REVIEW ARTICLE

INDONESIAN JOURNAL OF CANCER

Intermittent Fasting- A Paradigm Shift In Cancer Prevention and Treatment: A Scoping Review

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ARTICLE INFO

Received : 25 April 2024
Revised : 12 July 2024
Accepted : 18 July 2024
Published : 30 June 2025

Keywords:
autophagy, cancer, heme oxygenase-1, intermittent fasting, oncology

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ABSTRACT

Background: Cancer, a dreadful disease, is one of the most prominent and prevalent causes of mortality across the globe. The well-being of every human society is impacted by this serious issue. Intermittent fasting has gained popularity due to its potential in enhancing the efficacy of cancer treatment and limiting its detrimental effects.

Method: The literature review focuses on illuminating its beneficial role, suggesting that Intermittent fasting has the transformative potential to work as a complementary approach to cancer prevention and treatment.

Results: It has been observed that fasting can protect normal cells from the damaging effects of chemotherapy while stimulating the regeneration in normal tissues.

Conclusion: By elucidating its mechanisms of action and summarizing current evidence, this scoping overview aims to inform future research directions and clinical guidelines in the pursuit of improved outcomes for cancer patients.

INTRODUCTION

Cancer is a highly complex and terrifying disease whereby certain cells in the body grow out of control and invade other areas of the body. Irrespective of human growth, it is accountable for heightened rates of morbidity and mortality globally [1]. As per the cancer statistics report, there were an estimated 19.3 million cancer cases and almost 10 million deaths globally in 2020 [2]. Almost any area in the body might become the site of cancer. Trillions of cells comprise the human body. These cells are capable of proliferating through a process known as cell division. As cells develop, age, sustain injury, and eventually die, new cells replace the old ones. Anomalies or damaged cells can occasionally proliferate and expand. These damaged cells can create masses of tissue called tumors. They could be malignant or benign (non-cancerous). Cancerous or malignant tumors can spread to distant areas of the body and infiltrate neighboring tissues, a process known as metastasis. While many cancers progress into solid lumps, blood malignancies like leukemia usually do not. Benign tumors do not invade or disseminate into nearby tissues. These usually don't grow back after removal, although malignant tumors might be able to. Benign tumors occasionally have the potential to grow larger. Certain medical diseases, such as benign brain tumors, can cause severe symptoms or even be fatal.

The most recurrently and extensively used convention for cancer treatment includes chemotherapy, surgical tumor removal, and radiation, along with the newly discovered immunotherapy. The prognosis and overall survival time of patients remain dismal even after receiving the finest feasible treatment [1,3]. Standard therapy also carries several drawbacks and increases the chance of recurrence of the illness. Patient experiences physical, emotional, mental, financial, and social rifts. Numerous research projects are poised in line to look for a substitute. According to data from recent scientific studies, Intermittent fasting may boost the quality of life of cancer patients and boost the efficacy and tolerability of anticancer medications through a variety of biological adaptation processes. It might help with cancer therapy and prevention (**Table 1**) [4–7].

Table 1. Research studies analyzing the effect of intermittent fasting on cancer patients

