


REVIEW



## Trial watch: dietary interventions for cancer therapy

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### ABSTRACT

Dietary interventions have a profound impact on whole body metabolism, including oncometabolism (the metabolic features allowing cancer cells to proliferate) and immunometabolism (the catabolic and anabolic reactions that regulate immune responses). Recent preclinical studies demonstrated that multiple dietary changes can improve anticancer immunosurveillance of chemo-, radio- and immunotherapy. These findings have fostered the design of clinical trials evaluating the capacity of dietary interventions to synergize with treatment and hence limit tumor progression. Here, we discuss the scientific rationale for harnessing dietary interventions to improve the efficacy of anticancer therapy and present up-to-date information on clinical trials currently investigating this possibility.

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### Introduction

In the Western world, overnutrition has overcome undernutrition as a medical and societal problem.<sup>1–3</sup> Beyond quantitative considerations, it appears that the consumption of ultra-processed food (rich in carbohydrates, sugars, salt, and fat) and soft drinks coupled to a relative scarcity of fruit and vegetables affects the majority of individuals even in high-income countries.<sup>4–9</sup> Against this background, it is clear that the “normal diet” cannot be appreciated as a statistical norm (i.e., the diet of the average individual), but must be defined by public guidelines. Such guidelines, however, are overshadowed by political decisions and arguable observational epidemiology, meaning that they tend to differ among distinct countries.<sup>10</sup> Moreover, much of the preclinical research done with laboratory animals (mostly mice) is based on the comparison of different types of chemically non-defined regimens, meaning that the conclusions of such studies are often based on methodologically suboptimal approaches.<sup>11,12</sup> Indeed, in pharmacology, it is common practice to compare different experimental conditions that only differ with respect to the absence and the presence of a drug administered at different concentrations. This kind of rigor is absent from most nutritional studies, which ideally should be designed to test the effects of just one single macro- or micronutrient admixed as a chemically defined entity (e.g., sucrose, sodium chloride, cholesterol or specific vitamins).<sup>13</sup> Notwithstanding these limitations, it has become clear that the quantity and quality of nutrition plays

a major role in determining the risk of cancer.<sup>14–16</sup> Obesity is nowadays on the verge of beating tobacco as the principal avoidable risk factor for cancer.<sup>17–19</sup> Along similar lines, a high variety of food that supplies all necessary micronutrients appears to be one of the principal factors that link high socioeconomic status with low disease risk.<sup>20</sup> Finally, multiple animal studies favor the idea that nutritional interventions may curb the progression of established cancers and improve the efficacy of anticancer treatments.<sup>21–27</sup> These effects rely on the alteration of both oncometabolism (the anabolic and catabolic reactions that support oncogenesis, disease progression and resistance to treatment)<sup>28,29</sup> and immunometabolism (the metabolic features that regulate immune responses).<sup>30–34</sup>

Along the lines of our Trial Watch series,<sup>35,36</sup> we discuss the rationale for harnessing nutritional interventions in support of cancer therapy and the progress of recent clinical trials testing this therapeutic paradigm in cancer patients.

### Anticancer effects of dietary interventions – a cell-autonomous rationale

Cancer cells, especially those studied in the laboratory, are characterized by an increase in anabolic reactions that give rise to the so-called Warburg effect, the fact that such cells tend to take up large amounts of glucose even in conditions in which oxidative phosphorylation can proceed in an unlimited fashion.<sup>37–40</sup> This so-called ‘aerobic glycolysis’ allows glucose-derived carbon atoms to be used for biosynthetic reactions.

