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A Review of Morbidities and Long-Term Side-Effects After Chemotherapy Treatment

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Ashley R. Herington, Madelyn R. Claussen, Jennifer Moreno, Samuel P. Abraham[2*]

[1]Bethel University School of Nursing, Mishawaka, Indiana, USA

[2]Associate Professor of Nursing, Bethel University School of Nursing, Mishawaka, Indiana, USA*

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ABSTRACT

Background: Side effects of chemotherapy may occur during treatment and can appear years after treatment. Knowing the long-term side effects of cancer treatment can aid in identifying patients at an increased risk of developing morbidities. **Purpose:** The purpose of this review was to investigate the long-term effects of chemotherapy on the human body. **Method:** Research methods included a review of relevant literature along with quantitative and qualitative data. The question addressed in this review was, are adults with a history of cancer who have received chemotherapy at an increased risk for morbidity processes than those without chemotherapy treatment? The following review consists of 15 studies from 3 scholarly databases that give insight into the following ascertained topics: cardiovascular disease, neurological dysfunction, compromised reproductive function and decreased quality of life. **Results:** Findings of the literature review concluded that chemotherapy treatment leads to potential long-term effects such as cardiovascular, neurological, and reproductive morbidities. Also, a decrease in quality of life can be seen even years after receiving chemotherapy. **Conclusion:** Patients and families of cancer patients could benefit from improving the quality of life of patients by spreading adequate information about the risk of morbidities. The lack of research should also drive researchers to explore further risks for developing morbidities after chemotherapy.

INTRODUCTION

Chemotherapy is a type of drug used to reduce or destroy cancer cells. Chemotherapy can be used in the hopes of a curative outcome or to prolong life. Palliative chemotherapy may also be initiated to reduce symptoms of painful tumors. Chemotherapy does not discriminate in attacking fast-replicating cells in the body. This leads to short-term side effects such as immunosuppression, gastrointestinal distress, and alopecia [1]. Chemotherapy side effects can occur not only during treatment but may manifest years later. Understanding the long-term adverse effects of chemotherapy might help identify people at an increased risk of developing morbidities [2]. The purpose of this review was to investigate the long-term effects of chemotherapy on the human body. The question addressed in this review was, are adults with a history of cancer who have received chemotherapy at an increased risk for morbidity processes than those without chemotherapy treatment?

BACKGROUND

Cancer is the second leading cause of mortality in the United States with over 1.7 million individuals diagnosed and about 600,000 deaths each year [3]. Worldwide deaths account for nearly 10 million in 2020. Chemotherapy was invented around the turn of the twentieth century, although its original purpose did not intend to treat cancer. During World War II, those who were exposed to nitrogen mustard gas had dramatically lower white blood cell counts. Because of this discovery, investigations further determined whether mustard agents could be used to stop the growth of rapidly proliferating cells, such as cancer [4].

The side effects of chemotherapy can diminish the quality of one's life. As more patients live longer following chemotherapy, more information regarding the long-term effects of cancer treatment becomes more prominent. Long-term effects include difficulties that arise because of cancer treatment but do not manifest themselves for months or years after treatment. Due to its systemic effects, chemotherapy can affect many body systems. The types of side effects cancer survivors are at risk for may differ depending on the type of chemo drug used during treatment [2]. Patients need full disclosure of the risks of chemotherapy. Awareness of the long-term side effects may help patients decide the course of treatment. Additionally, knowledge of potential adverse effects can aid in the early detection and management of morbidities.

METHOD

This review was conducted using a review of the literature. This review included the use of the scientific databases Cumulative Index to Nursing and Allied Health Literature and Google Scholar to collect high-quality studies about the side effects of chemotherapeutic agents. The following keywords were used to find relevant studies: chemotherapy, side effects, morbidities, and long-term effects. Key terms are defined in Table 1. Results were limited to include studies published from 2018-2021. The results were further narrowed to only include peer-reviewed studies written in English.

Table No 1. Definition of keywords for long-term effects of chemotherapy

Keywords	Definition
Chemotherapy	Pharmaceutical agents used to treat cancer
Side effects	An unwanted or unintended effect of a medication or treatment
Morbidities	The presence of a disease or its symptoms, disability, or poor health; medical problems caused by treatment.
Long-term effects	An unwanted or unintended problem caused by a disease or its treatment that continues for months or years.

