

The Effects of Physical Activity on Adverse Side Effects in Chemotherapy Patients

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Abstract

Each year, more than 14 million people worldwide are diagnosed with cancer. Despite advancements in medicine, a cure for this disease has not been found. Chemotherapy, a common cancer treatment, is often used in an attempt to slow the progression of cancer and achieve remission, but it is also associated with several adverse reactions. Fatigue and reduced cognitive function are notable side effects that can decrease the quality of life for many patients and affect their ability to function as they did prior to the diagnosis. In the past, individuals treated for chronic illnesses were often told by their physicians to rest as much as possible and avoid physical activity to preserve their strength. However, current research suggests that exercise can mitigate many chemotherapy side effects. Adhering to the guidelines put forth by the American College of Sports Medicine in *Exercise Management for Persons with Chronic Diseases and Disabilities* (CDD4), individuals undergoing chemotherapy can and should participate in a regular exercise regime to avoid chemotoxicity, thus improving overall health. As cancer rates are expected to increase in the coming decades, physical activity should be integrated into the typical medication-based care plans of cancer patients to yield additional health benefits.

Introduction

As one of society's leading causes of death, the impact of cancer can be felt worldwide. Each year, approximately 14.4 million people are diagnosed with the disease (World Health Organization 2017). According to the American Cancer Society (2017), there were an estimated 1.68 million new cancer cases and 600,920 cancer deaths in 2017 in the United States alone. Given these high numbers, the likelihood of knowing an individual who is currently suffering or has suffered from cancer is considerable, and the disease is expected to become more prevalent in the coming decades. Even though the diagnostic rate continues to rise, cancer survivorship is also increasing. The National Cancer Institute (2016) states that the number of survivors who live five or more years following their diagnosis is projected to increase by approximately 35 percent in the next decade. Together, these trends demonstrate that considerable progress is being made against the disease, but the medical community will need to adapt to meet the needs of cancer patients at every stage of the disease, from diagnosis to remission.

While there is no cure for cancer, treatments such as radiation, chemotherapy, immunotherapy, or gene therapy can help prevent cancerous cells from spreading or even eradicate them. Despite these advancements, many cancer patients, especially those who undergo chemotherapy, experience unpleasant side effects. Fatigue and nausea are two of the most common and doctors often prescribe additional medications to curb their impact (American Cancer Society 2016). Research suggests that physical activity, although less allopathic, may be just as effective at mitigating adverse reactions. Other conditions, such as depression, dementia, and heart disease, have been found to improve with exercise, thus demonstrating the potential for physical activity to be an effective treatment. Cancer patients often experience some of the same symptoms associated with these other conditions. Therefore, the integration of a regular exercise program during and following chemotherapy may help to lessen common side effects, resulting in improved overall health and quality of life for cancer patients.

What is Cancer?

Cancer is a disease that occurs when a group of the body's own cells are mutated, causing them to divide at an especially high rate. When the human body is functioning normally, there is a system that replaces old or damaged cells with new ones. The development of cancer disrupts this orderly process; damaged cells continue to survive and new cells are formed when they are not needed (National Cancer Institute 2015). This surplus may clump together to form a tumor, which can be malignant (cancerous) or benign (noncancerous). A malignant tumor is one that metastasizes throughout the body and causes damage to other tissues, while a benign tumor is more easily controlled and not usually life-threatening (Cleveland Clinic 2016). Because malignant tumors feed on other parts of the body, it is not the cancer itself that leads to patient death; it is the failure of other organ systems, such as the intestines or kidneys.

Causes of Cancer

On the molecular level, cancer is caused by mutations or changes to the DNA within cells. Because DNA contains the set of instructions that determines the function and lifespan of a cell, any error in the genetic material can affect the cell's

behavior. A gene mutation can direct a healthy cell to allow rapid growth, fail to stop uncontrolled growth, or make mistakes when repairing DNA errors (Mayo Clinic 2015). Such mutations are either hereditary, which account for only a small portion of cancers, or the result of an environmental or lifestyle factor after birth. Although hereditary mutations cannot be controlled, many other factors can be. Common non-hereditary causes of cancer include smoking, poor diet, and lack of exercise. Cancer can also occur as a result of other environmental factors such as overexposure to harmful chemicals, radiation from the sun, or X-rays (Cleveland Clinic 2016). The gene mutations that an individual is born with, and those that may have been acquired throughout his or her lifetime, often interact to cause cancer, and the more mutations that accumulate, the higher the risk of developing the disease. While mutations occur repeatedly during normal cell development, complications arise when the system that identifies and corrects such errors is not functioning properly.

