Heliyon 9 (2023) e22814

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Take metabolic heterogeneity into consideration when applying dietary interventions to cancer therapy: A review

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ARTICLE INFO

Keywords:
Dietary interventions
Cancer
Metabolic heterogeneity
Precision nutrition
Anticancer therapy

ABSTRACT

In recent years, dietary interventions have attracted much attention in cancer therapy. Mechanistic studies suggest that dietary interventions can inhibit the progression of cancer through deprivation of essential metabolites, lowering the levels of protumor hormones, activation of anticancer immunity and synergistic effects with conventional anticancer therapies. The feasibility, safety and promising tumor outcomes have also been established in humans. However, the results from both preclinical and clinical studies are inconsistent or even conflicting, the reasons for which have not been extensively considered. In this review, we discuss the various heterogeneity, including dietary protocols, tissue of origin and cancer locations, spatial and temporal metabolic heterogeneity, and divergent combination treatment, that may affect the responses of different cancers to dietary interventions. Understanding this heterogeneity and taking them into consideration when applying dietary interventions to cancer therapy will allow us to deliver the right diet to the right patient at the right time to maximize compliance, safety and efficacy of conventional anticancer therapy and to improve the outcomes of patients with cancer.

1. Introduction

In the past several decades, beginning in the Western world, we have witnessed a dietary pattern transition from a traditional healthy diet, which is characterized by an appropriate energy intake and is mainly focused on the consumption of plant-based foods, to a Western diet, which mainly relies on animal source foods rich in calories, fat and protein [1]. Along with other unhealthy lifestyle changes, including low physical activity and sedentary behaviors, the dietary pattern transition leads to a global pandemic of overweight and obesity, which has been strongly established as the leading risk factor for various serious unmet public health challenges, including cancer [2,3]. Currently, the mechanisms through which an unhealthy dietary pattern, such as a high-fat diet (HFD) and excess adiposity, promotes the initiation and progression of tumorigenesis have been extensively investigated, including specific dietary components, inflammation, hormones and effects on cancer stem cells [4,5]. Therefore, several guidelines have been published to recommend a healthy dietary pattern for cancer prevention [6]. In addition, for the more urgent unmet need that numerous patients with established cancer lack effective therapies, the use of dietary interventions to enhance the efficacy of conventional cancer therapy, including chemotherapy, radiotherapy, targeted therapy and immunotherapy, has attracted much more attention.

Several dietary regimens, which are mainly formulated through restriction of specific dietary components or whole groups of

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https://doi.org/10.1016/j.heliyon.2023.e22814
Received 3 July 2023; Received in revised form 13 October 2023; Accepted 20 November 2023
Available online 23 November 2023

nutrients, have been tested in preclinical and early-phase clinical conditions. Dietary interventions, including fasting, a fasting-mimetic diet (FMD), calorie restriction (CR), a low-fat diet (LFD), a ketogenic diet (KD) and amino acid deprivation or supplementation, were shown to improve the efficacy of conventional cancer therapy and be feasible and safe in humans [7]. Based on this promising evidence, these dietary modifications are advancing well along the clinical translation, with an LFD already recommended for clinical practice for patients with breast cancer [8]. Nonetheless, evidence-based guidelines or clear dietary recommendations for patients with various cancers are still lacking. Furthermore, the observed effects of a given diet varied across studies. These variations and discrepancies warrant further mechanistic exploration and clinical work to determine the right dietary intervention, right patient and right time.

Designing the best dietary regimen for individual patients with cancer is very complex, and there is no one-size-fits-all dietary regimen for the treatment of cancer, as metabolic activity and nutrient preferences vary across cancers with different tissue origins and subtypes with different histological and molecular features [9]. Likewise, spatial and temporal metabolic heterogeneity makes cancers respond to changes in diet unequally [10]. Furthermore, various dietary modifications may differentially affect conventional cancer therapies. In this review, we will comprehensively discuss these context-dependent effects of dietary intervention on cancer and the underlying explanations, providing knowledge on how best and most effective to apply dietary interventions to manage patients with cancer. In this review, we mainly focused on strategies that are based on dietary restriction or supplementation of specific nutrient elements for therapeutic purposes, whereas others that are derived from regional and cultural dietary patterns, such as vegetarian diets and Mediterranean diets, are out of the scope of our discussion, as these diets are generally explored to improve cardiovascular and metabolic health but not to prevent cancer progression, largely attributing to the difficulty in implementing these 'ingredient-based' diets in preclinical models.

2. Anticancer mechanisms of dietary interventions

Currently, numerous data from preclinical and early clinical studies have shown that some dietary interventions have a powerful role in inhibiting tumor growth and enhancing the efficacy of conventional anticancer therapy. Although robust mechanistic conclusions are lacking and may differ across various dietary regimens, the anticancer effects of dietary interventions mainly rely on the physiological adaptations of the organism to dietary intake. In this section, we briefly describe the main proposed mechanisms through which dietary interventions can mediate anticancer effects (Fig. 1). For more detailed information, many excellent reviews are referenced [7,10,11].

Using preclinical models, studies have shown that through supplementation with energy and building blocks, mainly sugar, lipids and amino acids, diet supports the growth, proliferation, survival, metastasis and therapy resistance of cancer cells [7,12]. In addition, during transformation, the genetic background of tumors causes cancer cells to favor particular nutrients, making them vulnerable to

