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The Ketogenic Diet: Its Effectiveness as an Adjuvant Therapy for Cancer

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NURS 4500.2: Nursing Research and Senior Thesis

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Abstract

This paper explores a total of six research studies and will contain a literature review and proposal for further study regarding the effectiveness of the ketogenic diet as an adjuvant cancer therapy. Each study addresses a variety of different factors involved in KD implementation, ranging from effects on body composition and lipid profiles, to self-proclaimed quality of life, to tumor expression and progression under a KD regime. Ultimately, each were divided into three separate categories depending on the aspects of research that were covered. Two studies, by Hagihara et.al and Jansen and Walach respectively, discuss the potential benefits of KD in cancer patients, while two additional studies by Sremanokova et.al and Klement et.al address concerns regarding the implementation of KD in cancer populations. The final category and studies by Yang et.al and Erickson et.al claim a lack of significance in the use of KD in clinical practice, and examine why this is the case. The major findings and limitations of each study will be discussed in detail, alongside theme comparisons between studies. Based on the findings discussed, the new research question in the proposal for further study will address the anti-tumor effects of KD on glioblastoma specifically. The study will be a longitudinal mixed method design and will only involve participants diagnosed with glioblastomas. The data obtained through conducted interviews and surveys will be analyzed through audio recordings, written assessment scales, and questionnaires completed by participants. Additional lab work will be done for the statistical analysis portion and will observe changes in blood ketone levels, TKTL1 expression, and cfDNA blood levels respectively. The final portion will discuss the consensus between both the literature review and proposal for further study, which is that KD shows promise as an adjuvant therapy in cancer populations.

Acknowledgements

I dedicate this paper to my older cousin who passed from glioblastoma, as well as my relatives who have suffered from and are at risk for cancer. Their stories have inspired me to research this topic.

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Introduction: The Ketogenic Diet and Cancer Therapy

While many leaps and bounds have been made in the study of cancer and its subsequent treatment, there is still room for growth in the use of adjuvant therapies to increase efficacy and quality of life in patients. “In recent years, attention was drawn to the fact that diet-associated factors may be involved in the development and progression of cancer” (Jansen & Walach, 2016, para. 2). That said, one such avenue that shows promise is the ketogenic diet, a high-fat low-carbohydrate diet with increased protein consumption. The traditional ketogenic diet consists of a 4:1 ratio, which “delivers 90% of its calories from fat, 8% from protein and only 2% from carbohydrate” (National Center for Biotechnology Information, 2020, para. 9). Its practice has already been utilized as a second-line treatment for epilepsy in pediatric populations with much success.

However, there is debate in the scientific community regarding whether or not the implementation of KD is as effective in cancer populations as it is in epileptic populations. Many speculate that KD may provide an antitumor effect by creating an unfavorable environment for cancer cells through a decrease in carbohydrate consumption. Such cells thrive on the glucose contained in carbohydrates, and it is through this diet, alongside the use of standard cancer therapies such as chemo and radiotherapy, that tumor progression can be halted, increased tolerability to treatment, and improved quality of life for patients may be achieved. However, according to the National Center for Biotechnology Information (2020), “to further elucidate the mechanisms of the ketogenic diet as a therapy and evaluate its application in clinical practice, more molecular studies as well as uniformly controlled clinical trials are needed” (para. 3). The following thesis, including a comprehensive review of the research literature and proposal for

further study, is a way to provide additional insight into this area of interest, and to answer the question of how effective the ketogenic diet is for adjuvant cancer therapy in clinical practice.

Literature Review

The Dominican University databases were utilized in the search for information regarding the ketogenic diet and cancer treatment. All search terms were variants of these two descriptions, and the research was confined to the following databases: Iceberg, CINAHL, PubMed, and Cochrane. Six studies were used in total, and only ones that involved human trials and introduced KD as an adjuvant therapy were taken into consideration. Due to the versatility of KD effects on different cancer types, studies that only reviewed a single form of cancer were excluded from this review, but measures were taken to ensure that these studies provided evidence related to their respective cancer markers and how they correlate with KD. All studies involved were limited to either systematic reviews, randomized controlled trials, or meta-analyses.

