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The Impact of Fasting and Dietary Interventions on the Development and Treatment of Non-Hodgkin's Lymphomas and Other Cancers - a review

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Abstract

Introduction: The present study investigated the role of fasting and diet in the development and treatment of cancers, with a focus on non-Hodgkin's lymphomas. Dietary components and regimens have an impact on the risk of development of malignances as well as on the treatment of the disease. Cancerous subtypes react differently to various dietary compounds and regimes. Although not widely used- fasting can be valuable help in cancer treatment. In this article we show how diet modifications and restrictions can affect existing therapies.

Aim of the study: By analyzing current literature, the study aimed to understand how various dietary components and regimens influence cancer risk and treatment efficacy.

Methods: Extensive research was conducted using PubMed and Google Scholar. References from selected articles were included in the analysis.

Results: Consuming high amount of fruits and vegetables, unsaturated fats and supplementing vitamin D can reduce the risk of malignancies, with red meat, dairy products and saturated fats intake increasing it. Fasting affects lipid, glucose, protein and neuroendocrine metabolism in the way that helps the treatment of cancers. It slows down tumor growth, reduces some symptoms and improves the effects of chemotherapy. Exploring this topic further could propagate suitable diets for cancer subtypes as well as popularize fasting, which is not yet a widely known adition to standard anti-cancer treatments.

Keywords: diet; fasting , cancer, lymphomas, non-Hodgkin's lymphoma

1. Introduction and purpose

Cancer remains a leading cause of morbidity and mortality worldwide, with non-Hodgkin's lymphomas constituting a significant portion of blood cancers. Non-Hodgkin's lymphoma is a type of cancer that begins in the lymphatic system. In non-Hodgkin's lymphoma, lymphocytes grow abnormally and can form tumors throughout the body. Non-Hodgkin's lymphoma is a general category of lymphoma, that contains many subtypes from which diffuse large B-cell lymphoma and follicular lymphoma are most common. Amid the ongoing search for effective treatment strategies, the role of diet and fasting has garnered increasing attention. This study delves into the impact of various dietary components and fasting regimens on the development and treatment of cancers, particularly focusing on non-Hodgkin's lymphoma. It explores the potential of fasting and diet alterations in enhancing the efficacy of conventional cancer therapies which in case of non-Hodgkin's lymphoma are: chemotherapy, radiotherapy, targeted drug therapy, immunotherapy and bone marrow transplant, thereby offering insights into holistic cancer management approaches. By systematically analyzing current literature, this research aims to elucidate how dietary modifications can influence cancer risk and treatment outcomes. Fasting, although not widely adopted, shows promise in modulating lipid, glucose, protein, and neuroendocrine metabolism in a manner conducive to cancer treatment. This study underscores the importance of integrating dietary strategies with existing cancer treatments and advocates for further research to develop tailored diets for specific cancer subtypes and promote the benefits of fasting as an adjunctive therapy.

2. Diet

2.1 Fruits and vegetables

Consuming a variety of fruits and vegetables as part of a balanced diet is considered influential in maintaining overall health and well-being. They contain substances such as vitamins, minerals, fiber and phytochemicals which can serve as antioxidants, phytoestrogens, anti-inflammatory agents (Slavin & Lloyd, 2012). There is evidence that incorporating vegetables and fruits in a diet is associated with reducing risk of various types of neoplasms (Hurtado-Barroso et al., 2020; La Vecchia & Tavani, 1998), such as non-Hodgkin's lymphoma. They influence vary between subtypes of non-Hodgkin's lymphomas and specific products. General high consumption of fruits and vegetables lowered non-Hodgkin's lymphoma risk by 42% but the risk of Diffuse large B-cell lymphoma was lowered the most by high citrus fruit intake and the risk of follicular lymphoma was lowered the most by high intake of leafy green vegetables. High consumption of cruciferous vegetables together with green leafy vegetables showed the most beneficial effects in T- cell lymphoma. Zinc, lutein and zexanthin found in fruits and vegetables showed a beneficial effect across various subtypes (Skuladottir et al., 2006). Fruits and vegetables are an important dietary component and their inclusion in the non-Hodgkin's lymphoma patients and patients with increased non-Hodgkin's lymphoma risk should not be overlooked.

2.2 Diary products

Another major group of products consumed on a daily basis are dairy products.

