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IT'S NOT OVER WHEN IT'S OVER: LONG-TERM SYMPTOMS IN CANCER SURVIVORS— A SYSTEMATIC REVIEW*

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ABSTRACT

Background: The number of cancer survivors is steadily increasing. Following completion of primary cancer treatment and many years thereafter, specific symptoms continue to negatively affect cancer survivors. The purpose of this article is to review the evidence of symptom burden following primary treatment for cancer in survivors of the most common types of cancer (breast, gynecological, prostate, and colorectal). *Methods:* A systematic review of

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literature published between the years 2000-2008 that reported late-effects and/or long-term psychosocial symptoms associated with cancer survivorship post-completion of primary cancer treatment was conducted. The symptoms include physical limitations, cognitive limitations, depression/anxiety, sleep problems, fatigue, pain, and sexual dysfunctions. *Results:* Symptom burden associated with cancer survivorship was consistent among the four most common types of cancer (breast, gynecological, prostate, and rectal/colon), despite various types of treatment exposure. Generally, across the cancer groups, depressive symptoms, pain, and fatigue were commonly found in cancer survivors. *Conclusions:* Based on longitudinal and cross-sectional evidence, cancer survivors can experience symptoms for more than 10 years following treatment. These symptoms were present in survivors of all four cancer types who underwent a wide variety of treatment. The results indicate that these symptoms should be evaluated and managed to optimize long-term outcomes.

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Key Words: cancer survivorship, symptom burden, fatigue, depression, anxiety, late-effects, long-term

INTRODUCTION

The prevalence of cancer survivors has steadily increased over the past decade due to earlier detection, technological advances, and improved diagnostic procedures [1]. As survival rates improve, new challenges emerge. The presence of symptoms and emerging health problems, often secondary to the cancer, are experienced by a number of cancer survivors for years following primary cancer treatment [1, 2]. There are reports by survivors of many types of cancer that symptoms including fatigue, depression, anxiety, pain, and cognitive limitations persist for years post diagnosis [3-5]. These symptoms are presumed to be the consequence of both the malignancy and exposure to primary treatments including surgery, chemotherapy, and radiation [2]. Evidence suggests the contributory role of treatment exposure in these symptoms [6]. However, from an epidemiological perspective, a causal link between exposure and these outcomes remains to be confirmed [7]. By providing a general overview of current research related to the presence of various types of symptoms in different cancers at various times across the trajectory of cancer survivorship, we sought to further understand the presence of symptom burden that can affect the lives of cancer survivors.

The term symptom burden has been used to characterize distressing generic symptoms associated with medical conditions. Symptom burden is defined as the combined impact of symptoms related to a disease and disease-related treatment on function [8]. These symptoms are characterized in terms of prevalence, duration, and intensity. This article focuses on findings related to

patient-reported symptoms over time post-primary treatment in those diagnosed with cancers in adulthood. Specifically, this article examines symptoms in the four largest groups of cancer survivors; breast, prostate, colorectal, and gynecologic cancers [9].

METHODS

This review article examined the most current literature on patient-reported outcomes related to long-term or late effects of cancer and treatment exposures. The literature search comprised indexed papers in Medline and/or PubMed from 2000 to 2008 (December), including those published online before their print date that used either:

1. prospective/longitudinal designs that tracked symptoms over various time frames; or
2. cross-sectional designs.

Other parameters of the search included: cancer survivors were post initial primary treatments for cancer, papers addressed at least one of the symptoms of interest to this review, and the papers were written in English.

The symptoms searched were physical limitations, cognitive limitations, depression/anxiety, sleep problems, fatigue, pain, and sexual functions. The key terms used were: Cancer, long-term, late effect, and specific symptom (e.g., cognitive limitations, fatigue). Papers were excluded if they reported on long-term or late symptoms in survivors of childhood cancers. Study quality was not assessed in this review.

Two types of research were reviewed for associations between treatment exposure and patient-reported outcomes. First, the literature that addresses the temporal relationship between exposure (very generally defined) and symptoms (i.e., prospective/longitudinal studies) was reviewed. The goal was to provide an overview of prospective studies where symptoms were tracked prior, during, and/or after "treatment exposures" across various cancers. Second, cross-sectional studies where the causal link between exposure and symptom could not be determined but where we were able to observe associations were reviewed.

