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ASSOCIATIONS BETWEEN PERCEIVED STRESS AND CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY AND OTOXICITY IN ADULT CANCER SURVIVORS

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Abstract

Context—The most common adverse effects from neurotoxic chemotherapy are chemotherapy-induced neuropathy (CIPN), hearing loss, and tinnitus. While associations between perceived stress and persistent pain, hearing loss, and tinnitus are documented, no studies have examined these associations in cancer survivors who received neurotoxic chemotherapy.

Objectives—In this cross-sectional study, we evaluated for associations between perceived stress and the occurrence of CIPN, hearing loss, and tinnitus, in 623 adult cancer survivors who received platinum and/or taxane compounds.

Methods—Survivors completed self-report measures of hearing loss, tinnitus, and perceived stress (i.e., Impact of Events Scale-Revised (IES-R)). Separate logistic regression analyses were done for each neurotoxicity to evaluate whether each of the IES-R subscale (i.e., intrusion, avoidance, hyperarousal) and total scores made a significant independent contribution to neurotoxicity group membership.

Results—Of the 623 survivors in this study, 68.4% had CIPN, 34.5% reported hearing loss, and 31.0% reported tinnitus. Older age, higher body mass index, poorer functional status, being born prematurely, cancer diagnosis, and higher intrusion (p=.013), hyperarousal (p=.014), and total (p=.047) IES-R scores were associated with CIPN. Older age, being male, poorer functional status, a

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worse comorbidity profile, and a higher IES-R hyperarousal (p=.007) score were associated with hearing loss. Being male, having less education, a worse comorbidity profile, and a higher IES-R hyperarousal (p=.029) score were associated with tinnitus.

Conclusion—These findings suggest that increased levels of perceived stress are associated with the most common chemotherapy-induced neurotoxicities.

Keywords

stress; chemotherapy; peripheral neuropathy; hearing loss; tinnitus; cancer survivor

INTRODUCTION

"Stress" is a common, albeit ill-defined, human experience that can have significant negative effects on physical and emotional well-being.[1] Physiologically, stress is a process of increased arousal with the goal of maintaining homeostasis. The acute response to a stressor involves the activation of and interactions among sensory, autonomic, endocrine, and immune systems. This short term response is adaptive and has numerous health benefits.[1–3] However, long-term stress, without sufficient recovery, can lead to numerous health consequences including: depression,[4–7] anxiety,[6,8–10] chronic pain,[11–14] hearing loss,[15–17] and tinnitus.[15,18–22]

The diagnosis and treatment of cancer is a stressful experience for most patients.[8,23–25] High levels of stress can persist into survivorship as a result of unrelieved symptoms,[8,25–27] fears of disease recurrence,[28–31] and financial problems.[32–34] Some survivors report stress-related symptoms including: hyperarousal, emotional numbness, intrusive thoughts, and nightmares. These stress-related symptoms have a negative impact on survivors' overall health status, their ability to function, their mood, and their quality of life (QOL).[35,36]

Three of the most common adverse effects of neurotoxic chemotherapy that persist into survivorship are chemotherapy-induced neuropathy (CIPN),[26,37] hearing loss,[38–40] and tinnitus.[38,41–43] Approximately 30% to 70% of survivors experience CIPN.[44,45] While less well studied, occurrence rates for hearing loss and/or tinnitus range from 20% to 40%.[38,41]

A growing body of evidence suggests that perceived stress can trigger the development of, as well contribute to the persistence of musculoskeletal pain and headache.[11–14] In addition, stress may be a common underlying risk factor for persistent tinnitus.[15,18–22] Of note, increased stress exacerbates both persistent pain[46,47] and tinnitus[48,49] and evidence suggests that patients with these conditions have alterations in autonomic processing. In terms of hearing loss, most of the studies have focused on the deleterious effects of noise.[50,51] While less is known about the effect of perceived stress on the auditory system, recent work suggests that chronic stress is harmful to hearing and that normal functioning of the hypothalamic-pituitary-adrenal (HPA) axis is necessary for healthy hearing.[16,52] In addition, one needs to consider that persistent pain, hearing loss, and tinnitus are stressful to an individual because they have a negative impact on social interactions.[53–57] For example, individuals with hearing loss and/or tinnitus have difficulty engaging in conversations with colleagues and friends in a noisy environment.