S.NO.	Cancer Type	Patient Details	Fasting Protocol	Study Findings	References
1.	HER2-negative breast cancer, Stage II/III	Neoadjuvant chemotherapy was provided to 131 patients in total.	Diet that mimics fasting for 3 days before and during neoadjuvant chemotherapy	• Between the participants in the fasting and normal care groups, there were no differences in grade 3/4 toxicity throughout treatment. • In the FMD cohort, Miller-Payne 4/5 pathologic response is more prevalent. • Patients with a higher percentage of Miller-Payne 4/5 ratings were those who adhered to the FMD more carefully.	[42]
2.	2–4 grade astrocytoma	In an 8-week glioma Atkins diet, a total of 25 participants were included.	Five modified Atkins diet days (net carbs ≤ 20 g/d) are spaced out between two fasting days (calories < 20% calculated projected requirements) per week.	• The diet was largely well-tolerated, with the exception of two grade 3 adverse effects: seizures and neutropenia. • Lean body mass spiked while systemic activity metrics including insulin, hemoglobin A1c, and fat body mass all decreased. • Greater levels of ketones than at baseline in the brains of the contralateral and lesional regions.	[43]
3.	Gynecological cancers at any stage	30 patients undergoing the (neo)-adjuvant chemotherapy for at least four rounds	Half of the planned chemotherapy cycles will involve a ninety-six-hour fast, with the remaining cycles using a typical diet.	• Increased ketone bodies and decreased blood levels of insulin and IGF-1 are associated with fasting. • Reduced total toxicity score; less delays in treatment when fasting; and reduced stomatitis, headaches, and weakness. • There was no improvement in the tiredness, neuropathy brought on by chemotherapy, or patient-reported quality of life.	[44]
4.	Breast and ovarian cancer at any stage	Thirty-four people are receiving chemotherapy.	During the first half of chemotherapy, patients were randomized to either a normal calorie diet followed by a short-term fasting diet or a normal caloric diet followed by a short-term fasting diet.	• Patients on the fasting diet reported feeling more rested and having a better quality of life within eight hours after starting therapy.	[45]
5.	Breast cancer at an early stage	2413 patients performed 24-hour dietary recalls at baseline, year 1, and year 4.	The amount of time spent fasting at night was determined using dietary recalls.	• Individuals who fast for fewer than 13 hours per night are linked to a 36% higher risk of breast cancer recurrence in comparison to those who fast for at least 13 hours each night.	[46]
6.	Breast, ovarian, and uterine cancer at any stage	20 people are receiving chemotherapy based on platinum..	Fasting for 24 hours, 48 hours, or 72 hours before chemotherapy	• Fasting is doable and safe. • There were fewer cases of neuropathy and neutropenia in the fasting groups. • Those who fast have less harm to their DNA.	[47]

S.NO.	Cancer Type	Patient Details	Fasting Protocol	Study Findings	References
7.	HER2-negative breast cancer II/III	Chemotherapy (neo)-adjuvant treatment is being administered to 13 patients.	Patients were randomly allocated to either a diet that adhered to adequate nutritional requirements or a 24-hour fast before and after treatment.	• Fasting reduced hematologic toxicity and was well tolerated. • Fasting may help repair DNA damage brought on by chemotherapy.	[48]
8.	Breast, non-Hodgkin lymphoma, acute myeloid leukemia, nasopharynx, ovarian, and colon	Chemotherapy is given to 11 patients.	During Ramadan, patients received chemotherapy.	• Fasting is a safe and well-tolerated practice.	[49]

Intermittent fasting, a new and intriguing dietary paradigm, alternates between periods of fasting and feasting [8].Unlike traditional calorie-restriction diets, which focus on reducing overall energy intake, intermittent fasting places emphasis on when to eat rather than what to eat. This dietary pattern has currently become one of the world's most popular physical fitness and wellness trends. It has attracted widespread attention not only for its potential effects on weight management but also for its purported health benefits, including improvements in metabolic health, longevity, and disease prevention.

The concept of fasting has a long history and is ingrained in culture; it dates back to religious rituals and ancient civilizations. Fasting has been observed for various reasons, including spiritual purification, ritualistic traditions, and even therapeutic purposes. However, it is the recent surge in scientific interest that has shed light on the physiological mechanisms underlying intermittent fasting and its potential impact on human health.

There are multiple approaches to practice intermittent fasting, notably time-restricted feeding (TRF) and alternate-day fasting (ADF). 24 hours of fasting and 24 hours of feasting are part of the alternate-day fasting regimen [9]. Ramadan fasting is comparable to ADF since, depending on the season and region, the typical length of the feasting and fasting periods ranges from 12 to 18 hours [10]. A time-restricted feeder consumes all of the calories for the entire day in eight hours or less and fasts the remaining hours [11]. Since Islamic adherents only eat for about eight hours at night and fast from sunrise to sunset, TRF exhibits similarities with Ramadan fasting, therefore, it can be seen as a type of intermittent fasting because of this comparable pattern.

