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## Research Article

## The Physiological Basis of Quality of Life in Hematological and Solid Cancer Survivors: Implications From ALL, Hodgkin's Lymphoma, Breast, Pancreatic, And Gallbladder Malignancy

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### Abstract

Cancer survivorship has emerged as a focus of significant interest and study as progress has been made in early cancer detection, treatment modality refinement, and long-term patient survivorship. Despite improved survival across solid and haematological malignancies, a subset of cancer survivors will experience lasting physiological, psychological, and functional effects that negatively impact on their quality of life (QoL). A number of physiological factors play a role in determining QoL including interplay between autonomic nervous system (ANS), endocrine, immune and metabolic pathways, and behavioral response. Survivors of acute lymphoblastic leukemia, Hodgkin's lymphoma, breast, pancreatic and gallbladder cancers are more likely to experience a number of problems in relation to quality-of-life including cancer-related fatigue, autonomic dysfunction, sleep disturbance, ongoing inflammation and depression, reduced function and the physiological mechanisms will be discussed and illustrated in relation to these conditions. New understanding of the roles of the neuroimmune system and psychophysiology of the organism now make the biological mechanisms of these symptoms crucial in improving the care provided for the cancer survivor. In this narrative review we consider the underlying physiology that is important for QoL of both haematological and solid tumor survivors with an example from ALL, Hodgkin's lymphoma, breast cancer, pancreatic cancer and gallbladder cancer highlighting issues. A greater understanding of the mechanisms involved could help in the development of targeted therapies to manage specific symptoms and improve the experience and health of the survivor as well as developing novel biological markers of survivorship status.

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## 1. INTRODUCTION

As a consequence of increased screening for, diagnosis of, improved treatment for and survival of various cancers the cancer survivor population is rapidly expanding both in the western world and globally.<sup>12</sup> Quality of life in the cancer survivor population can no longer be defined as simply living without evidence of disease and now encompasses the multidimensional effects of living with and beyond cancer, physically, psychologically, socially and functionally.<sup>14</sup> QoL has become a pivotal measure in all oncology treatments and trials of new therapy now report QoL data along with clinical endpoints such as overall survival and disease-free survival<sup>12</sup> There is a wide range of physiological factors that can influence the quality of life in cancer survivors. Continuing and sometimes exacerbated long-term symptoms such as chronic inflammation, autonomic dysfunction, sleep disturbance, endocrine dysregulation and the effect of psychological stress can be present following treatment.<sup>11</sup> These will inevitably affect all aspects of a person's life, functioning and participation in everyday activities and may contribute to impaired quality of life.<sup>13</sup>

Specific populations of cancer survivors such as survivors of acute lymphoblastic leukemia or Hodgkin's lymphoma have been identified as suffering from longer term complications of cancer and its treatment, including long term cardiovascular, endocrine and neurocognitive sequelae of intense chemotherapy and radiotherapy.<sup>21</sup> Similarly, studies have investigated changes in autonomic regulation and an increased propensity for cancer related fatigue in survivors of breast cancer as a detriment to their health related quality of life.<sup>3</sup> Cancer survivors of pancreatic and gallbladder cancers suffer more typically from weight loss, anorexia, cachexia, pain and metabolic disturbances which clearly negatively impact quality of life.<sup>25</sup> In recent years there has been an increasing focus on the neuroimmune physiology that can affect quality of life in the cancer survivor population and interplay between nervous and endocrine and immune systems affecting response to stress, perception of symptoms and post-treatment recovery.<sup>16</sup> Measures of autonomic regulation, particularly vagal tone which can be determined by analysis of heart rate variability (HRV) has now become recognized as being an important predictor of overall quality of life and survival status in many cancer survivors.<sup>8</sup>

In this narrative review we aim to examine the underlying physiology that influences the quality of life in survivors of hematological and solid malignancies and in particular in relation to ALL, Hodgkin's lymphoma, breast, pancreatic and gallbladder cancers through a focus on neuroimmunology, autonomic regulation and the effect of symptoms on health-related quality of life.

### Quality of life and cancer survivorship

Survivorship is considered the whole aspect of physical, psychological, social and economic well-being of cancer survivors, starting from the time of diagnosis up to the rest of their lives. With ever improving survival rates for various cancers, it is becoming more critical than ever to understand

what determines wellbeing of cancer survivors throughout long-term survivorship<sup>12</sup>. Health-related quality of life (HRQoL) is an important survival measure that reflects how a certain disease state affects an individual's everyday functioning, his life satisfaction, well-being and physical/functional capacity<sup>13</sup> Multiple interdependent physiological systems are involved in the determinants of quality of life. During cancer treatment, several chronic changes are made to various physiological systems such as cardiovascular function, endocrine regulation, immune function, neuromuscular activity and metabolic homeostasis<sup>13</sup>. These effects may persist long after the termination of cancer treatment, leaving cancer survivors with symptoms and problems that may significantly reduce the quality of life such as chronic pain, fatigue, decreased cognitive function, sleep disturbances, anxiety, depression and poor exercise capacity<sup>1</sup>

