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Anxiety Disorders in Long-Term Survivors of Adult Cancers

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Abstract

Background—Little is known about the prevalence of anxiety disorders among long-term survivors of adult cancers. Using data from the National Comorbidity Survey-Replication (NCS-R), we compared rates of anxiety disorders between long-term cancer survivors and individuals without a history of cancer.

Methods—A nationally representative sample of 9,282 adults participated in a household survey to assess the prevalence of DSM-IV psychiatric disorders, a subset of whom also answered questions about medical comorbidities, including cancer. Long-term survivors were defined as those who received an adult cancer diagnosis at least five years before the survey. Multiple logistic regression analyses were used to examine associations between cancer history and anxiety disorders in the past year.

Results—The NCS-R sample consisted of 225 long-term cancer survivors and 5,337 people without a history of cancer. Controlling for socio-demographic variables, long-term cancer survivors were more likely to have an anxiety disorder (*OR:* 1.49, *95% CI:* 1.04-2.13), including specific phobia (*OR:* 1.59, *95% CI:* 1.06-2.44) and medical phobia (*OR:* 3.45, *95% CI:* 1.15-10.0), during the past 12 months compared to those without cancer histories. Rates for social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder and agoraphobia were not significantly different between groups.

Conclusion—Long-term survivors of adult cancers were more likely to have an anxiety disorder diagnosis, namely specific phobia, in the past 12 months compared with the general public. Further longitudinal study is needed to clarify the timing and course of anxiety relative to the cancer diagnosis.

Introduction

Notable advances in cancer screening and treatment over the last several decades have led to a dramatic increase in the population of long-term survivors, with more than seven million Americans currently living at least five years beyond the initial diagnosis of cancer.¹ Many of these individuals experience ongoing medical and psychosocial sequelae, even after the

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conclusion of anti-cancer therapy. Depending on the type of malignancy and nature of cancer treatment, survivors may report persistent problems with physical disability, chronic fatigue, infertility, sexual dysfunction, or neurocognitive deficits, as well as concerns regarding cancer recurrence, changes in interpersonal relationships, finances and employment status.² Although the burden of a cancer diagnosis, with its related treatment and complications, would certainly cause marked distress, the degree to which such stressors increase the risk of anxiety disorders in long-term survivors remains uncertain.

Reported prevalence rates of anxiety disorders in individuals with cancer vary widely, largely for methodological reasons. The frequency of diagnosable anxiety disorders in individuals with cancer ranges from approximately 10%-30%, based on reviews of studies that employ diagnostic criteria and standardized psychiatric interviews to assess anxiety symptoms.^{3, 4} Of all the anxiety disorders, posttraumatic stress disorder following a cancer diagnosis has been the most widely studied, with incidence rates ranging from 0% to 32%.⁵ The variation in these estimates is likely due to differences in not only methods for defining and assessing anxiety (e.g., use of symptom scales versus structured diagnostic interviews) but also types and stages of cancers sampled, as well as medical treatment factors and time from diagnosis.

The majority of the epidemiological studies on psychiatric morbidity in patients with cancer have sampled individuals either recently diagnosed with malignancy or during the treatment phase. For example, in an analysis of epidemiological data from the first National Comorbidity Survey, Honda and Goodwin⁶ investigated the frequency of anxiety and affective disorders in a representative sample of 5,877 adults aged 15-54, observing that individuals who had been diagnosed with cancer in the past year were more likely than those without cancer to have simple phobia and agoraphobia, adjusting for socio-demographic factors. However, the sample size of individuals with cancer in this study was small (n=45), limiting the reliability of the findings.⁷ Additionally, the degree to which such anxiety disorders abate over time or persist into survivorship requires further study.

Although previous research suggests that quality of life remains relatively normal for longterm survivors of cancer, anxiety symptoms may cause distress years after cancer diagnosis and treatment.⁸⁻¹² Two recent population-based cohort studies show that long-term survivors, defined as being alive at least five years post cancer diagnosis, are more likely to experience serious psychological distress, utilize outpatient mental health's services, and have anxiety and sleep disorders compared to either matched controls or a normative reference group without a history of cancer.^{13, 14} While these studies present compelling evidence about the long-term psychological effects of cancer and its treatment, they are limited in that they rely either on symptom scales or health care claims data to assess psychiatric morbidity.