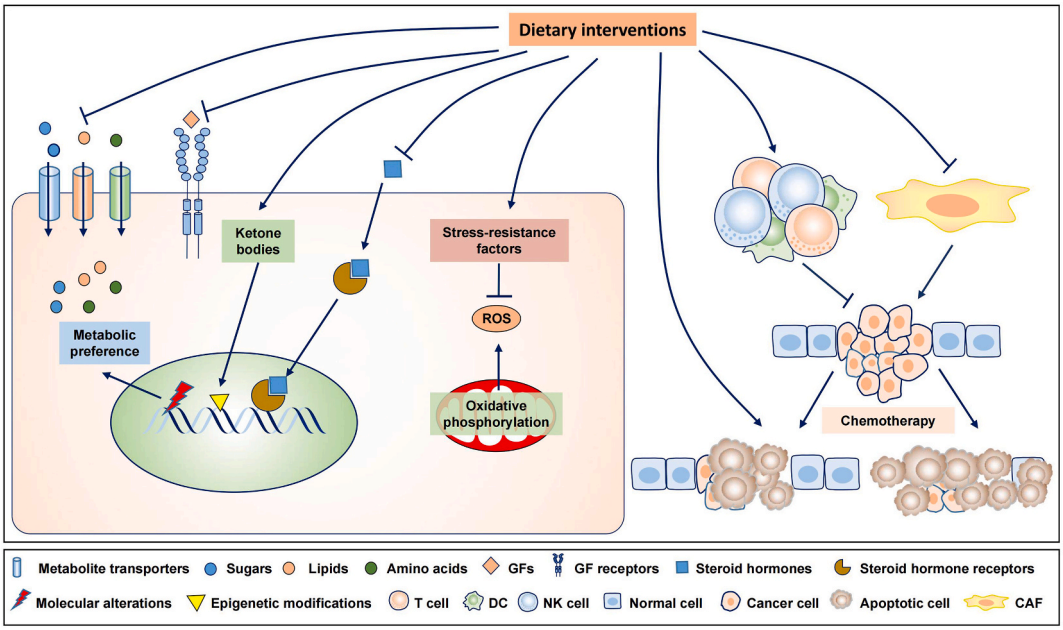

Fig. 1. Mechanisms for the anticancer effects of dietary interventions. Preclinical and preliminary clinical data indicate that dietary interventions reduce the levels of protumor metabolites and factors, including sugars, lipids, amino acids, growth factors (GFs) and steroid hormones. Dietary interventions can inhibit cancer progression through epigenetic modifications, stress-resistance factors, activation of anticancer immunity and inhibition of cancer-related fibroblasts (CAFs). Finally, the currently available evidence supports the synergistic effects of dietary interventions with conventional therapies, especially chemotherapy. DC, dendritic cell; NK cell, natural killer cell; ROS, reactive oxygen species.

Table 1
Completed clinical trials of dietary interventions with varied composition, duration and periodicity.

Diets	Cancer	Sample	Composition	Duration and periodicity	Dropout rate	Conclusion	Ref.
STF	Breast, ovarian	50	Unrestricted water, herbal tea, 2 × 100 cl vegetable juice and small standardized quantities of light vegetable broth; Daily calorie: <350 kcal	2.5 days	30 %	Well tolerated; improves quality of life and fatigue	[29]
STF	Breast	13	Water and coffee or tea without sugar	2 days	28.6 %	Well tolerated; reduces toxicity of chemotherapy	[30]
STF	Gynecological	24	Water, black coffee, or tea without sweetener; Daily calorie: 0 kcal	2 days	16.7 %	Well tolerated; improves quality of life scores	[31]
STF	Mixed	20	Ample water and beverages; Daily calorie: 0–200 kcal	3 days	23.1 %	Safe and feasible; reduces DNA damage	[32]
FMD	Mixed	101	Plant-based, low-carbohydrate, low-protein diet; Daily calorie: day 1, 600 kcal; days 2–5, 600 kcal	5 days per cycles (1–8 cycles)	1 %	Well tolerated; reshapes immunity	[33]
FMD	Mixed	90	Plant-based low-calorie and low-protein diet; Daily calorie: day 1, 1099 kcal (11 % protein, 46 % fat and 43 % carbohydrates); days 2–5, 717 kcal (9 % protein, 44 % fat and 47 % carbohydrates)	5 days per cycles (1–8 cycles)	10 %	Safe and feasible; reduces fat mass, insulin, IGF1 and leptin	[34]
FMD	Breast	131	Plant-based low amino-acid diet; Carbohydrates/proteins/fats energy ratio: day 1 (3.5/1/2), days 2–4 (complex carbohydrates >80 %); Daily calorie: day 1, ~1200 kcal, days 2–4, ~200 kcal	4 days	66.7 %	No difference in toxicity; reinforces the effects of neoadjuvant chemotherapy	[24]
FMD	Prostate	35	Plant-based low amino-acid diet; Carbohydrates/proteins/fats energy ratio: day 1 (3.5/1/2), days 2–4 (complex carbohydrates >80 %); Daily calorie: day 1, ~1200 kcal, days 2–4, ~200 kcal	4 days per month	17.1 %	Decrease in weight, abdominal circumference and blood pressure	[35]
IF	Breast	48	Fast for 18 h from 0 a.m. to 6 p.m., eat for 6 h from 6 p.m. to 0 a.m.; Daily calorie: <750 kcal	3 days	8.3 %	Decreases toxicity of chemotherapy	[36]
CR	Mixed	27	Calorie-free drinks such as water and tea/coffee without sugar, commercially formulated diet with 70 % protein restriction; Daily calorie: 30 %	5 days (2 cycles)	33.3 %	Improves therapeutic window	[37]
CR	ALL	120	Daily calorie: ≤80 % (Protein: ≥20 %; Fat: ≤25 %; Carbohydrate: ≤55 %)	NA	17.9 %	Augments chemotherapy efficacy	[38]
CR	Breast	338	Daily calorie: 500–1000 kcal deficit (Fat: ~25 %)	2 year	9.9 %	Potential beneficial effect on DFS	[39]
KD	Glioblastoma	172	Daily calorie: no restriction (fat, 70 %; carbohydrate, 3–5%)	12 weeks	25 %	Well tolerated; few side effects	[40]
KD	Glioblastoma	20	Daily calorie: no restriction (carbohydrate: 60 g/day)	6–8 weeks	15 %	Feasible and safe; no significant clinical activity	[41]
KD	Lung, Pancreatic	9	Daily calorie: no restriction (fat, 90 %; protein, 8 %; carbohydrate, 2 %)	5–6 weeks	66.3 %	Suboptimal compliance and poor tolerance	[42]
KD	Ovarian, Endometrial	73	Daily calorie: no restriction (fat, 70 %; protein, 25 %; carbohydrate, 5 %)	12 weeks	20 %	Loss of fat mass and retention of lean mass	[43]
LFD	Breast	1764	High vegetable, fruit, and grain intake (fat, 20 %)	8.5 years	NA	Decreased incidence of deaths	[44]
LFD	Breast	3088	High in vegetables, fruit, and fiber and low in fat (fat, 15–20 %)	6 years	NA	Did not reduce additional breast cancer events or mortality	[45]
STF + KD	Gynecological	30	STF: Daily minimum of 2.5 L of any calorie-free liquids, including water, herbal tea, and diet drinks without stimulants; Daily calorie: 25 % (400–600 kcal) KD: 75 % fat, 15 % protein and 10 % carbohydrates; Daily calorie: 100 %	4 days	41.2 %	Safe and feasible; reduces toxicities of chemotherapy	[46]