The physiological profile between hematological malignancies and solid cancers differ in terms of survivorship late effects. ALL and Hodgkin's lymphoma survivors may have problems related to cardiotoxicity due to chemotherapy, endocrine malfunction, second malignancies and neurocognitive decline<sup>21</sup> while breast cancer, pancreas and gall bladder cancer survivors may suffer from side effects related to surgery, nutritional deficiencies, altered metabolism, chronic pain syndromes<sup>25</sup>. Despite differences, the similar physiological pathways that contribute to diminished quality of life seem to be common in various cancers and these include inflammation, autonomic imbalance and stress responses.

### Neuroimmune physiology in hematological and solid cancers

The neuroimmune system is central to maintain and regulate physiological homeostasis and adapt to physiological stress such as disease. There is bidirectional communication between nervous and immune systems through complex pathways involving cytokines, neurotransmitters, hormones and cells<sup>16</sup>. Cancer and cancer treatment disturb normal neuroimmune function that leads to persistent physiological and psychological sequelae.

Inflammatory cytokines such as interleukin-1, interleukin-6 and TNF-alpha are known to be elevated in cancer patients and survivors<sup>11</sup>. This increase in cytokines may affect function of the brain through alterations of neurochemical pathways, neuroendocrine activity and neuronal networks and chronic inflammation has been clearly linked with reduced physical functioning and cognition, fatigue, depression and stress response<sup>1</sup>.

Activation of the hypothalamic-pituitary-adrenal axis as a result of chronic stress is responsible for dysregulated HPA function, increased inflammatory and immune dysregulation<sup>18</sup>. Such disruption has been related to changes in quality of life as well as tumor development and prognosis<sup>16</sup>.

Neuroimmune abnormalities in hematological survivors persist in some subjects for many years after treatment and in this patient population long-term inflammatory changes and neurocognitive problems are more relevant. For breast, pancreas and gall bladder cancer survivors' similar problems

are present but are not limited to the neuroimmune system, but other systems such as endocrine and autonomic regulation too are involved<sup>11</sup>.

#### **Autonomic dysfunction and Heart Rate Variability (HRV)**

The autonomic nervous system controls all physiological systems such as cardiovascular system, respiratory system, GI system, metabolic function. Both sympathetic and parasympathetic parts are essential for autonomic homeostasis. Autonomic system function can be impaired with cancer and cancer treatment<sup>5</sup>. Heart rate variability (HRV) is a widely used index of autonomic control that measures variability of interbeat interval in between subsequent heart beats. Low HRV generally reflects poor physiological resilience and adaptation<sup>29</sup>.

Many studies have revealed that, HRV values in cancer survivors is lower than those of healthy volunteers<sup>3</sup>. There are many signs that autonomic dysfunction can contribute to various complaints in cancer survivors such as reduced exercise capacity, fatigue, poor sleep quality, dizziness and inability to adapt to stress<sup>5</sup>. In breast cancer survivors, reduced HRV has been associated with decreased quality of life and increased intensity of fatigue<sup>3</sup>.

Similar findings have been reported in patients with cancer related fatigue syndromes as well as advanced cancers<sup>10</sup>. The role of the vagus nerve is important because of its anti-inflammatory properties, so reduced vagal activity may have an important role to play in inflammation and symptom management in cancer survivors<sup>8</sup>. Interventions like exercise training, mind-body therapy such as yoga, mindfulness-based interventions and biofeedback may have an effect on autonomic function and HRV as well as quality of life<sup>6</sup>.

#### **Physical Activity and Functional Recovery**

Physical activity is an important aspect of survivorship management following cancer treatment and helps improve the patient's cardiovascular fitness, muscle strength and overall functional capacity. Treatment for cancer usually results in fatigue, loss of physical function and reduced quality of life. Studies have indicated that exercise improves physical performance and well-being among cancer survivors<sup>6</sup>. Exercise also potentially improves autonomic function and decreases symptom load. Fatigue, disturbed sleep and psychological problems may all be positively influenced by exercise. Thus individual exercise programmes have been recommended as part of comprehensive survivorship care and management<sup>24</sup>

#### **Cancer related fatigue and energy regulation**

Cancer related fatigue is one of the most frequent and disabling side effects experienced by cancer survivors. It is an abnormal state where fatigue is abnormal as it is persistent, disproportionate to activity and inadequately relieved by rest<sup>1</sup>. Fatigue greatly impairs performance on daily activities, physical functioning, cognition, emotional well-being, social activities and overall quality of life. Chronic inflammation, autonomic dysfunction, hormonal imbalances, mitochondrial

dysfunction, anemia and stress responses are likely to be major contributing factors in cancer related fatigue<sup>1</sup>

Raised cytokines are found to alter central nervous system functioning leading to feeling of fatigue<sup>11</sup>. Reduced HRV also has shown to contribute significantly to the increased fatigue<sup>3</sup>. Muscle wasting due to chemotherapy and physical deconditioning after the treatment reduces physical fitness of cancer survivors and therefore increases the feeling of exertion and subsequent fatigue. The effectiveness of exercise in reduction of cancer related fatigue and improved physical fitness and quality of life has been well documented<sup>6</sup>. Thus, regular exercise is considered to be a fundamental intervention in survivorship care.