Once a cell becomes mutated, it differs from a normal one in numerous ways that allow it to metastasize and affect other organ systems and tissues. First and foremost, a cancer cell is less specialized than a normal one. While normal cells will differentiate into specific types or functions, a precancerous one typically remains undefined, which increases the risk of uncontrolled growth (National Cancer Institute 2015). In addition, cancer cells have the ability to influence the environment around them to their own benefit by prompting other cells and blood vessels nearby to supply a tumor with the nutrients it needs to thrive. Usually the immune system would work to destroy such cells to avoid this situation, but they are often able to conceal themselves in a way that the immune system does not recognize them as foreign (National Cancer Institute 2015). In fact, tumors can use the immune system to further promote their growth and survival, which ultimately leads to the spread of cancer.

Signs and Symptoms

Although patients experience different combinations of symptoms based on the types and severity of their cancer, the following symptoms occur most frequently among the majority of patients:

- Fatigue
- An unusual lump under the skin that can be palpated
- Weight loss or gain
- Skin changes, including a sore that does not heal or changes to existing moles
- Hoarseness of the voice or a persistent cough
- Unexplained bleeding or discharge
- Problems with indigestion and swallowing
- Changes in bowel or bladder habits

It is important to note that these symptoms are not exclusive to cancer, but can occur with a variety of diseases and conditions (Mayo Clinic 2015). Therefore, a physician or other medical professional needs to conduct a physical exam, as well as other laboratory tests, to diagnose an individual with cancer. Some of these tests include blood analyses, urine samples, X-rays, computed tomography (CT) scans, ultrasonography scans, and biopsy procedures (Cleveland Clinic 2016). The

progression of cancer will increase the severity of symptoms when left untreated, so it is not uncommon for an individual's cancer to have advanced to later stages when it is first diagnosed.

Cancer Types

As cancer research continues to progress with new medical developments and technologies, it has become easier to diagnose and identify the origin of an individual's cancer. Today, there are over 200 different types of cancer and each is named for the organ or tissue where the disease began or the class of cells that turned cancerous (National Cancer Institute 2015). Oftentimes the name of a certain cancer will end in the suffix “-oma,” which in medical terminology refers to a tumor or other abnormal growth. The three most common cancer types—lung, breast, and colorectal respectively—contribute to approximately 35 percent of all newly diagnosed cancer cases (Ferlay et al. 2015). All three of these cancers are considered to be carcinomas, a broad term for a cancer that is formed by epithelial cells. These cells compose one of the four major types of tissue and specialize in absorption and secretion. Epithelium covers the majority of both the external and internal surfaces of the body, which is why cancers of this type develop most frequently (National Cancer Institute 2015). Cancer treatments vary depending upon the location of an individual's cancer and the tissues that are affected.

Interventions and Treatments

The three most commonly used interventions for cancer are: surgery, chemotherapy, and radiation. Surgery is employed initially in an attempt to locally remove the tumor from the body. Chemotherapy and radiation are used as adjuvant therapies to further destroy cancerous cells and keep them from metastasizing. Like surgery, radiation is a local treatment that uses high-energy particles from X-rays or gamma rays to kill cancer cells. Radiation can either be internally placed through a radioactive implant or externally delivered by a machine (National Cancer Institute 2017). Using radiation postsurgically in an attempt to achieve remission is known as curative radiation, while utilizing radiation to reduce unwanted tumor effects is considered to be palliative. Chemotherapy is a systemic treatment, meaning it affects the body as a whole. This type of treatment uses powerful drugs administered orally or intravenously to destroy cancerous cells, so it can lead to additional undesirable side effects that were not present prior to the start of treatment. (Cleveland Clinic 2016). Patients are given a “chemotherapy cocktail” that includes several medications—given together or in a sequence—to produce the most efficient result.

While effective for treating cancer, chemotherapy can negatively impact the human body due to its destructive nature. The treatment uses medications known as chemostatics to target and kill rapidly growing cells. However, chemostatics are cytotoxic; they do not distinguish between cells that are foreign and those that are not (American Cancer Society 2016). As a result, chemotherapy drugs also destroy healthy cells that grow quickly: hair and blood cells and those of the mucous membranes in the mouth and throat. Destruction of these cells causes side effects such as hair loss, anemia, and nausea or vomiting (National Center for Biotechnology Information 2016). In addition, fatigue and nerve and muscle problems are also common (American

Cancer Society 2016). While each patient may experience any combination of these side effects in varying degrees, all occur frequently in those who undergo chemotherapy. Additional prescriptions are provided to combat side effects; however, these medications are associated with side effects of their own, further compounding the original problem. As a result, patients are often reluctant to begin or continue an exercise program for fear of exacerbating these side effects or due to a general feeling of lethargy.

