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Promoting Healthier Treatment Outcomes in Obese Cancer Patients Taking High Dose Methotrexate

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This is to certify that the doctoral dissertation by

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has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
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Abstract

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RD, University of New Hampshire, 2010

MA, Brown University, 2004

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Cancer and obesity rates continue to rise, creating enormous public heath burdens to the individual and at the national and global levels, reducing quality of life, and increasing spending. Moreover, the relationships between cancer and obesity are not well understood. A commonly used chemotherapy for several types of cancer is high dose methotrexate (HDMTX). Along with chemotherapy, especially at high doses, comes toxicity to specific organs and the entire body. However, limited research has been conducted on obese cancer patients as they are often excluded from clinical studies. Practitioners need to better understand how to dose these patients to provide the best treatment outcomes. The purpose of this retrospective cross-sectional analysis was to investigate the association between HDMTX and toxicity in the kidney and liver in cancer patients, controlling for body mass index (BMI), age, and sex as well as comedication for participants in the Guardian Research Network database with several types of cancer. Using the health belief model as a theoretical foundation, single and multiple logistic regression was used for this analysis. The results demonstrated that there was no association between BMI or BMI and comedication on liver toxicity or kidney toxicity without any other predictors. Females had a significantly higher odds ratio of liver toxicity as compared to males. There was a small association between kidney toxicity and age, although it was just under the significance level. This was the first study of its kind, so more research is needed to confirm these findings, adding more covariates to understand where the differences in toxicity lie to help promote better outcomes for the obese cancer patient.

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Dedication

This dissertation is dedicated to the people who have always supported me in furthering my education no matter what the cost--my mother and father. They have watched me start over numerous times, spending countless hours studying. They have supported me emotionally, educationally, professionally, financially, and in every way imaginable.

Completing this project has given me the confidence and strength to know that anything is possible. Even after getting Covid, going through a divorce, moving, starting a new job, all while parenting two young children, my parents did not give up on me. They knew this doctoral journey was of the utmost importance to me, and that I would succeed no matter what. They spent many hours helping to watch my children, nourishing my body and soul with healthy food, and providing me with endless compassion, which all enabled me to be successful and self-sufficient.

I hope I can be a role model for my children as my parents have been to me. I hope I can teach them that each day is a step in the right direction, even when steps often go backwards. No matter what we may lose along the way, we never lose the education we gain, and I hope to instill this in my children, the way my parents did for me.

Acknowledgments

This project could not have been possible without the tireless efforts of Dr. Margaux Guidry Zwierko and Dr. Scott Howard. Margaux is my best friend and a close colleague who also completed her PhD through Walden. I had many reservations after starting the doctoral process in 2005, dropping out of school, and then having two children as well as a full-time job. Margaux continuously supported me and at times had to talk me off the ledge when I was ready to quit. She not only encouraged me to continue through this journey, but in the meantime, she helped me use my education to springboard my career. It is because of her that I am still working towards this amazing goal after 16 years and not giving up. She is truly an inspiration.

Margaux not only supported me but also connected me with her colleague, Scott Howard. Scott Howard is one of the busiest professionals I have ever met. His life's mission is to address unmet patient and clinical needs in the oncology space. He is focused on educating patients globally as well as improving healthcare information technology. Dr. Howard took the time to explain his mission and share unpublished, up-to-date data with me that will be extremely useful in helping achieve the next step of his project, while assisting me in my educational goals. He answers my questions, no matter how rudimentary, and was eager to partner with me as a student and professional to complete our aligned goals. I am honored to be working with someone as smart as Dr. Howard who is making so many advances in the field of Oncology to change the lives of adults and children around the world.

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Chapter 1: Introduction to the Study

Background

Cancer and obesity are both potentially life-threatening diseases that are detrimental to quality of life at the individual level and to public health at the national and global levels (Agha & Agha, 2017; Centers for Disease Control and Prevention [CDC], 2021a). Due to the myriad of complications plaguing both obese people and those with cancer, it is imperative to understand the relationship between the two diseases. Obesity may have negative implications on cancer patients, and cancer may affect weight and body fat more so or differently than in non-cancer patients. These relationships are still not well understood. As cancer and obesity rates continue to rise (Mattiuzzi & Lippi, 2019; Tremmel et al., 2017), health care practitioners and policy makers must understand this association to provide the best treatment and strategies for combating both issues.

Generally, cancer is treated using chemotherapy, a drug treatment that uses chemicals to kill cancer cells. One type of chemotherapy that has been successful in treating several types of cancers is methotrexate (MTX). This drug, a dihydrofolate reductase inhibitor given orally or injected, has been available since the 1950s and is indicated for treatment of various types of cancer, autoimmune disease, and several other conditions (Malaviya et al., 2010). Along with its benefits in treating cancer, MTX comes with side effects such as the risk of toxicity (Alsdorf et al., 2020). MTX is often given at high doses (Kowalski, 2021) and can result in serious adverse events including but not limited to kidney failure, bone marrow suppression, hepatotoxicity, fibrosis, cirrhosis,

lung disease, tumor lysis syndrome, fatal skin reactions, tissue necrosis, and death (Teva Parenteral Medicines, Inc., 2021).

However, there is limited research on MTX toxicity in obese cancer patients. Currently, dosing is based on weight; however, fat tissue is different from other tissue as it is not as vascular (Howard et al., 2016). Therefore, obese patients may not be dosed correctly with MTX or other chemotherapy when only weight-based formulas are used. Practitioners need to understand how to best treat obese patients because high-dose methotrexate (HDMTX) may be needed to treat many types of cancer but is also potentially toxic. As cancer and obesity incidences rise, this relationship is becoming even more crucial to evaluate and understand.

Public health experts are faced with reducing the burden of both the overweight and obesity epidemics as well as the overwhelming costs of cancer care. Obesity is thought to be multifactorial in nature, as is cancer. The prognosis of obese patients with cancer is even worse than the cancer patient with a normal body mass index (BMI; Krupa-Kotara& Dakowska, 2021). This may be due to worsening chances of the cancer spreading or a lack of effective treatment in the obese patient (Krupa-Kotara& Dakowska, 2021).

Obesity

Obesity is a multifactorial disease defined by excess fat tissue, which ultimately leads to numerous and potentially serious health problems. In the year 1995, there were approximately 200 million obese adults, which rose to 300 million in 2000 (Agha & Agha, 2017). If the trend continues, half of all adults will be obese by 2030 (Tremmel et

al., 2017). The medical complications of obesity are ubiquitous, as are the social and economic implications. Medically, obesity is associated with stroke, heart disease, sleep problems, lung disease, liver disease, pancreatitis, gallstones, female disorders, cancer, arthritis, vein complications, gout, and many other conditions (CDC, 2021a).

In addition to the physical problems, obesity leads to social problems such as low self-esteem, lack of productivity, shame, depression, and overall lower quality of life (Mayo Clinic, 2021a). In addition, the direct medical cost of obesity in the United States alone for adults was 260.6 billion USD in 2016, which was more than double the cost in 2001 (Cawley et al., 2021). These physical, social, and other issues are among the many reasons obesity may add complications to other comorbidities.

When studying obesity, it is necessary to understand how it is classified and measured in the clinical setting. Obesity is characterized by a unit of measure known as BMI, which is calculated by dividing weight in kilograms by height in meters squared. A BMI of less than 18.5 is considered underweight, 18.5 to 24.9 is normal weight, 25 to 29.9 is overweight, and 30 or greater is obese (U.S. Department of Health and Human Services, n.d.).

However, BMI values are not truly a measure of body fat, as they do not distinguish between fat and muscle tissue (Gurunathan & Myles, 2016). Therefore, an elite athlete could be considered obese by this method. For example, a six-foot-tall football player that weighs 225 pounds might be extremely muscular and play professional sports, but his BMI would be 30.5 which is considered obese. That being said, BMI does provide value and is often used as a guideline by practitioners or

epidemiologists as it is a quick and inexpensive method to track trends of either an individual or a population over time (U.S. Department of Health and Human Services, n.d.)

Cancer

Like obesity, cancer rates are swiftly rising. The costs to the individual and public health are devastating. According to the World Health Organization (WHO), in terms of disability adjusted life years, cancer is responsible for the greatest global burden at 244.6 million disability adjusted life years (Mattiuzzi & Lippi, 2019). Most cancer patients are over the age of 60, and the aging population is growing while treatments are improving (Mattiuzzi & Lippi, 2019). The result of this is that more people are living with the disease and thus being treated for longer periods of time (White, 2015). In addition to prevalence, the incidence of cancer is also increasing. In 2018 alone, there were 18 million new cancer cases worldwide, making it the second highest cause of death following heart disease (Mattiuzzi & Lippi, 2019).

Cancer, like obesity, is multifactorial and may come with many comorbidities. Because cancer is defined by cells dividing uncontrollably, it can easily spread to other organ systems or parts of the body and present with fatigue, weight changes, skin lumps or changes, trouble breathing, joint pain, bleeding, bruising, or night sweats, among many other symptoms (Mayo Clinic, 2021b). The numerous types of cancer are outside of the scope of this paper; however, it is important to point out that there are more than 100 different subtypes (National Cancer Institute, 2021). With so many various sites of

infection and etiologies, there are also many types of treatments. In this study, I focus on one cancer treatment: MTX.

MTX

MTX has been used since the 1950s and is credited as being the first drug to cure cancer (a rare type of choriocarcinoma; National Cancer Institute, 2014). The mechanism of action is via inhibition of dihydrofolate reductase, an enzyme needed for synthesis of thymidine and purine deoxyribonucleic acid (DNA) bases. This inhibition prevents the formation of DNA and blocks cell division by acting during the S phase of the dividing cell. As MTX acts most readily on rapidly dividing cells, the bone marrow, mucosal lining, hair follicles, tumors, and other fast-growing cells are the most affected (Malaviya et al., 2010). This widely used pharmaceutical agent has several indications, but I focus on the high doses of MTX used to treat cancer, rather than lower, chronic dosing used for autoimmune disorders or other indications.

HDMTX is indicated for adult and pediatric patients with acute lymphoblastic leukemia, meningeal leukemia, non-Hodgkin's lymphoma, and osteosarcoma. It is indicated only in adults for breast cancer, squamous cell carcinoma, and gestational trophoblastic neoplasia. For all these indications, HDMTX is sometimes used alone and sometimes in conjunction with other chemotherapy agents (Teva Parenteral Medicines, Inc., 2021).

Like most pharmaceuticals and especially cancer drugs, HDMTX is not without risk. Doses range from 12 mg intrathecally and 20 mg/m^2 orally, intramuscularly (IM) or intravenously (IV), to as high as 33,000 mg/m^2 IV. As the dose increases, so do the side

effects. In this study, I focused on HDMTX, which is defined as a dose higher than 500 mg/m^2, which can be associated with more toxicity than that of lower doses used for noncancer indications (see Howard et al., 2016). However, there is a scarcity of information regarding MTX dosing in obese patients. Obese patients may have different pharmacokinetic parameters such as clearance and volume of distribution of chemotherapy drugs as compared to normal weight patients (Hall et al., 2013). This is most likely because obese patients are severely underrepresented in studies used by the Food and Drug Administration for new drug applications or biological license application approval (Jacques & Erstad, 2010; Martin et al., 2012; May et al., 2020).

The lack of obese patients in clinical trials coupled with the complex relationship between obesity and pharmacokinetics and pharmacodynamics makes dosing of MTX complicated in both overweight and obese patients. Because of the different amounts of fat tissue, it is difficult to know what method of dosing to use for these patients. Specifically, absorption, distribution, metabolism, and excretion of individual drugs may be altered in the obese patient (May et al., 2020). Very few studies exist examining the relationship of MTX and adverse events or toxicity in obese patients. Most studies have been conducted on noncancer patients or with cancer drugs other than MTX (Krüger et al., 2020; Maestas et al., 2015; Orgel et al., 2021). There is a lack of research regarding the impact of obesity on toxicity in obese patients. Thus, this study addressed this gap in knowledge by examining the relationship between body weight and MTX toxicity.

Problem Statement

As obesity rates increase, a rising number of people receiving HDMTX will be obese, so understanding the toxicities of this drug in obese patients is exceedingly important. There is a dire need to better understand the proper dosing for these patients (Hall et al., 2013) to be able improve health outcomes. Currently dosing of MTX is based on weight. However, fat tissue acts differently than other tissue and may lead to over or underdosing in obese patients (Howard et al., 2016). HDMTX may prolong lives by slowing the growth of many types of cancer but is also potentially toxic. As cancer and obesity rates climb, understanding this relationship is even more crucial.

Gennari et al. (2016) examined the effect of BMI on breast cancer patients and found that survival did not differ by BMI. Not all patients were taking MTX, and the authors reported the need for more information. In other research, Orgel et al. (2021) paved the way for future research as he examined 36 children with pediatric acute lymphoblastic anemia (ALL) who were given HDMTX to understand the pharmacokinetics related to body fat. The authors reported that larger body size and obesity resulted in twice the risk of delayed MTX elimination at 48 hours, but that the higher area under the curve of MTX was not associated with toxicity. As this study was just completed in 2021 and was one of the first of its kind, the authors reported the need for more research.

Purpose of the Study

The purpose of this quantitative retrospective cross-sectional study was to examine the association between HDMTX and toxicity in cancer patients, controlling for

BMI, age, and sex for participants in the Guardian Research Network (a large, integrated, de-identified database with patient data from 2010-2018) with several types of cancer. The independent variable was BMI while the dependent variable was toxicity. Age, and sex were assessed for confounding. This could lead to better outcomes in the obese cancer patient.

Research Questions

Research question (RQ)1: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{01}: There is no association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A1}: There is an association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

RQ2: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{02}: There is no association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A2}: There is an association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

RQ3: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{03}: There is no association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A3}: There is an association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

RQ4: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{04}: There is no association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A4}: There is an association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

Theoretical Foundation

The theory that grounded this study was the health belief model (HBM). It is difficult to pinpoint the original creator of this model, as it was first documented in the 1950s as a method to understand why individuals did or did not behave in certain ways, and the theory has morphed over time. It is most often credited to Hochbaum, Rosenstock, and Kegels (Rosenstock, 1974) who were social psychologists. It is based on the constructs of perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, and self-efficacy (Janz & Becker, 1984).

The logical connections between the framework presented and the nature of this study included the idea that overweight and obesity can be controlled by dieting, exercise, and will-power. However, obesity may also result from genetic or multifactorial causes that the individual may not have full or any control over (Janz & Becker, 1984). Obese patients may be more likely to develop serious illnesses like cancer and other comorbidities. In addition, there are many barriers that may prevent someone from losing

weight, especially when undergoing cancer treatment (Janz & Becker, 1984). Finding out what these barriers are may help provide better cancer treatment to obese or overweight patients while they attempt to lose weight. Finally, it may be impossible to lose weight in a timely manner prior to the need for HDMTX after a new cancer diagnoses. In some cases, HDMTX is the first therapy needed for a person with newly diagnosed cancer, so there would be no time for any interventions to reduce weight prior to HDMTX administration. Table 1 shows the variables and theoretical concepts of the study.

Table 1

Variables and Theoretical Concepts

Model	Concepts	Study variables
HBM	Behavioral beliefs	Obesity (dietary habits, exercise)
HBM	Cues to action	Obesity (knowledge of weight loss, motivation)
HBM	Susceptibility	Obesity (self or family history)
HBM	Severity	Obesity, comedication, toxicity
HBM	Outcomes	Toxicity

Note. HBM = health belief model.

Nature of the Study

To address the RQs in this quantitative study, the specific research design was a cross-sectional analysis using secondary data from the Guardian Research Network. These data included HDMTX dosing and regimen, height, weight, age, and toxicity data. Other personal information such as sex and comedication was also captured in this de-identified database of cancer patients.