Each study was divided into three separate categories. In the first category, the sources showed promising evidence for KD as a beneficial form of therapy alongside other cancer treatments. However, despite their many benefits, they also discuss how these results are not enough to support the practical use of KD in clinical settings. They merely serve as avenues for further study and provide valid evidence to support the idea that KD should continue to be researched as an alternative form of cancer therapy. The second category included sources that addressed the concerns regarding the use of KD on cancer populations and the potential barriers that need to be considered before it can be clinically implemented. The final source category described how KD implementation yielded inconclusive evidence and should not be considered for clinical practice.

Study Findings Show Promise in Primary Care

Hagihara et.al (2020) came together to conduct a study that evaluated the effectiveness of a new ketogenic diet regimen in patients with different types of stage IV cancer. The purpose was to determine whether KD could be used as a supportive therapy in clinical practice and to establish the extent that carbohydrate restrictions could be implemented in those with cancer. Fifty-five participants gave their consent in total, with data only being taken from 37 partaking in KD for three months or more. Major findings of the study yielded that the effects of KD differ depending on the cancer type, but across their respective lab markers and lipid profiles, KD in combination with chemotherapy or radiation was correlated with a decrease in tumor and metastases size. Paired with these standard cancer therapies, Hagihara et.al (2020) stated that “The present ketogenic diet regimen had better tolerability, with less nausea, fatigue, and constipation, and it induced stable adherence” (Discussion section, para. 5). In addition, “results suggest that weight loss is not a toxic effect of the ketogenic diet” (Discussion section, 2020, para. 5) despite weight loss risk in cancer patients. Many maintained adequate nutrition and muscle mass despite the change in diet.

These results indicate that adverse symptoms and body composition risks associated with the implementation of KD in cancer populations are not a primary concern. Overall, KD seems to have a positive effect on cancer patient’s long-term prognoses and may contribute to long-term survival with controlled use. However, some results may be controversial due to limitations in dietary restriction. If dietary restriction is insufficient, it may alter patient lab results and leave anti-tumor effects unclear. In summary, should future modifications and additional research be pursued, KD offers hope as a promising avenue for support therapy in cancer populations.

An additional study by Jansen and Walach (2016) wanted to evaluate whether the levels of TKTL1, a novel marker of tumor cell glycolysis, are affected by a ketogenic diet, and whether adherence to KD is associated with a better prognosis in patients with cancer. Seventy-two subjects diagnosed with any form of cancer since January 2001 were included in the study. According to Jansen and Walach (2016), “Results obtained suggest that there is a positive link between the expression of TKTL1 and cancer progression, and a negative link between ketogenic diet and TKTL1 expression” (Discussion section, para. 6). These results indicate that the expression of TKTL1 is associated with tumor progression. However, when KD was introduced, TKTL1 expression was observed to be halted. Jansen and Walach (2016) claim that “reduced expression levels of TKTL1, which are a negative predictor of cancer progression, may reflect the effect of a ketogenic diet” (Discussion section, para. 6). Noting these changes in lab values, Jansen and Walach surmised that it may be beneficial to advise individuals with cancer to adopt KD due to the altered expression of TKTL1.

However, despite altered TKTL1 values, patients are still at risk for recurrences or metastases. Additionally, not all individuals maintained a consistent regime while on KD, which may have skewed overall results.