A total of 3,601 studies were found through CINAHL using the keywords and limiters. After further review, we excluded 3,593 studies, leaving eight applicable studies. After searching Google Scholar with the same criteria, we found 12,746 studies, seven of which were used in this review. Studies were excluded for being too narrow or too broad, having too small of sample size, published before 2018, unable to access the study, and were not within the top four tiers of the evidence hierarchy (see Table 2).

Table no 2. Overview of search strategy and limiters for long-term effects of chemotherapy

Database Searched	Search Strategy and Limiters	Number of Studies Found	Reasons for Exclusion	Studies Used
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Keywords: chemotherapy, side effects, morbidities, and long-term effects Limiters: Last 3 years; English; Peer-reviewed	3,601	Too narrow or broad; small sample size; published before 2018; unable to access the study; not within the top four tiers of the evidence hierarchy	8
Google Scholar	Keywords: chemotherapy, side effects, morbidities, and long-term effects Limiters: Last 3 years; English; Review studies	12,746	Too narrow or broad; small sample size; published before 2018; unable to access the study; not within the top four tiers of the evidence hierarchy	7

The levels of evidence hierarchy for nursing literature were used to analyze and categorize the studies used in this review [5]. The first level contained the strongest level of evidence and included meta-analyses, systematic reviews, and current practice guidelines. Within this review, there were 11 studies from the first tier of evidence. The second level primarily consisted of randomized control trials (RCTs), and this study used one of them. This review had two studies in the third level, which consisted of non-randomized control trials.

Only one study belonged to the fourth level, which consisted of cohort and case-controlled studies. The fifth level in the evidence hierarchy consisted of systematic reviews of descriptive and qualitative studies and included correlational studies. Level six contained single descriptive and qualitative studies, case series studies, case reports, and concept analysis. Tier seven included the opinions of authorities, reports of expert committees, manufacturer's recommendations, and

traditional literature reviews [5]. Figure 1 outlined the level of evidence for the studies used in this review. As defined in nursing hierarchy of literature, level 1 is the highest, and level 7 is the lowest.

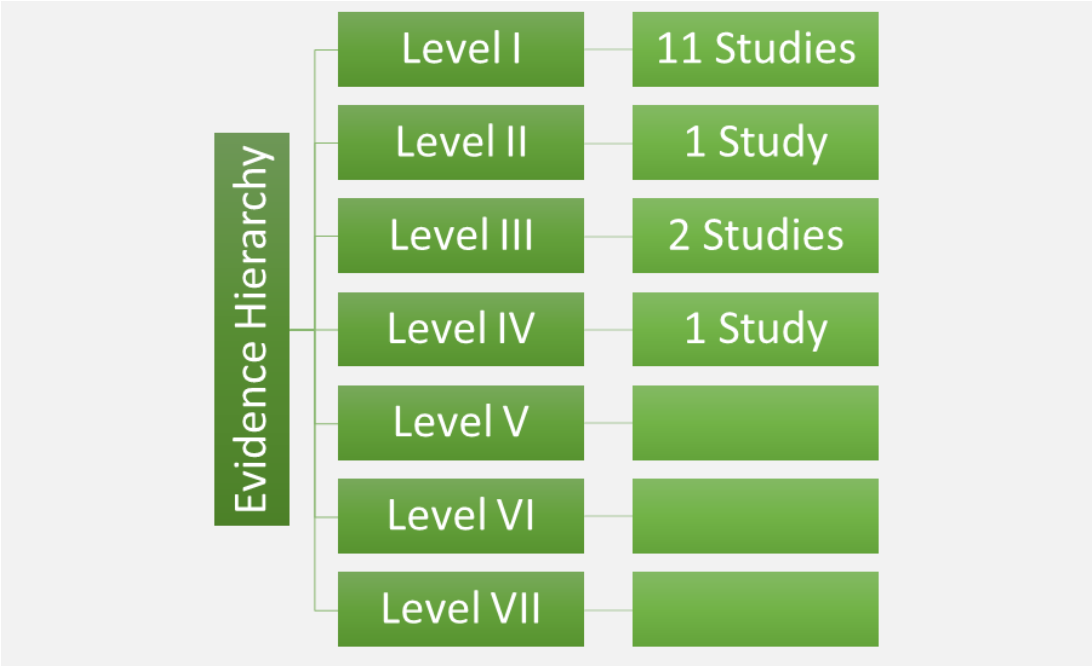

Figure no 1. Level of evidence of studies used in the study on long-term effects of chemotherapy.