In contrast, Gandubert and colleagues¹⁵ used standardized diagnostic assessments to investigate the onset and relapse of psychiatric disorders in a case-control study of female survivors of early-stage breast cancer who had completed treatment and were in remission for one to three years. Compared to women without a history of breast cancer, survivors were significantly more likely to have either a recurrent or initial episode of panic disorder and generalized anxiety disorder within the first three years of cancer diagnosis and treatment. Similar trends were observed for specific phobia and posttraumatic stress disorder. As these findings highlight, the first few years following cancer diagnosis and treatment appear to be an especially vulnerable time for the development or exacerbation of anxiety disorders in survivors. To overcome the limitations of previous research with respect to sample size, lack of diagnostic assessments, or focus on a single cancer types, we compared rates of anxiety disorders in the past 12 months between long-term cancer survivors and those without a history of cancer using data from the National Comorbidity Survey-Replication, a large-scale representative household survey of psychiatric disorders in the U.S.¹⁶ We hypothesized that long-term survivors would be more likely to be diagnosed with an anxiety disorder compared to a normative reference group given accumulating evidence from large-scale studies using symptom scales of anxiety and psychological distress.

Methods

Sample

Full details of the National Comorbidity Survey-Replication (NCS-R) sample and survey methods are described elsewhere.¹⁶ Briefly, the NCS-R is a large-scale epidemiological survey that utilized a multi-stage clustered area probability sample to investigate the prevalence and correlates of psychiatric disorders in the United States. From February 2001 to April 2003, diagnostic interviews were administered face-to-face in the homes of English-speaking adults ages 18 years or older residing in the 48 contiguous states. The overall response rate for the study was 74.6%. A total of 9,282 respondents completed the main survey, 5,692 of whom underwent a more comprehensive interview that included questions regarding risk factors, services, additional psychiatric diagnoses, and medical comorbidities such as cancer. More specifically, respondents were asked about a number of different chronic medical problems; those with a history of cancer also responded to questions about their age at diagnosis and current disease status, defined as either "in treatment," "cured," "in remission," or "don't know."

For the proposed analysis, we compared long-term survivors of adult cancers to individuals without a history of cancer. Using a methodology similar to Hoffman and colleagues,¹⁴ long-term survivors were defined as those participants who reported that they were diagnosed with cancer after age 18, were at least five years post diagnosis, and were either "cured" or "in remission." The comparison group included all individuals who never had a history of cancer. Participants who reported a history of cancer prior to age 18 were excluded from the sample.

Measures

Anxiety Disorders—Psychiatric diagnoses were determined using the World Health Organization's Composite International Diagnostic Interview based on the Diagnostic & Statistical Manual of Mental Disorders-IV. Employing strict diagnostic criteria, trained interviewers assessed the presence of anxiety disorders in the past 12 months and over the course of the participant's lifetime, including age of onset. In the present study, we examined the rate for any anxiety disorder as well as rates for particular disorders including specific phobia, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder and agoraphobia. When asked about specific phobia, respondents indicated the type(s) of fear they experienced; for the purpose of this analysis, we also separately examined those who met criteria for specific phobia and reported fears of a medical nature, labeling these as "medical phobia."

Mental Health Treatment—As part of the NCS-R structured interview, respondents indicated whether they were seeing a psychiatrist, general practitioner (or other medical doctor), psychologist, social worker, counselor, other mental health professional, etc. for problems with emotions, nerves or mental health. In addition, respondents indicated whether they had taken any anti-depressant medications or tranquilizers under the supervision of a

doctor in the past 12 months, which we combined into a single measure of psychotropic medication use (Yes/No).

