The Effect of Intermittent Fasting on Chemotherapy and Quality of Life in Cancer Patients

Thousand Oaks High School

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Abstract

The effects of intermittent fasting (IF) and chemotherapy were analyzed in comparison to patient quality of life (QOL) to determine which time length is the most feasible and beneficial fasting period for patients to complete, and if there is a correlation between glucose levels in the body and the decrease of chemotherapy related symptoms. Additionally, studies on chemotherapy effectiveness in relation to glucose levels were also analyzed in rats in order to evaluate if there is a potential correlation between these two factors. For human studies, the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) grade scale of 0-4 was used to determine the quality of life patients would experience while practicing IF versus Ad Lib eating. The likelihood of developing cancer was also examined and investigated a potential correlation between a person's average daily caloric intake and obesity in comparison to cancer rates through the years of 1976-2013. Papers included in this systematic literature review quantified chemotherapy symptoms experienced by patients after completing several different length fasting periods.

Introduction

Intermittent fasting (IF) is an eating pattern that has a series of eating and fasting periods throughout the week. IF can be performed in one of two ways: by not eating 1-3 days out of the week, or not eating for a certain period of time each day, such as fasting for the first 16 hours of the day, then intaking food for the last 8 hours of the day. This is commonly referred to as a 16/8 fasting plan. During fasting periods, no food is allowed; however, zero calorie drinks, such as black coffee, tea, or water, are allocated in order to maintain energy within the body and to avoid

dehydration. If the body is not properly hydrated throughout the fasting period, symptoms such as dizziness, fatigue, nausea, headaches, constipation, low blood pressure and low energy levels can be experienced. Most participants of IF have adopted this eating pattern in order to limit their caloric intake and to lose weight through creating a calorie deficit in their bodies. However, it has most recently been used to reduce the effects of toxins associated with chemotherapy so that larger doses can be administered to patients during a single session.

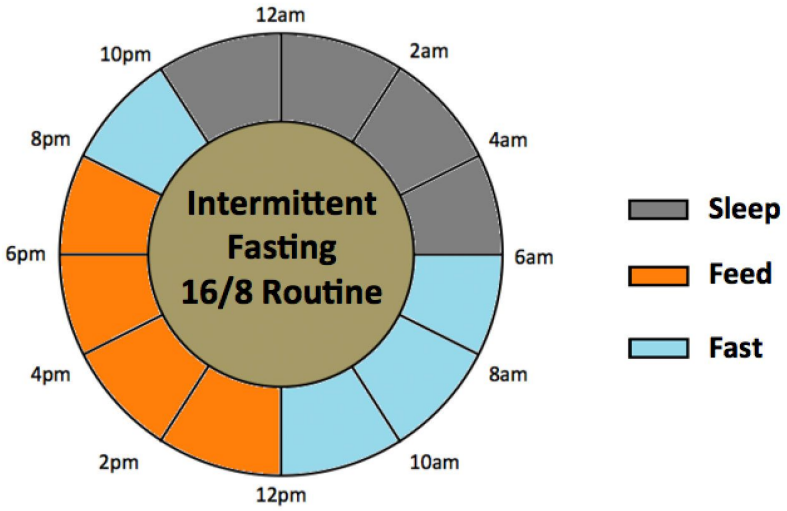

Fig. 1- The diagram above shows the 16/8 Intermittent fasting schedule, a popular fasting schedule. Fasting is observed between the hours of 8pm - 12pm (16 hours) and calorie consumption is allocated between 12pm - 8pm.

Platinum based chemotherapy, informally known as cocktail chemotherapy or combination chemotherapy, is a combination of drugs that oncologists use in order to target solid tumor masses in the body. Common drugs that are used include cisplatin, doxorubicin, rapamycin, carboplatin, and oxaliplatin. Platinum based chemotherapy is most effective and commonly used in lung cancer, testicular cancer, and ovarian cancer; it is the first treatment method for 80% of non-small cell lung cancer (NSCLC) patients (Tan et al., 2017). It provides

many benefits, such as reducing the risk of cancer recurrence after surgeries to remove the masses and has been known to extend the lifespan of patients who have developed advanced stages of cancer (Bauersfeld et al., 2018). However, while patients undergo chemotherapy treatments, they are subject to developing many symptoms and side effects, such as alopecia, fatigue, nausea, neutropenia, thrombocytopenia, neuropathy, and many more. These symptoms make it hard for patients with cancer to lead normal lives by restricting their ability to perform typical daily activities and functions that they previously would have been able to by altering their energy levels and attacking their immune system responses.