ALL, acute lymphoblastic leukemia; CR, calorie restriction; DFS, disease-free survival; FMD, fasting mimicking diets; IF, intermittent fasting; KD, ketogenic diet; LFD, low-fat diet; STF, short-term fasting.

changes in specific metabolites. Therefore, it is reasonable to manipulate dietary components according to metabolic preferences to starve cancer cells and inhibit cancer progression. For example, cancer cells commonly favor glucose as a primary nutrient for energy production and carbon sources of other building blocks, underlying the anticancer effects of dietary interventions with the ability to lower plasma glucose levels [13]. Some cancers are also dependent on serine and glycine for proliferation; thus, dietary restrictions inhibit tumor growth of intestinal cancer and lymphoma [14]. Adapting to dietary interventions, the organism also reprograms its metabolic hormones, such as insulin, insulin-like growth factor 1 (IGF-1), leptin, and steroid hormones, which play important roles in cancer proliferation and survival [10]. Dietary restriction can induce the expression of early growth response protein 1, a stress-resistance factor, while increased β-hydroxybutyrate (β-OHB) in KD diets activates the oxidative stress-resistance factors FOXO3A and MT2 [15,16]. These findings indicate that modulation of oxidative stress signaling is another factor underlying the anticancer effect of dietary interventions. Beyond supplying energy and building blocks, some metabolites, such as ketone bodies, can inhibit cancer progression and promote differentiation through epigenetic modifications [17]. In addition, dietary interventions and their systemic adaptations affect not only cancer cells but also their microenvironment. For example, recent evidence suggests that various dietary interventions can trigger the expansion of lymphoid progenitors and promote cancer immune attack via different mechanisms [18]. CR was shown to prevent fibrosis by downregulating TGF-β signaling, which further facilitates the interaction of immune cells with cancer [11]. Finally, the currently available evidence supports the synergistic effects of dietary interventions with conventional therapies, especially chemotherapy, which is based on the differential stress resistance (DSR) hypothesis that starvation would cause opposite effects in cancer versus normal cells in terms of their ability to withstand cell stressors, forcing normal cells to enter a highly protected state that prevents them from toxic insults while sensitizing cancer cells to anticancer drugs [18].

Despite these mechanisms being proposed to support the anticancer efficacy of dietary interventions, inconsistencies were also found in both preclinical model studies and early clinical trials. For example, different cancer types and even subpopulations arising from the same tissue showed different sensitivities to CR [19,20]. Under the same experimental conditions, CR significantly decreased the volume of tumors from colon cancer cell lines but not prostate and brain cancer cell lines, while for breast cancer, different cell lines displayed differential sensitivities to CR [19]. Similarly, although KD inhibits tumor growth and prolongs the survival of mouse models of brain, pancreatic, head and neck and stomach cancer, it can also enhance the progression of melanoma with the $BRAF^{V600E}$ mutation [21–23]. In clinical practice, studies have reported a lack of improvement in the survival of patients who used FMD before chemotherapy, while others have shown exceptional cancer responses [24,25]. Past trials of KDs in patients with cancer also found no survival benefits in recurrent glioblastoma or gliosarcoma but an improved survival rate in breast cancer [26,27]. However, these results were characterized by a high degree of heterogeneity regarding dietary regimens, duration, and prespecified health outcomes in conjunction with the timing of diet implementation, as well as the lack of the inclusion of control groups in most of the studies, which have likely obscured the efficacy of dietary interventions in patients who can benefit from them, warranting further understanding of the multifaceted heterogeneity when applying dietary interventions in cancer patients.

3. Protocol heterogeneity in dietary interventions

Diet supplies human body building blocks and energy mainly through three macronutrient categories: carbohydrate, fat and protein, as well as components that do not contribute to calorie sources but are indispensable for many biological processes, such as vitamins, minerals and fibers [28]. As mentioned above, these nutrients are also vital for cancer cells and can be utilized as cancer vulnerabilities. The numerous and complex food ingredients lead to heterogeneous dietary protocols modified for cancer treatment. Currently, dietary interventions for cancer therapy are mainly formulated through restriction of whole groups or specific dietary components of nutrients, aiming to eliminate nutrients exploited by cancer cells as fuel and signals for proliferation or therapy resistance. There are also some dietary regimens formulated by supplementing the standard diet with specific nutrients that have been suggested to have anticancer effects. The high degree of heterogeneity regarding dietary components, along with their varied duration and periodicity, determine the context-dependent effects of dietary interventions in patients with cancer (Table 1) [24,29–46].