Demographic Variables—The structured interview also included an assessment of the following demographic variables: age, sex, race/ethnicity (white, Hispanic, black, or other), marital status (married/cohabitating, divorced/separated/widowed, never married), education (less than 12 years, high school graduate, some college, or college graduate), and household income. For the NCS-R, the final data were weighted to have these socio-demographic variables approximate the distribution of the 2000 U. S. Census as well as to adjust for non-response and differences in the probability of selection within a household.¹⁶

Statistical Procedures—Given the multi-stage clustered area probability sample, we performed the statistical analyses with SUDAAN v. 9.0 using the final sample weights from part 2 of the NCS-R. Analyses began with descriptive summaries of the demographic factors and rates of anxiety disorders. To examine differences between long-term cancer survivors and the comparison group with respect to demographic characteristics and mental health treatment, we used the Pearson chi square test for categorical variables and the independent-samples t-tests for continuous variables. Unadjusted and adjusted multiple logistic regression analyses were then conducted to compare rates of anxiety disorders in the past 12 months between long-term cancer survivors and those without cancer histories. Adjusted models controlled for demographic factors that were significantly related to cancer long-term survivorship.

Results

In the NCS-R sample, 225 individuals met criteria for long-term survivorship, having been diagnosed with cancer after the age of 18 and at least five years prior to the survey. The cancer types represented in the sample were diverse and included: breast (24.0%), melanoma (18.7%), cervical (10.0%), prostate (8.0%), uterine (7.2%), colon (7.0%), ovarian (1.8%), lymphoma/ leukemia (1.8%), lung (0.7%), among others (25.6%). The comparison sample included 5,337 people without cancer histories. The demographic characteristics of both groups are presented in Table 1. Using the weighted data for all analyses, we observed that long-term cancer survivors were older and significantly more likely to be female, married, and white compared to those without cancer histories. Since the two groups were similar with respect to measures of socioeconomic status, we did not adjust for education level or mean household income in subsequent multiple logistic regression analyses of the anxiety disorders.

Table 2 lists the rates of anxiety disorders in the past 12 months for long-term cancer survivors compared to those without a history of cancer. Unadjusted logistic regression analyses revealed no differences in rates of specific disorders between the groups. Similar to previous studies, younger participants (p<0.001) and women (p<0.001) had higher rates of any anxiety disorder in the overall sample. After adjusting the analyses for age, sex, race/ ethnicity, and marital status, long-term survivors of adult cancer were significantly more likely to be diagnosed with any anxiety disorder in the past 12 months compared to those without cancer histories (OR: 1.49, 95% CI: 1.04-2.13, p=0.02). In particular, long-term survivors had higher rates for specific phobia, including medical phobia (see Table 2). The study groups did not differ significantly with respect to rates for social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder and agoraphobia. Nearly all anxiety disorders occurred prior to the diagnosis of cancer, except for 53.85% and 16.67% of cases for generalized anxiety disorder and posttraumatic stress disorder, respectively.

An analysis of mental health services revealed that, compared to the control group, longterm cancer survivors were more likely to have taken psychiatric medications, such as antidepressants and/or tranquilizers, in the past year (17.01%, *SE*=3.26 versus 11.36%, *SE*=0.44, p=0.06). However, survivors had significantly lower rates of psychiatric treatment that involved seeing a psychiatrist, psychologist, or other mental health professional (5.33%, *SE*=1.13 versus 7.87%, *SE*=0.44, p=0.05).

Discussion

We investigated 12-month prevalence rates of anxiety disorders in long-term survivors of adult cancers using a large-scale, representative dataset from the National Comorbidity Survey-Replication, observing that survivors were more likely to have an anxiety disorder in the past year compared to a normative reference group of individuals without a history of cancer, adjusting for socio-demographic variables. As noted in Table 2, survivorship status was not significantly associated with past-year diagnosis of the anxiety disorders in unadjusted analyses. However, participant age negatively confounds this association, given that anxiety disorders are more common in younger individuals,¹⁷ and the long-term cancer survivors in our sample were significantly older than the comparison group. Therefore, after adjusting for socio-demographic variables that were significantly different between the groups, long-term survivors had increased odds of being diagnosed with an anxiety disorder, including specific phobia and medical phobia, compared to those without cancer histories.