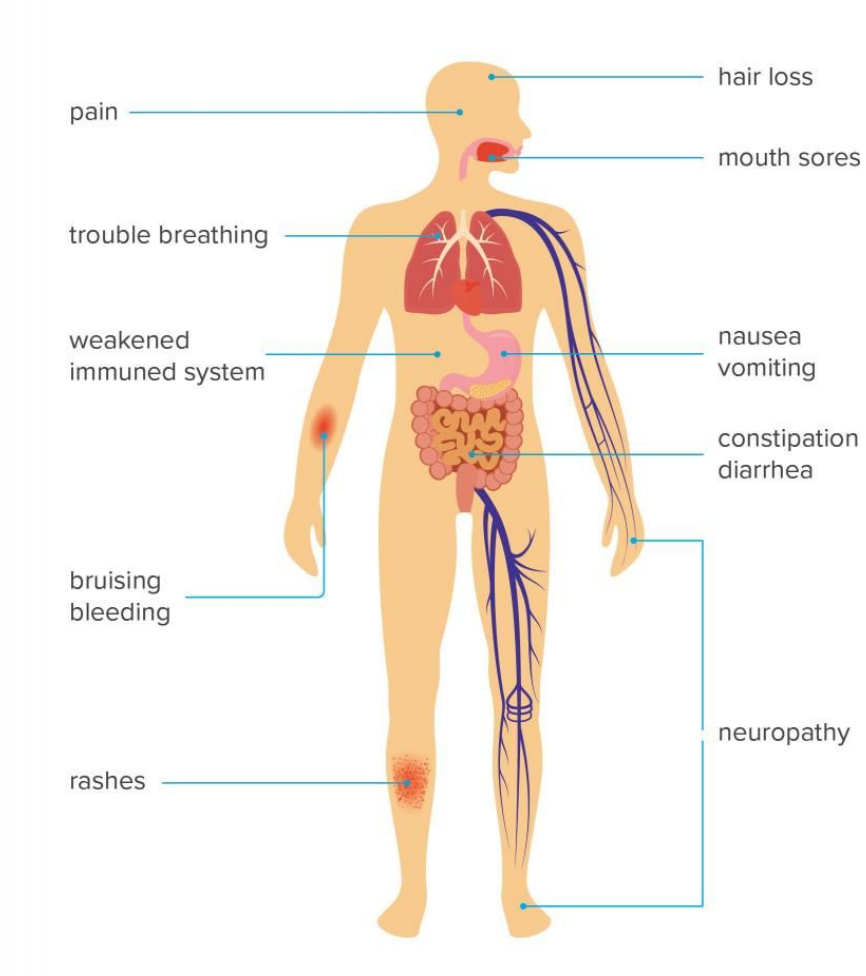

Fig. 2- The diagram above shows possible symptoms patients can develop after or during chemotherapy sessions.

Many cancer cases require the use of platinum based chemotherapy opposed to monotherapy, which is the use of a single drug during chemotherapy, because the tumors are further developed and have become more complex, so a single drug would not be a sufficient treatment plan because the tumors can become resistant to one drug (Gerber et al., 2005). However, due to the high toxicity levels of the combination of drugs, only small portions can be administered to patients at a time. If too large of a dose is administered, it can result in neurotoxicity, nephrotoxicity, and oxidative cellular damage, which is associated to many diseases that can range anywhere from Sickle-Cell disease, Alzheimer's disease, Attention deficit/hyperactivity disorder (ADHD), etc. (Dorff et al., 2016). Currently, most IF studies with chemotherapy focuses on two dominant drugs that are used in platinum based chemotherapy: doxorubicin and rapamycin.

Within the last decade, many populations have experienced severe poverty and starvation crises, while other populations have experienced growth and an influx of resources. However, within population groups that were not able to consume sufficient amounts of calories and were severely deprived of nutrients, it has recently been studied that their food deprivation has decreased the likelihood of developing age related diseases due to the lack of glucose intake. The normal physiological blood glucose level for both mice and humans is approximately 1.0 g/liter, but through fasting it can become 0.5 g/liter (Raffaghello et al., 2008). During World War II, many Europeans were not able to meet a sufficient caloric intake everyday, resulting in periods of unintentional fasting. Despite their starvation, in 2012 it was found that Norwegian women who underwent puberty during the WWII food shortages have far lower cancer incidences compared to populations during food surpluses (Hanjani er al., 2017). The medical

phenomenons experienced during these past events have led to studies on the effect of fasting with cancer and age related diseases.

Background

Calorie Restriction and Aging

Recent studies performed by the National Institute of Ageing and the University of Wisconsin show that when rhesus monkeys alter their diet by reducing their caloric intake, they have higher survival rates of cancer and other age related diseases, such as type 2 diabetes (O'Flanagan et al., 2017). Head researcher Dr. Ricki J. Colman completed a 20 year study on age related disease onset in rhesus monkeys by controlling their diets: a control group was fed normally, while another group was fed 10% less than the control group in order to restrict their calories and glucose levels. After 20 years, it was found that the effect of calorie restriction (CR) in reducing disease onset was statistically significant through a $p = 0.008$ value when compared to a $p = 0.05$ value (Colman et al., 2009).