Cancer cells also take up large amounts of amino acids through specific transporters in the plasma membrane, acquire increased amounts of proteins by pinocytosis, and even engulf their neighbors to cannibalize them.<sup>41–43</sup> In an analogous fashion, cancer cells are avid consumers of lipids.<sup>44</sup> Given their anabolic appetite, it is not surprising that nutritional interventions designed to reduce tumor growth involve a reduction in macronutrient uptake. Thus, it has been shown in mice that short-term starvation (STS, meaning no food supply for 1–2 days with access to drinking water *ad libitum*) and alternate-day fasting (ADF, meaning the alternation of 1-day intervals with and without access to food) can reduce tumor progression.<sup>25,27</sup> Moreover, the specific depletion of proteins (as well as selected amino acids) from nutrients can be harnessed to limit cancer growth.<sup>45,46</sup> One particular dietary intervention consists in a close-to-zero carbohydrate, low-protein, high-fat regimen that causes ketosis (*i.e.*, the accumulation of 3-hydroxybutyrate, acetoacetate, and acetone, commonly known as ketone bodies).<sup>47</sup> Ketone bodies can be used by multiple tissues in replacement of glucose for energy metabolism.<sup>48</sup> In mice, multiple variants of ketogenic diet slowdown the progression of some cancer types and boost the efficacy of targeted therapeutic agents,<sup>49,50</sup> an effect that (at least in some setting) is linked to reduced insulin signaling.<sup>50,51</sup>

One particular facet of these dietary interventions is their capacity to reduce the unwarranted side effect of genotoxic chemotherapy. For example, periodic fasting as well as the administration of a hypocaloric ‘fasting-mimicking diet’ (FMD) can enhance the efficacy of chemotherapy and, at the same time, limit chemotherapy-related weight loss and cardiotoxicity.<sup>27,52</sup> It has been theorized that transient calorie deprivation enhances the ‘differential stress resistance’ between chemotherapy-treated cancer cells (that would become more susceptible to the treatment) and normal, non-neoplastic cells (that would become more resistant to the toxic side effects to chemotherapy).<sup>53–56</sup>

### Anticancer effects of dietary interventions – an immunological rationale

Over the past years, an ever-expanding body of evidence pleads in favor of the notion that the long-term success of chemotherapy, targeted therapy and radiotherapy requires the reestablishment of immunosurveillance.<sup>57</sup> In other words, the efficacy of antineoplastic treatments, which has long been thought to exclusively rely on cancer cell-autonomous effects, now turns out to require the induction of a protracted anticancer immune response to be efficient.<sup>58–61</sup> Logically, the impact of dietary intervention on such immune-dependent antitumor effects has been studied in preclinical models.

In immunocompetent mice bearing transplantable tumors or carcinogen-induced breast cancer, chemotherapy with anthracyclines or oxaliplatin becomes more efficient if combined with shorts periods of starvation.<sup>22,24</sup> These combinatorial effects of chemotherapy and dietary intervention fully rely on a T lymphocyte-mediated anticancer immune response, meaning that they are lost upon T cell depletion.<sup>22,24</sup> Mechanistically, they have been linked to the

induction of heme oxygenase-1 (HO-1) in cancer cells, the stimulation of autophagy in cancer cells (which would enhance their immunogenicity),<sup>62–64</sup> a decrease in circulating insulin-like growth factor-1 (IGF1), as well as an increase in the frequency of common lymphocyte precursors (which would be immunostimulatory).<sup>22,24,65</sup> Whether such effects might involve major shifts in the gut microbiota has not been investigated thus far.<sup>66,67</sup> Moreover, the impact of dietary interventions on immunotherapies has been poorly explored, at least to our knowledge.<sup>68,69</sup> Available clinical evidence suggests that anti-melanoma immunotherapy with PD-1/PD-L1 blocking antibodies<sup>70,71</sup> is more efficient in obese than lean males,<sup>72</sup> casting doubts on the possibility to improve such therapies by brutal interventions designed to reduce overweight.

