Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0841

LETTER

Dietary restriction during active cancer therapy is associated with improved treatment response: a systematic review and meta-analysis

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Cancer remains a leading cause of death worldwide, despite advances in surgery, chemotherapy, radiotherapy, and immunotherapy[1]. Challenges, like treatment-related toxicities and resistance, limit the overall benefits of current cancer therapies, leading to increased interest in supportive strategies that can boost treatment effectiveness while maintaining tolerability.

Dietary restrictions, including calorie restriction (CR), a fasting-mimicking diet (FMD), and short-term fasting (STF), are emerging as promising adjuncts in cancer treatment by modulating tumour metabolism and the body's stress-response pathways[2]. CR is defined as a sustained reduction in daily caloric intake (typically 20%–40%). A FMD is defined as a low-calorie, low-protein, low-carbohydrate dietary regimen administered over 3–5 d per cycle. STF is defined as complete or near-complete fasting lasting 24–72 h surrounding therapy.

Cancer cells undergo significant metabolic reprogramming, primarily relying on aerobic glycolysis and growth factor signalling, a phenomenon known as the Warburg effect. This dependency makes malignant cells highly vulnerable to disruptions in the nutrient supply. Preclinical research has consistently shown that CR diets lower circulating insulin and insulin-like growth factor (IGF)-1 levels, activate AMP-activated protein kinase, inhibit mechanistic target of rapamycin (mTOR) signalling, and promote autophagy. While mTOR signalling is a key metabolic pathway implicated in several cancers, we acknowledge that cancer progression is heterogeneous and involves multiple parallel, context-specific pathways.

These effects help normal tissues develop resistance to stress, while making cancer cells more sensitive to treatment and improving therapy effectiveness without increasing collateral damage. However, the clinical evidence remains fragmented. Previous reviews frequently group together various dietary interventions, such as ketogenic, low-carbohydrate, or protein-restricted diets, each affecting different biological pathways.

To address this gap, we performed a systematic review and meta-analysis focusing on dietary restriction strategies in patients with cancer. These strategies were applied for at least 48 h during active cancer treatment. Our primary objective was to assess the response to oncologic therapy, while secondary outcomes included treatment-related toxicity, quality of life (QoL), and metabolic measures. The study followed PRISMA guidelines and was registered prospectively with PROSPERO (CRD42023460206).

Methodology

A thorough search of PubMed, Embase, and CINAHL from 1973 to October 2025 identified 12 eligible studies involving human participants undergoing dietary restriction during active cancer treatment (**Table 1**)[3-10]. These studies included

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Received March 20, 2026; accepted May 19, 2026;
published online July 13, 2026.
Available at www.cancerbiomed.org

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Table 1 Outcomes of included studies

Study ID	Change in QoL scores			Number of adverse effects			Treatment outcomes (Radiological response)		
	Control	Intervention	*P*	Control	Intervention	*P*	Control	Intervention	*P*
Bahrami et al. (2024)[3]				Grade I: 47 Grade II: 57 Grade III: 50	Grade I: 59 Grade II: 71 Grade II: 24		CR/PR: 8 SD/PD: 14	CR/PR: 15 SD/PD: 7	*P* 0.03
Demark-Wahnefried et al. (2017)[4]	+1.1	−0.04	0.68						
Demark-Wahnefried et al. (2020)[2]	+0.9	+0.3	0.58						
de Groot et al. (2015)[5]				3	6				
de Groot et al. (2020)[6]				36 (out of 64)	11 (out of 22)	0.54	CR/PR: 38* SD/PD: 14*	CR/PR: 47* SD/PD: 6*	0.039*
Lugtenberg et al. (2021)[7]	−4.7	−0.8	0.30						
Riedinger et al. (2020)[8]	+0.22	+5.1	0.01	2	0	0.49	CR/PR: 8 SD/PD: 2	CR/PR: 10 SD/PD: 0	0.47**
Zuccoli et al. (2010)[9]				No adverse side effects			No clear evidence of disease recurrence		
Study ID	Average QoL scores								
Li et al. (2015)[10]	M: 55.6	M: 67.8	<0.05						

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease. *intention to treat, **calculated using the Fisher's exact test. Quality of life scoring: (Demark-Wahnefried et al. (2017)[4]: RAND-36, Demark-Wahnefried et al. (2020)[2]: FACT B, Lugtenberg et al. (2021)[7]: EORTC-QLQ-C30, Riedinger et al. (2020)[8]: NCCN FACT FOSI-18, Li et al. (2015)[10]: SF-36).