Concerns Regarding KD for Cancer Populations

While benefits of the ketogenic diet are certainly present in study findings, there is still skepticism surrounding the safety of its use for individuals with cancer. Klement et.al (2020) were concerned with the skepticism regarding lack of adequate clinical research supporting the effectiveness of the ketogenic diet as a cancer therapy. They claim that a “lack of studies occupying higher levels in typical ‘evidence hierarchies’ has been emphasized by some authors...discouraging the clinical application of KDs” (Klement, p. 5, 2020). This is known as

“methodological skepticism” and serves as a strong barrier towards confidence in KD efficacy. In an effort to address such concerns, the subsequent study was executed and focused on research that had implemented KD in medical oncological treatments. Despite previous concerns, data found that there are large beneficial effects of KD on body composition in both overweight and frail populations, as well as those at risk for excessive weight loss due to cancer or while undergoing cancer treatment. Additional evidence by Klement et.al (2020) suggests that KD “acts synergistically with radiotherapy, chemotherapy, and other therapies” (p. 9), as well as “[deprives] cancer cells of important anti-oxidative substrates” (p. 9) to inhibit growth. The evidence supporting KDs as a supportive cancer therapy is steadily growing and suggests several benefits in clinical practice.

Sremanokova et.al’s (2018) study was concerned with the nutritional aspect of KD and aimed to determine its effects on cancer patient’s nutritional status, as they stated that “KD has the potential to influence many physiological processes...[incurring] weight loss, muscle wasting and severe inflammation, which can lead to morbidity and poorer quality of life” (Introduction section, para. 4). A total of 102 participants ranging 34 to 87 years old were included in the study, all with a variety of different cancer types at different stages. Based on analysis of anthropometry, lipid profiles, tumor effects, and adverse events, the study found that KD does not cause life-threatening events and may even be feasible as a therapy with the right parameters. However, Sremanokova et.al (2018) claim that KD “adherence is low and possibly linked to a limitation in diet delivery, as well as a lack of monitoring and follow-up” (Conclusion section, para. 1). This indicates that while no life-threatening events were observed, lack of proper KD implementation may have contributed to these results. Other barriers such as lack of ketone measurements, which is a staple value in evaluating ketogenic effectiveness, short KD duration,

and small sample sizes, were also noted, which made it difficult to reach a valid conclusion. Sremanokova et.al deduced that while there are sound theoretical bases for KD suppressing tumor growth across different cancer types, strong conclusive evidence in clinical practice is lacking.

No Statistical Significance

The following studies were some of the few that claimed there was inadequate evidence to support the beneficial effects of the ketogenic diet on antitumor therapy. In Yang et.al's (2021) study, rigorous comparison of different factors such as lipid profiles, tumor markers, level of satisfaction, and adverse effects found that "most evidence did not have any statistical significance and therefore the effects of LCKDs as an adjuvant therapy on cancer management was inconclusive" (Discussion section, para. 5). Yang et.al bring up a very important point in the study's discussion portion, claiming that it is difficult to accurately draw comparisons between studies because each follows its own set of protocols and are within different parameters. Data collection in one study may include qualitative aspects that give more depth to the patient's experience while others may choose to focus on statistical values seen in laboratory results or profiles. This lack of consistency in data, in the words of Yang et.al (2021), makes it "difficult to obtain an accurate conclusion to dictate the ketogenic diet as adjuvant therapy for cancer" (Discussion section, para. 10). As such, it cannot be exclusively proven whether KD is effective or ineffective as an adjuvant form of cancer therapy.

Erickson et.al (2017) take a similar approach to this claim, and ultimately they come to the same conclusion as Yang: "...evidence on [ketogenic] benefits regarding tumor development and progression as well as reduction in side effects of cancer therapy is missing" (p. 11). Similar to the previous study, their goal was to assess the effectiveness of a KD regime, specifically in

regards to weight maintenance, and acquire structure to determine how to implement this regime best in cancer patients. However, after the analysis of results related to tumor progression, regime duration, quality of life, and body composition, ultimately no statistically significant evidence could be found. Erickson et.al (2017) claim that “The studies are limited by their sample sizes and lack in homogeneity of type, location and cancer stage, and thus, results cannot be compared” (Results section, p. 2, 2017). In addition to this, “studies in the area of cancer lack consistency and do not utilize clearly comparable and consistent standardized dietary protocols” (Results section, p. 2, 2017). Validity and reliability of results are unable to be achieved in the case of inconsistent study implementation. For this reason, interpretation of the data presented for KD effectiveness in cancer therapy cannot be regarded as accurate. As a result, Erickson et.al (2017) suggest that “More robust and consistent clinical evidence investigating comparable patient groups with comparable methodology, dietary protocols and consistent results are warranted before the KD can be recommended for any single cancer diagnosis or as an adjunct therapy” (Conclusion section, p.1)

