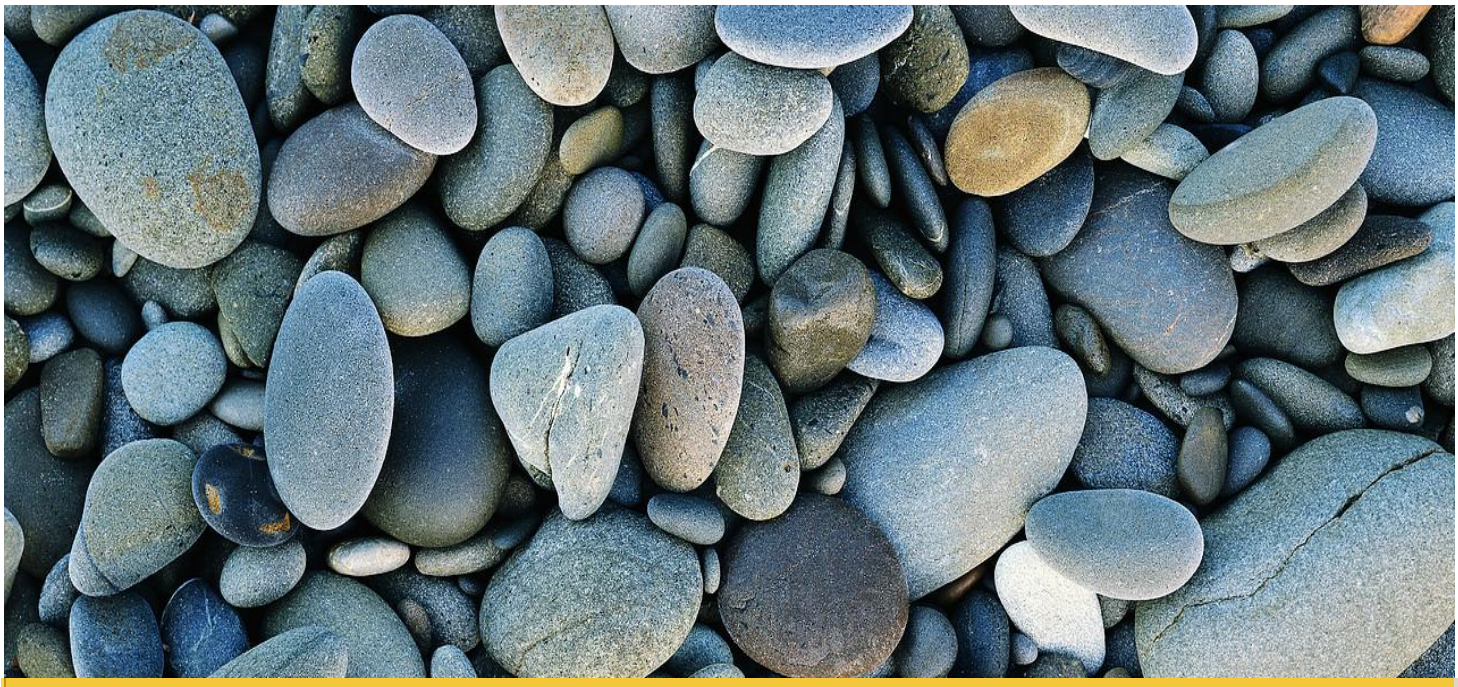

Knowledge Translation of Low Carbohydrate Diet Intervention in Cancer Survivorship: From Basic Science to Clinical Practice and Policy Making

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1. Introduction:

Cancer affects millions of people globally. Although there may be regional variation in the prevalence of various types of cancer, overall incidence and mortality rates are increasing worldwide [1]. The exponentially growing and aging population of the planet will pose a major global health burden unless drastic preventive measures are taken to reduce cancer-related infections, environmental exposures and to change eating patterns.

In Canada, approximately 180,000 new cases and 75,000 deaths from cancer are reported annually, and despite increasing incidence, there is a steadily decreasing trend in mortality, which suggests better survival for cancer patients (Canadian Cancer Society, Statistics Canada. www.cancer.ca) [2]. Survival rates are usually presented to indicate the percent of cancer patients who are alive after 5 years post diagnosis or treatment, and to estimate prognosis (National Cancer Institute. http://www.cancer.gov) [3]. The rates fluctuate depending on cancer type, sex, age, populations and cultural and environmental factors (Canadian Cancer Society, Statistics Canada. www.cancer.ca) [2]. For example, geographical location is an important factor among social determinants of health in influencing the survival rate. Differences in availability and types of health services, such as screening, detection methods and therapies exist in urban vs remote locations. In addition, individual preferences and/or behaviors within disadvantaged/vulnerable populations that remain unaddressed by the system are reflected in survival rate differences.