Individual metabolic functions may be significantly impacted by such alterations in the daily dietary pattern [12]. Numerous studies have documented the useful and advantageous effects of intermittent fasting, such as regulating blood pressure, energy metabolism, obesity, diabetes, and other diseases [13–17]. One of the key physiological responses to intermittent fasting is the activation of metabolic pathways that promote cellular repair and regeneration. The body switches during fasting periods from processing stored fat for power to using glucose as the primary source of energy.

This metabolic switch triggers a cascade of adaptive responses, including increased autophagy, a process by which cells break down and recycle damaged components, and enhanced mitochondrial function, which plays a crucial role in energy production and cellular resilience. Studies indicate that a person's general health is enhanced by fasting because it lowers oxidative stress and inflammation, lengthens life expectancy, triggers cellular repair processes, as well as enhances heart and brain function.

The objective of this scoping overview is to illuminate the finding that intermittent fasting has the transformative potential to work as a complementary approach to cancer prevention and treatment.While synthesizing the readily accessible scientific evidence, this review highlights certain clinical trials that have involved intermittent fasting for treating cancer.

Intermittent Fasting and Its Mechanism: Focusing On Cancer

Based on scientific studies, Intermittent fasting has been shown to influence various metabolic hormones and signaling pathways implicated in energy balance and homeostasis. Intermittent fasting is found to be associated with numerous healthcare benefits, including cardiovascular protection, cognitive enhancement, and inflammation reduction. Scientific research suggests that by repressing the levels of glucose, insulin, heme oxygenase 1, and insulin-like growth factor-1 (IGF-1), intermittent fasting could mitigate the risk of cancer. It elevates several factors that are crucial to the

