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NARRATIVE REVIEW

Safety and Feasibility of Intermittent Fasting During Chemotherapy for Breast Cancer

A Review of the Literature

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Intermittent fasting has been shown to protect healthy cells from chemotherapy toxicity while sensitizing cancer cells, but the extent to which fasting is safe and feasible for individuals during chemotherapy is unknown. The studies reviewed demonstrate that for well-nourished women with breast cancer, intermittent fasting between 24 and 72 hours can be safe and feasible as determined by treatment side effects, blood work, adherence to a fasting protocol, and quality of life. Fasting is not without potential adverse side effects and limitations. Further research is needed to standardize optimal length of fasting and determine whether limited caloric intake is beneficial while fasting during chemotherapy. **Key words:** *breast cancer*, *chemotherapy*, *feasibility*, *intermittent fasting*, *safety*, *toxicity*

BREAST CANCER is the second most common type of cancer in women, and the second leading cause of death from cancer among women in the United States.[1] Once diagnosed with breast cancer, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines have specific breast cancer treatment recommendations and algorithms that take into consideration pathology, stage of cancer, and hormone receptor status.[2] Traditional treatment options can include surgery, chemotherapy, radiation therapy, and/or endocrine therapy.[2] Cancer treatments are evolving to include targeted therapies as research is shedding light on human genomics and oncology biomarkers such as cells, molecules, genes, enzymes, and hormones that can be targeted for cancer treatments.[3] These targeted therapies involve drugs developed for specific cancer cellular mutations.[3] Immunotherapy is one type of targeted therapy.[3] The immune system does not always recognize cancer cells as harmful or is not strong enough to hinder the rapid growth of cancer cells. The goal of immunotherapy is to alter this immune response by increasing tumor-specific T cells, which control the immune response by either indirectly or directly causing immune-mediated cell death.[3]

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Immunotherapy can also use checkpoint inhibitors, which block proteins that otherwise prevent the immune system from killing cancer cells.[3]

Nutrition-specific side effects common with chemotherapy include decreased appetite, mouth sores, stomatitis, nausea, vomiting, and diarrhea.[4] Targeted therapies, on the other hand, have unique side effects including rash, diarrhea, hypertension, hypothyroidism, and proteinurea.[4] Side effects occur when the drug mechanism that targets cancer cells also affects the physiologic function of healthy cells, which can be indicators of the drug's efficacy.[4] Off-target side effects are not related to the drug's cancer fighting mechanism.[4] The degree of side effects from cancer therapy toxicities is measured using the Common Terminology Criteria for Adverse Events (CTCAE), which standardize adverse side effects by grade, with grade I being minimal adverse effect and grade V being death.[5] Of note, there is a higher incidence of grade III diarrhea with several targeted therapies used to treat breast cancer, particularly when used in combination with other systemic treatments.[4]

Nutrition recommendations for people being treated for breast cancer are individualized.[6] Treatment toxicities can lead to various nutrition-related side effects, which, in turn, can lead to suboptimal dietary intake and unintentional weight loss.[7] Therefore, it is important to formulate nutrition recommendations that will promote tolerance to treatment and improve the chance of a good prognosis. Registered dietitian nutritionists (RDNs) utilize specific diet recommendations for symptom management during treatment that may involve altering the consistency, taste, or nutrient content of food consumed.[8] Alternatively, when patients are not experiencing side effects related to treatment, the American Institute for Cancer Research (AICR) recommends a plant-based diet rich in fruits, vegetables, whole grains, beans, and legumes.[9]

At the same time, food intake during cancer treatment is integral to quality of life. For instance, Vance et al[10] acknowledged that food is a coping mechanism for some women with breast cancer and psychosocial factors such as stress and anxiety led to increased consumption of comfort foods. RDNs often help patients find a balance between the AICR plant-based recommendations and maintaining quality of life by not prohibiting comfort foods. A literature review by Reich et al[11] found that the prevalence of depression among patients with early-stage breast cancer is double that of what is seen in the general female population. Discussions about how their diagnosis and treatment impact quality of life contributed to increased anxiety and depression among patients with breast cancer.[11] As such, diet recommendations that impact quality of life and contribute to anxiety should be made with caution to women who are at a higher risk for depression after a breast cancer diagnosis than those without the diagnosis.[11]