Currently, 65% of adults and 80% of children who have cancer are expected to live at least 5 years after treatment in Canada [4]. Due to advancements in early detection and therapies, the total number of survivors is increasing in North America, reaching close to 1 million in Canada and 11.7 million in the United States (National Cancer Institute and Canadian Cancer Society, Statistics Canada. www.cancer.ca) [2, 3]. This reflects successful progress in cancer control in these countries.

While reduction in mortality suggests success in medical advancement, newly emerging issues such as the increasing number of cancer survivors and their quality of life require attention. The terms "survival rate" and "survivorship" are defined and used differently. In comparison to survival rate, which is used in a clinical/epidemiological context, survivorship implies "living beyond 5-year survival" and encompasses multiple stages of physiological and emotional changes that patients, families and care givers experience from the time of diagnosis till death (National Cancer Coalition for Cancer Survivorship). Traditionally, cancer research has focused heavily on the development of therapeutics or cures; however, with evolving cancer demographics, especially in developed nations, there is a need to shift today's cancer care to be more long term and focused on patients and families (Cancer Journey of Action Group: http://www.partnershipagainstcancer.ca) [5].

As stated in the 2005 report published by the Institute of Medicine, there is a substantial number of survivors today who feel "lost in transition" after cancer treatments or cannot make the proper transition from post treatment to long term care or health management because of the lack of resources and appropriate health services [6]. In order to sustain an effective healthcare system, the unmet needs of patients/families and the issues of poor accessibility and equity must be addressed. Improvements can be made through more extensive distribution and increased availability of information, health management services and psychosocial supportive care.

With the focus of current cancer research predominantly targeting therapeutic aspects of the illness, undesirable side effects or long term health effects associated with therapies are often overlooked. The duration, dosage and toxicity of a therapeutic agent that cancer patients are exposed to are as important as the therapeutic effects, because a new treatment that cannot be tolerated by patients is discontinued and the intervention is classified as a failure. Similarly, even if a specific therapy has an immediate benefit in treating cancer, it may produce long term-adverse health effects or may lead to the development of secondary cancers, creating a larger burden on our health care system.

Therefore, it is crucial for researchers and healthcare professionals to take into account the long term effects of current therapies and to integrate the full spectrum of the cancer journey, including palliation to minimize physical and psychological suffering and improve the overall health of patients and their families [4].

Palliation is often regarded as healthcare provided only at the end of life or for incurable diseases. The World Health Organization (WHO) defines it as the services provided to patients and their families to improve their quality of life through prevention and relief of physical, psychosocial and spiritual suffering [7]. The WHO emphasizes the significance of palliation and its need for integration into routine oncology care, regardless of prognosis (ie, curable vs incurable). In order to create a sustainable healthcare system in this era of rapidly evolving cancer demographics efforts should be invested in survivorship and palliation research and care. To this end, the exchange of research evidence, experience and knowledge is fundamental in identifying critical issues in cancer care [8]. In addition, appropriate application of innovation and systematic analysis of its effectiveness are important in establishing evidence-based clinical practice and health policy [8, 9]. Currently, there are several models and tools of knowledge translation (KT) aimed at facilitating the acceleration of this process.

i. Knowledge Translation Models

Traditionally, health research was thought to progress in a linear fashion - research was conducted, knowledge was gained and evidence was distributed to other researchers within the same field. Disciplines operated in silos, investing effort to acquire knowledge and gain expertise within their distinctive fields. This conceptualization lacks the recognition of the complex set of relationships between knowledge makers and users. As cancer demographics continue to evolve, there is a great need to strengthen interdisciplinary collaboration between academic research and service partners/organizations. Not doing so potentially fails to address real world problems, creating a large gap between bench (basic science) and bedside (clinical practice). To create an efficient and effective

health care system, a more integrative approach that promotes trans-disciplinary knowledge exchange, mutual learning and collaborative problem-solving relationships between researchers, clinical practitioners and decision makers is required.

The significance of KT in current health research is recognized as a national priority by policy makers in many countries, including Canada, USA, UK, Australia and the Netherlands. There are a number of models which integrate KT into action plans, including the Ottawa Model for Research Use (OMRU), the Knowledge-to-Action-Process (KTA) Model and the Knowledge Exchange-Decision Support Model (KE-DS) [8, 10]. While all these frameworks are structured to encourage interactive relationships/capacity building between different disciplines, there are subtle differences among these models. The main focus of the OMRU model is the implementation of existing evidence-based knowledge into practice and dynamic interactions between researchers and knowledge users [11, 12]. In comparison, the KTA model emphasizes the production and adoption of knowledge using evidence-based and practice/experience-based knowledge [8, 10]. The KE-DS model expands the approach further by conceptualizing the KT process in a holistic way, including not only epidemiological evidence, but also cultural, ethical and socioeconomic perspectives, and emphasizing the impact at the population level [8]. The KE-DS Model assesses the clinical and socioeconomic values of the knowledge-'product' and effectiveness of the implementation process by carefully examining each stage of knowledge mobilization, from synthesis of scientific evidence to clinical practice, and application at the population level [8]. The comprehensive approach of the KE-DS model is, therefore, ideal for the uptake of knowledge in a multidisciplinary setting where the values, beliefs and actions of individuals will impact the success of an intervention.