Discussion of the Literature

While there have certainly been benefits observed in the use of the ketogenic diet alongside cancer therapy, such as slowed tumor progression and maintenance of healthy body composition, concrete and measurable evidence of said benefits are still largely inconclusive. Many of these studies had limitations in their research that were not addressed or could not be overcome. A common theme in such limitations mainly had to do with small sample sizes, lack of homogeneity between cancer types, inconsistent diet implementation, and unequal study parameters. Smaller sample sizes indicate an inaccurate representation of the larger cancer population, and with each study conducting their research with different sets of parameters,

results indicate an unreliable portrayal of the effects of KD as an adjuvant cancer therapy. In addition, the purpose of including a variety of different cancers was to determine how KD affects each one individually. However, the broader the range of conditions to identify and research, the more difficult it becomes to accurately compare data. This lack of reliability and validity between studies creates a skewed cesspool of results, and despite the benefits observed, they are not enough to place sure confidence in clinical practice.

However, this does not mean that KDs lack promise in the potential to strengthen cancer therapy. If there is one thing that the studies share in common, it is the need for further research into this avenue of treatment, as many of them have claimed themselves. More controlled trials are necessary before KD can seriously be considered as an adjuvant therapy, and with new research being presented every year, the hope is that these future studies will address concerns that their predecessors have identified before them. Overall, while the research into KD is still in its infant stages among the cancer population, the aforementioned studies recognize that it is a valid adjuvant therapy to be pursued further, so long as limitations are addressed and attempted to be corrected.

Theoretical Framework

As briefly mentioned, a common theme across the studies was the participants' inability to utilize the ketogenic diet to completion. Many stopped KD a quarter or midway through, and others, despite using KD to completion, were not consistent with their diet's implementation. While this may have skewed data and results, it is important to understand that, especially in the case of cancer treatment, the patient always has the final say when it comes to decisions of care. According to Orem's Self-Care Deficit Nursing Theory, "People are distinct individuals" and "should be self-reliant, and responsible for their care, as well as others in their family who need

care” (Nursing Theory, n.d., p. 3). If there are deficits in a person’s ability to administer self-care, that is when nursing intervention must be implemented. This creates an interpersonal relationship between nurse and patient, where the nurse communicates accurate and reliable information regarding a patient’s condition and treatments, and the patient is enabled to make well-educated decisions about administration of self-care.

In the case of cancer populations, medical and therapeutic interventions will likely be implemented to better manage their conditions, no matter the cancer type. That being said, the patient will always be the final decision maker when it comes to actual implementation of these interventions. The nurse is responsible for “acting for and doing for others; guiding others; supporting another; providing an environment promoting personal development in relation to meet future demands; and teaching another” (Nursing Theory, p. 5). For ketogenic diet implementation, the role of the nurse is to provide an appropriate avenue for participants to be informed, and in doing so, encourage confidence in their care regardless of whether or not they choose to participate in the diet change. It is crucial that KD research considers this aspect of nursing, as it plays an important role in how data will be collected and to what extent it will be accurate.