### Published and ongoing clinical trials

Very few trials testing the ability of nutritional interventions to boost the efficacy of cancer therapy have been reported in the peer-reviewed literature so far. A series of anecdotal cases of self-imposed starvation during chemotherapy suggested an improvement of subjective well-being suggestive of a reduction of side-effects.<sup>73</sup> In the same line, fasting for 48 h prior and 24 h after platinum-based chemotherapy proved its safety and feasibility in patients treated for diverse cancer types.<sup>74</sup> A Phase I trial confirmed that STS for 60 h (from 36 h prior to chemotherapy to 24 h post-chemotherapy) improves quality of life and fatigue in patients with gynecological cancer.<sup>75</sup> In breast cancer patients treated with neoadjuvant multimodal chemotherapy,<sup>76</sup> a 48-h starvation period (from 24 h before to 24 h after chemotherapy) reduced hematological toxicity and accelerated recovery from DNA damage in circulating leukocytes.<sup>77</sup> Women with ovarian and endometrial cancer following a ketogenic diet for 12 weeks reported higher physical and energy status compared to the control group, highlighting the feasibility of this regimen.<sup>78</sup> A special ketogenic diet, the so-called ‘modified Atkins diet’, reportedly reduces the progression of some advanced cancer patients, especially individuals experience robust weight reduction.<sup>79</sup> Similarly, a ketogenic regimen has been reported to induce objective responses in 6 out of 7 patients with recurrent glioblastoma that simultaneously were treated with the antiangiogenic drug bevacizumab.<sup>80–82</sup> This effect appeared particularly strong in patients with stable ketosis.<sup>80</sup>

The website ClinicalTrials.gov informs on multiple clinical trials that are either ongoing or completed, yet generally lack published information on the outcome (Table 1). Many of these trials evaluate dietary interventions without further treatment (NCT01092247, NCT01865162, NCT02092753, NCT02286167, NCT03160599, NCT03194516, NCT03328858, NCT03785808, NCT00003367, NCT00020995, NCT00082732, NCT00444054, NCT01692587, NCT02129218, NCT02176902, NCT03221920, and NCT03679260). Such interventions include STS, intermediate fasting, FMD, multiple ketogenic and low-carbohydrate diets, low-fat/high-fiber regimens, protein-restrictive diets, low-calorie and low-glycemic regimens and a vegan diet in patients with a variety of advanced solid malignancies including glioblastoma (the most frequent indication),

Table 1. Clinical trials employing diet for cancer therapy.