Kruger et al. (2020) used kidney values such as creatinine clearance and glomerular filtration rate to examine MTX toxicity. Other researchers used liver function tests, overall survival, disease-free survival, as well as adverse events to quantify MTX toxicity (Conway & Carey, 2017; Gennari et al., 2017; Pai et al., 2020). On the other hand, researchers have also created their own algorithms or used other data points to explore toxicity (Orgel et al., 2021). Because there is no one agreed upon method, I focused on liver toxicity aspartate aminotransferase and alanine transaminase (AST and ALT) and acute kidney injury category to define MTX toxicity. The rationale for using these specific biomarkers is that these tests are readily available, commonly used, and well understood and represent kidney and liver toxicity as well as MTX clearance. As there is little if any research on this topic, the relationship between HDMTX and these clinical outcomes can provide valuable insight and much needed data points for these obese cancer patient toxicity outcomes.

Scope and Delimitations

Because BMI can be interpreted differently in children and adults (CDC, 2021b) only data points from patients 18 years or older were included in the study. No participants were excluded from the study except those under 18. MTX is also used for autoimmune disorders and other types of cancer, but the dataset used in this study only captured specific types of cancer patients at several institutions. Specifically, the patients in this dataset had been diagnosed with acute lymphoblastic leukemia, osteosarcoma, non-Hodgkin’s lymphoma, or primary central nervous system lymphoma.

Starting with this patient population will lay a foundation for further research studies in children with cancer as well as obese individuals who are taking MTX or HDMTX for other reasons. These data are generalizable to obese people with other types of cancer, which is imperative because obesity rates are continuing to rise in most countries.

Limitations

As with every study, there were several limitations to this project. First, data were previously collected, so missing data could not be recaptured. Also, it is not known if all comedications were captured by the physician because some medications may have been prescribed and dispensed by outside practitioners who do not participate in the Guardian Research Network. Patients may have been taking other medications that could have affected toxicity outcomes that were not recorded in the data set. Similarly, patients may have had other comorbidities that were not captured that may have affected toxicity outcomes.

In addition, these data were only gleaned from four types of cancer patients. Therefore, the relationships between obesity and toxicity may only apply to these cancer subtypes. MTX and HDMTX may act differently in other types of cancers or immune disorders. In addition, like all retrospective analyses, a limitation is that causal relationships could not be determined. The relationship between variables was assessed, but further studies will be needed to confirm this relationship and better understand the causes of various toxicities in obese cancer patients (see Wang & Katan, 2020).

Significance of the Study

The significance of this study was defined in several ways. First, this research helps fill a gap in the literature and improve understanding of proper HDMTX dosing for obese cancer patients. Next, this study could provide cancer and other health care centers information to facilitate potential weight loss counseling or other nutrition therapy for overweight and obese cancer patients. Third, decreased toxicity could reduce the length of hospital stay, which in turn may decrease healthcare costs while increasing quality of life for the obese cancer patient.

Significance to Practice

As previously mentioned, there is no agreed upon method for dosing obese cancer patients with chemotherapies such as MTX. Whichever protocol the institution follows, most practice therapeutic dose monitoring to constantly shift doses as a patient's weight changes (Abdah-Bortnyak et al., 2003; Arshad et al., 2021; May et al., 2020). Health care practitioners are always carefully balancing the amount of treatment with the side effect profile, attempting to interpret the ideal dosing regimen for each patient.

As the obese patient is not equally represented in clinical trials, understanding the specific needs of overweight and obese patients can provide significant knowledge advancement to oncology practices. Protocols may be updated to outline specific dosing regiments for patients who are obese and overweight using data from this research study. In addition, this research may be a springboard for further studies to investigate better methods of counseling overweight and obese cancer patients. This could include both weight loss strategies in addition to managing the side effects of HDMTX.

Promoting healthier treatment outcomes in obese cancer patients can have numerous positive outcomes. Most Americans are unaware that obesity has been linked with worsening cancer outcomes (Ligibel et al., 2014). The American Society of Clinical Oncology (ASCO) has created guidelines and priorities for the obese cancer patient. Specifically, the priorities are first to educate providers and patients regarding obesity/overweight and cancer. Next, they aim to instill specific protocols for the obese cancer patient both in the clinical setting and for patients at home. The guidelines promote research to foster better cancer prognosis and create policy for obese cancer patients (as cited in Ligibel et al., 2014).

Significance to Theory

As stated in the problem section, this project adds to a very scarcely understood body of knowledge regarding the obese cancer patient and treatment toxicity. This project has the potential to change dosing protocols and improve cancer treatment strategies in hospitals and other institutions. Additionally, although this study was limited to adults, the obesity rate in children is growing rapidly and should also be scrutinized. Specifically, in 2016, there were more than 340 million obese children and young adults (aged 5-19) and there were 39 million children under 5 years old classified as obese in 2020 (WHO, 2021).

Similarly, the rates of cancer in pediatric patients are sharply increasing. Cancer is the second leading cause of death in children under 15 years of age following accidents (American Cancer Society, 2021). Once adults with obesity can be properly counseled and doctors can be educated on the proper MTX dosing, children will also need and

benefit from this information. Therefore, there is enormous potential for the data from this project to assist in both adult and pediatric cancer centers to dose obese cancer patients.

Significance to Social Change

The knowledge gleaned from this research study could potentially reduce the length of stay for one oncology patient or even reduce the amount of time spent managing HDMTX toxicities. This could equate to an increase in overall survival, progression free survival, or overall quality of life, which are all measures of the success of cancer treatments (Hess et al., 2019). Similarly, this project improves strategies for counseling the obese cancer patient. This type of program could reduce public health costs to the individual and at the institutional level by providing better dosing strategies up front. Institutions may be able to transition obese patients off HDMTX faster, freeing up hospital beds for other patients.

Even though this is only the first step in the equation, more studies may use these data as a springboard to create diet counseling programs for obese and overweight adult and pediatric patients. Obesity and cancer are debilitating diseases that are extremely costly at many levels. Even a slight change can foster more research to be conducted so that the obese cancer patient can have better overall treatment outcomes.

Summary and Transition

There is no doubt that obesity and cancer are two important public health issues that are not only increasing in prevalence but are also driving up public health expenditures (CDC, 2021a; Mayo Clinic 2021; Park & Look, 2019; Tremmel et al.,

2017). While it is encouraging that cancer patients and obese individuals are living longer with the advancement in treatments and counseling programs, many treatments come with side effects that can be of devastating consequences to the individual. HDMTX is one treatment that is well studied and has positive treatment results, but it also comes with a myriad of toxicity outcomes and other adverse events (Howard et al., 2016). Therefore, practitioners would benefit from a better understanding of how the drug affects toxicity outcomes in the obese cancer patient. These data could be translated to obese pediatric cancer patients and may even be useful in patients taking HDMTX for other types of cancers or conditions.

Chapter 2: Literature Review

Introduction

The problem addressed is that the incidence and prevalence of both cancer and obesity are rising. Because many individuals have both comorbidities, this relationship needs to be better understood (Avgerinos et al., 2019). As people are living longer with both conditions, more people are treated with chemotherapy. There are numerous types of chemotherapy – one of which is HDMTX. However, little is known about the short- and long-term outcomes of this treatment in obese cancer patients. Toxicity is one way to examine this relationship. Understanding the association between HDMTX, cancer, and body composition can prepare health care providers to better treat these patients. In addition, understanding the epidemiological differences in obese cancer patients can provide better strategies for decreasing toxicity in obese cancer patients.

The literature that exists on this subject has been most often conducted using extremely small sample sizes and has often produced contradictory results. There have been several studies looking at the pharmacokinetic and pharmacodynamic profiles of HDMTX in various cancer patients (Gennari et al., 2016; Maesta et al., 2015; Orgel et al., 2021). Additionally, some researchers have examined chemotherapy in general and how this relates to toxicity in obese cancer patients with varying results. This literature review addresses studies done on obese cancer patients taking MTX with relationship to toxicity to provide a background for the next logical research steps. In addition, a literature review regarding the HBM in the obese cancer patient was conducted to understand the barriers to change and the factors that influence obesity.

Literature Search Strategy

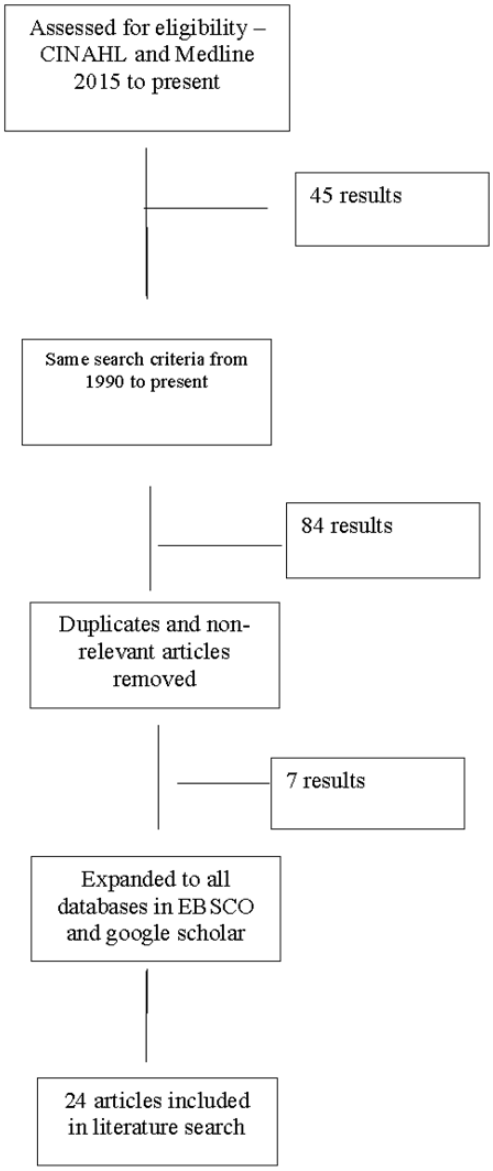
First, the Walden Library Health Sciences databases CINAHL and Medline were searched for *cancer* or *malignancy* or *neoplasm* or *cancer patients* or *oncology patients* or *patients with cancer* and *obesity* or *overweight* or *fat* or *obese* or *unhealthy weight* or *high BMI* and *methotrexate* or *Trexall* or *Xatmep* or *Otrexup* or *Rasuvo* and *toxicity* or *toxic* or *effects* or *risks* or *adverse events* or *side effects* or *hypersensitivity*. When limiting the search to 2015 or later, there were only 45 results. Next, the search window was increased to the same criteria from 1990 to the present. This search yielded 84 results.

Articles not relevant to cancer (regarding psoriasis or other autoimmune conditions and MTX) were excluded. Similarly, in vitro or animal studies were not used for this paper. Each article abstract was addressed, and I compiled a spreadsheet describing which articles were not relevant and why. An alert was sent to me every time a new article was published that met the criteria, and this was added to the Excel spreadsheet. After duplicates and nonrelevant articles were excluded, only seven of these articles were relevant and included in the paper.

Following this small turnout, the search was expanded to all database available at Walden, including Embasse, Proquest, and APA PsychInfo, Pubmed, TRIP, ProQuest, and Google Scholar. The same search words were used with the same date range, with duplicates excluded, yielding an additional 17 articles. Additional references were used for background and support regarding the theoretical frameworks. See Figure 1 for a consort diagram of this search.

Figure 1

Consort Diagram: Literature Search



Obesity Definition and Classification

Obesity can be defined in many ways but is most often classified as excess amounts of body fat for height (Hruby & Hu, 2015). Another definition is that obesity is classified as 20% or more of the calculated ideal body weight, leading to adverse health effects (Agha & Agha, 2017). In addition to diverse ways to define obesity, there are also several approaches to measure it. These methods use measurements such as waist circumference, waist-to-hip-ratio, bioelectrical impedance, skinfold thickness, and the most common, BMI. These techniques require simple equipment and are easy to calculate and conduct at office visits. While there are other ways to measure obesity and overweight such as dual energy X-ray, magnetic resonance imaging, or dual energy X-ray absorptiometry, these reference measurements, as they are often called, are more difficult and much more costly. They are, therefore, normally only used in research or for specific case studies (Harvard School of Public Health, 2021).

BMI is available for all patients and is mostly used in clinical practice. In adults, the standard formula for BMI is weight in kilograms divided by the height in meters squared. There are several on-line calculators to help individuals compute this value, and it is easily done in a doctor's office to assess values over time or look at population comparisons. Table 2 lists the various categories used for BMI in adults, according to the National Institute of Health.

Table 2

BMI Categories for Adults

Category	BMI range (kg/m^2)
Severely underweight	< 16
Underweight	< 18.5
Normal weight	18.5-24.9
Overweight	25-29.9
Obese	≥ 30
Obesity Class I	30-34.9
Obesity Class II	35 to 39.9
Obesity Class III	≥ 40

Note. BMI = body mass index. Adapted from "US Department of Health & Human Services." (n.d.). *Calculate your body mass index*. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

Like every measurement method, there are positives and negatives to BMI. As previously mentioned, BMI is easy to calculate, free to perform, and strongly correlated with body fat. However, this is only a measurement of height and weight, and does not distinguish between body fat and lean body mass. Therefore, BMI is not an accurate measurement in athletes or anyone with high muscle mass who is not overfat. Also, someone with decreased lean mass such as people with Prader-Willi syndrome may be misclassified with this method (Daniels, 2009).

Another difficulty with BMI is that the calculation differs in adults and children. BMI is not used for children under 2 (they follow growth charts based on weight and

length only). It is only defined for children and adolescents 2 to 19 years old. BMI in children is also based on age and sex, not just height and weight (CDC, 2021b). In children and young adults, it is not a diagnostic tool but can be used with growth charts to observe trends. The BMI is expressed only as a percentile and is compared to those who were part of a 1963 to 1965 or 1988 to 1994 survey. This is done mainly because children are constantly growing and, therefore, their body composition changes rapidly. Comparing the BMI to other children of the same sex and age may be helpful for physicians and parents to understand how a child compares to other children to understand if there may be any medical issues (see Table 3; CDC, 2021b).

Table 3

BMI Categories for Ages 2-18

Category	Percentile range
Underweight	< 5th
Healthy weight	5th - < 85th
Overweight	85th - < 95th
Obesity	≥ 95th

Note. Adapted from "Centers for Disease Control and Prevention." (2021b, March 17). *About child and teen BMI*. Obesity Incidence, Prevalence, Risk Factors, and Complications.

Currently, more than 33% of the adult worldwide population is either overweight or obese. This equates to more than 1.9 billion overweight adults and 650 million obese children. If this trend continues, 85% of the adult population will be overweight or obese by the year 2030 (Hruby & Hu, 2015). More specifically, according to the CDC (2021a),

between 2017 and 2018, the prevalence of obesity in the United States alone was 42.4, which was up from 30.5% in 1999-2000. Obesity was recognized as a disease in 2013 by the American Medical Association and has been deemed an epidemic and a pandemic by many sources (see Ludwig et al., 2021; Meldrum et al., 2017).

Of course, there is no one simple cause of obesity, and researchers continue to study the risk factors as well as how they interact with each other. Currently, there have been links to more than 60 genetic markers for obesity. However, when further examined, all these genetic risks may only lead to a 15-pound difference between low and high genetic obesity risk (Hruby & Hu, 2015). More recently, the environment and its connections are being investigated. Environmental factors may be part of the household environment, such as TV watching and sedentary lifestyle, or the larger environment. For example, most people are driving long distances to work and driving to stores instead of walking. Many jobs require sitting at a desk in front of a computer for long hours rather than moving around. In addition to the environment, there are behavioral, socioeconomic, biological, and mostly preventable links to obesity (CDC, 2021a).

