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Psychiatric comorbidities in cancer survivors across tumor subtypes: A systematic review

Bach A *et al.* Psychiatric disorders cancer survivors

Abstract

BACKGROUND

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD).

AIM

To identify studies that examined the prevalence of clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD for patients with one or more tumor sites and compared those prevalences between cancer subtypes.

METHODS

Four databases (PubMed, PsycInfo, PubPsych and the Cochrane Database) were searched and resulted in a total of 2387 articles to be screened. To be included, a study must have investigated cancer-free and posttreatment survivors using tools to assess clinically relevant levels of the listed psychiatric comorbidities. All articles were screened by two authors with a third author reviewing debated articles.

RESULTS

Twenty-six studies on ten different tumor types fulfilled all inclusion criteria and were included in the review. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Generally, all four comorbidities show higher prevalences in cancer survivors than the general population. Brain tumor survivors were reported to have a relatively high prevalence of both depression and anxiety. Studies with melanoma survivors reported high prevalences of all four psychiatric comorbidities. Regarding comorbidities, a wide range in prevalence existed across the tumor types. Within one cancer site, the prevalence also varied considerably among the studies.

CONCLUSION

Psychiatric comorbidities are more frequent in cancer survivors than in the general population, as reflected by the prevalence of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor subtypes. Developing generalized screening tools that examine psychological distress in cancer survivors up to at least ten years after diagnosis could help to understand and address the psychological burden of cancer survivors.

Key Words: Cancer survivor; Cancer type; Prevalence; Psychiatric disorder; Psychiatric comorbidity; Survivorship; Tumor site

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Core Tip: Psychiatric disorders are a common comorbidity in cancer survivors, even years after diagnosis. Studies have found that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder. This systematic review compared the prevalence of these four psychiatric disorders in cancer survivors among tumor types. The results suggest that there are variations in the prevalence of all comorbidities across and within cancer types. A future direction should be the development of a screening tool to regularly assess cancer survivors' psychological distress for at least 10 years after the initial disease.

INTRODUCTION

Before, during and after treatment, patients with cancer are exposed to a variety of factors (physical constraints, fatigue, financial problems, *etc.*) that may impact their psychological state. This is in addition to the possible trauma caused by a cancer

diagnosis and treatment. With the number of cancer survivors growing due to longevity and medical progress, the evaluation of long-term psychological aftereffects and their predispositions becomes more relevant^[1]. Over the last decades, the examination of psychiatric comorbidities in cancer survivors has become a growing research field. According to several studies, tumor type can have an impact on the risk of developing a psychiatric comorbidity^[2-4]. This paper aimed to review the literature about psychiatric comorbidities in cancer survivors across cancer types to identify their commonalities and differences.

Cancer survivors experience several challenges even after finishing acute treatment. Chemotherapy, radiation and other kinds of treatment often bear the risk of long-term side effects. This can lead to clinically relevant levels of psychological distress, and survivors have an increased risk for mood alterations compared to the general population^[5]. The simultaneous presence of two or more clinical conditions is referred to as comorbidity, which requires special attention when strategizing treatment^[6]. Some of the most frequent psychiatric comorbidities in long-term cancer survivors are depression, generalized anxiety disorder and posttraumatic stress disorder (PTSD), all of which can depend on the type of cancer.

The response to each cancer type calls for unique treatment plans and exposes survivors to a particular risk of recurrence. Therefore, cancer survivors of different tumor types are exposed to several burdens, not only during the acute treatment phase but also after the treatment is finished. Studies have found that patients with specific tumor types may experience more psychological distress than others. Muzzatti *et al*^[4] found that survivors with a history of breast cancer showed more anxiety and depression than those with a history of lymphoma or genitourinary tumors. Similarly, Götze *et al*^[3] described that breast and skin cancer survivors showed the highest levels of anxiety and depression, whereas prostate cancer survivors showed the lowest levels. Another study showed significant variation in psychological distress across cancer types^[7]. In contrast, there are studies that did not find a significant difference between cancer sites and clinical levels of depression, anxiety or PTSD^[8-10]. In these studies, other

patient characteristics, such as sex and age at the time of diagnosis, were proposed to have an influence on the prevalence of psychiatric comorbidities. Another argument by Deimling *et al*^[10] is that with increasing time since diagnosis, cancer type and treatment-specific stressors are removed, and psychological stressors become more homogeneous.

