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Plant-Based and Ketogenic Diets As Diverging Paths to Address Cancer A Review

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Abstract

IMPORTANCE—As the incidence of cancer and metabolic disorders, such as obesity, concurrently rise, there has been increasing awareness of the pervasive effect of nutrition. The whole foods plant-based diet (WFPBD) and ketogenic diet (KD) have gained popularity in oncology, and this topic is increasingly permeating clinical dialogue.

OBSERVATIONS—Dietary intake is associated with multiple pathways involved in carcinogenesis and tumor progression. Consumption of a plant-enriched diet is associated with reduced cancer incidence and is recommended by dietary guidelines for cancer prevention. Despite a starkly different nutrient composition, a WFPBD and KD can be associated with weight loss, decreased inflammation, and decreased insulin levels. In addition, a WFPBD is associated with increased fiber, phytochemicals, and butyrate levels and decreased insulin-like growth factor 1 levels, whereas a KD exerts potential anticancer effects by increasing β hydroxybutyrate levels. A KD may be of interest in select, less common settings, such as tumors treated with phosphatidylinositol 3-kinase inhibitors, which induce hyperinsulinemia and hyperglycemia. Completed interventional trials have focused on increasing fruit and vegetable intake or reducing fat intake but have not specifically tested WFPBD or KD for cancer prevention or treatment.

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Currently available data support plant-based diets as opposed to KD as part of a lifestyle associated with reduced cancer risk. In the postdiagnosis setting, there are currently no rigorously tested approaches that support the recommendation of any diet to treat cancer.

CONCLUSIONS AND RELEVANCE—The results of this review suggest that the collective evidence supports plant-enriched diets vs KD for the reduction of cancer risk and the improvement of metabolic disorders in survivors. Additional prospective randomized clinical trials are needed to encourage use of dietary modification across the cancer continuum. Rigorous trial designs that adapt classical oncologic end points may identify populations that are likely to benefit from starkly contrasting diets. Current data support prioritization of plant-based diets, and future data could further personalize dietary recommendations in cancer populations.

The link between nutrition and health has long been of interest, dating back to the saying, "Let food be thy medicine and let medicine be thy food." As human dietary patterns have evolved based on the availability of processed foods, we have seen a rise in chronic diseases, including cancer. A National Health and Nutrition Examination Survey study attributed more than 80 000 new cancer cases to a poor diet in the US.[1] Simultaneously, we have seen nutrition research evolve to match new diet trends. Substantial emphasis has recently been placed on 2 popular diets for cancer prevention/treatment that have divergent dietary macronutrient and micronutrient profiles: the whole foods plant-based diet (WFPBD) and the ketogenic diet (KD). The merits are debated, despite the evidence available to support WFPBD for cancer prevention. This topic is increasingly permeating clinical dialogue with patients.

The WFPBD maximizes nutrient-dense plant foods and minimizes processed foods, oils, and animal foods, focusing on micronutrient density rather than a fixed macronutrient proportion. Thus, it is a minimally processed, low-fat, moderate-to-high–carbohydrate (unrefined) diet. The KD challenges the dogma that meat intake should be reduced and reverses the dietary macronutrient profile with fat and protein as major macronutrients instead of carbohydrates. The KD aims to promote the production of ketone bodies from fatty acids, typically through very low carbohydrate (approximately 5% calories), high fat (approximately 75% calories), and moderate protein (approximately 20% calories) intake. Most calories in a KD are obtained from meat, dairy, fish, oils, and eggs, with some nuts, seeds, and nonstarchy vegetables. These calculations typically translate to fewer than 40 g of carbohydrates per day compared with the standard Western-style diet (>250 g/day). In contrast, low-carbohydrate diets (LCDs), although also low in carbohydrates, usually have modest carbohydrate reductions of less than 26% calories or fewer than 100 to 130 g per day.