While a growing body of literature has demonstrated associations between stress and persistent pain,[11–14] hearing loss,[50,51] and tinnitus,[48,49] no studies were found that examined these associations in cancer survivors who received neurotoxic chemotherapy. In this cross-sectional study, in a sample of 623 adult cancer survivors who received either a platinum and/or a taxane compound, we conducted a preliminary evaluation of the associations between perceived stress and the occurrence of CIPN, hearing loss, and tinnitus.

METHODS

Survivors and Settings

The methods for the larger study which was designed to evaluate for differences in subjective and objective characteristics associated with CIPN are described in detail elsewhere.[37] In brief, survivors with and without CIPN were recruited from throughout the San Francisco Bay area. Survivors in the CIPN group were included if they: had received a platinum and/or a taxane compound; had completed their course of chemotherapy ≥3 months prior to enrollment; reported changes in sensation and/or pain in their feet and/or hands of ≥3 months duration following the completion of chemotherapy; had a rating of ≥3 on a 0 to 10 numeric rating scale (NRS) for any one of the following sensations from the Pain Qualities Assessment Scale (i.e., numb, tender, shooting, sensitive, electrical, tingling radiating, throbbing, cramping, itchy, unpleasant);[58,59] and if they had pain associated with the CIPN, had an average pain intensity score in their feet and/or hands of ≥3 on a 0 to 10 NRS. Survivors without CIPN were included if they: had received a platinum and/or a taxane compound; had completed their course of chemotherapy ≥3 months prior to enrollment; and did not have persistent changes in sensation and/or pain in their hands or feet at the time of enrollment.

Survivors with and without CIPN were excluded if they had: peripheral vascular disease, vitamin B12 deficiency, thyroid dysfunction, HIV neuropathy, another painful condition that was difficult for them to distinguish from their CIPN, a hereditary sensory or autonomic neuropathy (60), and/or a hereditary mitochondrial disorder.[61] A detailed patient history was obtained to evaluate for the presence of these conditions. Of the 1450 survivors who were screened, 754 were enrolled and 623 completed the self-report questionnaires and the study visit. This study was approved by the Committee on Human Research at the University of California, San Francisco.

Study Procedures

Research nurses screened and consented the survivors over the phone; sent them the questionnaire booklet, and asked them to complete the self-report questionnaires prior to their study visit; and scheduled the in person assessment. At this assessment, written informed consent was obtained, questionnaires were reviewed for completeness and objective tests were performed.

Study Measures

Demographic and Clinical Characteristics—Survivors provided information on demographic characteristics and completed the Karnofsky Performance Status (KPS)

scale[62–64] and the Self-Administered Comorbidity Questionnaire (SCQ).[65,66] Medical records were reviewed for disease and treatment characteristics.

Hearing Loss and Tinnitus—Two items from the Functional Assessment of Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) subscale were used to evaluate hearing loss (i.e., I have trouble hearing) and tinnitus (i.e., I get ringing or buzzing in my ears).[67] Each item was rated on a 0 (not at all) to 4 (very much) scale. Survivors who reported a score of 0 were classified in the no hearing loss or no tinnitus groups. Survivors who reported a score of ≥1 on these questions were classified into the hearing loss or tinnitus groups.

Perceived Stress—The Impact of Event Scale-Revised (IES-R) was used to evaluate perceived stress. The IES-R is a 22 item instrument that was used to measure distress associated with cancer and its treatment.[68,69] Patients rated each item based on how distressing each potential difficulty was for them during the past week 'with respect to their cancer and its treatment'. Each item was rated on a 0 to 4 Likert scale (i.e., 0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, 4 = extremely). Three subscales were created using the mean of the responses. These mean scores allow the user to identify the degree of symptomatology because the subscale scores are presented on the same metric as the item responses. A total IES-R score is created by summing the responses to the 22 items. The three subscales evaluate the levels of intrusion (8 items), avoidance (8 items), and hyperarousal (6 items) perceived by a patient. The total IES-R score can range from 0 to 88. For the total IES-R score, a cut-off is set at 33, while a score between 24 and 29 is cited as a sign of a partial PTSD and a score of ≥37 indicates a high presence of post-traumatic symptomatology.[70] The IES-R has well established validity and reliability.[70–72] In this study, the Cronbach's alphas were 0.85 for intrusion, 0.80 for avoidance, 0.81 for hyperarousal, and 0.92 for total IER-S scores.