Although some previous reports have suggested that levels of anxiety do not differ between patients with cancer versus normal controls,¹⁸ our results present a more complicated picture of anxiety disorders in long-term survivors of adult cancers. The elevated rate of past-year specific phobia in our sample of survivors is consistent with findings by Honda and Goodwin,⁶ who reported in their examination of the first National Comorbidity Survey that individuals recently diagnosed with cancer were more likely to be diagnosed with simple phobia compared to those without cancer. We were able to conduct further analyses to determine the nature of such phobias, demonstrating that medically-related fears may partially account for the differences in specific phobia between survivors and those without a history of cancer. Considering that patients undergo frequent medical procedures, ranging from major surgery to routine venipuncture, during the course and follow-up of anticancer treatment, the increased rates of specific phobia, and in particular medical phobia, may be expected. While specific phobias are among the most common anxiety disorders in the general population, they generally go undiagnosed, and few individuals seek treatment for the disorder.¹⁹ Among cancer survivors, such anxiety symptoms may become problematic if they interfere with adherence to medical care and treatment decision-making.

In addition to documenting the prevalence and nature of phobias, our study extends the literature by showing that long-term survivors are no more likely to have social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder or agoraphobia compared to those without cancer histories. In contrast, the study of breast cancer survivors by Gandubert and colleagues¹⁵ revealed that during the initial years following diagnosis, individuals were more likely to have generalized anxiety disorder and panic disorder, with similar trends for posttraumatic stress disorder and specific phobia, compared to matched controls. However, by year three of survivorship, rates of these disorders no longer differed significantly between groups. Thus, the first few years after cancer treatment appear to represent a critical period for increased psychological symptoms, whether through an exacerbation of a premorbid anxiety disorder or new onset of anxiety symptoms post cancer diagnosis. Our data point to the former explanation, as most cases of anxiety disorders in the sample of long-term survivors occurred prior to the diagnosis of cancer. Moreover, such anxiety symptoms may abate over time either spontaneously or

through mental health treatment, perhaps accounting for the generally modest differences observed between groups in rates of anxiety disorders. Indeed, although long-term survivors were less likely to seek consultation from a mental health professional, they were more likely to report taking psychotropic medications in the past year compared to those without cancer histories.

Our definition of long-term survivor and sample characteristics are quite similar to the recent population-based study by Hoffman and colleagues,¹⁴ who examined data from the National Health Interview Survey and found that survivors are significantly more likely to report serious psychological distress compared with controls. Since previous research shows that long-term survivors are no more likely to have major depressive disorder,²⁰ our study suggests that the elevated rates of psychological distress observed by Hoffman and colleagues¹⁴ may be better accounted for by anxiety symptoms. However, the mediating mechanisms underlying the development of anxiety disorders in long-term survivors still need to be elucidated. The parameters of the clinical interview and cross-sectional nature of the NCS-R prohibit drawing conclusions about whether the onset of any anxiety disorder was the consequence of having cancer. For example, although the rate of past-year PTSD in our sample of long-term survivors is similar to those previously reported in people with cancer,^{5, 21} only 16.7% of cases occurred after the cancer diagnosis, and we were unable to conclude whether the precipitating trauma was associated with the initial cancer diagnosis or its sequelae. Therefore, findings of the present study highlight the need for longitudinal research to determine the nature of anxiety in relation to cancer diagnosis among survivors.

