Review Article :

The Effect of Carbohydrates Intake, Free Sugars, and Ketogenic Diet on Cancer Development; Critical Review of the literature.

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Abstract

In 1920, Otto Warburg established the Warburg Effect which is defined as the unusual fuel generation by the cancer cells through their dependence on glucose metabolism. The aim of the current review is to present the evidence for the association between cancer development and carbohydrate intake and the ketogenic diet usefulness for these patients. Search was conducted in PubMed, Scopes, and Wiley Online Library during 5th November 2021 to 1st December 2021 with searching terms of sugar and cancer, carbohydrates intake and cancer, the ketogenic diet and cancer. RefWorks was used for managing the references. One hundred and seventy studies were found based on inclusion criteria. There are limited metabolic ward randomized clinical trials (RCT) that investigated cancer development with carbohydrates intake, free sugar, or the ketogenic diet. Most studies used food frequency questionnaire (FFQ) as a dietary assessment tool for intake collection however, this method is not intended for this purpose. Results were inconsistent some studies reported carbohydrate intake with adverse effect on endometrial cancer, pancreatic cancer, or overall cancer. On the other hand, some studies reported no effect or a possible protective effect for fibers and low glycemic index carbohydrates. Overall, the relationship is debatable. However, carbohydrate is an important macronutrient for optimum health. In conclusion, there is not enough high-quality evidence to support the hypothesis of carbohydrates and free sugar association with cancer progression additionally the ketogenic diets studies had some limitations. This paper suggests the need for interventional metabolic ward studies with appropriate dietary assessment methods.

Key Words:

Ketogenic diet (KD), Glycemic index (GI), Glycemic Load (GL), Sugars, Warburg Effect, Alkaline phosphatase (ALP)..

Introduction

Cancer is a disease reported in the history. For example, anecdotal reports were documented for skull necrosis and bone lesions for a female skeleton during the period of 3500 to 3000 BC in Tepe Hissar, Iran.[1]

Kaiser (2021, pp.871-874) defines cancer as "a family of diseases unique to multicellular animals that are characterized by the uncontrolled cellular growth and proliferation".[2] In the past decade, there was a rapid development in cancer statistics.[3,4]For example, in 2021 the United States (US) reported 1,898,160 new cases with 608,570 deaths.[3] Nevertheless, cancer mortality plummeted in the US to almost 31% due to many factors such as smoking cessation policies and improved medical care.[3]

In addition, there were public health prevention programs for some cancer types such as the cervical cancer prevention programs through vaccination against Human Papillomavirus (HPV) [5-7] which is a documented as a cause for it.[5,7]For example, in the United Kingdom (UK) they vaccinate females aged 12-13 years against HPV.5 The result of that public health intervention is cervical cancer reduction by 62 % for those who aged 14-16 years and 34 % for females aged 16-18 years in comparison with unvaccinated sample.[5]

Genes are major area of interest within the field of oncology.[8] Given the fact that there are two forms of tumor related genes; the oncogenes which favor tumor formation, and the tumor suppressor genes which are described as anti-oncogene.[8,9] Therefore, genes play an important role in cancer development. Thereby, any possible alternations within them either through environmental factors or genetic susceptibility inherited from the parents could result in cancer development.[10]

Moreover, nutrition and cancer relationship reported in the literature.[11,12] For example, there are some nutrition risk factors documented as carcinogens in which they increase the chance for cancer development, or possibly increase cancer mortality. Notable examples are excessive sodium and exposure to aflatoxins.[13,14,15]Excessive sodium intake in the form of salt is correlated with gastric cancer.[13] In addition, there are food contaminants that are reported as risk factors for specific cancer types.14-15 For instance, aflatoxins reported as a risk factor for hepatic cancer by European Food Safety Authority (EFSA).

The cancer cells metabolism is distinct.[16]In 1920 , Otto Warburg established what is defined as "The Warburg Effect".[17] This phenomenon is described as the unusual fuel generation by the cancer cells; in which they use aerobic glycolysis at higher rate instead of mitochondrial respiration.16-17Howev-

er, glycolysis is not effective in generating adenosine triphosphate (ATP) compared to the mitochondrial respiration.18This concept raised the question for researchers if weather carbohydrates intake could fuel cancer cells.[19-20] Furthermore, considerable reviews in the literature suggested that to kill cancer cells an elimination of glucose may be required.[21] Several attempts made to review the literature on carbohydrates intake and cancer development[19, 22] however, most studies have only focused on carbohydrates intake and the Warburg effect[19], no previous reviews investigated carbohydrates intake, free sugar, and the ketogenic diet relationship with cancer development. Thus, the aim of this review is to examines the literature on carbohydrates intake, the ketogenic diet, and free sugar consumption in cancer development. In addition, to critically appraise the ketogenic diet usefulness studies for cancer patients. This review hypothesizes that there is a protective relationship between some types of carbohydrates such as fibres and cancer incidence.