Effect of Exercise on Fatigue

The destruction of healthy cells throughout the body often leads to increased fatigue in chemotherapy patients. This can be a deterrent to comply with an exercise program, but research has shown that regular physical activity can potentially decrease fatigue during chemotherapy treatment. Terson de Paleville, Topp, and Swank (2007) examined the effects of aerobic training on a 42-year-old breast cancer patient. She began a home-based walking program one week prior to the start of her chemotherapy treatment and continued the program for eight additional weeks. Initially, each exercise session included a 5-minute warm-up, a 15-minute walk, and a 5-minute cooldown. As the weeks passed, the patient was able to increase the duration of the exercise session until a maximum of a 35-minute walk was achieved. Using a rating of perceived exertion (RPE) scale, the patient rated her fatigue after each exercise session and after various activities of daily living (ADLs). At the end of week nine, she reported a score of 0 out of 10 for all categories. A rating of 0 on the RPE scale correlates to no exertion felt by the patient, whereas a rating of 10 indicates maximal exertion. This information, combined with the improvements in distance traveled during walks, led to the conclusion that aerobic exercise boosts peak exercise capacity and reduces lethargy in breast cancer patients undergoing chemotherapy (Terson de Paleville et al. 2007). Though this was a case study that only examined the effects of exercise on one patient, the results are consistent with research that has been done with larger sample sizes.

Although a different type of physical activity compared to walking, a seated exercise program can also reduce fatigue in cancer patients. Headley, Ownby, and John (2004) conducted their own study to investigate exercise interventions on fatigue over time in females suffering from advanced metastatic breast cancer. There were a total of 32 patients in the study who met all inclusion criteria: at least 18 years of age, diagnosed with stage IV breast cancer, and scheduled for outpatient chemotherapy. The patients were randomized into either the control group or the intervention group; those in the intervention group participated in a 30-minute seated exercise program three times each week. The study utilized a videotape called "Armchair Fitness: Gentle Exercise," which included a warm-up period, 20 minutes of various flexion and extension exercises, and a cooldown. No strength or resistance exercises were included in the patients' regimes. Using the Functional Assessment of Chronic Illness Therapy—Fatigue Version IV (FACIT-F), researchers assessed patients' reported fatigue after each chemotherapy course for a total of four measurements. After 12 weeks and four rounds of chemotherapy, both groups experienced an increase in fatigue and decrease in overall well-being. However, those cancer patients who were in the intervention group reported less increase in fatigue and less decrease in well-being compared to the control group who did not participate in the seated exercise program (Headley et al. 2004). The

fact that this study resembles the results of the previous case study with a larger sample size helps to solidify the advantages of physical activity during chemotherapy. These results also demonstrate that exercise can be beneficial for patients whose cancer is more advanced and not just those in the early stages.

Closely behind breast cancer, colorectal cancer is the third most common cancer worldwide (Ferlay et al. 2015). Like its counterpart, colorectal cancer is often treated with chemotherapy, whether as the sole treatment or in conjunction with other treatments. Research completed at seven Dutch hospitals between 2010–2013 reported that approximately 46 percent of those undergoing treatment for colorectal cancer suffered from moderate to vigorous fatigue, which often increased during chemotherapy treatment (van Vulpen et al. 2016). Similar to the previous studies, this research showed that the implementation of regular physical activity had beneficial effects on the overwhelming fatigue experienced by these patients. Thirty-three patients who had recently been diagnosed with colorectal cancer were selected to participate in the study. Each was randomly assigned to one of two groups: one group participated in an 18-week exercise program and the other did not engage in any exercise outside of ADLs. Cancer patients who took part in the exercise program were required to attend two supervised exercise sessions per week and were instructed to exercise on their own on three other days (van Vulpen et al. 2016). The findings of this study indicated that participants in the intervention group experienced significantly less physical fatigue after 18 weeks when compared to the cancer patients in the control group. In addition, the experimental group reported higher physical functioning than the control group (van Vulpen et al. 2016). These outcomes demonstrate that an exercise regime for chemotherapy patients is not only manageable but also effective at reducing fatigue and lethargy.