3.1. Heterogeneous dietary compositions

Dietary interventions that limit nutrients higher in calorie production are the most common protocols used for cancer therapy, which include fasting and CR diets that differ in the extent of calorie reduction. Fasting, during which people no longer consume any food except for water voluntarily, has been advocated by some populations following their own beliefs for thousands of years, although with varied norms. The most common strategy is short-term fasting (STF), a technique that involves a fasting duration from 1 to 3 days, and some reports support its safety when the duration is extended to five days [47]. STF has been extensively investigated in animal models and has shown pleiotropic anticancer effects and the ability to potentiate the activity of conventional cancer therapies while protecting multiple normal cells from their side effects [18]. SFT has also been tested in combination with chemotherapy in clinical settings, and although the majority of studies suggest its feasibility and possible role in normal cell protection, no cancer outcomes have been reported [48]. Based on preliminary clinical evidence, a fast of at least 48 h is needed to achieve clinically meaningful outcomes, which results in relatively high dropout rates and potential malnutrition risk, making STF difficult to implement in clinical practice [18]. Therefore, several modified fasting regimens were medically designed through dietary component manipulation or the timing of food intake to achieve better long-term compliance and safety [49]. One such modified fasting regimen is the FMD, which consists of cycles of calorie-restricted, low-sugar and protein diets for several consecutive days (commonly 5 days, with day 1 consuming 50 % of normal daily intake and days 2–4 consuming 10 % of normal daily intake) each month, while nutrient uptake is not restricted during the remainder of the month. Animal and preliminary clinical studies have shown that FMD recreates the efficacy of

water-only fasting [33]. Another dietary modification, similar to FMD but with a higher calorie intake and long-term duration, formulated through restriction of whole groups of nutrients, is CR. Typically, CR involves a chronic 15–30 % reduction in standard caloric intake except for vitamins and minerals, which can improve metabolic activity but keep body weight within normal ranges [50]. As early as the 1990s, research found that CR can prevent or retard the growth of transplanted cancers in mice [51]. Since then, numerous studies have suggested a protective role of CR in slowing the growth of established cancers and reducing their distant metastasis [52,53]. Limited human data also suggest the safety and possible survival benefits of CR as an adjuvant cancer therapy [37, 39]. Although both fasting and CR were carried out through total calorie restriction and were shown to affect cancer progression, there were distinct differences in their metabolic effects. For example, fasting can significantly decrease glucose and IGF-1 levels and increase ketone bodies in humans, while CR does not, reflecting their different anticancer mechanisms, which should be taken into consideration when designing clinical trials [18]. In addition, different CR protocols showed significant differences in anticancer efficacy and mechanisms. For example, compared with intermittent CR, chronic CR had a more significant effect on oxidative stress protection and methylation levels of genes for adipokines, which play important roles in the development of breast cancer [54,55].

Different from fasting and CR, there have been dietary modifications focused on the ratio alteration of macronutrients, such as KD and LFD, two regimens with opposite fat proportions. The KD was clinically described in the 1920s as a dietary intervention in children with epilepsy but was also increasingly applied in patients with cancer. Typically, the KD has very low sugar consumption of less than 15 g per day but enough fat uptake to meet the calorie demand (≥95 % calories) [9]. In contrast, calories provided by fat account for less than 30 % of the LFD, which emphasizes the consumption of vegetables, fruits and whole grains [9]. Despite their distinct nutrient compositions, KD and LFD both showed anticancer effects and are advancing well along the clinical development pipeline. A systemic review including 13 clinical studies concluded that a KD in subjects with various cancers is safe and can improve metabolic parameters, but no effects on cancer outcomes have been reported [56]. Unlike KD, LFD has been examined for long-term benefits and risks in large prospective, randomized controlled trials (RCTs) including breast cancer, and a lowered incidence of deaths was observed [8,44]. Although both are effective at inhibiting cancer progression, KD and LFD have unique features underlying their anticancer effects, making them more feasible and effective in specific cancers. For example, an LFD typically has no effects on glycemic and ketone body levels but is effective at inhibiting weight gain and adiposity, which have been shown to promote cancer progression [57,58]. Therefore, LFD may be more promising in cancers that are rigorously influenced by obesity. However, a KD triggers anticancer metabolic adaptations mainly through the restriction of carbohydrate consumption; therefore, when applying a variation of a KD that has a high-protein component, the type of amino acids must be carefully considered to avoid the *de novo* synthesis of glucose through compensatory anaplerotic reactions [10].

In addition to restriction of sugar and lipids, there are also many other means to modify diet by depletion or addition of certain sugars, vitamins and amino acids. For example, serine, glycine or methionine deprivation from diets showed promising anticancer effects in preclinical models [7,12]. However, there is no clinical evidence yet, and further mechanistic and clinical studies are

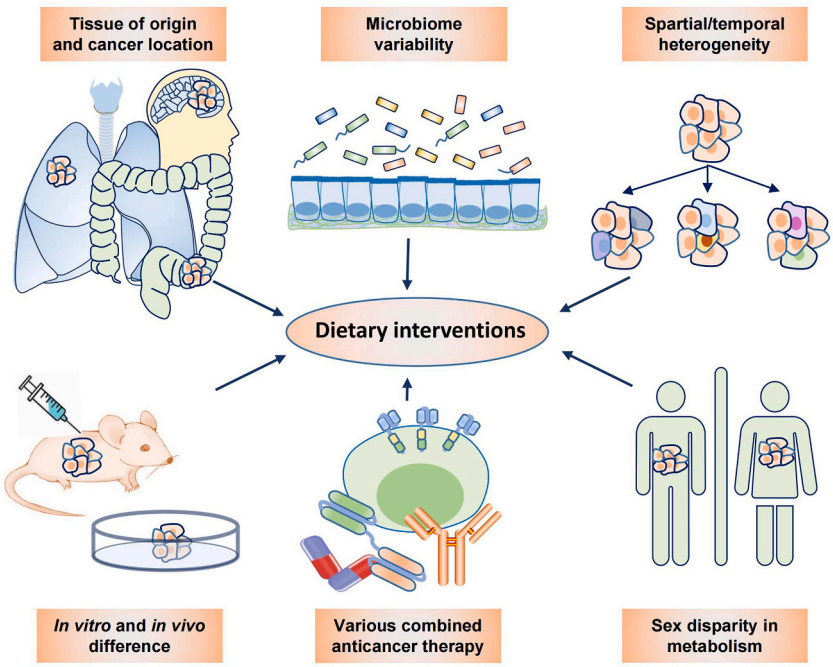

Fig. 2. Factors that may affect the responses of cancer to dietary interventions. In addition to the heterogeneous protocols regarding composition, duration and periodicity of diets, the responses of cancer to dietary interventions are determined by many factors, including tissue of origin and cancer location, microbiome variability, spatial and temporal metabolic heterogeneity, *in vitro* and *in vivo* differences, various combined anticancer therapies and sex disparity in metabolism.

warranted. Recently, the role of fructose in intestinal cancer progression was revealed, indicating that fructose restriction may be beneficial to patients with colorectal cancer (CRC) [59]. Unlike nutrient restriction, the addition of a diet with specific elements, such as histidine and mannose, may also be applied as a complement to cancer therapies [7]. However, research on this type of dietary intervention lags far behind that on the regimens mentioned above.