Identifying whether there are specific influences on distress depending on a survivor's cancer site could help to identify necessary adjustments to survivorship programs and medical follow-up treatments. To do so, it is important to know which patient characteristics and tumor entities have an effect on psychological distress and further effects on the development of psychiatric disorders due to disease-related burdens. Additionally, this could provide more insight into cancer site-specific psychological guidelines for the psychological care of cancer survivors after treatment.

Therefore, this systematic review aimed to identify studies that examined clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD across tumor types.

MATERIALS AND METHODS

The systematic review was conducted according to the PRISMA statement criteria^[11]. The review protocol is registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42021253430).

Literature search

We searched four databases between February 8th and 19th, 2021: PubMed, PsycInfo, PubPsyc and the Cochrane Database. Articles published in any year were included. Our search terms were as follows: [(Psychiatric OR psych*) AND (comorbidity OR disorder)] AND (cancer OR tumor OR neoplasm OR oncolog*) AND (survivor OR survivorship OR long-term).

Inclusion and exclusion criteria

The eligibility criteria were based on the five PICOS dimensions. P: The participants were cancer survivors with the following characteristics: Adults at the time of cancer diagnosis and not in (primary) acute treatment. Survivors were defined according to the World Health Organization (WHO) as patients who have had cancer and are, following treatment, now cured of the disease^[12]. This implies that all studies where all/a subpopulation(s) of survivors were still in active treatment were excluded. I: Studies with any kind of intervention were excluded. C: A control group was not necessary. O: The outcomes were the prevalence of psychiatric comorbidities, more specifically, the clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD. S: The study designs included in the review were observational, cross-sectional and longitudinal designs.

The exclusion criteria were: (1) Studies with no cancer patients; (2) Studies with no survivors; (3) Studies with no psychiatric/psychological assessment; (4) Studies with a patient group < 18 years old at the time of cancer diagnosis; (5) Studies not in accordance with the predefined study designs; (6) Articles with missing information or not written in English; (7) Studies including an intervention; and (8) Studies that did not separate the different tumor types.

Data extraction

After removing duplicates, the articles were screened for relevant titles by two authors. For papers where the first two authors did not agree, a third author decided. The remaining articles were screened for abstracts again by the two authors, with the third author reviewing debated articles. Then, all three authors came to a consensus. One author screened the remaining articles for the full texts. The studies that were considered eligible were included in the review, and the relevant data were extracted.

Quality assessment

The quality of each study was assessed according to the study design, participant selection and method of patient evaluation^[13].

Statistical analyses

The included papers showed high heterogeneity in the number of participants, time since diagnosis and assessment tools used (Table 1). Furthermore, there were a limited number of articles per tumor site (*e.g.*, 4 articles related to breast cancer *vs* 1 article related to brain tumors). Therefore, this review aimed to perform a descriptive data analysis rather than a meta-analysis. The descriptive analysis focused on the prevalence of the mentioned psychiatric comorbidities in cancer survivors with a focus on similarities and differences among the tumor types.

RESULTS

The literature search of the four scientific databases provided 2968 results. After removing duplicates, 2387 articles were left for screening. Title screening reduced the number to 102 articles, which was further filtered to 72 for full text screening. Finally, 26 studies were considered relevant to the topic and were included in the review (Figure 1). Table 2 shows the extracted data (reference, tumor type, study population, time since diagnosis, screening tools to assess psychiatric comorbidity, prevalence of comorbidity and potential bias) of the included articles. Several studies had to be excluded after full text screening because of missing reports of the prevalence in percentages and instead reporting the mean results of the questionnaires.

Quality assessment

The studies included in the review were assessed for possible risks of bias. The natures of the study designs analyzed here are known to favor certain biases^[13]. Table 2 shows the reviewed studies with the study design (self-report questionnaire, personal interview, *etc.*) and possible type of bias. All studies used a cross-sectional design, with only some having a matched comparison group, and therefore bear the risk of selection bias. Two qualities of the reviewed studies presented a risk of response bias: Cancer survivors with specific (psychological or physical) symptoms may be more likely to

respond to a study invitation, and most studies were self-report questionnaires. Performance bias may have occurred in the studies that used personal interviews. Exclusion bias may be present in the studies where a specific group of participants was not included in the results (Table 2).