Methodology

2.1 search strategy

Search was conducted in PubMed, Scopes, and Wiley Online Library during 5th November 2021 to 1st December 2021. The key terms that used were based on a Boolean method with AND, OR and which were sugar and cancer, carbohydrate intake and cancer, ketogenic diet, and cancer.

2.2 Inclusion and exclusion criteria

Table 1 summarizes the inclusion and exclusion criteria. RefWorks, ProQuest LLC was used to manage the resources.

Table 1. The inclusion and exclusion criteria.

Inclusion	Exclusion
Systematic reviews and metanalysis, prospective and retrospective cohort, interventional studies.	Not within the hierarchy of evidence editorial letters, critical and narrative reviews.
Published within the data bases.	Not published.
Human studies.	Animal's studies, in vivo studies, cellular culture studies.
In English language.	Not in English.
Related to the dietary intake.	Not related to the dietary intake.

Results

3.1 Initial overall papers results

Total of 236,462 results were preliminary found, Figure 1. Then, refined by the study design and title. Finally, abstract screening resulted in 238 studies out of them 68 were duplicates; the final results were 170 studies.

3.2 Sugar and cancer

Sugar is a disaccharide that is comprised of glucose and fructose.[23] There is mounting

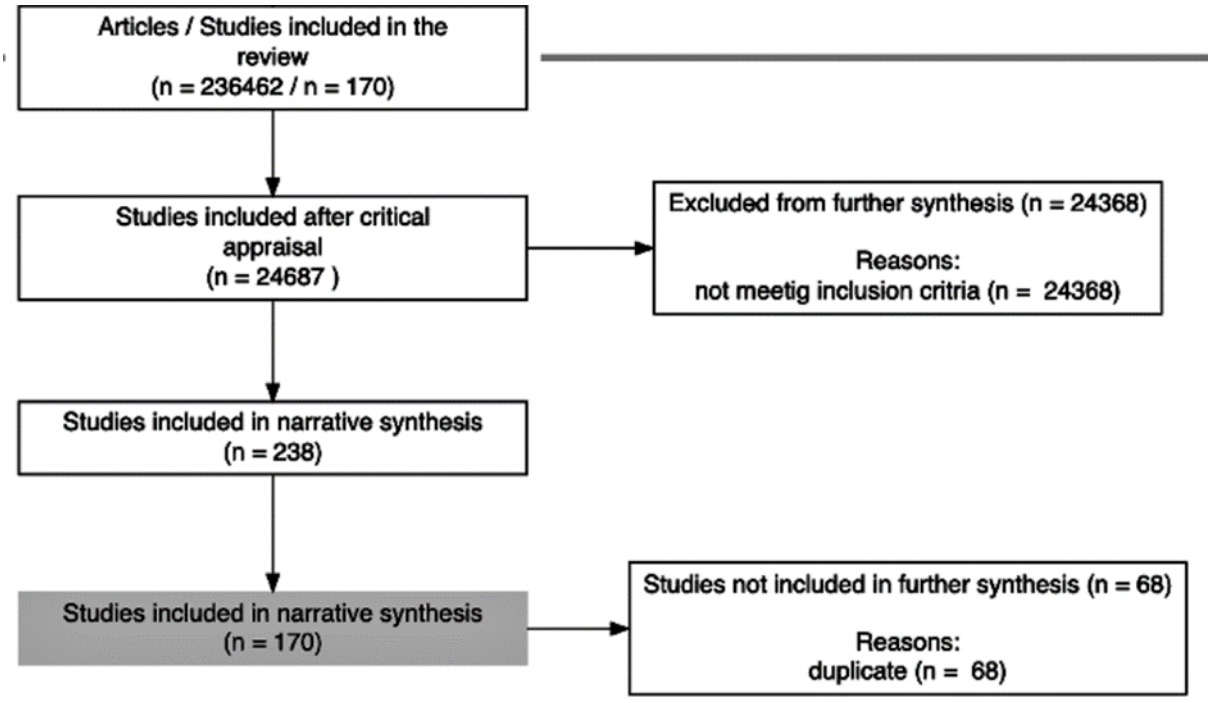


Figure 1 Summary of the literature findings.

evidence postulated that free sugar plays a role in feeding the cancer cells.[20,24,25] There are some studies linked sugar intake with increased chance for specific cancer development risk.[26,27] However, they were not human interventional trails rather they were done on cellular models. For example, Monzavi-Karbassi et al.[26] used MDA-MB-468 cultured breast tumor cells for humans and substituted glucose with fructose. They suggest that fructose in a nutritional micro-environment might pose negative outcomes for the patients. Nevertheless, these data were on cultured isolated tumor cells and the nutritional environment was manipulated by eliminating glucose and substituting it by fructose. However, the human body does not work in isolation rather it is orchestrated.[28]Moreover, Liu et al.[27] found similar findings with a different cancer type which is the pancreatic cancer. They found that fructose promotes tumor growth. Nonetheless, the main limitation of that study was the design. Given the fact these two studies used the same dependent variable which is fructose with different cancer types; the former was with breast cancer cells and the latter was with pancreatic cancer this indicates the urgent needs to investigate fructose's role with cancer cells proliferation in metabolic ward interventional studies. Which leads to Nöthlings et al.[29] findings of high sucrose intake may play a role which was with 162,150 human subjects. Furthermore, Aune et al.[30] conducted a systematic review and meta-

