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Impact of Fast-Mimicking Diet and Fasting Dietary Interventions on Cancer Outcomes in Adult Patients: A Scoping Review of Clinical Evidence

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Abstract

Background: *Cancer poses a significant global burden in terms of both morbidity and mortality. Conventional cancer therapies often come with adverse effects that significantly impair patients' quality of life. Recently, there has been a growing interest in the potential of fasting interventions to improve cancer treatment outcomes and reduce treatment-related effects.*
Purpose: *This scoping review aims to assess the clinical evidence regarding the effects of fasting mimicking diets (FMD) and other fasting interventions on cancer outcomes in adult patients.*
Methods: *The research focused on clinical studies involving patients diagnosed with cancer who were 18 years of age or older. These studies compared the effects of different fasting regimens to those of standard cancer treatment. The search was conducted across PubMed, the Cochrane Library, and Embase databases, resulting in 5,776 articles. After removing duplicates and screening titles and reviewing full text, 10 studies (six randomized controlled trials, one control clinical trial, and three single-arm studies) met the inclusion criteria involving 696 patients. Data extraction and risk of bias assessment were conducted using Covidence and the Cochrane ROB1 tool, respectively.*
Results: *The review included a variety of fasting protocols, such as FMD, short-term fasting, and ketogenic diets combined with intermittent fasting. Some studies suggest that fasting may improve overall survival, quality of life (QoL), inflammatory biomarkers, and a decrease in chemotherapy-induced toxicities, although the results were not entirely consistent.*
Conclusions: *FMD and other fasting interventions show promise as adjunct therapies in cancer treatment, potentially improving treatment efficacy and reducing side effects. However, the current evidence is limited by methodological heterogeneity and small sample sizes.*

Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, driving the need for continuous advancements in therapeutic strategies to improve patient outcomes. According to the National Cancer Institute (2024), the estimated global incidence of cancer is 440.5 per 100,000 people, with a mortality rate of 146 per 100,000 people. Conventional treatments

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often come with numerous side effects, including severe fatigue, nausea, cognitive decline, immunosuppression, and damage to healthy organs and tissues, which significantly impact patients' quality of life (QoL) (Debela et al., 2021; National Cancer Institute, 2024). These side effects eventually limit both the effectiveness of cancer therapies and patients' ability to tolerate them.

Fasting Mimicking Diet (FMD) is a dietary intervention that has been investigated in cancer patients over the past decade to enhance QoL, regulate tumor growth, and improve tolerance to cancer treatment side effects. FMD is based on the understanding that tumor progression relies on the availability of sugars and amino acids to regulate key signaling pathways, including IGF-1, Ras, AKT, PI3K, and PKA, which may undergo mutations due to oncogenic activity (Blaževitš et al., 2023).

Fasting may benefit cancer patients through several mechanisms. It has been shown to reduce chemotherapy toxicity, enhance immune responses, and improve overall QoL. One key mechanism is "differential stress resistance," where fasting protects healthy cells from chemotherapy's toxic effects by promoting a protective, low-growth mode, while cancer cells remain vulnerable due to their rapid proliferation. This selective protection reduces DNA damage and side effects in healthy tissues (Safdie et al., 2009).

Additionally, fasting enhances immune function by stimulating autophagy and facilitating immune cell regeneration, which strengthens the body's response to infections and improves the efficacy of cancer treatments by reducing tumor immunosuppression (Vernieri et al., 2022). Furthermore, fasting improves metabolic profiles, lowering insulin, glucose, and inflammatory markers, thereby reducing treatment-related fatigue and potentially slowing tumor progression and positively influencing survival and quality of life (Valdemarin et al., 2021).

It is hypothesized that reducing the availability of nutrients like glucose through dietary approaches such as FMD, short-term fasting (STF), modified short-term fasting (mSTF), and the ketogenic diet (KD) may inhibit tumor proliferation and promote the body's self-healing mechanisms that could ultimately revolutionize patients' health outcomes and improve their QoL. In contrast to chronic dietary restrictions, which can be difficult to sustain and may lead to malnutrition, FMDs are designed to provide similar metabolic benefits while being easier to adhere to and less likely to cause long-term nutritional deficiencies. This makes FMD a promising intervention compared to chronic dietary restrictions, being seen as a safer option for cancer patients. However, studies are inconclusive, and the evidence is still limited, particularly concerning different types of cancer and fasting interventions.

The objective of this scoping review is to categorize the clinical trials that have investigated FMD and other fasting interventions in cancer patients and assess their impact, identifying gaps in outcomes such as survival, QoL, tumor biomarkers, metabolic changes, and immune function. Additionally, we aim to evaluate the methodological quality of the studies and assess the potential implications of the findings for clinical practice and future research.

The research question was defined using the PCC framework (Population: adult cancer patients; Concept: intermittent fasting; Context: different types and stages of tumor under contemporary treatments): What is the impact of intermittent fasting on patients with different types and stages of cancer under contemporary oncological treatments?