Diet can also strongly impact obesity risk and is itself the result of culture, socioeconomic status, and other nongenetic factors that interact to influence food choices. For example, healthy food is often more expensive than unhealthier, more calorie dense food. Therefore, low socioeconomic status is often linked to obesity (Mayo Clinic, 2021). Similarly, if specific nutrition education is not provided, it is difficult to know what foods or how much of them to eat. Consequently, more affluent individuals and populations tend to have a better diet and reduced rates and risk of obesity as compared to those with

less money and education (Mayo Clinic, 2021). The reason obesity is deemed preventable, even though some risk factors are not controllable, is that many of the risk factors are behavioral and can be changed. Eating high fat and calorically dense foods, eating in restaurants, and eating more meals per day are associated with overweight and obesity (Sahib et al., 2016). In addition to eating behaviors, lack of physical activity is also associated with higher weight and is most often preventable. Of course, if someone is handicapped or has physical limitations, physical activity may not be an option (Sahib et al., 2016).

Medical complications of obesity are numerous. Obese individuals are more likely to have hypertension, stroke, Type 2 diabetes, high cholesterol, gallbladder disease, low quality of life, mental illness, sleep apnea, and cancer (CDC, 2021a). This is not an exhaustive list of comorbidities. More specific analyses have been done to understand the increase risks of specific types of cancer in obese patients. Breast, endometrial, ovarian, colorectal, kidney, pancreatic, and prostate cancer are all more likely to occur in obese and overweight patients as compared to their normal weight counterparts (Guh et al., 2009). The myriad of causes and complications of obesity make it a complex and multifactorial public health problem of enormous magnitude.

Cancer Definition and Classification

Like obesity, cancer is a common health problem with various causes, typology, and complications. Cancer is defined as the uncontrollable growth of cells that may spread to other parts of the body (known as metastasis) and form tumors (National Cancer Institute, 2021). Cancer can occur anywhere in the body, even in the blood, which

is termed leukemia. Cancer can lead to both benign and malignant tumors. Benign tumors generally do not grow back when removed and are not typically as dangerous as malignant tumors. Cancer cells are different from the normal cells that they derive from. First, they do not undergo apoptosis, and therefore continue growing when normal signaling would otherwise stop cells from further division. Normal cells do not typically move to other areas of the body, but cancer cells may spread and even grow new blood vessels, which is known as angiogenesis (National Cancer Institute, 2021).

In addition, cancer cells are normally not recognized by the immune system as foreign. Therefore, they keep growing and may proliferate even more quickly than normal cells without any repercussions from the immune system. They can even cause chromosomal changes in cells that propagate to daughter cells as mutated cells divide (National Cancer Institute, 2021). Cancer is caused by genetic abnormalities that can occur as cells are dividing or by environmental carcinogens such as smoke and ultraviolet rays. Proto-oncogenes are specific types of genes that can lead to abnormal growth and division of cancer cells. Tumor suppressor genes may also be downregulated in cancer patients (National Cancer Institute, 2021).

To date, there are over 100 distinct types of cancer. They are grouped by the types of cancer cells and the location of the cancer. The most common types of cancer, carcinomas, are made up of epithelial cells and are differentiated into adenocarcinoma, basal cell carcinoma, or squamous cell carcinoma. Breast, prostate, and colon cancers are often adenocarcinomas, which are cell types that produce fluid. Basal cell carcinomas are

associated with the skin outer layer, and squamous cell carcinomas involve cells that line organs such as the stomach and intestines (National Cancer Institute, 2021).

Another type of cancer, sarcoma, is rarer and occurs in tissues and bones. Sarcomas are even further broken down to osteosarcoma, leiomyosarcoma, Kaposi sarcoma, and several other types. Leukemia is the type of cancer that begins in tissues that form blood cells. This leads to a buildup of white blood cells which take away blood supply for other cells (National Cancer Institute, 2021). Lymphoma (divided into Hodgkin's and non-Hodgkin's) is a type of cancer that originates in T or B lymphocytes. Next, more cancer epidemiological factors are explained.

Cancer Incidence, Prevalence, Risk Factors, Complications, and Public Health Costs

Cancer is a public health problem not only in the United States, but worldwide. According to the World Cancer Research Fund International (WCRFI), in the year 2020, there were approximately 18.1 million cases globally, with slightly over half occurring in men. Most of these cases were made up of breast and lung cancer, making them the first and second most prevalent types of cancer worldwide, respectively (WCRFI, n.d.). Colorectal, prostate, and stomach cancer are third, fourth and fifth in prevalence, globally. The number of new cancer cases worldwide is also staggeringly large. According to 2020 data from the Global Cancer Observatory (GLOBOCAN), there were 19.3 new cases of cancer worldwide in 2020 alone and ten million deaths attributed to this disease (2022).

These statistics are similar in the United States and global populations, as breast, lung, and prostate cancer make up the top three cancer types in the United States. In the United States alone, the estimated new cancer cases in 2021 were 1,898,160 with the estimated deaths being 608,570. More specifically, 450.5 new cases per 100,000 were reported based on 2014-2019 data. In 2021 alone, there were an estimated 281,550 new cases of breast cancer along with 43,600 deaths (National Cancer Institute, n.d.). According to another source, there were eighteen million cases of cancer globally in 2018, with 9.5 million occurring in men and 8.5 million occurring in women. (Saini et al., 2020).

Because of the nature of this paper, it is important to point out rates of certain cancer types that are part of the Guardian Research Network and thus included in the current study. Leukemia, for example, had an estimated 1,898,160 new cases in 2021 alone while non-Hodgkin's lymphoma had 81,560 new cases (National Cancer Institute, n.d.). As for the prevalence of leukemia, in 2018, there were 459,058 people in the United States with this type of cancer.

Like obesity, cancer has a myriad of causes. Cancer is caused by abnormal DNA in cells, known as mutations. Mutations can have different effects on a normally healthy cell, such as overgrowth and more mutations. Similarly, there are normally genes known as tumor suppressors, which instruct the cell to stop growing. When these do not work properly, cancer may result (National Cancer Institute, n.d.). The causes of cancer can be broken down into 3 categories. First, there are physical carcinogens. These include things like ultraviolet rays, uranium, radon, and X-ray emissions. The next category of causes

are the biological carcinogens, including infections from viruses or bacteria, or pathogens including hepatitis B and C and Epstein-Barr (Saini et al., 2020).

The last category of cancer-causing agents are the chemical carcinogens. These can be found in water or food, such as arsenic or aflatoxin, or can be chemicals such as those found in cigarette smoke, benzene, and many others (Saini e al., 2020). In addition to these categories, lifestyle factors also play a role in cancer development. For example, alcohol and diet such as processed meats can contribute to cancer risk as does aging. The higher aging population equates to more people living longer with multiple comorbidities who may develop genetic mutations as their time for exposure is increased (Saini et al., 2020). Therefore, the upstream causes of cancer are varying and often intertwined, whereas the downstream cause is DNA damage.

As for the public health cost, in 2018 alone, the US cancer expenditures totaled 150.8 billion USD, which is projected to increase with the growing elderly population and rise in treatment options. In addition, patient survival is increasing leading to multiple lines of costly therapy. In 2019, national costs rose to 190.2 billion USD with the highest financial burden coming from myeloma and chronic myeloid leukemia (National Cancer Institute, n.d.). The cost of care is often calculated across the treatment timeline. For example, in 2020, average lung cancer costs per patient were $68,293 for initial care, $12,386 for continuing care, and $110,247 for the last year of life. Leukemia costs were $47,263 initially, then $12,700 for continuing care, and $169,588 in the last year of life on average for the individual. This is only the cost to the patient, but there are other costs that may be incurred as well (National Cancer Institute, n.d.).

Looking at public health care costs globally, cancer has the highest economic impact on the world compared to any other cause of death, with the total impact being 895 billion USD in 2008. This does not include direct medical costs and is equivalent to 1.5% of the gross domestic product for the entire world (American Cancer Society, 2021). The financial burden can be difficult to measure as it is different for distinct types of cancer and in various locations. In low-income countries, breast, mouth, throat, and cervical cancer have the largest fiscal impact, but there is also an immeasurable effect on quality of life to the individual and family. These situations can cripple an entire family financially, making the cost of cancer even greater (American Cancer Society, 2021). Different sources calculate the financial burden differently, but however the calculation is performed, it is apparent that public health care costs of cancer are astronomical.

Theoretical Foundation

As explained in chapter 1, the theory associated with this project is the HBM. The HBM originated in the 1950s and was initially designed to understand why people chose to or not to receive tuberculosis screening (Rosenstock, 1974). This theory has evolved considerably since then, but still relates to an individual's understanding or belief of how susceptible they are to disease, the severity of the disease, and the actions that may be taken to reduce the susceptibility. Some assumptions of the HBM are that the individual perception of barriers or benefits to a health behavior will influence intentions and confidence in the health behavior (Yuen et al., 2021).

Several studies have demonstrated the HBM in relation to obesity and losing weight. In 2020, Saghafi-Asl & Asghari-Jafarabadi reported that college students were

more likely to lose weight if they perceived being overweight as a threat and believed that diet and exercise could reduce this threat. Similarly, Abdeyazdan et al (2017) reported that elementary school students and their mothers displayed better obesity reducing behaviors after completing an education-based program that utilized the factors of the HBM. In addition, Al-Hassan et al (2020) reported that college students who had a high level of perceived benefit of exercise were less likely to be obese. Therefore, the HBM has previously been used in relation to obesity to explain barriers and seriousness of the disease.

Like obesity, cancer has been studied in relation to the HBM. Zare et al. reported that cancer programs using the HBM helped promote better cancer outcomes (2016). Similarly, Azriful et al (2021) examined behavior in female breast care survivors to understand how the HBM was relevant. They reported that early cancer screening helped women to believe they had the ability and chance to overcome breast cancer with more favorable outcomes. Even though these cancer patients may face many obstacles during treatment, a dedicated support system can help overcome these barriers.

Another example of the HBM in oncology was in a group of colorectal cancer patients. An educational intervention was implemented for one month. The group given the HBM based education demonstrated significantly higher scores in knowledge, perceived susceptibility, perceived benefits, perceived severity, and perceived self-efficacy as compared to the control group (Rakhshanderou et al., 2020). These examples of the HBM establish how obesity and cancer are both influenced by beliefs surrounding barriers to treatment and utilizing self-efficacy to reduce the disease state and reduce risk.

The current study aimed to understand how to improve HDMTX treatment outcomes for obese cancer patients. The HBM was chosen because it addresses factors that can promote or prevent treatment of a multifactorial disease such as cancer and obesity. When discovering the differences in toxicity or any treatment outcomes in these patients, health care practitioners can benefit from utilizing the HBM to better understand why patients seek treatment and follow it, and how the outcomes are affected by beliefs (Zare et al., 2016).

MTX Background and Mechanism of Action

As previously stated, MTX is used to treat cancer, arthritis, psoriasis, and several other conditions. This drug goes by the brand names Otrexup, Xatmep, Trexall, Rasuvo, and RediTrex in the United States and additional names in Canada. In the Unites States, MTX is indicated for acute lymphoblastic leukemia, breast cancer, gestational trophoblastic disease, lung cancer, non-Hodgkin lymphoma, osteosarcoma and is under investigation for other cancer types (Koźmiński et al., 2020). This folic acid analog is a synthetic biopharmaceutical that was first synthesized in the 1940s as it could treat children with less side effects than aminopterin. MTX is often used in conjunction with other products to treat cancer and autoimmune disease. This paper focused on cancer, specifically leukemia and lymphoma.

This product is still widely used and is dosed in either low/normal dosing of 7.5-25 mg/week or at high doses of 1-5 g per cycle in cancer patients (HDMTX). MTX works by inhibiting the formation of tetrahydrofolate from dihydrofolate, therefore blocking methylation reactions in DNA synthesis (Koźmiński et al., 2020). MTX is

extremely effective in treating various types of cancer but can also come with dangerous side effects. Side effects or adverse reactions can be via reduction of blood cells, reduction in immune function, or respiratory and liver complications. Skin reactions can also be extremely serious, affecting the mouth, stomach, and intestines. (Koźmiński et al., 2020).

Another issue of importance is the narrow range in which MTX is therapeutic, with a small minimal concentration. Because of this, monitoring is extremely important. Adverse reactions can occur in up to 10% HDMTX courses, and dose modifications, rescue treatment, or even discontinuation of HDMTX may be necessary when toxicities occur (Koźmiński et al., 2020). Because of the effectiveness of MTX and HDMTX in combination with the adverse event profile, it is critical that cancer centers and hospitals or treatment locations have adequate knowledge of monitoring and potential dose changes during treatment.

Clinical Outcomes for Obese Patients

Poor clinical outcomes in obese patients are not a new phenomenon. These patients often have co-morbidities and are taking several medications. Although obesity and overweight have been associated with lower mortality in acute respiratory distress (ARDS) patients, this is the exception and not the norm (Ni et al., 2017). There are a few other cases where higher BMI is associated with better clinical outcomes (Grigsby et al., 2017). However, there is a copious amount of research on clinical outcomes for obese patients with various diseases which are statistically worse than their non-obese counterparts. This section will point out just a few examples.

In heart failure patients, weight loss by either bariatric surgery or other methods has been shown to improve heart failure outcomes. This may be due to the improved metabolic regulation, the improved cardiac electrical function, the reversal of adverse cardiac remodeling, hemodynamic improvement, or several other effects of the weight loss in these patients (Tabucanon et al., 2020). Not only does weight loss in heart failure patients result in better biochemical markers, but there is also a decrease incidence of new heart failure, an increase in exercise capacity, an increase in quality of life and a decrease in in-hospital mortality, among other positive outcomes. It is clear from this study done in 2020 that these patients benefit from a reduction in BMI (Tabucanon).

In a retrospective cohort study done on 569 patients between 2011-2018, Khan et al. (2019) reported that patients who entered a hospital for posterior lumbar spine fusion who were also obese were more likely than their non obese counterparts to have diabetes ($p < .001$), longer operating time ($p < .001$), and a higher Classification system score from the American Society of Anesthesiology ($p < .001$). This is just a selection of the literature demonstrating that obese patients have worse clinical outcomes than their non-obese counterparts. This is another reason to support promoting healthier outcomes for these patients, such as those taking HDMTX.

Chemotherapy Dosing in Obese Patients

Because there is a dearth of information regarding MTX in obese patients, it is helpful to review other cancer drugs and how they are used in the obese patient. In general, the current clinical landscape recommends chemotherapy dosing based on body surface area (BSA). This does not account for type of tissue (fat or muscle), but solely

relies on an equation with height and weight and several constants (Lyman & Sparreboom, 2013). Unfortunately, these recommendations came from antiquated mouse and human studies in which dosing for obese cancer patients was extrapolated. This may explain why so many obese patients are underdosed and experience higher toxicity or worse quality of life outcomes (Howard et al., 2016). Even a 20% decrease in the amount of chemotherapy has been linked to reduced remission and cure rates by 50% in some animal models (Lyman & Sparreboom, 2013).

Even the use of BSA to calculate dosing of chemotherapy is inconsistent. There are several different algorithms in which body surface area is multiplied by different factors with no agreed upon standard of care. Among these methods are the DuBois & DuBois (1916), the Boyd method (cited in Bois et al., 1935), the Gehan & George Method (1970), the method described in Haycock et al (1978) and Mosteller method (1987). While the intricacies of all these formulas is outside the scope of this paper, it is important to stress that BSA estimates are all based on height and weight only and do not take muscle or fat mass info effect.