FINDINGS OF LITERATURE REVIEW

Data gathered from the literature varied, although concepts related to the long-term effects of chemotherapy were consistent. After careful consideration and analyzing the literature, we identified overarching themes of the long-term effects of chemotherapy treatment. Cardiovascular disease, neurological dysfunction, and changes in reproductive function comprised the findings. The main findings are further described below.

Cardiovascular Toxicity of Chemotherapeutic Agents

The most prevalent long-term side effects of chemotherapy were related to the cardiovascular system. A systematic review of anthracyclines indicated potential mechanisms of cardiotoxicity (see Figure 2) in chemotherapeutic agents, oxidative stress, DNA damage, senescence, and cell

death [6]. The development of cardiotoxicity was once thought to happen in different stages, but recent findings indicated that anthracycline-induced cardiotoxicity occurs on a continuum and leads to heart failure [6]. An increased risk of myocardial infarction, cerebrovascular morbidity, and venous thromboembolism exists shortly after cisplatin-based chemotherapy. The risk decreased one year after treatment, but it increased again 10 years after treatment [7]. Adding anthracycline chemotherapy to radiation increases the patients' risk of developing congestive heart failure 10 years after treatment [7].

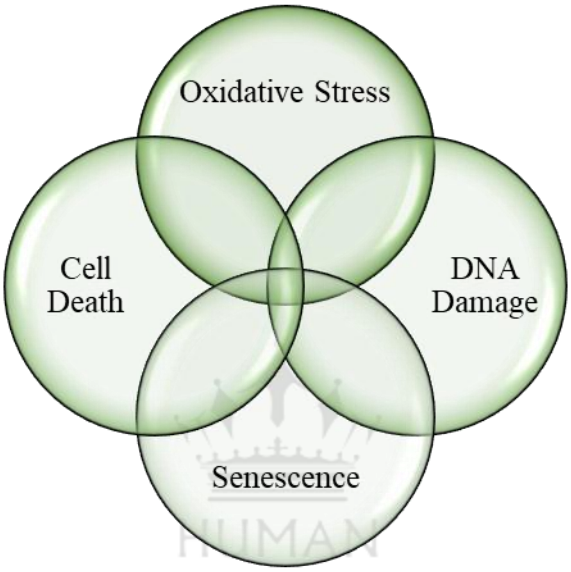

Figure no 2. Potential mechanisms of cardiotoxicity in chemo agents.

Results of a nonrandomized control trial to evaluate cardiopulmonary fitness after breast cancer chemotherapy indicated a reduced oxygen uptake during the peak of exercise that did not show significant improvement over 16 months [8]. However, participants who underwent specialized exercise training showed better cardiac function than those who did not. This reduced VO_{2peak} was associated with progressive impairments in cardiac function, an increased risk of heart failure, cardiovascular morbidity, and mortality [8].

In a retrospective study, Peddi *et al.* [9] assessed the pretreatment evaluation of left ventricular ejection fraction (LVEF). They discussed the known cardiotoxic effects of chemotherapy, specifically anthracyclines. Acute effects included electrocardiographic changes, transient left ventricle dysfunction, chest pain from myocarditis, and supraventricular arrhythmias. Chronic

problems ranged from subclinical cardiac dysfunction to apparent symptoms of heart failure [9]. They determined that assessing pre-chemotherapy LVEF was a widely accepted practice, despite the lack of clinical evidence to support this practice. As seen thus far, chemotherapeutic agents can increase the risk of cardiovascular morbidities, so assessing a patient's cardiac function before starting treatment was a commonly adopted practice. However, patients with two or fewer risk factors such as hypertension, diabetes mellitus, and smoking had a lower chance of having an altered LVEF that would warrant a change in the chemotherapeutic agent. Pretreatment evaluation of LVEF may not be necessary for every patient and certainly not ones with low risk and receiving lower doses of chemotherapeutic agents [9].