Epidemiologic Studies

In the prevention setting, plant-based diets are consistently associated with a reduced cancer incidence; seminal large epidemiologic studies include the Adventist Health Study–2 (hazard ratio [HR], 0.84; 95% CI, 0.72–0.99),[2] EPIC Oxford and Oxford Vegetarian Cohort (HR, 0.88; 95% CI, 0.82–0.95)[3] and NutriNet-Santé (HR, 0.85; 95%CI,0.76–0.97).[4]To our knowledge, long-term epidemiologic evidence for a KD is not available, but participants with diets low in plant foods had an increased cancer incidence in these

studies. Furthermore, 2meta-analyses showed thatLCDs are associated with higher mortality, especially for those whose diets favored animal-derived protein and fat.[5,6] Low protein intake (<10% calories) has been associated with a 4-fold reduction in cancer mortality compared with high protein intake (>20% calories) in adults aged 50 to 65 years in the National Health and Nutrition Examination Survey III study. This association was abolished or attenuated if the source of proteinswere plant-based,[7] similar to other studies in which plant proteins were associated with lower all-cause mortality.[8]

Consistent with these data and many other studies, the American Institute of Cancer Research/World Cancer Research Fund and the American Cancer Society recommend a diet comprising primarily whole plant-based foods and limited sugary drinks, highly processed foods, refined grains, and red and processed meats based on cumulative generalizable evidence for cancer.[9] The World Cancer Research Fund also summarized the evidence for individual cancers. Few US adults meet these dietary recommendations, irrespective of body mass index.[10]

Pathophysiology

Nutrition may play a substantial role in cancer prevention and treatment via multiple mechanisms. Although there are considerable differences in the KD and WFPBD, there are some common mechanisms by which they may be associated with a decrease in cancer risk. A summary of potential mechanisms is shown in the Figure.

Weight Loss

Obesity is a risk factor for several cancers,[11] and its incidence is rising in younger adults.[12] Both diets eliminate processed foods and refined carbohydrates, dietary components that are associated with increased mortality and weight gain, although there are some differences.[13,14] Fiber-rich foods in a WFPBD are low in calories and lead to early satiety,[15] whereas KDs can suppress appetite,[16] similarly reducing calorie intake.

An inpatient randomized clinical trial (RCT) of 20 healthy patients assessed an ad libitum WFPBD or KD for 2 weeks each. The WFPBD led to significantly less energy intake. Despite this, patients adhering to the KD lost more weight, and most of this weight loss was owing to a decrease in fat-free (lean) mass, whereas the WFPBD had a significant decrease in fat mass.[13]

In the postdiagnosis setting, in the KETOCOMP study, 29 patients with breast cancer who were adhering to a KD lost total body weight and fat mass after initial water loss compared with patients following a standard diet.[17] Similar weight loss was seen in astrocytoma[18] and prostate cancer populations.[19] Similar significant weight loss with a WFPBD intervention was seen in a randomized study in patients with prostate cancer.[20]

Despite the KD being an effective weight loss strategy, concerns have been raised about its long-term adverse effects. A nonketogenic LCD compared with a KD was equally effective in reducing body weight and insulin resistance, but the KD was associated with higher low-density lipoprotein (LDL) cholesterol levels and fatigue-inertia scores.[21] Studies have

shown variable long-term changes in LDL cholesterol levels and evidence of dyslipidemia in those adhering to a KD; thus, the association with long-term cardiovascular outcomes is unclear.[22] In contrast, a WFPBD led to significantly lower LDL and total cholesterol levels compared with a standard low-fat diet.[23] It is unclear whether loss in lean mass and increase in fatigue occur consistently while following a KD; if so, it is also unknown whether this could represent a long-term risk for patients with cancer cachexia.