Proposal for Further Study

Due to the limitations that have been identified by ketogenic diet research, specifically in relation to cancer populations, more controlled measures will need to be taken for further study in this area of interest. Small sample sizes were a common barrier seen among the studies. In particular, participant's inability to continue KD to completion led to attrition, leading to inconclusive results. Additionally, insufficient data collection was largely due to the incomparability of different cancer types, all of which were studied at different stages and with

different biomarkers. With such large inconsistencies in research, it is essential to implement a more concise method of study to analyze the specific effects of KD on cancer populations. For more accuracy and consistency across data, the subsequent study will address the following research question: What are the effects of a ketogenic diet on tumor progression in those with glioblastoma?

While changes will be implemented in the study's protocols to address these concerns, it will still be difficult to fully control all extraneous variables. Participants have a right to informed consent, and we cannot blind them to the study's implementation methods without proper education of the risk-benefit analysis of KD. Margins of error related to how involved participants will be will also need to be considered. From an ethical standpoint, we cannot force a patient to undergo any form of treatment no matter the benefits, and in the case of KD, the participant has the final say in whether or not they want to complete the trial. With this in mind, the following parameters were designed to carry this research study forward.

Study Design

A longitudinal mixed method design will be implemented for this study. Collection of data to determine the effects of the ketogenic diet in patients diagnosed with glioblastoma will need to take place over a longer period of time. Both qualitative and quantitative data will be collected for analysis of holistic effects of KD on cancer patients.

Specific Aims

The primary objective of collecting quantitative data will be to precisely measure changes in lab values specific to glioblastoma tumor progression during a ketogenic diet and achievement of ketogenesis over a six-month period. The secondary objective will be to assess participants' perception of pain and changes in symptoms related to ketogenic diet implementation not

associated with other forms of cancer treatment. Qualitative data will additionally be collected to explore participant feelings before and after adoption of a ketogenic diet

Methodology

A total of ninety participants will be included for KD implementation, and due to the conflicting data of different cancer types, this study will only consist of those with glioblastomas. Advertising will be administered both physically through paper flyers posted at the UCSF Brain Tumor Center in San Francisco and electronically on the News and Blog section of the National Brain Tumor Society website. Both advertising campaigns will signify that trial screening is open for a two-month window. To meet criteria for the design, participants must be over the age of eighteen and have been diagnosed with glioblastoma for at least two weeks. As mentioned previously, we cannot force participants to undergo KD for any length of time they do not wish to. To decrease the likelihood of this occurrence, an educational session will be held during the screening process to inform the participants of the parameters this study will implement. The session will include education on what KD is, what specific KD type will be implemented and for how long, the potential effects it may have on tumor progression, and the lab work and data collection that will be done throughout the study to observe the effects of KD.

Selection of participants will be conducted as a rolling admission, meaning that all applications from participants will be evaluated as they are received rather than altogether once a deadline is reached. Participants will be given a three-week period after the study's educational session to decide whether they want to be involved in the study. Should they choose to participate, they will partake in a thirty minute interview session before KD implementation to discuss feelings regarding their current treatment and what they are hoping to achieve through implementation of KD. Another thirty minute interview session will take place at the end of the

study asking the same questions now having received KD and whether or not their expectations were met, and to what extent. Each interview session will be recorded and analyzed at the study's conclusion to determine significance of KD implementation.

Data Collection

The ketogenic diet will be administered over a six month period, and among that time four blood tests will additionally be given. The lab work will be to obtain biomarkers related to KD effects, with ketogenesis being observed through ketone levels in the blood and glioblastoma tumor progression being observed through TKTL1 expression and cfDNA levels in the blood respectively. The tests will take place before the KD diet is implemented to obtain participant baselines, again two months into the study, then four months in, and finally at the study's conclusion. Additionally, at the two month and four month intervals, a survey will be given to determine current feelings on KD's implementation, symptom assessment using the short form of the Brief Pain Inventory (BPI) assessment tool, changes in health and/or quality of life, and how confident they feel that they will continue KD to completion. Overall, the total length of enrollment, diet implementation, and data collection will take place over the span of two years.