Dairy products are foods produced from or containing the milk of mammals such as cows, goats, sheep, and buffalo. These products are rich in essential nutrients and are a significant part of many diets around the world.

They have different influence on neoplasm occurrence, while they seem to lower the risk of breast cancer (Arafat et al., 2023) they are found to increase the risk of non-Hodgkin's lymphoma. Highest reduction of non-Hodgkin's lymphoma risk was observed in high ice cream, milk and cheese consumption. High cheese consumption showed a lesser influence on non-Hodgkin's lymphoma risk, while intake of yoghurt showed no connection to non-Hodgkin's lymphoma risk. Each 200 g/day increment of total dairy product and milk consumption increased non-Hodgkin's lymphoma risk by 5% and 6%, respectively (Wang et al., 2016).

Dairy products are a diet compound that should generally be avoided in patients endangered by non-Hodgkin's lymphomas.

2.3 Vitamin D

Vitamin D regulates bone metabolism and calcium absorption. It is found in various products like: citrus fruits, eggs, fish and vegetables. Vitamin D can also be supplemented dissolved in oil. Apart from supplementation and diet sunlight/UVR exposure is important in maintaining appropriate vitamin D levels. It has a lot of other functions such as regulating arterial blood pressure, modulation of immunological responses, regulation of insulin production and protection against cancer (Urena-Torres & Souberbielle, 2014).

Vitamin D deficiency has been linked to an increased risk of developing non-Hodgkin's lymphomas. Chemotherapy combined with vitamin D supplementation was found to increase the chemosensitivity of tumors, reducing tumor growth rates more effectively than either vitamin D or chemotherapy alone. It had a protective effect for patients with diffuse large B-cell lymphoma undergoing R-CHOP (chemoimmunotherapy plus steroid drug administration) treatment. Vitamin D insufficiency was also linked to impaired rituximab treatment efficacy and worse clinical outcomes in CAR-T (chimeric antigen receptor) cell therapy recipients. A therapy that uses genetically modified limfocytes T (Potre et al., 2023).

Potential mechanism explaining vitamin D's role in the occurrence of non-Hodgkin lymphoma involves the presence of vitamin D receptors and the enzyme 1α-hydrolase in activated B and T lymphocytes. This enzyme converts the circulating form of vitamin D (25(OH)D) into its active form (1,25-dihydroxyvitamin D). Through this conversion, vitamin D can regulate cell growth, induce cell death, and promote cell differentiation (Potre et al., 2023).

In non-Hodgkin's lymphoma patients it is important to prevent vitamin D deficiency, because of its influence of non-Hodgkin's lymphoma treatment and protective properties of vitamin D. It can be done by supplementation, diet and sunlight/UVR exposure, which should be recommended to non-Hodgkin's lymphoma patients.

2.4 Meat consumption

High meat consumption is associated with number of cancers (31), it also has a connection with occurrence of non-Hodgkin's lymphomas (Aschebrook-Kilfoy et al., 2012; Fallahzadeh et al., 2014; Rohrmann et al., 2011; Skibola, 2007). (1,3,4,10) as well as saturated fat consumption, which is often associated with meat consumption (Skibola, 2007).

There is significant risk association between the red meat, meat protein, processed meat, broiled meat, fried red meat and non-Hodgkin's lymphoma risk. Regarding non-Hodgkin's lymphoma subgroups- a significant positive association was noted between diffuse large B-cell lymphoma and red meat intake (Fallahzadeh et al., 2014). A high intake of poultry is also related to an increased risk of B-cell lymphomas (Aschebrook-Kilfoy et al., 2012; Rohrmann et al., 2011; Skibola, 2007). Follicular lymphoma was borderline associated with a higher intake of total fat and oleic acid (Aschebrook-Kilfoy et al., 2012). The etiologic heterogeneity is visible here- diffuse large B-cell lymphoma is linked with red meat consumption in contrast to follicular lymphoma which has not got affiliation to red meat but to oleic acid.

Research shows that the immune system responds to the amount of dietary fat and the level of fatty acid saturation. Saturated fats consumption results in increased production of proinflammatory agents as well as higher nuclear factor activation and decrease T-cell apoptotic tendencies. Polyunsaturated fats on the contrary, decrease the production of proinflammatory agents and increase apoptosis in T- cells (Aschebrook-Kilfoy et al., 2012; Skibola, 2007).