As one of the first investigations of the rates of anxiety disorders in long-term survivors of adult cancers, the present study possesses notable strengths, namely the examination of a nationally-representative epidemiological survey that included a fairly large sub-sample of respondents diagnosed with heterogeneous cancers as well as the use of standardized assessments to diagnose psychiatric disorders by trained interviewers. However, several methodological considerations warrant cautious interpretation of the results. First, since our primary aim was to examine the between-group difference in the overall rate of anxiety disorders, we chose not to adjust the study-wide significance level to correct for multiple testing in the exploratory analyses of particular anxiety disorders. Also, as a secondary analysis of a cross-sectional survey, we were limited in determining the course of anxiety disorders over time within participants for each group. Moreover, retrospective accounts of medical and mental health histories are not ideal, given problems with the validity of such self-report data,²² though any bias in recalling symptoms would likely be similar across groups. Finally, while the study may generalize to a broader range of individuals with cancer, the relatively small numbers of patients within each cancer type, as well as the lack of data on cancer stage and components of treatment, prohibited subgroup analyses that may have yielded more subtle variations.

As part of comprehensive care for long-term survivors of cancer, screening for anxiety symptoms in both oncology and primary care settings may lead to improved access to psychological treatment and ideally enhanced outcomes for patients. Consistent with the recommendations of the recent Institute of Medicine report, "From Cancer Patient to Cancer Survivor: Lost in Transition," survivorship care plans²³ should not only address the morbidity associated with cancer treatment but also patients' psychosocial concerns, including anxiety.

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	Cancer Survivors	No Cancer History	
	N=225	N=5337	p value
Age M (SE)	62.93 (0.98)	43.79 (0.49)	<.001
Male N (%)	66 (37.86)	2272 (47.43)	.007
Marital Status N (%)			<.001
Married	126 (58.47)	2583 (49.36)	
Divorced	89 (38.34)	1297 (22.73)	
Never Married	10 (3.19)	1453 (27.91)	
Race/Ethnicity N (%)			<.001
White	187 (86.05)	3868 (71.65)	
Hispanic	9 (5.55)	519 (11.58)	
Black	13 (4.46)	700 (12.93)	
Other	13 (3.94)	250 (3.84)	
Education Level N (%)			ns
>12 years	43 (18.14)	778 (16.50)	
High school grad	65 (30.20)	1597 (32.40)	
Some college	57 (25.90)	1635 (27.94)	
College grad	60 (25.76)	1327 (23.16)	
Household Income M (SE)	\$57,016 (3105)	\$59,605 (1640)	ns

	Table 1
Sample Demographic Characteris	tics

Note: Percentages are based on data from weighted NCS-R sample.

	Table 2
12-Month Rates and	Odds Ratios for Anxiety Disorders

	Cancer Survivor	No History of Cancer	Unadjusted Odds	Adjusted ^{***} Odds Ratios
	N, % ^{**} (SE)	N, % ^{**} (SE)	Ratio (95% CI)	(95% CI)
Psychiatric Disorder				
Any Anxiety Disorder	68, 18.83	1558, 18.19	1.04	1.49 [*]
	(2.72)	(0.67)	(0.72-1.49)	(1.04-2.13)
Specific Phobia	37, 10.97	782, 9.08	1.23	1.59 [*]
	(1.91)	(0.45)	(0.83-1.82)	(1.06-2.44)
Medical Phobia	6, 2.60	101, 1.30	2.04	3.45 [*]
	(1.15)	(0.16)	(0.87-4.76)	(1.15-10.0)
Social Anxiety Disorder	26, 6.91	631, 7.22	0.95	1.49
	(1.87)	(0.34)	(0.54-1.69)	(0.85-2.63)
Generalized Anxiety Disorder	13, 3.39	236, 2.57	1.33	1.45
	(0.92)	(0.19)	(0.73-2.33)	(0.76-2.78)
Posttraumatic Stress Disorder	18, 4.33	298, 3.54	1.23	1.72
	(1.19)	(0.31)	(0.64-2.38)	(0.93-3.23)
Panic Disorder	8, 2.22	243, 2.79	0.79	1.10
	(1.00)	(0.25)	(0.29-2.17)	(0.39-3.03)
Agoraphobia	5, 1.18	134, 1.49	0.79	1.19
	(0.57)	(0.12)	(0.31-2.00)	(0.46-2.94)

* p<.05

** Note: percentages are based on data from the weighted NCS-R sample

*** Adjusted for age, sex, race/ethnicity, and marital status