This review will extrapolate the therapeutic dietary intervention traditionally used for glioma patients and investigate its applicability to breast cancer patients and survivors. Guided by the KE-DS

Model, its efficacy, effectiveness and value will be assessed by incorporating epidemiological, economic and socio-cultural perspectives [8].

ii. Epidemiology

Body weight issues are a major health concern in North America since they are linked to decreased self-reported quality of life and increased morbidity and mortality from chronic diseases like diabetes, cardiovascular diseases and cancer [13-15]. In the US, the number of obese or overweight individuals has steadily risen in the last couple of decades, reaching almost two-thirds of the whole population today [16]. Next to tobacco smoking, obesity is the second most preventable cause of death from cancer in the US [16].

Currently, breast cancer (BrCA) is the most common cancer after non-melanoma skin malignancies among North American women [17, 18]. It is reported that the majority of BrCA survivors have excess weight or weight problems [19, 20]. Epidemiology studies show that women with Body Mass Index, BMI, >25 (overweight and obese) have twice the risk of recurrence [18, 21, 22] and 1.5 times the risk of death of those with a normal BMI (18.5-24.9)[17, 18, 23, 24]. This translates into an alarming number of BrCA survivors at risk of recurrence, and this poses a significant populational health issue [13, 17, 18, 23-26]. Given this positive association, it is concerning that weight gain is commonly observed among female patients after diagnosis [27, 28].

Despite the well established link to cancer risk, very little attention is placed on weight control as part of cancer care/management for BrCA survivors. One reason for the lack of effort in this area is that a woman's weight is perceived as a sensitive cultural issue and one that many physicians are reluctant to address [26]. Also, lifestyle modification is challenging as it requires a lot of time, effort and commitment from patients and their families/supporters. Effective implementation strategies or care models that take into consideration the social and economic contexts of the population are needed to support this approach.

2. Basic Science: Low Carbohydrate Diets and Cancer

i. History of carbohydrates and cancer

The link between carbohydrates (CHOs) and cancer was first established in the early 1920s when little or no glucose (CHO) was detected in the urine samples of diabetic patients with cancer, compared to diabetic patients without cancer [29, 30]. When Braunstein incubated malignant and benign tissues in culture media containing glucose, he noticed a higher glucose consumption in cancer cells than normal liver and muscle cells [29]. Further, Warburg *et al.* in 1924 observed that the high amount of glucose used by cancer cells was converted to lactate even in the presence of oxygen (this process is called "aerobic glycolysis" or the "Warburg effect") [30, 31]. This effect is relatively unique to malignant cells since most normal cells decrease glucose uptake and lactate production in the presence of oxygen [30]. High consumption and metabolism of glucose by cancer cells leads to lactate secretion into the microenvironment of the tumour and this plays an important role in the invasion of malignant cells into surrounding tissues [32, 33]. Since the early 1920s when a high reliance of tumours on CHO was first reported, there has been a significant amount of research conducted and evidence generated to support this claim. Today, the Warburg effect is known as a hallmark of cancer [34].

ii. Mechanism: *In vitro* data

Every cell in our body requires energy in the form of ATP, and cells can switch from an efficient oxidative metabolic process called oxidative phosphorylation (OXPHOS) (which generates 34 ATPs/ glucose molecule) to a far less efficient process called glycolysis (which generates only 2 ATPs/glucose), when the availability of oxygen is markedly reduced [31, 35, 36]. Thus, the total energy production per glucose is far less with glycolysis than OXPHOS; yet most tumour cells prefer glycolysis [36, 37]. One of the hypotheses for this preference is that because glycolysis does not metabolize glucose completely to carbon dioxide as in OXPHOS, cancer cells can use the carbon-chain intermediates as building blocks for

nucleic acid, fatty acid and protein synthesis, all needed for rapid proliferation [35, 36]. Pfeiffer *et al.* argue that tumor cells can generate ATP at a much faster rate through glycolysis than oxidative phosphorylation, compensating for inefficiency and meeting the higher demand for energy [38]. Moreover, glycolysis leads to accumulation of lactic acid, which decreases the pH from 7.4 to 6.0 in the extracellular compartment [36]. Normally, acidification is toxic and leads to *p53*-mediated apoptosis (cell death) in normal tissues [39, 40]; however, *p53* is inactivated in approximately 50% of human cancers, which allows for survival under acidic (toxic) conditions [41]. Furthermore, this acidic environment creates a favorable condition for cancer cells to invade since lactic acid has been shown to promote metastasis by inhibiting immune response to tumour antigens and by inducing angiogenesis (formation of new blood vessels) and extracellular matrix degradation via activation of proteases [32, 33, 42-45].