It could be useful for the non-Hodgkin’s lymphoma patients to reduce meat and saturated fats consumption in favor of unsaturated fats and plant diet.

This evidence shows us that incorporating a diet based on scientific studies in the non-Hodgkin’s lymphoma treatment and recommending this diet to patients with increased lymphoma risk could benefit their health and treatment with simple dietary modifications. Influence of various dietary components on non-Hodgkin’s lymphoma subtypes should be studied further in order of establishing the most beneficial diets. These diets should always be accompanying a therapy and groups that are at risk of developing a non-Hodgkin’s lymphoma should introduce them into their daily lives.

3. Fasting

Fasting, as a therapy, has been promoted and practiced throughout history due to its alleged physical, mental and emotional benefits. Since Hippocrates it has been recommended for the treatment of acute and chronic diseases. Both clinical and epidemiological observations indicate that dietary interventions are valuable strategies that can be applied to promote healthy life. Caloric diets and sedentary lifestyles increase the incidence of obesity, diabetes, cardiovascular disease, stroke, and dementia in modern societies. From the above diseases the obesity and diabetes have been associated with an increased incidence of cancer, (including colorectal, kidney, esophageal, endometrial, breast, pancreatic, thyroid, liver, ovarian, gallbladder, and prostate cancers, and non-Hodgkin lymphoma) (Calle et al., 2003). Emerging evidence suggest that fasting , limiting cancer cells' adaptability, survival, and growth., can be associated with improved outcomes in cancer.

What and how much we eat, when we eat is also of critical importance. Fasting schedules may vary, however, broadly, three types can be distinguished: time-restricted, which limits daily intake of food to a 4- to 12-hour window , intermittent fasting, a periodic decrease in food intake or prolonged fasting which may benefit cell repair, weight loss, and blood sugar levels.

Despite caloric restriction provides beneficial effects on health and survival prolonged fasting has been reported to exert adverse effects for a number of mouse strains and could push humans to what one may consider a near anorexic state underlying some cautionary negative outcomes pointed out by the eating-disorders field as well (Di Francesco et al., 2018).

3.1 Systemic effects of fasting

Fasting is dependent on three types of energy metabolism: glycogen, lipid, and amino acid and the most immediate organ affected by a fast is the pancreas, liver and skeletal muscles.

3.1.1 The effect of fasting on human lipid metabolism

During fasting the body reaches the point of negative energy balance, when the liver's glycogen reserves are depleted and free fatty acids are mobilized. Fasting-induced depletion of glycogen in hepatocytes increases lipolysis in adipose tissues resulting in increased fatty acid-derived ketones in the liver, kidney, astrocytes, and enterocytes as an energy supply (de Cabo & Mattson, 2019; Puchalska & Crawford, 2017; Zubrzycki et al., 2018). Brown adipose tissue plays a key role in energy homeostasis and thermogenesis producing energy being released in the form of heat, which increases energy expenditure and ultimately reverses the hyperlipidemia (Kim et al., 2019). Studies have shown that fasting can decrease blood lipids. Alternate-day fasting appear to be effective at reducing total cholesterol (10%–21%) and triglycerides (14%–42%) (Tinsley & La Bounty, 2015; Varady et al., 2013).

3.1.2 The effect of fasting on human glucose metabolism

The degree of influence of fasting on glucose metabolism is inconsistent, however prolonged fasting tended to decrease glucose and insulin level in the blood and increases the insulin sensitivity and β cell responsiveness in obese patients (Sutton et al., 2018).

3.1.3 The effect of fasting on human protein metabolism

Fasting regulates protein synthesis and breakdown, proteins in the body are oxidized and decomposed to produce energy. Fasting can cause changes in the content and types of amino acids. Despite some risk of a negative effect on skeletal muscle protein metabolism, at least intermittent fasting tends to the maintenance of skeletal muscle mass while reducing body fat (Yoshii et al., 2023).

3.1.4 The effect of fasting on human neuroendocrine metabolism

Prolonged fasting leads to an increase in the concentration of growth hormone, glucagon and a decrease in the blood levels of thyrotropin and T3/T4 (Palmblad 1997). Endorphins (Komaki 1990), catecholamines and glucocorticoids are released in large quantities during the first 7 days of fasting (Michalsen, 2010) .