Study characteristics

There was a wide range of study characteristics within the included articles. We extracted data for ten different broad tumor sites. For each site, the number of articles included were as follows: Breast (5), gynecological/cervical (2), hematological (4), testicular (5), prostate (1), head and neck (3), stomach (1), melanoma (3), brain (1) and lung (1). The number of participants ranged between 17^[13] and 1260^[14]. The studies were published between 2002 and 2020. The age of the participants ranged between 18 and 93 years. Seven studies included only women, and six studies included only men because of the specificity of the cancer site. The remaining thirteen studies included both men and women.

Assessment tools

In the studies, psychiatric comorbidities were evaluated with a variety of assessment tools, including questionnaires and personal interviews. Table 1 shows all the assessment tools and their abbreviations with regard to the study they were used in. The most common questionnaire was the Hospital Anxiety and Depression Scale (HADS), which was used in eleven of the 26 studies. The assessment tool used in each article is shown in the summary of the findings (Table 2). Most articles included the screening of more than one psychiatric comorbidity (*e.g.*, depression and anxiety), while others focused on only one.

Time since diagnosis

The studies included in this review ranged from 144 d^[16] to more than 11 years since diagnosis^[17-19]. Some studies found an effect of time since cancer diagnosis and

psychological distress. According to Mols *et al*^[20], depressive symptoms declined over time, whereas anxiety scores stayed stable across a 4-year period.

Depression

Twenty-one of the 26 articles assessed the prevalence of depression in cancer survivors, including for all ten tumor sites. Table 3 shows the studies organized by tumor site and the extracted percentages for clinical levels of depression. Comparing the prevalences among tumor types, a high variability, between 7.9% and 48%, can be seen. Whereas most tumor sites showed a range between 8% and 22% for clinical levels of depression, four cancer subtypes showed a much higher prevalence (above 40%): Head and neck^[21], stomach^[22], melanoma^[14] and brain^[23] cancer.

Furthermore, within one cancer site, the prevalence varied. For testicular cancer survivors, the prevalence of depression was relatively stable across the four studies included in the review (between 7.9%^[19] and 9.7%^[15,24]). For patients with breast cancer, the prevalence varied between 8%^[16] and 22%^[25].

Anxiety

Fifteen of the eligible studies assessed the prevalence of clinical levels of anxiety in cancer survivors. Among these, six different tumor types were assessed: Breast, testicular, hematological, cervical/gynecological, melanoma and brain tumors (Table 3). The percentage for anxiety ranged between 3.5% and 58.5%. A study on brain tumor survivors showed a high prevalence of clinical levels of anxiety of almost 60%^[23], whereas across the other tumor sites, the prevalence ranged between 6.1%^[19] and 20.2%^[15].

Comorbid anxiety-depression

Only four of the 26 articles assessed the prevalence of comorbid anxiety-depression in cancer survivors (Table 3). The included tumor types were breast, testicular and melanoma (2 studies). The two studies assessing the prevalence in melanoma patients

showed a prevalence of comorbid anxiety-depression in up to 40%^[14] of survivors. The smallest prevalence was found in breast cancer survivors, with a study indicating a prevalence of comorbid anxiety-depression of 1.5%^[26].

PTSD

Ten studies assessed PTSD in cancer survivors across 6 different tumor types. Whereas testicular cancer survivors showed a comparably low level of full PTSD with a prevalence of 4.5%^[17], the two studies including melanoma patients showed numbers as high as 48%^[14,27]. For breast cancer survivors, the prevalence ranged from 6.3%^[16] to 18%^[28].

DISCUSSION

This systematic review aimed to describe differences and commonalities between psychiatric comorbidities in cancer survivors across ten tumor types. Twenty-six studies that matched all the inclusion criteria and provided the prevalence of at least one of the four psychiatric comorbidities as a percentage were included.

Studies on psychological distress in cancer survivors found that there are risk factors for developing clinical levels of mood disorders. A systematic review on the prevalence of depression in breast cancer survivors reported several factors associated with depression: Fatigue, low income or poor financial status, low education level and younger age^[29]. A review with testicular cancer survivors found that poorer psychological health was related to living alone, being unemployed or having a low socioeconomic status and experiencing worse symptoms/side effects^[30].