nine randomized controlled trials, one prospective single-arm study, and one case report involving various solid tumours with breast and prostate cancers the most common. The dietary interventions studied were CR in six studies, a FMD in four studies, and STF in two studies. Treatment outcomes were assessed using RECIST criteria and classified as favourable (complete or partial response) or non-favourable (stable or progressive disease). Bias risk was evaluated with RoB 2, ROBINS-I, and Joanna Briggs Institute tools, depending on the study type. Importantly, dietary restriction interventions in the included studies were applied under controlled conditions and patients with malnutrition or cachexia were generally excluded from the included studies.

Binary outcomes (e.g., treatment response) were summarized using odds ratios (ORs), which are appropriate for dichotomous event data. Continuous outcomes (e.g., QoL and metabolic markers) were analysed using standardized mean differences (SMDs) to account for variability in measurement scales across studies. Pooling was performed only when at least three studies reported comparable outcomes with similar definitions and measurement approaches. Detailed methodology is included in the Supplementary Material.

A meta-analysis was performed when at least three studies reported the same outcome, utilizing standardized mean differences with 95% confidence intervals within a random-effects model. Heterogeneity was evaluated with the I^2 statistic and considered with a narrative synthesis. A correlation coefficient of 0.5 was assumed in accordance with Cochrane guidance for studies reporting change-from-baseline outcomes without paired raw data. Although varying this assumption may have influenced the estimated variance, sufficient paired summary statistics were not consistently available to allow formal sensitivity analyses using alternative correlation coefficients. Therefore, this was considered a limitation of the study.

A random-effects model was used *a priori* due to the expected clinical heterogeneity across studies. Fixed-effect estimates were also examined and yielded similar results for outcomes with low statistical heterogeneity (I^2 = 0%). Sensitivity analyses and narrative synthesis were prioritized and pooling was interpreted cautiously for outcomes with substantial heterogeneity (I^2 >75%). Data were inverted by multiplying effect sizes by −1 to ensure consistency in interpretation, such that negative values uniformly reflected improvement across all analyses for outcomes where higher values indicated improvement (e.g., QoL scores). Multiple cancer types were included to provide a comprehensive overview of current evidence given the limited number of available studies. However, subgroup analyses by cancer type

were not feasible due to insufficient data. Notably, hormone-sensitive cancers predominated in the included studies, which may have influenced the generalizability of findings to other cancer types.

Results

A meta-analysis of studies on the oncologic response showed that patients undergoing dietary restriction had a significantly higher probability of favourable treatment outcomes compared to controls [OR: 4.55; 95% confidence interval (CI): 1.64, 12.58]. The analysis exhibited low heterogeneity ($I^2 = 0\%$; $P = 0.87$) and a significant Z-score ($P = 0.004$; **Figure 1**).

These findings are consistent with individual clinical trials showing that patients undergoing FMD during neoadjuvant chemotherapy experience more significant pathologic responses, including higher rates of Miller–Payne grade 4/5 responses and better radiologic outcomes.

With respect to treatment-related toxicity, multiple studies reported numerically fewer adverse events, including neutropenia, neutropenic fever, and gastrointestinal symptoms, in the dietary restriction arms compared to controls. While pooled analyses did not demonstrate statistically significant reductions in toxicity, heterogeneity in reporting methods, toxicity grading, and treatment regimens limited quantitative synthesis. No study reported an increase in serious adverse events attributable to dietary restriction, supporting the short-term safety of these interventions when implemented in controlled settings.

QoL outcomes were evaluated using validated instruments across five studies. Although pooled analyses did not show statistically significant differences between dietary restriction and control groups (SMD: 0.18; 95% CI: −0.22 to 0.59; $P = 0.37$), point estimates generally favoured dietary restriction and sensitivity analyses suggested that small sample sizes and methodologic heterogeneity were key contributors to imprecision ($I^2 = 39\%$; $P = 0.18$).