nalysis of prospective human studies cohort to explore prostate cancer risk with different carbohydrates sources including fructose and they found that fructose intake is associated with a positive association with pancreatic cancer development with relative risk (RR) of 1.22 (95% CI: 1.08–1.37, I2 = 0%) in an amount of 25 g of fructose per day. Figure 2 depicts the frost plot adopted from the source.

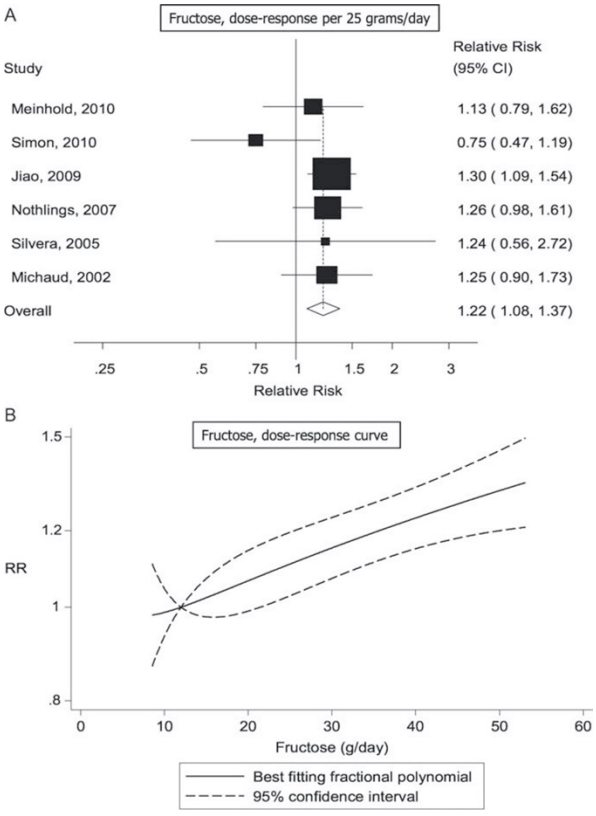


Figure 2: Aune et al., frost blot for fructose intake association with pancreatic cancer. Source: Aune et al., 29

Interestingly, honey which is an extrinsic sugar [31] found to pose a protective effect against cancer development,[32,104] Porcza, Simms & Chopra[32] point out that it has antiproliferative features that may protect against cancer through various mechanisms. Figure 3 summarises them adopted from the source.

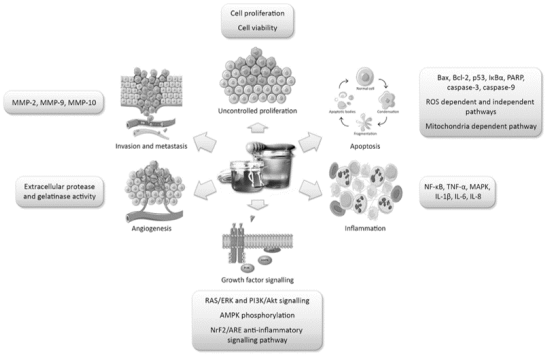


Figure 3: Summary for the potential benefits of honey in carcinogenesis suppression. Adapted from Porcz et al.,[31] with their permission.

They point out that among cellular studies that used honey as a treatment resulted in an inhibition at the cellular phases of S and M. However, honey's beneficial roles are dependent on factors such as climate, nectar source, and bee species. Therefore, the generalization of the findings might be problematic.

Moreover, McCullough et al.[33] conducted a prospective cohort study to examine the association between sugar sweetened beverages (SSB) and lymphoid neoplasm among 100,442 human participants. They used a food frequency questionnaire (FFQ) as a dietary tool to collect the intake. They establish that there is no association of it with non-Hodgkin lymphoma (NHL) development. Table 2 depicts the relevant findings in the literature. The main limitations were the dietary assessment tool which has its own biases.[34] In addition,

the study design was not interventional. Thereby double-blinded clinical control trails with washout period may illustrate a robust conclusion.