Materials and Methods

Inclusion and exclusion criteria

The population included patients diagnosed with cancer who were older than 18 years old. The interventions encompassed different types of fasting, such as FMD, intermittent fasting, alternate-day fasting, water fasting, and caloric restriction. Comparison groups were restricted to standard care treatments. Studies that reported outcomes related to survival rate, QoL, and other surrogate markers, such as biomarkers, were included. This scoping review included the following: (1) randomized clinical trials (RCTs), controlled clinical trials (CCTs), and other interventional studies with (2) patients diagnosed with cancer, (3) over 18 years, (4) who submitted to any of these fasting modalities: FMD, intermittent fasting, alternate-day fasting, water fasting, and caloric restriction, (5) which present any of the outcomes of interest. Comparison groups were restricted to standard-of-care treatments. We excluded (1) observational studies, (2) case reports, (3) reviews, (4) nonclinical trials, (5) studies involving animals, (6) pediatric patients, and (7) pregnant participants.

Search strategy

To ensure a comprehensive search covering all eligible literature, the research question was translated into a search strategy (Appendix 1) across three electronic databases: PubMed, Cochrane Library, and Embase. The search included clinical trials available up to the date of access, which was conducted on May 1, 2024. No restrictions were set regarding the date of publication, geographical location, or

language.

Selection of studies

Studies were included if they involved preschoolers, children, and adolescents (less than or equal to 18 years old), diagnosed with ADHD, investigating the intake of Omega-3 fatty acids through diet or supplementation and its impact on the severity of ADHD symptoms. Only RCTs published in peer-reviewed journals in English or Spanish over the past 30 years were considered.

Data extraction and synthesis

A standardized data extraction form was developed collaboratively after consensus and review by all participants using the Covidence platform to ensure data collection accuracy across all reviewers. After an initial review of the relevant literature, a draft version of the form was created outlining the key variables to capture, such as fasting intervention type, study settings and duration, participant characteristics, intervention details, and outcomes.

In cases where data were missing or ambiguously described, study investigators were contacted for clarification. To ensure systematic capture of relevant information and minimize potential data selection bias, any discrepancies in data extraction were addressed through discussions between the reviewers to reach a consensus and make a final decision. Any discrepancies in data extraction were addressed through discussions between the reviewers to reach a consensus and make a final decision. The extracted data were organized into tables and charts, and the main findings from each study were summarized.

Endpoints

Our primary endpoints were survival rate, quality of life, and side effects of chemotherapy

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Risk of bias assessment

The quality of the 10 studies included in this review was assessed using the Cochrane Risk of Bias (RoB 1.0) Tool (Higgins et al., 2011). To minimize bias, each included clinical trial was independently assessed by two reviewers using the Covidence platform. Discrepancies were resolved through discussion and detailed analysis until consensus was achieved. The entire process, from study selection to conflict resolution, was facilitated solely by the Covidence platform, and no additional automation tools were used through the PRISMA criteria process.

Results

Description of the studies

The systematic search initially identified a total of 5776 articles. After thorough screening and assessment, 10 articles met the eligibility criteria (Figure 1 PRISMA). These studies collectively encompassed data from 696 patients. Most of the studies were conducted in Europe (n=9), and only one was done in the United States. Locations were single-center (n=5), multicenter (n=4), and unreported (n=1). Withdrawals were reported in nine studies (n=102) due to medical intelligibility, personal preference, or treatment-related discomfort. All the 10 selected studies were clinical trials. Participants derived from small pilot studies (De Groot et al., 2015; Bauersfeld et al., 2018; Zorn et al., 2020), multicenter randomized-controlled trials (De Groot et al., 2020; Lugtenberg et al., 2021) or large single-arm studies (Valdemarin et al., 2021; Vernieri et al., 2022; Ligorio et al., 2024). Table 1 contains the details of each study design.

Fasting Interventions

Fasting treatment regimens varied among different studies and clinical trials with no standardization. FMD regimens could involve a 5-day cycle of progressively decreasing caloric intake repeated every 21-28 days (Ligorio et al., 2024; Vernieri et al., 2022). This contrasts with shorter-term protocols (Bauersfeld et al., 2018), such as fasting for 36 hours before and 24 hours after chemotherapy.

Duration

The average study duration varied greatly by country, the shorter being in Germany (10 months) and the longer Netherlands (47 months). The duration of these trials varied depending on the aim of the study. Studies focusing on the effects of fasting on patients averaged about 47 months, while trials focusing on the safety, feasibility, and metabolic effects of fasting lasted an average of 30 months. Feasibility and impact studies averaged 19 months, while anti-tumor efficacy trials, which require more rigorous follow-up, lasted the longest with an average duration of 156 months. In contrast, studies of short-term fasting and chemotherapy toxicity averaged 10 months. Trials evaluating the effect of fasting on both toxicity and efficacy lasted an average of 47 months, while those focusing on the safety and acceptability of fasting lasted an average of 13 months.