Data Analysis

Data were analyzed using SPSS version 23.[73] Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics. All of the analyses used actual values. Differences in demographic and clinical characteristics between each of the neurotoxicity groups (i.e., no CIPN versus CIPN, no hearing loss versus hearing loss, and no tinnitus versus tinnitus) were evaluated using Independent sample t-tests and Chi Square analyses.

To evaluate whether each of the IES-R subscale and total scores made a significant independent contribution to neurotoxicity group membership, separate logistic regression analyses were done for each neurotoxicity group in which all of the demographic and clinical characteristics that differed significantly between the groups were entered in Block 1 and the IES-R score was entered in Block 2 (i.e., to assess its unique contribution). No adjustments were made for multiple testing.[74,75] A p-value of <.05 was considered statistically significant.

RESULTS

CIPN Group Membership

Of the 623 adult cancer survivors enrolled in this study, 68.4% had CIPN. Compared to survivors without CIPN, survivors with CIPN were significantly older; had a higher BMI, a higher SCQ score, and a lower KPS score; were more likely to be born prematurely, and more likely to have a diagnosis of ovarian cancer, and more likely to have received a platinum and taxane containing chemotherapy regimen (Table 1). Compared to the survivors without CIPN, survivors with CIPN had significantly higher IES-R subscale and total scores (Table 2). As shown in Table 3, after controlling for age, BMI, KPS score, whether or not the survivor was born prematurely, and cancer diagnosis, while no association was found for the IES-R avoidance scale, for each one unit increase on the IES-R intrusion, hyperarousal, and total scales, survivors were 1.627 (p=.013), 1.834 (p=.014), and 1.020 (p=.047) times more likely to be in the CIPN group, respectively.

Hearing Loss Group Membership

Of the 613 adult cancer survivors who completed the hearing loss item, 34.5% reported hearing loss. Compared to survivors without hearing loss, survivors with hearing loss were significantly older; had a higher SCQ score and a lower KPS score; and were more likely to be male (Table 1). Compared to the survivors without hearing loss, survivors with hearing loss had significantly higher IES-R hyperarousal and total scores (Table 2). As shown in Table 4, after controlling for age, gender, KPS score, and SCQ score, while no associations were found for the IES-R intrusion, avoidance, and total scores, for each one unit increase on the IES-R hyperarousal scale, survivors were 1.569 (p=.007) times more likely to be in the hearing loss group.

Tinnitus Group Membership

Of the 609 adult cancer survivors who completed the tinnitus item, 31.0% reported tinnitus. Compared to survivors without tinnitus, survivors with tinnitus had significantly fewer years of education, a higher SCQ score, were more likely to be male, and were more likely to have another type of cancer (i.e., compared to breast, colon, lung, and ovarian), and more likely to have received a platinum containing chemotherapy regimen (Table 1). Compared to the survivors without tinnitus, survivors with tinnitus had significantly higher IES-R hyperarousal scores (Table 2). As shown in Table 5, after controlling for gender, years of education, and SCQ score, while no associations were found for the IES-R intrusion, avoidance, and total scores, for each one unit increase on the IES-R hyperarousal scale, survivors were 1.383 (p=.029) times more likely to be in the tinnitus group.

DISCUSSION

This study is the first to demonstrate associations between cancer survivors' perceptions of disease-specific stress and the occurrence of CIPN, hearing loss, and tinnitus. For all three neurotoxicities, scores on the hyperarousal subscale of the IES-R were associated with increased risk for having CIPN, hearing loss, or tinnitus. Given the cross-sectional nature of this study, the causal relationships between perceived stress and these three neurotoxicities

cannot be determined. Longitudinal studies are warranted to examine the directionality of these associations in more detail.