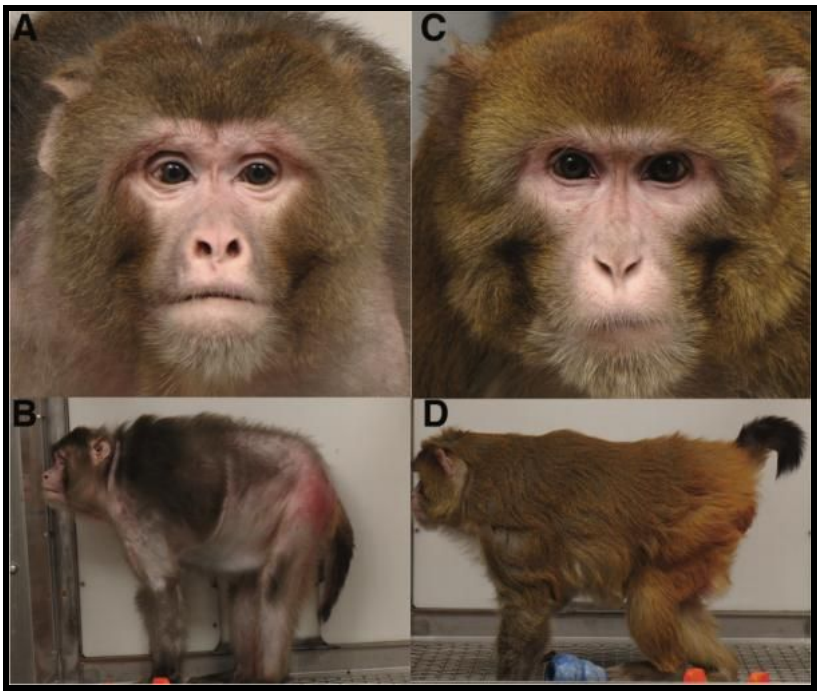

Fig. 3: Colman, R., 2009- Animal appearance in old age. (A–B) Photographs of a typical control animal at 27.6 years of age. (C–D) Photographs of animal at 27.6 years on a CR diet.

In figure two, photos A and B show a rhesus monkey that is 27.6 years old, which is towards the end of an average rhesus monkey lifetime in captivity. Photos C and D show a rhesus monkey that is also 27.6 years old; however, this monkey had a calorie restricted diet compared to the monkey in photos A and B. The monkey that had a calorie restricted diet is evidently much more healthy than the monkey fed a normal diet, who is showing signs of alopecia and old age through the decrease of elasticity in the skin. Moreover, overall energy levels and motivation to do activities was also observed in the monkeys, and the C/D rhesus monkeys led more of an active life than the A/B monkeys.

Calorie Restriction and Cancer

Research completed on fasting in mice shows it is beneficial to them and they are able to withstand higher doses of chemotherapy at a time; overall, the likelihood of cancer returning is lower. In a trial done on mice with a model of human metastatic cancer, mice underwent a series of five 48 hour fasting periods in a time span of 34 days. By the end of the 34 day period, mice that were starved had tumor sizes that were half of those in the control groups (Naveed et al., 2014). Through having the mice fast for a total of 240 hours, it proved beneficial to them in that they had less metastasis of their cancer and it reduced the size of their tumors.

In certain studies, metastasis, which is the spreading of cancer from the initial, primary site to a secondary site in the organism, was also analyzed in mice. In 2012, Researcher Chen X found that ad libitum feeding of mice with lung cancer had a metastasis rate of 100%, while mice who fasted has a metastasis rate of 6.25% (Chen et al., 2012). Ad Libitum feeding is eating as one desires and stops eating once they are satisfied in no particular pattern. Through lowering metastasis rates within the organism's body, it prevents further damage to the cells and other vital aspects of the body; overall it prevents further damage to the body. Furthermore, there were no physical or visible symptoms of the effects of chemotherapy seen in the mice.

In 2014, intermittent fasting was then tested to see if the incidence of delayed-type vomiting (vomiting after chemotherapy sessions, opposed to during) associated with doxorubicin could improve treatment in dogs with lymphatic cancer, which is cancer in the infection-fighting cells in the immune system. From this study, a control group of dogs that had cancer had an average of 67% for incidences of vomiting after given two doses of doxorubicin, while the group of dogs that fasted before their two doses of doxorubicin only had an average of 10% vomiting

incidences (Withers et al., 2014). There was a significant difference between the two groups with a p=0.020, indicating that fasting before chemotherapy sessions would be beneficial. By reducing the amount of nausea and vomiting the dogs experienced during chemotherapy, researchers began to hypothesize whether of not through IF human patients could decrease their amount of grade of chemotherapy symptoms experienced and improve their quality of life.

During preliminary research in humans, a potential relationship between the effects of glucose in the human body and how it increases the levels of toxicity in chemotherapy was investigated. Studies show that the toxins in chemotherapy are intensified by glucose and harm normal cells; on the other hand, when the glucose levels are lower, it starves the cancer cells of nutrients and causes them to shut down faster. Due to this relationship, IF is utilized to lower the level of glucose in the body naturally (Anson et al., 2003).