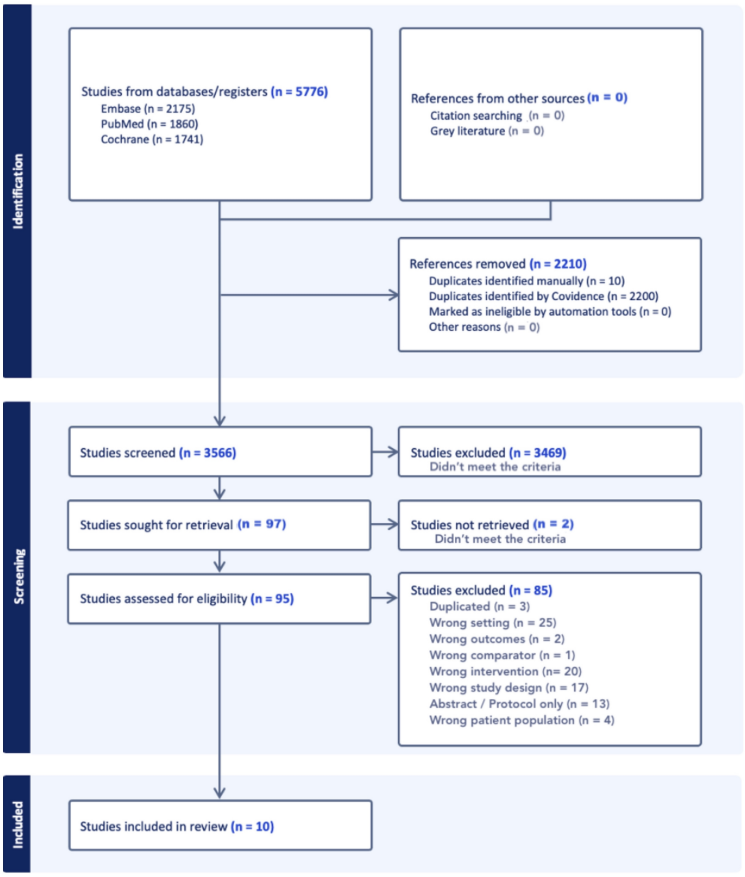

Figure 1: *PRISMA flowchart of study selection.*

Effectiveness

The effectiveness of these regimens varies, with some studies suggesting that FMD may improve chemotherapy tolerance and quality of life. Lugtenberg et al. (2021) reported more favorable QoL outcomes in patients who completed at least half of their chemotherapy cycles when following an FMD. There is a noticeable low adherence to extended and prolonged fasting cycles among patients.

Population

Patients harbored various malignancies, with breast and gynecological cancers being the most frequent (breast n=4, ovarian/uterine/cervical n=2, breast/ovarian n=1). The median age was 51 years. Seven studies included only females, and the rest included both genders (Vernieri et al., 2022: 27% male; Valdemarin et al., 2021: 24% male). None of the studies focused exclusively on males. The demographic characteristics and the type of cancer can be found in Table 1. The interventions and the cancer therapies vary in most of the studies, as shown in Table 2.

Fasting interventions

The studies explored a variety of fasting interventions without standardization. Four main types of fasting interventions were examined, namely FMD (Ligorio et al., 2024) (Vernieri et al., 2022) (De Groot et al., 2020) (Valdemarin et al., 2021) (Lugtenberg et al., 2021); short-term fasting only (Riedinger et al.,), Short-Term and Water-Only Fasting (De Groot et al., 2015), Combined Ketogenic Diet and Intermittent Fasting (KD-IF) (Voss et al., 2020) and Modified Short-Term Fasting (mSTF) (Zorn et al., 2020) (Bauersfeld et al., 2018). Additional details about the interventions are described in Table 2.

Outcomes

The studies present a range of findings, from survival rates to side effects and quality of life improvements (Table 3), illustrating both the potential benefits and the limitations of these dietary strategies.

