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Pain. Author manuscript; available in PMC 2009 November 30.

Published in final edited form as:
Pain. 2008 November 30; 140(2): 323–331. doi:10.1016/j.pain.2008.09.004.

Metallic Taste Phantom Predicts Oral Pain among 5-year Survivors of Head and Neck Cancer

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Abstract

Chronic pain following cancer-related treatment is emerging as a major concern. Heretofore, the pain level among 5-year survivors of head and neck cancer has received limited attention. This study proposes a predictive model for understanding factors associated with elevated levels of chronic oral pain. Cancer survivors were drawn from a pool of 5-year survivors. A listed sample matched on sex, age, and zip code was purchased and served as a comparison group. Telephone interviews were conducted by a professional call center. Oral pain levels and the presence of metallic taste phantoms were significantly higher in the cancer survivor group than among the comparison group. The prevalence of chronic oral pain among the 5-year survivors was 43% compared to 13% for the comparison group. Hierarchical linear regression showed that among the 5-year survivors, the predictive model for spontaneous pain accounted for 24% of the variance, and for function-related pain the model accounted for 34% of the variance, with the presence of a phantom metallic taste making a significant independent contribution in both models. In the function-related pain model, depression and level of oral function quality of life (QOL) made significant independent contributions. The presence of oral pain is a significant problem among head and neck cancer survivors. The presence of metallic phantoms is an important new piece of evidence suggesting neural damage following cancer-directed treatment. Routine assessment of oral pain levels could improve current analgesic approaches among head and neck cancer survivors.

1. Introduction

For older adults who beat the odds and survive head and neck cancer [1], the likelihood of experiencing treatment-related chronic pain approaches 40% in the first year and at least 15% at 5 years [9,30,43]. Burton and colleagues identified sources of ongoing pain as multifactorial concluding that in most cancer survivors, pain is a result of the cancer treatment [8]. Treatment for head and neck cancer involves surgery, radiation, and chemotherapy treatments. These therapies cause side effects including facial deformity, taste changes, speech and swallowing difficulties, and chronic pain. Radiation-induced neural damage and pain may surface decades

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Conflict of interest statement
We declare that we have no conflict of interest.

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after radiotherapy completion, making identification of the pain source difficult. Postsurgical pain syndromes come in many forms, ranging from loss of sensation to loss of function. Consequent deteriorated functional status, inability to cope and depressive symptomatology are all associated with poor outcomes [26,44]. Among both cancer and non-cancer patients an association between chronic pain and depression has frequently been reported [13–15].

Heretofore, pain has received limited attention in the study of long-term survivors of head and neck cancer with the exception of work by Connelly and colleagues [9,30]. To understand the significance of chronic pain in this population, it is worth noting that of all oral diseases, head and neck cancer produces the greatest morbidity and mortality rates. Survival from head and neck cancer is one of the lowest among all malignancies, including other more commonly occurring cancers such as prostate, breast, colon, rectum and skin; the 5-year survival rate for head and neck cancer has not improved in recent decades and remains about 58% [1,42]. In the U.S., there are more than 7,550 deaths per year from head and neck cancer vs. 3,670 for cervical cancer [1]. In short, for those who survive head and neck cancer, the prospect of years of chronic pain must be devastating.

1.1. Radiotherapy

Radiotherapy used as an adjunctive therapy in head and neck cancer increases the incidence of chronic pain [8]. Radiation toxicity is divided into early and late effects. Early or acute effects including nausea, skin reactions, diarrhea, and neutropenia are self-limited. Late effects including connective tissue fibrosis, neural damage, secondary malignancies, and pain can occur long after completion of radiotherapy. Neural damage from radiotherapy is well documented, as is the presence of taste phantoms (taste sensations in the absence of stimulation), particularly metallic [23,33]. Phantom taste is believed to be a proxy for oral structure damage (e.g., neural). We chose to assess metallic taste phantom because we reasoned that it would be most recognizable and salient to survivors. Metallic taste phantoms are associated with taste damage produced by conditions ranging from tonsillectomy to third-molar extraction [10,18,46,48]. Burning mouth is associated with the presence of metallic taste phantoms, suggesting a linkage between oral pain and taste phantoms [22]. What has not been considered are associations between the presence of metallic taste phantoms and the presence of oral pain among long-term survivors of head and neck cancer.