The ASCO guidelines from 2021 most recently stated that cytotoxic chemotherapy should be dosed by weight regardless of obesity status, but the evidence quality is low (Griggs et al., 2021). ASCO does not suggest one formula for BSA over another, as they are all similar (within 10%), but the quality of evidence is low for this recommendation as well (Griggs et al., 2005). Unfortunately, even using these validated methods can result in a wide array of toxicity and efficacy among patients. Therefore, BSA is not always agreed upon as the best dosing method (Horowitz & Wright, 2015).

It is difficult to pinpoint exactly why obese patients may have higher morbidity and mortality with MTX or HDMTX treatment, but it is noted that these patients are often undertreated due to rounding down or dose-capping (Lyman & Sparreboom, 2013). For any cancer patient, it is imperative to understand how the drug is cleared to determine proper dosing. Most chemotherapy drugs are cleared by the liver. Obese patients may carry fat tissue at a higher concentration. The kidneys are also critical in filtering out these chemotherapy drugs, and obesity may have effects on glomerular filtration rate or creatinine clearance. These are a few of the reasons that chemotherapy dosing in the obese patient is difficult (Lyman & Sparreboom, 2013)

There are some chemotherapies for which fixed dosing is known to be ideal such as carboplatin. For most chemotherapies, there is limited data on the pharmacokinetics in obese patients, including MTX. As previously mentioned, this may be due to the lack of phase 1 and other pharmacokinetic (PK) studies in this population. (Horowitz & Wright, 2015). Additionally, the PK studies of obese patients taking cancer drugs have shown different volume of distribution and clearance as compared to non obese patients. As there is a limited amount of data on obese patients and chemotherapy, some health care professionals and institution protocols choose to cap the dose at a certain level, to prevent further toxicity. This may result in fewer adverse events, but also could result in worse cancer prognosis (Hall et al., 2013; Jenkins et al., 2006).

The next section of this chapter will focus on what is currently known about toxicity and other outcomes in obese patients dosed with several types of chemotherapy. It is important to note for this and further studies that the correlation between BSA and

BMI is extremely high (correlation ranges between 0.97 and 0.99) (Verbraecken et al., 2006). Therefore, the literature review includes articles using both BMI and BSA to understand the rates of toxicity in overweight and obese patients. Since both measurements are based on height and weight, without regard for type of tissue, the information is comparable.

Clinical Studies in Breast Cancer

Many of the studies examining toxicity outcomes in obese cancer patients were done in breast cancer patients. In 2007, Jenkins et al examined data from 662 female breast cancer patients given 5-fluorouracil (600mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) which is also referred to as FEC treatment. The treatment was given IV every 3 weeks over a 4-year period at a minimum of six treatment cycles. The authors analyzed BMI compared to relative dose intensity (RDI) which is defined as the dose received or planned divided by the overall treatment time. RDI is considered less than optimal if it is below 85%. The authors also wanted to examine myelosuppression as it related to body size (Jenkins et al., 2007).

The study resulted in a significantly higher RDI in overweight/obese patients as compared to normal weight patients (p = .03). Myelosuppression leading to dose reduction occurred in 26% of patients and 13% failed to reach RDI due to toxicity (Jenkins et al., 2007). The authors purported that this difference in RDI between overweight and obese patients may have been due to excess body fat which could have altered PK of these drugs. They concluded that obese patients should not be given

reduced doses of this chemotherapy regimen, as they were not more likely to suffer toxicity as compared to normal weight patients (Jenkins et al., 2007).

Another study by Gennari et al in 2016 reported similar outcomes. The authors examined 959 women with high-risk early breast cancer (EBC) in a phase three trial to investigate the impact of BMI on EBC prognosis. In these patients, taken from an Italian multicenter chemotherapy trial, 21% were obese and 34% were overweight at baseline with a median age of 52. Obesity had previously been shown to result in shorter survival and worse prognosis for those with EBC (Gennari et al., 2016). The authors postulated the reason for this association may have been due to insulin resistance, leading to cancer cell proliferation and the inflammatory state of obesity. The BMI of all patients was calculated prior to treatment.

To assess treatment outcome, disease free survival and overall survival were measured using univariate analysis with Kaplan-Meir curves and the respective hazard ratio. Disease-free survival (DFS) was calculated as the time from entering the study to death from any cause, development of contralateral breast cancer, or disease recurrence. The median follow up was 103 months with a five-year disease free survival (DFS) of 80% in all patients. There were slight differences in DFS when patients were grouped by BMI, which were not statistically significant. The five-year DFS was 81% in normal weight patients, 82% in overweight patients, and 76% in obese patients (p =.44). The authors further reported that there was no difference between women who were pre or postmenopausal (Gennari et al., 2016).

To gain a further understanding of the difference in treatment outcomes based on BMI, overall survival (OS) was also examined. The five-year OS was 95% for all patients, with no significant difference between BMI groups (p = .60). The only factors that were associated with poor survival were nodal status, age, and biological subtype. Although this article did not investigate the specific types of toxicity in these obese cancer patients, it is helpful to look at DFS and OS to understand the treatment outcomes of these cancer patients (Gennari et al., 2016).

Patients in the aforementioned study were dosed with a combination of epirubicin or CMF (cyclophosphamide, MTX, and 5-flurouracil). Although the mean RDI for both types of therapy was similar across all BMI groups, the obese patients were given a significantly higher dose of epirubicin (Gennari et al., 2016). Therefore, it may be difficult to conclude that BMI does not factor into prognosis. As there is extremely limited data on MTX specifically, this study provided some background for why future studies are needed.

Other similar studies did not result in the same clinical outcomes, even when they were conducted on the same types of cancer patients. Breast cancer has been studied in obese patients perhaps more than other cancers because of the known connection between the two (Jiralerspong & Goodwin, 2016; Lauby-Secretan et al., 2016). Another study examining breast cancer and BMI and the association between the two looked at two lipophilic drugs- docetaxel, and paclitaxel. These are both taxanes which can be associated with high toxicity (Desmedt et al., 2020). The patients were retrospectively analyzed from the Breast International Group (BIG) 2-98 trial (n=2887) between 1998

and 2001. Participants were randomly assigned to either doxorubicin followed by CMF, doxorubicin, and CMF concurrently, docetaxel followed by CMF, or docetaxel and CMF concurrently (Desmedt et al., 2020).

The authors reported no difference in the proportion of patients with an RDI of <85% in the non-docetaxel groups but there were significantly more patients with an RDI of <85% in those taking the docetaxel regimens (p =.003, p = .009). Similarly, there was no difference in DFS for the non-docetaxel groups but significantly lower DFS in lean vs overweight or obese patients in one of the docetaxel regimens (p =.002). There was also a significantly higher hazard ratio in the docetaxel group than the non-docetaxel groups. The authors also examined differences in BMI and survival status according to estrogen receptor status. They found no difference in BMI and ER status in the non-docetaxel groups, while there was a lower DFS in the overweight and obese group compared to normal weight in the ER negative group (p = .005). ER positive women only demonstrated lower DFS in the obese group as compared to normal, but there was no difference from the overweight to normal groups (p = .036) (Desmedt et al., 2020).

The authors concluded that docetaxel-containing regimens in these breast cancer patients led to worse outcomes as far as DFS and OS as well as an increased risk for metastasis. While this is not directly relevant to MTX, the authors explained that there is little research on cancer therapy in the obese patient and more research needs to be conducted.

Along with MTX toxicity, there has also been research done on breast cancer recurrence related to BMI. In a Belgian phase 3 study with 734 patients, patients were

given epirubicin-cyclophosphamide, a lower dose of the same treatment, or MTX, cyclophosphamide, and fluorouracil (CMF). Fisher's exact test was utilized to understand the relationship between BMI and various clinical outcomes. Survival was measured using Cox semi parametric regression (Biganzoli et al., 2017). The authors also looked at a composite endpoint including whichever outcome came first (second primary tumor, tumor recurrence) with death being a competing event. Like other studies, the authors reported a positive relationship between increased BMI and older age, post menopause, and tumor size. They found that higher BMI was correlated with worse outcomes for relapse in breast cancer patients (Biganzoli et al., 2017).

Even though most research on chemotherapy and toxicity outcomes in obese patients was done in breast cancer, there is still a limited amount of information. The variation in results previously explained elucidates the need for more targeted studies with specific types of chemotherapy and toxicity outcomes as they differ across BMI. Next, additional relevant research will be addressed.

Other Cancer Types and MTX Toxicity With BMI

Recently, a poster presentation at the American Society of Hematology reported the analysis of the effects of BMI on HDMTX toxicity. The authors examined retrospective data from 147 patients at Washington University in St. Louis, MO taking >1000 mg/m^2 of MTX. Patients had either central nervous system lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma, mantle cell lymphoma, sarcoma, or breast cancer. The authors reported no difference in BMI and MTX toxicity (defined by delayed MTX clearance, acute kidney injury, liver function abnormalities,

mucositis, and survival) (p =.898) (Bhaskar et al., 2020). The authors also reported that more research needs to be done regarding obese cancer patients and MTX toxicity.

A non-concurrent cohort study was conducted between 1973 and 2012 in patients taking MTX (97.3%) or actinomycin D with gestational trophoblastic neoplasia (GTN). This study was conducted on three hundred patients at the New England Trophoblastic Disease Center who were classified as obese/overweight or non-obese/overweight to understand how responses and toxicities varied according to BMI (Maesta et al., 2015). It is important to note that patients were given doses based on actual body weight, regardless of BMI status. The authors reported no difference in time to remission (p =.961), resistance (p = .438), or toxicity (p =.669) in obese/overweight vs non-obese/overweight patients (Maesta et al., 2015).

The authors also discussed the concept that obesity increases adipokines and therefore tumorigenesis, requiring higher doses of various chemotherapy drugs (Maesta et al., 2015). As there is limited research done on leukemia and lymphoma, this study could be extrapolated to better understand dosing regiments for MTX patients who are obese. Again, the variable results point to more research needed on this topic.

Further Analysis

In 2021, the American Society of Clinical Oncology performed a literature review based on sixty articles from Nov 1, 2010, to March 27, 2020, involving chemotherapy, immunotherapy, and targeted therapies for adult cancer patients. They concluded that full weight-based dosing should be used without adjustment for obesity (Griggs et al., 2021). The researchers did recommend fixed dosing for some agents and reported the evidence

for this as low as well. It is not clear from the analysis if MTX was included in this study or what specific agents were evaluated (Griggs et al., 2021). This further supports that more research needs to be done regarding specific chemotherapies like MTX.

The clear message is that there is a paucity of information regarding HDMTX (as well as MTX and other chemotherapy agents) dosing and toxicity in obese patients. Little is known about MTX specifically, but a retrospective analysis reported 24% of cancer centers using actual body weight for dosing calculations, while 15% used ideal body weight (Navarro, 2003). The remaining centers in the survey used other various methods to calculate dosing. This may not seem like much of a concern, but the difference in dosing with these methods was greater than 100% in some cases. Since too much chemotherapy is toxic and too little may be ineffective, more prospective studies are needed to determine the best outcomes for these patients.

Nearly all studies that were performed on obese chemotherapy patients were done over 15 years ago. However, Navarro conducted one of the very few relevant research studies available, and therefore this data may be useful when determining the approach for future studies. Table 3 is a compilation of studies from Navarro's retrospective meta-analysis done in 2003, reporting the outcomes of cancer patients receiving autologins and allogenic hematopoietic stem cell transplant (HCT) receiving chemotherapy. Table 4 elucidates the lack of consistent results between obese and nonobese patients and the discrepancies related to type of cancer and dose adjustments. It is apparent from this table that there are vast differences in mortality and survival between obese and non-obese

patients depending on the study and type of cancer. Table 4 illustrates that the outcomes of chemotherapy in obese patients are variable and required further study.

Table 4

Chemotherapy Outcomes for HCT Patients in Adults

Disease	Obese/Total (%)	Dose adjustments	5-year event free survival percentage (obese vs nonobese)	5-year overall survival obese/nonobese
AML	13/32 (%)	Yes	51 vs 57 (p = NS)	68 vs 68 p =NS) 22 vs 55 (p =.012)
AML	9/54 (%)	No	22 vs 53 (p = .021)	38 vs 65 (p<.002)
NHL	28/121 (%)	Various	23 vs 55 (p < .002)	Not reported
Various	104/473 (%)	Yes	39 vs 33 vs 47 (p = NS)	
Various	76/242 (%)	Not reported	Not reported	Not reported
Various	250/1475 (%)	No	Not reported	Not reported
CML	44/196 (%)	No	Not reported	Not reported

Note. Adapted from "Navarro, W. H. (2003). Impact of obesity in the setting of high-dose chemotherapy. *Bone Marrow Transplantation, 31*(11), 961-966. doi:10.1038/sj.bmt.1704052"

AML = acute myeloid leukemia; NHL = non-Hodgkin's lymphoma; CML = chronic myeloid leukemia; NS = non-significant.

Summary and Conclusions

It is clear from that more research is needed to better understand the impact of obesity on outcomes for people receiving HDMTX and other cancer treatment. Some studies looked at survival while some reported toxicity, but measure in different ways. In

addition, the types of cancer and types of chemotherapy from study to study have great variation. All of these factors, along with the scarce evidence, demonstrate the need for more research on HDMTX and how it affects the obese cancer patient.

The only available evidence is on combination therapy, mostly done in breast cancer patients on small sample sizes and is not focused on leukemia. Of course, it is difficult to find patients taking only HDMTX as many are often on combination therapies. This paper provided a much-needed analysis of specific toxicity outcomes in patients of various BMIs to better understand how HDMTX is tolerated across different sized patients. This study added to the currently miniscule amount of research done on HDMTX toxicity in the obese cancer patient to hopefully fill in the many research gaps.

Chapter 3: Research Method

Background

The purpose of this quantitative retrospective cross-sectional study was to promote healthier outcomes in obese cancer patients by examining the association between HDMTX toxicity after controlling for BMI, age, sex, and comedications. The first section of this chapter addresses the research design and rationale, including the concepts and reasoning for the study design. Next, the role of the researcher is described, and finally, the methodology is described in detail. The trustworthiness of the study is examined by understanding the credibility and transferability and finally, the ethical principles and potential ethical concerns are addressed.

Research Design and Rationale

There were four distinct RQs addressed in this study.

1. RQ1: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex?
2. RQ2: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex?
3. RQ3: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex?
4. RQ4: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex?

To address these questions, the independent variable was BMI, the standard measure of overweight and obesity, while dependent variables included liver (ALT and

AST) and kidney (AKI) toxicity measurements. In addition, age, sex, and comedication with other chemotherapy agents were assessed for confounding. Liver and kidney toxicity were each analyzed as dichotomous variables based on whether toxicity occurred or did not occur. For liver toxicity, *yes* was defined as a category of 3 or 4 in either AST or ALT, which is the standard definition of "severe toxicity" on the Common Technology Criteria for Adverse Events scale from 0 (*no hepatic toxicity*) to 4 (*very severe hepatic toxicity*). For kidney toxicity, *yes* was indicated by an acute kidney injury category of 2 or 3, on the acute kidney injury network scale, which ranges from 0 (*no kidney toxicity*) to 3 (*severe kidney toxicity*; National Cancer Institute, 2023).

The sex of patients was defined as either male or female, as these are the only two categories that were recorded in the Guardian Research Network Database. Comedication was restricted to the treatments that the patient received from 1 week prior to HDMTX administration through 2 weeks after because these were the time periods in which combined toxicity could occur. Only concomitant cancer treatments were included in the analysis, such as rituximab, vincristine, doxorubicin, cisplatin, and cyclophosphamide.

The research design was a cross-sectional quantitative study using secondary data collected from the Guardian Research Network, a nonprofit clinical research consortium. Anonymized, de-identified data were obtained from 101 oncology practices in the United States that participated in the Guardian Research Network from 2011 to 2019. Patients included in the database had complete transfer of medical records to the Guardian Research Network data lake, where the data were processed and harmonized before being transferred to the knowledge system, which was anonymized and de-identified. This

process was governed by data use agreements and an Institutional Review Board (IRB)-approved protocol waiving informed consent.