Table 2. Summary for the studies investigating sugar intake and cancer

Gender	Sample size	Study type	Findings	Authors	Diet collection methods	Statically analysed (Y\N) Examples of the statical tests
Men	22,720	Prospective cohort with follow up of 9 years	Sugar intake is associated with prostate cancer. Reduced sugar intake recommended.	Miles et al.,[24]	FFQ	Yes (Quartile distribution, COx proportional hazards regression)
N\A	37 prospective cohort studies	Systematic review	Majority of studies showed no association. Possible detrimental association worth study	Makarem et al.,[35]	N\A	N\A
N\A	13 cohort studies, (731441 subjects, followed for 6-20 years)	Pooled analysis of prospective cohort studies	Coffee and sugary drinks were not associated with colon cancer risk	Zhang et al.,[36]	N\A	Yes (Relative risks (RRs) and 95% CIs were estimated using Cox proportional hazards models).
N\A	71 observational articles, 32 case-control, 39 cohort studies	Systematic review and dose-response meta-analysis of observational studies	Sugar consumption increases cancer risk especially for breast, hepatic, colorectal and prostate cancer	Li et al.,[37]	N\A	Yes (Cochran's Q-test and I2)
Men and Women	7056	Prospective cohort study from the PREDIMED trial	Sugar consumption is associated with increased cancer development and mortality	Laguna et al.,[20]	FFQ	Yes (Multivariable-adjusted, time-dependent Cox proportional hazard models).
Men and women	1463	Prospective cohort study	The relationship needs further examination	Zoltick et al.,[38]	FFQ	Yes (hazard ratios (HRs) with 95% CIs.
Men and women	3184	Prospective cohort study (1991-2013)	Excessive sugar consumption is associated with higher risk for prostate and colorectal cancer	Makarem et al.,[39]	FFQ	Yes (Cox proportional for hazard ratios (HR) with 95% CI.
Men and women	435674	Prospective epidemiologic data	Sugar intake is associated with higher risk of oesophageal adenocarcinoma, fructose intake with high risk of intestinal cancer, and overall sugars intake with high risk of pleural cancer. An inverse association seen in ovarian cancer in women. No associations with colorectal cancer.	Tasevska et al.,[40]	FFQ	Yes (Cox proportional for hazard ratios (HR) with 95% CI.
Men and women	35 593	Data from the Melbourne Collaborative Cohort Study	Increased obesity related cancers with high sugar-sweetened soft drinks	Bassett et al.,[52]	FFQ	Yes (Cox proportional for hazard ratios (HR) with 95% CI.
Men and women	1435 (738 cases and 697 control).	Case control	No association between sugar intake and colorectal adenoma	Cho et al.,[42]	FFQ	Yes (t test, Wilcoxon rank-sum test, and $\chi 2$ test).
Women	8863	Prospective cohort study	Excessive consumption of (SSB) increases breast cancer mortality	Farvid et al.,[43]	FFQ	Yes (Cox proportional for hazard ratios (HR) with 95% CI.

Men and women	101279	Prospective cohort study	A positive relationship between sugar intake and cancer risk particularly for breast cancer seen. Sugar could be a modifiable risk factor in cancer prevention measures.	Debras et al.,[44]	Two 24-h dietary records	Yes (Cox proportional hazard models).
Women	10713	Prospective cohort study	Positive association between SSB intake and breast cancer risk among postmenopausal women.	Romanos-Nanclares et al., [45]	FFQ	Yes (Cox proportional hazard models).
Men and women	100442	Prospective cohort study	No association between sugar-sweetened and artificially sweetened carbonated drinks or aspartame with non-Hodgkin lymphoma (NHL)	McCullough et al.,[33]	FFQ	Yes (Cox proportional for hazard ratios (HR) and 95% CI.
Women	23039	prospective cohort study	Excessive SSB consumption is associated with greater risk for type I endometrial cancer. No association with type II endometrial cancer	Lnoue-Choi et al.,[46]	FFQ	Yes (Spearman correlation coefficients, Cox proportional hazards regression for HR and their 95% CI.
Women	822 (424 cases and 398 controls).	Case–control study	Further studies are needed to eradicate sugar relationship with endometrial cancer development	King et al.,[47]	FFQ	Yes (Descriptive analysis, ANCOVA, logistic regression models for OR and 95 % CI).
Women	595 (205 cases and 390 controls).	Case–control study	No association between sugar intake and ovarian cancer.	King et al.,[48]	FFQ	Yes (Multiple logistic regression models for odds ratios and 95% CIs estimations).
N\A	14 prospective cohort studies (853,894 subjects with follow-up) 2,185 incident pancreatic cancer diagnoses	Pooled Analysis of 14 Cohort Studies	Moderate positive association between SSB intake and pancreatic cancer risk	Genkinger et al.,[49]	N\A	Multivariate (MV) study-specific relative risks (RR) and 95% CI.