| Dietary intervention  | Additional details (when available)                              | NCT                   | Therapeutic intervention  | Cancer type  | Phase                   | Status                    |
|---|--|-----------------------|---|--|-------------------------|---------------------------|
| Short-term starvation   | 24, 48, or 72 h of fasting or 48 h of FMD                        | NCT00936364           | Platinum chemotherapy   | Advanced solid tumors                                  |                         | Recruiting                |
|   | 24, 36, or 48 h of fasting before chemotherapy                   | NCT01175837           | Chemotherapy  | Breast cancer  | Pilot study             | Completed                 |
|   | STS 24 h before and 24 h after chemotherapy                      | NCT01304251           | Docetaxel, Doxorubicin, Cyclophosphamide                                      | Breast cancer  | Pilot study             | Completed                 |
|   | STS 24 h before and 24 h after chemotherapy                      | NCT02379585           | Doxorubicin, cyclophosphamide, paclitaxel, docetaxel, trastuzumab, pertuzumab | Breast cancer  | Phase 1/2               | Terminated, has results   |
|   | FMD 36 to 48 h before and 24 h after chemotherapy                | NCT01954836           | Chemotherapy  | Gynecological  | Pilot study             | Completed                 |
| Fasting-mimicking diet  | FMD  | NCT02126449           | Neoadjuvant chemotherapy  | HER2-negative breast cancer                            | Phase 2/3               | Terminated                |
|   | FMD 36 h before and 24 h after chemotherapy                      | NCT02710721           | Chemotherapy  | Prostate   |                         | Recruiting                |
|   | FMD or vegan diet 36 to 48 h before and 24 h after chemotherapy  | NCT03162289           | Chemotherapy  | Breast and ovarian                                     |                         | Recruiting                |
|   | FMD (low calorie, low protein, and low carbohydrates) for 5 days | NCT03340935           | Standard therapies  | Any malignancy except small-cell neuroendocrine tumors |                         | Recruiting                |
|   | 5 days of FMD 13 to 15 days before or 1 month after surgery      | NCT03454282           | Surgery   | Breast and melanoma tumors                             |                         | Recruiting                |
|   | FMD for 5 days   | NCT03595540           | Chemo, hormonal, targeted or immuno-therapies                                 |  |                         | Recruiting                |
|   | FMD 72 h before and 24 h after chemo-immunotherapy               | NCT03700437           | Carboplatin/pemetrexed and pembrolizumab                                      | NSCLC  |                         | Not yet recruiting        |
|   | FMD for 5 days   | NCT03709147           | Metformin   | Advanced LKB1-inactive lung adenocarcinoma             | Phase                   | Not yet recruiting        |
|   | KD   | NCT00575146           | Bevacizumab   | Recurrent glioblastoma                                 | Phase 1                 | Completed, has results    |
|   | Ketogenic diet   | KD for up to one year | NCT01092247   | No   | High-grade glial tumors |                           |
| KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment  |  | NCT01419483           | Chemoradiation  | Pancreatic   |                         | Terminated                |
| KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment  |  | NCT01419587           | Chemoradiation  | Carcinoma, non-small cell lung cancer                  |                         | Terminated                |
| Energy-restricted KD starts after surgery and continues through radio and chemotherapy, ending 6 weeks after treatments completion                      |  | NCT01535911           | Surgery followed by chemo- and radiotherapy                                   | Brain tumors   |                         | Active, not recruiting    |
| 2 cycles of 3 days calorie-restricted KD separated by 3 days fasting  |  | NCT01716468           | No  | Metastatic cancer                                      |                         | Completed                 |
| KD with calorie restriction for 6 months  |  | NCT01754350           | Reirradiation   | Recurrent glioblastoma                                 |                         | Active, not recruiting    |
| KD starts 2 days before chemoradiation and last at least during 5 weeks throughout the treatment  |  | NCT01865162           | No  | Refractory/end-stage glioblastoma                      | Phase 1                 | Recruiting                |
| KD starts after surgery and continues through radio and chemotherapy. A modified Atkins diet is implemented during the following month of chemotherapy. |  | NCT01975766           | Chemoradiation  | Head and neck cancer                                   | Phase 1                 | Terminated (poor accrual) |
| KD or low glycemic and insulinemic diet for 20 weeks  |  | NCT02046187           | Chemoradiation  | Glioblastoma   | Phase 1/2               | Terminated                |
| Modified Atkins-based with intermittent fasting diet  |  | NCT02092753           | No  | Breast cancer  |                         | Completed                 |
| KD starts at the radiation initiation and continues 6 months throughout the entire period of chemoradiation   |  | NCT02286167           | No  | Glioblastoma   |                         | Recruiting                |
| Low-carbohydrate vs low-fat diet before surgery   |  | NCT02302235           | Radiation and temozolomide  | Glioblastoma multiforme                                | Phase 2                 | Recruiting                |
| Modified Atkins diet  |  | NCT02516501           | Chemoradiation  | Breast ER+ cancer                                      | Pilot presurgical study | Recruiting                |
| KD  |  | NCT02744079           | Surgery   | Glioblastoma   | Early Phase 1           | Active, not recruiting    |
|   |  | NCT02768389           | Bevacizumab   | Recurrent glioblastoma                                 | Phase 1/2               | Unknown                   |

(Continued)

Table 1. (Continued).