Only cancer patients 18 years old or older and only four cancer diagnoses (acute lymphoblastic leukemia, osteosarcoma, non-Hodgkin's lymphoma, or primary central nervous system lymphoma) were included for the purpose of this study. The unit of analysis was each course of HDMTX because toxicities are associated with a specific course of treatment. A patient may receive multiple cycles of HDMTX, but the toxicities differ with each course, so all variables (except demographics) were measured for each course, including the BMI, which could have changed over time as a person gained or lost weight. Therefore, each row of data was analyzed as a new entry to understand how toxicity was associated with BMI. The use of this secondary data set eliminated time and resource constraints as the data were already collected and anonymized.

This research design was used to advance the knowledge in this discipline as most other studies have been extremely small or reported disparate outcomes with various primary endpoints. Similarly, previous studies were not focused on MTX and were done on breast cancer patients. This research design concentrated on specific toxicity outcomes instead of overall survival and disease-free survival as in other studies. Looking at specific toxicity markers was used to better explore the relationship between HDMTX and toxicity.

Role of the Researcher

As the researcher, I analyzed data previously collected at several health care institutions. I had no professional relationships with any of the participants, nor did I

know their names or identities. This eliminated any researcher bias. There were no other ethical issues as I did not use data from my place of work or any former affiliated work environment. I partnered with a physician who organized the data collection, but we did not have any overlap in our work domains as he was a university-based doctor/researcher, and I work(ed) in regulatory affairs at a pharmaceutical company.

Methodology

The target population was adults (participants aged 18 years or older) whose HDMTX treatment and outcome data were captured in a subset of the Guardian Research Network database. This network is a nonprofit group in a health system consortium that provides de-identified data from electronic health and medical records to help researchers and institutions better understand treatment outcomes and how to promote better health outcomes for patients (Guardian Research Network, 2022). In this data set, patients with acute lymphoblastic leukemia, osteosarcoma, non-Hodgkin's lymphoma, or primary central nervous system lymphoma were included. For this analysis, 944 courses of HDTMX were available for potential inclusion.

Participant Selection Logic

Participants were included as part of a larger dataset for cancer patients treated at several participating centers that administer chemotherapy. No identifying data were included. There were no specific exclusion criteria, and the inclusion criteria were that patients must have received at least one course of HDMTX, defined as > 500 mg/m^2. Data were available from patients treated from January 1, 2011, through December 31, 2019.

Instrumentation

The instrumentation used for data collection was the electronic health record. Data from each participant were then deidentified and transferred to an Excel spreadsheet for research purposes. I was able to gain access to this dataset via the chief data science officer at the Guardian Research Network. These were unpublished data used for research purposes shared with students or researchers upon request.

Data Analysis Plan

To analyze the data, they were first trimmed down into the appropriate columns with data elements needed for the study. The dataset was next transferred from Excel into the Statistical Package for Social Sciences (SPSS), which was used to analyze the data. The first step was to perform a power analysis. For RQs one and two, because there was one independent continuous variable (BMI), and one dichotomous outcome variable (toxicity yes or no), a binary logistic regression was used (Harris, 2021). For RQs 3 and 4, because there were two independent variables (obesity is continuous, as indicated by BMI, and comedication is dichotomous) and a dichotomous outcome variable (toxicity yes or no), a multiple logistic regression was used (Boston University of Public Health, 2013).

Figure 2 displays the G power calculator for the sample size needed for all four RQs because they all employed logistic regression. The alpha level of 0.05 was chosen as this is a typical level chosen for research, meaning that a .5% chance exists that the result does not represent the entire population (see Serdar et al., 2021). The power chosen was

0.8, meaning there was an 80% chance of rejecting a false null hypothesis (Serdar et al., 2020).

An effect size converter was used to convert between Cohen's *d* and odds ratio. A Cohen's *d* of 0.500 was chosen as a medium effect size, which resulted in an odds ratio of 2.477. These values using G power analysis resulted in a sample size of 142 needed for each RQ. This was well below the number used in this study (944 collected with some missing as reported in chapter 4). Figure 2 shows the *z* test to determine the sample size needed. The RQs are restated below for clarity.

RQ1: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex?

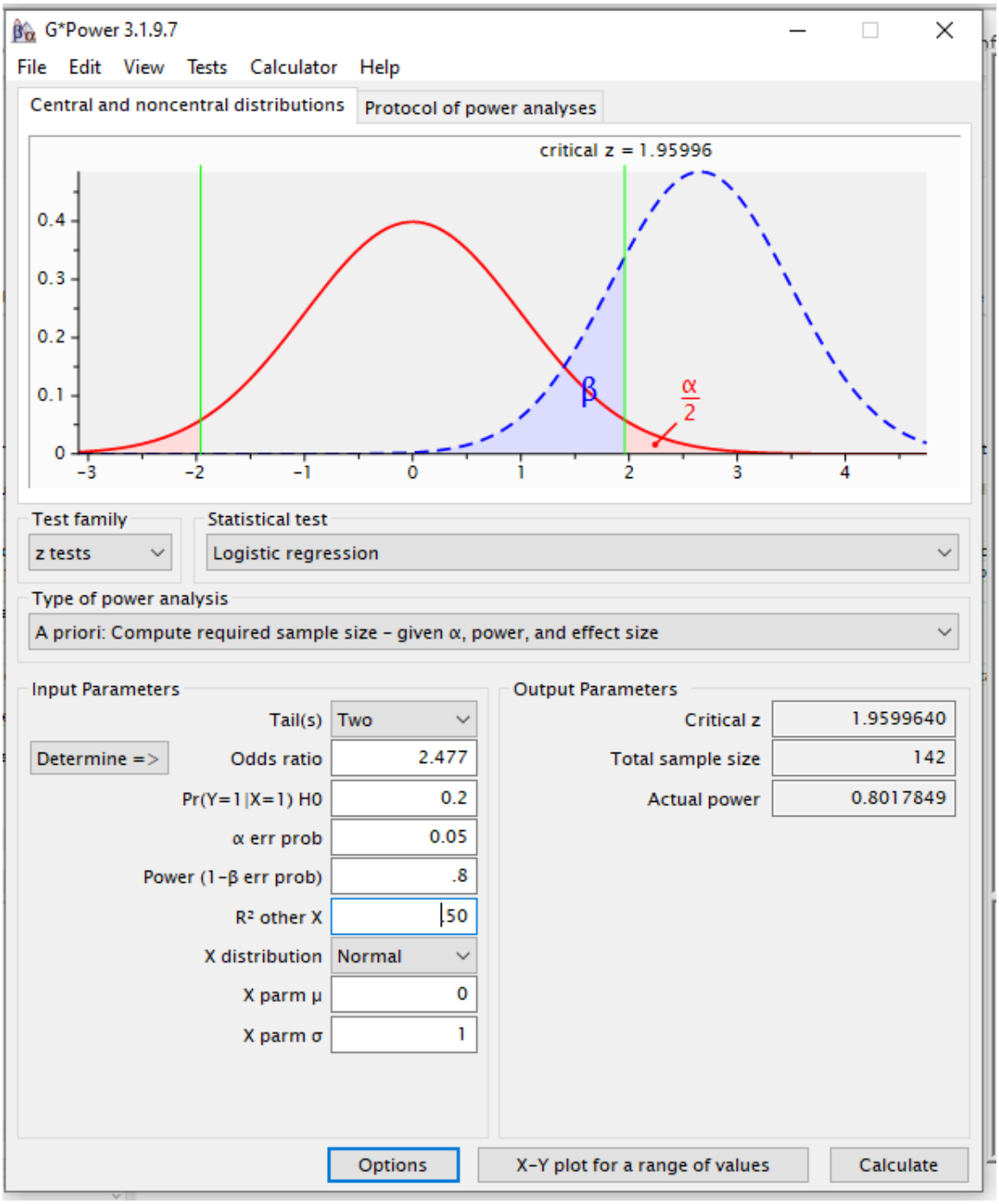
RQ2: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex?

RQ3: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex?

RQ4: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex?

Figure 2

G Power Sample Size Calculator



All data were cleaned and saved in an Excel file. The analysis was performed in SPSS. Table 5 displays the type of data, coding, and connection to all RQs.

Issues of Trustworthiness

Credibility

Another term for credibility is internal validity. Internal validity is the idea that any conclusions made from a specific study using that design are warranted, controlling for extraneous and confounding variables (Kaya, 2014). In other words, internal validity is supported by reducing threats of a false conclusion being made. For this study, there were limited threats to validity. One threat was history, meaning that events may have happened between the first and next measurements in the study that may have influenced the dependent variable (see Kaya, 2014). Because the independent and dependent variables were all taken at a snapshot in time (cross-sectional), there was limited likelihood that history would confound the results. Each data point was related to the specific course of HDMTX. Therefore, the BMI measurement that coincides to the toxicity outcome would have been taken at the same time, as it was calculated from height and weight only, which were measured prior to each cycle of HDMTX.

Maturation was a similar threat, which means that outcomes were different due to the passage of time (see Kaya, 2014). Again, because this was a cross sectional study, there was little risk that maturation could be an issue. There was also a very low risk of testing effect, which is the risk that better outcomes occur over time because the patient becomes better at the test. This would not be an issue as the toxicity outcomes were taken by a doctor at the same point in time and were not repeated for that data point.

Instrumentation was also a threat to internal validity as different tools may be used in different patients. Because the methodology searched for an association between the independent and dependent variables using regression, the statistical method took outliers into account (see Kaya, 2014).

Transferability

Like internal validity, it is important to protect the external validity of a research study. This study can be transferable to other populations such as children with cancer or adults with various types of cancer that were not captured in the Guardian Research Network database. This project is both transferable and generalizable to the greater population as the data were captured from varying institutions and settings (see Findley et al., 2021). Because this was the first study to investigate the relationship between obesity and outcomes for patients taking HDMTX, more research will need to be conducted on varying cancer types and to a large group of patients, including children. At that point, it will be clearer how generalizable the current study is to the broader population. The components of external validity include mechanisms, settings, treatments, outcomes, units, and time (Findley et al., 2021). More research will need to be conducted to account for all these dimensions.

Ethical Procedures

IRB approval was received for this project as all data were de-identified and cannot be linked to participants. There are no conflicts of interest as I am not affiliated with the Guardian Research Network and the data were kept confidential and only

provided to me by the lead researcher. These data are stored only on my laptop computer, with both a password protected file and computer system.

Summary and Conclusions

The methodology outlined in this chapter facilitated understanding of how the independent variable (BMI) was associated with the dependent variable (toxicity), while also examining comedication as related to treatment outcomes. The cross-sectional study and secondary dataset provided a large sample of data points that could be relatively easily analyzed for association.

Although cause and effect conclusions could not be drawn from this methodology, it provides a starting point for further researchers to continue analyzing treatment outcomes in obese patients. This may lead to better understanding of chemotherapy dosing as well as dietary interventions to best prepare obese patients for HDMTX and other cancer treatments.

Chapter 4: Results

Introduction

The purpose of this quantitative, retrospective, cross-sectional analysis was to examine the association between BMI and toxicity from HDMTX in cancer patients controlling for age, sex, and comedication. There were four RQs and related hypotheses that are restated below.

RQ1: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{01}: There is no association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A1}: There is an association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

RQ2: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{02}: There is no association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A2}: There is an association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

RQ3: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{03}: There is no association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A3}: There is an association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

RQ4: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{04}: There is no association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A4}: There is an association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

After this brief introduction, the data collection method is described. The descriptive and demographic baselines statistics are reported, and statistical assumptions are discussed. Next, the logistic regression results are reported and graphed for each RQ. The results are explained in detail in the final chapter, along with the discussion and conclusion.

Data Collection and Cleaning

As previously stated, these data were gleaned from a secondary data set of 944 cancer patients of four types from 101 oncology practices in the United States between 2011 and 2019. All data were anonymized and sent via email in an Excel file. Before importing into SPSS, the extremely large data set was trimmed down into the needed columns of height, weight, comedication, ALT category, AST category, gender, and age (More detail is provided in Table 5). An equation was created in Excel to calculate BMI based on height and weight (BMI = weight in kilograms / height in meters squared). At this point, the data were imported into SPSS and coded as described in Table 5. Missing

data points were given a value of 999, and no deviations from the planned methodology were needed.

Table 5

Data Table for all Collected Variables

Variable name	Type of variable	Research questions applied	Coding
Height	Continuous	NA	NA
Weight	Continuous	NA	NA
BMI	Continuous	All	NA
Cyclophosphamide	Dichotomous	3,4	1=Yes, 2= No
Cytarabine	Dichotomous	3,4	1=Yes, 2= No
Doxorubicin	Dichotomous	3,4	1=Yes, 2= No
Vincristine	Dichotomous	3,4	1=Yes, 2= No
Rituximab	Dichotomous	3,4	1=Yes, 2= No
AST cat	Categorical	All	1=Toxicity, 2=No toxicity
ALT cat	Categorical	All	1=Toxicity, 2=No toxicity
AKI cat	Categorical	All	1=Toxicity, 2=No toxicity
Sex	Dichotomous	All	0=Male, 1= Female

Note. NA = not applicable, used for calculations only; BMI = body mass index; AST = aspartate transaminase; ALT = alanine aminotransferase; AKI = acute kidney injury.

Statistical Output – Descriptive Statistics

BMI was reported for all 944 samples, with a range of 16.3 to 55.1 kg/m^2 (*M* = 28.1, *SD* = 6.38). Age was also reported for all samples, with a range of 18 to 69 (*M* =

55.7, *SD* = 0.50). Liver toxicity was only reported for 638 patients, meaning that 306 data points were missing from the dataset. As this was a dichotomous coded variable (Y/N), no other statistics are discussed for liver toxicity. Kidney toxicity was only reported for 690 patients, meaning 254 data points were missing. Again, this was a dichotomous variable, and, therefore, range and *SD* were not meaningful. Comedication and sex were also reported as dichotomous variables and were included for all 944 patients. Table 6 provides a visual representation of these results.

Table 6

Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	*SD*	Variance	Kurtosis	*SE*
BMI	944	38.80	16.29	55.09	28.1018	6.38421	40.758	1.843	.159
Age	944	69	18	87	55.65	15.070	227.092	-.333	.159
Sex	944	1	0	1	.49	.500	.250	-2.003	.159
Liver toxicity	638	1	0	1	.92	.274	.075	7.425	.193
Kidney Toxicity	690	1	0	1	.07	.250	.062	10.154	.186
CoMed	944	1	0	1	.96	.202	.041	18.750	.159
Valid *N* (listwise)	613								

Note. CoMed = Comedication

RQ1

RQ1: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{01}: There is no association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A1}: There is an association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex.

For this RQ, a binary logistic regression was conducted to investigate if BMI, gender, and age were associated with the outcome of interest, liver toxicity. The possible predictor variables were BMI, age, and gender. The Hosmer-Lemeshow goodness-of-fit for block 1 (BMI only) was significant ($p > 0.05$), indicating the model was correctly specified. Additionally, the Nagelkerke *R* squared = .003, meaning that only 0.3% of the change in liver toxicity is due to BMI. However, because this is only a pseudo-*R*-squared, it should be interpreted with caution (see Laerd Statistics, 2018). In Block 1, the model resulted in the independent variable, BMI, not being a significant predictor of liver toxicity [($p > 0.05$), CI (0.768, 1.072)]. Therefore, I fail to reject the null hypothesis in this case.