3.4 Carbohydrates intake and Cancer

There is a large body of evidence investigating the carbohydrates intake relationship with breast cancer in different ethnic groups.[63,86,87] However, the data were confusing because some studies suggested positive effects while others suggested adverse effects. In addition, the design for most studies was observational. For example, Nielsen et al.[87] examined carbohydrates intake and breast cancer risk amongst 23,870 postmenopausal Danish women. The overall carbohydrates intake was examined, glycemic index (GI) and glycemic load (GL) via 192-items FFQ. Furthermore, to evaluate the breast cancer incidence with the estrogen receptors considered. The median carbohydrates intake was 119 g\day. They found a trend of an inverse correlation between (GI) and the positive estrogen receptor (ER+) breast cancer. They found that there is no obvious association between carbohydrates and its corresponding subtypes with breast cancer among postmenopausal Danish women although when they considered the estro-

gen receptors. Silvera et al.[86] found the opposite findings with Canadian subjects. Intake was collected by the FFQ with a follow up period of 16.6 years. They found out that excessive consumption of high GI foods poses a high risk for breast cancer amongst them. Interestingly, Giles et al., [63] point out the insulin role in breast carcinogenesis. The researchers conducted a prospective cohort study with 12,273 post-menopausal women. They found that increased dietary fibers and carbohydrates consumption could be associated with favorable outcomes. In alternative words, fibers consumption could be protective. Nonetheless, they used 121 item FFQ as a tool to collect the intake data. To summaries, most of the evidence used dietary assessment tools to collect the intake and these methods provide a sort of bias in making a solid conclusion.107For instance, there is a chance for under and\or over reporting by individuals.

In terms of colorectal cancer (CRC) and carbohydrate intake, Larssonet al.[76] investigated CRC development among 61,433 Swedish females in a prospective study by FFQ to collect the intake. They found that carbohydrates are not associated with the hypothesis that high carbohydrate consumption, GI or GL poses a risk in CRC development.

In terms of endometrial cancer and carbohydrates intake, Larsson et al.[75] examined endometrial cancer risk among 61,226 Swedish women who completed FFQ. They found that excessive carbohydrates consumption poses higher risk for endometrial cancer among the physically inactive overweight and obese women with RR of 1.68; 95% CI, 0.86–3.29. Furthermore, Cust et al.58 investigated carbohydrates intake in relation to endometrial cancer risk in 288,428 females in multiple European countries with different dietary assessment tools. They found that there is no association between carbohydrates intake, GL, or GI with endometrial cancer risk, however there was a slight increased risk with sugar intake, carbohydrates and overall high glycemic load meals among women who did not use hormonal therapy.

In terms of pancreatic cancer, Patel et al.[89] point out that there is a no association between overall carbohydrates intake GL or GI with pancreatic cancer risk among 124,907 cohort based on FFQ data. To sum up, the literature shows unclear relationship that needs investigation. Table 3 summarizes some of the findings.

3.5 Ketogenic diet and cancer

The ketogenic diet is a major area of interest within the field of nutrition.[95,56,97] Historically, it used as a treatment for epileptic patients during the 1920's.[108] Nonetheless, given the fact the Warburg effect discovery

Table 3. Summary for the studies investigating carbohydrate's intake and cancer risk relationship.

Gender	Sample size	Study type	Findings	Authors	Diet collection methods	Statically analysed (Y\N) Examples of the statical tests that used.
Men and women	Total of 854 (cases of renal cell carcinoma RCC), 1255 healthy (controls)	Case–control	High glycaemic index (GI) food is associated with greater risk of RCC and inverse association with fibers intake and RCC risk	Zhue et al.,[116]	FFQ	Yes (Student t-test, Pearson chi-squared, logistic regression for odds ratios (ORs) and 95% Cis.
Men and women	3184	Prospective cohort study	Carbohydrate intake is associated with 41 % breast cancer risk reduction. A total intake of low GI food associated with cancer risk reduction in breast, prostate, and colorectal cancers.	Makarem et al.,[82]	FFQ	Yes (Descriptive analysis, Cox proportional hazards for hazard ratios (HR) and 95 % CI).
Men and women	26 Publications with 540,000 subjects	Meta-analysis	No association between carbohydrates intake, GI and GL in gastric cancer development	Ye et al.,[112]	N\A	Yes (Chi-square and I2 test, OR, RR, Meta-regression analyses, Funnel plots, Begg's and Egger's tests).
Women	1015 subjects (406 cases, 609 controls).	Case–control	High GI carbohydrates are associated with increased risk for ovarian cancer while fibres intake is protective among African American women	Qin et al.,[92]	FFQ	Yes (Multivariable logistic regression for OR, CI of 95 %).
Women	19 publications	Systematic review and dose response meta-analysis	Carbohydrate intake, GI and GL relationship between breast cancer risk could be explained by the menopausal and hormonal status	Schlesinger et al.,[119]	N\A	Yes (Natural logarithm of the RRs and 95%CI, person-years or non-cases, quantiles, I2 statistics
N\A	15 publications	Systematic review and meta-analysis	Fibres are protective against endometrial cancer (negative relationship) in the 12 case-control studies. Nevertheless, cohort studies found positive relationship.	Chen et al.,[55]	N\A	Yes (logarithm RR/OR, Q test, I2, DerSimonian Laird random effects for OR, RRs, and 95% CI).
Women	13 publications with 5,777 ovarian cancer cases and 142,189 overall subjects	Meta-analysis	Inverse association between dietary fibres and ovarian cancer risk.	Zhang et al.,[36]	N\A	Yes (DerSimonian and Laird random-effects, Forest plots, I2, Egger's regression test and funnel plot).
N\A	13 publications	Meta-analysis	Protective effect of carbohydrates consumption against oesophageal cancer with some differences among various ethnicities.	Xuan et al.,[111]	N\A	Yes (Random-effects model, OR, RR with 95 % CI, I2, Egger's test and Begg's funnel plots).
N\A	21 publications for observational studies	Meta-analysis	No association between carbohydrates consumption and prostate cancer (PC) risk.	Fan et al.,[71]	N\A	Yes (hazard ratio (HR), funnel plot, Egger's test, relative ratio (RR), CI with 95%, Forest plots, Cochrane Q statistic (significance level of $p < 0.10$) I2, DerSimonian and Laird inverse-variance-weighted random-effects models).
N\A	16 publications with total of 6,563 endometrial cancer cases	Meta-analysis	Fibres are protective against endometrial cancer	Li et al.,[37]	N\A	Yes (Random-effects models of RR, Newcastle-Ottawa Scale (NOS) score).
N\A	18 publications 13 case-control, 5 cohort studies)	Meta-analysis	No association between carbohydrates intake and prostate cancer risk	Zhai Cheng & Zhang,[114]	N\A	Yes (RR with 95 %CI with random effects model)
Men	30482	prospective cohort study	This study found that there is no association between carbohydrates intake, GI and GL with prostate cancer (PC) development. Further elucidation needed	Shikany et al.,[98]	FFQ	Yes (Descriptive analysis, COx proportional hazards).