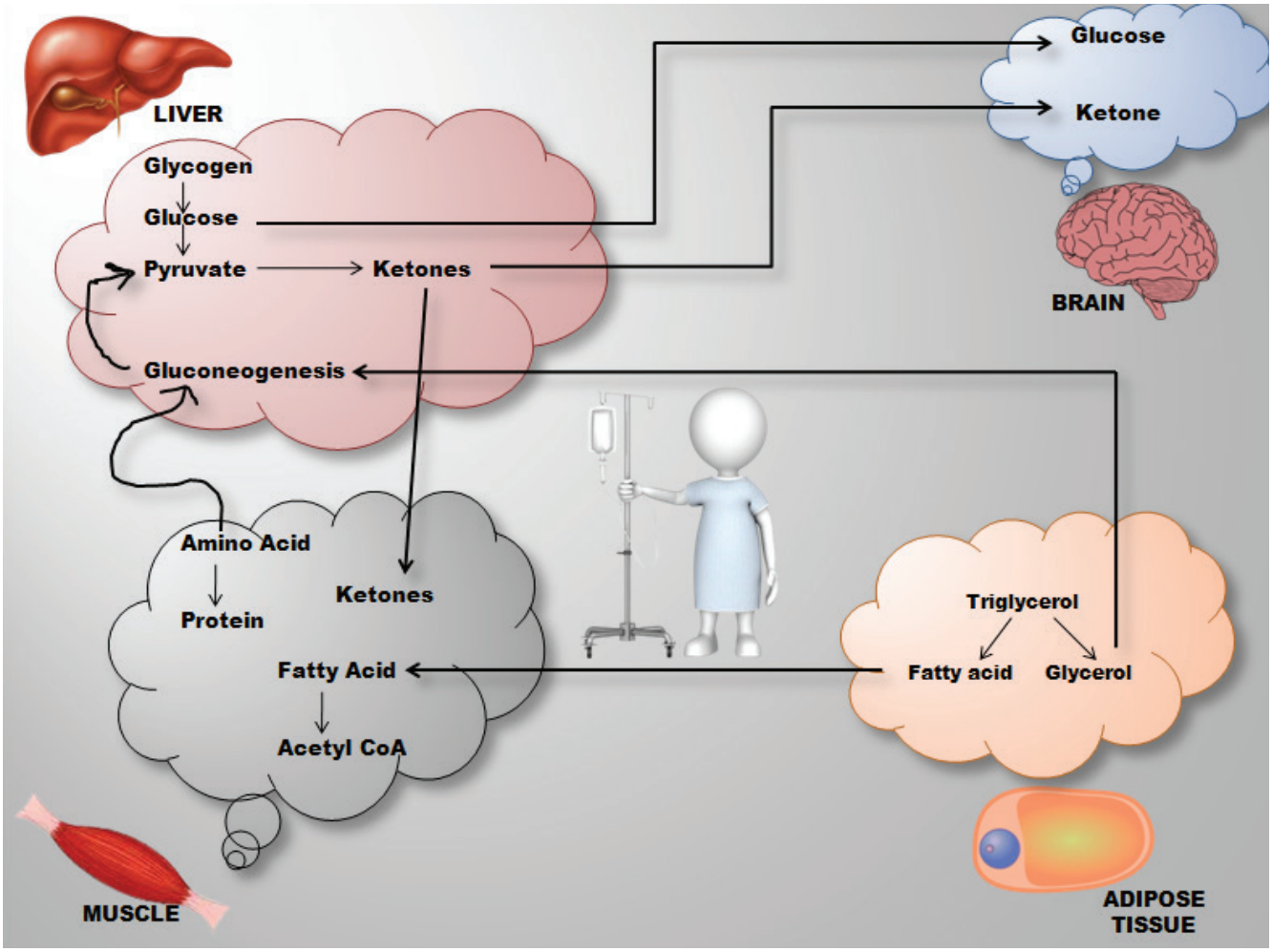

Figure 1. Impact of prolonged fasting on patients' different body systems. During prolonged fasting, the body undergoes a series of metabolic adaptations aimed at sustaining energy levels and supporting vital functions. As liver glycogen reserves are depleted and triglycerides are broken down into their constituent components—glycerol and free fatty acids—the brain shifts progressively towards utilizing ketone bodies alongside glucose to meet its energy demands. Meanwhile, other tissues predominantly rely on fatty acids as an energy source. Notably, gluconeogenesis, the synthesis of glucose from non-carbohydrate precursors, is facilitated by ketone bodies generated in the liver during the ketogenic phase of fasting, drawing upon fatty acids, fat-derived glycerol, and amino acids to maintain glucose levels and metabolic equilibrium.

regulation of autophagy, which include the autophagy-regulating elements such as Atgs, LC3, P62, and LAMP2.

Research indicates that Intermittent fasting makes healthy normal cells divide more slowly, shielding them from the harmful shocks caused by anticancer drugs. Nevertheless, it also increases the susceptibility of cancer cells to medication, so limiting their potential to adapt, endure, and multiply. It reduces insulin, glucose, and insulin-like growth factor-1 (IGF-1), which limits cell division and speeds up the death of injured cells to shield the cells in opposition to DNA damage [18].

Since there is no regular food intake during fasting, the body meets its energy needs by using stored reserves. The dissolution of liver glycogen stores into glucose and triglycerides to glycerol and free fatty acids is triggered by this metabolic strain, which also raises glucagon and lowers insulin levels. Through various biological mechanisms, fasting benefits various organs in the long run. There occurs ketone production and an increase in insulin sensitivity in the liver, brain observes improved neurogenesis, improved cognition, enhanced autophagy and reduced inflammation, further fatty acid oxidation and reduced inflammation take place in adipose tissue and the muscle observes enhanced autophagy and increased insulin sensitivity (**Figure 1**) [19–21].The brain uses glucose and ketone bodies as sources of energy, whereas other tissues use fatty acids.