However, when moving to Block 2, the predictor variables now included BMI, age, and sex. In this scenario, The Hosmer-Lemeshow test was not significant ($p < 0.05$). While BMI ($p = 0.589$) and age ($p = 0.245$) were not significant predictors of toxicity (CI 0.966, 1.062 and 0.992, 1.030 respectively), sex was a significant predictor of liver toxicity. The unstandardized $B = 0.771$, $SE = 0.319$, $Wald = 5.853$, $p < 0.016$. The estimated odds ratio favored an increase of 116% in liver toxicity for females compared to males (*Exp B* = [2.163], 95% CI [1.158, 4.041]). See Table 7.

Table 7

Variables in the Equation RQ1

								95% C.I.for EXP(B)	
		B	*S.E.*	Wald	*df*	*p*	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	.013	.024	.292	1	.589	1.013	.966	1.062
	Age	.011	.009	1.352	1	.245	1.011	.992	1.030
	Sex(1)	.771	.319	5.853	1	.016	2.163	1.158	4.041
	Constant	1.151	.772	2.226	1	.136	3.162		

[a]. Variable(s) entered on step 1: Age, Sex.

RQ2

RQ2: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{02}: There is no association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A2}: There is an association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex.

For this RQ, a binary logistic regression was conducted to investigate if BMI, gender, and age were associated with the outcome of interest, kidney toxicity. The possible predictor variables were BMI, age, and gender. The Hosmer-Lemeshow goodness-of-fit for Block 1 (BMI only) was significant ($p > 0.05$), indicating the model was correctly specified. In Block 1, the model resulted in the independent variable, BMI, not being a significant predictor of liver toxicity ($p > 0.05$), CI (0.933, 1.031). Therefore, I fail to reject the null hypothesis in this case. See Table 8.

Table 8

Variables in the Equation RQ2

								95% C.I. for *EXP(B)*	
		B	S.E.	Wald	*df*	Sig.	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	-.019	.025	.574	1	.448	.981	.933	1.031
	Constant	-2.108	.709	8.847	1	.003	.121		

a. Variable(s) entered on step 1: BMI.

However, when moving to Block 2, the predictor variables now included BMI, age, and sex. In this scenario, The Hosmer-Lemeshow test was still significant ($p > 0.05$). While BMI ($p = 0.437$) and sex ($p = 0.097$), were not significant predictors of toxicity (CI [0.929, 1.033] and [0.318, 1.110] respectively), age was a marginally significant predictor of kidney toxicity. The unstandardized $B = 0.022$, $SE = 0.011$, $Wald = 3.818$, $p = 0.051$. The estimated odds ratio favored an increase of 2.3% in liver toxicity for every year of age ($Exp\ B$ = [1.023], 95% CI [1.000, 1.046]).

RQ3

RQ3: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex?

H_{03}: There is no association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A3}: There is an association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex.

For this RQ, a multiple logistic regression was conducted to investigate if BMI, comedication, gender, and age were associated with the outcome of interest, liver toxicity. The Hosmer-Lemeshow goodness-of-fit for block 1 (BMI and comedication) was significant ($p > 0.05$), indicating the model was correctly specified. Additionally, the Nagelkerke *R* squared = .006. In Block 1, the model resulted in the independent variables, BMI and comedication, not being significant predictors of liver toxicity ($p > 0.05$), CI (0.975, 1.071) and $p > 0.05$, CI (0.532, 6.660) respectively. Therefore, I failed to reject the null hypothesis in this case. See Table 9.

Table 9

Variables in the Equation RQ3

								95% C.I.for EXP(B)	
		B	S.E.	Wald	*df*	Sig.	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	.022	.024	.825	1	.364	1.022	.975	1.071
	Comedication(1)	.628	.642	.958	1	.328	1.875	.532	6.600
	Constant	1.222	.882	1.921	1	.166	3.395		

[a]. Variable(s) entered on step 1: BMI, Comedication.

However, when moving to Block 2, the predictor variables now included BMI, age, and sex. In this scenario, The Hosmer-Lemeshow test was not significant ($p < 0.05$). While BMI ($p = 0.624$), comedication (p = 0.374), and age ($p = 0.234$) were not significant predictors of toxicity, sex was significant predictor of liver toxicity. The unstandardized $B = 0.762$, SE = 0.319, Wald = 5.692, $p = 0.017$. The estimated odds ratio favored an increase of 114% in liver toxicity for females compared to males (*Exp B*= 2.142, 95% CI [1.146, 4.004]). See Table 10.

Table 10

Variables in the Equation RQ3 Continued

								95% C.I.for EXP(B)	
		B	S.E.	Wald	*df*	Sig.	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	.012	.024	.241	1	.624	1.012	.965	1.061
	Comedication(1)	.578	.650	.790	1	.374	1.782	.498	6.375
	Age	.011	.010	1.416	1	.234	1.011	.993	1.030
	Sex(1)	.762	.319	5.692	1	.017	2.142	1.146	4.004
	Constant	.619	.971	.406	1	.524	1.858		

[a]. Variable(s) entered on step 1: Age, Sex.

RQ4

RQ4: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex?

H_{04}: There is no association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

H_{A4}: There is an association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex.

For this RQ, a multiple logistic regression was conducted to investigate if BMI, comedication, gender, and age were associated with the outcome of interest, kidney toxicity. The Hosmer-Lemeshow goodness-of-fit for Block 1 (BMI and comedication) was significant ($p > 0.05$), indicating the model was correctly specified. Additionally, the and the Nagelkerke R squared = .004. In Block 1, the model resulted in the independent variables, BMI and comedication, not being significant predictors of liver toxicity ($p > 0.05$), CI (0.933, 1.030) and $p > 0.05$, CI (0.247, 14.102) respectively. Therefore, I failed to reject the null hypothesis in this case. See Table 11.

Table 11

Variables in the Equation RQ4

								95% C.I.for *EXP(B)*	
		B	S.E.	Wald	*df*	Sig.	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	-.020	.025	.610	1	.435	.980	.933	1.030
	Comedication (1)	.623	1.032	.365	1	.546	1.865	.247	14.102
	Constant	-2.696	1.216	4.916	1	.027	.067		

a. Variable(s) entered on step 1: BMI, Comedication.

However, when moving to Block 2, the predictor variables now included BMI, age, and sex. In this scenario, The Hosmer-Lemeshow test was still significant ($p > 0.05$). While BMI ($p = 0.426$), comedication ($p = 0.554$), and sex ($p = 0.095$) were not significant predictors of toxicity, age was a mildly significant predictor of kidney toxicity. The unstandardized $B = .022$, $SE = 0.011$, $Wald = 3.796$, and $p = 0.051$. The estimated odds ratio favored an increase of 2.2% increase in kidney toxicity every year of aging $Exp\ B = 1.0220$, 95% CI =1.000, 1.046. See Table 12.

Table 12

Variables in the Equation RQ4 Continued

								95% C.I.for EXP(B)	
		B	S.E.	Wald	*df*	Sig.	*Exp(B)*	Lower	Upper
Step 1[a]	BMI	-.022	.027	.634	1	.426	.979	.928	1.032
	Comedication(1)	.612	1.035	.349	1	.554	1.844	.242	14.025
	Age	.022	.011	3.796	1	.051	1.022	1.000	1.046
	Sex(1)	-.529	.317	2.786	1	.095	.589	.317	1.097
	Constant	-3.675	1.380	7.098	1	.008	.025		

a. Variable(s) entered on step 1: Age, Sex.

Because I failed to reject the null hypothesis in all four research questions, I looked further into the independent variable of obesity to see if higher BMI was affecting

the association. I then divided the data points by category of overweight. I subdivided the BMI into categories 1-4. Category 1 was underweight, Category 2 was normal weight, Category 3 was overweight, and Category 4 was obese. Table 12 demonstrates that 30% of the 944 data points were from obese patients.

Table 13

Weight Category

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	UW	34	3.6	3.6	3.6
	Normal	298	31.6	31.6	35.2
	overweight	324	34.3	34.3	69.5
	obese	288	30.5	30.5	100.0
	Total	944	100.0	100.0	

To better understand if the obese patients may have skewed the results, another analysis was conducted looking at weight category as an ordinal independent variable (See Table 14) and obesity as a dichotomous variable of yes or no (See Table 15). In both of these scenarios, Obesity was still not associated with liver toxicity as the p values were all greater than .05.

Table 14

Variables in the Equation – Weight Category and Liver Toxicity

		B	S.E.	Wald	*df*	Sig.	*Exp(B)*
Step 1[a]	Category			.769	3	.857	
	Category(1)	-.298	.770	.150	1	.699	.742
	Category(2)	-.120	.776	.024	1	.877	.887
	Category(3)	.012	.788	.000	1	.988	1.012
	Constant	2.565	.734	12.218	1	<.001	13.000

[a]. Variable(s) entered on step 1: Category.

Table 15

Variables in the Equation – Obesity and Liver Toxicity

		B	S.E.	Wald	*df*	Sig.	*Exp(B)*
Step 1[a]	Obese *Y/N*(1)	.212	.333	.406	1	.524	1.236
	Constant	2.365	.167	199.350	1	<.001	10.641

[a]. Variable(s) entered on step 1: Obese *Y/N*.

I repeated the same analysis with kidney toxicity (See Tables 16 and 17). In both cases, there was no association between obesity and kidney toxicity.

Table 16

Variables in the Equation – Weight Category and Kidney Toxicity

		B	S.E.	Wald	*df*	Sig.	*Exp(B)*
Step 1[a]	Category			2.991	3	.393	
	Category(1)	*.698*	1.054	.439	1	.508	2.010
	Category(2)	*1.014*	1.042	.946	1	.331	2.756
	Category(3)	*.412*	1.068	.149	1	.699	1.510
	Constant	*-3.367*	1.017	10.961	1	<.001	.034

[a]. Variable(s) entered on step 1: Category.

Table 17

Variables in the Equation – Obesity and Kidney Toxicity

		B	S.E.	Wald	df	*Sig.*	*Exp(B)*
Step 1[a]	Obese Y/N	-.425	.368	1.334	1	.248	.654
	Constant	-2.530	.173	213.461	1	<.001	.080

[a]. Variable(s) entered on step 1: Obese Y/N.

Because this is the first study of its kind in these cancer types, the external validity cannot be assessed at this time. In summary, in all four RQs, I failed to reject the null hypotheses, as BMI was not associated with kidney or liver toxicity in any of the four RQs. However, aging was marginally associated with kidney toxicity, and females were at a significantly higher risk for liver toxicity than males. Chapter 5 provides support for these results and ties back to the HBM framework while also providing direction for future research.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction to the Study

The purpose of this study was to understand the association between BMI and kidney/liver toxicity in obese cancer patients taking HDMTX with comedication, age, and sex as covariates. There is a large gap in the literature on this subject, making it extremely important for physicians to know how to properly dose this widely growing population. Different oncology institutions have different protocols on HDMTX dosing, and the outcomes are not well understood. The literature is sparse and inconsistent. Providing more knowledge around this association can help physicians and other clinicians to promote better health outcomes for this largely growing demographic of obese cancer patients.

This chapter provides a discussion of the findings on each RQ as well as the assumptions made for this analysis. Next, the information is tied back to what has been published in the literature and to the HBM. Also, social change is addressed as well as future directions and limitations of the study.

Table 6 in the previous chapter showed that 944 data points were available, but 306 data points were missing for liver toxicity, leaving 638 data points for analysis. For kidney toxicity, there were 254 data points missing, leaving 690 data points available to be analyzed. BMI ranged from 16.29 to 55.09 and age ranged from 18 to 87.

Discussion of Findings for RQ1 Analysis

The first RQ was as follows: What is the association between BMI and liver toxicity in patients receiving HDMTX after controlling for age and sex? For this RQ,

BMI was not associated with liver toxicity. Therefore, I failed to reject the null hypothesis. This RQ had not previously been investigated. Obesity is highly correlated with cancer, and there are often poorer outcomes in these patients, which is not completely understood (Silvestris et al., 2021). The previous literature focused mainly on other cancer drugs and different cancer types than this study. The literature review had to be expanded to 1990 or later because of the dearth of literature on this subject. In 2007, Jenkins et al. reported a higher relative dose intensity in overweight or obese patients compared to normal patients and concluded that obese patients should not be given reduced doses of chemotherapy. Although this study was done with antineoplastic drugs other than MTX and in breast cancer, it is consistent with the current study findings that obesity is not associated with worse toxicity outcomes.

Similarly, Gennari et al. (2016) reported no statistically significant difference in overall survival or disease-free survival in breast cancer patients taking epirubicin between BMI groups. As previously stated, there has been no research on HDMTX in the four cancer types in this study (acute lymphoblastic anemia, osteosarcoma, non-Hodgkin's lymphoma, and primary central nervous system lymphoma). Most research to date has been done on breast cancer patients and has not looked at specific toxicity outcomes and or MTX. However, this study supports the findings that BMI is not associated with worse toxicity outcomes in cancer patients taking HDMTX and that full dosing can be used. Maesta et al. (2015) supported these findings with a nonconcurrent cohort study of 300 patients taking MTX or actinomycin D with various types of cancer.

The authors reported no statistical difference in toxicity, time to remission, or resistance in these patients when stratified by BMI.

Upon adding in age and sex in this analysis, the estimated odds ratio favored an increase of 116% in liver toxicity for females compared to males (see Table 7). This is a significant association between being female and HDMTX liver toxicity. This is in alignment with previous research that stated that women experience more overall toxicity and adverse drug reactions in general across all types of medications. This may be due to pharmacokinetics, gut flora, polypharmacy, and sex hormones, to name a few (Ozdemir at al., 2022). Mennecozzi et al. (2015) also supported this finding, reporting that females experience worse liver toxicity outcomes from xenobiotics, but the reasons are not fully understood.

Therefore, even though there was no association between BMI and liver toxicity in this study, there was a clear difference in sex as it relates to liver toxicity specifically. Practitioners could adjust HDMTX dosing for females to reduce this toxicity, but more research is needed to discover if lower doses would result in cancer spreading or other worse outcomes. Dosing should never be adjusted without significant clinical studies. Similarly, practitioners may decide to monitor females more heavily and earlier for liver toxicity as compared to males.

Discussion of Findings for RQ2 Analysis

The second RQ was as follows: What is the association between BMI and kidney toxicity in patients receiving HDMTX after controlling for age and sex? For this RQ, BMI was not associated with kidney toxicity. Therefore, I failed to reject the null

hypothesis. However, age was slightly associated with kidney toxicity. There was only a 2.3% increase in kidney toxicity for every year of age. Therefore, this difference would be compounded over time, and older patients would be more likely to have kidney toxicity.

This is supported by data from the National Kidney Foundation, which reported that people over the age of 60 are the most likely to develop kidney disease. Specifically, over half of people over 75 may have kidney disease (National Kidney Foundation, 2023). Even though the statistical association found in this study was small, it is important information adding to the subject of HDMTX and toxicity outcomes. Another recent study by Latcha et al. (2023) examined risk factors for AKI in patients taking HDMTX. They reported that older patients taking HDMTX had higher rates of AKI as compared to younger patients ($p < .001$).

Discussion of Findings for RQ3 Analysis

The third RQ was as follows: What is the association between comedication and BMI on liver toxicity in patients receiving HDMTX after controlling for age and sex? The multiple logistic regression resulted in no significant association between comedication and BMI on liver toxicity. For this question, I failed to reject the null hypothesis. This was a bit surprising, as comedication is often associated with worse liver toxicity outcomes, as most medications are metabolized by the liver (Francis & Navarro, 2022). The comedications included in this study were only a select type of antineoplastic medications.

Because HDMTX is primarily metabolized by the kidney, liver toxicity may not be significantly affected by the addition of other antineoplastic agents (Howard, 2016). Amitai et al. (2018) conducted a retrospective analysis of 160 patients who received HDTX for 265 courses. Patients were taking the drug for primary CNS lymphoma, CNS prophylaxis, and other types of lymphoma or leukemia. Howard reported that age over 40 years resulted in a significantly greater kidney toxicity than those under 40 (p = .05, OR = 7.6, 95%, CI = 1-57; 2016).