Neurological Dysfunction Associated with Chemotherapy

Another finding throughout this review consisted of neurologic dysfunction associated with chemotherapy. In a systematic review and meta-analysis, Ciernikova *et al.* [7] found that long-term cancer survivors experienced memory loss, attention problems, difficulty processing information, poor organizational and decision-making skills, white brain matter changes, and chemotherapy-induced peripheral neuropathy. Additionally, there was a significant correlation between changes in intestinal microbiota and chemotherapy-related comorbidities [7].

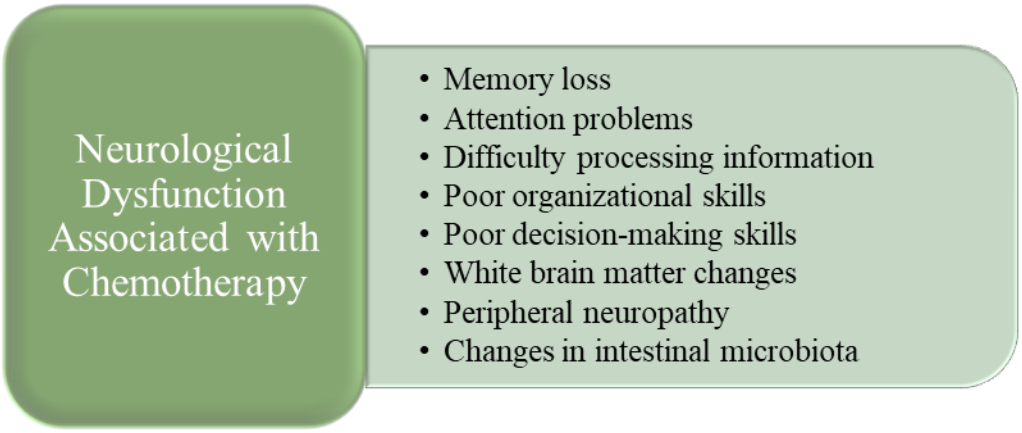

Figure no 3. Neurological dysfunction associated with chemotherapy.

In a cross-sectional study of survivors of childhood acute lymphoblastic leukemia (ALL), Phillips *et al.* [10] discovered that exercise intolerance related to chemotherapy treatment correlated with neurocognitive impairment. The participants had lower averages of intelligence, executive

functioning, processing speed, memory, and academics. After chemotherapy, children with ALL may benefit from specialized exercise regimens to support neurocognitive and academic performances [10].

Chemotherapy-induced peripheral neuropathy was a side effect experienced by colorectal cancer survivors who took oxaliplatin. Peripheral neuropathy can significantly impair a patient's quality of life. In a systematic review, Teng *et al.* [11] found that after chemotherapy, the average prevalence of neuropathy fell by 26% every year. They concluded that while patients may experience long-term effects of neuropathy from treatment, the change of symptoms over time will help clinicians and patients estimate risk [11].

Effects of Chemotherapy on the Reproductive System

Testicular cancer can cause irreversible damage to fertility because of cancer treatment. Chemotherapy adversely affects reproductive functioning, leading to infertility, impaired body self-esteem, and decreased sense of masculinity [12]. This can cause men to feel inadequate or impotent when trying to begin a family. An inability to conceive could poorly affect marital relationships if semen specimens were not collected and stored before treatment. In addition, Wiltink *et al.* [13] stated that physical abilities, social, and overall well-being were altered because of chemotherapy in men.

In a systematic review, Gerstl *et al.* [14] investigated the long-term impact of cancer therapy on pregnancy and birth outcomes after a childhood cancer diagnosis. The average age for cancer diagnosis was ten and a half years old. Researchers discovered that survivors had reduced birth rates with a higher risk of preterm birth. The risk of infertility was considerably higher in survivors than women in the public [14].