To compensate for the inefficient energy production of glycolysis, cancer cells require a higher level of glucose than normal cells [36, 37]. This excess demand of cancer cells is met by increasing expression of glucose transporters, GLUTs, which are located on the cell membrane and facilitate cellular glucose uptake [37, 46-48]. The functional involvement of these proteins in human malignancies is evident since they are overexpressed in many cancers such as brain, breast, lung, pancreatic, renal, gastric, and esophageal cancers [37, 46-48]. Similarly, increased expression or activation of oncogenes such as *Ras, Myc, PI3K* and *Akt* results in induction of hypoxia inducible factor-1α (HIF1α), which is a major transcription factor that regulates energy metabolism [49-51]. Loss of the tumour suppressor genes, *PTEN* and *p53,* is also known to up-regulate HIF1α levels even when normal levels of oxygen are present within a tumour [52-54].

Stabilization and/or increased expression of HIF1α leads to inhibition of enzymes involved in OXPHOS and activation of enzymes involved in glycolysis, leading to increased glucose uptake and glycolysis in cancer cells [55]. For example, it has been demonstrated that rapidly proliferating cells have

a higher expression level of PFK2, a phospho-fructokinase, which activates a critical glycolysis driver, PFK1, that converts Fructose-6-Phosphate into the Fructose-1,6-biphosphate (Figure 1) [37, 56]. Also, cancer cells often express pyruvate kinase isoform 2, PKM2, rather than PKM1, and this leads to increased glycolysis, which, in turn, increases the tumour forming capacity of these cells (Figure 1)[37, 57].

Because cancer cell survival and growth depends on the availability of glucose, targeting pathways involved in glucose metabolism holds promising potential in cancer therapy. To this end, drugs have been developed to inhibit enzymatic activities involved in glycolysis. For example, small interfering RNA (si RNA) targeting PKM2 (Fig 1) have been shown to induce cell death *in vitro* and inhibit tumour growth *in vivo* (in mice) [58]. Similarly, 3-bromopyruvate (3-Br-PR) limits glycolysis by inhibiting hexokinase (HK. Fig 1)[59, 60]. ^{18}F-labeled 2-deoxyglucose (2DG) is a glucose analogue which has been used as a diagnostic tool for PET imaging [61]. This analogue competes with glucose and is phosphorylated by HK upon uptake. It then accumulates within the cell and inhibits normal glucose uptake, reducing energy production and lactate accumulation [60]. Although these molecules showed very promising anti-tumour effects in preclinical studies [61-63], clinical application has not been feasible due to stability or toxicity issues since dosages required for clinical efficacy are too toxic to humans [59, 60]. Another glycolysis inhibitor, dichloroacetate (DCA) is a pyruvate analogue that promotes cancer cells to switch from glycolysis to OXPHOS, but clinical trial results are not yet available and there are toxicity concerns with this chemical as well [64].