3.2. Varied duration and periodicity

Caloric and nutrient intake are not the only determining factors for the effects of dietary interventions, as the timing of food intake also plays a key role in mediating anticancer activity. Therefore, after the first modern intermittent fasting (IF) was introduced in the 1950s, numerous studies have been performed to elucidate the effects of the timing of food intake on cancer progression [60]. IF is an eating pattern characterized by a brief period of fasting with considerable calorie restriction or no food consumption and a subsequent period of unrestricted eating, focusing on when to eat rather than what to eat. The frequency and duration of eating and fasting also varied, leading to several different approaches to IF interventions. Alternate-day fasting (ADF) entails eating every other day and consuming no or less than 600 kcal calories on the days between [60]. A modified ADF is a 6:1 or 5:2 diet with fasting on 1 or 2 nonconsecutive days per week [60]. A third method, time-restricted eating (TRE), requires limiting the intake of all foods to a 4- to 12-h window [60]. Finally, some forms of fasting advocated by Christianity, Judaism, Buddhism, and Islam also showed benefits in patients with cancer [60,61].

IF has been extensively investigated in rodent models and cancer patients with promising yet conflicting results. For example, 2 separate 24-h fasting periods nonsignificantly decreased the growth of prostate cancer xenografts and improved the survival of mouse models [62]. However, such anticancer effects were not observed in a larger follow-up study [63]. In hematologic malignancies, alternate 1-d or 2-d fasting delayed the progression of both B-cell and T-cell acute lymphoblastic leukemia but not acute myeloid leukemia in mouse models [64]. Furthermore, in some rodent models, quite a few IF interventions with different designations were shown to promote the growth and aggressiveness of cancer cells [65,66]. There have been a few clinical studies that were conducted only to test the effects of IF on metabolic and hormonal parameters that are associated with cancer initiation and progression, and the findings are also inconsistent [60]. The negative or even potentially harmful effects of IF may be attributed to the timing and length of the fasting schedules or to refeeding after fasting, which has a detrimental impact on insulin regulation and maladaptive molecular responses [60]. Therefore, some researchers have modified diet regimens to overcome these negative effects. For example, when feeding was controlled on nonfasting days to prevent excessive calorie intake, p53-deficient mice showed delayed tumor onset, reduced tumor metastasis and increased overall survival [67]. Interestingly, although not tested in patients with cancer, clinical practice in other conditions showed that the effects of TRE on metabolic response may be better when food intake is restricted to the middle of the day than to the late afternoon or evening periods [68,69].

However, it is difficult to draw strong conclusions about which patients respond best to a given dietary intervention, as observations are typically spread across different studies rather than being investigated within a single well-controlled experiment. Therefore, many modified IF regimens also reflect that the interactions between diet and cancer are complex, and there is no one dietary intervention that fits all patients, calling for further investigation to determine the right diet and the right patient.

3.3. Compliance and adverse events

Compliance differences are another important heterogeneity that must be taken into consideration in clinical practice, as a high dropout rate may dilute the benefits of diet interventions. In contrast to preclinical studies in which dietary interventions can be completed in the majority of animals, in clinical situations, compliance with each regimen varies widely. For example, TRE results in nearly 100 % compliance with no adverse events, while for CR trials on body weight management, the dropout rates can reach as high as 30–40 %, even when participants have been highly motivated [68,70,71]. There are data to compare the compliance differences between individual dietary interventions, and the highest dropout rate was 38 % in the ADF group, followed by the daily CR group (29 %) [72]. In another study also conducted in obese patients, the dropout rates were 20 % and 13 % for FMD and continuous CR, respectively [73]. These variations also apply to cancer patients; even with adequate participant activation and demonstrated safety, dietary modifications are hardly maintained for a considerable portion of patients. In a clinical trial utilizing CR in patients with breast cancer, a 22 % dropout rate was also reported, although the medical events were not increased [39,74]. After 3 FMD cycles in patients with cancer, the grade 3 or 4 adverse events and dropout rate were reported to be 13 % and 24 %, respectively [33,34,75]. Even when using the same dietary intervention, the compliance varied. For example, adherence was reported to be excellent (dropout rate 19 %) in women with ovarian or endometrial cancer prescribed KD [43]. However, unsatisfactory tolerance was also reported in other situations, such as in patients with head and neck, lung and pancreas cancers, which may be due to the high cachexia incidence in these cancer types [42,76,77]. The reasons for significant differences in compliance across different dietary interventions and cancer patients are multifaceted. Almost all clinical trials have demonstrated the safety and feasibility of dietary interventions in patients with various clinical conditions; however, the vulnerability to the side effects of dietary interventions may vary across individuals. For example, no adverse events were reported when a KD was tested in patients with diabetes, while many mild adverse events have been reported in patients without obesity or metabolic disease and in older people [78–80]. Furthermore, systemic adaptations to dietary interventions, such as hypoglycemia and excessive circulating triglycerides and cholesterol, can also result in inflammation of the liver and pancreas [9]. In addition, varied eating behaviors and cultures among individuals may also affect the compliance of patients with specific dietary modifications [9].

In summary, current data suggest that TRE has the highest degree of adherence, while other therapeutic diets, such as prolonged

fasting, FMD and CR, tend to have higher dropout rates. Although dropout rates were reported by many trials, no study has analyzed the effects of dropout on treatment efficacy. One trial reported that a longer continuation of the KD improved the prognosis of advanced cancer patients, which may support the conclusion that a high dropout rate may dilute the benefits of diet interventions [81]. However, current evidence is based on secondary analyses, retrospective or observational studies, or preliminary RCTs. Therefore, more well-controlled trials and context-dependent diet selection are needed to improve the efficacy of dietary interventions in cancer patients.