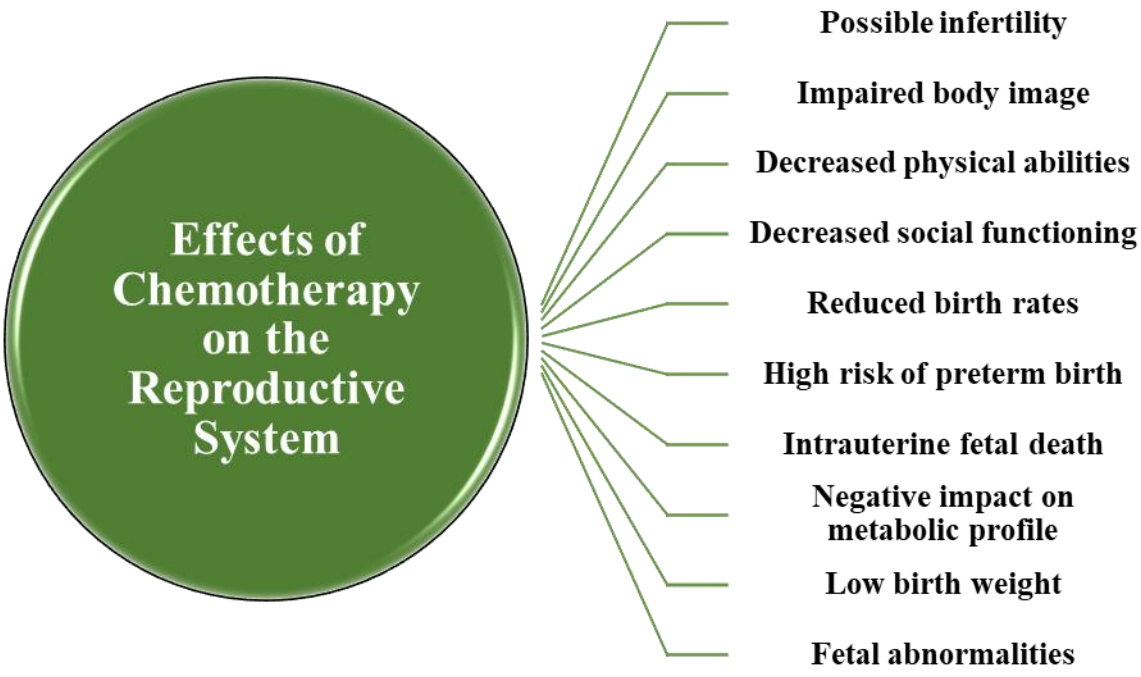

Figure no 4. Effects of chemotherapy on the reproductive system.

In another study, Godinho-Mota *et al*. [15] found that premenopausal women who received chemotherapy for breast cancer had an increased total and central adiposity, insulin resistance, and all lipid-related indicators. The chemotherapy harmed their metabolic profile. The negative impact on the body could contribute to developing future morbidities.

Infertility related to chemotherapy in breast cancer survivors is a concern for reproductive-aged women. In a systematic review and meta-analysis, D'Ambrosio *et al.* [16] found that women who have a history of breast cancer had a greater incidence of obstetrical complications when compared to controls. Preterm birth, low birth weight, cesarean section, intrauterine fetal death, and fetal anomalies were significantly higher in those who underwent chemotherapy for breast cancer than in the control group [16]. In another study, Peigne and Decanter [17] elaborated, for people who may need chemotherapy, the necessity for fertility preservation strategies, fertility counseling, and future family planning due to ovarian toxicity mechanisms of chemotherapy.

Cancer Survivors Living with Morbidities

In a meta-analysis, Firkins *et al.* [18] compared the reported quality of life of those who had chemotherapy with those who did not undergo chemotherapy. The study found that the quality of life was significantly impacted 26 years after a cancer diagnosis (see Figure 5). The analysis found that both physical and mental health were lower than acceptable levels years after chemotherapy. The ability to work was impacted for about six years, and research studies addressed the short-term effects of chemotherapy, but only a fraction of these after diagnosis [18].