Treatment response rates and progression-free survival

Regarding treatment response rates, De Groot et al. (2020) found that the intervention group had higher

Author (Year)	Country	Type of Study	Patients with Cancer (n)	Gender	Age (Mean and SD)
Ligorio et al. (2024)	Italy	Single-arm trial with retrospective cohort for comparison (subanalysis of Vernieri 2022)	90	-Female (n=90): 100%	-Fast Mimicking diet(n=14): 54 (51.59)
				-Male (n=0): 0%	-Control (n=76): 56 (47,68)
Vernieri et al. (2022)	Italy	Single arm trial	101	-Female (n=73): 72.3%	- ≥ 60 (n=28): 27.7%
				Male (n=28) 27.7%.	- <60 (n= 73): 72.3%
Lugtenberg et al. (2021)	Germany	Multicenter, randomized controlled trial, parallel group (subanalysis of De Groot 2020)	131	-Female (n=131): 100%	-Fast-Mimicking diet (FMD) (n=65): 49(31-71)
				-Male (n=0): 0%	-Regular diet (n=64): 51 (27-71)
Valdemarin et al.(2021)	Italy	Single-arm, phase I/II clinical trial	90	-Female(n=77): 86%	Single arm: 50.4 ± 8
				-Male (n=13) 14%	
De Groot et al. (2020)	Germany	Multicenter, randomized controlled trial, parallel group	129	-Female (n=129): 100%	-Fast-Mimicking Diet: (n=65):49.0 (31–71)
				-Male (n=0): 0%	-Regular diet (n=64): 51.0 (27–71)
Riedinger et al. (2020)	United States of America	Randomized controlled trial, parallel group	20	-Female (n=20): 100%	-Fasting group (n=10): 59.5 +- 10.33
				-Male (n=0): 0%	-Control group (n=10): 59 +- 10.23
Voss et al. (2020)	Germany	Randomized controlled trial, parallel group	50	-Female and male (n=50) (not specified)	-Fast-Mimicking Diet (ketogenic diet or intermittent fasting): 56 (39-71)
					-Regular diet: 58 (26-75)
Zorn et al. (2020)	Germany	Randomized, Controlled, cross-over pilot study	30	-Female (n=30): 100%	Cross-over: 54 ± 11 (30-74)
				-Male (n=0): 0%	
Bauersfeld et al.(2018)	Germany	Randomized cross-over pilot study	50	-Female (n=50): 100%	-Group A mean: 49.8+- 9.1
				-Male (n=0): 0%	-Group B mean: 53.6 +-7.3
De Groot et al.(2015)	Netherlands	Randomized, controlled pilot study	13	-Female (n=13): 100%	-mSTF(modified short term fasting) (n=7): 51(47-64)
				-Male (n=0): 0%	-non-STF (non modified short-term fasting) (n=6): 52 (44-69)

FMD = Fast Mimicking Diet; **mSTF** = modified Short-Term Fasting; **non-STF** = non-modified Short-Term Fasting; **HER2** = Human Epidermal Growth Factor Receptor 2; **NC** = Normocaloric Diet; **KD** = Ketogenic Diet.

Table 1: *Demographic characteristics, type of study and cancer.*

radiological complete or partial response rates (OR 3.168, P=0.039). However, Ligorio et al. (2024) did not find a statistically significant difference in objective response rate (ORR) or disease control rate (DCR) between intervention and control groups (ORR: 71.4% vs 56.6%, P = 0.46; DCR: 78.6% vs 78.9%, P = 1).

Progression-free survival (PFS) outcomes were reported by Voss et al. (2020), showing no differences in the PFS at 6 months post-radiotherapy (PFS6) of 20% in the intervention group versus 16% in the control group (P = 0.713). Similarly, Ligorio et al. (2024) found no significant PFS differences between groups (median PFS: 7.09 months, 95% CI: 4.01-NR, vs 6.61 months, 95% CI: 5.30-8.95; log-rank test P value = 0.3).

Biomarkers related to tuor, metabolic, or immune function

Five of the selected studies analyzed the impact of dietary intervention on biomarkers related to the tumor or immune system. Vernieri et al. (2022) showed a reduction in peripheral blood immunosuppressive myeloid cells and an increase in lymphoid cells, including certain T cells and natural killer cells. Additionally, functional changes were observed, such as increased expression of immune-activating molecules and a reduction in immunosuppressive markers. Cytokine expression changes included reductions in several inflammatory markers, while some cytokines like IL-8 increased.

Valdemarin et al. (2021) measured the impact on peripheral markers such as growth factors, adipokines, and cyto/chemokines. Leptin, IGF1, and IGFBP3 levels were found to be lower compared to baseline, while adiponectin and IGFBP1 levels were higher. Regarding the protective effect related to chemotherapy toxicity, De Groot et al. (2015, 2020) found in two studies that FMDs were associated with a significantly lower increase in DNA damage, as measured by *gamma*-H2AX intensity.

Due to the restrictive nature of the diet, metabolic changes were commonly identified, such as reductions in plasma glucose, insulin, and IGF-1 (Valdemarin et al., 2021; Ligorio et al. 2024; Zorn et al. 2020). Besides this, other changes were identified, such as reductions in Mean Corpuscular Volume and Mean Corpuscular Hemoglobin, and reduced mean free T3 levels, while mean free T4 rose significantly (Zorn et al. 2020).

Assessment of risk of bias in individual studies

Paired reviewers performed the quality assessment of included trials using the Cochrane Risk of Bias (RoB 1.0) Tool (Higgins et al., 2011). The appraisal of

the risk of bias of each included study is summarized in Figure 2.

