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Anxiety and Depression in Cancer Survivors

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Synopsis

Most cancer survivors adjust well to life after cancer but some experience persisting negative mood such as cancer-related fears, post-traumatic stress, anxiety, or depression. Mood fluctuations may not reach criteria for a clinical diagnosis but sub-clinical symptoms can interfere with quality of life. Females, and adolescents and young adults are particularly at risk for mood disturbances. Behavioral interventions such as cognitive behavioral therapy and pharmacological treatments can effectively treat these distressing emotions. Much of the research on managing emotional needs after cancer has been completed with breast cancer survivors and more work is needed with diverse groups of survivors.

Keywords

Anxiety; depression; distress; cancer survivors

INTRODUCTION

Due to improvements in cancer detection and treatment, two-thirds of those diagnosed with an invasive cancer today will live more than five years, with a resulting rising population of long-term survivors.^{1,2} With the increasing visibility of survivors has come an awareness that mental health concerns are prominent among survivors' unmet needs, not only anxiety and depression but also various aspects of cancer-related distress. Many survivors adjust to cancer and its associated treatments but a subgroup struggles with emotional adjustment in

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the survivorship period. It is important to address these mood concerns because they can be barriers to engaging in survivorship care in addition to disrupting quality of life and return to usual activities.³ This article will examine anxiety and depressive symptoms as well as other cancer-related sources of distress in adults who may be survivors of childhood cancer, adolescent and young adult cancer survivors, or mature adult cancer survivors, with a brief discussion of treatment options in these populations.

SYMPTOMS

After cancer treatment, many survivors report feeling alone or even abandoned following the intensive support provided during their treatment. Survivors often are fearful and hypervigilant to physical sensations, especially prior to regularly scheduled testing for recurrence. These intermittent, preoccupying anxieties are called ‘fear of recurrence,’ (FOR) although they can also extend to include symptoms of post-traumatic stress, with hyperarousal when exposed to reminders of cancer, avoidance of situations that remind them of treatment, or numbing of emotions.

Many survivors experience emotional distress that does not meet the clinical criteria for anxiety disorder or major depression. Because cancer survivors have numerous sources of distress that increase their potential for adjustment reactions, and to reduce the negative stigma of mental health terms, these common reactions are categorized as ‘distress.’ The National Comprehensive Cancer Network (NCCN) Distress Guideline describes distress as extending along a continuum, ranging from common feelings of vulnerability, sadness, and fears of recurrence to disabling depression, anxiety, trauma, panic, and existential crisis.⁴ According to psychiatric diagnosis criteria⁵, a generalized anxiety diagnosis requires excessive anxiety or worry that is difficult to control and impairs function, along with at least three of the following symptoms most of the time for the past six months:

- Restlessness or feeling keyed up or on edge
- Being easily fatigued
- Difficulty concentrating
- Irritability
- Muscle tension
- Sleep disruptions

A major depression diagnosis requires at least five of the following symptoms most of the time in the past two weeks:

- Sadness, feeling hopeless or empty, or depressed
- Loss of interest or pleasure in most activities
- Significant changes in weight or appetite
- Sleep disruptions including sleeping too much or too little
- Psychomotor slowing or agitation that is observable by others

- Fatigue or loss of energy
- Feelings of guilt or worthlessness, or feeling like a burden
- Difficulty concentrating or indecisiveness
- Thoughts of being better off dead or active suicidal thoughts or plans