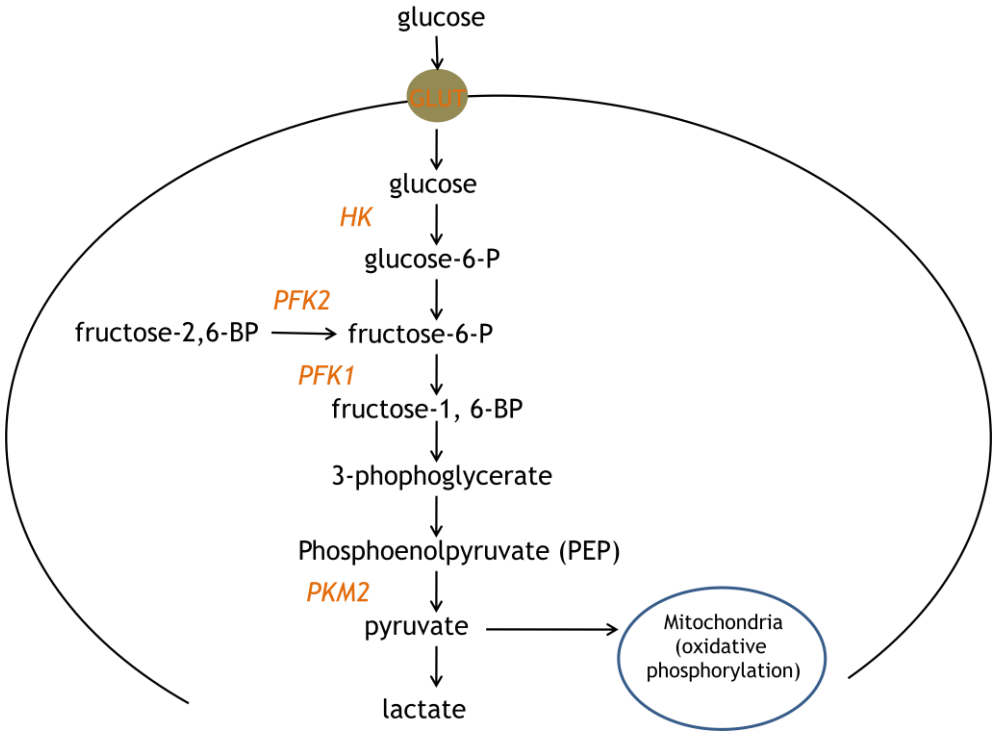

Figure 1. Glucose metabolism: during glycolysis, glucose is taken up by glucose transporters (GLUTs), and metabolized to pyruvate (generating 2 ATPs/glucose) and then to lactic acid, which is secreted . In the presence of oxygen, pyruvate is further broken down to carbon dioxide and water through oxidative phosphorylation (OXPHOS) within mitochondria, producing 34 additional ATPs [36]. In the absence of oxygen or when cells are transformed into cancer cells, the cells stall at glycolysis. The resulting high levels of extracellular lactic acid both suppress the ability of the immune system to kill the cancer cells and promote their metastasis [36, 37]. Italic: kinases involved in glycolysis. (Diagram modified from Hamanaka and Chandel *J Exp Med* 2012;209:211-215)

iii. *In vivo* data

The first classic animal study using a CHO-restricted diet was conducted in 1913 [30]. While rats in the control group were fed bread only or casein, lard and lactose, those in the treatment group were placed on a CHO-free diet with casein and lard weeks before implantation of Buffalo sarcoma cells [65]. The results showed reduced tumour growth and mortality in the treatment group compared to the control [65]. The beneficial effect of a CHO-restricted diet shown in this study was indicative of a significant role that diet plays in cancer control. As shown in Table 1, there have been numerous studies conducted to investigate the effects of various dietary interventions using animal models [30]. Although macromolecule compositions vary among the studies, ketogenic or low CHO diets (eight out of ten

studies) showed positive outcomes such as decreased mortality, slower tumour growth, longer survival and inhibition of metastasis in melanoma, colon, glioma, prostate and mammary cancers. Recently, Ho *et al.* showed synergistic effects of low CHO diets with anti-cancer drugs in further slowing tumour growth and extending life expectancy of mice [36]. This combinatorial effect of anti-cancer drugs with low CHO diets may allow lower doses of drugs to be used in future and thus may reduce the toxicity of chemotherapeutic agents.

Authors	Year	Cancer	Mouse strain	Dietary composition (CHO/Protein/Fat)	Duration (days)	Results
Magee *et al.* [66]	1979	Melanoma	C57BL/6	0/0/100	14	Decreased lung metastases
Santisteban *et al.* [67]	1985	Mammary tumour	BALB/c	30/60/5	70	Decreased mortality
Tisdale *et al*. [68]	1987	Colon cancer	NMR1	80% of energy from fat	20	Reduced tumour
Zhou *et al.* [69]	2007	Mouse astrocytoma	C57BL/6	3/17/80	>8	No difference in tumour weight
Venkateswaran *et al.* [70]	2007	Prostate cancer	Swiss nu/nu	10/45/45	63	Reduced tumour
Freedland *et al*. [71]	2008	Prostate cancer	SCID	0/16/84	>40	Reduced tumour growth & longer survival
Otto *et al.* [72]	2008	Gastric adenoma	NMRI	0/14/86	>16	Reduced tumour growth & longer survival
Masko *et al.* [73]	2010	Prostate cancer	SCID	NCKD: 0/16/84 10% diet: 10/16/74 20% diet: 20/16/64	>80	All three diets reduced BG and tumour, thus zero-CHO diet unnecessary
Ho *et al.* [36]	2011	Prostate cancer	C3H/HeN Rag2M NOP	16/58/26	16	Reduction in tumor growth & longer lifespan without weight loss
Maurer *et al.* [74]	2011	Glioma cancer	Foxn1nu	0/13/36	>63	No significant difference

Table 1: Summary of animal studies on ketogenic or low-CHO diets.

3. Human Studies:

Because epidemiological evidence gathered over the past 20 years has strongly implicated diet as an important player in cancer morbidity and mortality, numerous interventional trials have been carried out to study this in more detail [75, 76]. However, because obesity has been shown to be a

major risk factor for many cancers, traditional diet-modification studies have concentrated on restricting total calories, by either lowering dietary fat intake or by increasing fiber (by increasing vegetable and fruit intake) [77]. More recently, low CHO, high protein diets have been found to be effective in weight control and prevention of diabetes and cardiovascular disease (CVD) in studies with obese or overweight patients [77-81]. The results showed that low CHO, high protein diets were more effective than traditional low fat diets or high CHO, low protein diets [77-81]. Evidence from *in vitro* and *in vivo* studies suggests that this diet intervention has promising potential in cancer prevention and therapy.