Discussion

The results of this scoping review provide evidence regarding FMD and other fasting interventions as adjunct treatments to cancer therapies, exploring the potential to improve cancer outcomes. Consistent with recent reviews by Drexler et al. (2023) and Anemoulis et al. (2023). The analysis of this study indicates minor adverse effects and, although limited, promising evidence suggesting potential benefits in reducing chemotherapy-induced toxicities and improving overall QoL, survival, progression free survival (PFS), and treatment response rates. The heterogeneity of study designs, patient populations, and fasting protocols highlights the complexity of this research area and underscores the need for more standardized methodologies in future investigations.

Animal studies suggest possible biological mechanisms associated with increased tolerance to the toxic effects of chemotherapy-related to FMD. In vitro and animal studies indicate that normal and tumor cells have opposite response mechanisms to dietary deprivation, known as differential stress resistance (DSR). In fasting conditions, healthy cells downregulate proliferation, enhancing their protection against oxidative damage from chemotherapy, radiotherapy, and other toxic agents. Conversely, tumor cells are more susceptible to stress due to the inhibition of pathways associated with stress response control (Di Base & Longo, 2016; Tiwari et al., 2022; Longo et al., 2018).

Another mechanism involves the regulation of insulin-like growth factor (IGF), with its reduction associated with protection from cyclophosphamide and pro-oxidative damage to glial cells and neurons but not to glioma and neuroblastoma cells, according to Longo et al. (2018). The studies by Liborio et al. (2024) and Vernieri et al. (2022) point to the protective effects of FMD against chemotherapy. Bauserfeld et al. (2018) demonstrated that fasting interventions might improve QoL, particularly when combined with a normocaloric diet. Additionally, De Groot et al. (2015,2020) showed that FMD intervention is linked to a significantly lower increase in DNA damage as measured by *gamma*-H2AX intensity. Consistent reductions in serum IGF-1 levels were noted, suggesting another possible protective mechanism (Valdemarin et al., 2021; Ligorio et al., 2024; Zorn et al., 2020). The protective effect of FMD is likely pleiotropic, affecting several systems simultaneously through different mechanisms. The scarcity of clinical studies showing improved chemotherapy tolerability may stem from the wide heterogeneity of studied pathologies and the various chemotherapy and dietary regimens used.

The included studies presented diverse designs and patient populations, predominantly focusing on female participants with breast or gynecological cancers, such as clinical studies by De Groot et al. (2015) and Bauersfeld et al. (2018). Variations in the modality, duration, and frequency of fasting contributed to outcome variability, complicating direct comparisons and emphasizing the need for standardized methodologies in future research. Different types of cancer exhibit distinct biomolecular behaviors, making it difficult to generalize therapeutic outcomes across various cancer types. Each type of cancer can have unique genetic mutations, molecular pathways, and immune system interactions, leading to varying responses to treatment.

We analyzed 10 clinical studies with various designs, mostly focused on breast and gynecological cancers. However, two studies included malignant and solid or hematological cancers (Vernieri et al., 2022; Valdemarin et al., 2021). Most studies included only female participants due to the focus on breast and gynecological cancers, aligning with literature showing breast cancer as the most common cancer in women in 157 countries out of 185 in 2022, accounting for 1 in 8 cancer diagnoses and a total of 2.3 million new cases in both sexes (Sung et al., 2021; Heer et al., 2020; Arnold et al., 2022).

Participant numbers varied widely from small pilot studies (De Groot et al., 2015; Bauersfeld et al., 2018; Zorn et al., 2020) to multicenter randomized-controlled trials with more than 120 patients (De Groot et al., 2020; Lugtenberg et al., 2021) or large single-arm studies (Valdemarin et al., 2021; Vernieri et al., 2022; Ligorio et al., 2024). Del Paggio et al. (2021) noted that RCTs have been the standard to establish the efficacy of new cancer therapies for the past five decades. However, variations in study design in this field highlight the need for a framework for next-generation clinical trials, focusing on an optimal balance of operational efficiency, scientific impact, and value to patients (Spreafico et al., 2021). Ilerhunmwuwa et al. (2024) recently published a systematic review of dietary interventions in cancer, noting that most RCTs had small samples too.