DIAGNOSTIC TESTS

Given the scope of mood problems cancer survivors may experience, clinicians need easy to administer methods for screening so that they can make appropriate recommendations and referrals. Numerous methods for screening and diagnosing mental health needs in survivors have been validated that balance ease of use and sensitivity and specificity for defining treatment needs. Many of these measures can be administered in print or online versions, although clinical interview is equally useful and allows for more nuanced understanding of a patient's sources of concern, possible medical or pharmacologic factors affecting mood, and potential responses to recommendations. The NCCN has guidelines for screening distress to assist health care professionals.⁶ A commonly recommended measure is the Distress Thermometer (DT), a simple oral or printed measure that asks the patient to rate their distress from 0 = no distress to 10 = extreme distress. The DT can be used as a screening tool to determine need for further screening using a cut point of 5. However, when compared to structured clinical interviews, the DT lacks sensitivity and specificity and the high rate of false positives could render the single item difficult to use in practice.⁷ Therefore, the DT should not be used as a stand-alone screening tool, but if a patient scores 4 or higher a further screening may be needed.^{8,9} An alternative is the Patient Health Questionnaire (PHQ)-4, designed with the two key depression and anxiety items required for diagnosis.¹⁰ For this measure a cut point of 3 or more provides optimal sensitivity and specificity. However, it is important to recognize that both the DT and PHQ-4 indicate a need for further screening and do not in themselves constitute sufficient evaluation for diagnosis or treatment.

Somewhat longer measures provide more diagnostic details for depression, anxiety, or post-traumatic stress disorder.¹¹ In a randomized trial using the Patient Health Questionnaire-9 (PHQ-9) to screen hematopoietic cell transplant (HCT) survivors, the survivors with higher scores wanted the measure to be used in future visits.¹² Screening can stimulate discussions between survivors and providers about these concerns. Furthermore, providers report more satisfaction with the management of psychological issues and of the overall visit.¹² Table 1 is a list of potential screening tools to use, some of which will be mentioned in this article:

DIFFERENTIAL DIAGNOSIS

Making a differential diagnosis can be critical with cancer survivors as many of the symptoms of anxiety and depression overlap with other problems survivors report such as cognitive difficulties and fatigue. Because mood symptoms overlap with each other, clinicians need a thoughtful screening plan to allow differential diagnosis that can help to determine a specific treatment strategy. It is important to recognize that a survivor may have an agitated depression with symptoms of both anxiety and depression. Similarly, some of the

symptoms for post-traumatic stress also indicate depression or anxiety, e.g., loss of interest, irritability, restlessness, difficulty concentrating or insomnia. Therefore, it is important to either use diagnostic tools that allow for distinguishing these syndromes or the ability to refer to qualified mental health specialists after a more broad screening such as with the DT or PHQ-4.

ANXIETY AND DEPRESSION IN DIFFERENT POPULATIONS OF SURVIVORS

This section will review the literature on anxiety and depression in adult survivors of childhood cancer, adolescent and young adults and adult survivors. Within each section, prevalence, risk factors and trajectories for various mood issues will be discussed.

Adult Survivors of Childhood Cancer

Survivors of childhood cancers have been most extensively studied by the Childhood Cancer Survivor Study (CCSS), which has tracked over 20,000 survivors across the United States. Analysis from the CCSS cohort found that 11% of the survivors had both elevated anxiety and depressive symptoms compared to 5% in the sibling controls.¹⁸ While most survivors did not meet criteria for a diagnosis of post-traumatic stress disorder (PTSD), many survivors did report post-traumatic stress symptoms (PTSS) which do not meet clinical criteria for a diagnosis of PTSD. PTSS can be thought of as a subclinical syndrome relative to PTSD, where some of the symptoms of PTSD are present and disrupt quality of life but do not meet clinical criteria. In contrast to CCSS, a cohort of Dutch childhood cancer survivors found no difference in anxiety or depression between the survivors and controls.¹⁹ In the CCSS cohort, those with chronic health conditions such as cardiovascular, endocrine or pulmonary issues also had higher levels of anxiety and PTSS.²⁰

CCSS has examined the longitudinal course of anxiety and depressive symptoms in childhood survivors who are now adults.²¹ While most report few to no mood symptoms, almost 9% reported persistent depressive symptoms suggesting a clinical diagnosis of depression and almost 5% reported anxiety symptoms suggesting a clinical diagnosis of anxiety. Another group reported increasing symptoms over time: 10% for depression and almost 12% for anxiety. Increasing mood symptoms were related to the survivors' perceptions that their health was worsening. This finding underlines the need for continuing evaluation of mood in young adult survivors.

