing health behaviors, IL-6 secretion from monocytes could be reduced in the tumor microenvironment thereby inhibiting tumor proliferation.

Limitations of the study

The study was cross-sectional, hence it is possible the correlations between the health behaviors and IL-6 may be bidirectional. Moreover, the study did not look at changes in health behaviors over time. BMI was used as a proxy for nutritional status. While the smaller study found the mean IL-6 of healthy controls to be 6.0 pg/mL (range, 0–52), no normal controls were available for comparison in this study. The MOS Sleep scale is a global measure of sleep disturbances and does not identify the etiology of the sleep problems. Future research is needed to determine if treating health behaviors can modify IL-6 levels, decrease recurrence, and increase survival among patients with head and neck cancer.

Conclusion

DNA damage resulting from chronic inflammation has been shown to affect several critical pathways regulating cellular homeostasis (e.g., cell-cycle regulation, apoptosis, DNA repair; ref. 80). The elevated IL-6 levels among patients with head and neck cancer are likely due to multiple causes many of which are difficult to control, including the fact that head and neck cancer cells themselves secrete IL-6 (1) and the inflammatory process may be further attenuated by subsequent surgery, radiation, and chemotherapy. However, treating modifiable poor health behaviors that increase IL-6 levels may be one way to decrease the inflammatory load and add prognostic value to the treatment of patients with head and neck cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.A. Duffy, T. Teknos, K.E. Fowler, G.T. Wolf, J.E. Terrell
Development of methodology: S.A. Duffy, K.E. Fowler, M. Islam, J.E. Terrell
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.A. Duffy, T. Teknos, K.E. Fowler, G.T. Wolf, S. McLean, T.A. Ghanem
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.A. Duffy, J.M.G. Taylor, K.E. Fowler, G.T. Wolf
Writing, review, and/or revision of the manuscript: S.A. Duffy, T. Teknos, J.M.G. Taylor, K.E. Fowler, G.T. Wolf, T.A. Ghanem, J.E. Terrell
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.A. Duffy, K.E. Fowler, G.T. Wolf
Study supervision: G.T. Wolf, J.E. Terrell

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