Fasting treatment regimens varied among different studies and clinical trials with no standardization. The studies employed varying durations, frequencies, and types of fasting, leading to inconsistent results and making it difficult to draw definitive conclusions. For example, FMD regimens such as those used by Ligorio et al. (2024) and Vernieri et al. (2022) typically involve a 5-day cycle of progressively decreasing caloric intake repeated every 21-28 days. This contrasts with short-term fasting protocols, such as those

Author (year)	Type of cancer	Cancer therapy	Fasting scheme	Fasting duration
Ligorio et al.(2024)	-Advanced triple-negative breast cancer	First line	FMD: calorie-restricted diet with low carbohydrate, low protein dietary intervention	5-day FMD repeated every 21-28 days, up to a maximum of 8 c
		Carboplatin.gemcitabine for 8 consecutive cycles	-Day 1: 600 kcal -Day 2,3,4 and 5: 300 kcal	consecutive cycles
Vernieri et al.(2022)	-Breast: 56 (55.4%)	-Chemotherapy (n=73):72.3%	FMD: calorie-restricted diet with low carbohydrate, low protein dietary intervention	5-day FMD repeated every 21-28 days, up to a maximum of 8 consecutive cycles
	-Colorectal: 10 (9.9%) -Lung: 7 (6.9%) -Prostate: 4 (3.9%) -Pancreas: 3 (3%) -Melanoma: 3 (3%) -Germinal: 3 (3%) -Ovary: 2 (2%) -Thyroid: 2 (2%) - Hematological: 4 (4%) -Others: 7 (7%)	-Endocrine (± targeted therapies) (n=13): 12.9% -Immunotherapy (n=3): 2.9% -Targeted therapy (n=2): 2% -Radiotherapy (n=1): 1% -Radionuclide treatment (n=1): 1% -Best supportive care (n=8): 7.9%	-Day 1: 600 kcal -Day 2,3,4 and 5: 300 kcal	
Lugtenberg et al.(2021)	-HER2-negative stage II/III breast cancer	4 cycles: Doxorrubicin + cyclophosfamide.	FMD (Xentigen™): plant-based, low amino-acid substitution diet, consisting of soups, broths, liquids and tea	4-day FMD for 3 days prior to and on the day of each cycle neoadjuvant chemotherapy
		4 cycles: docetaxel. or 3 cycles fluorouracil, epirrubicin, cyclophosfamide+ 3 cycles docetaxel	Calorie content: -day 1 (~1200 kcal), -days 2–4 (~200 kcal)	
Valdemarin et al.(2021)	-Breast cancer: 68%	Chemotherapy: doxorubicin, paclitaxel, carboplatin, cisplatin, capecitabin, XELOX, FOLFOX.	FMD (L-Nutra™): plant-based ingredients, low-calorie and low-protein diet	5-day FMD cycles every 3 or 4 weeks, depending on the standard treatment received (chemotherapy, radiotherapy, endocrine therapy, etc).
	-Other cancers: 13.4%	Radiotherapy.	Day 1: 1099 kcal (11% protein, 46% fat and 43% carbohydrates)	
	-Hematologic: 6.7%,	Endocrine therapy: letrozole, exemestane, anastrozole.	Days 2-5: 717 kcal (9% protein, 44% fat and 47% carbohydrates)	
	-Colorectal cancers: 4.4%	target therapies: TKI, ruxolitinib,		
	-Prostate cancer 3.3%	biological drugs, BCG, immune checkpoints inh.		
	-Lung cancer 3.3%			
De Groot et al. (2020)	-HER2-negative stage II/III breast cancer patients	4 cycles: Doxorrubicin + cyclophosphamide.	FMD (Xentigen™): plant-based, low amino-acid substitution diet, consisting of soups, broths, liquids and tea Calorie content:	4-day FMD for 3 days prior to and on the day of each cycle neoadjuvant chemotherapy
		4 cycles: docetaxel. or 3 cycles fluorouracil, epirrubicin, cyclophosphamide 3 cycles docetaxel	-day 1 (~1200 kcal), -days 2–4 (~200 kcal)	
Riedinger et al.(2020)	Fasting group vs Control group: -Ovary:50%/60% -Uterus:40%/40% -Cervix: 10%/0%	Bevacizumab, carboplatin, cisplatin, docetaxel, doxorubicin, gemcitabine, paclitaxel	Short term fasting: abstain from all caloric nutrition intake	24h before to 24hs following chemotherapy
Voss et al. (2020)	FMD: -Glioblastoma: 23 -Lesser grade brain tumor: 2 Regular diet: -Glioblastoma:18 -Lesser grade brain tumor: 7	Radiotherapy: 5 x 4 Gy from day 4 to 8.	KD (21-23 kcal/kg/d), followed by fasting and again KD.	Ketogenic diet on days 1 to 3, fasting on days 4 to 6 and ketogenic diet on days 7 to 9 associated with radiotherapy from day 4 to 8.
Zorn et al.(2020)	-Breast Cancer: 22 (73,33%)	>4 cycles chemotherapy: Epirubicin/cyclophosphamide, (Breast cancer) for 2-3 cycles in each cross-over period	Interventions: 1.modified Short-Term Fasting (mSFT) based on 25% caloric requirement of each patient (400 and 600 kcal/day)	mSTF started 3 days prior to chemotherapy, and ended 1 day after chemotherapy (fasting period of 96 hours)
	-Endometrial Ca: 2 (6,7%) -Ovarian Ca: 2 (6.7%)		2. 6-day normocaloric diet (NC) 3.Ketogenic Diet (KD) prior to each mSFT.	
	-Cervical Ca 4 (13,3%)		4 cross over groups: A:mSFT/NC B: NC/mSTF C: KD+mSTF/NC D: NC/KD+mSTF	
Bauersfeld et al.(2018)	Group A: -Primary breast cancer: 12 (66.7%) -Advanced breast cancer 3 (16.7%) -Ovarian cancer 2 (11.1%) -Advanced ovarian cancer 1 (5.6%) Group B: -Primary breast cancer 13 (81.3%) -Advanced breast cancer 2 (12.5%) -Ovarian cancer 1 (6.3%) -Advanced ovarian cancer 0 (0%)	Chemotherapy: taxanes, paclitaxel, platinum agents,cyclophosphamide, anthracyclines, doxorubicin, methotrexate, bevacizumab, trastuzumab for 6 cycles	Short term fasting in the first half of chemotherapies followed by normocaloric diet or vice-versa	60 hours of short-term fasting (36 hours before to 24 hours after chemotherapy).
De Groot et al.(2015)	HER2-negative stage II/III breast cancer.	3-weekly cycle (six in total), docetaxel, adriamycin and cyclophosphamide + granulocyte-colony stimulating factor + dexamethasone	Short Term Fasting - only allowed to drink water, and coffee or tea without sugar	24h before until 24h after chemotherapy.