| Dietary intervention  | Additional details (when available) | NCT         | Therapeutic intervention                   | Cancer type  | Phase       | Status                  |
|---|-------------------------------------|-------------|--|--|-------------|-------------------------|
| KD  |                                     | NCT02983942 | Methotrexate                               | Primary central nervous system lymphoma                  | Phase 1/2   | Not yet recruiting      |
| Modified KD or medium-chain triglyceride KD for 12 weeks                                      |                                     | NCT03075514 | Chemo- and/or radiotherapy                 | Glioblastoma   | Pilot study | Active, not recruiting  |
| Restricted calorie KD for 12 weeks  |                                     | NCT03160599 | No   | Glioblastoma multiforme                                  |             | Recruiting              |
| KD for 8 weeks  |                                     | NCT03171506 | No   | Ovarian and endometrial cancer                           |             | Completed               |
| Modified Atkins KD for 7 days before surgery  |                                     | NCT03194516 | No   | Prostate cancer  |             | Enrolling by invitation |
| KD for at least 1 year  |                                     | NCT03278249 | Temozolomide and radiation                 | Malignant glioma   |             | Recruiting              |
| KD for 16 weeks throughout chemoradiation treatment   |                                     | NCT03285152 | Surgery                                    | Endometrial cancer                                       |             | Recruiting              |
| KD for 3 months   |                                     | NCT03328858 | No   | Brain tumors   |             | Recruiting              |
| Low-carbohydrate high-fat ketogenic-type diet vs low-fat high low-glycemic carbohydrates diet |                                     | NCT03451799 | Radiation and temozolomide                 | Glioblastoma   | Phase 1     | Recruiting              |
| Low-fat high-fiber diet   |                                     | NCT03535701 | Paclitaxel                                 | Stage IV breast cancer                                   |             | Recruiting              |
| Specific low-nutrient   |                                     | NCT03785808 | No   | Lung cancer  |             | Recruiting              |
| Low-fat high-fiber diet   |                                     | NCT00003367 | No   | Prostate cancer  | Phase 3     | Completed               |
| Low-fat high-fiber diet for 3 weeks   |                                     | NCT00020995 | No   | Prostate cancer  | Phase 2     | Completed               |
| Low-fat high-fiber diet   |                                     | NCT00082732 | No   | Hormone-refractory prostate cancer                       | Phase 1     | Completed               |
| Very low-carbohydrate diet for 28 days  |                                     | NCT00444054 | No   | Advanced cancer  | Pilot study | Completed               |
| Low-fiber vs high-fiber diet  |                                     | NCT01170299 | Radiation                                  | Gynecological, bladder, colorectal, or anal cancer       |             | Completed               |
| Protein-restrictive diet  |                                     | NCT01692587 | No   | Prostate cancer  |             | Completed               |
| Low-calorie diet from 3 days before to 2 days after the 12 weeks of chemotherapy              |                                     | NCT01802346 | Chemotherapy                               | Breast, hormone-resistant, and recurrent prostate cancer | Phase 2     | Recruiting              |
| Carbohydrate-restricted diet  |                                     | NCT02019979 | Metformin with platinum-based chemotherapy | Non-squamous non-small cell lung cancer                  | Phase 2     | Terminated, has results |
| Low- or medium-glycemic diet for 12 weeks   |                                     | NCT02129218 | No   | Colon cancer   | Pilot study | Completed               |
| Low-fat omega-3 supplement diet for one year  |                                     | NCT02176902 | No   | Prostate cancer  | Phase 2     | Recruiting              |
| Vegetarian vs vegan diets for 6 months  |                                     | NCT02437474 | Prescribed therapy                         | Any cancer type  | Pilot study | Completed               |
| Very low-carbohydrate and high-fat diet   |                                     | NCT03221920 | No   | Colorectal adenocarcinoma                                |             | Not yet recruiting      |
| Low protein diet from 1 week before to 10 days after treatment                                |                                     | NCT03329742 | Sipuleucel-T                               | Metastatic castrate-resistant pancreatic cancer          |             | Recruiting              |
| Carbohydrate restricted diet for 6 months   |                                     | NCT03679260 | No   | Prostate cancer  | Phase 2     | Recruiting              |