Gluconeogenesis is driven by ketone bodies that are created in the liver during a ketogenic state from fatty acids, glycerol generated from fat, and amino acids. Histone deacetylases are inhibited by ketone bodies, which may prevent tumor growth [22,23]. Moreover, the endogenous inhibitor of histone deacetylase is the ketone molecule β-hydroxybutyrate. By blocking the impulses, this inhibitor shields the organism from oxidative damage [24]. Adrenaline and glucocorticoids also play a role in the immediate metabolic reactions to fasting, helping to promote lipolysis and sustain blood

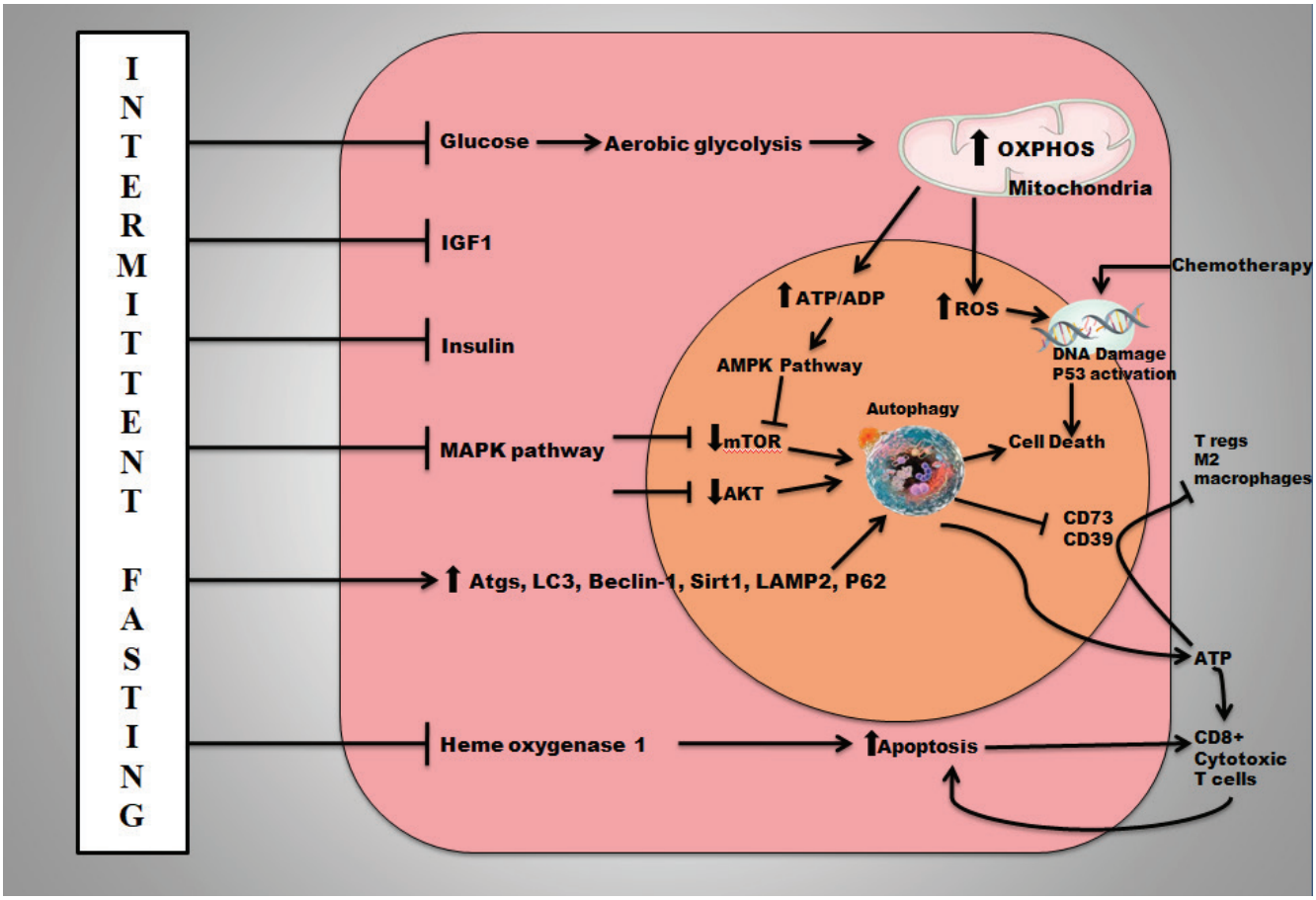

Figure 2. Elucidating the multifaceted mechanisms of fasting impact on cancer cells. Abbreviations: FGF21- Fibroblast growth factor 21; IGF1- Insulin-like growth factor 1; SHBG- Sex hormone binding globulin; RAS- Reticular activating system; DNA- Deoxyribonucleic acid; CD8+ - Cytotoxic T Lymphocytes; ROS–Reactive oxygen species; SIRT3- Sirtuin 3; SIRT4–Sirtuin 4; AKT-Protein Kinase B; mTOR- Mechanistic target of rapamycin; TKIs- Tyrosine Kinase inhibiters; IGFBP1- Insulin-like growth factor binding protein 1; PAX5–B cell specific activator protein; STAT5–Signal transducer and activator of transcription; IGFBP1- Insulin-like growth factor-binding protein 1; NAD+ - Nicotinamide adenine dinucleotide; NAMPT- NicotinamidePhosphoribosyl transferase.

sugar levels [25]. When fasting intermittently, FGF21 is upregulated and inhibits phosphorylated STAT5 in the liver, which is a major factor in reducing IGF1 levels [26]. Moreover, elevated insulin-like growth factor-binding protein 1 (IGFBP1) restrains the biological activity of IGF1 during periods of intermittent fasting by adhering to systemic IGF1 and blocking its interaction with the appropriate cell surface receptor [20,27]. IGF1 downregulation is a fundamental mechanism via which fasting increases chemotherapy endurance and minimizes significant side effects. Increased levels of IGF1 in breast, prostate, and colon cancer are thought to be caused by more substantial proliferating cells, unstable genetics, and repressed apoptosis [28,29]. The IGF-1/mTOR signaling cascade is altered, and the concentrations of adiponectin are subsequently raised by fasting, whereas levels of glucose, IGF1, insulin, and circulating leptin are reduced.