With the addition of the hyperarousal items to the original IES, the IES-R was designed to assess current subjective distress associated with specific stressful life events (i.e., in this study, the effects of cancer and its treatment).[68] The IES-R assesses three symptomatic responses from exposure to traumatic life events, namely: intrusion, avoidance, and hyperarousal. Intrusion is characterized by intrusive thoughts about various aspects of the traumatic event, sequelae, or self-conceptions; disrupted sleep, and repeated visual images. Avoidance is characterized by deliberate efforts to not think or talk about the event or to avoid reminders of the event. Hyperarousal is characterized by anger and irritability, jumpiness and an exaggerated startle response, difficulty concentrating, and hypervigilance.[69]

In our study, higher intrusion, hyperarousal, and total IES-R scores were associated with an increased odds of having CIPN. In fact for intrusion and hyperarousal, for each one unit increase in these scale scores, survivors were 1.6 and 1.8 times more likely to report CIPN. While the total IES-R scores for our survivors with CIPN did not reach the cutoff score that is suggestive of partial PTSD, their scores are comparable to those of patients with rheumatoid arthritis (13.4 ± 14.5) but lower than those of patients with fibromyalgia (24.6 ± 18.9)[76] or low back pain (median score 23.0).[77]

It should be noted that the significant associations with IES-R scores and CIPN remained significant after controlling for additional potential sources of stress that could contribute to the CIPN phenotype.[26,78–80] First, despite relatively small number of survivors in our study who were born prematurely, this risk factor, which is known to be a major stressful life event,[81,82] increased the odds of being in the CIPN group between 8.5 and 9.0 times. This finding is congruent with previous reports that suggest that early life stress is associated with the development of persistent pain.[83] In addition, consistent with previous findings on stress-induced obesity,[84,85] a higher BMI was associated with CIPN group membership. Finally, in the multiple logistic regression analyses, survivors with colon (OR range = 2.8 to 3.0) and ovarian (OR range = 3.6 to 4.0) cancer were more likely to be in the CIPN group compared to those in the “other” diagnosis group that included patients with cancers other than breast, colon, lung, and ovarian. These increases may reflect additional stressors associated with diagnosis-specific chemotherapy regimens (e.g., variations in cycle length, single agent versus combination drug regimens) and/or differences in overall treatment regimen. However, it should be noted that while in the univariate analyses, differences were found between the two CIPN groups in the types of chemotherapy regimens received, this characteristic did not remain significant in the multivariate analyses.

In contrast to the findings for CIPN, only the IES-R hyperarousal score was associated with hearing loss and tinnitus. However, the odds ratios for these two outcomes were similar to those for CIPN (i.e., for each one unit increase on this subscale, survivors were 1.6 and 1.4 times more likely to report hearing loss or tinnitus, respectively). The items included in the hyperarousal subscale were added to the IES-R after the American Psychiatric Association published their formal diagnostic criteria for PTSD in 1980 to capture the phenomenon of

hypervigilance.[69] The symptoms evaluated on this subscale include: irritability, anger, jumpiness, difficulty falling asleep, difficulty concentrating, and heightened watchfulness. Because of the cross-sectional nature of this study, the causal relationships between these hyperarousal symptoms and each of these common chemotherapy-induced neurotoxicities cannot be determined. In addition, it is not entirely clear why the intrusion and avoidance subscales, as well as the total scores of the IES-R were not associated with hearing loss or tinnitus. Additional, longitudinal research, with larger samples, may identify causal relationships between these aspects of perceived stress and chemotherapy-induced ototoxicity.

The demographic and clinical characteristics included in the final models differed for CIPN, hearing loss, and tinnitus. However, the associations that were identified are consistent with previous reports. Briefly, the occurrence of CIPN[37] and hearing loss increases with age.[86] In addition, males are at increased risk for both hearing loss[87] and tinnitus.[88] Finally, individuals with a worse comorbidity profile are more likely to report hearing loss[89,90] and tinnitus.[91] It should be noted that in the multivariate analyses, neither cancer diagnosis nor chemotherapy regimen were associated with hearing loss or tinnitus group membership.