A unique nutrition intervention that is gaining popularity in clinical practice and could potentially negatively impact quality of life is fasting.[12] While the term *fasting* is defined as "to eat sparingly or abstain from some foods,"[13] it has been used inconsistently as a nutrition intervention and can occur in several different ways.[12] For the purpose of this literature review, fasting refers to intermittent fasting where calorie intake is restricted on certain days and unrestricted on other days during a chemotherapy cycle.[12] Fasting protocols vary by when they occur during the chemotherapy cycle as well as the extent and duration of the fast.[12]

MECHANISMS OF INTERMITTENT FASTING IN CANCER

Cancer occurs through a combination of mutations and damage to deoxyribonucleic acid (DNA) that lead to atypical rapid reproduction of cells.[14] Those mutations in cancer cells make them less able to adapt to extreme environments such as those created during fasting.[15] Conversely, healthy cells enter a self-maintenance phase in response to

fasting.[15] The primary mechanisms explaining the benefits of fasting related to cancer are known as differential stress resistance (DSR), which protects healthy cells from chemotherapy toxicity, and differential stress sensitization (DSS), which sensitizes cancer cells to the chemotherapy.[15] This occurs because fasting reduces the levels of circulating hormones and metabolites in the body including glucose, insulin, and insulin-like growth factor-1 (IGF-1), which signals healthy cells to reduce cell division and growth, thereby protecting them from chemotherapy.[15] In addition to protecting healthy cells against chemotherapy toxicity, fasting has also been shown to promote the regeneration of stem cells in the nervous system, muscle and liver damaged by chemotherapy, as well as regenerate white blood cells.[16]

Furthermore, fasting reduces the expression of heme oxygenase-1 (HO-1), a protein that protects cancer cells from cell death, thereby sensitizing the cancer cells to chemotherapy and inducing apoptosis.[15] Fasting also inhibits the development of new blood vessels in tumors that prevents tumor growth in animals.[14]

In vitro and animal studies suggest that fasting protects healthy cells from chemotherapy toxicities.[17-20] In a case series report, Safdie et al[21] compiled some of the initial data on fasting in humans and described its effects on 10 cases of patients who were diagnosed with a variety of cancers. The participants voluntarily fasted for 48 to 140 hours prior to chemotherapy and for 5 to 56 hours after chemotherapy.[21] The only reported side effects were hunger, lightheadedness, and headaches, and these reported side effects did not interfere with daily life.[21] Weight that was lost was quickly regained, and self-reported chemotherapy toxicities were fewer and less severe than the expected side effects from each respective chemotherapy regimen.[21] This case series report provided valuable preliminary information upon which to base future randomized controlled trials. The purpose of this review is to evaluate the recently published literature to determine whether intermittently fasting during chemotherapy is safe and does not contribute to adverse side effects or malnutrition in women with breast cancer. This review also evaluates feasibility of intermittently fasting as defined by the ability to adhere to the fasting protocol without significantly impacting quality of life.

SEARCH STRATEGY

PubMed and CINHAL databases were used to search the literature with the MeSH terms "Fasting AND (chemotherapy OR treatment OR toxicity) AND (breast neoplasm OR breast cancer)." Articles were filtered to include studies of human adults 18 years or older that were published in English after 2013. Studies were excluded if participants had breast cancer but were not undergoing chemotherapy and if the studies only looked at breast cancer risk or breast cancer prognosis. Other studies were excluded if fasting was limited to fasting blood work and if they did not involve an intermittent fasting protocol. Reference lists were reviewed for additional articles, and systematic reviews were used to provide background information. A total of 3 studies met the inclusion criteria and were reviewed. A second search was later conducted to identify studies on fasting and targeted therapies; however, no results were found that met the inclusion criteria.

While this review specifically evaluated patients with breast cancer, studies that included patients with other cancers, in addition to patients with breast cancers, were included when relevant. The study by Bauersfeld et al[22] was chosen for this review despite including 4 patients with ovarian cancer in addition to 29 patients with breast cancer and 1 patient with advanced breast cancer as they studied the effects of intermittent fasting on quality of life.

The study by Dorff et al[23] was also included in the review despite including men and several other cancers (urothelial, non–small cell lung cancer, ovarian, and uterine)

in addition to breast cancer in the same analysis because those with breast cancer were all treated with docetaxel, carboplatin, and trastuzumab, which represented the standard-of-care chemotherapy for patients with HER2-positive breast cancer.[2] Pertuzumab was not added to the NCCN guidelines until 2017, which was after this study was published in 2016.[2] This study, in addition to the study by de Groot et al,[24] provided valuable insight into fasting in relation to 2 different standard-of-care chemotherapy regimens for patients with breast cancer.