KD = Ketogenic Diet; **XELOX** = Capecitabine plus Oxaliplatin chemotherapy; **FOLFOX** = Chemotherapy regimen containing Folinic Acid, Fluorouracil, and Oxaliplatin; **TKI** = Tyrosine Kinase Inhibitor; **BCG** = Bacillus Calmette-Guérin vaccine.

Table 2: *Fasting schemes and cancer treatments.*

Study	Survival	Side Effects of chemotherapy	Quality of Life
Ligorio 2024	Intervention group: 30.3 months (95% CI 18-NR) Control group: 17.2 months (95% CI 15.3-25.1), log-rank p=0.041.	N/A	No QoL data
Vernieri 2022	No survival data	Fatigue (90.2%) ; Grade III/Grade IV (4%)	No QoL data
Lugtenberg et al. 2021	No survival data	N/A	More favorable QoL outcomes in patients adherent to at least half of the chemotherapy cycles
Valdemarin 2021	No survival data	Enhanced tolerance to chemotherapy Headache (26 patients, 29%) and fatigue (23 patients, 26%), followed by diarrhea (3 patients, 3%), abdominal pain (2 patients, 2%), nausea (1 patient, 1%), constipation (1 patient, 1%), decreased libido (1 patient, 1%) and symptomatic hypoglycemia (1 patient, 1%).	No QoL data
De Groot 2020	No survival data	Grade III/IV toxicity similar	No QoL data
Riedinger 2020	No survival data	Reduced side effects	Improved QoL
Voss 2020	Intervention group: 331 days (95% CI:124-538), Control group: 291 days (95% CI:165-417), p=0.978	Headache, nausea, or possible epileptic seizures with short-lasting aphasia.	No QoL data
Zorn 2020	No survival data	1. Reduction in chemotherapy-induced toxicities such as stomatitis, headaches, weakness, and overall toxicity score. 2. Improved tolerance to chemotherapy with fewer postpones.	No QoL data
Bauersfeld 2018	No survival data	(headache, hunger, slight nausea). Less Fatigue	Better QoL only in the first crossover group
De Groot 2015	No survival data	No significant difference in incidence of grade III/IV side effects between the STF and non-STF group.	No QoL data

QoL = Quality of Life; **CI** = Confidence Interval

Table 3: *Study outcome.*

Study ID	D1	D2	D3	D4	D5	D6	D7	Overall
Valdemarin 2021	!	!	-	-	-	-	-	-
Ligorio 2024	-	-	-	!	+	!	-	-
Lugtenberg 2021	+	!	-	-	!	-	-	-
De Groot 2020	+	+	-	!	+	+	+	+
Riedinger 2020	+	+	-	!	+	+	!	+
Voss 2020	!	!	-	!	!	+	+	!
Bauersfeld 2018	+	!	-	-	+	+	-	+
De Groot 2015	!	!	-	-	+	+	-	!
Zorn 2020	-	-	-	!	+	+	+	+
Vernieri 2022	-	-	-	-	!	!	-	-

***D1**: Sequence Generation; **D2**: Allocation concealment; **D3**: Blinding of participants and personnel for all outcomes; **D4**: Blinding of outcome assessors for all outcomes; **D5**: Incomplete outcome data for all outcomes; **D6**: Selective outcome reporting; **D7**: other sources of bias; + low risk; ! unclear risk; - high risk.*

Figure 2: *Overall survival, quality of life of cancer patients, and chemotherapy-induced toxicity.*

of Bauersfeld et al. (2018), which involve fasting for 36 hours before and 24 hours after chemotherapy.