Effect of Exercise on Cognitive Function

While fatigue is cited most often as a physical side effect, chemotherapy agents can also have an effect on cognitive function. Impairments in memory, processing speed, and executive function can endure for decades following the completion of adjuvant cancer treatments (Crowgey et al. 2014). It has been found that a decreased risk of dementia is associated with higher levels of physical activity among cancer-free adults, but less is known about how exercise following chemotherapy can affect the resulting cognitive function loss. A study conducted at Duke University recruited 37 breast cancer patients in an attempt to examine the relationship between exercise and cognitive function after chemotherapy. The cognitive function of each patient was gauged using a computerized test that employed the following subtests: reaction time, complex attention, cognitive flexibility, processing speed, executive function, and verbal memory, among others (Crowgey et al. 2014). Comparing these test results to the self-reported exercise data provided by patients, the authors of this study noted that breast cancer patients who had not participated in regular, structured physical activity performed more poorly on the majority of the cognitive tests. Therefore, there was a positive correlation between levels of exercise and cognitive function in those who had previously undergone chemotherapy.

It is routine for cancer patients to be treated with more than one chemical agent throughout the course of their chemotherapy, which can amplify the subsequent

cognitive deficits. Despite this supplementation, exercise may still prove effective in reducing such impairments. According to Fardell et al., 5-fluorouracil (5FU) and oxaliplatin (OX), two common medications used during the treatment of colon cancer, induce “a profile of peripheral neurotoxicity in both rodents and humans indicating that potentially both peripheral and central nervous systems may be affected by systemic treatment” (Fardell et al. 2012, 184). Using rats as subjects, several researchers sought to examine the impact of each of these chemotherapy agents alone and together and to investigate the therapeutic remediation of exercise on resulting cognitive function loss. Each of the 60 male rats were treated with a single dose of chemotherapy, but each dose varied in its chemical composition; some rats received only 5FU, some only OX, and others a combination of the two (Fardell et al. 2012). By subjecting the rats to a variety of memory and recognition tests, researchers were able to measure their cognitive function before and after chemotherapy and after exercise. They found that rats treated with 5FU or OX alone experienced impaired object recognition following the administration of chemotherapy. On the other hand, rats that were given a 5FU/OX-combined treatment experienced a decrease in spatial memory and contextual fear recall, in addition to object recognition. Even though the combination of two chemotherapy agents resulted in additional consequences compared to single agent treatments, exercise proved to be effective for improving cognitive function in all subjects. (Fardell et al. 2012). Since rats and humans exhibit similar reactions when exposed to these particular medications, it is reasonable to assume the results of this study could be applied to humans as well.

Effect of Exercise on Immune Susceptibility

Just as chemotherapy drugs mistakenly target healthy cells in the blood and mucous membranes of cancer patients, they also destroy cells that are essential to the immune system. Both T-lymphocytes and B-lymphocytes can be damaged by the chemicals present in chemotherapy drugs and are slow to return to normal levels (Hutnick et al. 2005). A study published by Hutnick et al. (2005) examined the effects of exercise on lymphocyte activation in patients with breast cancer following chemotherapy. A total of 49 patients were gathered to participate in the study and divided into two groups: one group had a formal exercise intervention and the other did not. The exercise group participated in a three-month exercise regime that was composed of one-on-one sessions with a trainer three times per week. At the end of three months, some participants chose to continue with a trainer, while others fulfilled their exercise requirements in their own homes (Hutnick et al. 2005). Blood samples were collected from all patients before chemotherapy, after chemotherapy but before starting the exercise program, after three months of exercise, and after six months of exercise. The samples were tested for the presence of various lymphocytes and the results indicated that CD4⁺ T-helper activation was greater in exercisers compared to non-exercisers (Hutnick et al. 2005). T-helper cells stimulate other immune cells to destroy foreign bodies and kill infected cells. Because a high level of T-lymphocyte activation is associated with an active immune system, exercise may prove to be an effective treatment for boosting the immune system of cancer patients.

As a result of their immunodepressed state, cancer patients are at a significantly higher risk for secondary infections following chemotherapy treatment. Because they

can lead to further complications, infections are “the leading cause of treatment-related mortality in cancer patients” (Baumann et al. 2012, 638). Research conducted at the University Hospital of Cologne in Germany sought to investigate if infections—particularly non-fungal, nosocomial pneumonia and fever—can be prevented with the implementation of routine, moderate physical activity. Rather than breast cancer or colon cancer patients, subjects for this particular study suffered from leukemia or lymphoma. Subjects were paired based on sex, age, stage, and risk profile to obtain the most accurate results. One member of each pair was designated as the control, and the other member participated in an exercise program that was conducted on a stationary bicycle two to three times per week. Following the completion of the exercise regime, pneumonia was observed in seven individuals in the control group, but only in two from the intervention group. In addition, 16 individuals in the control group were diagnosed with fever, while only 11 in the intervention group experienced the same symptoms (Baumann et al. 2012). Therefore, cancer patients who exercised following the completion of chemotherapy displayed a reduced risk of developing a fever and pneumonia.