LITERATURE REVIEW

Safety of intermittent fasting

de Groot et al[24] randomized 7 women with HER2-negative stage II and III breast cancer to fast for 24 hours before their chemotherapy regimen of docetaxel, doxorubicin, and cyclophosphamide until 24 hours after the chemotherapy. These women were permitted to drink water and sugarless coffee and tea during the fasting time period.[24] Six women were randomized to the nonfasting group and instructed to eat a healthy diet with a minimum of 2 pieces of fruit each day.[24] Tolerance to fasting was measured by finishing all 6 cycles of chemotherapy and adjusting the chemotherapy regimen was not needed.[24] There were no statistically significant differences in grade I/II or grade III/IV toxicity between the 2 groups, and no grade V toxicity occurred in either group as measured by CTCAE version 4.03.[24] While fasting did not contribute to toxicities, fasting also did not lessen patient-reported chemotherapy toxicities.[24]

Similarly, Bauersfeld et al[22] conducted a randomized crossover study where participants were instructed to fast around chemotherapy, but their protocol differed in several important ways. Participants had breast cancer (n = 29), advanced breast cancer (n = 1), and ovarian cancer (n = 4) and were randomized to one of 2 groups.[22] The first group (n = 18) was instructed to fast for 36 hours before chemotherapy and for 24 hours after chemotherapy for the first 3 chemotherapies and then follow a Mediterranean diet for the last 3 chemotherapies.[22] The second group (n = 16) was instructed to follow a Mediterranean diet for the first 3 chemotherapies, followed by the fasting protocol for the final 3 chemotherapies.[22] Those participants with breast cancer were treated with several different regimens that included cyclophosphamide, epirubicin ± paclitaxel; fluorouracil, epirubicin, cyclophosphamide, docetaxel ± trastuzumab; doxorubicin, cyclophosphamide, paclitaxel; and docetaxel, pertuzumab, trastuzumab.[22] There were no significant ($P > .3$) changes in weight in the fasting group versus the nonfasting group.[22] All reported side effects of fasting in both groups were low grade (grade I or II) and included headache, hunger, nausea after intake of broth or juice, and one orthostatic reaction.[22]

Dorff et al, on the other hand, took a systematic approach by increasing the length of the fast at each platinum-based chemotherapy cycle only when the participants (n = 20) met certain criteria demonstrating tolerance to the fast.[23] The first criterion for safety was defined as 3 or more compliant participants who did not experience a fasting-related side effect requiring hospitalization during the fasting period unless it was related to the disease or treatments.[23] A second criterion of safety was whether 3 or more compliant participants did not experience grade III+ adverse events not related to the disease or treatments as measured by CTCAE version 4.0.[23] Participants started with fasting for 24 hours before chemotherapy.[23] If safety criteria were met, the length of the fast was gradually increased in each cycle, with the maximum length of fasting being 72 hours.[23] No evidence of malnutrition was found in this study, which was measured by prealbumin.[23] However, in the 48-hour cohort, one of the 6 participants did not regain 25% of the weight that was lost during the rest of the treatment cycle so that participant could not fast again.[23] Fasting-related

symptoms were grades I and II and included headache, dizziness, hypoglycemia, grade I weight loss, hyponatremia, and hypotension.[23] There were no grade III or IV fasting-related toxicities reported.[23] The number of participants with reported nausea and vomiting significantly decreased as the length of the fast increased ($P = .019$, for nausea; $P = .003$, for vomiting).[23]

Each of these studies concluded that intermittent fasting is safe during the respective chemotherapy regimens where safety was measured or defined by lack of toxicity, weight loss, and malnutrition (measured using prealbumin as a surrogate marker).[22-24] Of note, while fasting did not contribute to toxicity, de Groot et al[24] were unable to demonstrate a benefit to fasting in reducing symptoms of toxicity as compared with following a healthy diet, whereas Dorff et al[23] demonstrated a significant decrease in nausea and vomiting toxicities as the length of fasting increased.

In addition to measuring safety in terms of measurable toxicity, de Groot et al[24] and Dorff et al[23] also evaluated safety by analyzing biochemical blood work. de Groot et al[24] found that in the fasting group, glucose was significantly increased between the baseline value at randomization and the median value immediately before each chemotherapy ($P = .042$), but there was no significant difference in median insulin level between the 2 time points. Similarly, Dorff et al[23] included biochemical blood work and found that among compliant participants, blood glucose and insulin did not change significantly between fasting cohorts. The proposed mechanisms of fasting indicate that fasting reduces the levels of glucose and insulin circulating in the body.[15] Although glucose and insulin levels were not reduced in these 2 studies as would be expected by the proposed mechanisms of fasting,[15] de Groot et al[24] demonstrated that fasting was safe in that insulin levels were not significantly increased as a result of fasting and Dorff et al[23] demonstrated safety as neither blood glucose nor insulin was increased as a result of fasting.