4. Metabolic heterogeneity affects cancer responses to dietary interventions

In addition to the heterogeneous protocols regarding composition, duration and periodicity of diets, the responses of cancer to dietary interventions are determined by metabolic heterogeneity, which is shaped by tissue of origin and cancer location, molecular and histological features, and spatial and temporal metabolic heterogeneity (Fig. 2).

4.1. Tissue of origin and anatomical location

During development, lineage-determined and differentiated cells acquire distinct metabolic preferences to accommodate various metabolic environments determined by the functional purposes of individual tissues, which are also shaped by blood supply and physical barriers [82]. Therefore, the tissue of origin and anatomical location inevitably affect the behaviors of cancer, including metabolite abundance and metabolic activity, reflecting the diverse effects of dietary interventions with different compositions [83]. For example, in the brain, the blood–brain barrier (BBB) provides selective permeability between parenchymal cells and systemic circulation, which prevents nonselective nutrients from freely diffusing into the brain, supporting a unique metabolic feature of the brain. The expression of solute carrier family 2 member 3 (SLC2A3), which has high affinity and transport activity for glucose, makes glucose the chief source of energy for the brain [84]. In contrast, neuronal cells seldom rely on fatty acids for energetic demands, while during glucose restriction, they are also capable of metabolizing ketone bodies [85–87]. Therefore, to adapt to the specific environment, tumors in the brain show high expression of genes involved in glycolysis, including hexokinase, pyruvate kinase, and pyruvate dehydrogenase (PDH) [88]. Therefore, glucose restriction in the diet may be a useful therapeutic approach for glioma through glucose deprivation from the brain while maintaining neuronal survival depending on ketone body consumption [89]. In contrast, isotope labeling studies in pigs found that metabolism in the lung is notable for relatively high consumption of ketone bodies, saturated fatty acids and glutamine [90]. Such metabolic features provide a set of advantages to cancer cells within the lung, reflecting the reported small effect of a KD on lung cancer growth [91]. In some conditions, a KD even promotes the growth of renal cancer and melanoma [22, 92]. Differences in amino acid availability across tissues may also affect the responses of cancer cells to dietary interventions. For example, a serine and glycine-free diet retarded the growth of breast cancer in mammary fat pad tissue but not in pancreatic tissues, as the total tissue serine content is lower in the mammary fat pad, while the pancreas is a more serine-replete tissue [93].

Another important factor that affects the metabolic features of various tissues and cancers arising from them is hormones. Some tissues are hormone-responsive, such as the breast, endometrium, ovary and prostate, whose nutrient uptake and metabolism are regulated by IGF-1, insulin, estrogens, progesterone and testosterone, while the metabolic activity of other tissues, such as the lung and pancreas, is not particularly sensitive to systemic hormones [86,94–96]. For cancers arising from the first type of tissues, systemic hormone changes caused by dietary modifications may affect the metabolic activity of cancer cells and thus their biological behavior, while the effects may be weak on cancers originating from the latter type of tissues. In addition to systemic hormones, the cellular components or the adjacent cell types of a cancer also shape a distinct local hormonal environment, which may also benefit cancer metabolism. The breast is a fat-rich organ in which adipocytes generate estrogen, making its levels much higher in breast cancers than in serum [97]. Therefore, clinical data suggest that LFD only has beneficial effects in patients with breast cancer, which may be due to decreased estradiol concentrations [98,99].

Despite affecting the response of primary tumors to dietary interventions, the local metabolic environment within specific tissues also provides an opportunity to control metastasis through dietary interventions. For example, the levels of serine and fatty acids are relatively low in the brain, and metastases from breast cancer need to synthesize these nutrients *de novo* for survival, indicating that restriction of these components in diets combined with the inhibition of key enzymes involved in *de novo* synthesis may prevent or delay the growth of metastatic cancers in the brain [100,101]. Brain metastases from cancers in various primary tissues can adapt to acetate as an energy source; therefore, a KD, which increases ketone bodies in the circulation and brain, may not be beneficial in such patients [102]. Physiologically, seminal fluid is rich in fructose, which is *de novo* synthesized from glucose via the polyol pathway [103]. Therefore, human primary prostate cancer was shown to increase the expression of fructose transporters and may directly invade the seminal vesicle filled with fructose-dense fluid, revealing the therapeutic potential of fructose restriction in prostate cancer [104,105].

There are also cancer types that do not obey the metabolic features of tissues they arise from but acquire new metabolic activity to adapt to the local tumor microenvironment (TME). For example, although normal prostate cells are highly glycolytic but have a diminished capacity for oxidative phosphorylation, which is driven by testosterone to produce citrate and lactate for seminal fluid generation, prostate cancer cells from both mice and humans regain the ability to consume these locally produced metabolites [96, 106]. Another illustration comes from the pancreas, the primary role of which is anabolic, thus showing the greatest use of amino acids [90,107]. However, pancreatic ductal adenocarcinomas (PDACs) consume fewer branched chain amino acids (BCAAs) [108].

4.2. Molecular features

A hallmark of cancer is the remodeling of their metabolic state through dysregulation of various molecular pathways, diverting central metabolites such as glucose and glutamine toward biosynthetic processes that underlie cancer progression. These molecular alterations contribute to metabolic heterogeneity, as the oncogenotype can drive particular metabolic features in cancers. For example, dysregulation is mostly involved in the WNT, PI3K and KRAS pathways, and each pathway alteration may impose distinct metabolic changes in CRC. WNT signaling hyperactivation impairs oxidative phosphorylation but increases the transition of glucose into pentose phosphate pathway (PPP) flux and fatty acid synthesis [109,110]. Mutations in the PI3K pathway convert substantially more glutamine to α-ketoglutarate to replenish the tricarboxylic acid cycle (TAC) and generate ATP in CRC [111]. Finally, CRC cells with *KRAS* and *BRAF* mutations can be selected under low-glucose conditions, as these molecular changes enhance glucose uptake by upregulating the expression of glucose transporters [112]. Similar to alterations in different pathways, divergent effects on metabolism may be present in cancers driven by the same molecular change but with different mutant loci. In preclinical studies, cancer cells with $KRAS^{G12V}$ were less dependent on glutamine than cancer cells expressing $KRAS^{G12C/D}$ [113]. The effects of molecular changes on metabolism may also be influenced by the location of cancer. For example, *KRAS*-mutant pancreatic cancer avidly scavenges their microenvironment for nutrients via macropinocytosis, while non-small cell lung cancer (NSCLC) driven by the same mutation takes up relatively less [114,115]. MYC induces glutamine synthesis in lung cancer but glutamine catabolism in liver cancers [116]. Similarly, both are driven by KRAS; NSCLCs incorporate free BCAAs into tissue proteins and use BCAAs as a nitrogen source, whereas PDACs have decreased BCAA uptake [114].