Data Analysis

For analysis of quantitative data, descriptive statistics will be used to describe demographic characteristics along with multiple regression, which will examine differences in lab values over time. Analysis will additionally be correlation based to determine the relationship between KD diet implementation and tumor progression, as measured by the Pearson r correlation technique. For analysis of qualitative data, content analysis will be used and measured by Colaizzi's method of data analysis, as described below in Fain's (2021) sixth edition *Nursing Research* text:

1. Describe lived experience under study.
2. Collect participant descriptions of the lived experience.
3. Read all participant's descriptions of the lived experience.
4. Extract significant statements.
5. Articulate the meaning of each significant statement.
6. Aggregate the meanings into clusters of themes.
7. Write an exhaustive description.
8. Return to participants for validation of the exhaustive description.
9. Incorporate any new data revealed during validations into final exhaustive description.

Conclusion

While there have been a variety of different research designs and scrutiny regarding the ketogenic diet as a cancer therapy, the consensus among the scientific community is this: the ketogenic diet, while still in its infancy as a therapeutic cancer intervention, shows promise in its effectiveness and potential for long-term benefit. Its influence on tumor progression seems notable when paired with additional intervention such as chemo or radiotherapy, and this effect extends across a wide variety of cancer types. However, these benefits can only be considered with partial strength due to the extensive limitations the study designs faced. Most sample sizes were too small to accurately represent KD effects on all cancer populations. Additionally, each type of cancer used different methods of measurement that were incomparable with each other. Each study also had their own set of parameters that could not be replicated or were not properly explained. This lack of homogeneity between cancer types, implementation, and observation makes it difficult to reach a joint conclusion.

As it stands, KD cannot be properly implemented into clinical practice without further research and study analysis. While it has clearly shown promising results in the avenue of adjuvant cancer therapy, there are still too many uncertainties that may put patients at risk if implemented with the current knowledge we have. That being said, the ideas that KD has introduced serve as an exciting opportunity for cancer populations in the pursuit of alternative therapy, all with the goal of improving quality of life. More controlled trials will need to be conducted to ensure that results are obtained within similar design frameworks, which will build validity and reliability that can pave the way for future studies. For nurses and patients alike, knowing the effects on different cancers is certainly beneficial, but in the best interest of consistent research and data collection, studies should strive for homogeneity in cancer types to allow for more authentic variety in KD effects. Tumor progression, body composition, and adverse symptoms seem to be the avenues that are most promising for KD implementation.

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adjuvant cancer therapy: A systematic review and meta-analysis of randomized

controlled trials. *MDPI*, 13(5). <https://doi.org/10.3390/nu13051388>

Appendix A

Authors/Citation	Purpose/Objective of Study	Sample- Population of Interest, Sample Size	Study Design	Major Findings(s)	Strengths	Limitations
<p>Yang, Y.-F., Mattamel, P. B., Joseph, T., Huang, J., Chen, Q., Akinwunmi, B. O., Zhang, C. J. P., & Ming, W.-K.</p>	<p>Investigate the efficacy of the low carb keto diet as an adjuvant therapy in antitumor treatment compared to non-keto diets</p> <p>Establish the role of the low carb keto diet in cancer treatment more clearly</p>	<p>216 subjects who underwent the keto diet to completion (4–24-week range)</p>	<p>Systematic review and meta-analysis</p>	<p>Results show inadequate evidence to support beneficial effects of LCKD on antitumor therapy. Not enough studies on the mechanism of the keto diet, need more</p> <p>Need more practical guidance on use in cancer patients such as timing of the intervention, patient age, the severity of the disease, and nutritional status. These factors may affect the efficacy of KD, but many previous studies have not addressed this.</p> <p>Include a bigger population to precisely compare the KD group and the non-KD group: same or similar types of cancers affecting the same</p>	<p>All studies involved human subjects</p> <p>Excluded trials that were non-randomized, had no comparison group, were non-human species, were conference abstracts, book chapters, reviews, or other forms without detailed empirical data and have no exposure or outcome of interest</p> <p>Included extensive coverage of lipid profiles to analyze the range of effect of the ketogenic diet across multiple factions</p>	<p>All the papers were mostly heterogeneous, leading to inaccurate comparison between results and studies</p> <p>All the included papers had different types of cancers and treatment, made it difficult to compare and provide a conclusive result (different cancer pathogenesis and pathophysiology may cause different responses to LCKDs)</p> <p>All had small populations</p> <p>Difficult to compare all the papers in the same sequence because each measured a different type of parameter</p>