Metabolic outcomes demonstrated biologically consistent trends. Several studies reported reductions in insulin, glucose, and IGF-1 levels in the dietary restriction groups, supporting mechanistic plausibility. Meta-analyses of these parameters did not reach statistical significance, largely Due to substantial heterogeneity in glucose reporting, including absolute

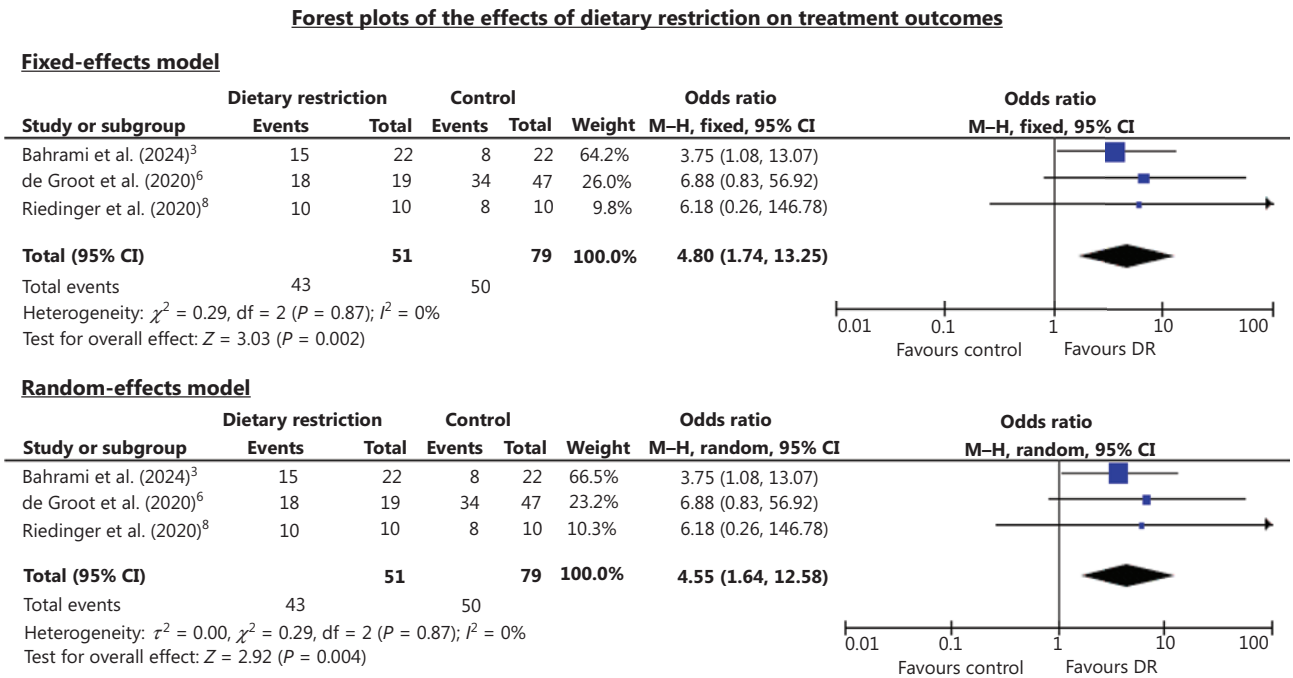


Figure 1 Effect of dietary restriction on clinical outcomes: Forest plots comparing the effect of DR *vs.* control across included studies. Fixed-effects model (Mantel–Haenszel method): The pooled OR demonstrated a significant association favouring dietary restriction (OR = 4.80, 95% CI: 1.74, 13.25; $P = 0.002$). There was no evidence of heterogeneity among studies ($\chi^2 = 0.29$, df = 2, $P = 0.87$; $I^2 = 0\%$). Random-effects model: Using a random-effects model, the overall effect remained significant (OR = 4.55, 95% CI: 1.64, 12.58; $P = 0.004$), with similarly low heterogeneity ($\tau^2 = 0.00$; $\chi^2 = 0.29$, df = 2, $P = 0.87$; $I^2 = 0\%$). Each square represents the effect estimate for an individual study with size proportional to study weight and horizontal lines indicating 95% confidence intervals. The diamond represents the pooled effect estimate. Values to the right of the line of no effect (OR = 1) favour dietary restriction. CI, confidence interval; DR, dietary restriction; OR, odds ratio.

concentrations, change scores, median values, and percentage changes without corresponding measures of variance, a quantitative meta-analysis of glucose outcomes was not feasible [insulin (SMD: −0.83; 95% CI: −1.86, 0.21; $P = 0.12$) or IGF-1 (SMD: 1.16; 95% CI: −0.79, 3.11; $P = 0.24$)]. Both analyses demonstrated substantial heterogeneity [insulin ($I^2 = 88\%$) or IGF-1 ($I^2 = 92\%$)]. Sensitivity analyses excluding outlier studies reduced heterogeneity and attenuated effect sizes toward neutrality, suggesting that variability in intervention protocols, baseline metabolic status, and concurrent therapies influenced observed effects.