2. Materials and methods

The purpose of this investigation was to contrast oral pain levels of a matched non-cancer comparison group to 5-year survivors of head and neck cancer and to test predictive models of oral pain among 5-year survivors. More specifically, we predicted that evidence of taste damage would be greater among the 5-year cancer survivors compared to the non-cancer group. Regression analysis to determine whether taste damage showed predictive utility above and beyond the previously reported associations including a) function and pain level and b) depression and pain level was conducted.

The study protocol conformed to the ethical guidelines of The 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the University of Florida. A professional survey research center conducted the 20-minute telephone interviews. Participants received a $25 gift card.

2.1. Selecting survivors

The survivors were drawn from 378 individuals treated for head and neck cancer at the institution’s radiation oncology clinic who had survived 5 years (plus or minus 3 months since completing treatment). Inclusion criteria included squamous cell carcinoma of the head and

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neck including oral cavity, oral pharynx (oropharynx), or larynx. (The final group of survivors included only those diagnosed with squamous cell carcinoma of the oropharynx, hypopharynx, and larynx.)

Eligible survivors were based on those alive at last contact from the Department of Radiation Oncology and confirmed through the Tumor Registry of Shands at the University of Florida. After verification of status (dead or alive) and confirmation of address and telephone number, individuals were sent a letter describing the study, which indicated that researchers would be calling them in the near future. A toll-free telephone number was provided for those who did not wish to participate in the study. In response to the letter, seven survivors called the toll-free number, requesting not to be called. After multiple attempts to obtain a corrected telephone number, six names had to be dropped from the list. When the calls were made by the survey research center, 20 individuals refused to participate and 83 either repeatedly requested we call back or the telephone call was never answered. Six individuals had died and 14 were either too mentally or physically compromised to participate in the survey. Four partially completed the survey but were never available to finish the questionnaire. All but six telephone numbers from the original 378 survivors were used to complete the 100 surveys (100/372=27%).

2.2. Selecting listed sample

A commercial list was purchased that matched the survivors by age (within 5 years), sex, and geographical location. For each survivor, 10 people of the same sex and age (+/− 5 years) were selected from the survivors' zip code. Numbers were chosen randomly from this list of 10 until one individual completed the survey. Each participant was screened to exclude those with a history of cancer. Of the original list of 980 telephone numbers, 544 numbers were used to complete 101 surveys.

2.3. Measures

Measures were drawn from published methodology and instruments including co-morbidities as measured by the Seattle Index of Co-morbidities [12], tumor staging and location [47], measures of function-based quality of life [41], and oral pain [9]. Additional measures of depression [24], anxiety [16], and tobacco use [2] were collected.

2.4. Data reduction

Using previously published methodologies, the University of California San Francisco (UCSF) Oral Cancer Pain Questionnaire was scored to establish two subscales: spontaneous pain and function-related pain [9,30]. Scaling was modified slightly for ease in administering the questionnaire to older participants in a telephone-based survey. A 10-point scale was used, with 0="no pain" and 10="the most intense pain sensation imaginable."

For purposes of this investigation, the Functional Assessment of Cancer Therapy – Head and Neck scale (FACT H&N) was modified to exclude the single item related to pain; this was done to eliminate the potential confound of predicting pain from a scale that included a question about pain. Our goal was to include those items related to oral functioning and potential damage to the oral structure that might be influenced by cancer-directed treatment. The scale was designed to assess disease and treatment-related experiences of head and neck cancer patients [36–39]. The content of the items, however, is related to function that can be influenced by a number of health conditions of older persons (e.g., "My mouth is dry" and "trouble breathing" can reflect medication effects) and were judged suitable for use with both the 5-year survivor group and the age and sex-matched comparison group. According to published methodology, three items were reversed prior to calculating the final 9-item sum, with higher scores equivalent to higher function/less impairment (range 0–36).

