We are among the majority of people who experience fatigue throughout our battle with cancer. It is a near universal problem that affects approximately three-fourths or more of us and is the most common side effect of our cancer experience. More than half of us experience fatigue on most days, and it affects our daily lives more than pain or nausea. Fatigue associated with cancer is not the kind that will resolve after we take a nap or get a good night’s sleep, but tends to be more severe and ongoing. For those of us who are fortunate, our fatigue is mild and temporary. For others, it can last for months or sometimes years after treatment and makes going about our daily activities nearly impossible. The impact of our fatigue is profound and affects our ability to work, walk short distances, be intimate, and meet the needs of our families. We often have difficulty performing even the most simple tasks such as cooking, cleaning, or showering. Some of us experience difficulty concentrating or making relatively simple decisions. Fatigue even causes us to feel distant from our friends and social networks.

We refer to our specific type of fatigue as CRF (cancer-related fatigue). It is one of the most debilitating yet least understood or addressed side effects of cancer treatment.

The exact cause of our CRF is unknown. Sometimes the root of our fatigue is caused by the cancer itself; in other instances, it is caused by the treatment. What we do know is that cancer-related fatigue can be caused by a variety of other factors such as dehydration, depression, anemia, electrolyte imbalances, decreased nutrition, and medications. There is often more than one contributing cause. It is not predictable by tumor type, treatment or stage of illness. Usually, our CRF comes on suddenly, does not result from activity or exertion, and is not relieved by rest or sleep. We often describe it as “paralyzing” and may continue even after our treatment is complete.

Causes/Etiology
- Cancer-related fatigue (CRF) is a multi-factorial, multi-dimensional phenomenon that consists of physical, psychological, social, cognitive, and behavioral aspects.
- Possible causes of fatigue after completion of cancer treatment are still not confirmed.
- The exact cause of cancer-related fatigue is unknown; however, anemia and lack of sleep have both been strongly associated with its onset.
- Depression has been positively associated with CRF. Psychostimulants used in the treatment of depression have been shown to decrease fatigue levels.
- Stress has been shown to increase fatigue in healthy individuals and could be a contributor to the fatigue levels in cancer patients.
- The most well-identified causes of CRF in adults and children include the natural progression of the disease, poor nutrition, depression, and anemia. Specifically, some studies have found that in addition to other physiological factors, CRF might be induced by the loss of nutrients as a result of anorexia, nausea, vomiting, or hyper-metabolism.
- At present, the etiology of CRF is poorly understood and the relative contributions of the neoplastic disease, various forms of cancer therapy, and comorbid conditions remain unclear.
- Patients with lung cancer have self-reported higher levels of fatigue than patients with cancers of other organs.
- Mild cases of cancer-related anemia have been shown to increase patients’ levels of fatigue; however, high levels of CRF have also been reported by cancer patients without anemia.
Fatigue is the most prevalent symptom of individuals with cancer who receive radiation therapy, cytotoxic chemotherapy, or biological response modifiers. \(^{(6, 10)}\)

Physiological factors that contribute to the development of CRF are interrelated. These proposed mechanisms include abnormal metabolism function related to increased energy requirements (e.g., due to tumor growth, infection, fever, or surgery); decreased availability of metabolic substrate (e.g., due to anemia, hypoxemia, or poor nutrition); or the production of substances that impair metabolism or normal functioning of muscles (e.g., cytokines or antibodies). \(^{(6, 10)}\)

Okuyama et al. reported no relationship between fatigue and stage of disease. However, others have reported that patients whose cancer has metastasized have described higher levels of cancer-related fatigue. \(^{(11)}\)

Cancer-related fatigue is believed to be caused by cancer and compounded by the effects of cancer therapy. Studies have shown that fatigue is usually noticed before treatment begins. \(^{(12)}\)

The occurrence of cancer-related fatigue has been linked to physiological and psychological disorders including anemia, stress, insomnia, and depression. \(^{(13)}\)

Symptoms of cancer-related fatigue have shown a high correlation to the blood levels of circulating cytokines. \(^{(14)}\)

Multiple studies have found the greatest amount of fatigue to be during periods of less daytime activity (more daytime sleep) and less nighttime rest (more nighttime activity). \(^{(15, 16)}\)

Barriers to effective management of cancer-related fatigue include a lack of awareness that fatigue is the most prevalent symptom, a lack of physician and patient knowledge of its causes, and a lack of proven treatment methods. \(^{(17)}\)

**Screening**

Authors report there is a lack of adequate assessment instruments for measuring the different subjective dimensions of fatigue whose properties have been sufficiently psychometrically tested. \(^{(11, 17)}\)

Most clinical assessments of CRF rely on self-reports by patients, although this assessment method is both an asset and a liability. While these symptoms are best measured by patients themselves, the sickest patients may not be able to complete these assessments. \(^{(17)}\)

Assessment should include discussion about common symptoms experienced by cancer patients. Repeated assessments for these symptoms should continue over the course of the illness. \(^{(17)}\)

Although multidimensional assessment instruments for CRF exist, they are often not feasible for use in cancer care. Brief symptom rating scales are preferred in clinical practice settings. \(^{(17)}\)

Cancer-related fatigue is left unaddressed by physicians because it is a condition that can persist long after treatments have ended. \(^{(18)}\)

Fatigue scales used to measure the severity of fatigue do not account for the patients’ perception of fatigue. Therefore, a quantitative measure of fatigue is usually not possible. \(^{(19)}\)

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**DEFINING CANCER-RELATED FATIGUE**

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology \(^{(1)}\) defines cancer-related fatigue (CRF) as: “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.”