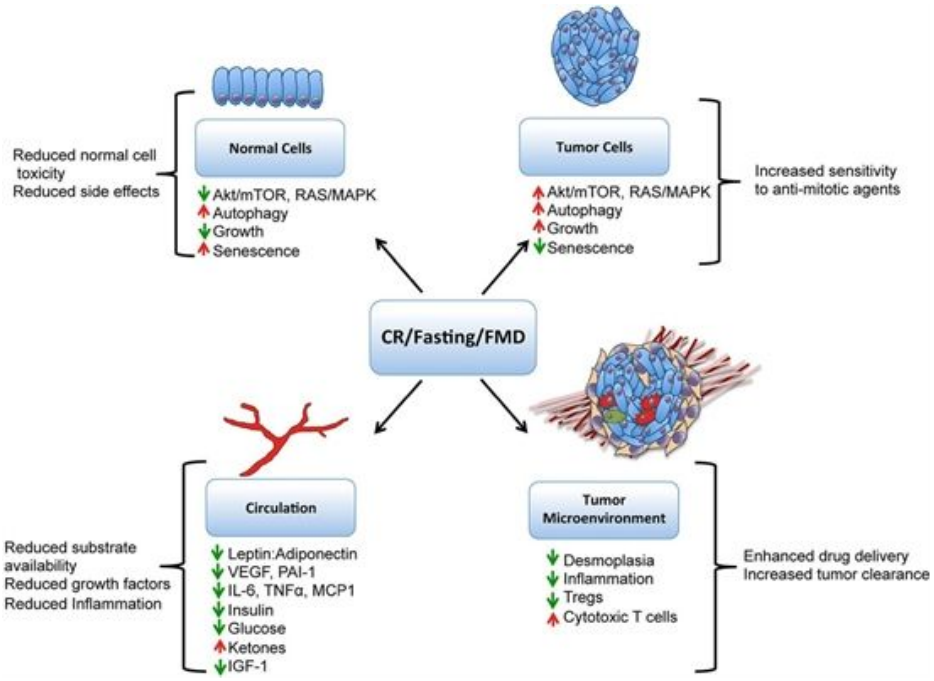

Fig. 4: O'Flanagan, 2017- Calorie restriction and Intermittent Fasting on Tumor Microenvironment, Circulation, Normal Cells, and Tumor Cells (cancerous).

Platinum based chemotherapy is the combination of multiple types of toxins during treatment, opposed to just one. These drugs dramatically elevate glucose levels in the body, causing damage to the patient's overall health. By fasting, it naturally lowers the glucose levels of the body and causes the body to become less sensitive to the toxins, as well as making the cancer cells more susceptible to chemotherapy, which is referred to as differential stress resistance (DSR) (Bauersfeld et al., 2018). Researcher Dr. Valter Longo, from University of Southern California (USC) Keck School of Medicine, found that by fasting before chemotherapy sessions, the body naturally decreased glucose levels and creates an extreme environment that the cancer cells are not able to adapt to, which ultimately leads to the decline of the reproduction of cancerous cells. During IF, the body becomes starved, and in this process the organisms will use their energy for cell maintenance, and decrease the amount of energy available for growth and reproduction (Naveed et al., 2014). Metastasis can only occur in cancer cells through growth and reproduction, so during starvation, since the body reduces the amount of energy the cells are allocated for growth, they die quickly. The cells die due to a process in the body known as autophagy, a physiological process in which cells disassemble older cells in order to start to make new ones (Bauersfeld et al., 2018). When cells are placed in stressful environments, autophagy allows cells to survive from the stress, like nutrient deprivation, and allows them to withstand internal stresses as well. However, when cancer cells enter the autophagy process they are not able to reproduce once they have destroyed themselves. The use of alternate day fasting has been proven to increase the radiosensitivity of mammary tumors in mice, or how well the tumors are able to be attacked during radiation treatments, which is due to the phenomenon of increased oxidative stress within the cancerous cells (O'Flanagan et al., 2017). During the

oxidative stress, the cancerous cell's DNA strands break apart because the cell is not able to properly function without sufficient amounts of glucose. Furthermore, it was studied in yeast that the PKA Msn2/4 pathway is activated by glucose, which makes the cells more resistant to stress. Additionally, Dr. Longo theorized that this pathway is similar to the PKA/EGR1 pathway in its reaction to glucose during chemotherapy; when more glucose is present, the cell becomes more resistant to stress (Biase et al., 2017).

Additionally, the specific effects of Rapamycin in mTOR signalling pathways were examined. mTOR pathways are the "master regulators of cell growth and metabolism" in the human body, which is why they play an important role in chemotherapy toxins (Li et al., 2015). These pathway regulators are found to be involved in many diseases, including cancer and diabetes.

Similar to the fasting trials tested on rhesus monkeys, the department of Cellular and Structural Biology at the University of Oxford studied the drug Rapamycin in mice with an IF diet. They reduced the caloric intake of the mice by 40% and they were given 14 ppm of Rapamycin. In result analysis, they found that dietary restriction (DR) altered nutrient pathways in the body and each pathway changed in different ways, but ultimately it increased the lifespan of the mice being tested (Fok et al., 2012). The mice that had elongated lifespans were able to stay alive longer than the control group that did not fast due to resistance against the development of age related diseases and the prevention of metastasis within their bodies. The mice that had metastasis had cancer spread quickly throughout the body and reduced their lifespan by taking over their healthy cells.

Purpose

The purpose of this study to evaluate whether or not IF can be utilized to to decrease the amount of chemotherapy symptoms cancer patients have and overall improve patient quality of life. Moreover, it examines which length time period is the most beneficial and feasible to complete: 24 hours, 48 hours, or 72 hours. This study also investigates if there is a correlation between daily caloric intake and obesity rates to determine if glucose is a common factor in cancer rates increasing.