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The Seattle Index of Co-morbidities (SIC) is an index using age and smoking status plus doctor-confirmed presence of chronic condition indicators. SIC was developed to predict clinical events, was validated against 2-year mortality and hospital admission [12], and has been used to assess health expenditures[40]. In this study, the SIC was used to adjust for the potential confounding effects of age, heart disease, lung disease, diabetes mellitus, pneumonia, stroke, and current and past smoking. Using published scoring procedures, higher scores (range 2–17) indicate greater co-morbidities [12].

The CESD is a 20-item scale of depressive symptoms, on which patients rate the frequency of depressive symptoms in relation to how they felt during the past week. Previous studies have shown that the scale has good predictive validity among patients in chronic pain [17].

A single yes or no item, “Do you ever have a metallic taste in your mouth for no apparent reason?” was used to capture potential damage to the taste mechanism associated with cancer-directed treatment. Lower score indicates greater damage (1=yes and 2=no). Although other questions about changes in taste in the past 5 years were asked of both cancer survivors and the comparison group, the presence of a metallic phantom was selected as most likely to capture taste dysfunction. Patients can experience taste phantoms that are sweet, salty, sour or bitter; however, metallic appears to be the most common. In addition, metallic tastes are not commonly experienced and so are very salient experiences to patients.

Treatment data such as location of tumor, stage of tumor, and type of treatment were abstracted from the medical record using well accepted criteria for classification [19,20,25,47].

2.5. Analytic Strategy

Data analysis used the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) version 15.0 for PC. Descriptive statistics are presented as percentages, means, and standard deviation. To establish the best set of predictor variables prior research was reviewed and Pearson correlation analyses were conducted on key baseline and study variables. Finally, hierarchical regression analysis was used to determine potential predictors of pain using subscales of the UCSF Oral Cancer Pain Questionnaire among the 5-year survivor group. Ancillary analyses included discriminant function and chi square analysis.

3. Results

3.1. Characteristics

One hundred cancer survivors and 101 matched controls (comparison group) are included in this report. Characteristics of these study participants are shown in Table 1. There were equivalent numbers of men and women in both study groups, the mean age (standard deviation) of the survivor group was 64.9 (10.9) years, and the comparison group was 64.1 (10.7) years. Education levels were comparable across groups. The proportion of survivors and the comparison group who were former smokers was similar (48.9% versus 46.5%, respectively); however, the proportion who never smoked was higher among the comparison group (43.6%) than among survivors (35.1%) (chi square=8.58, $p<.05$). There were no significant differences among the never smokers, former smokers, and current smokers on the pain score subscales ($p>.2$), the key dependent variables in this report, nor were there significant associations between smoking status and the presence of metallic taste phantoms (chi square<1, $p>.9$). As such, smoking status was excluded from subsequent analyses.

Table 2 shows the means, standard deviations, and results of t-test analyses for the survivors and comparison group on key variables. The 5-year survivor group reported significantly lower function scores on the modified FACT H&N module, which assesses oral health as well as the presence of a metallic taste, which specifically relates to damage to taste. The cancer survivor

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group had significantly higher scores than the comparison group on the spontaneous pain and function related pain questionnaire subscales, the key dependent variables in this investigation. There were no significant differences between the two groups on depression, trait anxiety, or the co-morbidities scales although there was a non-significant trend for greater depression and anxiety among the 5-year survivor group compared to the non-cancer comparison group.

Results of initial analyses yielded significant correlations for pain and selected psychosocial variables and function/dysfunction measures and the modified FACT H&N module (Table 3). Sex, tumor stage at diagnosis, tumor site, and co-morbidities were not significantly associated with the pain scores. Nonetheless, we forced these variables into the first step of the hierarchical regression model to control for potential differences based on disease at diagnosis and general health conditions. Sixty-nine percent of the survivors had received only radiation, 15% had received radiation and chemotherapy, 13% had received radiation and surgery, and 3% had received radiation, chemotherapy, and surgery. Using established categories [19], 74% of the tumors were classified as oropharynx (base of tongue, soft palate, uvula, tonsilar region, lateral or posterior oropharyngeal wall), 7% hypopharynx (pyriform sinuses, postcricoid area, lateral or posterior hypopharyngeal wall), and 19% larynx (supraglottis, glottis, or subglottis). There were no significant differences among the individuals with tumors in the three locations on the FACT H&N function scale [37], spontaneous, or function-related pain [9]. In addition, there were no significant differences among the three locations on the presence of a metallic taste in the mouth (chi square<.8).