4. The effect of fasting on cancer patients

4.1 The role of fasting in promoting anti-cancer treatment

Fasting and fasting-mimicking diets have been consistently found to promote additive or synergistic antitumor effects when combined with standard anticancer treatments, including ovarian, breast, colorectal, and lung cancer. In clinical trials, fasting has demonstrated reductions in chemotherapy-related side effects and improved treatment tolerability in breast cancer, gynecological cancers, astrocytoma as well ovarian and colon cancers (Table 1). In addition, recent clinical reports have shown that combining different form of fasting with chemotherapy, endocrine therapies, or immunotherapy improves tumor responses in patients with early-stage neoplasms, and it induced complete and long-lasting tumor remissions in some patients with highly aggressive advanced malignancies (Raucci et al., 2024). In patients with cancer, fasting was safe and well tolerated when combined with standard antineoplastic therapies, and it also resulted in metabolic modifications, such as a reduction of blood glucose, insulin, and insulin-like growth factor 1 (IGF1) concentration, which recapitulate metabolic changes responsible for the antitumor effects of nutrient starvation in preclinical experiment.

Table 1. The effect of fasting on cancer patients

Author	Type of diet	Type of cancer	Outcome
Goldhamer (Goldhamer et al. 2015)	Water-only fasting	stage IIIa, low-grade, grade 1 follicular lymphoma	At 6 and 9-month follow-up visits, the patient's lymph nodes were non-palpable and she remained asymptomatic.
Myers (Myers et al., 2018)	Water-only fasting SOS-diet	stage IIIa, grade 1 follicular lymphoma	Lymph node size reduction after water-only fasting and dietary adherence was sustained for 3 years
Schreck (Schreck et al. 2021)	8-week Glioma Atkins-Based Diet	2–4 grade astrocytoma	better systemic activity
de Groot (de Groot et al. 2020)	Intermittent fasting	HER2-negative breast cancer, Stage II/III	tumor-cell loss was more likely to occur in patients using the fasting mimicking diet
Bauersfeld (Bauersfeld et al. 2018)	Intermittent fasting	Gynecological cancers at any stage	improved quality of life and fatigue during chemotherapy
Badar (Badar et al., 2014)	Intermittent fasting	Breast, non-Hodgkin lymphoma, acute myeloid leukemia, nasopharynx, ovarian, and colon	growth of tumors retared
Safdie (Safdie et al., 2009)	Fasting before /or after treatment.	Breast, prostate, ovarian, uterine, non-small cell lung, and esophagus	Fasting has been linked to decreased tiredness, weakness, and gastrointestinal side effects

4.2 The role of fasting in anti-cancer treatment of lymphomas

The most common form of lymphoma are non-Hodgkin lymphomas that account for about 90% of the lymphomas diagnosed. Patients are more likely to develop non-Hodgkin lymphomas in older age, although it can occur at any time. Non-Hodgkin lymphomas are divided further into two categories: B-cell lymphomas and T-cell lymphomas. B-cell lymphomas make up most (about 85%) of the non-Hodgkin lymphomas in the United States. These types of lymphomas start in early forms of B lymphocytes (B-cells). The most common types of B-cell lymphomas involve diffuse large B-cell lymphoma, and follicular lymphoma (about 1 out of 5 lymphomas is a follicular lymphoma), Burkitt lymphoma, as well as chronic lymphocytic leukemia /small lymphocytic lymphoma, mantle cell lymphoma, and lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia).

B-lineage and myeloid leukemia cells are often transformed by the same oncogenes, but have different biological and clinical characteristics. Although B-lineage acute lymphoblastic leukemia cells are characterized by a state of chronic energy deficit, myeloid leukemia cells show abundant energy reserve. Interestingly, fasting has been demonstrated to inhibit selectively the development of B-all but not myeloid leukemia, further suggesting that lineage identity may be linked to divergent metabolic states in hematopoietic malignancies (Chan & Müschen, 2017).

Diet and dietary restrictions play a crucial role in the management and prognosis of lymphomas. In the limited studies of weight cycling and cancer, no independent effect on post-menopausal breast cancer but a modest enhancement of risk for renal cell carcinoma, endometrial cancer, and non-Hodgkin’s lymphoma have been reported (Thompson & McTiernan, 2011).