The NCCN Consensus Panel further states that: “Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing, and less likely to be relieved by rest. In terms of the defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on patients’ descriptions of their fatigue and accompanying distress. Fatigue that interferes with usual functioning is another substantial component of the definition for cancer-related fatigue and the source of much distress for patients.” \(^{(1)}\)
Generally, fatigue scales rely on patients’ self-report, which can be problematic as clinical interpretation of the scores can vary from patient to patient and among the various scales.\(^{19-21}\)

**Disparities**

- CRF symptoms, alone or in combination, may be perceived and managed differently in children and adolescents, older adults, those from low-income or low-educational backgrounds, and those from ethnically and culturally diverse groups.\(^{17}\)

- Evidence regarding the treatment of fatigue in children and adolescents, older persons, and other special populations is insufficient.\(^{17}\)

- Although the relationships between fatigue and demographic characteristics, physiologic factors, and psychosocial factors are not well-defined, findings from Eversley et al. show that increased levels of post-treatment symptoms, including fatigue, exist among minorities and are also associated with decreased income.\(^{22}\)

- Eversley et al. found that Latinas reported significantly higher rates of fatigue than African American/black and non-Hispanic/Latino women with breast cancer.\(^{22}\)

- Fatigue is a commonly reported symptom among children and adolescents with cancer. However, the mechanisms, risk factors, clinical features, prevalence and duration are poorly understood. At present, no therapeutic interventions are available.\(^{23}\)

**Outcomes**

- Fatigue is one of the most prevalent side effects during chemotherapy, usually persisting for more than two weeks; also, it has been shown to have the greatest and most long-lasting impact after chemotherapy.\(^2\)

- Patients who experience daily cancer-related fatigue are also more likely to be experiencing pain and other psychosocial symptoms such as depression, lack of motivation, and disturbances in mood and cognition.\(^2\)

- Cancer-related fatigue has occupational repercussions, sometimes causing patients to discontinue or change employment, go on disability, or use unpaid family and medical leave because of their extreme fatigue.\(^2\)

- Research has shown that non-pharmacological interventions can be beneficial by providing patients with preparatory knowledge about their disease and treatment. Non-pharmacologic treatments for CRF include: patient education, exercise, modification of activity and rest patterns, stress management and cognitive therapies, and adequate nutrition and hydration.\(^6\)

- In some women with breast cancer who are receiving chemotherapy, a home-based exercise program of low to moderate intensity has shown to be a feasible and effective way to reduce the effects of fatigue as well as improve quality of life and functional ability.\(^6, 15, 26, 28\)

- Patients receiving radiotherapy begin with a lower level of fatigue that rises gradually as treatment progresses and decreases once treatment ends.\(^{15}\)

- The large range found for CRF prevalence (4-91\%) suggests a lack of uniformity in measurement methodology. Lack of consistency in estimates of symptoms across studies could be attributed to an inability to agree on the criteria to define these symptoms. There is also a lack of consensus on the most valid and reliable measures.\(^{17}\)

- At present, published studies on CRF have focused on prevalence data because there are no reliable studies on its incidence.\(^{17}\)

- Studies have shown that patients adapt to their condition during treatment to distance themselves from the disease. They begin to consider their condition normal and may report their fatigue as less severe.\(^{24}\)

- Often, patients do not report episodes of cancer-related fatigue to their physicians and/or other health professionals due to its lack of perceived severity. These patients tend to adjust to more sedentary activities, change their daily schedules, and decrease their productivity.\(^2, 3, 15, 23\)
Some patients do not discuss their fatigue with a health care professional because they assume CRF is a normal and expected outcome of their cancer treatment, that it would not continue to persist, that it was caused by the cancer itself, or that nothing could be done to alleviate their fatigue.\(^3, 25\)

Studies report that the number of people affected by cancer-related fatigue falls between the range of 60-100%; many report an average of 75%.\(^6, 25\)

Cancer-related anemia, a symptom highly associated with cancer-related fatigue, can be effectively treated without the use of blood transfusions. Epoetin alfa, the most clinically used drug intervention for cancer-related anemia, has been shown to increase hemoglobin levels in anemic cancer patients receiving chemotherapy.\(^8, 15, 17, 26, 27\)