RESULTS

An emerging series of empirical work highlighting the long-term symptom burden associated with cancer and cancer treatment exists. The body of literature on breast cancer is the most abundant including diagnosis, treatment, and late- or long-term effects. The breast cancer literature currently serves as the standard by which to model research on symptoms over time among other types of cancer (see Table 1).

Table 1. Symptom Burden in Breast Cancer Survivors

	Time since primary treatment completion					
	Immediately following	Up to 6 months	6 to 12 months	1 to 2 years	2 to 5 years	> 5 years
Fatigue	X* [10, 12, 14] X [12, 14]	X [22] O [12, 14, 16, 114]	X [11] O* [18]	X* [10, 19, 20] X [18]	X* [10, 16, 19, 21] X [19]	X [23]
Sleep disturbance	x* [23]	X* [15] X [23]	X* [23]	X* [24] X [20] O [24]	X [23]	—
Depressive symptoms	X* [25] X [29] O* [23]	X* [22, 25-28] X [30] O [23]	X* [16, 25] X [27, 30] O [23]	X* [26] X [18] O* [20, 24, 30] O [16, 26, 30]	X [18] O* [24, 31] O [31]	O [23]
Anxiety symptoms	X* [23]	X* [26, 28] X [23]	X* [26] X [23]	X* [26] X [26]	X [33, 35]	—

Cognitive limitations†	X* [10] X [32, 34-37]	X* [39] O* [38, 40]	X* [10] X [39, 41] O* [33, 34]	X* [37] O* [10] O [18, 23]	—	—
Pain/functional limitations	X* [11] O* [23, 43]	X* [30, 42, 44, 45] X [27, 46] O [23]	X* [30, 42, 54] X [11] O* [27, 46] O [18, 23]	X* [20, 30, 42, 44] X [46] O [18]	X* [30, 31, 42, 44] X [31]	X [23, 47]
Sexual dysfunction	X* [11] O* [23, 47, 48]	X* [23, 48]	X* [11] O* [23, 48]	X* [24] X [48]	X* [24, 31] X [31]	X [49]

Note: All studies in table are longitudinal studies (2000-2008).
X = Symptoms present; O = No association found; - - = No studies found
*Investigations that included assessment prior to treatment initiation.
†Cognitive limitations symptoms are determined via neuropsychological assessment.

Symptoms are reported in both longitudinal and cross-sectional studies in various types of cancer. Table 2 provides an overview of the studies that reported either prospective/longitudinal or cross-sectional associations between these symptoms and cancer-related treatments. The symptoms (i.e., physical limitations, cognitive limitations, depression/anxiety, sleep problems, fatigue, pain, and sexual functions) were consistently seen in both cross-sectional and longitudinal studies over the most common groups of cancer survivors (breast, prostate, colorectal, and gynecologic) who received standard primary treatments (i.e., surgery, chemotherapy, and radiation). The literature presented is organized by symptoms present following primary treatment. Table 3 describes the number of studies by length of follow-up time.

Breast Cancer

A summary of research on symptoms over time in breast cancer survivors can be found in Table 1. A relatively large number of longitudinal studies (39) were found in the search on breast cancer survivors and, despite many more cross-sectional studies, this table attempts to identify a pattern based exclusively on longitudinal studies. Breast cancer survivors treated with some combination of surgery, chemotherapy, radiation, and hormone therapy reported fatigue immediately following treatment [10-14] at prevalence rates of 26-28% [12, 13], up to 6 months post-treatment [12, 14, 15] at a reported rate of 17% [12], 6 to 12 months post-treatment [12, 14, 16, 17] at rates of 16-49% [12, 14, 17], 1 to 2 years post-treatment [10, 18-20] at rates of 20-35% [18, 19], 2 to 5 years post-treatment [10, 16, 18, 19, 21] at rates of 20-56% [16, 18, 19, 21], and points up to more than 5 years post-treatment [19] at a rate of 34%. A minority of studies dispute the presence of fatigue in survivors of less than 1 year [11, 22].

Sleep disturbance was also found to be a problem in the majority, but not all [20], studies from the end of treatment [23] up to 5 years post-treatment [15, 23, 24] at a rate of 59% of survivors experiencing difficulties with sleep 1 to 2 years out [24] and 14% of survivors reporting problems 2 to 5 years post-treatment [24]. The presence of depressive symptoms was found to be prevalent more often [16, 22, 23, 25-28] than not [22, 29, 30] in the first year post-treatment, with rates of approximately 30% immediately following treatment [25], 21-48% up to 6 months post-treatment [22, 25, 26, 28], and 21-34% 6 to 12 months post-treatment in studies that reported a significant presence of depressive symptoms [16, 25]. However, when considering the time beyond 1 year post-treatment, findings have been more mixed [16, 18, 20, 23, 26, 30, 31]. In studies that assessed levels of depressive symptoms that were elevated but failed to meet diagnostic threshold, the rates were 23% 1 to 2 years post-treatment [26], and 15-32% in survivors 2 to 5 years post-treatment [16, 26].