The effectiveness of these regimens varies, with some studies suggesting that FMD may improve chemotherapy tolerance and quality of life. For example, Lugtenberg et al. (2021) reported more favorable QoL outcomes in patients who completed at least half of their chemotherapy cycles when following an FMD. However, the heterogeneity of fasting protocols complicates direct comparisons and underscores the need for standardized regimens. There is a noticeable low adherence to extended and prolonged fasting cycles among patients, which could impact the results of studies on fasting and cancer (Lugtenberg et al., 2021; Vernieri et al., 2022). The systematic review by Drexler et al. (2023) also reported that while IF and FMD can reduce chemotherapy-related toxicity, patient adherence varied widely depending on the fasting duration and support systems in place. They highlighted the importance of personalized fasting regimens to improve adherence and outcomes.

One of the main limitations of the studies is the generalizability of results, particularly those evaluated subjectively, such as QoL. l. This issue arises primarily from the lack of blinding, which is a consequence of the nature of the intervention and the impossibility of concealing it. Participants who are aware they are undergoing a fasting regimen may report changes in their quality of life based on their expectations or preconceived notions about fasting. Similarly, researchers who know which participants are fasting may unintentionally influence the assessments of subjective outcomes. Our risk of bias assessment conducted using the RoB 1 tool revealed several areas of concern. Sequence generation and allocation concealment were often inadequately described, leading to potential selection bias. The lack of blinding in many studies introduces performance and detection bias due to subjective outcomes. High dropout rates and incomplete data were also common, generating concerns that studies with significant missing data may not accurately reflect the intervention effects. Therefore, we recognize the need for studies with a low risk of bias on this topic. The methodological limitations or high risk of bias of these studies, while informative for understanding the overall research landscape, can generate less reliable results. This necessitates a cautious interpretation of the review's findings, particularly concerning generalizability to broader contexts.

Our findings suggest that while fasting interventions appear promising, the current evidence is insufficient to justify their widespread clinical adoption. Future research should focus on larger, well-designed randomized controlled trials with standardized protocols and consistent outcome measures. Investigations into the underlying mechanisms of fasting, such as the role of autophagy and hormesis, could provide a greater understanding and amplify the therapeutic potential of fasting in cancer treatment. Autophagy, a cellular degradation process activated by fasting, aids in the removal of damaged cells and the maintenance of cellular homeostasis, which could improve the efficacy of cancer treatments (Antunes et al., 2018). Additionally, hormesis—the concept that mild stress from fasting can trigger protective pathways (Zimmermann et al., 2014)—might be important in reducing chemotherapy-induced toxicity and improving overall treatment outcomes.

The primary strength of this scoping review is the inclusion of a diverse set of clinical trials, providing a comprehensive overview of fasting interventions in cancer treatment. Following PRISMA guidelines, our search strategy included three major databases: PubMed, Embase, and the Cochrane Library. However, many studies had small sample sizes, high dropout rates, and potential biases inherent in open-label designs. The heterogeneity of the included trials limits the generalizability of our review, as most trials were conducted in Europe, which may affect the applicability of the results to other regions. Additionally, the diversity of patient populations, cancer types, and fasting protocols requires caution when extrapolating these findings to broader clinical practice. Furthermore, the review was limited to English-language studies and included some at high risk of bias, which may introduce bias into the overall results and affect their generalizability.

Conclusion

Although fasting interventions show promise in improving cancer treatment outcomes, the current evidence is insufficient to ensure their efficacy for clinical implementation. The results remain controversial, and fasting as an adjunct to standard therapy is not yet a general recommendation. Future research should aim to standardize fasting protocols, including larger and more diverse patient populations, and employ rigorous methods to minimize bias and enhance the reliability of results.

Additionally, prioritizing the assessment of each cancer as a unique pathology should be an important consideration each time an intervention is evaluated for neoplasms. This is important because each cancer varies in the organ system affected and, in its pathophysiology, leads to different responses to the same therapy. Further rigorous studies are essential to validate the potential benefits of fasting interventions and to explore the underlying biological mechanisms, such as autophagy and hormesis, that may contribute

to their therapeutic effects.

Furthermore, the Fast-Mimicking Diet (FMD) regimen may serve as a coadjuvant treatment worthy of further investigation, given its known potential to provide a standardized dietary intervention that combines the benefits of fasting regimens with an established and consistent dietary intake.

Authors Contributions

All the authors contributed equally to the conceptualization, design, formal analysis, methodology, interpretation of data, writing, and critical revision of the original draft and approved the final version to be published. Therefore, the authorship order was determined alphabetically using the given name of each author.

Supplementary Materials

Search Strategy Used in Each Database

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