There is some research supporting that MTX toxicity can be seriously exacerbated by other medications (Jafari et al., 2023). However, the medications in this study that counted as comedication were not specifically called out in these articles. In the current study, if a patient was taking cyclophosphamide, cytarabine, doxorubicin, vincristine, or rituximab, they were given a code of "Yes – comedication." Therefore, the exact dose and length of the comedication was not specified. More research must be conducted to determine if the doses or length of time taking these medications may have a significant association with liver toxicity.

Discussion of Findings for RQ4 Analysis

The fourth and final RQ was as follows: What is the association between comedication and BMI on kidney toxicity in patients receiving HDMTX after controlling for age and sex? Again, no association was found between comedication and BMI on kidney toxicity. As previously explained, this could be because of the small number of medications that were deemed comedication in this study analysis. Also, the dose and

length of treatment were not assessed in this study. More research needs to be conducted to better understand any drug interactions with HDMTX and these cancer drugs.

There are no specific studies looking at how comedication interacts with BMI to affect toxicity, but it is known that several drugs have negative interactions with MTX (Cudmore et al., 2014). The medications from Cudmore et al.'s study (2014) were trimethoprim-sulfamethoxazole, penicillin, high dose acetylsalicylic acid, indomethacin, and ibuprofen; none of which were included in this research study. Additionally, levetiracetam may slow the elimination of MTX (Bain, 2014).

Reintroduction of the Problem Statement

The problem is that obesity and cancer rates are rising, and many patients are taking HDMTX without proper understanding of the best way to promote the healthiest treatment outcomes. The current study substantially contributes to this gap in the literature and provides some understanding regarding proper HDMTX dosing to promote the best outcomes in obese cancer patients. Although the issue is not completely solved and more research needs to be done, there were no studies in this specific cancer type looking at liver and kidney toxicity in these patients previously.

There has been little to no research regarding toxicity outcomes in obese cancer patients taking HDMTX. The information published has been mostly in breast cancer and is conflicting in nature, meaning that some studies reported worse outcomes, and some studies showed no difference in outcomes (Howard, 2016; Maesta et al., 2015). The current research project supports the idea that the current method of dosing, which is calculated by weight, is not more toxic to these cancer patients because they have a

higher amount of fat tissue. Because of the lack of obese patients in Food and Drug Administration studies, it has been difficult for oncology practices to understand how to properly dose the obese cancer patients.

Positive Social Change Impact

This study helps fill a large knowledge gap regarding how HDMTX obese cancer patients can experience the best treatment outcomes. As more and more obese cancer patients present with multiple types of cancer, public health resources such as hospital beds, practitioners, and medicines are increasing (National Cancer Institute, 2022). Understanding how to provide the best treatment outcomes for these patients may result in shorter hospital stays, less resource usage at the clinical level, and better treatment outcomes. These could include better quality of life, increased overall survival, increased disease-free survival, and even less time on treatment meaning less side effects. Understanding the factors that affect treatment outcomes is paramount to creating the best possible outcomes for these patients. As more and more adults and even children are obese and needing HDMTX, this study may even lead to additional research regarding sex differences or even the effects of different dietary regimens on these patients' treatment outcomes.

Because the current literature was so sparse, focusing mainly on breast cancer, this is the first assessment of the factors that play into toxicity outcomes of the four types of cancer patients examined in this study. Also, the previous literature is very divided. There is now more support that full HDMTX dosing is not associated with worse liver and kidney toxicity in these patients. Additionally, because being female is associated

with worse liver toxicity, practitioners can be more aware of liver function testing early on in these patients and further investigate what other factors in females are associated with worse treatment outcomes.

Theoretical Framework

The HBM was the selected theoretical framework for this study. This model examines how choices that people make about health behaviors such as treatments affect health outcomes. This model has been used extensively to understand treatment outcomes in cancer patients (Zare et al., 2016). Because the doctor and not the patient chooses the dose of MTX for treatment, this model works best seen from the eye of the practitioner. The patients themselves are not changing their behaviors to affect toxicity outcomes. However, the different practitioners and different treatment institutes have been choosing how to best provide treatment for their patients. Some were using dose capping, and some were following the prescribing information as written by the HDMX manufacturer.

This research is aligned with the HBM because the practitioner can have more certainty that they are using the correct dose of HDMTX, even for the obese cancer patient. The health care practitioner may feel that there are less perceived barriers to treating these patients because of this research. They may also see more benefits to HDMTX in the obese patients and even be able to monitor women and older patients more carefully, as this research demonstrated worse outcomes in liver toxicity in women and in kidney toxicity in the elderly. This further examination may lead to less perceived severity of comorbidities.

Similarly, health care practitioners may feel less barriers to treating a patient with comedications as this study revealed no association between specific comedications and toxicity outcomes. The practitioner may feel that they can promote the healthiest treatment outcomes with this knowledge and assure patients that even though obese patients are not well studied, there is some information supporting the use of full dosing in these cancer patients.

Future Research

As this study is the first of its kind, there are many recommendations for future research. First, the study should be repeated with additional cancer patient types (in addition to acute lymphoblastic anemia, osteosarcoma, non-Hodgkin's lymphoma, and primary central nervous system lymphoma, which were studied in this study). Because there are over 100 types of cancer as previously discussed, there is much more research to be done. Also, more studies should be conducted or stratified across the different types of cancer, rather than grouping them together to understand which patients may experience more toxicity due to obesity. Next, the study could be expanded to children. Many of the patients seen in these cancer centers are young and suffer from many comorbidities. Understanding how to promote the best outcomes for patients at this age can lead to better outcomes in general, as patients start to have cancer younger.

Comedication is another area that should be explored further. This study only included five antineoplastic drugs. Other medications such as blood pressure drugs, pain medication, or anything that is metabolized in the kidneys or liver may have a significant association with toxicity. In that same realm, smoking and other unhealthy behaviors may

be associated with worse outcomes. There are many different directions and studies that can be done to support this and add to the body of knowledge regarding HDMTX and healthy outcomes.

It would also be interesting to look at dietary differences and toxicity outcomes. Differences in protein intake or specific nutrients may be associated with better or worse outcomes, which could provide more information to the team of practitioners trying to treat for all the comorbidities these patients may face. Along with age and sex, it would be interesting to understand if there are differences in toxicity outcomes based on race or socioeconomic status. Many of these studies could be conducted with the already existing dataset collected by the Guardian Research Network.

Summary of Chapter 5

This study is the first of its kind to understand the factors that can lead to better overall health outcomes in the obese cancer patient. As the prevalence of these comorbidities continues to rise, it is difficult for healthcare practitioners to navigate all the nuances in treatment for each individual patient. Finding that there was no association between BMI and liver or kidney toxicity outcomes in these obese cancer patients is a positive finding for oncologists and other health care practitioners. Also, learning that females have a much greater risk of liver toxicity should be considered. Although the finding regarding age and kidney toxicity is marginal, it is also important information to note.

As patients are living longer, they will present with more and more comorbidities that are difficult for their healthcare team to manage. Promoting shorter hospital stays,

better quality of life, and less toxicity can reduce the public health burden to both the nation and the individual. Hopefully, the obese cancer patient will be included in more clinical trials as new drugs emerge. In the meantime, oncology practitioners can push back against dose capping for these patients.

References

Abdah-Bortnyak R., Tsalic M., & Haim N. (2003). Actual body weight for determining doses of chemotherapy in obese cancer patients: evaluation of treatment tolerability. *Medical Oncology*. *20*(4), 363-8. https://doi.org/10.1385/MO:20:4:363

Abdeyazdan, Z., Moshgdar, H., & Golshiri, P. (2017). Evaluating the effect of lifestyle education based on health belief model for mothers of obese and overweight school-age children on obesity-related behaviors. *Iranian Journal of Nursing and Midwifery Research*, *22*(3), 248–252. https://doi.org/10.4103/1735-9066.208163

Agha, M., & Agha, R. (2017). The rising prevalence of obesity: Part A: Impact on public health. *International Journal of Surgery Oncology, 2(*7), e17. https://doi.org/10.1097/IJ9.0000000000000017

Al-Hassan, Y. T., Fabella, E., Estrella, E., Al-Ramadan, H. A., & Bujbara, A. H. (2020). Utilizing the health belief model in determining the association between perceptions on obesity and exercise behavior of Saudi University Students. *The Open Public Health Journal, 13*(1), 87-93. https://doi.org/10.2174/1874944502013010087

Alsdorf, W. H., Karagiannis, P., Langebrake, C., Bokemeyer, C., & Frenzel, C. (2020). Standardized supportive care documentation improves safety of high-dose methotrexate treatment. *The Oncologist*, *26*(2), e327-e332. https://doi.org/10.1002/onco.13603

American Cancer Society. (2021). *Key statistics for childhood cancer.*

https://www.cancer.org/cancer/cancer-in-children/key-statistics.html

Amitai, I., Rozovski, U., El-Saleh, R., Raanani, P., Gafter-Gvilli, A., & Gurion, R. (2018). High dose methotrexate and acute kidney injury—Is it predictable? *Blood, 13(*2*)*, (Supplement 1) https://doi.org/10.1182/blood-2018-99-113755

Arshad, U., Taubert, M., Seeger-Nukpezah, T., Ullah, S., Spindeldreier, K. C., Jaehde, U., Hallek, M., Fuhr, U., Vehreschild, J. J., & Jakob, C. (2021). Evaluation of body-surface-area adjusted dosing of high-dose methotrexate by population pharmacokinetics in a large cohort of cancer patients. *BMC Cancer*, *21*(1),719. https://doi.org/10.1186/s12885-021-08443-x

Avgerinos, K. I., Spyrou, N., Mantzoros, C. S., & Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism*, *92*, 121-135. https://doi.org/10.1016/j.metabol.2018.11.001

Azriful, B., E., Nildawati, R., R., Mallapiang, F., & Suyuti, S. (2021). Health belief model on women's cancer recovery (a phenomenological study on cancer survivors). *Galeta Sanitaria*, *35*. https://doi.org/10.1016/j.gaceta.2020.12.003

Bain, E., Birhiray, R. E., & Reeves, D. J. (2014). Drug-drug interaction between methotrexate and levetiracetam resulting in delayed methotrexate elimination. *Annals of Pharmacotherapy*, *48*(2), 292–296. https://doi.org/10.1177/1060028013511951

Bhaskar, B., Pullarkat, P., Wan, F., Butler, S., & Mehta-Shah, N. (2020, December 6). BMI is not associated with toxicity to high dose methotrexate: A single institution retrospective study of 147 patients [Poster presentation.] *American Society of*

Hematology, Virtual. https://ash.confex.com/ash/2020/webprogram/Paper137536.html

Biganzoli, E., Desmedt, C., Fornili, M., de Azambuja, E., Cornez, N., Ries, F., Closon-Dejardin, M.-T., Kerger, J., Focan, C., Di Leo, A., Nogaret, J.-M., Sotiriou, C., Piccart, M., & Demicheli, R. (2017). Recurrence dynamics of breast cancer according to baseline body mass index. *European Journal of Cancer*, 87, 10–20. https://doi.org/10.1016/j.ejca.2017.10.007

Boston University. (2013). *Multiple logistic regression analysis*. https://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704_multivariable/bs704_multivariable8.html

Cawley, J., Biener, A., Meyerhoefer, C., Ding, Y., Zvenyach, T., Smolarz, B. G., & Ramasamy, A. (2021). Direct medical costs of obesity in the United States and the most populous states. *Journal of Managed Care & Specialty Pharmacy*, *27*(3), 354-366. https://doi.org/10.18553/jmcp.2021.20410

Centers for Disease Control and Prevention. (2021a, March 23). *Overweight & obesity*. https://www.cdc.gov/obesity/index.html

Centers for Disease Control and Prevention. (2021b, March 17). *About child and teen BMI*. https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

Conway, R.,& Carey, J. J. (2017). Risk of liver disease in methotrexate treated patients. *World Journal of Hepatology*, *18* (26),1092-1100.

https://doi.org/10.4254/wjh.v9.i26.1092

Cudmore, J. A., Seftel, M. D., Sisler, J., & Zarychanski, R. (2014). Methotrexate and trimethoprim-sulfamethoxazole: toxicity from this combination continues to occur. *PubMed*. https://pubmed.ncbi.nlm.nih.gov/24452563

Daniels, S.R. (2009). The use of BMI in the clinical setting. *Pediatrics, 124* Suppl 1:S35-41. doi: 10.1542/peds.2008-3586F. PMID: 19720666

Desmedt, C., Fornili, M., Clatot, F., Demicheli, R., De Bortoli, D., Di Leo, A., Viale, G., de Azambuja, E., Crown, J., Francis, P.A., Sotiriou, C., Piccart, M., & Biganzoli, E. (2020). Differential Benefit of Adjuvant Docetaxel-Based Chemotherapy in Patients with Early Breast Cancer According to Baseline Body Mass Index. *Journal of Clinical Oncology*. *38*(25):2883-2891. doi: 10.1200/JCO.19.01771

Du Bois, D., & Du Bois, E.F. (1916). A formula to estimate the approximate surface area if height and weight be known. *Nutrition 5*(5):303-11; discussion 312-3.

Findley, M.G., Kikuta, K., & Denly, M. (2021). External validity. *Annual Review of Political Science*, *24*, 365-393. doi/10.1146/annurev-polisci-041719-102556

Francis P., & Navarro, V.J. (2023). Drug-induced hepatotoxicity. *Treasure Island (FL): StatPearls Publishing*; https://www.ncbi.nlm.nih.gov/books/NBK557535/

Gehan, E.A., & George, S.L. (1970). Estimation of human body surface area from height and weight. *Cancer Chemotherapy Reports.* 54(4):225-35.