Table 2. Symptoms Post Primary Treatment by Cancer Type

	Cognitive limitations	Depression/ anxiety	Fatigue	Pain/functional limitations	Sexual function	Sleep problems
Gynecologic cancer	—	X^A [49-53] X^B [58-62]	X^A [49] X^B [65, 67-69] O [70]	X^A [57] O^B [69, 72, 73]	X^B [69-74]	—
Prostate	X^A [75-77] X^B [86]	X^A [83-84] X^B [87]	X^A [74, 78, 79] X^B [85, 87]	X^A [83, 85] X^B [86, 87]	X^A [79-82] X^B [86-88]	X^B [87]
Rectal/ colon	—	X^A [89, 90] X^B [85, 93]	X^A [89, 90]	X^A [89-91] X^B [85, 93, 94]	X^A [92] X^B [6, 94, 95]	X^A [93]

X = Symptoms present; O = No association found; - - = No studies.
[A]Longitudinal or Prospective
[B]Cross-sectional

Table 3. Symptoms Observed in Cancer Survivors by Duration of Follow-Up

Time since treatment (ranges)	References	Number of studies
Up to 6 months	[49, 51-53]	4
6 to 12 months	[75-77, 83, 84]	5
1 to 2 years	[53-57]	5
2 to 5 years	[50-55, 77-84, 86]	15
> 5 years	[6, 58, 60, 61, 65, 67-72, 79-83, 85-87, 93, 94]	21

Feelings of anxiety were consistently found to be present in the first year post-treatment [23, 26, 28], with rates of 45-48% up to 6 months post-treatment [26, 28]. Less work has been performed from 6 months post-treatment on [23, 26], but one study approximates a rate of 23% 1 to 2 years post-treatment and 15% 2 to 5 years post-treatment [26].

Some degree of cognitive decline was reported up to 6 months following treatment [10, 32-37] at rates of 31-61% [32, 34, 36, 37]. As time progressed for survivors, the presence of cognitive limitations was not as clear [10, 33, 34, 37-41], but where reported, studies suggested that 25% experienced a cognitive decline at 6 to 12 months [38, 40] and 50% at 1 to 2 years post-treatment [34].

Pain and functional limitations were related to prior treatment for breast cancer in the first 6 months post-treatment [23, 30, 42-45] with rates ranging from 26-47% [42-45]. For 6 to 12 months, the presence of pain or a functional limitation related to breast cancer treatment ranged from 20-23% where a prevalence rate was reported [42, 43], 21-41% 1 to 2 years post-treatment [18, 42, 44], and 19-41% 2 to 5 years post-treatment [18, 42, 44]. There were also some null findings for symptoms of pain and functional limitations [11, 27, 46].

Finally, sexual dysfunction was included as a symptom that may impact breast cancer survivors. Several studies indicated the presence of symptoms (e.g., vaginal dryness, dyspareunia, decreased sexual desire) from the end of treatment to more than 5 years post-treatment [23, 24, 31, 47, 48], with one exception [11]. One study reported prevalence rates of 51% of survivors experiencing some "problem related to sexual functioning" 1 to 2 years post-treatment, and 28% of survivors reporting problems 2 to 5 years post-treatment [24].

Gynecological Cancers

Gynecological cancers include ovarian, cervical, endometrial/uterine, vaginal, and vulvar cancers. Studies reviewed here focused on ovarian (13 articles), cervical (nine articles), uterine (one article), and heterogeneous gynecologic cancer survivors (seven articles).

Longitudinal studies tracked depression from immediately following treatment to 18 months post-treatment [49-53]. Some studies found an increase in depressive symptom scores over time [49, 51] while another one found that the prevalence of depression decreased from end of treatment to 3-month follow up [53]. Between 11%-19% of survivors experience depression at 3-months post-treatment [52, 53] and 5.7% of survivors showed depression at 18 months post-treatment [50]. Fatigue was found to increase over the course of treatment, correlating with an increase in depression [49].