Importance

Recently, the World Health Organization discovered that cancer is the second leading cause of death in the world, and will soon become the primary cause of death due to the increasing amounts of cancer cases each year; with this, more than half a million people in the United States alone endure chemotherapy sessions (Eslami et al., 2012). The long term importance of this study is to lead to the improvement of tolerance and the effectiveness of chemotherapy to decrease the risk of tumor reappearances, along with increasing the quality of life patients experience while having treatment. Fasting has been reported by patients to reduce nausea, fatigue, and overall discomfort while receiving the treatment, and they feel as if they have more energy to continue normally with their lives in the days post treatment. In 2012, there were more than 14 million new cases of cancer, along with 8.2 million cancer related deaths; by improving the QOL during chemotherapy, it would be assisting millions of people worldwide annually (Nair et al., 2016).

Research Question

What period of intermittent fasting is most effective in chemotherapy and beneficial to quality of life in cancer patients?

Hypothesis

Null Hypothesis: There is no indication that intermittent fasting is beneficial to chemotherapy patients in regards to both their quality of life and effectiveness.

Alternative Hypothesis: Glucose alters the effectiveness of chemotherapy, therefore a fasting period would be sufficient to lower glucose levels and improve patient quality of life.

Methods

The research study design was conducted through systematic literature review. All included articles and sources were collected from published, online databases, which included Ebscohost, PubMed- NCBI, PLOS, Google Scholar, NIH and BMC Cancer and Medicine. The articles used in this paper and online databases were given access to by Thousand Oaks High School and mentors at the Casa Colina Research Institute, as well as mentors who are of Ph.D. level and experts on the topic of intermittent fasting and caloric restriction in regards to aging.

Keywords such as intermittent fasting, caloric restriction, starvation, platinum-based chemotherapy, glucose levels, cancer rate trends, chemotherapy symptoms, differential cell resistance, Rapamycin, Doxorubicin, quality of life, and oxidative stress were used to search the databases for pertinent information. Of all the academic, peer reviewed papers, 30-40 were then selected to be analyzed, annotated, and summarized.

The entirety of the research has been conducted within the last decade, as the oldest article used in this study was written in 2003, while a majority of the papers fall within the years of 2012-2016. Because IF is a fairly new topic in the scientific field, all relevant data that was used was collected within the last five years.

Systematic literature review was used for data collection because secondary data analysis did not provide enough information in order to find relevant information to the research question in one research paper. Multiple sources were used and data sets relating to quality of life and changes in glucose levels after IF or chemotherapy sessions were used.

Additional data was collected in order to analyze cancer rate trends compared to daily caloric intake from the years of 1976-2013 in graphs, and found correlations between the two to show how glucose has impacted cancer throughout history.