Because cancer cells are well known for their heavy reliance on glucose for survival and growth, a few clinical trials have been carried out to assess the effectiveness of low CHO diets in cancer management as summarized below.

i. **Nebeling *et al*. *J Am Coll Nutr* 1995. Pediatric astrocytoma case report.**

Ketogenic diets (KDs), which are CHO-restricted and are normally comprised of 80% fat and 20% CHO and protein, have been used to treat epileptic seizures in pediatric patients since the 1920s [82]. In the absence of glucose (in famine or in KDs), normal cells in the brain use ketone bodies, which are by-products of fatty acid metabolism, for energy production, while brain tumour cells are solely dependent on glycolysis (glucose) [83, 84]. Therefore, by restricting glucose intake, KDs limit glucose uptake to the tumour, inhibiting its growth and survival, while minimizing effects on healthy tissues, which can use an alternative energy source or ketone bodies from dietary fat.

Nebeling *et al*. conducted the first CHO-restricted intervention in two advanced stage pediatric astrocytoma patients in 1995. Their diet regimen, which lasted 8 weeks, was comprised of 70% Fat (60% medium-chain triglyceride (MCT) oil & 10% other dietary fat), 10% CHO, and 20% protein, supplemented with vitamins and minerals [84]. They reported a reduction in blood glucose (BG) after seven days with no weight loss [84]. After eight weeks of intervention, PET scan results showed a 22% reduction in glucose uptake by tumour sites [84].

The major limitation of this study was the number of patients and no non-ketogenic controls to compare the effectiveness of the diet. Although the KD decreased glucose uptake into the astrocytomas, there was no report on tumour size, which would have provided more of a direct indication of effectiveness.

Moreover, this KD regimen had a very high proportion of fat, since it was designed to increase the body weight of pediatric patients [84]. If this intervention was used to treat BrCA or PrCA patients, where increased body weight is in itself a risk factor, the diet needs to be modified or proportion of fat decreased (and protein increased) while keeping CHO low.

Compared to other studies using KD, side effects such as nausea and vomiting were minimized and limited only to the initial stage of the study since their MCT-KD was introduced to the two patients very gradually, with regular food [84]. The minimization of side effects may have facilitated the compliance of this diet regimen. Also, their intervention was based on a well-planned diet, taking into account the patients' food preferences to favor compliance and the strong commitment and support of the patients' families [84]. One patient reported significant improvement in mood and skill development, which led to continuation of this intervention for 12 months. No disease progression was observed in this patient during those 12 months, and the patient survived for the next 10years (verbal communication and reported by Schmidt *et al. Nutr Metab* 2011)[85].

ii. **Zuccoli *et al., Nutr Metab* 2010. Case study with a female glioblastoma patient.**

Following Nebeling *et al.,* another case study with a 65-year old female glioma patient was conducted using a calorie-restricted KD [83]. In this study, a patient followed a 600kcal/day-diet comprised of 80% fat and 20% CHO and protein for two months, at which point the tumour regressed significantly [83]. Due to hyperuricemia, this KD was discontinued after 2 months and the patient switched to a calorie-restricted but-non-KD (of unspecified composition) [83]. Although complete regression of the tumour occurred, this could have been due to weight reduction rather than the KD. Another limitation was that this was a case report without any controls; comparison with patients with standard therapy alone and no therapy but KD alone would be needed to validate their findings.

The standard therapy for glioblastoma includes radiation with temozolomide, which is an alkylating agent that damages DNA [83]. The female patient in this study and many others lack enzymes that can repair such DNA damage due to *MGMT* hypermenthylation, thus they are more sensitive to temozolomide treatment [83]. However, even in patients with this epigenetic profile, there has not been any report of rapid tumour regression with standard treatment alone or in older patients to date. Moreover, significant reduction in edema observed in this case suggests that KDs may have anti-inflammatory effects that may function synergistically with therapy. Therefore, the practice-based observation made here suggests that this diet intervention may enhance cytotoxic/apoptotic effects of standard therapy.

iii. **Schmidt *et al. Nutr Metab* 2011. A pilot trial with 16 metastatic patients**

Recently, a pilot clinical trial was conducted to evaluate the compliance and effectiveness of a CHO-restricted diet in advanced stage or metastatic patients [85]. Sixteen patients with various cancers and no therapeutic options were recruited to a low CHO diet (limited to less than 70g CHO/day) for 3 months [85]. However, only five out of the sixteen patients completed the entire 3 month study period, creating a high dropout rate.