These conditions, which include anti-tumor effects, reduced formation of free radicals, and enhanced bodily tolerance to stress, are all known to influence the genesis of cancer (**Figure 2**) [20,21]. Furthermore, reduced insulin and IGF1 levels may shield healthy cells from adverse consequences [30]. Significant therapeutic effects of fasting have been shown through molecular processes, including increased sirtuin activity and autophagy (**Figure 2**). Using a lysosome-dependent regulated mechanism, autophagy is a naturally occurring process that breaks down unnecessary or defective cellular components to enable systematic disintegration and repurposing [31,32]. Autophagy has been linked to pro- and anticarcinogenic pathways. It controls tumor suppressor genes and oncogenes and has an intricate connection with cancer. It carries out several functions in properly functioning cells that work together to halt malignant transformation, including maintaining oxidative metabolism and enough energy, eliminating harmful, mutagenic, and carcinogenic substances, battling infections that can cause cancer, and protecting the integrity of stem cell organelles [32–34].

ULK1 and ULK2, which regulate autophagy, are inhibited by the protein kinases AMPK and mTOR [21–23]. Moreover, the control of autophagy is crucially influenced by Atgs, Beclin-1, LC3, P62, Sirt1, LAMP2, and the class III PI3K pathway (**Figure 2**) [32–34]. Autophagy

has the potential to alter the way cancer treatments are administered because it has been shown to make cancer cells more receptive to chemotherapy [35]. On the other hand, increased autophagy might contribute to resistance to cancer treatments [34]. More research is required to fully comprehend the benefits and hazards of fasting-instigated autophagy in malignant patients, as there is uncertainty whether intermittent fasting could enhance autophagic activities in humans. Furthermore, sirtuins, which are NAD+-dependent deacetylases, provide safeguards and implications that prolong life in model species [36,37].