Results

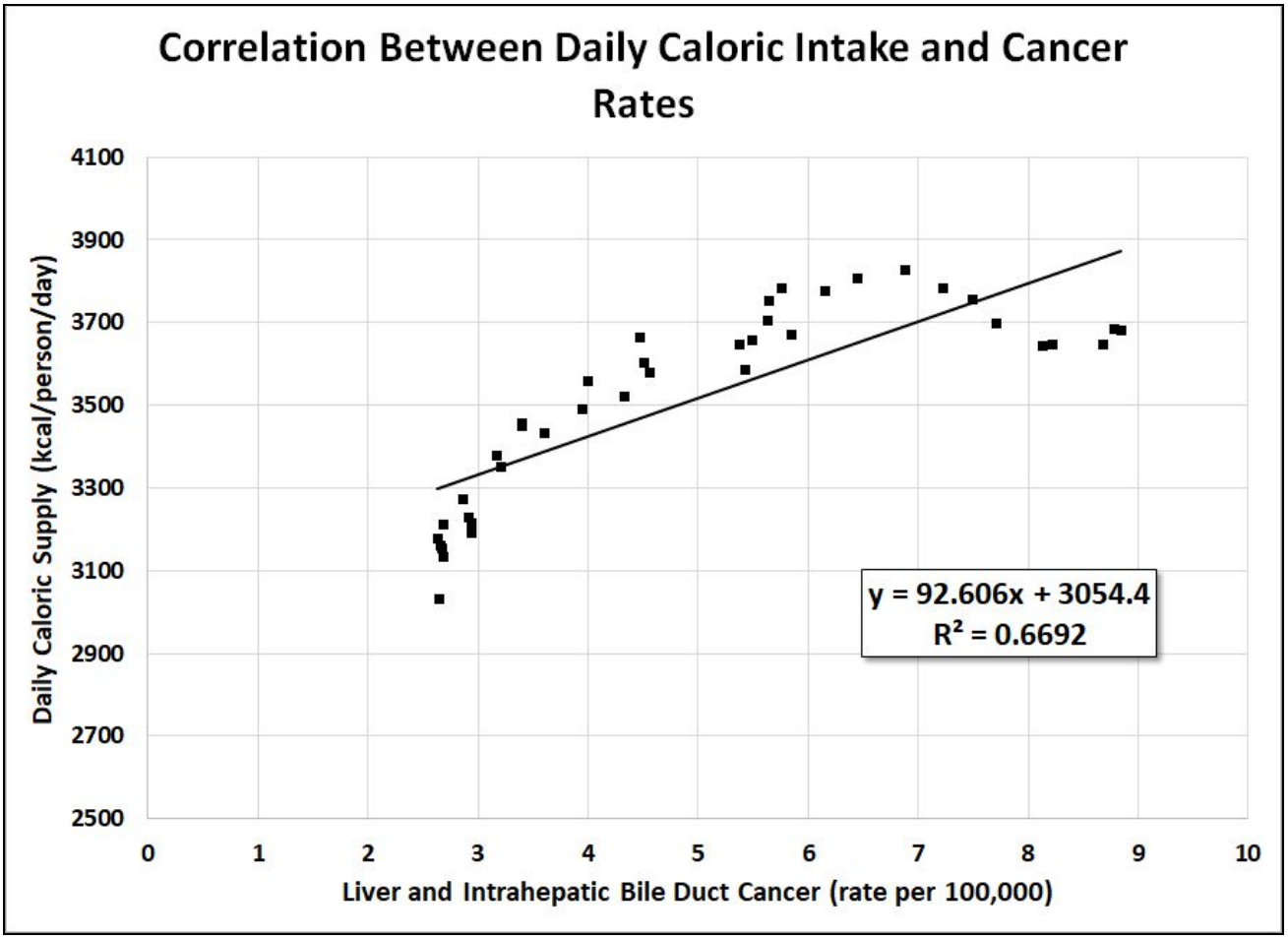

Fig. 5- R^2=0.6692; The correlation between Liver and Intrahepatic Bile Duct Cancer (rate per 100,000) and daily caloric intake (kcal/person/day) through the years of 1976-2013.

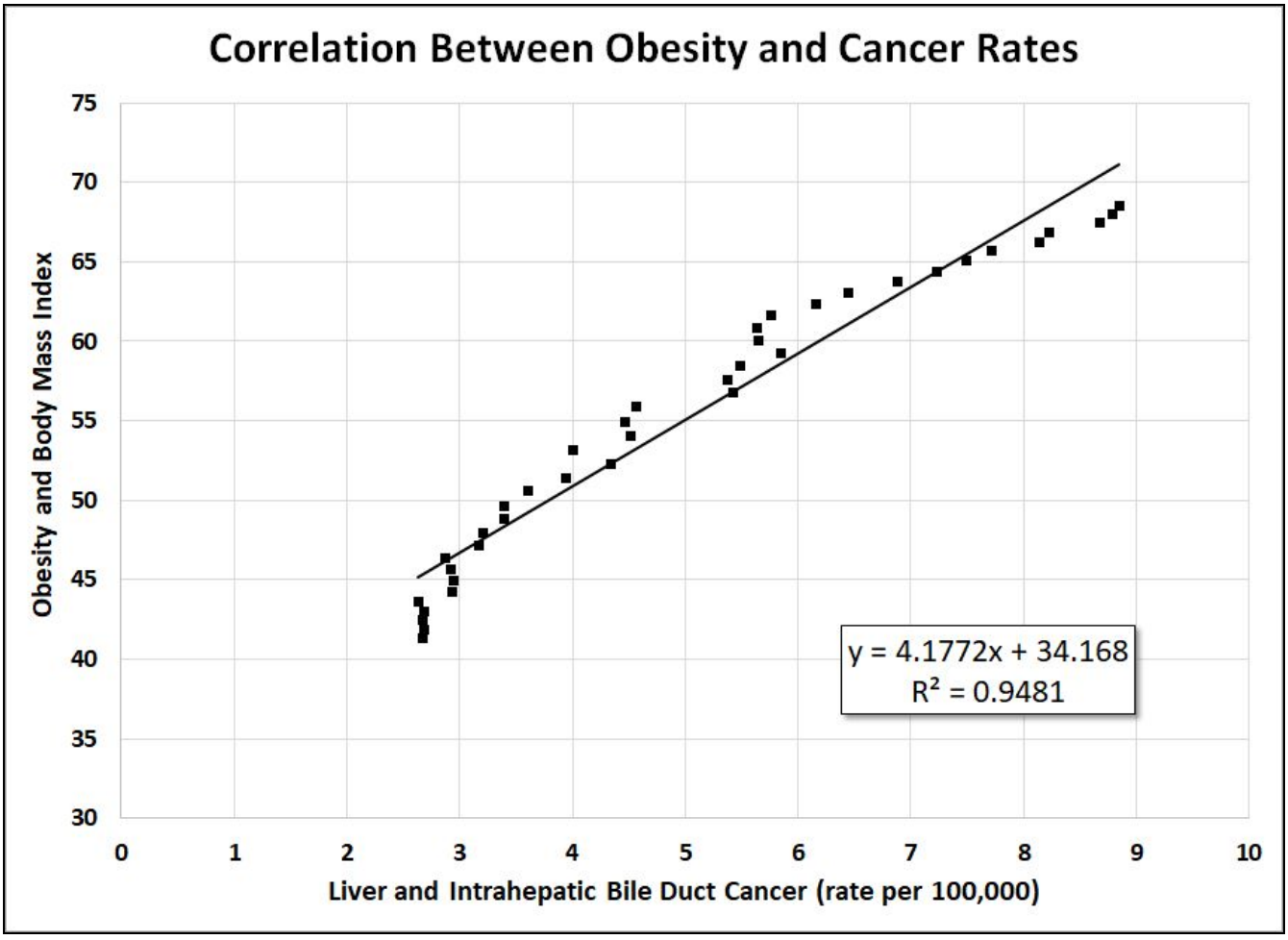

Fig. 6- R^2=0.9481; The correlation between Liver and Intrahepatic Bile Duct Cancer (rate per 100,000) and obesity and body mass index in the United States through the years of 1976-2013.