				organ, such as the ovaries, uterus, prostate, pancreas, etc., to have a precise comparison group		
Hagihara, K., Kajimoto, K., Osaga, S., Nagai, N., Shimosegawa, E., Nakata, H., Saito, H., Nakano, M., Takeuchi, M., Kanki, H., Kagitani-Shimono, K., & Kijima, T.	<p>Study the effectiveness of a new keto diet regimen in patient with different types of stage IV cancer</p> <p>Determine the effectiveness of the keto diet as a support therapy and establish the degree and duration of carb restriction more clearly in those with cancer</p>	<p>55 gave consent, 37 took the keto diet</p> <p>Patients diagnosed with cancer by histology or cytology and evaluated as stage IV on computed tomography (CT), magnetic resonance imaging (MRI), or surgery by their attending oncologist; performance status <2; and could take foods orally</p> <p>15M 22F Age 54.8 ± 12.6</p>	Case series study	<p>The effects of the ketogenic diet alone differ depending on the type of cancer, but the combined effect of the ketogenic diet with chemotherapy or radiation is promising</p> <p>Demonstrated that the ketogenic diet regimen showed stable adherence and induced functional ketosis with high reproducibility and was well controlled in advanced cancer patients receiving chemotherapy.</p> <p>Seems to have an effect on long-term survival of advanced cancer patients</p>	<p>Evaluated effects of the ketogenic over a longer course of time</p> <p>Addressed concerns regarding dietary restrictions in cancer patients and included so in their study</p>	<p>Lack of homogeneity between cancer types and treatment, leading to inaccurate comparison between results</p> <p>Lack of control group makes it difficult to draw meaningful conclusions after implementation of independent variable (keto diet)</p>
Jansen, N., & Walach, H.	Evaluate whether the levels of TKTL1 are associated with tumor status and progression, and are affected by a ketogenic diet, and whether adherence to a ketogenic diet is associated with a better prognosis in patients with cancer	78 subjects diagnosed with any form of cancer since Jan 2001. Diagnosed with any type of tumor, or had experienced the recurrence of a tumor or metastasizing disease during the 10 years previous to the initiation of the study	Systematic prospective cohort study	<p>Results suggest that it may be beneficial to advise tumor patients to adopt a ketogenic diet, and that those who adhere to it may have positive results from this type of diet</p> <p>Keto diet as a complementary</p>	<p>Present study is the first to describe the effects of a ketogenic diet in patients with cancer in primary care</p> <p>Levels of TKTL1 were measured continuously in the patients</p>	<p>No control condition or control group matched for important predictors</p> <p>Difficult to preclude that the effects observed are not confounded</p>

				<p>treatment to tumor therapy must be further studied in rigorously controlled trials</p> <p>Negative link between ketogenic diet and TKTL1 expression</p> <p>In summary, the present study has demonstrated that a ketogenic diet is feasible and likely beneficial for patients with cancer in primary care, who have been treated for their primary cancer, since it altered the expression of TKTL1, a novel and potentially useful marker to monitor the metabolic state of the body regarding aerobic glycolysis, and to evaluate the potential progression of non-end stage tumor disease</p> <p>Results should serve as guidance to encourage further research</p>		
Sremanakova, J., Sowerbutts, A. M., & Burden, S.	KDs have the potential to influence many physiological processes. It is	102 participants ranged 34 to 87 years old. Brain, rectal, or mixed cancer sites at an early or	Systematic review	KD is potentially feasible and does not cause life-threatening events in patients with cancer. However,	Included randomized and nonrandomized control trials, prospective cohort studies, retrospective	limited information on eligibility of participants, and details of recruitment were only reported in