Reduction in Insulin-Like Growth Factor 1 Levels

Insulin-like growth factor 1 (IGF-1) is positively associated with the risk of several cancers by stimulating proliferation and inhibiting apoptosis.[24,25] Individuals who consume a vegan diet have significantly lower levels of IGF-1 and higher levels of IGF-binding proteins 1 and 2,[26] which may be associated with the specific effects of plant proteins and lower overall protein intake compared with a Western diet.[27] Ketogenic diets have shown a reduction in insulin levels but the reduction in IGF-1 was not significant.[18,28]

In vivo studies with a lymphoma mouse model also suggested that a low-protein diet compared with an LCD was associated with a decrease in tumor growth and increase in tumor-infiltrating lymphocytes, which were followed by ananticancer immuneresponse.[29] Similar findings were seen in hepatocellular cancer rat models.[30]

Reduction in Insulin Resistance

Insulin and some of the most prevalent genomic alterations in human cancers (such as *PIK3CA* variations and *PTEN* loss) activate the phosphoinositide 3-kinase (PI3K) signaling cascade. This pathway regulates cellular metabolism as well as cell survival and proliferation. Thus, high insulin levels can promote and sustain tumor growth.[31] A WFPBD is associated with decreased fasting plasma insulin concentrations and improved insulin sensitivity.[32] Decrease d insulin levels have also been reported in KD clinical trials,[18,28] although some preclinical studies showed contrary findings, suggesting increased insulin resistance.[33]Treatment with a KD had variable effects on different tumor mouse models (including accelerated disease progression in acute myeloid leukemia).[31] Therapeutic targeting of the PI3K signaling cascade with PI3K inhibitors leads to systemic feedback with acute insulin release and hyperglycemia that impairs the efficacy of these agents. Approaches that reduce insulin exposure might increase the efficacy of these inhibitors. Inmouse models, KDs deplete hepatic glycogen content, which prevents the degree of hyperglycemia and hyperinsulinemia observed following PI3K inhibitor treatment, thus enhancing the drug's effectiveness.[31] It may be possible that a WFPBD may also have some benefit for managing PI3K inhibitor–induced hyperglycemia, althoughtoourknowl-edge this has not been studied.[32]

Increased Fiber

A large meta-analysis showed a decrease in cancer mortality (relative risk [RR], 0.85; 95% CI, 0.80–0.91) and all-cause mortality (RR, 0.83; 95% CI, 0.77–0.90) per 90-g per day increase in whole grain intake.[34] Fiber intake was inversely correlated with the risk of cancers in the EPIC study as well.[35]

In patients with melanoma who were treated with checkpoint inhibitors, patients with sufficient dietary fiber intake ([H11350]20 g per day) and no probiotic use had higher odds of responding to treatment with programmed cell death 1 (PD-1) inhibitors as well as a longer progression-freesurvival.These findings were confirmed in preclinical animal models, and mice that received a low-fiber diet or probiotics had a lower frequency of interferon γ–positive cytotoxic T cells in the tumor microenvironment and an impaired response to anti–PD-1 therapy.[36] A preclinical model with anti–cytotoxic T-lymphocyte associated protein 4 inhibitors showed contrasting results.[37] Similar positive effects of fiber have been observed in the setting of colon cancer prevention. Given higher rates of colon cancer in African American individuals compared with African individuals living in rural areas, 20 healthy African American individuals and 20 African individuals from rural areas were administered a 2-week dietswitch(high-fiber, low-fat,AfricanstyledietadministeredtoAfrican American individuals and a high-fat, low-fiber, Western stylediet to African individuals from rural areas). The high-fiber diet was associated with decreases in cell proliferation (Ki67) and $CD3^+$ lymphocytes in colon mucosa, as well as an increase in butyrate in the stool.[38] These positive effects of high-fiber diets are typically not achieved in KDs because the recommended dietary fiber intake is rarely met compared with a WFPBD.[39]

Reduction in Inflammation

When weight loss was achieved via either diet or exercise, parallel reductions in circulating inflammatory molecules were observed.[40] Additionally, a WFPBD was associated with lower levels of oxidative stress and inflammation.[41,42] While data are limited, some clinical studies of KD suggested proinflammatory effects, such as an increase in Creactive protein and a decrease in fibroblast growthfactor 21 levels, which are regulators with anti-inflammatory properties compared with the average US diet.[43]