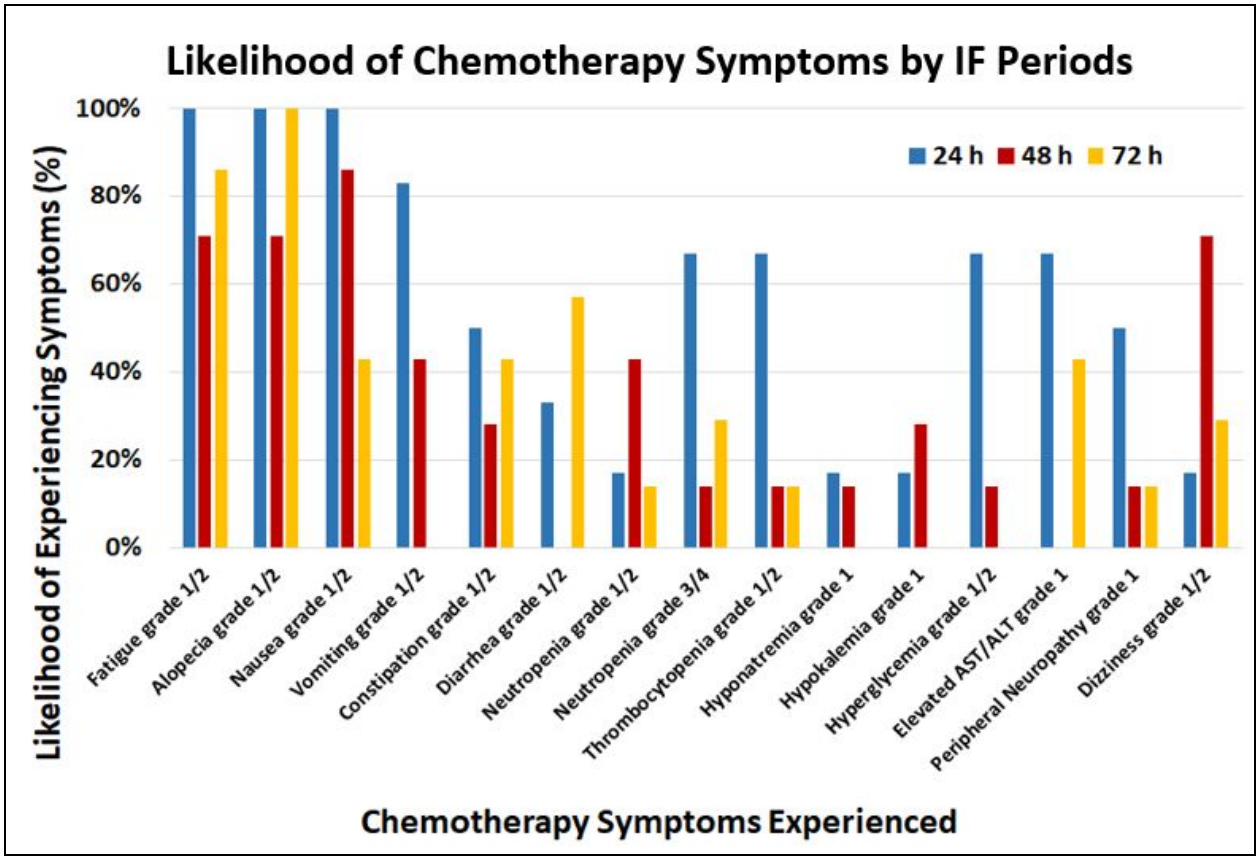

Fig. 7- Chemotherapy toxicity patient symptom occurrence shown at 24 hours, 48 hours, and 72 hours.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No symptoms	Asymptomatic, mild symptoms	Moderate symptoms, does not completely affect daily routine	Severe symptoms, associated with pain, affects daily routine	Extreme symptoms, intervention necessary

Fig. 8- Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) grade scale of 0-4

Chemotherapy Symptom	Ad Lib (CTC Grade)	STF (CTC Grade)
Fatigue	3	1.5
Weakness	2.9	1.5
Alopecia (Hair Loss)	2.5	1.85
Headaches	1	0.85
Nausea	1.6	0.55
Vomitting	1.2	0.15
Diarrhea	0.5	0.25
Abdominal Cramps	1	0.55
Mouth Sores	1.3	0.55
Dry Mouth	1.7	0.75
Short-Term Memory Impairment	1.3	0.95
Numbness	1.6	1.35
Tingling	1.6	1.35
Neuropathy-motor	1	1
Mean	1.585714286	0.939285714
Standard Deviation	0.738873511	0.511099332
Variance	0.545934066	0.261222527
n	14	14
t-test	0.012252	

Table 1- p=0.012252; Average of chemotherapy symptoms experienced by patients according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI)

Discussion

In figure four, a correlation with an r-squared value of 0.9481 was found between the rates of obesity and body mass index and liver and intrahepatic bile duct cancer through the years of 1976-2013. Both variables showed an increase of values through the years and as obesity rates have increased, cancer rates have also increased. Obesity is caused by more caloric intake compared to energy expenditure, which can cause extra glucose to remain in the body. Because

of this, the higher glucose and caloric rates have a correlation between cancer rates; as the daily caloric intake of people increase, cancer rates increase as well.