While this study is the first to describe associations between disease-specific stress and -induced neurotoxicities, several limitations warrant consideration. First, because of the cross-sectional nature of this study, the causal relationships between stress and these three neurotoxicities cannot be determined. Prospective, longitudinal studies, that enroll patients prior to the initiation of chemotherapy, are warranted to determine the relationships between subjective and objective measures of stress and the development of CIPN, hearing loss, and tinnitus. Second, in this study, the characterization of hearing loss and tinnitus were based on self-report. While patients' self-report of hearing problems is acceptable,[92] future studies need to do a detailed characterization of ototoxicity in cancer survivors. In addition, we did not assess whether these survivors had hearing loss and/or tinnitus prior to the initiation of chemotherapy. Prospective studies are needed to evaluate pretreatment levels of all three neurotoxicities and the time to onset of each toxicity relative to the other two. Given the evidence that early life stress predisposes to the development of chronic pain,[83] future studies should obtain self-reports on cumulative life stress using measures like the Life Stressor Checklist-Revised.[93] In addition, prospective studies are needed to evaluate the impact of cumulative life stress on the development of chemotherapy-induced neurotoxicities. While the IES-R has excellent psychometric properties, future studies should include a battery of biomarkers of stress.[94] In combination with longitudinal evaluations of chemotherapy-induced neurotoxicities and reports of perceived stress, the use of biomarkers will allow for an exploration of the causal mechanisms that underlie CIPN, hearing loss, and tinnitus in oncology patients who receive neurotoxic chemotherapy.

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Table 1

Differences in Demographic and Clinical Characteristics Between Each of the Neurotoxicity Groups

Characteristic	Chemotherapy-induced Neuropathy			Hearing Loss			Tinnitus		
	No 31.6% (n=197)	Yes 68.4% (n=426)	p-value	No 65.5% (n=401)	Yes 34.5% (n=211)	p-value	No 69.0% (n=420)	Yes 31.0% (n=189)	p-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	58.4 (12.3)	60.9 (10.5)	.013	58.6 (11.1)	62.7 (10.6)	<.001	60.0 (11.0)	59.9 (11.3)	.893
Education (years)	16.4 (2.6)	16.4 (2.8)	.839	16.4 (2.7)	16.3 (2.6)	.572	16.6 (2.7)	15.9 (2.7)	.006
BMI (kg/m^2)	24.8 (5.0)	26.6 (5.5)	<.001	25.9 (5.2)	26.4 (5.9)	.311	26.2 (5.6)	25.8 (5.1)	.508
KPS score	91.2 (9.3)	83.2 (10.2)	<.001	87.1 (10.2)	83.4 (10.7)	<.001	86.4 (10.3)	84.6 (10.8)	.050
SCQ score	2.9 (3.0)	4.2 (3.4)	<.001	3.3 (2.9)	4.7 (3.6)	<.001	3.6 (3.2)	4.2 (3.4)	.031
	% (n)	% (n)		% (n)	% (n)		% (n)	% (n)	
Female	80.7 (159)	86.6 (368)	.072	87.5 (351)	79.5 (167)	.012	88.8 (372)	75.7 (143)	<.001
Ethnicity									
White	82.2 (162)	77.2 (329)		78.8 (316)	80.1 (169)		80.7 (339)	75.7 (143)	
Asian/PI	6.1 (12)	7.0 (30)	.539	7.2 (29)	6.2 (13)	.937	7.4 (31)	5.8 (11)	.160
Black	4.1 (8)	5.2 (22)		4.2 (17)	4.7 (10)		3.6 (15)	6.3 (12)	
Hispanic/other	7.6 (15)	10.6 (45)		9.7 (39)	9.0 (19)		8.3 (35)	12.2 (23)	
Born prematurely	1.1 (2)	6.6 (26)	.002	5.1 (19)	4.6 (9)	.842	5.1 (20)	4.5 (8)	.837
Cancer diagnosis			.002						
Breast	57.4 (113)	54.9 (234)		58.9 (236)	50.2 (106)		58.3 (245)	49.7 (94)	
Colon	4.6 (9)	9.6 (41)		8.0 (32)	7.6 (16)		7.6 (32)	8.5 (16)	
Lung	5.6 (11)	1.9 (8)	No significant pairwise contrasts	3.2 (13)	2.8 (6)	.184	3.1 (13)	3.2 (6)	.010
Ovarian	4.6 (9)	10.6 (45)		8.2 (33)	9.0 (19)		10.0 (42)	5.3 (10)	
Other	27.9 (55)	23.0 (98)		21.7 (87)	30.3 (64)		21.0 (88)	33.3 (63)	