When cells are denied nourishment, their intracellular NAD+ levels rise, which activates SIRT3 and SIRT4, two sirtuin mitochondria that safeguard cells from chemotherapy [36,37]. Overall, fasting slows down the rate at which healthy normal cells divide, shielding them from the harmful shocks caused by anticancer drugs while making cancerous cells more susceptible to their effects. Fasting can drive cancerous cells to transition from aerobic glycolysis to mitochondrial oxidative phosphorylation, which increases reactive oxygen species (ROS) by minimizing glucose uptake and enhancing fatty acid oxidation. Therefore, increased activity of mitochondrial respiratory and cellular redox capabilities may arise from decreased glutathione formation from the pentose phosphate and glycolysis process (**Figure 2**) [19,20]. Increased ROS and lowered antioxidant defense work together to cause oxidative stress in malignant cells, which amplifies the effects of chemotherapy. Additionally, fasting triggers REV1 modification mediated by SUMO2 and/or SUMO3, which amplifies p53-driven transcription of pro-apoptotic genes and ultimately causes malignant cells to die [20,21,38,39]. Fasting enhances MAPK signaling inhibition, which increases the effectiveness of TKIs in limiting the growth and killing of malignant cells [21,39,40]. In the end, fasting may modulate the leptin receptor through the protein PRDM1, thereby inhibiting and reversing the progression of acute lymphoblastic leukemia in T and B cells [20,21,27,38,40].

The metabolic variability that distinguishes different tumors increases the likelihood that cancerous cell types will become resilient by eschewing the cellular changes brought on by fasting [41].As such, utilizing biomarkers to pinpoint the tumors most amenable to these nutritional interventions will be a major area of emphasis in the days to come. One of the major challenges of the future will be to determine which tumors are best candidates for the benefits of fasting. It may be possible to identify the origins of resistance and provide medication to cure it, even in cases when malignant cells are less sensitive to fasting. In contrast, in cancer preclinical investigations, fasting has rarely resulted in the formation of resilience when paired with conventional therapy [20,21,35,38].

Intermittent Fasting, Cancer Prevention and Treatment

According to recent investigations, individuals who practice intermittent fasting may have a lower chance of developing cancer by adopting healthier diet and lifestyle choices. Tolerated fasting regimens with low adverse effects and good clinical efficacy for malignant patients still need to be discovered and put into practice. One variant of fasting that has been demonstrated to be beneficial in reducing tumor formation in rats is calorie restriction, which includes lymphomas and breast cancers [38,50–52]. A 30% calorie-restricted diet was found to minimize the likelihood of recurrent cancer in rhesus monkeys, which share almost identical DNA with humans, by 50% when contrasted with ad libitum-fed animals [53,54].Thesame outcomes have been shown in human experiments. After a median of 20 follow-ups, Carlsson et al. observed a 20% reduction in cancer-related mortality and a 29% decline in the prevalence of cancer. A lower chance of developing malignancies was linked to a decreased prevalence of malignancy, especially tumors affecting women. Those who underwent bariatric surgery and had higher baseline blood insulin levels benefited more significantly from this association [55,56].

A fasting, low-calorie diet can prevent the development and spread of cancer by targeting multiple interrelated pathways. Major metabolic and hormonal changes linked to a decreased risk of cancer were brought about by energy restriction. These alterations encompassed alterations in insulin susceptibility, raised levels of IGFBP1 and SHBG, reduced levels of estrogen and testosterone, and attenuated oxidative and inflammatory processes [20,21,27,38]. Extended calorie-controlled diets, which are the variations of fasting, reduce cell growth and senescence markers while increasing antioxidant activity, autophagy, molecular repair in the DNA and heat-shock protein chaperone pathways [19–21,34]. Other mechanisms include increased immune suppression against tumors, decreased reactive oxygen, and reduced production of different growth factors.