Therefore, the effects of dietary intervention are also influenced by the histological and molecular features of cancer. Preclinical and human studies have found that triple-negative breast cancers (TNBCs) rely more on glycolysis and consume more exogenous fatty acids, while estrogen receptor (ER)-positive breast cancers are relatively oxidative and consume citrate and lactate; therefore, an LFD may improve the efficacy of therapies in patients with TNBC but not ER-positive breast cancer [117,118]. PI3K pathway activation, mainly through mutations in the *PI3KCA* gene, is common in breast cancer [119]. In preclinical studies, cancers with PI3K pathway mutations are resistant to the effects of CR, whose anticancer effects are mainly mediated through insulin and the PI3K pathway [19,20]. In mouse models of melanoma, a KD induces a 3-hydroxybutyrate (3HB)-mediated antineoplastic effect that relies on T-cell--mediated cancer immunosurveillance [120]. However, when melanoma cells harbor a $BRAF^{V600E}$ mutation, they become resistant to KD, as acetoacetate, one metabolite elevated under KD, can augment BRAF signaling [22,121]. $BRAF^{V600E}$ mutation underlying the tumor-promoting effects of KD in melanoma was argued by another animal study, in which KD slowed melanoma growth *in vivo* regardless of genetic background [122]. The authors attributed this difference to two reasons: first, the dietary regimens used by two studies differed in their ketogenic ability; second, the timing of KD administration was also different: one study started the KD intervention once the xenografts had reached a measurable size, while the other study started the KD intervention 1 week before tumor initiation [122]. These differences in study design may significantly influence the response, which needs to be addressed in further studies. In addition, a serine and glycine-restricted diet showed an inhibitory effect on models of Eμ-*Myc*-driven lymphoma and *Apc* loss-driven intestinal cancer but not *Kras*-mutant pancreatic cancer and CRC [14]. This may result from molecular changes that contribute to *de novo* synthesis of the limited nutrients in the modified diet. For example, *KRAS* mutation increases the expression of enzymes involved in *de novo* serine synthesis, rendering cancer cells resistant to diets deprived of serine and glycine [14]. Furthermore, cancer cells that lack the expression of ketone body metabolism genes were sensitive to KD, whereas cancer cells that expressed these genes were resistant to KD [123].

4.3. Spatial and temporal metabolic heterogeneity

Despite variations in their molecular nature and between cancers with different tissues of origin, metabolism also varies widely between regions of the same cancer, between primary and metastatic cancer and between cancers at different stages. This spatial and temporal heterogeneity in tumor metabolism is attributed to the combined effects of intrinsic factors (e.g., cell lineage and molecular features, which were mentioned above) and extrinsic factors (e.g., metabolite availability, blood supply, and interaction with stromal cells). Understanding these heterogeneities will help in selecting appropriate diets for tumor treatment. However, the metabolic milieu of cancers *in vivo* is still poorly defined. Current methods measuring metabolic activity in cancer, such as metabolite detection of tumor interstitial fluid (TIF), only represent an average level in the extracellular fluid and thus fail to capture the heterogeneity between different subdomains [124]. The primary data obtained using state-of-the-art technologies have identified substantial spatial metabolic heterogeneity within single tumors, suggesting that assigning a specific metabolic profile to a single tumor may overlook important aspects of tumor metabolism [125]. The vascularization variations between subdomains of a cancer, which make oxygen and nutrient availability different for cancer cells within different subdomains, have been well characterized. Therefore, cells located close to the blood supply tend to generate ATP aerobically and upregulate anabolic pathways to support proliferation, while cells distant from the blood supply will experience hypoxia and activate catabolic pathways such as autophagy to provide energy and biosynthetic precursors [126]. However, whether and how this spatial heterogeneity in cancer metabolism will affect the efficacy of dietary interventions for cancer therapy is still unknown.

Despite the contributions of differences in molecular alterations and nutrient supply, the metabolic plasticity and flexibility of cancer cells also contribute to significant intratumoural metabolic heterogeneity. Metabolic plasticity refers to the ability of cancer cells to utilize one metabolite to fuel various metabolic requirements, while metabolic flexibility describes cancer cells that can use different metabolites to meet the same metabolic requirement [127]. Therefore, cancer cells adjust their metabolic activity and preference dynamically according to the changing microenvironment. Theoretically, when there are cancer cells with the ability to

reprogram their metabolism, dietary interventions that focus on specific nutrient restriction will not work. For example, although both CR and a KD lowered blood glucose and insulin levels, only CR impaired the growth of allografts formed from a PDAC cell line and an NSCLC cell line [128]. The failure of a KD to inhibit the growth of cancer was attributed to the higher lipid levels in plasma and TIF, which can be used by cancer cells to support proliferation upon glucose deprivation [128].