Gennari, A., Amadori, D., Scarpi, E., Farolfi, A., Paradiso, A., Mangia, A., Biglia, N., Gianni, L., Tienghi, A., Rocca, A., Maltoni, R., Antonucci, G., Bruzzi, P., & Nanni, O. (2016). Impact of body mass index (BMI) on the prognosis of high-risk

early breast cancer (EBC) patients treated with adjuvant chemotherapy. *Breast Cancer Research and Treatment*, *159*(1), 79–86. https://doi-org.ezp.waldenulibrary.org/10.1007/s10549-016-3923-8

Global Cancer Observatory. (2022). *Cancer Today*. https://gco.iarc.fr/today/home

Griggs, J.J., Sorbero M.E.S, & Lyman, G.H. (2005). Undertreatment of obese women receiving breast cancer chemotherapy. *Archives of Internal Medicine. 165*(11):1267–1273. doi:10.1001/archinte.165.11.1267

Grigsby, P., Elhammali, A., Ruiz, F., Markovina, S., McLellan, M.D., Miller, C.A., Chundury, A., Ta, N.L., Rashmi, R., Pfeifer, J.D., Fulton, R.S, DeWees, T., & Schwarz, J.K. (2017). Clinical outcomes and differential effects of PI3K pathway mutation in obese versus non-obese patients with cervical cancer. *Oncotarget*. *23*;9(3):4061-4073. doi: 10.18632/oncotarget.23664. PMID: 29423104; PMCID: PMC5790521

Guardian Research Network. (2022). *Health systems what we do*. https://www.guardianresearch.org/healthcare-what-we-do/

Gurunathan, U., & Myles, P.S. (2016) Limitations of body mass index as an obesity measure of perioperative risk, *BJA: British Journal of Anaesthesia*, *116*, (3), 319–321. https://doi.org/10.1093/bja/aev541

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*, *9*(1). https://doi.org/10.1186/1471-2458-9-88

Hall, R. G., Jean, G. W., Sigler, M., & Shah, S. (2013). Dosing considerations for obese patients receiving cancer chemotherapeutic agents. *The Annals of Pharmacotherapy*, *47*(12), 1666–1674. https://doi-org.ezp.waldenulibrary.org/10.1177/1060028013509789

Harris J. K. (2021). Primer on binary logistic regression. *Family Medicine and Community health*, *9*(Suppl 1), e001290. https://doi.org/10.1136/fmch-2021-001290

Harvard School of Public Health. (2021). *Measuring obesity*. https://www.hsph.harvard.edu/obesity-prevention-source/obesity-definition/how-to-measure-body-fatness/

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. (1978). Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. *The Journal of Pediatrics*, *93*(1), 62–66. https://doi.org/10.1016/s0022-3476(78)80601-5

Hess, L. M., Brnabic, A., Mason, O., Lee, P., & Barker, S. (2019). Relationship between progression-free survival and overall survival in randomized clinical trials of targeted and biologic agents in oncology. *Journal of Cancer*, *10*(16), 3717–3727. https://doi.org/10.7150/jca.32205

Howard, S. C., Mccormick, J., Pui, C., Buddington, R. K., & Harvey, R. D. (2016). Preventing and managing toxicities of high-dose methotrexate. *The Oncologist*, *21*(12), 1471-1482. doi:10.1634/theoncologist.2015-0164

Horowitz, N. S., & Wright, A. A. (2015). Impact of obesity on chemotherapy

management and outcomes in women with gynecologic malignancies. *Gynecologic oncology*, *138*(1), 201–206. https://doi.org/10.1016/j.ygyno.2015.04.002

Hruby A., & Hu, F.B. (2015). The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics*, *33*(7):673-89. doi: 10.1007/s40273-014-0243-x. PMID: 25471927; PMCID: PMC4859313

Jacques, K. A., & Erstad, B. L. (2010). Availability of information for dosing injectable medications in underweight or obese patients. *American Journal of Health-System Pharmacy*, *67*(22), 1948-1950. doi:10.2146/ajhp100226

Janz, N.K. & Becker, M.H. (1984). The health belief model: A decade later. *Health Education Quarterly*, *11*(1), 1-47. https://deepblue.lib.umich.edu/bitstream/handle/2027.42/66877/10.1177_109019818401100101.pdf

Jenkins, P., Elyan, S., & Freeman, S. (2007). Obesity is not associated with increased myelosuppression in patients receiving chemotherapy for breast cancer. *European Journal of Breast Cancer*, *43*(3), 544–548. https://doi-org.ezp.waldenulibrary.org/10.1016/j.ejca.2006.10.013

Jiralerspong, S., & Goodwin, P.J. (2016). Obesity and breast cancer prognosis: Evidence, challenges, and opportunities. *J Clin Oncol. 10*;34(35):4203-4216. doi: 10.1200/JCO.2016.68.4480

Kaya Y, Aki OE, Can UA, Derle E, Kibaroğlu S, Barak A. (2014). Validation of Montreal cognitive assessment and discriminant power of Montreal cognitive

assessment subtests in patients with mild cognitive impairment and Alzheimer dementia in Turkish population. *Journal of Geriatric Psychiatry and Neurology*. 27(2):103-109. doi:10.1177/0891988714522701

Khan, J. M., Basques, B. A., Kunze, K. N., Grewal, G., Hong, Y. S., Pardo, C., Louie, P. K., Colman, M., & An, H. S. (2019). Does obesity impact lumbar sagittal alignment and clinical outcomes after a posterior lumbar spine fusion? *European Spine Journal*, *29*(2), 340–348. https://doi.org/10.1007/s00586-019-06094-y

Kowalski, A., Jaszczur, S.M., Nadeau-Nguyen, M., & Merl, M.Y. (2021). Assessment of high-dose methotrexate management guideline in adults with caner at an academic medical center. *Journal of Hematology Oncology Pharmacy*. *11*(2), 69-73.

Koźmiński, P., Halik, P. K., Chesori, R., & Gniazdowska, E. (2020). Overview of dual-acting drug methotrexate in different neurological diseases, autoimmune pathologies and cancers. *International journal of molecular sciences*, *21*(10), 3483. https://doi.org/10.3390/ijms21103483

Krupa-Kotara, K., & Dakowska, D. (2021). Impact of obesity on risk of cancer. *Central European Journal of Public Health*, *29*(1), 38-44. doi:10.21101/cejph.a5913

Krüger, C., Engel, N., Reinert, J., Alsdorf, W., Fiedler, W., Dierlamm, J., Bokemeyer, C., & Langebrake, C. (2020). Successful treatment of delayed methotrexate clearance using glucarpidase dosed on ideal body weight in obese patients. *Pharmacotherapy*, *40*(5):479-483. doi: 10.1002/phar.2390. Epub 2020 Apr 20.

PMID: 32239519

Laerd Statistics. (2018). *Binomial logistic regression using SPSS.* https://statistics.laerd.com/spss-tutorials/binomial-logistic-regression-using-spss-statistics.php

Latcha, S., Gupta, M., Lin, I., & Jaimes, E. A. (2023). High dose methotrexate-induced acute kidney injury: Incidence, risk factors, and recovery. *Kidney International Reports, 8*(2), 360-364. https://doi.org/10.1016/j.ekir.2022.10.029

Lauby-Secretan, B., Scoccianti, C. Loomis, D. Grosse, Y. Bianchini, F. & Straif, K. (2016). Body fatness and cancer--Viewpoint of the IARC working group. *New England Journal of Medicine., 375*(8):794-8. doi: 10.1056/NEJMsr1606602. PMID: 27557308; PMCID: PMC6754861.

Ligibel, J.A., Alfano, C.M., Courneya, K.S., Demark-Wahnefried, W., Burger, R.A., Chlebowski, R.T., Fabian, C.J., Gucalp, A., Hershman, D.L., Hudson, M.M., Jones, L.W., Kakarala, M., Ness K.K., Merrill, J.K., Wollins, D.S., & Hudis, C.A. (2014). American Society of Clinical Oncology position statement on obesity and cancer. *J Clin Oncol., 32*(31):3568-74. doi: 10.1200/JCO.2014.58.4680. Epub 2014 Oct 1. PMID: 25273035; PMCID: PMC4979237.

Ludwig, D. S., Aronne, L. J., Astrup, A., de Cabo, R., Cantley, L. C., Friedman, M. I., Heymsfield, S. B., Johnson, J. D., King, J. C., Krauss, R. M., Lieberman, D. E., Taubes, G., Volek, J. S., Westman, E. C., Willett, W. C., Yancy, W. S., & Ebbeling, C. B. (2021). The carbohydrate-insulin model: A physiological perspective on the obesity pandemic. *The American Journal of Clinical Nutrition*.

https://doi.org/10.1093/ajcn/nqab270

Lyman, G. H., & Sparreboom, A. (2013). Chemotherapy dosing in overweight and obese patients with cancer. *Nature Reviews Clinical Oncology, 10*(8), 451-459. doi:10.1038/nrclinonc.2013.108

Maesta, I., Horowitz, N. S., Goldstein, D. P., Bernstein, M. R., Ramirez, L. A. C., Moulder, J., & Berkowitz, R. S. (2015). Response to chemotherapy in overweight/obese patients with low-risk gestational trophoblastic neoplasia. *International Journal of Gynecological Cancer, 25*(4), 734–740. https://doi-org.ezp.waldenulibrary.org/10.1097/IGC.0000000000000398

Malaviya, A. N., Sharma, A., Agarwal, D., Kapoor, S., Garg, S., & Sawhney, S. (2010). Low-dose and high-dose methotrexate are two different drugs in practical terms. *International Journal of Rheumatic Diseases*, *13*(4), 288-293. doi:10.1111/j.1756-185x.2010.01564.x

Martin, J. H., Saleem, M., & Looke, D. (2012). Therapeutic drug monitoring to adjust dosing in morbid obesity - a new use for an old methodology. *British Journal of Clinical Pharmacology*, *73*(5), 685-690. doi:10.1111/j.1365-2125.2011.04159.x

Mattiuzzi C, Lippi G. (2019). Current cancer epidemiology. *J Epidemiol Glob Health, 9*(4),217-222. doi: 10.2991/jegh.k.191008.001. PMID: 31854162; PMCID: PMC7310786.

May, M., Schindler, C., & Engeli, S. (2020). Modern pharmacological treatment of obese patients. *Therapeutic advances in endocrinology and metabolism, 11*, 1-19. https://doi.org/10.1177/2042018819897527

Mayo Clinic. (2021a). *Obesity*. https://www.mayoclinic.org/diseases-conditions/obesity/symptoms-causes/syc-20375742

Mayo Clinic. (2021b). *Cancer*. https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588

Meldrum D.R., Morris M.A., & Gambone, J.C. (2017). Obesity pandemic: Causes, consequences, and solutions-but do we have the will? *Fertility and Sterility*. *107*(4):833-839. doi: 10.1016/j.fertnstert.2017.02.104. Epub 2017 Mar 11. PMID: 28292617

Mennecozzi, M., Landesmann, B., Palosaari, T., Harris, G., & Whelan, M. (2015). Sex differences in liver toxicity—Do female and male human primary hepatocytes react differently to toxicants in vitro? *PLOS ONE*, *10*(4), e0122786. https://doi.org/10.1371/journal.pone.0122786

Mosteller, R.D. (1987) Simplified calculation of body-surface area. *The New England Journal of Medicine*, *317*, 1098. http://dx.doi.org/10.1056/NEJM198710223171717

National Cancer Institute. (2014, April 30). *Treatment of solid tumor cancers with the chemotherapy drug methotrexate*. https://www.cancer.gov/research/progress/discovery/methotrexate

National Cancer Institute. (2021, May 5). *What is cancer?* https://www.cancer.gov/about-cancer/understanding/what-is-cancer

National Cancer Institute. (2022, Apr). *Financial burden of cancer care*. https://progressreport.cancer.gov/after/economic_burden

National Cancer Institute. (2023). Common terminology criteria for adverse events : (V4.03 ed.). U.S. Department of Health and Human Services. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

National Cancer Institute. (n.d.). *Cancer stat facts: Cancer of any site*. https://seer.cancer.gov/statfacts/html/all.html

National Kidney Foundation. (2023). Aging and kidney disease. https://www.kidney.org/news/monthly/wkd_aging#:~:text=Kidney%20disease%20can%20develop%20at,believed%20to%20have%20kidney%20disease.

Navarro, W. H. (2003). Impact of obesity in the setting of high-dose chemotherapy. *Bone Marrow Transplantation, 31*(11), 961-966. doi:10.1038/sj.bmt.1704052

Ni, YN., Luo, J., Yu, H. *et al.* (2017). Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Critical Care, 21*, (36). https://doi.org/10.1186/s13054-017-1615-3

Orgel, E., Nabais, T., Douglas, C., Mittelman, S. D., & Neely, M. (2021). Effect of body fat on population pharmacokinetics of high-dose methotrexate in pediatric patients with acute lymphoblastic leukemia. *Journal of Clinical Pharmacology, 61*(6), 755–762. https://doi-org.ezp.waldenulibrary.org/10.1002/jcph.1799

Özdemir, B. C., Gerard, C. L., & Espinosa da Silva, C. (2022). Sex and Gender Differences in Anticancer Treatment Toxicity: A call for revisiting drug dosing in Oncology. *Endocrinology, 163*(6). https://doi.org/10.1210/endocr/bqac058

Pai, M.P., Debacker, K.C., Derstine, B., Sullivan, J., Su, G.L., Wang SC. (2020). Comparison of body size, morphomics, and kidney function as covariates of high-dose methotrexate clearance in obese adults with primary central nervous system lymphoma. *Pharmacotherapy*, *40*(4):308-319. doi: 10.1002/phar.2379

Park, J., & Look, K. A. (2019). Health care expenditure burden of cancer care in the United States. *Inquiry: The Journal of Health Care Organization, Provision, and Financing*, *56*, 004695801988069. doi:10.1177/0046958019880696

Rakhshanderou, S., Maghsoudloo, M., Safari-Moradabadi, A., & Ghaffari, M. (2020). Theoretically designed interventions for colorectal cancer prevention: a case of the health belief model. *BMC Med Educ 20,* 270. https://doi.org/10.1186/s12909-020-02192-4

Rosenstock, I. M. (1974). Historical origins of the health belief model. *Health Education Monographs, 2*(4), 328–335. http://www.jstor.org/stable/45240621

Sahib, A. S. (2016). Eating behavior in a sample of overweight and obese: A cross sectional study. *Journal of Obesity and Weight-Loss Medication*, *2*(2). https://doi.org/10.23937/2572-4010.1510014

Saini, A., Kumar, M., Bhatt, S., Saini, V, & Malik, A. (2020). Cancer causes and treatments. *International Journal of Pharmaceutical Sciences and Research, 11*(7). 3109-3122.

Serdar, C. C., Cihan, M., Yücel, D., & Serdar, M. A. (2021). Sample size, power and effect size revisited: Simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochemia Medica*, *31*(1), 27–53.

https://doi.org/10.11613/bm.2021.010502

Silvestris, N., Argentiero, A., Natalicchio, A., D'Oronzo, S., Beretta, G. D., Acquati, S., Adinolfi, V., Di Bartolo, P., Danesi, R., Faggiano, A., Ferrari, P., Gallo, M., Gori, S., Morviducci, L., Russo, A., Tuveri, E., Zatelli, M. C., Montagnani, M., & Giorgino, F. (2021). Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper. Annals of Oncology, 32(3), 319-329

Tabucanon, T., Wilcox, J., & Tang, W. H. (2020). Does weight loss improve clinical outcomes in overweight and obese patients with heart failure? *Current Diabetes Reports*, *20*(12). https://doi.org/10.1007/s11892-020-01367-z

Teva Parenteral Medicines, Inc. (2021). Methotrexate: Prescribing information. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=346ec9ce-dc98-4a55-b55e-d3af11f2d703

Tremmel, M., Gerdtham, U.G., Nilsson, P.M., & Saha, S. (2017). Economic burden of obesity: A systematic literature review. *Int. J. Environ. Res. Public Health*, *14*(4), 435. https://doi.org/10.3390/ijerph14040435

US Department of Health & Human Services. (n.d.). *Calculate your body mass index*. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

Verbraecken, J., Van de Heyning, P., De Backer, W., & Van Gaal, L. (2006). Body surface area in normal-weight, overweight, and obese adults. A comparison study.

Metabolism, 55(4), 515–524. https://doi.org/10.1016/j.metabol.2005.11.004

Wang, X., & Kattan, M.W. (2020). Cohort studies: Design, analysis, and reporting. *Chest, 158* (1), S72-S78. https://doi.org/10.1016/j.chest.2020.03.014

White E. (2015). The role for autophagy in cancer. *J Clin Invest*. *125*(1):42-6. doi: 10.1172/JCI73941

World Cancer Research Fund. (n.d.). *Worldwide cancer data*. https://www.wcrf.org/dietandcancer/worldwide-cancer-data/#:~:text=There%20were%20an%20estimated%2018.1,listed%20in%20the%20tables%20below.

World Health Organization. (2021). *Obesity and overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Yuen, K. F., Bin Saidi, M. S., Bai, X., & Wang, X. (2021). Cruise transport service usage post covid-19: The Health Belief Model application. *Transport Policy, 111*, 185–196. https://doi.org/10.1016/j.tranpol.2021.08.002

Zare, M., Ghodsbin, F., Jahanbin, I., Ariafar, A., Keshavarzi, S., & Izadi, T. (2016). The effect of health belief model-based education on knowledge and prostate cancer screening behaviors: A randomized controlled trial. *International Journal of Community Based Nursing and Midwifery*, *4*(1), 57–68.