Regularly fasting for longer than a day may improve health by protecting normal, healthy cells from the damaging effects of radiation and chemotherapy. While healthy standard cells surrounding them may not be affected, malignant cells may be prevented from entering a high-stress endurance phase during fasting by RAS, AKT, and mTOR[33,38–40]. Through the differential stress response, fasting may improve the therapeutic outcomes for malignant cells while protecting normal tissue from the deleterious effects of chemotherapy [35,40,57]. Moreover, the Warburg effect—a metabolic anomaly in malignant cells—is caused by an abnormal metabolism mostly centered on glycolysis, which

increases the absorption of glucose and its breakdown into lactate [58,59]. Thus, glucose deprivation may enhance apoptosis and make malignant cells more susceptible to the deleterious effects of chemotherapy medications, as demonstrated by prolonged fasting and ketogenic diets [29,35,40,51]. Extended fasting resulted in a decrease in IGF-1, which subsequently enhanced the rejuvenation of hematopoietic stem cells and counteracted immunosuppressive action by increasing the receptivity of tumor cells to chemotherapy [60,61]. This prolonged duration of fasting was associated with lower levels of IGF-1 and insulin, in addition to a reduction in headaches, weakness, and stomatitis [44]. Additionally, there were significantly fewer treatment delays and a significant reduction in the total toxicity score during the fasting periods.

One of the main concerns in the research on intermittent fasting and cancer is the possibility that this diet plan could cause malnourishment, sarcopenia, and cachexia in vulnerable or frail people [62]. Nevertheless, so far, no published medical investigation examining the effects of fasting in combination with chemotherapy medications has shown any instances of substantial weight loss or inadequate nourishment that could be considered meaningful.

CONCLUSION

Through numerous metabolic, biochemical, and immunological alterations, intermittent fasting has been demonstrated to profoundly affect malignant etiology and efficiently reduce body mass. Research on its possible application in the prevention and treatment of cancer is still underway as a result. Nevertheless, there hasn't been any solid evidence from human research on how intermittent fasting affects insulin-stimulated growth and other hormone and inflammatory indicators linked to cancer. The precise effects of intermittent fasting on clinically significant cancer outcomes are still unknown due to the paucity of clinical studies. Because of its low cost, few side effects, and possible broad-spectrum tumor benefits, intermittent fasting is still regarded as a promising topic of research despite the obstacles and gaps in our understanding of dietary habit modifications.

According to some studies, extended periods of fasting may be useful, doable, and practical in improving the effectiveness of tyrosine kinase inhibitors (TKIs) and chemoradiotherapy. This will activate anticancer immunity and lower the risks of chemotherapy-induced tumor development in some cancer patients. In particular, prolonged intermittent fasting may not be very useful in treating malignancies that already exist if it is taken in isolation without other therapies. Better outcomes and increased cancer-free survival are frequently seen when fasting is combined with cancer medicines. As such, we suggest combining extended interval fasting with traditional treatments.

There is currently little proof that weight loss, exercise, and a balanced diet alone can enhance cancer outcomes when combined with intermittent fasting. Like any other therapy choice, patients should be informed about the possible dangers and advantages of fasting. Clinical trials involving fasting should not be conducted on patients who are weak, malnourished, or at risk of malnutrition. Throughout the study, patients' general physical and mental well-being should be thoroughly observed. Patients can optimize the advantages of fasting and prevent malnourishment by implementing a well-rounded eating plan. The long-term advantages of fasting for cancer patients require more investigation. Overall, intermittent fasting is safe for cancer patients when followed appropriately under the guidance of a dietitian or doctor. It may even be used in conjunction with conventional anticancer therapies to increase their efficacy and lessen side effects.

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