Feasibility of intermittent fasting

In the study by de Groot et al,[24] inconsistent feasibility of the fasting protocol was demonstrated by participant adherence. Although 2 of the 7 (28.5%) participants did withdraw from the fasting group after the third chemotherapy cycle due to heartburn and neutropenia, these side effects persisted on the regular diet as well, so the authors had difficulty determining causation of the side effects and could not attribute them directly to fasting.[24]

While the protocol by Dorff et al[23] may have improved adherence and feasibility by allowing some caloric consumption, adherence to the protocol was also inconsistent and difficult for some participants. If participants experienced symptoms as a result of fasting such as feeling weak or dizzy, they were instructed to consume rescue food in the form of a small amount of food or juice while staying under 200 calories in 24 hours.[23] Thirteen of the 20 (65%) total participants reported consuming less than 200 calories in 24 hours.[23] In the 72-hour cohort, all of the participants consumed some calories but only 4 of the 20 (20%) participants consumed less than 200 calories in 24 hours as they were instructed.[23] In the other cohorts, reasons for noncompliance with the fasting protocol included forgetting and social limitations of fasting.[23] Fasting was also not feasible for 1 participant in the 48-hour cohort who did not regain 25% of the lost weight and could not fast again.[23]

Similarly, Bauersfeld et al[22] allowed for calorie consumption as part of their protocol. While fasting, participants were allowed water, herbal tea, 2 × 100 calorie vegetable juice, and small standardized amounts of light vegetable broth for a maximum total caloric intake of 350 calories per day.[22] Bauersfeld et al[22] also demonstrated inconsistent results with regard to adherence and feasibility. On the one hand, 5 of 50 (10%) participants who were recruited to the study withdrew from fasting due to side effects including headaches, hyperventilating during the first chemotherapy, general subjective weakness,

and a self-reported aversion to fasting.[22] These 5 participants were not evaluated as part of the statistical analysis, which possibly led to reporting false-positive benefits of fasting.[22] An additional 8 of the 50 (16%) subjects recruited could not be evaluated because of noncompliance with the study.[22] Telephone interviews determined reasons for not completing the study, which were time restrictions and unwillingness to fill out study documents.[22] It was determined that those 8 subjects did not dropout related to the fasting protocol.[22] On the other hand, when looking at the patients who completed the study and who were statistically evaluated (n = 34), 5 of the 18 (28%) participants who started in the fasting group declined to switch to the Mediterranean diet, which supports feasibility.[22]

In these 3 studies, intermittent fasting was generally feasible for the majority of participants who were able to adhere to the fasting protocol but not for all.[22-24] de Groot et al[24] were able to demonstrate that fasting by the traditional definition of allowing no calories[13] was feasible for 5 of the 7 participants in the fasting group.[24] Alternatively, the articles by Dorff et al[23] and Bauersfeld et al[22] suggested that a minimal amount of calories may promote feasibility in that 200 to 350 calories were allowed in their fasting protocols.

Impact of fasting on quality of life

Bauersfeld et al[22] addressed quality of life, using the Functional Assessment of Chronic Illness Therapy tool, which addresses relevant disease-, treatment-, or condition-related issues by using a total of 4 different scales and subscales. Those participants who started with fasting reported better quality of life and less fatigue than those following the Mediterranean diet on each of the 4 scales ([95% CI, 65.9-76.3] $P = .041$; [95% CI, 30.2-37.6] $P = .006$; [95% CI, 59-72.9; $P = .009$; [95% CI, 96.6-113.5 $P = .013$).[22] This same benefit was not found with the group that fasted for the last 3 chemotherapy treatments after following the Mediterranean diet.[22] Benefits on quality of life can support both the safety and feasibility of intermittently fasting. If there is a benefit to quality of life, it is unlikely that participants are experiencing significant nutrition-related side effects (demonstrating safety), which, in turn, potentially makes it more feasible to comply with the fasting protocol.