Characteristic	Chemotherapy-induced Neuropathy			Hearing Loss			Tinnitus		
	No 31.6% (n=197)	Yes 68.4% (n=426)	p-value	No 65.5% (n=401)	Yes 34.5% (n=211)	p-value	No 69.0% (n=420)	Yes 31.0% (n=189)	p-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
CTX regimen									
Only platinum	28.6 (56)	22.3 (95)		22.0 (88)	28.9 (61)		20.0 (84)	34.4 (65)	
Only taxane	51.0 (100)	46.9 (200)	.020	49.8 (199)	45.5 (96)	.167	49.9 (209)	44.4 (84)	<.001
Both platinum and taxane	20.4 (40)	30.8 (131)		28.2 (113)	25.6 (211)		30.1 (126)	21.2 (40)	

Abbreviations: BMI = body mass index, CTX = chemotherapy kg = kilograms, KPS = Karnofsky Performance Status, m^2 = meter squared, PI = Pacific Islander, SCQ = Self-administered Comorbidity Questionnaire, SD = standard deviation

Table 2

Differences in Impact of Event Scale-Revised Scores Between Each of the Neurotoxicity Groups

Stress scales	Chemotherapy-induced Neuropathy			Hearing Loss			Tinnitus		
	No 31.6% (n=197)	Yes 68.4% (n=426)	p-value	No 65.5% (n=401)	Yes 34.5% (n=211)	p-value	No 69.0% (n=420)	Yes 31.0% (n=189)	p-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
IES-R intrusion	0.5 (0.5)	0.7 (0.7)	<.001	0.6 (0.6)	0.7 (0.7)	.075	0.6 (0.6)	0.7 (0.7)	.090
IES-R avoidance	0.6 (0.6)	0.7 (0.7)	.048	0.6 (0.6)	0.7 (0.7)	.163	0.7 (0.6)	0.7 (0.7)	.790
IES-R hyperarousal	0.3 (0.4)	0.5 (0.7)	<.001	0.4 (0.5)	0.5 (0.7)	.002	0.4 (0.6)	0.5 (0.7)	.020
IES-R total score	9.9 (9.5)	14.2 (13.5)	<.001	12.0 (11.3)	14.4 (14.5)	.033	12.3 (11.6)	14.0 (14.3)	.156

Abbreviations: IES-R = Impact of Event Scale – Revised, SD = standard deviation

Table 3

Logistic Regression Analyses for the Association Between Impact of Event Scale-Revised Scores and Chemotherapy-induced Neuropathy Group Membership

Predictor	OR	95% CI	p-value
IES-R Intrusion Subscale (n=543)			
Age	1.032	1.013, 1.051	.001
BMI	1.051	1.008, 1.096	.020
KPS score	0.914	0.889, 0.940	<.001
Born prematurely	9.214	2.042, 41.575	.004
Cancer diagnosis *			.007
Breast	1.312	.805, 2.139	.276
Colon	2.967	1.191, 7.395	.020
Lung	0.660	0.200, 2.178	.495
Ovarian	3.989	1.588, 10.020	.003
IES-R intrusion	1.627	1.110, 2.385	.013
Overall model - $X^2 = 127.74$, p<.001			
IES-R Avoidance Subscale (n=542)			
Age	1.027	1.009, 1.046	.003
BMI	1.050	1.007, 1.095	.022
KPS score	0.907	0.883, 0.932	<.001
Born prematurely	8.460	1.864, 38.402	.006
Cancer diagnosis *			.010
Breast	1.247	0.767, 2.029	.374
Colon	2.837	1.140, 7.058	.025
Lung	0.593	0.179, 1.967	.393
Ovarian	3.627	1.452, 9.058	.006
IES-R avoidance	1.090	0.785, 1.514	.605
Overall model - $X^2 = 120.89$, p<.001			
IES-R Hyperarousal Subscale (n=543)			
Age	1.033	1.014, 1.053	.001
BMI	1.050	1.007, 1.095	.022
KPS score	0.916	0.891, 0.942	<.001

Predictor	OR	95% CI	p-value
Born prematurely	8.926	1.969, 40.462	.005
Cancer diagnosis *			.008
Breast	1.268	0.779, 2.063	.339
Colon	2.930	1.174, 7.310	.021
Lung	0.608	0.186, 1.989	.411
Ovarian	3.804	1.524, 9.498	.004
IES-R hyperarousal	1.834	1.133, 2.969	.014
Overall model - $X^2 = 127.93$, p<.001			
IES-R Total Score (n=543)			
Age	1.031	1.012, 1.050	.001
BMI	1.051	1.008, 1.096	.020
KPS score	0.913	0.888, 0.938	<.001
Born prematurely	9.186	2.029, 41.585	.004
Cancer diagnosis *			.008
Breast	1.312	0.806, 2.136	.274
Colon	2.918	1.173, 7.260	.021
Lung	0.649	0.197, 2.138	.477
Ovarian	3.912	1.564, 9.782	.004
IES-R total score	1.020	1.001, 1.041	.047
Overall model - $X^2 = 125.24$, p<.001			