Longitudinal studies of anxiety found mixed results. Two studies found that anxiety did not increase significantly from immediately post-treatment to 3 months post-treatment [49, 51], but one study reported that clinical cases of anxiety, increased during that period [53]. Between 22%-47% of survivors experienced anxiety at 3 months post-treatment [52, 53].

Longitudinal studies of sexual dysfunction found that sexual problems persisted up to 1 or 2 years post-treatment. Between 12 and 24 months post-treatment, survivors experienced greater levels of dyspareunia, lower interest in sex, more difficulty with lubrication, and greater dissatisfaction with their sex lives compared to matched controls or population norms [54-56]. One study found that pain was found to decrease slightly by 6 months post-treatment then remain stable up to 24 months post-treatment [57].

Cross-sectional studies found that 5.5-15% of gynecological cancer survivors had clinical levels of depression an average of 2 to 6 years post-diagnosis, with an additional 4.5-11% showing sub-clinical but significant levels of depressive symptoms [58-62]. In a sample of survivors who became infertile as a result of treatment, 40% had depression an average of 2 years post-treatment [63]. Studies that compared depression cases with comparison groups found mixed results: four studies found that the cancer survivors did not have higher depression scores than referenced norms [58, 64, 65] or age-matched controls [58, 66], but one study reported that survivors did show greater depression an average of 8 years post-diagnosis [67].

Anxiety and fatigue were more prevalent than depression in cross-sectional studies. Between 14%-28% of gynecological cancer survivors experienced anxiety and an additional 14.6% demonstrated sub-clinical anxiety symptoms an average of 3.7-8 years post-diagnosis [58, 60, 61]. Fatigue was found in 17-33% of survivors an average of 3-8 years post-diagnosis [65, 67-69]. Two studies reported that survivors had higher levels of fatigue than the general population [62, 65] but one study found no such difference [70].

Sexual dysfunction was the most widely studied problem among gynecologic cancer survivors in cross-sectional studies. Eleven studies consistently demonstrated that cases had higher levels of sexual dysfunction than referenced norms [69-72] up to 27 years post-diagnosis. Among the most prevalent types of sexual problems were pain during intercourse (34%-58%) [69, 72, 73]; decreased interest in sex (56%-70%) [72, 73]; difficulty with orgasm (43%-53%) [71, 73]; and anxiety about performance (31%-71%) [74].

Studies are absent in the areas of cognitive limitations and sleep disturbances.

Prostate Cancer

The most common treatments for prostate cancer are surgery, radiation (including brachytherapy), and chemotherapy [75, 76]. Treatment for prostate cancer was associated with most of the searched symptoms (i.e., cognitive limitations, depression/anxiety, fatigue, pain/functional limitations, and sexual function). In longitudinal studies, treatment for prostate cancer was associated with cognitive limitations in assessments post-treatment [75-77] with studies showing up to 48% of the sample experiencing at least one cognitive deficit (e.g., spatial memory, attention, and ability) from baseline to 12 months post-treatment. Sixty percent of the sample in one study reported an increase in fatigue from baseline to 3 months following treatment [74, 78, 79]. Survivors of prostate cancer reported problems with sexual function from 1 month to 8 years, ranging from 25 to 80% of patients reporting sexual function problems [79-82]. Depression was present for 12 months post-treatment with 14% of the sample meeting criteria for clinical depression and 26% of the sample reporting at least one depressive symptom or emotional distress [83, 84]. Pain while urinating was present in 22% of the sample up to 15 years post-treatment [83, 85].

In cross-sectional studies, prostate cancer treatments were associated with cognitive limitations up to 5 years post-treatment [86]. Clinical depression was reported by approximately 17% of cancer survivors [87] and depressive symptoms were present in up to 32% of survivors more than 2 years post-treatment [87]. Over half (53%) experienced fatigue [85, 87] following completion of primary treatment. Pain/functional limitations were reported by 54% of survivors from immediately following to more than 5 years post-treatment [86, 87]. Sexual function impacted 50 to 70% of survivors up to 5 years post-treatment [86-88]. Last, sleep problems affected up to 40% of samples from 6 months to greater than 2 years post-treatment [87].

Rectal/Colon Cancers

Post-treatment symptoms in rectal/colon cancer also include depression, fatigue, pain/functional limitations, sexual function, and sleep. In longitudinal studies, fatigue was reported 2 to 5 years post-treatment [89, 90], pain/functional

limitations 2 to 5 years post-treatment [89-91], sexual function 12 months to 37 months post-treatment [92], and sleep problems 4 years after treatment [93].