We observed differences across the studies in the prevalence of psychiatric comorbidities after a cancer diagnosis, even when patients were no longer in treatment and there was no sign of disease recurrence. It was not clear whether these differences were partly caused by the type of cancer. Other factors, such as the time since diagnosis, participant demographics, and the assessment tool, may have similarly influenced the prevalence of clinical levels of depression, anxiety, and PTSD. Andrykowski *et al*^[31]

found a wide range of reported anxiety and depression levels in cancer survivors, which was due to challenges in identifying the rate of psychological distress in cancer survivors. One of the difficulties is the variation in detecting a psychiatric disorder due to the range of screening tools and criteria. The studies in this review used a variety of assessment tools. Furthermore, the studies demonstrated a wide range of sample sizes and participant demographics, including the risk factors mentioned above. The country of origin has similarly been shown to have an effect on cancer survivors' psychological distress. For example, a ² comparison between Hong Kong Chinese and German Caucasian women with breast cancer showed that greater unmet psychological needs were detected in Germany^[32].

Depression

Our results show a higher prevalence of depression in cancer survivors than in the general population. Whereas some of the studies reported prevalences in the normal range, more than half of the prevalences were 15% or higher. Furthermore, one longitudinal study^[33] found that the prevalence of depression did not differ significantly over the course of five years for head and neck cancer survivors. A comparison of cancer types regarding depression showed consistently lower levels of depression in testicular cancer survivors than in breast cancer survivors, where the prevalence varied from 8% to 22%. Patients with several tumor entities, namely, head and neck, stomach, melanoma and brain tumors, demonstrate higher levels of depression, between 41% and almost 50%, indicating the need for special support for these groups of cancer survivors.

Anxiety

Anxiety scores were reported by 15 studies and showed a very wide range of prevalences from 3.5% to almost 60%. Moreover, our review showed that anxiety prevalence was higher than the prevalence of clinical levels of depression. Similarly, among United States adults, data on anxiety disorders shows a higher prevalence than

the prevalence of depression^[34]. The highest prevalences of anxiety were seen in breast, melanoma and brain tumor survivors, although one study on breast cancer survivors reported a prevalence as low as 3.5%. The study by Nicol *et al*^[23] with brain tumor survivors reported an especially high number of survivors showing clinically relevant levels of anxiety, with a prevalence of 58.5%.

Comorbid anxiety-depression

Comorbid anxiety-depression was assessed in only four of the 26 included studies. A useful comparison among cancer types is therefore difficult. In contrast to the two studies on breast and testicular cancer survivors that reported a prevalence of 1.5% and 6.8%, respectively, the prevalences in two studies with melanoma survivors were higher (up to 40%)^[14,27]. For all three of the previously mentioned psychiatric comorbidities, melanoma survivors seemed to show relatively high prevalences, which might indicate a distinctive demand for psychological support for this survivor group.

PTSD

Ten studies examined posttraumatic stress syndrome in cancer survivors. Geffen *et al*^[35] compared survivors who either had Hodgkin's disease or non-Hodgkin's lymphoma with a matched control group that had experienced at least one traumatic life event. They did not find significant differences between the survivors and control group in the occurrence of posttraumatic stress symptoms, suggesting that a cancer diagnosis might have the same impact as experiencing a traumatic event. Again, studies on melanoma cancer survivors showed a particularly high prevalence of PTSD (35% and 48%), which was assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Clinical Version, at a median time of 30 mo and 5.6 years after the diagnosis, respectively^[14,27]. Another study investigated the occurrence of PTSD in testicular cancer survivors 11 and 19 years after diagnosis and found that the prevalence of clinically relevant PTSD symptomatology was reduced by more than half at the latter time point^[17].

Limitations

This review contains some limitations, with the most obvious being the limited number of studies per cancer site. Since we employed stringent inclusion and exclusion criteria, many studies were not included in the review. It was important to include only cancer survivors based on the WHO definition, meaning that the survivors were not going through acute treatment. This exclusion criteria were chosen to ensure that the prognosis and side effects of the treatment were not likely to influence the results of a psychiatric assessment. Several studies included a noteworthy number of survivors who still received some kind of treatment, from radiotherapy to immunotherapy^[3,36]. This limitation is likely influenced by the lack of a unique definition of cancer survivorship^[37], which may have complicated the literature search.