Our next goal was to test predictive models for the two subscales on oral cancer related pain among the 100 head and neck cancer survivors.

3.2. Regression analysis

Hierarchical linear regression analysis was conducted to examine the combined and unique contribution of psychosocial, function, damage, and control variables to two subscales, spontaneous pain and function-related pain, as measured by the USCF Oral Cancer Pain Scale, among the 5-year cancer survivors. Location of tumor and type of treatment were entered as dummy coded variables using oropharynx as the referent for location and radiation-only as referent for type of treatment.

3.2.1. Spontaneous pain level—The analysis was conducted in three steps and the results of the final model are shown in Table 4. The first step entered sex, location of tumor (dummy variables hypopharynx and larynx using oropharynx as the referent), and early (Stage I and II) versus advanced (Stage III and IV) and co-morbidities. In the same step, the type of treatments (dummy variables: 1) radiation + chemotherapy, 2) radiation + surgery, 3) radiation + chemotherapy + surgery with radiation-only as the referent) were also entered as control variables. Earlier analysis had shown that depression and anxiety were highly correlated (r=. 84, p<.0001). , and for that reason depression was used in Step 2 of the modeling analysis with the modified FACT H&N scale which assesses function-related quality of life. The presence or absence of a metallic taste for no apparent reason was entered in the final step of the analysis.

The first step of the analysis accounted for 7% of the variance in the spontaneous pain scale. The second step added depression as a measure of psychosocial well being and function-related quality of life to the predictive model and accounted for a significant change in the variance (12%, p≤.01). The final step added the presence of a metallic taste which accounted for an additional 6% of the variance (p≤.01). The presence or absence of a metallic taste and function-related quality of life were both significant independent predictors of spontaneous pain in this final step; overall the model accounted for 24% of the variance.

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3,2.2. Function-related pain level—Again the linear hierarchical analysis was conducted in three steps and the results of the final model are shown in Table 5. In the first step, sex, location of tumor (oropharynx as the referent location as in above analysis), tumor stage (Stages I and II versus Stages III and IV), and co-morbidities were entered as control variables, and type of treatment, with radiation-only as the referent. Depression and the modified FACT H&N were entered in Step 2 of the modeling analysis. The presence or absence of a metallic taste for no apparent reason was entered in the final step. The first step of the analysis accounted for 9% of the variance in the pain scale. The second step added depression as a measure of psychosocial well being and function-related quality of life to the predictive model and accounted for a significant change in the variance (21%, $p<.01$). The final step added the presence of a metallic taste phantom (4%, $p<.05$). In the final model, depression, function-related quality of life, and the presence or absence of a metallic taste were significant independent predictors. Overall the model accounted for 34% of the variance in the function-related pain subscale.

Discriminant analysis was used to further confirm the relationship between the risk factors identified in the hierarchical regression analysis and pain report by classifying the survivor group into two categories, pain present or no pain using the dichotomized intensity item. The following variables were entered into the discriminant function: sex of subject, early versus late stage diagnosis, tumor site, co-morbidities scale, depression, presence of metallic taste for no apparent reason, modified FACT H&N module. Variables that failed to achieve a p-value of .15 or less were eliminated from the model. Subjects who did not have complete data were excluded from the analysis. The overall model correctly classified 76% of the survivors with pain and 89% of the survivors without pain. As before, depression, presence of metallic taste and modified FACT H&N scale were significant independent variables ($F=21.9$, $p<.0001$; $F=6.7$, $p<.05$; and $F=26.9$, $p<.0001$, respectively).

To expand our understanding of the association between the presence of a metallic taste and pain level, chi square analysis using dichotomized pain intensity and presence or absence of metallic taste was conducted. Results showed that 62% of those with a metallic taste present also reported pain, compared to 34% of those who reported no metallic taste (chi square=6.65, $p<.05$), further increasing our confidence in the association identified in this study.