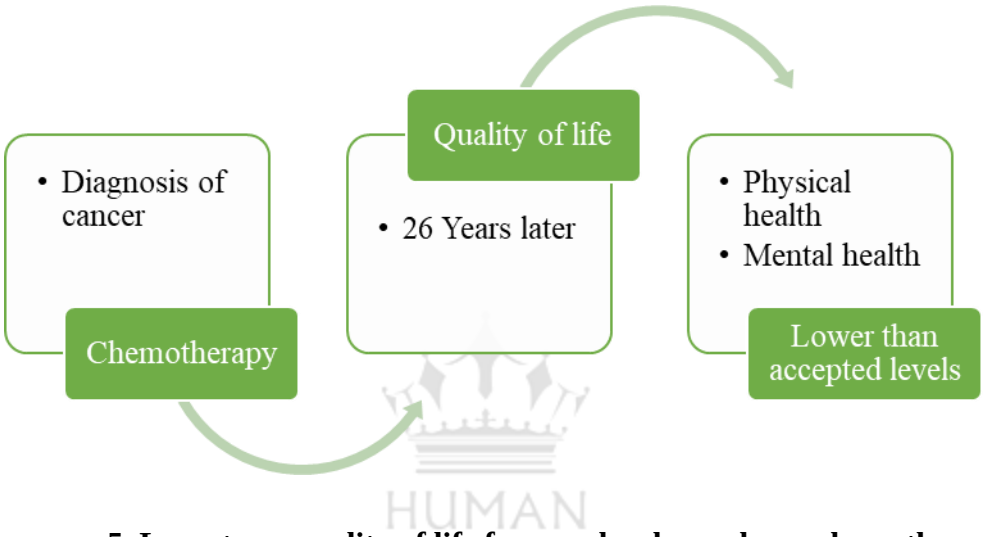

Figure no 5. Long-term quality of life for people who undergo chemotherapy.

Klonoff-Cohen and Polavarapu [19] discovered that researchers lacked information regarding the impact of adverse effects from chemotherapy on the body of cancer survivors. Since chemotherapeutic agents target highly proliferative cells and use potent chemicals to do this, side effects cannot be completely avoided. Long-term side effects of treatment were referred to as signs and symptoms that were not present at the end of the individual's treatment but arose months or years later [19]. In another cross-control study, it was noted that chronic fatigue, quality of life, and long-term side effects of chemotherapy are common in patients treated for ovarian cancer [20].

Additionally, Streefkerk *et al.* [21] noted that childhood cancer survivors had difficulty with physical morbidities, but a lack of consistency between studies made it difficult to interpret findings accurately. The focus of another study was how having cancer survivors participate in

physical activity would save them money and increase their quality of life [22]. However, inconsistency in activities performed by survivors made it difficult to compare findings between a patient who used different levels of activities.

Summary of Findings

A variety of research techniques were used to locate and analyze studies regarding the long-term effects of chemotherapy on the human body. Many of the studies addressed the short-term effects of chemotherapy, but only a fraction of them addressed the long-term effects it has on the body. All studies used in this review fell into the top four tiers of the evidence hierarchy. This review consisted of systematic reviews, meta-analyses, randomized control trials, nonrandomized control trials, cross-sectional studies, retrospective studies, and cohort studies. Studies covered a variety of cancer types, chemotherapeutic agents, and populations. The main findings in the research include cardiovascular disease, neurological dysfunction, and reproductive dysfunction (see Figure 6).