Phytochemicals

Plant foods contain phytochemicals, such as flavonoids, that have anti cancer properties; therefore, they are more abundant in a WFPBD than a KD. Large epidemiologic studies have shown that moderate habitual intake of flavonoids is inversely associated with all-cause and cancer-related mortality.[44] Flavonoids have anti-inflammatory effects (via the mitogen-activated protein kinases, nuclear factor-κB (NF-kB), nodlike receptor pyrin domain–containing 3 inflammasome, signal transducer and activator of transcription 3 pathways) and antioxidant effects (via the Warburg effect, nuclear factor erythroid 2–related factor 2, and hypoxia-inducible factor 1 α signaling)and lead to apoptosis and cell cycle arrest, alter cell growth and metabolism (via protein kinase B/mammalian target of rapamycin and renin-angiotensin system/extracellular signal-regulated kinase inhibition), and modulate autophagy.[45]

Short-Chain Fatty Acids

Some of the beneficial anticancer effects of both diets were associated with an increase in short-chainfattyacids(SCFAs)bydifferent mechanisms. Fiber-rich plant-based diets were associated with increased butyrate producers while animal-based diets were associated with increased bile tolerant organisms in the gut microbiome.[46,47]The butyrate producers facilitate production of SCFAs (butyrate/acetate), which inhibit the nuclear factor-KB

pathway and histone deacetylases (HDACs), leading to anticancer and anti-inflammatory effects.[48,49] Higher stool butyrate concentrations and the relative abundance of butyrate producers were associated with minimal residualdisease negativity in patients with multiple myeloma who were receiving maintenance therapy in a small single-center study.[50]

Conversely, KDs were associated with increased blood ketone body levels(mainlyβ-hydroxybutyrate[βHB]), aSCFA.AlthoughβHB also has HDAC inhibitory effects, butyrate is a stronger HDAC inhibitor.[51] There is conflicting evidence as to whether βHB has anticancer effects vs proinflammatory and tumor proliferative effects in in vitro and in vivo models.[51–53] The discrepant findings may be because of a βHB paradox. In transgenic mice bearing a spontaneous mouse mammary tumor virus NEU-NT model, tumors that were inhibited by βHB preferentially utilized glucose vs βHB and accumulated high βHB levels that inhibited HDAC, whereas some tumors preferentially utilized βHB, which enhanced their growth rate andreducedβHBconcentrationstolessthanthethresholdforHDAC inhibition.[53] Therefore, tumor screening for ketone body metabolizing enzyme activation may identify those likely to benefit from a KD; however, concerns remain that the tumor could metabolically adapt and eventually develop tolerance to the KD.

Limited preclinical data suggest that KD may enhance the effects of specific cancer treatments and/or have tumor subtype–specific effects. For example, KDs induced tumor growth retardation in models in which anti–PD-1 treatment alone or in combination with anti–cytotoxic T-lymphocyte associated protein 4 failed to reduce tumor growth via alterations in the gut microbiome.[54] Pre-clinical data in *BRAF V600E*–expressing melanoma suggested that a KD upregulated 3-hydroxy-3-methylglutaryl coenzyme A lyase (a key enzyme in ketogenesis), which raised levels of acetoacetate that then activated *MEK1* and fueled tumor growth. Additionally, hypolipidemic agents attenuate tumor growth by reducing serum acetoacetate.[55] The βHB promotes anabolic growth of breast cancercells(approximately2.5fold)andmetastaticdissemination.These data led to the study of ketone inhibitors for cancer treatment.[56,57]

Ketogenic diets have shown antitumorpotentialinsomemouse studies(especiallybraintumormodels[18])[58]and variable effects in other studies.[31] To date, definitive human clinical trial data are awaited.[59]