Gender	Sample size	Study type	Findings	Authors	Diet collection methods	Statically analysed (Y\N) Examples of the statical tests that used.
Women	61433	Prospective cohort study	Limited information on Helicobacter pylori. The finding suggests there is no positive association between GI, GL, and carbohydrates consumption on gastric cancer development.	Larsson Giovannucci & Wolk,[76]	FFQ	Yes (Cox proportional hazards model, HR with 95% CI, 2-sided P-value).
Women	61226	Prospective cohort study	Excessive carbohydrates consumption, high GL and GI is associated with increased risk of endometrial cancer among physical inactive overweight females.	Larsson Friberg & Wolk,[75]	FFQ	Yes (Cox proportional hazards models, RR and 95% CI, median value for trends assessment).
Women	526 (263 Cases, 263 Control)	Case–control	There is a significant relationship between GI,GL with breast cancer risk among postmenopausal women	Shin, Kim and Sung,[99]	FFQ	Yes (Odds Ratio, 95% CI)
Men	430 (274 cases, 156 control).	Case-control	High carbohydrates intake might be associated with overall prostate cancer risk reduction in addition to high grade PC	Vidal et al.,[105]	FFQ	Yes (Tertiles for the dietary component, continuous variables done by Wilcoxon rank sum test, in terms of categorical variables X2 test was used, OR, CI 95 %, logistic regression and the contrast statement).
N\A	17 Publication	meta-analysis	The meta-analysis showed that carbohydrate intake may lead to high colorectal cancer risk among men.	Huang et al.,[66]	N\A	Yes (random-effect model, RR with 95% CI, Egger's regression, funnel plot).
N\A	44 Publications	Meta-analysis	High GI carbohydrates are associated with moderate risk for gastrointestinal cancer	Li et al.,[37]	N\A	Yes (meta-regression coefficient, Pooled RR or OR with CI 95%, Q test, I2,Mantel–Haenszel, DerSimonian & Laird, forest plots, funnel plots, Begg's test, Egger test, Greenland & Longnecker).
Men and Women	1151	Prospective cohort study	Fructose intake poses high risk for pancreatic cancer. Further research recommended. No association between pancreatic cancer risk and carbohydrates intake, GI or GL	Jiao et al.,[67]	FFQ	Yes (Pearson correlation coefficients (r), Cox proportional hazards regression models, RR with CI 95 %).

led the researchers to investigate the ketogenic diet effect on cancer. Schmidt et al.[95] conducted a pilot study in the light of the Warburg effect among cancer patients who followed the ketogenic diet for 3 months. The carbohydrate dose was 70 g\day with urinary ketosis as an objective tool for adherence measurements. The sample was 16 cancer patients however, this diet is notoriously difficult to follow therefore, not all the subjects completed assigned period. The study had considerable patients who dropped out. The research had only 5 patients who stuck to the assigned 3 months. The researchers found that the ketogenic diet improves the quality of life for cancer patients and could be suitable for them. However, most subjects could not follow the diet either for tolerability or personal reasons while others felt unable to stick to it, thus recommending this dietary pattern is still questionable because of the small sample size.