breast and gynecological cancer, melanoma, head and neck cancer, non-small cell lung carcinoma, ovarian cancer, pancreatic adenocarcinoma, and prostate cancer. Several trials also aim at investigating the combination of dietary interventions with (1) chemotherapy (NCT01175837, NCT02379585, NCT02126449, NCT02710721, NCT03162289, NCT03340935, NCT03595540, NCT03700437, NCT01419483, NCT01419587, NCT01975766, NCT02046187, NCT02302235, NCT02516501, NCT02939378, NCT02983942, NCT03075514, NCT03278249, NCT03451799, NCT03535701, NCT01802346, NCT02019979, and NCT02437474), (2) radiotherapy (NCT03340935, NCT01419483, NCT01419587, NCT01754350, NCT01975766, NCT02046187, NCT02302235, NCT02516501, NCT03075514, NCT03278249, NCT03451799, NCT0170299, and NCT02437474), (3) metformin, a medication for type II diabetes with pleiotropic effects on cancer cells<sup>83–85</sup> (NCT03709147 and NCT02019979), (4) targeted-therapies (NCT02379585, NCT03595540 and NCT02768389), and (5) immunotherapies such as immune checkpoint blockers targeting PD-1<sup>86,87</sup> (NCT03595540 and NCT03700437) or the dendritic cells based-vaccine Sipuleucel-T<sup>88,89</sup> (NCT03329742). Interestingly, one study also sets to monitor anticancer immune responses induced by an FMD (NCT03454282).

It will be interesting to see whether any of these studies will document a clinical benefit linked to a specific nutritional intervention.

## Concluding remarks

Knowing the importance of nutrition and metabolism for human physiology, including the crosstalk between malignant and immune cells, it is not surprising that dietary interventions are attracting attention as safe means to limit tumor progression or restore disease control by the host immune system.<sup>90–92</sup> While evidence from preclinical studies suggests that reducing total calorie intake (and perhaps specific macronutrients) may stimulate anticancer immunity, such evidence has not yet been obtained in clinical trials. Multiple trials testing these possibilities in patients with multiple types of cancer are on the way (Table 1). Unfortunately, it will be difficult to compare results from different studies for at least two reasons that add upon the usual heterogeneity of clinical trials. First, dietary interventions are quite heterogeneous in nature.<sup>13</sup> Thus, the term ‘ketogenic diet’ may refer to distinct regimens differing in quantity, composition and even in the gross protein:fat ratio.<sup>93</sup> Second, the control arms of the studies, when exist, usually receive consulting on ‘healthy dietary habits’, which (1) is a non-standardized notion (with major cross-continental and cross-cultural divergences), (2) is usually not enforced, and (3) is extremely complex to monitor.

Thus, the studies listed in Table 1 might examine the differences between salutary (interventional) and poor (control) regimens, meaning that control regimens can be expected to have a negative impact on health status. For this reason, it will be important to standardize control diets, ensure compliance, and to define interventional regimens in an accurate fashion. This implies strict guidelines, their enforcement by connected objects and phone app-mediated

control, as well as monitoring of multiple metabolic parameters (such as plasma metabolome, cytokine and hormone status, stool microbiota). Moreover, it will be important to monitor immune parameters in the tumor and the peripheral blood to gain insights into therapeutically relevant anticancer immune responses. Without this information, it will be difficult to obtain any useful knowledge on the impact of nutritional interventions on cancer therapy.

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## Disclosure of Potential Conflicts of Interest

LG provides remunerated consulting to OmniSEQ (Buffalo, NY, USA), Astra Zeneca (Gaithersburg, MD, USA), VL47 (New York, NY, USA) and the Luke Heller TECPR2 Foundation (Boston, MA, USA), and he is member of the Scientific Advisory Committee of OmniSEQ (Buffalo, NY, USA). GK and LZ receive a research grant by Elior.

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