Adolescent and Young Adult (AYA) Cancer Survivors

AYA survivors are increasingly recognized as a group with emotional needs that differ from either childhood cancer survivors or older adults. Although definitions of AYA age range may vary, the most widely used definition is those diagnosed between ages 15–39.²² In a cohort of hematologic malignancy survivors that used semistructured interviews, 23% met criteria for anxiety, 28% met criteria for depression and 13% met criteria for PTSS.²³ In a sample of Australian AYA's, almost half were classified as being above the cutoff score for PTSS.²⁴ FOR is also common in young adult cancer survivors. Just over half of young adult breast cancer survivors in one study reported moderate to high levels of FOR.²⁵ Another study comparing AYA survivors to controls found no differences in anxiety or depressive

symptoms but the AYA survivors did report more PTSS.²⁶ Other cohorts of AYA's that were much larger (between N=300 and N=6000) found that AYA's reported more distress than controls.^{27–29} These inconsistent findings may be due to differing populations of survivors, methodologies or measures used.

In considering risk factors for impaired mood in AYA survivors, females consistently report more depressive symptoms than young women without a history of cancer or than male survivors. This was found in the National Longitudinal Study of Adolescent Health³⁰ and the Australian cohort study described above.²⁴ The Australian study identified additional risk factors for elevated distress, which included lower social support, low self-image, and identity issues. More intensive treatment also is predictive of more distress.³¹ FOR may be maintained in survivors if they are unable to talk about the cancer experience with their partners.²⁵ This highlights the importance both of opportunities to process the cancer experience and of tracking these symptoms at least annually in AYAs to identify those with a need for treatment before negative moods become chronic.

Adult Cancer Survivors

Anxiety Symptoms—Most survivors are diagnosed as mature adults (over age 40). Approximately 18 to 20 percent of long-term cancer adult survivors report anxiety symptoms.^{32–35} Using the Hospital Anxiety and Depression Scale with a cohort of survivors 6 and 12 months post-diagnosis, 22% and 21% respectively were higher than the cutpoint of 8.³³ Having higher scores at 6 months predicted higher scores at 12 months. Females had twice the relative risk of anxiety than males. Other identified risk factors for anxiety in adult survivors have included shorter time since diagnosis and a higher number of comorbid conditions,³⁶ as well as younger age, living alone and a diagnosis of lung cancer or melanoma.³⁵ A prospective, longitudinal study that documented trajectories of mood symptoms over time found 4 different trajectories in breast cancer survivors assessed over a 2 year follow-up: 1) High Stable, 2) High Decrease, 3) Mild Decrease and 4) Low Decrease.³⁷ Financial difficulties, lower global health and functional status were predictive of being in the High Stable trajectory.

Post-Traumatic Stress Disorder (PTSD)—PTSS are common in cancer survivors although full PTSD diagnosis is seen less often. Reported rates vary depending on the population studied because risk factors depend on the intensity of treatment and age among other factors. A meta-analysis of PTSD comparing survivors and controls found that survivors were more likely to have PTSD (OR=1.66, 95% CI 1.09-2.52).³⁸ In a sample of long-term testicular cancer survivors who were 11 years post-diagnosis, just over 10% had either subclinical or full PTSD.³⁹ In a sample of hematopoietic cell transplant survivors, 15% met criteria for PTSD over a period from pre-transplant to one year post.⁴⁰ Survivors who were younger, diagnosed with later stage disease and recent completion of cancer treatment were at risk for PTSD.³⁸ Pain was associated with higher PTSD levels as well as being female.