In a systematic review by Römer, Dörfler

& Huebner [93] the researchers found that cancer patients lost weight after following this diet with mild to moderate side effects. The researchers conclude that the effectiveness of the ketogenic diet for these patients is still unclear due to the limited high-quality evidence. In the same vein, another systematic review found similar results.[117] It is important to point out that cancer patients are at higher risk for malnutrition in the form of cancer cachexia.[106] Therefore, achieving their energy, macronutrients, and micronutrients requirements is a paramount important.[50]

What is interesting is some studies investigated the ketogenic diet effectiveness in brain tumors and glioma.[56,94,97,109,110] Moreover, it is a burgeoning area of research in the literature based on animals or cellular experiments.[97,80] Perez et al.[91] investigated the effect of the ketogenic diet in diffuse intrinsic pontine glioma (DIPG) among pediatrics. The researchers conclude that this diet could be suitable for them in a period of 3 months. However, the study design was retrospective analysis not interventional. In addition, poor free living subjects' adherence is documented in the literature.[73,62]

In terms of the breast cancer and the ketogenic diet, Khodabakhshi et al.[68] conducted an interventional study with 40 patients in each group to investigate the ketogenic diet effects for breast cancer patients. Interestingly, the ketogenic diet arm had almost 10 subjects who dropped out from the trail. Therefore, the study was based on 30 subjects. Among the intervention group, a decreased energy intake was observed with a value of 498 however, a similar finding with value of 189 kcal difference in the intake was observed in the control group. Furthermore, prior to the trail the carbohydrates intake was 235±52 g for the intervention group, while it reduced to 22±11 g post trail. In terms of the control, it was 238±54 g which reduced to 208±60 g post intervention. The researchers found that the ketogenic diet does not pose any benefits in terms of the quality of life (QoL) and physical exertion to these patients. However, it reduces the lactate levels and alkaline phosphatase (ALP). Table 4 summaries the resulted studies.

Discussion

The effect of carbohydrate intake, free sugar, and the ketogenic diet on cancer development was explored. Based on the presented data, there is not enough high-quality evidence in the literature to document a direct relationship between carbohydrate intake and the risk of cancer development. In contracts to Branco et al.[53] review which found that low carbohydrates diet may be suitable for some diseases such as can-

Table 4. Summaries the studies investigating the ketogenic diet and cancer

Gender	Sample size	Study type	Findings	Authors	Diet collection methods	Statically analysed (Y\N) Examples of the statical tests that used.
N\A	46 publications	Systematic review	There is no good scientific evidence for the ketogenic diet application for cancer patients	Römer et al.,[93]	N\A	N\A
Women	80 of cancer patients	RCT (open-label clinical trial)	No difference between the ketogenic diet group and the control the only difference was decreased ALP levels among the KD group.	Khodabakhshi et al.,[68]	24-h dietary recall for 3 days (one weekend day and two weekdays)	Yes (Kolmogorov-Smirnov test, either Student t-test or Mann–Whitney U test, Paired sample t-test or Wilcoxon for variable comparison between groups, ANCOVA and Pearson correlation analyses).
Women	45 subjects which were randomized to (American Cancer Society diet (ACS): n 1⁄4= 20; Keto genic diet (KD): n 1⁄4 =25).	RCT (parallel-arm design)	Ketogenic diet (KD) might be safe for certain types of cancer. The study was on ovarian and endometrial cancer patients	Cohen et al.[57]	4 days dietary records.	Yes (t-tests and correlation analyses)
Men and women	Total of 19 pancreato-biliary cancer patients who underwent pancreatectomy, General diet (GD) = 9 KD=10	Prospective controlled intervention	KD could be used as anti-cancer therapy.	Ok et al.,[88]	daily diet record	Yes (Shapiro–Wilk test,2 ways ANOVA, student t-test or Fisher's exact test and 1 way ANOVA and Tukey–Kramer test)
Still under progress.	50 patients	RCT	The DREAM study is going to test the effect of ketogenic diet and exercise and caloric restriction for chemotherapy patients.	King et al.,[47]		Yes (one-way analysis of covariance, generalized linear mixed models, Kaplan-Meie, Cox proportional hazard models).

cers.[53] The current paper suggests that the relationship between these two variables is equivocal because of the limited high-quality research. Given the fact that carbohydrates are staples for many cultures across the world. For example, in 1998 Okinawa nation who is known to have high longevity consume carbohydrates in the form of vegetables and fruits.[84] In addition, the Eat Well guide in the UK[90], and My Plate guidelines in the US [72] do not suggest excluding carbohydrates in the form of fruits, vegetables, and whole grain cereals for the general population. Furthermore, the recommendation by the European Society for Clinical Nutrition and Metabolism (ESPEN) for cancer patients is to provide energy and macronutrients requirements.[50] It is worth to discuss that term sugars have diverse types; there are intrinsic sugars which are naturally present in food while the extrinsic sugar that is added to the food.[23] Notable examples for extrinsic sugars are honey, syrups, and table sugars.[23]In the UK, in 1989 the department of health committee used the term of non-milk extrinsic sugars (NMES) which refers to them. Now, the term "free sugars "is used

to describe the added sugar.100 Most of the free sugar and cancer studies (Table 2) did not mention if the sugar was free sugar or intrinsic sugars.