4. Discussion

This is one of the first studies to assess spontaneous and function-related pain level among 5-year survivors of oral and pharyngeal cancer and compare pain levels to those of an age-, sex-, and geographic region-matched comparison group. Pain report was significantly higher in the cancer survivor group than among the comparison group, as was the presence of a metallic taste. Not surprisingly, the survivor group reported lower scores related to function (e.g., eating, dry mouth, or breathing) than the comparison. Hierarchical linear regression showed that among the 5-year survivors, the predictive model accounted for 24% of the variance in spontaneous pain and for 34% of the variance in function-related pain, with the presence of a metallic taste making a significant independent contribution in both models. In the function-related pain model, depression and level of oral function quality of life also made significant independent contributions.

We found that 43% of the 5-year survivors surveyed in this study reported pain. This compares to 15% at 5 years reported by Burton et al. [8]. That difference may lie in treatment differences in the patient groups. Every participant (100%) in our survivor group had received radiotherapy, whereas the percentage receiving radiotherapy in the study by Burton and colleagues may have been less. Connelly and Schmidt studied pain levels in newly diagnosed and treated oral cancer patients [9]; similar to our findings, they found little association between

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stage (e.g., tumor size) and pain levels. Although our findings and those of others [29] are based on assessing pain at different time points in the lives of the cancer patient, it supports our contention that the presence of pain is a serious concern to those diagnosed with and surviving head and neck cancer.

Our findings suggest that subclinical levels of depression [28] may play different roles in spontaneous pain and function-related pain. Depression was a significant independent predictor of function-related pain but not spontaneous pain. It seems reasonable that function-related pain may produce greater interference with daily activities and may reduce their enjoyment, which may produce depression. It is also possible that those with greater depression have more pain, resulting in lower function. This latter explanation seems less likely because depression was not a significant independent predictor of spontaneous pain. We acknowledge, however, that our scales and design do not allow for causal conclusions.

One of the most interesting outcomes of this study was the association between pain and the presence of a metallic phantom taste. Chi square analysis indicated that pain was associated with the presence of the metallic taste phantom. Localized damage to taste has been hypothesized to produce taste phantoms because of inhibitory interactions among areas in the central nervous system which receive input from the cranial nerves mediating taste. Interruption of input from one taste nerve releases its inhibition thus intensifying neural signals from other taste nerves [34] and producing taste phantoms [5,48]. The taste phantoms associated with taste damage can be any of the “four basic tastes” (sweet, salty, sour, bitter) or combinations of these. In addition, the phantom is often described as “metallic.” Metallic taste is produced by a variety of sources in addition to the phantoms described above: particular taste stimuli (e.g., ferrous sulfate), electrical stimulation of the tongue [32], direct stimulation of the chorda tympani taste nerve [10], damage to the chorda tympani during stapedectomy [7] , or anesthesia of the chorda tympani [48]. As noted above, metallic phantoms are also associated with a variety of conditions in which taste is damaged, including radiation therapy. Metallic perceptions may also include non-taste stimulation; olfactory sensations appear to play a part in some metallic sensations [27,31]. Because metallic sensations do not play important roles in daily taste experience, metallic phantoms are easily noticed by patients and offer a good index of damage to the taste system. Central inhibitory interactions also appear to occur between taste and oral pain [45]; damage to taste releases that inhibition leading to intensification of oral pain and oral pain phantoms [21].

Given the location of the tumors in this survivor group, it is highly plausible that radiotherapy injured either or both of the cranial nerves VII or IX. Thus, the presence of a metallic taste may represent a marker of damage from cancer-directed treatment. Pain among head and neck survivors may reflect greater treatment-related damage. An alternative explanation, supported by our laboratory studies, is that the release of inhibition resulting in taste phantoms may be associated with release of pain inhibition [45].