DISCUSSION

All 3 studies indicated that intermittently fasting was safe in terms of not contributing to measurable side effects of chemotherapy.[22-24] In fact, Dorff et al[23] demonstrated that the number of participants with nausea and vomiting decreased as the length of the fast increased and Bauersfeld et al[22] demonstrated an improvement in quality of life and fatigue in participants who started chemotherapy after following the fasting protocol. In addition, de Groot et al[24] and Dorff et al[23] evinced safety when analyzing biochemical laboratory work as insulin was not increased in the first study[24] and neither glucose nor insulin was increased in the second study.[23] Most, but not all, of the participants in each study were also able to adhere to the fasting protocol, demonstrating inconsistent feasibility of fasting during chemotherapy.[22-24] Each of the 3 fasting protocols also included provisions of adequate hydration,[22-24] which is important because severe dehydration can be life-threatening and should be avoided even if caloric intake is restricted.[25]

However, each study differed in several important ways that make it difficult to compare and make recommendations for clinical practice as a result of this review. One such limitation is related to the nutritional status of participants. In each study, participants only met eligibility criteria if they were not malnourished before starting the fasting regimen. de Groot et al[24] and Bauersfeld et al[22] excluded participants with a body mass index (BMI) of less than 19 kg/m^2. Dorff et al[23] excluded participants with a BMI of less than 20.5 kg/m^2 or with greater than 10% weight loss in the previous year. Therefore, the results of these

studies cannot be generalized to anyone with a low BMI.

Although many clinicians characterize malnutrition based on weight, making unintentional weight loss and low BMI important safety criteria to consider, Dorff et al[23] also used prealbumin as a marker of malnutrition. Prealbumin is a negative acute-phase protein that is affected by physiological stress, among other factors, and should not be used to independently define malnutrition.[26] However, prealbumin is commonly used to determine the severity of inflammation, which may shed light on the cause of malnutrition, especially in those with cancer.[26-29] While Dorff et al[23] did not find any significant differences in prealbumin, they did not have prealbumin values available for every patient, which impacts validity, so concluding that there was no evidence of malnutrition is questionable.

A second limitation of all 3 studies was the small sample sizes used (de Groot et al[24]: n = 13; Bauersfeld et al[22]: n = 34; Dorff et al[23]: n = 20). Before intermittent fasting can be routinely applied in clinical practice, larger randomized controlled trials will need to be completed.

The final limitation is that both Bauersfeld et al[22] and Dorff et al[23] allowed for minimal caloric intake as part of their fasting protocol. Bauersfeld et al[22] specified the types of calories allowed in their protocol and indicated that caloric intake was not to exceed 350 calories per day, but Dorff et al[23] only specified the amount of calories allowed. Therefore, in the study by Dorff et al,[23] calories consumed were likely variable. Standardizing both the types and quantity of calories allowed would minimize confounding variables that could potentially impact measurable outcomes. Furthermore, if a fasting protocol is only feasible because caloric intake is required to mitigate side effects and prevent weight loss, it is questionable whether that protocol is in fact fasting. Consuming calories could contribute to perceived improved quality of life, which may be an important aspect for acceptability.

Also of note, in the Bauersfeld et al[22] study, only the group that started with the fasting protocol, before switching to the Mediterranean diet, demonstrated a significant benefit on quality of life. One explanation offered by the authors is that fasting can prevent negative effects before they happen rather than after they happen.[22] This could be related to the DSR.[15] If fasting is known to protect healthy cells, the cumulative damage from chemotherapy could have already happened in the second group during the first 3 cycles of nonfasting.

In addition, DSR is said to occur because fasting limits the amount of glucose and insulin (among other hormones and metabolites) circulating in the body.[15] However, neither de Groot et al[24] nor Dorff et al[23] were able to demonstrate reduced levels of insulin and glucose when analyzing biochemical blood work. In fact, glucose was significantly increased ($P = .042$) in the study by de Groot et al.[24] Dexamethasone is a corticosteroid that was used as a chemotherapy premedication in these 2 studies to decrease emesis, fluid retention, and hypersensitivity to docetaxel.[23,24] Dexamethasone causes hyperglycemia and hyperinsulinemia, so dexamethasone could have hindered the benefit of fasting on glucose and insulin levels.[23,24] In addition, if decreases in glucose and insulin levels are part of the mechanisms behind the DSR benefit to fasting,[15] giving dexamethasone could explain why de Groot et al[24] showed no beneficial effects of fasting on toxicity.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