Exercise Recommendations for Cancer Patients

Given the positive implications of physical activity on several side effects in chemotherapy patients, the integration of a regular exercise regime is recommended to improve overall patient health. According to the American College of Sports Medicine [ACSM] (2016), both current patients and cancer survivors should be following these recommendations for exercising set forth in *Exercise Management for Persons with Chronic Diseases and Disabilities* (CDD4):

- Every person with a chronic condition should be physically active, accumulating a minimum weekly total of:
 - 150 minutes of preferably moderate-intensity physical activity or, if that is too difficult then,
 - 150 minutes of light-intensity physical activity may be substituted.
- At least two days per week of flexibility and muscle strengthening activities that should minimally involve:
 - Chair sit-and-reach stretches on the left and right,
 - At least 8 consecutive sit-to-stand exercises,
 - At least 10 step-ups (or a flight of steps), leading with each foot, and
 - At least 8 consecutive arm curls with a minimum of 2 kg held in the hand; 4 kg is recommended (ACSM 2016, 19–20).

Though these recommendations are established, it is important to individualize exercise sessions to patients’ wants and needs. This is especially necessary for those who are undergoing chemotherapy, as additional adverse effects must be taken into account. As with any chronic condition, the ultimate goal when implementing an exercise regime is to increase the physical activity and fitness level of the patient while minimizing the risk of exercise-related complications (ACSM 2016). For this reason, patients should begin exercising at a light to moderate intensity and progress

to higher intensities if they are able. If needed, the typical 30-minute exercise sessions can be broken up into smaller, more frequent sessions as long as the 150-minute goal is reached (Bleck 2017). An exercise session should be discontinued if cancer symptoms become exacerbated or if the patient develops any new or unusual reactions. Despite these limitations, however, cancer patients should unquestionably avoid inactivity. The ACSM (2016) states that progression is necessary and that some individuals may need to be pushed beyond their perceived limitations to see improvement.

Barriers to Exercise Implementation

Cancer patients who have been prescribed an exercise regime and who were avid exercisers before cancer may be eager to return to their previous level of training. Due to a general feeling of malaise and weakness caused by chemotherapy, many cancer patients lead a sedentary lifestyle despite prior involvement in physical fitness. Because deconditioning occurs very rapidly, this often leads to exercise-related setbacks. Lying in a hospital bed for seven days results in a 20 percent loss of total system strength, and after ten days, three pounds of muscle will be lost in a healthy individual (Bleck 2017). A loss of muscle mass and strength weakens the musculoskeletal system, thus resulting in a decrease in overall ability to withstand physical activity (ACSM 2016). To avoid injury and benefit overall health, previously active individuals need to begin at lower intensities and gradually increase to rebuild muscle mass before returning to their prior training level.

In addition, patients may cite boredom or lack of time as reasons for not participating in exercise. Encouraging aerobic fitness during normal daily activities can help to increase adherence to an exercise regime. Many different types of activities meet recommendations set forth by the ACSM and can be done without access to an exercise facility or expensive equipment. Some examples of moderately intensive activities include walking, dancing, in-line skating, bicycling, or yoga. In addition, household chores like mowing the lawn or gardening qualify. Manual labor as part of an individual's job can also contribute to the recommended 150 minutes of aerobic physical activity (Bleck 2017). The more that patients enjoy exercising, the more likely they are to continue with the regime. Therefore, it is important to individualize patients' plans to include activities that are already part of their daily routines or are of interest to them.

Conclusion

As one of the leading causes of death around the globe, cancer is a major concern for medical professionals and civilians alike. Despite the upward trend in the total number of cancer cases in the United States, the death rate declined by 25 percent from 1991 to 2014 (Simon 2017). New treatments and technologies in the medical field have contributed to this decrease, but some current treatments, mainly chemotherapy, can cause harsh side effects. Although traditional recommendations for cancer patients included excess rest and energy preservation, new research suggests that physical activity can ameliorate the typical side effects of chemotherapy without additional medications. According to many studies, a structured, regular exercise regime is likely safer than polypharmacy and still effective at reducing fatigue, increasing cognitive function, and boosting the immune system in cancer patients who have undergone

chemotherapy treatment. When compared to individuals who do not participate in an exercise program, individuals who do exercise are more likely to have increased energy, greater memory and recognition, and a higher level of lymphocyte activation. This evidence indicates that participating in physical activity both during and following chemotherapy can help to combat some of the typical chemotherapy side effects; therefore, exercise can be used to guide the future treatment of cancer patients.

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