#### **Sleep disturbances and circadian physiology**

Sleep disturbances are prevalent in many cancer survivors and can significantly compromise the quality of life. Commonly reported sleep disorders are insomnia, fragmentation of sleep, excessive daytime sleepiness, disturbance of sleep-wake cycle and circadian rhythms<sup>13</sup>. Sleep is known to be a critical process for immune regulation, memory formation, restoration of body tissues, emotional state, and homeostasis. Poor sleep can impair daily functions and worsen symptoms of fatigue, reduce cognitive functioning, affect emotional status, promote inflammation, and aggravate neuroimmune dysregulation<sup>18</sup>.

Treatments such as chemotherapy, radiotherapy, radiation therapy and medications contribute to sleep disturbances through pain, anxiety, hormonal changes, effects of drugs, stress and anxiety. Long term sleep disturbances have been frequently reported by breast cancer survivors, which can affect their quality of life<sup>13</sup> and a similar pattern may be observed in hematological survivors due to treatment induced neuroendocrine changes<sup>21</sup>. Thus, addressing sleep disturbances may represent an important therapeutic target. Behavior modification therapy, sleep hygiene, exercise programs and relaxation techniques can have favorable impacts on survivors' quality of life<sup>6</sup>.

#### **Psychological stress, depression and physiological response**

Psychological distress remains a pervasive problem among cancer survivors where many subjects will continue to experience anxiety, depression, worry about recurrence of cancer and social isolation even after completion of the treatment<sup>18</sup>. These conditions also have a profound link to the physiological response. Activation of the autonomic system as a result of chronic psychological stress leads to elevation of catecholamines and cortisol and increases inflammatory responses<sup>16</sup>. Chronic HPA axis stimulation leads to prolonged immune suppression and autonomic dysfunction. Depression has been found to be correlated with higher inflammatory markers and altered endocrine pathways<sup>19</sup>. Higher stress levels are found to decrease the HRV and increase autonomic dysfunction<sup>29</sup>. Such findings emphasize the need for an integrated survivorship program where psychological and physiological issues are looked at together.

### Organ-specific concerns

Survivors of ALL may have long term morbidities including cardiovascular sequelae, endocrine disorders and neurocognitive impairments from chemotherapy exposure<sup>22</sup> which can affect their quality of life into adulthood. Long term sequelae in Hodgkin's lymphoma survivors predominantly include cardiotoxicity, second malignancies, pulmonary abnormalities, and endocrine disorders<sup>21</sup>.

Breast cancer survivors frequently suffer from fatigue, autonomic nervous system dysfunction, lymphedema, disrupted sleep and psychological sequelae<sup>3</sup>. These multiple factors interact, with physical and emotional health intertwined.

Pancreatic cancer survivors present with problems such as malnutrition, exocrine pancreatic deficiency, cachexia, chronic pain and metabolic derangement<sup>25</sup>. Many of these issues are likely to have a significant impact on quality of life, even in long-term survivors.

Gallbladder cancer survivors form a smaller patient group, but have a clinically significant profile. Issues including nutrition, hepatobiliary deficiency, complications of surgery and persistent symptoms may affect their quality of life.<sup>28</sup>

### Future directions

Future survivorship studies must examine what objective physiological factors can be identified to predict outcomes in relation to quality of life. Measures such as heart rate variability, inflammatory cytokines, cortisol diurnal rhythm, wear sensors and digital biomarkers have the potential to uncover more about physiological reserve and recovery<sup>6</sup>.

Wearable sensors provide a new method of tracking the autonomic system, sleep, physical activity and the body's response to stress on a continuous basis. In survivorship this may allow personalized care and identification of those at risk of poorer outcomes<sup>6</sup>.

### CONCLUSION

Quality of life in survivors of hematological and solid tumors is influenced by a complex interaction between neuroimmune, autonomic, endocrine, metabolic and psychological systems. Chronic inflammation, autonomic nervous system dysfunction, cancer-related fatigue, disrupted sleep patterns and psychological distress may contribute significantly to long-term symptomatology and a diminished quality of life. Shared issues and also unique pathophysiological effects are experienced by survivors of ALL, Hodgkin's lymphoma, breast cancer, pancreatic cancer and gallbladder cancer. More understanding of these mechanisms may lead to better supportive care interventions and ultimately to an improved quality of life for cancer survivors.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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