	<p>therefore important to determine whether KD adversely affects nutritional status in individuals with cancer.</p> <p>Evaluate the current evidence on anthropometry, metabolic changes and systemic inflammation in individuals with cancer who were following a KD</p>	<p>advanced disease stage. Intervention ranges from 2.4-134.7 weeks (0.5-31 months)</p>		<p>adherence is low and possibly linked to a limitation in diet delivery, as well as a lack of monitoring and follow-up</p> <p>sound theoretical bases for KDs suppressing tumor growth. However, strong conclusive evidence in clinical practice is still lacking</p>	<p>cohort studies, observational and case studies</p>	<p>two studies</p> <p>Unspecified inclusion criteria, had a short duration on a KD that would not result in any potential benefits that could be attributed to ketosis, some studies didn't report or measure ketones</p> <p>Studies lacked precision and reliability, had a small sample size, insufficient statistical analysis, limitations in the design, methodology and outcomes reported</p> <p>none of the studies assessed the quality of evidence using risk assessment tools</p>
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<p>Klement, R. J., Brehm, N., & Sweeney, R. A.</p>	<p>Summarize data from clinical studies that have tested KDs along with other treatments used within medical oncology to determine the effectiveness of KD as a complementary treatment</p>	<p>Sample size unknown</p>	<p>Systemic review</p>	<p>Large beneficial effects of KDs on body composition for both overweight patients who benefit by losing body weight and fat mass while maintaining fat-free mass and patients at risk for excessive weight and lean mass loss such as head and neck cancer patients undergoing radio chemotherapy or pancreatic cancer patients KDs as a supportive cancer therapy is growing and suggests several beneficial effects. The largest evidence so far is for beneficial effects on body composition in both overweight and frail patient populations</p>	<p>Analyzed the effects of a ketogenic diet across a range of different cancers</p>	<p>Only two of the studies had an a priori published study protocol</p> <p>The majority of studies included in this review suffered from different sources of bias</p> <p>Small sample sizes</p> <p>Lack of a control group, or lack of randomization giving rise to self-selection, allocation, and performance bias</p>
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<p>Erickson, N., Boscheri, A., Linke, B., & Huebner, J.</p>	<p>Assess clinical evidence of isocaloric keto diet regimes and determine evidence-based recommendations for treating cancer patients with diet regime</p>	<p>330 total patients included, but only 177 followed KD at any duration of the study</p> <p>Only 67-177 adhered to dietary recommendations of study</p>	<p>Systematic review</p>	<p>Evidence of benefits on tumor development and reduction in side effects is missing</p> <p>Need more robust and consistent clinical evidence</p> <p>Need more comparable methodology, dietary protocols, and consistent results</p>	<p>Only involved original, peer-reviewed articles</p> <p>Addressed many concerns regarding KD use and discussed lack of evidence in literature to support</p>	<p>Low adherence to diet by cancer patients</p> <p>Inconsistent and poorly described protocols</p>
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Appendix B

Sample survey questionnaire regarding participant involvement in the ketogenic diet. Includes a rating scale ranging from 1-5 and brief margins to describe personal feelings more in depthly.

- Have you felt any changes in health since starting KD?

1 - I feel no different 2 - I feel worse 3 - I feel better

If you circled 2 or 3 in the previous question, please explain:

- How difficult has it been maintaining KD regularly?

1 - Not Difficult 2- Slightly Difficult 3 - Neutral 4 - Difficult 5 - Very Difficult

Briefly explain why:

- Have you experienced symptoms separate from your cancer treatment since starting KD?

YES NO

If yes, please state them below:

- How confident do you feel about completing the KD diet?

1 - Not Confident 2- Slightly Confident 3 - Neutral 4 - Confident 5 - Very Confident