Confirmatory discriminant analysis using the dichotomized intensity item yielded similar results to the hierarchical linear regression analysis. In addition, conducting the analysis with this dichotomous variable mitigated a potential scaling error. Comparisons across groups made with labeled scales are valid only when scale labels denote the same perceived intensity, on average, to all groups [4,11]. For example, the visual analogue scales in the UCSF Oral Cancer Pain Scale are labeled from “No pain” to “The most intense pain sensation imaginable.” For valid comparisons, “The most intense pain sensation imaginable” would have to denote the same pain intensity, on average, to cancer patients and controls. This might not be the case if the scale labels used with the UCSF scale do not denote the same intensity experiences to cancer patients and controls (a discussion of this error is elucidated in [3]. It is of note that the items from the UCSF Oral Cancer Pain Scale ask about the effect of eating, drinking, or talking

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on oral sensation (e.g., sharp or ache). Previous research has shown that eating is associated with pain suppression across the age span and food types [6,35,49]. We are unaware of any such published results showing a similar pain inhibition in the presence of talking. Thus it is possible that these seemingly similar activities (talking and eating) may have opposite effects among cancer survivors, one causing pain through movement and touching of the tissue and the other reducing pain. This potential confound raised our concern and additional confirmatory analysis was conducted. We dichotomized the single item intensity of pain (with no eating, drinking, or talking) into pain present or not present categories; our reasoning was that this item would minimize the potential confound and be a conservative test for the predictive utility of our model. It is probable that using the conjunction "or" in the UCSF scale lessens the likelihood of misunderstanding among respondents in answering the items with eating, drinking, or speaking and most of the effect is being driven by the act of talking. Although we still believe that including the effect of eating and speaking in the same item may be problematic, our results show that the scale is probably robust against this potential confound. In addition, the similarity of results using the UCSF scale as well as the dichotomized intensity item suggests that the scale labels denoted similar pain intensities for both the cancer patients and controls.

More than half of the sample of 5-year survivors (64%) were diagnosed in earlier stages of tumor development. The 5-year survival rate for head and neck cancer is less than 60%, suggesting that this study group who survived for 5 years may not be representative of all individuals diagnosed with squamous cell carcinoma of the head and neck. In addition the 27% response rate may have yielded a 'healthy survivor effect' the result of which might be an underestimation of pain levels among a more representative sample. It is also possible that those who survived for the 5 years were diagnosed at an earlier stage. As such, our results may underestimate the amount of damage resulting from cancer-directed treatment had we conducted this study sooner after treatment. On the other hand, it is possible that neural damage from radiation treatment may not manifest until later, regardless of the stage of the tumor.

Our data show that chronic pain is a significant issue among survivors of head and neck cancer, and greater than previously reported. The prevalence of chronic oral pain among the 5-year survivors was 43%, compared to 13% of an age-, sex-, and region-matched comparison group. Routine assessment of pain levels could improve current analgesic approaches among long-term survivors. The presence of taste phantoms, particularly metallic, may provide important new evidence about the nature of the late effects from radiation treatment and should also be routinely assessed.

5. Conclusion

This is one of the first studies of 5-year survivors of head and neck cancer to attempt to build a predictive model of chronic oral pain. Even after controlling for depression and function related quality of life, the presence of metallic taste significantly contributed to the level of both function related pain and spontaneous pain. We conclude that the presence of metallic phantoms is an important new piece of evidence about neural damage following cancer-directed treatment and routine assessment of taste phantoms would aid understanding of late effects of cancer treatment.

Acknowledgement

This research was funded by NCI grant CA111593 awarded to H. Logan.

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Table 1

Selected characteristics of study participants

	5-year Survivor Group (n=100		Non-Cancer Comparison Group(n=101)	
	n	**%**	**n**	**%**
Sex				
Male	72	72.0	72	71.3
Female	28	28.0	29	28.7
Age, 15-year increments* (y)				
32–45	5	5.0	5	5.0
46–61	36	36.0	38	37.6
62–77	47	47.0	51	50.5
78–90	12	12.0	7	6.9
Race*				
White+	92	92.0	93	92.1
Other racial groups**	8	8.0	8	7.9
Education*				
Less than high school diploma	7	7.1	11	10.9
High school diploma or GED†	21	21.2	22	21.8
Some college	35	35.4	36	35.6
Bachelor's degree or higher	36	36.4	32	35.6
Smoking Status* (Chi Square 8.58 p=. 035)				
Current	15	16.0	10	9.9
Former	46	48.9	47	46.5
Never	33	35.1	44	43.6

*Categories may not sum to 100% due to missing data

†GED = general educational development diploma

+White 5 year survivor group was composed of 3 Hispanic and 89 Non Hispanic Whites; non-cancer comparison group 1 Hispanic and 100 Non Hispanic Whites

**Other category was composed of 3 Blacks, 2 Asians, 3 American Indians; non-cancer comparison group was composed of 4 blacks 2 Asians, 2 American Indians.