Cancer types and stages were not specified in the recruitment criteria and this generated heterogeneity among the study subjects, which may have contributed to difficulty in compliance. Family life involvement may have added to the resistance to lifestyle changes in adults compared to pediatric patients as in the Nebeling *et al*. study [85]. In addition, even with a food allowance of 70g CHO or 20g/meal, some patients failed to adhere due to severity of the

disease [85]. However, those who completed the study reported less insomnia, and improved blood profiles and emotional health [85]. The improvement in quality of life reported in this study is promising, especially in palliative care targeted for metastatic patients. Also, no reports of major side effects such as vomiting and nausea makes this dietary intervention ideal for advanced stage cancer patients or to be used as an adjunct therapy.

iv. **Lin et al. Cancer Epi Biomarkers Prev 2007. Feasibility study using gene expression analysis to evaluate efficacy of low fat & low CHO diet in PCa.**

To evaluate if a short-term diet intervention could have an effect on tumour biology, Lin *et al*. conducted a study with eight PrCA patients. Four men were randomized either to a low fat/low CHO diet group or a control group and followed for six weeks [86]. Differential gene expression in biopsy samples (before intervention) and prostatectomy samples (after intervention) was analyzed. The results showed that men in the intervention group consumed 46% less fat and 42% less CHO (39% less total energy), resulting in weight lost compared to the control group. While there was no change in gene expression in the control group before and after the intervention, there was significant change in expression of 23 genes in the intervention group. Some of these genes are linked to cell migration and tissue remodeling, which may be important in tumour progression [86, 87]. The significant weight loss and gene expression changes observed in the intervention group were likely due to the combinational effects of fat-, CHO- and caloric-restrictions.

Despite the small number of subjects recruited and short intervention time, the study demonstrated that the dietary modification altered PrCA outcome at the molecular level. Unlike the other three studies, this study included a control/comparison group and used a new scientific tool (gene expression profile) as a biomarker to predict prognosis, adding significance to their finding.

v. **Ongoing studies/ results yet to be published.**

Larger clinical trials are currently underway to assess the effect of low CHO diets on glioblastoma [88] and advanced solid-cancer patients [89].The preliminary data from both studies show promising results, including disease stability and partial regression [88, 89]. Also, randomized studies with BrCA survivors [26], prostate and lung cancer patients are being recruited for phase I- low-CHO-diet studies in the US [30]. Results are yet to be published.

Dietary intervention in cancer therapy has been predominated by low-fat/high CHO diets; however, the evidence of the efficacy of Atkin's-like diets for human cancer is slowly emerging. As discussed in the aforementioned cases of low CHO diet trials, most of them are case-reports, and a few larger randomized, controlled trials are currently underway. Promising preliminary clinical results together with preclinical (*in vitro* and *in vivo*) data provide solid evidence to support anticancer activity of low CHO diets. The evidence from case reports strongly suggests the benefit of this intervention as

long as there is compliance and the diet is followed properly. In order for this type of intervention to succeed, proper strategies from recruitment of patients, dietary guidelines, implementation plans, monitoring and follow-up assessments are needed.

Summary of Cochrane Library Database: "low CHO and cancer"

Authors	Year	Intervention	Study Duration	Outcome Measures	Results
Martin *et al.*	2011	Reduced fat (to 15%) & Increased CHO	10 years	Invasive BrCA	Fat intake: no association
Russell *et al.*	2011	High protein & low CHO (low fiber) *	4 weeks	Anti-cancer metabolites in colon health	Decrease in protective metabolites and increase in hazardous metabolites in colon
Meinhold *et al.*	2010	Cohort study: assessed dietary intake through questionnaires	6.5 years	Pancreatic cancer incidence	High glycemic load and **High CHO intake**: associated with **pancreatic cancer risk**
Thomson *et al.*	2010	2 diets: 1)Low CHO * 2)Low Fat	6 months	Body weight, BG, insulin and blood lipids	**BW, BG,** insulin and cholesterol reduction in both diet groups
Howard *et al.*	2006	Low Fat & high CHO	7.5 years	Body weight	Reduction in body weight
Berrino *et al.*	2001	Reduction in animal fat, high in complex CHO and high in phytoestrogen	4.5 months	Serum hormone levels, BW, BG	Serum testosterone and estrogen levels reduced. BW & BG also reduced.
Knight *et al*.	1999	Low fat & high CHO diet	2 years	Mammographic density	Reduced density: reduced BrCA risk
Leyenaar *et al.*	1998	Low fat & high CHO diet	2 years	Adverse effects on physical and emotional health (self-reported)	No adverse effects on physical or emotional health
Boyd *et al*.	1997	Low fat & high CHO diet	2 years	Mammographic density	Reduced density: reduced BrCA risk
Sopotsinskaia *et al.*	1992	Total caloric restriction: reduced fat (by 30%) & reduced CHO (by 9%) *	3 years	BCa progression	**Reduced metastatic progression.** Control: 25%. Intervention group: only 7%.

Table 2: Cochrane database results: 25 randomized trial studies that are related to diet intervention and cancer. Most of the studies are based on reduced fat intake, not on reduced CHO, and some are not related to cancer (thus omitted from this table). *: low CHO diet intervention used in the study.