PTSS does not meet the level of the clinical diagnosis of PTSD yet can still be troubling for survivors and interfere with functioning. A study of non-Hodgkin lymphoma survivors found that 37% reported PTSS.⁴¹ Factors associated with PTSS include the following^{41–43}:

- Lower educational attainment
- Single relationship status
- Lower income (<\$20,000)
- Unemployment
- Poor social support
- Racial minorities
- More recent diagnosis
- Younger age at diagnosis
- Greater perceived negative impact of cancer
- Intensity of cancer treatment

Fear of Recurrence (FOR)—As previously mentioned, FOR is common in cancer survivors. Almost 80 percent of respondents to a national survey of cancer survivors reported some level of FOR as a concern.⁴⁴ Even for long-term cancer survivors (median 5 years post-treatment), 38% of colorectal cancer survivors reported high levels of FOR.⁴⁵ In another very large cohort (>10,000 participants), 50% reported FOR.⁴⁶ Attentional bias, a tendency to focus on threat-related stimuli, could be a factor that explains FOR in breast cancer survivors.⁴⁷ As an example, Custers and colleagues evaluated women who were either high or low in FOR and found that regardless of the level of FOR, these women had longer reaction times to a task that required them to process cancer threatening words than healthy controls. This study was conducted in a hospital setting so the breast cancer survivors may have been mentally primed for these cancer words. In another study, breast cancer patients were assessed prior to surgery and 6 months post-surgery for risk factors associated with higher FOR.⁴⁸ Risk factors for higher FOR scores at 6 months after treatment included, paradoxically, living with someone as compared to living alone, as well as greater changes in spiritual life, higher state anxiety, more self-reported difficulty coping, or reported more distress due to family members. The authors recognized that living with a partner may be counterintuitive to higher levels of FOR, but they did posit that if a person has low coping self-efficacy, this person may have difficulty navigating the relationships in the context of cancer. Other research has defined risk factors as female, less than 60 years of age, 5-7 years post-diagnosis, social isolation, less than 10 years of education, and survivors who had a recurrence.⁴⁹ Women who had the greatest declines in their FOR scores over time were those who had better physical health along with higher FOR scores at the time of enrollment⁴⁸. In breast cancer survivors who were getting their mammograms, women who reported greater perceived risk, lower coping self-efficacy and greater reassurance-seeking behaviors were more likely to be in the higher FOR group.⁵⁰ Unsurprisingly, FOR tends to increase around the time of scans or other testing for recurrence.⁵¹ FOR may be important to

address as it has been related with negative health behaviors such as smoking and lower levels of physical activity.⁴⁶

Distress—The emotional distress many survivors may experience may not reach the level of a clinical disorder such as depression or anxiety. Preoperative levels of distress as measured by the DT has predicted post-operative pain 4 and 8 months after breast surgery.⁵² Thus, distress may be important to monitor to prevent other symptoms or other behaviors such as smoking in survivors.⁵³ The DT is not just a single item question but also offers respondents the opportunity to mark which aspects of their lives are distressing. Financial concerns, limited mobility, and sleep problems are associated with distress.⁵⁴ Other risk factors for elevated distress vary depending on the population being studied. The Health Information National Trends Survey (HINTS) study has found that African American survivors report higher levels of distress compared to other survivors and non-cancer controls.⁵⁵ Gay and bisexual prostate cancer survivors also report more distress than heterosexual prostate cancer survivors.⁵⁶ Married prostate cancer survivors with lower levels of partner support and unmarried survivors reported more distress than married survivors with high levels of partner support.⁵⁷ Distress can be a long-term problem for cancer survivors as a longitudinal study of colorectal cancer survivors who were 5 years post-diagnosis found that one third of the sample reported high levels of distress.⁵⁸ The study also found that younger men who had late stage disease, lower educational attainment and poorer social support were likely to have higher levels of distress over the course of survivorship.