Some studies have already investigated psychiatric comorbidities across different cancer types^[4,9]. These studies did not include the separate prevalences per tumor type in their papers and therefore could not be reported in this review. Several studies reported the mean results on the questionnaires; however, the prevalence of clinical levels of depression, anxiety or PTSD could not be extracted. This review focused on four types of psychiatric comorbidities in cancer survivors, which represent the most common mental health disorders. Less common psychiatric comorbidities, such as acute psychosis, are likely present in cancer survivors (although at very low prevalence) but were beyond the scope of this review. Future work should address these.

We explored the extracted data with a focus on differences among cancer types. The studies that were reviewed displayed a high heterogeneity in key study characteristics (*e.g.*, the number of participants, time since diagnosis, assessment tools), which may have had a significant influence on the results and was not considered in our review. The various screening tools possibly measure psychological distress and clinical relevance in a way that cannot be easily compared^[31]. A systematic review on the HADS indicated that the assessment tool might underestimate true levels of anxiety and

depressive symptoms because it does not include somatic symptoms^[38]. This may have impacted the generalizability of the HADS-based results.

Future directions

The increased prevalence of clinical levels of psychological distress for cancer survivors remains an issue to be adequately addressed. Whereas many survivorship programs are being developed, the specific needs of cancer survivors depending on their own personal experiences have not yet been widely explored. Beutel *et al*^[39] suggest general screening even 10 years after diagnosis, which would show the objective and subjective needs of each cancer survivor. Götze *et al*^[40] supported this recommendation following their examination of emotional distress in cancer survivors. They compared a group of survivors five years after diagnosis with a group 10 years post-diagnosis and found no significant difference in emotional distress between the groups. However, a significant difference between tumor entities was detected, with breast and skin cancer survivors showing the highest levels of anxiety and depression and prostate cancer survivors showing the lowest levels. Furthermore, Kypriotakis *et al*^[41] compared long-term cancer survivors of different tumor sites at four different time points. They found that cancer stage at the time of diagnosis was a significant predictor of initial depressive symptoms. Therefore, a future direction could be the development of screening tools to repeatedly measure cancer survivors' psychological distress up to 10 years after the last acute treatment phase. According to Beutel *et al*^[39], such screening would include survivors who are below the threshold of a mental disorder but still have difficulties adjusting to being a cancer survivor.

CONCLUSION

The articles included in this review showed high heterogeneity in several study characteristics (the number of participants, time since diagnosis, assessment tools, *etc.*) and showed that psychological distress in survivors is dependent on multiple factors. We aimed to describe the differences among tumor types, which were limited by

missing data and/or the lack of a clear definition for survivorship. More research is needed that evaluates the specific psychological needs of cancer survivors and how to address them in survivor programs. Future research should have a clear definition of cancer survivorship and take participant characteristics such as the tumor subtype, the time since diagnosis and demographics into account. Furthermore, our results strongly suggest future guidelines for psychiatric and distress screenings for at least ten years after a cancer diagnosis, even when there is no sign of recurrence.

ARTICLE HIGHLIGHTS

Research background

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD) symptoms.

Research motivation

Detecting differences in the prevalence of four common mental disorders that can occur as a comorbidity in cancer survivors might lead to a better understanding of cancer survivors' psychological distress. This might help to address the psychological concerns of cancer survivors more effectively.

Research objectives

The aim of this review was to identify studies in which clinically relevant levels of common mental disorders in cancer survivors were examined. The prevalence rates were compared among different cancer types.

Research methods

Four databases were searched for studies that investigated cancer-free, posttreatment survivors with screening tools that assess clinically relevant levels of four common

mental disorders. Two authors screened all articles, with a third author reviewing debated articles.

Research results

Twenty-six studies were included in the article and indicated the prevalence of one or more of the four mental disorders. Ten different tumor types were examined in the included papers. Generally, all four comorbidities show higher prevalences in cancer survivors than in the general population. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Each comorbid disorder had a variable prevalence across tumor subtypes. Within one cancer site, the prevalence also varied considerably among the studies.

Research conclusions

Psychiatric comorbidities are high in cancer survivors relative to the general population, as reflected by the prevalences of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor types. This enhanced distress is clinically relevant even years after a cancer diagnosis. The lack of a concise definition of cancer survivorship likely contributes to the high heterogeneity among studies focusing on cancer survivors' psychological distress, which might hinder significant comparisons among studies.

Research perspectives

Developing generalized screening tools that examine psychological distress in cancer survivors for at least ten years after diagnosis could help to understand and address the psychological burdens of the survivors.

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