A correlation with an r-squared value of 0.9481 was also found between the rates of obesity and daily caloric intake through the years of 1976-2013. As society has grown and evolved through time, food has become a focal point in people's lives, and it has become a commodity that is no longer hard to obtain. In 1970, the malnourishment rates in developing countries was 34.75%, while in 2015 it was found to only be 12.5% (Rosner et al., 2019). With the decline in malnourishment seen across the world, there has also been a staggering increase in rates of cancer; the correlation found in figure five shows that cancer rates are correlated to daily caloric intake, with an r-squared value of 0.6692. With a correlation between caloric intake and cancer rates, intermittent fasting is shown as a beneficial way to reduce glucose levels in the body. By reducing caloric intake, it would likely decrease cancer rates seen in the United States as well.

Furthermore, as seen in table one, a total of six patient cases were compiled and cancer patients were asked to self evaluate their chemotherapy symptoms for fasting for a time period of 72 hours prior to the session and non-fasting prior to their session using Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI). The CTCAE grading scale, as described in figure eight, is from 0-4, where four is experiencing the symptom the most and zero is no experience of the symptom. Table one is an average of all the patient cases that were collected for each symptom. During chemotherapy with Ad Lib eating, patients had an overall average CTC value of 1.5857, while during intermittent fasting time periods, they had an overall decreased average CTC value of 0.9392. Using a t-test, it was found that the

p-value of the intermittent fasting and Ad Lib eating was 0.012252, and when compared to a p-value of 0.05, the alternative hypothesis must be accepted and the null hypothesis is rejected. This means that intermittent fasting is a feasible way of lowering the body's glucose levels and overall improves patient quality of life through lowering the grade of chemotherapy symptoms experienced.

In figure seven, there was a decrease in almost all patient symptoms from the 24 h to the 48 h fasting period, but from the 48 h to the 72 h fasting period results varied from having both positive and negative effects. From this, it was concluded that a 48 h fasting period would be the most beneficial IF length for patients to complete because it is the most efficient time period for lowering chemotherapy symptoms, so it would overall be increasing the quality of life for patients. Although the 72 h fasting period did provide some additional benefits for symptoms such as Hyponatremia and Hypokalemia, symptoms such as fatigue (grade 1), Alopecia, and Diarrhea (grade 1 and 2) increased (Dorff et al., 2016).

Moreover, it was observed that it is more feasible for patients to complete a 48 h fasting period than a 24 h period; this is shown through the number of participants who were able to fully complete a 48 h IF period versus a full 72 h IF period. In certain studies evaluated, data sets for the 72 hour time period had to be revised in order to take out data from patients who were not able to fully fast for 72 hours before every chemotherapy session. When patients were questioned whether or not they fully completed their fasting session, if they were not able to even for one chemotherapy session, it could affect their CTCAE level experienced, so their data was taken out of the sets. Ultimately, by decreasing the amount of patient symptoms

experienced, it can be concluded that the overall quality of life that the patients have is increased dramatically through fasting period of 48 hours.

The results shown above means that a 48 h fasting period is worthwhile to patients, but in different cases only sometimes would a 72 h fasting period be beneficial. Moreover, this was completed on a small pool of patients so if one was an outlier it could throw the data set off. In the graph, it shows a substantial difference (a decrease) from the 24 h to 48 h fasting period.

Conclusions

The 48 hour fasting period is overall the most favorable time period for cancer patients to fast for because it maximizes the decrease of chemotherapy symptoms experienced by patients when compared to a 24 hour or 72 hour time period. Additionally, the 48 hour time period is a more feasible time length for patients to fast for opposed to a 3 day fast, which is the 72 hour time period. There is also a correlation between obesity and cancer rates; as both obesity and caloric intake rates increased throughout the years of 1976-2013, there was also a correlation between the two and cancer rates increasing likewise.

Limitations

No research was completed on Insulin levels as an artificial way to lower the glucose levels in the body, which limited findings on which method would be the most beneficial way to lower glucose levels. Although it was found that the 48 h time period would be the most efficient and feasible time period, due to limitations of data the fasting time period efficiency could not be compared to insulin being used to lower glucose levels, which could potentially be a

better method for patients. If insulin had been tested and proven to be more efficient with lowering patient symptoms during chemotherapy and sufficiently lowered glucose levels, it would be a better option for patients because it would increase their quality of life through allowing them to eat and not have to fast for two days.

Additionally, this project only focuses on glucose as an independent variable to cancer rates and chemotherapy symptoms, or the dependent variables. However, there are more factors that can affect cancer rate increases; for instance, smoking is a major cause of lung cancer and alcohol is a main factor of liver and bowel cancer. This project was not able to take into account these other outside factors when examining the correlations between obesity, daily caloric intake, and cancer rates through the years of 1976-2013; other outside factors could have affected the rise of cancer rates during certain time periods.

Finally, the number of papers and patients that were available to this study was limited due to minimal research on this fairly new topic in the scientific field; intermittent fasting during chemotherapy has only been analyzed in humans within the last ten years. For future research on this subject, larger data sets would be necessary. With larger data sets, cancer types can be isolated for separate data tables to ensure that the type of cancer that the patient has does does not affect the types of symptoms that they are experiencing.

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