Depressive Symptoms—Negative mood symptoms such as anxiety, FOR, PTSS and depression often co-occur. In a population-based, longitudinal study, 9% of survivors had both anxiety and depressive symptoms.³³ In a sample of colorectal and head and neck cancer survivors, exposure to childhood trauma was associated with higher depressive symptoms.⁵⁹ When screening depression alone, the prevalence of these symptoms that are above cutpoints for depression range from 12% to 14%.^{33,60–66} A meta-analysis of major depression diagnosed with interviews in the non-palliative care setting found a prevalence of 16%.⁶⁷ This was confirmed in women with breast cancer who were followed 4 months after their diagnosis and over the course of 1 year were assessed a total of 7 times using a clinical interview and questionnaire. In these closely tracked women, 17% met criteria for a major depressive episode.⁶⁸

Physical symptoms can be associated with depressive symptoms.⁶⁹ As an example, oral cancer survivors who reported dental health, problems with smelling, and issues with range of motion were associated with both depressive and anxiety symptoms.⁷⁰ In prostate cancer survivors, men with higher levels of urinary and androgen deprivation therapy symptoms reported higher levels of depressive symptoms.⁶⁴ Reduced sexual function by head and neck cancers also has been associated with depressive symptoms.⁶⁶ In a Medicare sample of colorectal cancer survivors, ethnic minorities, having two or more comorbidities and difficulties in daily living were associated with more depressive symptoms.⁷¹ Lack of receipt of a survivorship care plan (SCP) which is mandated by the American College of Surgeons⁷² has also been associated with higher depressive symptoms.⁷³

Risk factors for depressive symptoms include:

- In a heterogeneous sample of adult cancer survivors, a diagnosis of melanoma, survivors not in remission, and smoking³³
- Females⁶¹
- A higher number of comorbid conditions^{36,63,74}
- Negative body image for women^{75,76}
- Financial problems^{64,71,77,78}
- Within the first 2 years of survivorship⁷⁹
- Prior history of depression^{33,35}
- A sedentary lifestyle^{33,35}
- Loneliness⁸⁰

Longitudinal studies have examined the different trajectories of depressive symptoms following a cancer diagnosis. Breast cancer survivors (N=653) were assessed 4 times (baseline, 6, 12, and 18 months) and 6 trajectories were identified.⁸¹ Most of the sample could be classified as having very low or low depressive symptoms while 29% had consistently borderline scores. Another 11% had high depressive scores at baseline and declined over time but was still above the cutoff; 7% had increasing depressive symptoms while a very small percentage (1%) reported very high scores at all of the timepoints. Stanton and colleagues found similar trajectories in their sample of breast cancer survivors.⁶⁸

TREATMENT OPTIONS

Evidence from randomized controlled trials indicate that several behavioral approaches are effective in improving mood in cancer survivors, although a majority of studies have been done in female breast cancer survivors. Therefore, all of these interventions need further testing with diverse groups of survivors, particularly men. Cognitive behavior therapy (CBT) is effective in reducing mood symptoms in cancer survivors.^{82–84} Mindfulness-based approaches also has demonstrated efficacy in reducing anxiety and depressive symptoms.^{85–89} In a small study, hypnosis has reduced anxiety symptoms in breast cancer survivors.⁹⁰ Self-management strategies also are effective in decreasing distress.^{91–93} Modes of intervention delivery are rapidly changing and the internet and social networking modalities may be attractive options for psychosocial interventions because many survivors already use these resources for cancer information.^{70,92–99} Telehealth approaches may improve access to mental health resources especially for those with limited online access or lack of online skill.^{84,100,101} Physical activity interventions also reduce depressive and anxiety symptoms in breast cancer survivors.¹⁰² However, in a study of prostate cancer survivors in which depressive symptoms and anxiety were secondary outcomes, there was no effect of the physical activity intervention on mood.¹⁰³