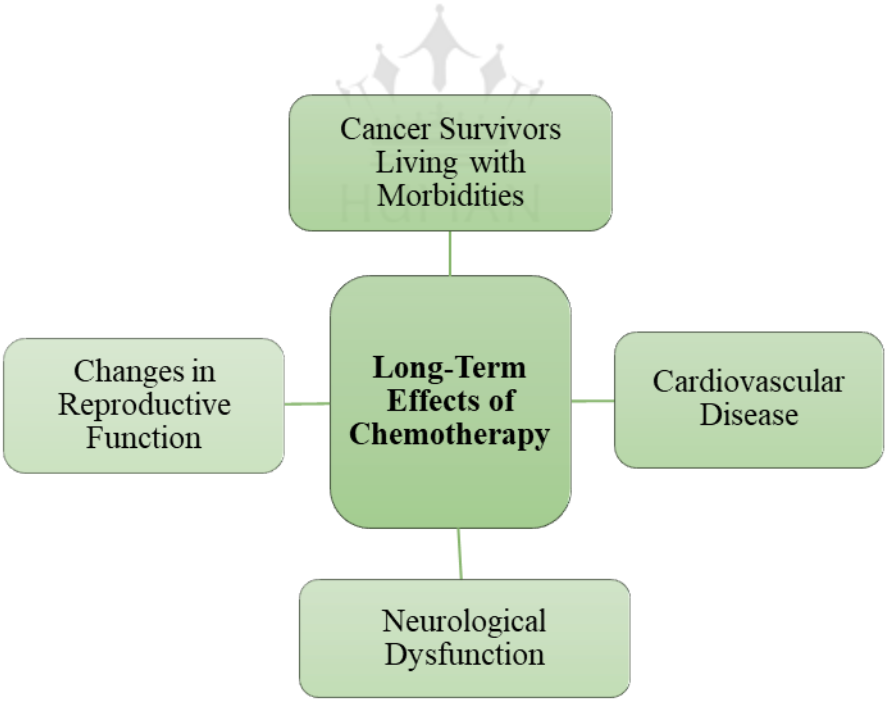

Figure no 6. Main findings for long-term effects of chemotherapy.

The cardiovascular toxicity from chemotherapeutic agents increased the risk of electrocardiographic changes, transient left ventricle dysfunction, myocarditis, supraventricular

arrhythmias, myocardial infarctions, cerebrovascular morbidity, venous thromboembolism, heart failure, and mortality. Neurologic dysfunction consisted of memory loss, attention problems, difficulty processing information, poor organizational and decision-making skills, white brain matter changes, chemotherapy-induced peripheral neuropathy, lower averages of intelligence, poor executive functioning, slower processing speed, and poor academic performance. Chemotherapy affected the reproductive system by decreasing fertility in both men and women, increasing the risk of sexual dysfunction, increasing the risk of early menopause and osteoporosis in women, and decreasing self-esteem related to body image.

DISCUSSION

Parameters throughout the research were limited, as few studies sufficiently covered this topic. Many studies focused on cancer itself but not the long-term effects that followed these patients. Research lacks implementation of the impact of long-term effects on individuals who received cancer treatment. Chemotherapy was found to be impactful and damaging to people's bodies resulting in complex and sometimes incurable symptoms.

The findings from this review indicated an increased risk of cardiovascular-related complications [6-9]. Promoting patient education regarding these potential risks, especially those patients with pre-existing cardiovascular disease is imperative decision making. Cardinale *et al.* [6] found an increased risk of cardiotoxicity, specifically with the use of anthracycline chemotherapeutic agents. It may be beneficial to administer alternative chemotherapeutic agents for those patients with pre-existing cardiovascular disease to prevent the worsening of the disease.

Ciernikova *et al*. [7] noted peripheral neuropathy in people who received chemotherapy and who also experienced neurological-related alterations. People with pre-existing neurological deficits should be provided advocacy to promote the correct treatment choices. Families should become aware of the intellectual challenges that may arise from treatment to cope with disabilities.

Several studies identified fertility issues in patients with breast or testicular cancer because of chemotherapy [12,16]. Discussing with patients, non-modifiable factors such as the family history of reproductive cancers, age, gender, and genetics can aid in identifying risks for comorbidities related to fertility. Bringing focus to the patient's wishes regarding having children can help

patients make decisions about possibly storing eggs or sperm for future reproduction (see Figure 7).

Potential Interventions	Teach impact of long-term effects of chemoptherapy
	Administer alternate chemo for those with cardiac problems to prevent deterioration
	Families should be aware of intellectual challenges that may arise from treatment
	Help with decisions about possibly storing sperm and eggs for future reproduction
	Specialized exercise training

Figure no 7. Potential interventions for patients who may undergo long-term effects of chemotherapy.

Implications for Nursing Practice

Nursing practice can benefit from education about the degenerative process of cancer morbidities. Chemotherapy can harm a patient's quality of life, and they may not be aware of what life could be like after treatment. Incorporating effective teaching to potential chemotherapy candidates would allow them to understand the advantages and disadvantages of treatment. The patient may choose to continue with treatment if the advantages outweigh the potential risks of treatment.