A case report in the British Medical Journal described how stage III follicular lymphoma resolved after a 21-day water-only fast combined with a with a whole plant food diet (Goldhamer et al., 2015). In a follow-up study (Myers et al., 2018) reported no evidence of hypermetabolic neoplasm. Lymph node size reduction after water-only fasting and dietary adherence was sustained for 3 years in a case of stage IIIa, grade 1 follicular lymphoma suggesting that exclusively whole plant food diet appears to maintain an asymptomatic period in a case of stage IIIa, grade 1 follicular lymphoma. The beneficial effects mediated by fasting and calorie restriction appear to be due to a reduction in oxidative stress, glucose levels, insulin resistance, insulin-like growth factor-1 (IGF-1), and growth hormone (GH) levels that occur in normal cells.

Fasting and calories restriction have stronger impacts on cancer cells that are expressing proto-oncogenes. Additionally, it has been demonstrated that fasting promotes cancer immunosurveillance and T-cell-mediated tumor cytotoxicity, modify the activity of natural killer cells, and may even cause immunogenic cell death (Cancemi et al., 2023).

The results showed that fasting is safe and feasible in terms of a high compliance rate and stable nutritional status. The fasting was associated with benefits in post-chemotherapy hematological parameters (Tang et al., 2021).

Cancerous cell types are likely to develop resilience by avoiding the cellular alterations induced by fasting, and the metabolic heterogeneity that characterizes various tumors adds to this probability.

4.3 Key mechanisms of the effect of fasting on cancer

As shown on the **Figure 1** basic systemic effects of fasting overlap and interact with systemic effects of cancers. In particular :

Insulin sensitivity improves. Fasting is the most effective way to lower insulin levels and improve insulin sensitivity. Insulin is responsible for energy utilisation and storage. However some proteins, especially some animal proteins, notably whey, can raise insulin almost as much as carbohydrates, though interestingly (marine) collagen has been found to improve insulin sensitivity. Ketosis reaches a plateau after four days of fasting by which time 75% of the brain's energy is being supplied by ketones.

Leptin has been shown to regulate cancer cell proliferation, alongside insulin resistance there is a high leptin level but low satiety because of leptin resistance. When leptin levels rapidly drop during fasting it should improve leptin sensitivity and therefore appetite regulation

Fasting also boosts growth hormone levels (maximal at day five) which ensure conservation of muscle mass.

Cellular 'cleansing' – autophagy**.** When the body switches to using ketones as a fuel during fasting this signals several mechanisms in the body including autophagy. Autophagy is the cellular process whereby the body recycles old and damaged parts. Autophagy acts in an anti-metastatic role via limitation of cancer necrosis and inflammation responses in early stages of cancer metastasis. In early metastasis, autophagy also reduces invasion and migration of cancer cells from origin sites.

Fasting also appears to stimulate biological mechanisms in humans that may potentiate tumor regression, such as decreasing levels of leptin and insulin-like growth factor 1.

4.4 Contra-indications

Fasting is not recommended for children, pregnant or breastfeeding women, the frail elderly or anyone with a history of eating disorders. Caution is also advised for anyone with a low BMI and for people taking certain medications, in particular meds for diabetes and blood pressure would probably need to be reduced.

5. Conclusions

Resilience to fasting combined with chemotherapy is even more rare in vitro research studies, thus stressing the necessity of discovering therapies that result in significant cytotoxic actions on cancerous cells with negligible adverse effects on normal healthy cells. Although data on the effects of fasting on the treatment of human cancer are lacking, animal research suggests that fasting affects cancer cells by reducing nutrients necessary for sustained growth leading to oxidative stress and cell death, activating the immune system or facilitating immune cells to kill cancer cells, and promoting autophagy. Identifying the cancers most sensitive to the dietary regimens will be a critical future problem. Even with cancerous cells that are less sensitive to fasting, it might be feasible to discover the causes of resilience and assist with medication that can reverse the resilience. Fasting, in contrast, has just a few times led in the development of resilience when combined with standard therapies in cancer preclinical studies. Fasting may have aided in the healing process of chemotherapy-induced DNA damage. Fasting for a brief time was observed to minimize hematologic damage in female cancer patients receiving chemotherapy. Despite the information gaps and problems involved with modifying human dietary habits, fasting remains an appealing modality to investigate in a research environment since it has few side effects, is inexpensive, and is likely tumor agnostic.

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