While each of the studies differed in protocols and chemotherapy regimens and included some additional types of cancers, they still contribute to the current knowledge about fasting during chemotherapy. Breast cancer diagnosis and treatment are multifaceted, and these studies provided insight into the safety and feasibility of fasting in relation to 2 different standard-of-care

chemotherapies. One of the studies[22] also took quality of life into consideration in a population at a higher risk for depression.[11] While overall the studies did show that intermittently fasting is safe and generally feasible for the majority of participants who were able to adhere to the fasting protocol, given the limitations previously discussed, there is not enough evidence to routinely recommend fasting. These studies demonstrated some preliminary benefits to fasting during chemotherapy, but larger-scale randomized, clinical, controlled trials will need to be conducted. If a patient with breast cancer is interested in fasting and is not malnourished, it is worth a discussion with an RDN who can discuss safety and help the patient stay hydrated and who can monitor for tolerance based on toxicity, laboratory values, and acceptable parameters of weight loss.

CONSIDERATIONS FOR FUTURE RESEARCH

The current research on intermittently fasting during chemotherapy provides important preliminary information, but a randomized controlled trial with a much larger sample size should be completed to provide the best insight into the safety and feasibility of intermittently fasting during chemotherapy for breast cancer. The ideal study design would include only patients with breast cancer undergoing one of the standard-of-care treatment regimens. Future research should also include protocols that study the optimal length of fasting and that standardize whether caloric intake is beneficial while intermittently fasting. Current studies are variable in allowing caloric intake and present too many confounding variables on outcomes studied. Future research should consider whether decreasing the length of fasting but consuming no calories is more or less beneficial than a longer fast that allows some caloric intake on the fasting day.

Another important consideration for future research is taking into account the nutritional status of study participants. While overweight and obesity are risk factors for postmenopausal patients with breast cancer,[9] there is also a risk for malnutrition in oncology patients undergoing treatment.[7,26-29] Fasting is a restrictive way of eating, and it is reasonable to exclude participants who are malnourished at the start of chemotherapy, given poor outcomes and prognosis associated with malnutrition in oncology.[27,29] By excluding these patients, the results of a high-quality randomized controlled trial would not be applicable to malnourished patients.

Patients with breast cancer who are considered overweight or obese, on the other hand, could present an interesting population to study fasting in relation to breast cancer prevention, given what is known about the mechanisms of fasting and the association of metabolic syndrome and breast cancer.[15,30] If fasting is associated with health benefits that can reduce risk factors associated with metabolic syndrome, fasting could also have important implications on cancer prevention.[16] Future research has the potential to study not only fasting during chemotherapy but also the safety and feasibility of long-term fasting in relation to cancer prevention among those at high risk.

Finally, as the knowledge of targeted therapies continues to grow and become more widely used in cancer treatments, there is significant opportunity to study the role of diet and fasting in relation to those targeted therapies. After an extensive literature search, no studies were found to date on intermittent fasting in patients receiving immunotherapy for any cancer type.

Given what we know about cancer cellular metabolism and targeted therapies, there may be opportunities to further study the effects and possible benefits of intermittent fasting in this population. Normal cells produce energy through oxidative phosphorylation in the mitochondria.[31] However, the Warburg effect of aerobic glycolysis is a well-studied mechanism for how tumor cells adapt their metabolism to produce energy by converting glucose to lactate both with and

without the presence of oxygen to sustain the high-energy demands necessary for growth and survival.[31] Targeted therapies that disrupt this cancer cell metabolism could potentially be more effective when given in conjunction with fasting. Fasting decreases circulating glucose,[15] which is the preferential energy source of cancer.[31] Similar to other systemic treatments, fasting, through the DSS mechanism, could potentially make targeted therapies more effective by sensitizing cancer cells to targeted therapies.[15] Fasting could also potentially have a positive impact on the unique side effects associated with targeted therapies through the DSR mechanism, by protecting healthy cells from treatment toxicity.[4,15]

One such example is trastuzumab, which is a monoclonal antibody used to treat human epidermal growth factor receptor 2 (HER2) breast cancer.[2] Trastuzumab is hindered by overexpression of IGF-1 receptor (IGF-1R), a protein-coding gene, which is elevated in almost 80% of breast cancers.[32] IGF-1 binds to IGF-1R, which activates various tumor development pathways, and a high expression of IGF-1R in HER2-positive breast cancer is associated with a poorer prognosis.[32] Therefore, therapies that target IGF-1R could be potentially beneficial. Fasting could have important implications on targeted therapies by decreasing circulating IGF-1 and potentially limiting tumor development pathways.[5,32]

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