Cross-sectional studies reported the presence of depressive symptoms [93], depression [85], and pain [85] all more than 5 years following diagnosis [93] or the completion of primary cancer treatments [93]. The prevalence rate for depression was 14% [85] and pain was 27.1% with 11.5% of the colorectal cancer survivors attributing the pain to the cancer [94]. A cross-sectional association between treatment for colorectal cancer and sexual function was found 37 months following colon or rectal resection [95] and 6 and 13 years post-diagnosis [94]. At 37 months, 24% of participants with a history of colon or rectal cancer reported sexual dysfunction related to feeling weak, less pleasure, and less sexual desire [95]. Sexual problems at 6 and 13 years post-diagnosis were similar for colon (64%) and rectal (63%) cancer survivors, however, more women (77%) than men (52%) reported problems [6]. The type of sexual problems was not indicated.

DISCUSSION

Prolonged fatigue, cognitive limitations, depression/anxiety, sleep problems, pain, and sexual function are consistently present in heterogeneous cancer survivors following primary treatment. The purpose of this review was not to determine the relationship between type of treatment and symptoms, but to identify patterns of symptoms among cancer survivors. This review suggests that symptoms are prevalent throughout the trajectory of survivorship for up to 10 years following primary treatment, across multiple and diverse types of cancer (see Table 3). Although specific incidence rates and risk factors for these symptoms remain to be determined, it is important to highlight that survivors exposed to various treatments experience these same symptoms. As with any complex set of health outcomes there is reason to assume that the origin of symptoms experienced by some cancer survivors are multi-factorial [96-99]. It is simply too premature to specify the etiological factors related to these symptoms but the literature does provides a series of likely suspects. Despite multiple predisposing factors, there may be a common mechanism (e.g., biological) for the etiology of these symptoms [100].

The symptoms most commonly reported by the studies reviewed, regardless of cancer type and treatment, included fatigue and symptoms of depression and anxiety. Fatigue is one of the most common and distressing concerns among many types of cancer survivors. It is estimated that 50 to 100% of cancer patients experience fatigue across the trajectory of cancer survivorship [101]. Fatigue is present well past treatment completion [102] and has potential effects on function and quality of life [103]. Symptoms of depression and anxiety also impact the quality of life in cancer survivors. It has been suggested that stressors experienced over the long-term differ from the stressors during treatment or immediately

following diagnosis [104], meaning that the etiology of depressive and anxiety symptoms may change throughout the course of treatment and recovery.

There are several challenges to consider when compiling such disparate research. Precise data regarding the time from primary treatment is often not available and therefore, the time from diagnosis is often used as a proxy. These time intervals can be quite different as evident in Tables 1-3. Also, there are multiple measures used to assess symptoms; the various tools used across studies may not measure the same dimensions of the construct or symptom, introducing a significant source of measurement error [100]. This review included any study that included the terms searched, quality of the study or measurement technique was not a factor in the decision process. The purpose of this review was, to provide a general summary of the types of patient reported outcomes over time across many different exposures and potential etiological factors and alert all involved in the care of these cancer survivors that problems can persist for years.

Clinical Implications

What does all this mean for current and future management of cancer survivors? First of all it is clear that symptoms of various types are present post-primary treatment. For those responsible for the long-term care of cancer survivors it is critical that we realize that once treatment for the cancer has ended, there are many challenges (e.g., symptom burden) that these cancer survivors may face. These symptoms need to be carefully evaluated and when they occur, whether tumor pathology is present or not, they need to be considered as targets for management. This is particularly the case for symptoms that interfere with either the physical and psychosocial dimensions of function. Providers need to stay vigilant for these symptoms and realize there are options (i.e., pharmacological, educational, self-management, psychosocial interventions) for their more aggressive management [7].

This review clearly indicates that a percentage of cancer survivors treated for one of the top four cancer diagnoses can experience symptoms of fatigue, mild cognitive limitations, depressive- or anxiety-related symptoms. Many of these clinical problems can be managed within your existing practices with time allocated and proper evidence-based care for these problems until cancer survivor specific evidence-based care is developed. Quality care for cancer survivors does not only include surveillance of cancer over time, but better preventive health and better management of long-term and late-effects from cancer and its aggressive and often toxic treatments [11, 13].

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