In addition, they were completely based on the food composition tables analysis which do not differentiate between intrinsic or extrinsic sugars [69] and that is a major limitation for understanding the relationship. The intrinsic sugar is present in fruits, vegetables, and pulses, and these are pivotal for optimum health. Other biomarkers such as urinary sugar excretion marker could provide an objective view rather than the food composition tables.[103,113]

In terms of carbohydrates intake and cancer, there is a documented role of carbohydrate consumption on the appetite and fullness which if not achieved weight gain may occur. In addition, obesity is a risk factor for considerable types of cancer.[51] Carbohydrate consumption aids in fullness sensation and thus energy intake reduction. For example, carbohydrates in terms of fibers play a role in satiety through mechanoreceptors in the stomach.[54]In addition, glucagonlike peptide-1 (GLP-1) is a satiety hormone which is stimulated by carbohydrate intake.[77,81] Moreover, low carbohydrate diets definition is still not exist, hence there is no scientific consensuses about the accurate carbohydrate percentage in these diets rather it is varied across different studies.100 Feinman et al.[61] suggested that high carbohydrates diets could be defined as more than 45 % of energy requirement, while moderate carbohydrates intake are 26 – 45 % of the total energy, and low carbohydrates diets are those who provide less than 130 g \ day or 26 % of the total energy intake while very low carbohydrates are those that provide 20-50 g\ day or less than 10 % of total energy intake. Moreover, carbohydrates in terms of oligosaccharides are a well-known source for prebiotics that play a role in feeding the probiotics in the gut.[101] In addition, prebiotics produce short chain fatty acids (SCFA) such as butyrate, acetate, and propionate.[118] Moreover, the literature shows that butyrate has a protective role against colon cancer; it reduces the activity of enzymes such as glucuronidases and 7-alpha-hydroxylases which are co-carcinogenic enzymes.[118] Thus, gut microbiota (GM) has considerable benefits; additionally, diet is a recognizable environmental factor for their survival, through prebiotics which are obtained from fibers intake.[65]

In terms of the ketogenic diet or low carbohydrates diet, the current paper findings suggests that the evidence is still unclear and that is similar to Elisia & Krystal [60] paper which suggested that our knowledge is still in its infancy hence there is not enough evidence for its safety and efficacy. Fur-

thermore, as previously presented; there are some patients who lost weight while following this diet therefore, it might pose the risk for malnutrition. In which limiting carbohydrates options implies in limited intake because of limited choices. In addition, ketogenic diets are high in fat and high fat diets have been shown in the literature to cause chronic low-grade inflammation.[59,64,96]

In terms of the dietary assessment tool that is used by the previously presented studies. Most of the studies used FFQ as a nutritional tool to collect the absolute intake data (Table2&3&4) while some studies [44] used 24-hour recall. The former is not intended for this purpose; it is a tool to assess the frequencies of consumption for certain food items.[74,62] For example, how frequently this population consumes fruits and vegetables.[74] In addition, it depends on the memory.[74,62] Nonetheless, Crichton et al.[34] point out long-term subject adherence as a challenge in using the dietary assessment tools in research. Thereby, the metabolic ward studies could be a suitable option with minimum bias. If that was not possible, using other accurate dietary tools is suggested; these tools are the weighted dietary diary or estimated dietary diary for period of 7 days or for 4 days. [62,74]

To our knowledge, this is the first critical review to investigate the effect of sugar, carbohydrates, and ketogenic intake with cancer risk. The primary limitation of the current paper is the heterogeneity of the studies.

Conclusion

In conclusion, this paper discussed the carbohydrate intake and cancer risk and argued that there is not enough high-quality evidence in the literature to support the association. In terms of free sugar and cancer development most studies used food composition tables through FFQ tool which may not show the full unbiased picture. Secondly, the overall carbohydrate intake and cancer development is unclear in the literature hence carbohydrates are source for fibers and prebiotics which are needed for an optimal health. Finally, our knowledge for the ketogenic diet and improved cancer outcomes is scant because this diet is notoriously difficult to adhere. In addition, high fat intake is associated with inflammation, and there is large evidence in the literature that linked high fat intake with increases inflammation and that is a known risk for cancer. Overall, carbohydrates are important to achieve healthy gut microbiota, body weight, and satiety. This paper suggests the need for interventional studies with an appropriate dietary assessment tool.

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Author contribution:

JSMA was conceived and designed the study, conducted the research, and provided the materials, collected, and organized the data. LMAG analyzed and interpreted the data. JSMA wrote the initial and final draft for the manuscript. All authors have critically reviewed and approved the final draft.

Key Points

- Free sugar and cancer studies were based on FFQ and food composition data which could be biased in estimating the accurate intake.
- Fiber intake is associated with protective health outcomes.
- Ketogenetic diet studies were based on small sample size with some subjects lost weight. Therefore, it is safety for such patient is still unclear.
- Metabolic ward interventional studies could provide a robust view for the relationship.

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