Many patients report experiencing physical manifestations of fatigue at least a few days each month, such as a significantly diminished energy level, a need to slow down from a normal pace, a general sense of sluggishness or tiredness, and an increased need for sleep or rest.\(^2, 28, 29\)

Exercise reduces fatigue by improving physical efficiency and performance through gains in muscle mass and plasma volume, improved pulmonary ventilation and perfusion, increased cardiac reserve, and higher concentrations of oxidative muscle enzymes.\(^29\)

Ancoli-Israel et al. have found that women with breast cancer report disruptions in sleep and higher levels of fatigue prior to receiving treatment.\(^30\)

Fatigue causes substantial functional and psychological impairment, and is rarely discussed or treated. Many patients report that fatigue affects the quality of their daily lives by preventing them from leading a normal life and forcing them to alter their daily routine.\(^2, 31\)

Berger and Higginbotham found that patients most often experienced pain along with their fatigue. The next highest association was found to be between sleeping problems and depression.\(^11, 31\)

Breast cancer patients experience a “roller coaster” pattern of fatigue, in which the experience of fatigue is significantly greater at the start of each treatment cycle than it is at the midpoint.\(^32\)

In patients receiving multiple forms of treatment for cancer, a “response shift” during the initial treatment may influence perceptions of fatigue during the second treatment, as patients become accustomed to their fatigue. Response shift is defined as a re-conceptualization of the quality of life brought about by a change in health status.\(^10, 32\)

Studies suggest that fatigue gradually decreases after the last treatment. However, fatigue is still a frequent complaint by disease-free cancer patients months and years after curative treatment for cancer has ended.\(^3, 6, 11, 32\)

Lung cancer patients report that fatigue was the most frequent symptom that interfered with their daily lives.\(^33\)

During the first 24 to 48 hours of chemotherapy, a sharp rise in fatigue levels has been observed.\(^34\) After the first two weeks of therapy, fatigue levels continue to rise slightly and begin to decrease once treatment ends.\(^10, 15, 32\)
WEB RESOURCES

American Cancer Society
www.cancer.org
The American Cancer Society is the nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer, through research, education, advocacy, and service.

American Pain Foundation
www.painfoundation.org
As a nonprofit information resource for people with pain that provides practical information for patients, the American Pain Foundation raises public awareness and understanding of pain and promotes better pain management.

American Society of Clinical Oncology
www.asco.org
The American Society of Clinical Oncology (ASCO) is the world’s leading professional organization representing physicians who treat people with cancer. ASCO’s efforts are directed toward advocating for policies that provide access to high-quality care for all patients with cancer and at supporting the increased funding for clinical and translational research.

CancerCare
www.cancercare.org
CancerCare is a national non-profit organization that provides free professional support services to anyone affected by cancer: people with cancer, caregivers, children, loved ones, and the bereaved.

Chemo Care
www.chemocare.com
A program of the Scott Hamilton CARES Initiative (the Cancer Alliance for Research Education and Survivorship), this is Scott Hamilton’s personal program designed to promote cancer awareness while raising significant funds for cancer research.

Department of Pain Medicine & Palliative Care at Beth Israel Medical Center
www.stoppain.org
This is a resource that provides patients and the medical community with information about pain management and palliative care. Also addresses the physical, psychosocial, and spiritual concerns of patients with lifethreatening illnesses (i.e. facts, treatments, educational programs, resources, clinical trials).

National Cancer Institute
www.cancer.gov
The National Cancer Institute (NCI) is a component of the National Institutes of Health (NIH), one of eight agencies that compose the Public Health Service (PHS) in the Department of Health and Human Services (DHHS). The NCI, established under the National Cancer Act of 1937, is the Federal Government’s principal agency for cancer research and training.

National Comprehensive Cancer Network
www.nccn.org
The National Comprehensive Cancer Network (NCCN), an alliance of 19 of the world’s leading cancer centers, is an authoritative source of information to help patients and health professionals make informed decisions about cancer care.

National Ovarian Cancer Coalition (NOCC)
www.ovarian.org
The NOCC provides patients and the medical community with information about ovarian cancer, (i.e. facts, treatments, peer-support forum, database of cancer-related resources).

OncoLink
www.oncolink.upenn.edu
Founded by University of Pennsylvania cancer specialists, Oncolink provides cancer patients, families, healthcare professionals and the general public with comprehensive information about cancer, its treatments and research initiatives.

Oncology Nursing Society
www.ons.org
The ONS provides oncology nurses, healthcare professionals and patients with access to educational programs, cancer-care resources and peer-support networks.

People Living With Cancer
www.plwc.org
People Living With Cancer, the patient information website of the American Society of Clinical Oncology (ASCO), is designed to help patients and families make informed health-care decisions. The site provides information on more than 85 types of cancer.

The purpose of this and other ICC Fact Sheets is to draw attention to the cancer disparities that exist among various medically underserved populations. With specific regard to cancer-related fatigue (CRF), at present there is a dearth of scientific research on this subject reported in the medical literature.
References