*Compared to other cancer diagnoses

Abbreviations: BMI – body mass index in kilograms/metered squared, CI = confidence interval, IES-R = Impact of Event Scale – Revised, KPS = Karnofsky Performance Status, OR = odds ratio

Table 4

Logistic Regression Analyses for the Association Between Impact of Event Scale-Revised Scores and Hearing Loss Group Membership

Predictor	OR	95% CI	p-value
IES-R Intrusion Subscale (n=589)			
Age	1.045	1.026, 1.064	<.001
Gender	1.931	1.181, 3.156	.009
KPS score	0.977	0.958, 0.996	.017
SCQ score	1.094	1.030, 1.162	.003
IES-R intrusion	1.185	0.884, 1.589	.255
Overall model – $X^2 = 61.82$, p<.001			
IES-R Avoidance Subscale (n=587)			
Age	1.043	1.025, 1.062	<.001
Gender	1.884	1.151, 3.084	.012
KPS score	0.975	0.956, 0.993	.008
SCQ score	1.097	1.033, 1.164	.003
IES-R avoidance	1.068	0.808, 1.413	.642
Overall model – $X^2 = 60.95$, p<.001			
IES-R Hyperarousal Subscale (n=589)			
Age	1.050	1.030, 1.069	<.001
Gender	1.960	1.196, 3.212	.008
KPS score	0.982	0.963, 1.001	.065
SCQ score	1.085	1.021, 1.154	.009
IES-R hyperarousal	1.569	1.129, 2.179	.007
Overall model – $X^2 = 67.86$, p<.001			
IES-R Total Score (n=589)			
Age	1.046	1.027, 1.065	<.001
Gender	1.901	1.163, 3.108	.010
KPS score	0.978	0.959, 0.997	.022
SCQ score	1.093	1.029, 1.161	.004
IES-R total score	1.011	0.996, 1.027	.150
Overall model – $X^2 = 62.60$, p<.001			

Abbreviations: CI = confidence interval, IES-R = Impact of Event Scale – Revised, KPS = Karnofsky Performance Status, OR = odds ratio, SCQ = Self-administered Comorbidity Questionnaire

Table 5

Logistic Regression Analyses for the Association Between Impact of Event Scale-Revised Scores and Tinnitus Group Membership

Predictor	OR	95% CI	p-value
IES-R Intrusion Subscale (n=592)			
Gender	2.662	1.669, 4.243	<.001
Education	0.923	0.864, 0.987	.020
SCQ score	1.050	0.994, 1.109	.081
IES-R intrusion	1.242	0.947, 1.629	.117
Overall model – $X^2 = 30.82$, p<.001			
IES-R Avoidance Subscale (n=589)			
Gender	2.696	1.691, 4.298	<.001
Education	0.932	0.872, 0.997	.041
SCQ score	1.060	1.004, 1.119	.034
IES-R avoidance	0.961	0.730, 1.265	.775
Overall model – $X^2 = 27.94$, p<.001			
IES-R Hyperarousal Subscale (n=592)			
Gender	2.688	1.685, 4.288	<.001
Education	0.925	0.865, 0.989	.023
SCQ score	1.043	0.986, 1.102	.142
IES-R hyperarousal	1.383	1.033, 1.852	.029
Overall model – $X^2 = 33.06$, p<.001			
IES-R Total Score (n=592)			
Gender	2.610	1.640, 4.154	<.001
Education	0.924	0.864, 0.987	.020
SCQ score	1.052	0.996, 1.111	.070
IES-R total score	1.008	0.994, 1.023	.251
Overall model – $X^2 = 29.70$, p<.001			

Abbreviations: CI = confidence interval, IES-R = Impact of Event Scale – Revised, OR = odds ratio, SCQ = Self-administered Comorbidity Questionnaire