Interventional Clinical Trials

Plant-Enriched Dietary Interventions

Several trials have demonstrated that weight loss and dietary modification are feasible in cancer populations and have been reviewed elsewhere.[60]Although most completed interventional studies have not incorporated a whole foods approach or, more specifically, a WFPBD, several trial interventions aimed to increase fruit and vegetable intake or reduce fat intake. In this article, we discuss some of the largest dietary studies in oncology that have tested interventions that are most representative of WFPBD or KD.[60]

In the postdiagnosis setting, for patients with prostate cancer on observation, aWFPBDcompared with control was associated with a significantly reduced incidence

of conventional prostate cancer treatment.[61] The growth of prostate cancer cells was significantly inhibited almost 8 times by serum from patients adhering to a WFPBD vs the control group in vitro.[20] Favorable changes were also found in tumor gene expression, and an increase in relative telo mere length was observed with a WFPBD.[62,63]TheMen'sEating and Living (MEAL) Study (CALGB 70807 [Alliance]), a larger RCT promoting 7 or more servings of vegetables daily, showed no difference in the time to cancer progression, possibly owing to low dietary adherence, and points to the challenges of changing dietary habits with counseling alone.[64]

In breast cancer, several trials have tested plant-enriched diets, although not strictly WFPBD. In the prevention setting, the Women's Health Initiative (WHI) Study compared the effect of a reduced fat dietary intervention with a usual diet group in 48 835 postmenopausal women and showed that those in the low-fat group had improved breast cancer–specific and overall survival.[65] In the postdiagnosis setting, the 2 largest RCTs of dietary interventions are the Women's Healthy Eating and Living (WHEL) Study and the Women's Intervention Nutrition Study (WINS). The WHEL Study tested a diet comprising 5 vegetable servings, 3 fruit servings, and 30 g of fiber with a 15% to 20% energy intake from fat vs a control arm diet (usual care). The primary outcome measures were recurrent or new invasive breast cancer or death of any cause. During a 7.3-year follow-up period, the dietary intervention did not reduce breast cancer events or mortality.[66] The WINS study tested the effect of reduced fat intake (<15%) in women with resected, early-stage breast cancer who were receiving conventional cancer treatment. In contrast to the WHEL study, participants in the low-fat diet arm of this trial experienced a 24% reduction in breast cancer relapse events compared with the usual diet group, although this effect was attenuated in long-term follow up.[67,68] The conflicting results of these seminal dietary trials highlight the need for further research and do not adequately test the efficacy of a WFPBD.

Ketogenic and Similar Dietary Interventions

A systematic review and meta-analysis of 6 RCTs evaluating the efficacy of KD as antitumor therapy concluded that there was inconclusive evidence. Completion rates for KD interventions ranged from 45%to75%, highlighting the challenges of ensuring compliance with KDs.[69] To date, to our knowledge, no KD RCTs powered to cancer-specific outcomes have been reported.

An LCD study in patients with prostate cancer with biochemical recurrence, elevated body mass index, and a prostate-specific antigen doubling time of 3 to 36 months showed no difference in the mean prostate-specific antigen doubling time, although there was significant weight loss and improvements in high-density lipoprotein cholesterol, triglyceride, and hemoglobin A_{1c} levels in the interventional arm.[19] More recently, a nonrandomized study (KOLBIRI) tested the feasibility of a KD, LCD vs standard diet in survivors of breast cancer and showed significant weight loss and improved quality of life in all arms, although breast cancer–specific end points were not studied.[70] Similar findings were reported in non-cancer populations. Currently, there are 46 KD trials (20 active, 10 completed, and 6 terminated [poor accrual/compliance]; 5 with unknown status)

and only 8 WFPBD trials (6 active, 2 completed, and 0 terminated) (eTables 1 and 2 in the Supplement).