5. Improve the efficacy of conventional therapy through appropriate dietary interventions

It is unlikely that dietary interventions alone will be efficacious enough to combat cancer progression. Therefore, to date, the majority of studies testing the anticancer effects of dietary interventions have also been combined with conventional therapies, including chemotherapy, radiotherapy, targeted therapy and immunotherapy (Fig. 2). However, the anticancer mechanisms and adverse effects of each treatment approach may be very complex or even contradictory. Only combination therapy based on a detailed and exact mechanistic understanding has the potential to achieve promising clinical translation. For example, in patients with dysregulation of metabolic enzymes such as phosphoglycerate dehydrogenase (PHGDH) and stearoyl-CoA desaturase (SCD), amino acid-depleted diets and diets low in unsaturated fats may increase the efficacy of inhibitors of dysregulated enzymes [128,129]. ER-positive breast cancers develop resistance to hormonal therapy mainly by acquiring *PI3KCA* mutations, indicating the benefits of conventional therapies combined with a KD, which decreases insulin levels to reduce the nutrient uptake of cancer cells [75,130]. In addition, although a diet deprived of serine and glycine can enhance the anticancer activity of metformin in some contexts, this combination showed no effect or even promoted cancer growth in other conditions [14,131]. Similarly, in cell culture conditions, reduced glucose but not amino acids was shown to synergize with metformin to reduce cell viability, suggesting that the *in vivo* efficacy of dietary intervention combined with metformin to inhibit tumor growth is mediated by blood glucose reduction [132]. Therefore, to achieve synergistic effects, metformin should be combined with dietary regimens that have the ability to reduce blood glucose, such as fasting but not LFD [57].

Although numerous studies have suggested a protective role of dietary interventions in normal cells while sensitizing cancer cells to chemotherapy through DSR, in some conditions, specific diets even aggravate the adverse effects of drugs and select for cancer cells with drug resistance [18]. For example, a recent publication reported that sustained ADF can worsen the cardiotoxicity of doxorubicin due to the increased myocardial nuclear transcription factor EB, which promotes the development of doxorubicin-induced cardiotoxicity [133]. In a preclinical study, when the FMD was combined with chemotherapy (oxaliplatin plus 5-fluorouracil) to treat CRC models, although the tumor mass was dramatically reduced, transcriptomic and metabolomic analysis demonstrated that the residual cells entered a drug-tolerant persister (DTP) [134]. However, as these cancer cells also show high autophagic activity, they are exquisitely sensitive to ferroptosis inducers, the addition of which can circumvent the negative effects of FMD [134]. Overall, these findings indicate that the context may matter when combining dietary interventions and conventional therapy to treat cancer.

6. Other sources of heterogeneity

A large population of microbes colonize the human body, especially in the intestinal tract, which is the first point of contact for orally ingested diet components. The dysbiosis of the intestinal microbiota is strongly linked with some types of cancer, and such mechanistic associations, together with the observed microbiome variability between individuals, present challenges for successful cancer control by dietary interventions [135]. For example, although both CR and IF can lead to gut microbiota remodeling, only CR can increase the abundance of *Bifidobacterium*, which mediates the CR-induced antitumor effect through acetate production and thus the accumulation of interferon-γ^{+}CD8^{+} T cells in the TME [136]. Therefore, characterizing the gut microbiome and identifying specific beneficial and detrimental bacteria would assist in precision dietary intervention.

Many metabolic processes differ between healthy males and females. For example, plasma glucose concentrations are higher in healthy males than in females, leading to increased liver and colon cancer incidence in males but not in females [137]. Accordingly, cancer cells rewire metabolism differently between sexes to meet the demands of proliferation. Data on 13 nonreproductive cancers in The Cancer Genome Atlas Program (TCGA) suggest significant sex differences in pathways involved in glucose, fatty acid and bile acid metabolism [138]. These sex-dependent metabolic preferences may define the response differences of cancer to therapies targeting metabolism, including dietary interventions. However, current evidence on dietary interventions is derived from trials including both sexes, warranting the inclusion of patient sex as an outcome determinant in future studies.

Other types of unconventional heterogeneity have always been overlooked. One is the differences in metabolite changes between the blood and TME. Currently, numerous efforts have been made to measure the alterations in metabolite availability in the blood imposed by diet modifications [93,139,140]. However, the metabolic alterations induced by diet modification within the TME are not always consistent with those in the blood, which is supported by the findings that the metabolite composition of TIF was distinct from that of plasma, implying that the TME may not be as deprived of all nutrients as is sometimes assumed [141,142]. The other is the metabolic differences in cancer cells observed between *in vitro* cultures and *in vivo* growth. For example, when lung cancer cells are cultured in medium, they heavily consume glutamine as the carbon source for the TCA cycle, while when these cancer cells are transplanted into mice, they do not depend on glutamine for growth [143,144]. Therefore, any finding derived from *in vitro* studies must be verified *in vivo* before dietary interventions are designed to affect the metabolic activity of cancer (Fig. 2).

7. Conclusions

Overall, dietary interventions have been extensively studied in the context of cancer, and safety and feasibility have been established in humans. Despite this, various sources of heterogeneity make the anticancer effects inconsistent across previous studies, indicating that precision nutrient approaches are needed to maximize anticancer efficacy while limiting adverse effects of dietary interventions. The ideal therapy is to deliver the right diet to the right patients at the right time. Before achieving this goal, numerous mechanistic and clinical studies are needed. First, the detailed metabolic changes across cancer (sub)types with distinct histological and molecular features and during cancer progression must be elucidated. Second, the mechanisms through which dietary interventions affect the metabolic activity of cancer cells and their surrounding and systemic environments are important determinants of the successful application of dietary interventions in clinical practice and are also the principle for appropriately designing the components, duration and periodicity of individual dietary protocols. Third, taking culture and specific patient clinical conditions into consideration will also improve the efficacy of dietary interventions in cancer therapy, for example, to provide cultural meals to support subject adherence and to exclude subjects who may suffer severe side events based on key effects of dietary interventions. Finally, although elucidating the effects of specific factors on cancer metabolism is still a challenge, an even larger challenge is to elucidate the combined effects when several causes coexist. Therefore, dietary interventions combined with conventional anticancer therapies based on the tissue of origin, anatomical location, genetic alteration of cancer cells and the systemic and local hormonal environment and their dynamic remodeling will likely ensure the success of dietary interventions in cancer management.

Source of funding

This study was supported by the Medical Research Project of The Third Hospital of Mianyang (202222).

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Chun Ni: Writing – original draft, Formal analysis, Conceptualization. **Jian Li:** Writing – review & editing, Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the Health Commission of Mianyang City for their support. We apologize to authors whose papers could not be cited due to space limitations.

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