However, some patients may decide to forgo chemotherapy after being made aware of the potential disadvantages, especially those long-term effects. It may not be possible to know which morbidities a patient could face after receiving chemotherapy, so it can be challenging to distinguish actual or potential risks of treatment. The will to live influences this decision for many. Teaching patients and their families about the side effects of chemotherapy, such as infertility, is important so patients can consider how it will affect their daily lives.

For example, infertility is a potential side effect of some chemotherapy agents, so patients need to consider their options before choosing treatment. Children with cancer may not consider the impact of chemotherapy on their fertility, and there may be ethical dilemmas that arise when bringing the attention to the child's parents. Nurses advocate for patients, so informing patients of potential morbidities can help them decide what is best for that patient. Some patients may lack sufficient support systems, so the nurse takes on a stronger role to support the patient through their treatment or non-treatment process.

Strengths

Strengths included having high-tiered research, effective feedback, and specifically oriented research. The literature review contained 15 studies all within the top four tiers of evidence, meaning it was highly reliable. The use of meta-analyses, randomized controlled trials, and systemic reviews display the diversity of studies used. Each study was selected based on its relevance, level of reliability, and its congruence to the purpose of this review. The research was analyzed to assess the main findings such as cardiovascular, neurological, and reproductive changes.

Weaknesses

Weaknesses included a variety and inconsistency in sample sizes, variety of cancers, and databases used focused on the success of treatment by lacking long-term effects. Other weaknesses include the use of studies from other nations and the collection of studies for a longer period of over five years. Some researchers came across a lack of consistency with sample sizes and were unable to compare within its broad parameters in certain studies. The variation of cancers that exist made it challenging to find current research to thoroughly examine each body system in this review. Some databases used to conduct research focused more on the success or failure of treatment and less on the effects after treatment. Many of the studies were too broad or too specific, so the search for applicable and accurate data was difficult. Analyzing these strengths and weaknesses helps to identify the relevancy, applicability, and authority of this review.

Recommendations

To improve nursing relevance in the influence of chemotherapy treatment, further research is necessary to fully determine all possible morbidities that could result from chemotherapy-related treatments. Evaluating and comparing findings from this review can help distinguish similarities and differences of certain cancers. Investigating effects on each body system can aid in the development of less harmful treatments. Further research could help develop other forms of treatments for cancer to improve the quality of life of the patient affected. Nurses need specialized training and certification to administer chemotherapy drugs because of the risk of developing serious adverse effects from the administration.

Patient education regarding the long-term effects of chemotherapy can better equip patients to make the most appropriate decision for their care. The patients who continue with treatment could benefit from support groups, rehabilitation programs, and an appropriate nutritional diet to meet their unique needs. The use of screenings to determine pre-existing comorbidities can help identify patients who have an increased risk of developing long-term effects from treatment. Since chemotherapy can impair fertility, nurses need to use caution and sensitivity when addressing this concern with parents of children with cancer. Some patients and families may decide to preserve reproductive function or reproductive cells, such as the ova or sperm. These recommendations would innovate the cancer association to improve patient outcomes and patient satisfaction.

CONCLUSION

Chemotherapy results in side effects that can manifest months or years after treatment. Discovering long-term side effects of treatment helps to identify individuals at an increased risk for developing morbidities because of treatment. Patients and families of cancer patients could benefit from improving the quality of life of patients by spreading adequate information about the risk of morbidities. In conclusion, the lack of research should drive researchers to explore further risks for developing morbidities after chemotherapy.

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	**Ashley R. Herington** *Bethel University School of Nursing, Mishawaka, Indiana, USA*
	**Madelyn R. Claussen** *Bethel University School of Nursing, Mishawaka, Indiana, USA*
	**Jennifer Moreno** *Bethel University School of Nursing, Mishawaka, Indiana, USA*
	**Dr. Samuel P. Abraham– *Corresponding Author*** *Associate Professor of Nursing, Bethel University, 1001 Bethel Circle, Mishawaka, Indiana, USA*