Discussion

From a mechanistic standpoint, the improvement in treatment response without increased toxicity supports the biological concept of differential stress resistance and stress sensitization. CR reduces systemic insulin and IGF-1 levels, which downregulates pro-growth pathways, such as PI3K–AKT–mTOR, and activating stress responses, including AMP-activated protein kinase pathways and autophagy[7]. These shifts lead to cell-cycle arrest, better oxidative stress resilience, and improved cellular repair in healthy tissues. Conversely, cancer cells, defined by constant oncogenic signalling and poor stress response, cannot activate protective mechanisms, making cancer cells more vulnerable to damage from chemotherapy and radiotherapy. This difference helps explain the positive treatment outcomes observed in studies, even when patient-reported toxicity and QoL change little.

Notably, the high prevalence of hormone-sensitive cancers, like breast and prostate cancers, in the reviewed studies may partly account for the treatment responses observed. These tumours rely heavily on metabolic and endocrine signalling pathways, making the tumours potentially more responsive to transient nutrient deprivation. In addition, evidence from both preclinical and clinical research indicated that even brief interventions can lead to significant decreases in insulin and IGF-1 levels, supporting the biological basis for the minimum duration of intervention examined in this review.

Several factors likely explain the lack of statistically robust findings across secondary outcomes, including heterogeneity in cancer types, treatment modalities, dietary protocols, and adherence monitoring. Compliance varied widely, particularly in the FMD studies, and contamination of control groups was observed in some trials. In addition, most studies enrolled small sample sizes with a short duration of follow-up, limiting the ability to detect modest but clinically meaningful effects. The predominance of hormone-sensitive cancers may further restrict generalizability because these tumours could be particularly responsive to metabolic interventions. Long-term clinical outcomes, including progression-free and overall survival, remain underreported in the current literature and represent a key gap in knowledge. Future studies should incorporate these endpoints to better evaluate the clinical impact of dietary restriction strategies in cancer therapy.

Despite these limitations, this analysis provides a focused synthesis to date of calorie-based dietary restriction during active cancer therapy, distinct from broader dietary modification strategies. To our knowledge, this is the first systematic review to isolate CR, a FMD, and STF and examine clinical responses and metabolic biomarkers within a unified framework.

Conclusions

In conclusion, dietary restriction implemented during active cancer treatment was associated with a favourable response without evidence of increased toxicity or compromised quality of life. While secondary outcomes did not demonstrate statistically significant pooled effects, observed trends and mechanistic coherence support further investigation. These findings highlight key considerations for future trials, including standardized dietary protocols, objective adherence monitoring, and incorporation of metabolic and immune biomarkers to identify responders. Long-term oncologic endpoints, such as progression-free and overall survival remain largely unexplored. Together, these data suggest that calorie-based dietary restriction is a biologically coherent adjunct to cancer therapy and warrants evaluation in adequately powered randomized trials.

Grant support

The project was supported by the Lee Kong Chian School of Medicine Center for Microbiome Medicine, the Wang Lee Wah Memorial Fund, and the Student Scholarly Project. We would like to thank the Ong Tiong Tat Endowed Chair Professorship for Yusuf Ali. Dr. Rupesh Agrawal (Grant No. MOH-001287-00) is supported by the Clinician Scientist Grant from the National Medical Research Council (NMRC). Sunny Wong is supported by the Singapore National Medical Research Council Clinician Scientist Individual Research Grant (Grant No. CIRG23jan-0004), Large Collaborative Grant (Grant Nos. OFLCG22may-0009, OFLCG23may-0031, and OFLCG24may-0025).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Ee Chern Ng: Investigation, Data curation, Writing – review & editing.
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William K.K. Wu: Writing review & editing, Supervision.
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Sunny H. Wong: Conceptualization, Supervision, Project administration, Writing review & editing.

Data availability statement

The data relevant to this article are available in the published articles and supplementary material.

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Cite this article as: Agrawal K, Goh DSY, Ng EC, Tan SY, Cifuentes-González C, Kang JX, et al. Dietary restriction during active cancer therapy is associated with improved treatment response: a systematic review and meta-analysis. Cancer Biol Med. 2026; 23: 1193-1197. doi: 10.20892/j.issn.2095-3941.2025.0841