Other Diets

Other dietary patterns with limited data for cancer prevention and controlincludeLCD,Mediterranean, andmacrobioticdiets.The macrobiotic and Mediterranean diets are very similar to a WFPBD, as they are enriched for plant foods and fiber. The LCDs are similar to KDs bylimiting carbohydrate intake, although they are less restrictive and typically do not achieve ketosis. Several of these dietary patterns have garnered attention in popular literature, although the evidence for benefit in cancer populations is sparse. Some additional data are anticipated from ongoing trials. For example, the Diet and Androgen-5 (DIANA-5) study is an ongoing RCT in 1344 women aimed at testing whether a Mediterranean-macrobiotic dietary pattern can reduce the incidence of breast cancer–related events.[71]

Time-restricted eating via fasting or fasting-mimicking diets has also gained increasing popularity inrecent years.Preclinical and preliminary clinical data indicate that these approaches are associated with alterations in metabolites, growth factors, and antitumor immunity that limit the ability of cancer cells to adapt and survive within the host environment.[72]While fasting approaches have been shown to induce weight loss, it is unclear whether fasting is superior to caloric restriction, and caution is advised in patients with low lean mass.[73] The mechanisms and applications of fasting approaches in the setting of cancer have been reviewed elsewhere.[74]

Challenges

Nutrition trials with cancer-specific primary objectives often require large sample sizes and long intervention periods to see changes, especially given that long-term adherence to dietary changes during clinical trials is difficult. Other challenges with nutrition studies in oncology include differences inintervention duration, lack of standardization of macronutrient content, conflation of weight loss effect vs nutrient intake effect, and suboptimal adherence. For example, if ketosis is not achieved, a KD essentially amounts to carbohydrate restriction. Personal food preferences, psychosocial issues around a cancer diagnosis, adverse effects of cancer and its treatment (such as appetite loss, nausea, and cachexia), and other medical comorbidities can further accentuate these challenges, making it harder to initiate and sustain dietary changes.

Plant-based KDs are a potential alternative, with benefits from both dietary patterns.This approach may be difficult to sustain given the limited number of high-fat plant foods. Limited food variety is also associated with decreased microbial diversity.[75]

Conclusions and Future Directions

A large body of evidence suggests that dietary intake is associated with cancer outcomes (Box). The preponderance of available data supports plant-enriched diets for cancer prevention and control, although confirmatory prospective trials are required. The WFPBD

is part of established, universally recommended healthy lifestyle habits. Adherence to a WFPBD is associated with reduced cancer risk and has been shown to confer additional benefits for cardiovascular disease, diabetes, body weight, and body composition.[32,76–78]

Accordingly, several professional organizations recommend dietary patterns that are consistent with WFPBD for primary risk reduction. In contrast, far fewer data support the KD for cancer prevention or survivorship. Exceptions may be supported by data from well-designed prescriptive KD studies in specific tumors that have an underlying mechanistic basis, such as *PIK3CA*-mutated tumors, if ongoing trials are affirmative.

Data from prospective RCTs are required to change clinical recommendations. Currently, to our knowledge, no such data exist to support the recommendation of specific diets for adjunctive cancer treatment. The National Cancer Institute's translational framework provides a blueprint for lifestyle intervention development and should guide future WFPBD and KD trials.[79] The safety and tolerability of these specific diets could be substantially affected by ongoing cancer therapy, which underscores the need to start with phase 1 safety studies, followed by phase 2 preliminary efficacy trials (biologic and/or cancer-related) that confirm safety, and finally, confirmatory phase 3 trials testing classical oncologic end points.[80]

Despite the epidemiologic evidence supporting plant-enriched diets, there are currently more ongoing trials testing KDs than WFPBDs in cancer populations. The data reviewed in this article support an urgent call to investigators, clinicians, and funding agencies to prioritize interventional WFPBD trials in oncology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box.

Summary of Current Evidence, Limitations, and Future Directions in Nutrition for Cancer

Current Evidence

- Epidemiologic studies suggest that there is a reduced cancer incidence with plant-based dietary patterns.
- Mechanistic evidence for both diets includes weight loss, decreased inflammation, and decreased insulin levels.
- Mechanistic evidence for WFPBD alone includes increased fiber, phytochemicals, and butyrate levels and decreased IGF-1 levels.
- Mechanistic evidence for KD alone includes increased β hydroxybutyrate levels.
- Large RCTs have tested low-fat and weight loss interventions in cancer populations, although trials with WFPBD or KD interventions with cancer-specific outcomes are not available.