Medications provide additional options for regulating mood. A small study using selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRIs) for the treatment of hot flashes in breast cancer survivors found reductions in depressive symptoms with both types of medications.¹⁰⁴ In a medical chart review of over 16,000 breast cancer survivors, there was no indication of an increased risk of recurrence when concurrently taking tamoxifen and antidepressants although caution is still recommended for prescribing medications with cytochrome P₄₅₀ interactions, specifically fluoxetine, paroxetine, sertraline, bupropion, fluvoxamine and nefazodone.^{6,105} Gabapentin has been tested in a 3 arm RCT with breast cancer survivors comparing 300 mg, 900 mg and a placebo and the 300 mg dose condition had the best outcomes except for those with the highest levels of anxiety.¹⁰⁶ Gabapentin, like venlafaxine, is also effective for hot flashes so these medications could be beneficial in reducing multiple symptoms. With the options available to treat mood symptoms, and the lack of evidence for the superiority of one treatment over another, asking survivors their preferences for treatment can be a way to engage in shared decision-making and potentially to improve adherence. See Table 2 for a summary of evidenced-based interventions in cancer survivors.

FUTURE CONSIDERATIONS/SUMMARY

Many survivors cope well with cancer and its associated treatments. However, for a subgroup of survivors, anxiety, depression, fears and distress can linger for up to 10 years after treatment.¹⁰⁷ For some of the issues discussed such as FOR, no standardized definitions exist, which makes comparing research results difficult.¹⁰⁸ More research is needed with diverse survivors on many levels: types and stages of cancer, racial/ethnic diversity, sexual minorities, and rural survivors to name a few groups. We also need to develop and validate improved screening methods so that we can monitor survivors' symptoms over time and make appropriate referrals. When looking at the various treatment options, it is clear that most interventions have been tested only with breast cancer survivors, and we need to test treatments with patients who have other diagnoses. Information also is lacking about survivors who were not treated at large cancer centers.¹⁰⁹ In short, cancer survivors have long-term increased risk for mood disruptions and evidence-based treatments exist that can relieve their distress.

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Key Points

1. Many cancer survivors experience cancer-related fear of recurrence, post-traumatic stress symptoms, anxiety, or depression after completing treatment.
2. Anxiety and fear are more common than depression.
3. We are beginning to understand risk factors for these issues. Females, adolescents and young adults and those who receive intensive treatment are more vulnerable.
4. Most of what we know is from breast cancer survivors; more research is needed with diverse cancer survivors.
5. Evidence supports a number of interventions to assist cancer survivors in coping with emotional distress including behavioral and pharmacological treatments.

Table 1

Potential Screening Tools for Anxiety and Depression

Measure Name	Concept Measured	Number of Items	Cutoff Score
Patient Health Questionnaire – 9 (PHQ-9) ¹³	Depressive symptoms	9	10
Generalized Anxiety Disorder Screener (GAD-7) ¹⁴	Anxiety symptoms	7	>10
Hospital Anxiety and Depression Scale (HADS) ¹⁵	Anxiety and depressive symptoms, total distress score	14	HADS-Depression 5 HADS-Anxiety 7
PTSD Checklist for DSM-5 ¹⁶	Post-Traumatic Stress Symptoms	20	>33
Impact of Events Scale (IES-R) ¹⁷	Post- Traumatic Stress Symptoms	22	24

Data from Refs^{13–17}.

Table 2

Evidence-based Interventions for Cancer Survivors

Type of Intervention	Modality	Cancer Populations with Evidence	Outcomes
Cognitive Behavioral Therapy (CBT) ^{82–84}	Face to face, Telehealth	Breast, hematopoietic cell transplant	Depressive symptoms, anxiety, post-traumatic stress
Mindfulness-Based Stress Reduction (MBSR) ^{85–89}	Face to face	Breast	Depressive symptoms, anxiety, fear of recurrence
Hypnosis ⁹⁰	Face to face	Breast	Depressive symptoms
Self-Management ^{91–93}	Web-based	Breast, mixed cancer sites	Distress
Physical Activity ^{95,102}	Face to face, Web-based	Breast	Depressive symptoms, anxiety
Gabapentin ¹⁰⁶	Face to face	Breast	Anxiety

Data from Refs^{82–93; 95, 102, 106}.