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Table 2

Comparisons between study groups on key variables

	5-year Survivors (n=100)		Comparison Group (n=101)		Analysis	
Construct	**Mean**	**SD**	**Mean**	**SD**	**T test**	**p-value**
Depression (CES-D)	12.6	11.3	10.0	8.6	1.8	.07
Trait Anxiety	34.2	11.6	31.4	10.2	1.8	.08
Seattle Co-morbidities	7.5	3.5	7.3	3.3	.4	.70
Modified FACT H&N module[+]	22.7	7.8	30.8	4.9	8.7	<.0001
Presence of Metallic Taste[*]	1.7	.46	1.92	.27	4.0	<.0001
Spontaneous pain subscale of (SCFOCPQ)[++]	4.5	6.4	1.1	3.9	4.6	<.0001
Function-related pain subscale of (SCFOCPQ)[++]	5.3	7.1	1.2	4.2	5.0	<.0001

[+] Function- based Quality of Life (modified FACT-Head and Neck Module) modified scale does not include item related to pain level

[*] lower score indicate presence of metallic taste

[++] University of California San Francisco Oral Cancer Pain Questionnaire

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Table 3

Correlations* among key study variables (cancer survivors, n=100)

	Sex	Early versus Late Stage tumor	Tumor site	Co-morbidities	Depression (CES-D)	Trait anxiety	Presence of metallic taste	Function-based Quality of Life (modified FACT-H&N)
Spontaneous pain subscale+	.16	<.1	<.1	<.1	.33**	.28**	−.28**	−.31**
Function-related subscale +	.15	<.1	.13	<.1	.43	.39	−.26	−.40

*Pearson correlation coefficients

**p<.01

+UCSF oral cancer pain scale

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Table 4

Result of the hierarchical regression analysis testing regression model[a] predicting spontaneous pain level

	Final Model		
	β	p-value	Cumulative R^2
Sex of Subject	.096	.3	
Early versus Late Stage	.082	.4	
Treatment location[+]			
Hypopharynx Only	−.046	.6	
Larynx Only	.026	.8	
Co-morbidities (SIC)	−.093	.4	
Treatment Type[++]			
Radiation & Chemotherapy	−.192	.09	
Radiation & Surgery	−.050	.6	
Radiation, Chemotherapy & Surgery	−.091	.3	
Depression (CES-D)	.165	.1	
Function-based Quality of Life (modified FACT-Head and Neck Module)	−.220	.05	
Presence of metallic taste	−.244	.01	
			24%

[a] Using enter regression procedure in 3 steps

CES-D = Center for Epidemiological Studies Depression Scale SIC = Seattle Index of Co-morbidities

[+] Oropharynx is referent location

[++] Radiation-only treatment is referent group

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Table 5

Result of the hierarchical regression analysis testing regression model[a] function-related pain level

	Final Model β	p-value	Cumulative R^2
Sex of Subject	.091	.3	
Early versus Late Stage	.062	.5	
Treatment location[+]			
Hypopharynx	−.011	.9	
Larynx	.071	.5	
Co-morbidities (SIC)	−.164	.1	
Treatment Type[++]			
Radiation & Chemotherapy	−.179	.09	
Radiation & Surgery	−.065	.4	
Radiation, Chemotherapy & Surgery	−.114	.2	
Depression (CES-D)	.250	.02	
Function-based Quality of Life (modified FACT-Head and Neck Module)	−.286	<.01	
Presence of metallic taste	−.209	<.05	
			34%

[a] Using enter regression procedure in 3 steps

[+] Oropharynx is referent location

[++] Radiation-only treatment is referent group