Limitations

- Nutrition trials with cancer-specific outcomes require long intervention periods and large sample sizes to be able to identify a meaningful difference.
- Long-term adherence to dietary changes on clinical trials is challenging.

Future Directions

- Cancer nutrition research is likely to benefit from trial designs adapted from drug development.
- Develop clinical trials with prescriptive meal delivery services to improve compliance and be better able to study the outcomes of interest.
- Design clinical trials with mechanistic translational correlatives, such as epigenetic, immune, and microbiome changes.
- Prioritize studies that evaluate the role of a WFPBD in cancer populations given the limited number of trials that are currently ongoing.

Abbreviations: IGF, insulin-like growth factor; KD, ketogenic diet; RCT, randomized clinical trial; WFPBD, whole food plant-based diet.

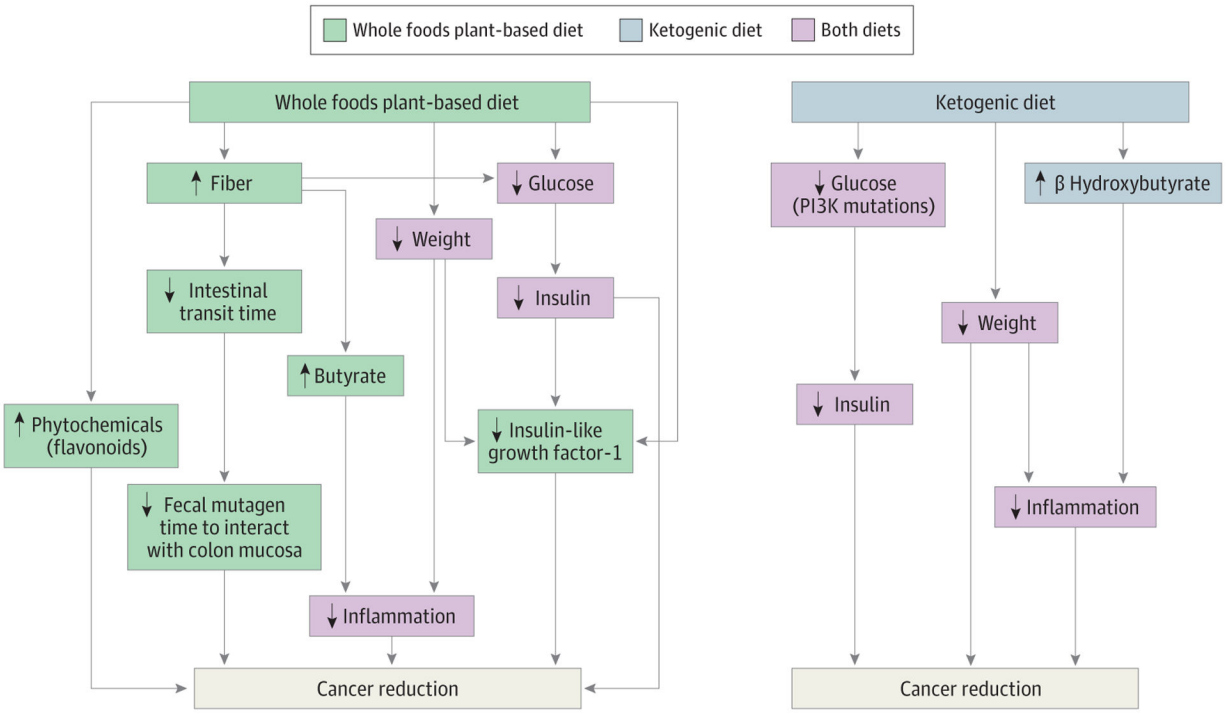

Figure.

Association of Plant-Based Diets With Multiple Additional Pathways That Suppress Cancer Growth Compared With Ketogenic Diets