4. Discussion: implementation processes in the socio-cultural and economic contexts: impact on healthcare system

In vitro and *in vivo* evidence showing that tumour cells in general take up more glucose than normal cells has led to the development of diagnostic Positron Emission Tomography using a glucose analog, ^{18}fluorodeoxyglucose [90, 91]. This technology has advantages over other conventional detection tools since small, hard-to detect tumours and/or micrometastases can be visualized. The development and application of PET imaging with ^{18}fluorodeoxyglucose is a very successful example of knowledge translation at work. Our review of the clinical and epidemiological literature suggests the effectiveness of a CHO-restricted diet in cancer management. As directed by the KE-DS Model, we will now consider the socio-cultural and economic contexts associated with implementing this intervention.

i. Socio-cultural context

Food provides us with necessary nutrients and energy to survive and maintain optimal health. In many cultures, however, food is viewed beyond its biophysical context and holds psychosocial and spiritual meaning [92] as it is used as part of rituals, medical practice and social occasions [93-95]. To many patients, the act of eating represents overall wellness, and to their families and care-givers, food is often a form of support and care for the patients [92, 96, 97]. Therefore, modification of eating habits as a means of therapeutic intervention may present cultural challenges.

Compared to children, adults are more resistant to change due to lack of adaptability and other life commitments [85]. Furthermore, wide variation in food preferences and people's willingness to adhere to a specific diet regimen are additional barriers in implementing dietary intervention for adult

participants [84, 85]. Cancer survivors are, however, more motivated to change their lifestyle to promote better health and prevent recurrence compared to healthy individuals [98]. This is particularly true for breast and prostate cancer patients who have undergone drastic changes in their eating habits after diagnosis [99-102].

Another aspect of note is that health professionals from different disciplines (eg, basic science and clinical researchers, nurses and oncology dietitians and physicians) may possess disparate or sometimes conflicting opinions about certain nutrients and their value, creating differential interpretation of research data.

ii. Economic Impact

For a new 'product' or knowledge to be implemented into clinical practice and policy, scientific merits need to be weighed against the principles of social justice and socioeconomic factors. Despite the tendency to be over-shadowed by clinical significance, economic impacts of health research play a critical role in the decision making process, where health care investments are made to gain the highest return. Clinical significance of the research knowledge needs to be synchronized to economic significance where it can have a positive impact on the highest number of people possible through equitable access to effective interventions [8].

Lifestyle is one of the major risk factors of cancer, thus modifying the behavior of the public has great potential in healthcare cost saving. Dietary changes to promote healthy living or prevention of primary and recurrent tumours generally produce minor, if any, adverse effects, requiring no secondary intervention to treat side effects. Often, positive emotional and psychological effects are reported to coincide with the clinical benefits of this intervention [84, 103].

Obesity is a major health concern in western countries as it is associated with a number of diseases and affects a large number of people. Despite challenges of adopting and complying with

dietary/lifestyle modifications [84, 85], reducing obesity and the diseases associated with it would greatly reduce morbidity and mortality in today's society.

There are several studies showing efficiency and effectiveness of dietary intervention in cancer prevention. For example, Campbell *et al.* evaluated the efficacy of health communication interventions to increase fruit and vegetable consumption in colorectal cancer survivors in North Carolina [98]. The results of their analysis showed that motivational communication methodology was cost effective in promoting dietary changes in colorectal cancer patients [98].

Similarly, the Women's Health Initiative Randomized Control Dietary Modification Trial (WHI-DM) was conducted to evaluate whether a low fat dietary change may prevent cancer in women. 49,000 post menopausal women aged 50 to 79 were recruited and followed up at forty centres across the United States for eight years [104]. For two cohorts of women; those with high dietary fat intake and those who are at high-risk for BrCA, Bos *et al.* measured quality-adjusted life years that patients would have being disease-free (QALY) and incremental cost effectiveness ratio (ICER), which indicates the cost associated with the intervention [104]. The ICER for the 50 year old cohort of women with high fat intake was $13,773/QALY and $19,199/QALY for the high risk-BrCA group [104]. Because these ratios were below the commonly set cost-effectiveness threshold of $50,000/QALY [105, 106], this low fat diet intervention was very cost-effective as it successfully reduced the dietary fat intake and risk for breast and ovarian cancers in the intervention groups compared to the control group [104]. Even though this study was conducted in the United States and no cost effective analysis has been carried out as yet in Canada, we can estimate similar costs for such dietary intervention studies given that inclusion resources (ie orientation, counseling, dietitian salaries etc) for cost calculation would be similar between these countries.

As demonstrated in the aforementioned studies, dietary intervention is one of the most cost-effective strategies in cancer prevention. Newly emerging clinical data for the effectiveness of low CHO

diets together with solid preclinical data (both *in vitro* and *in vivo*) strongly support this intervention be implemented in oncology nutrition/therapy plans. The synergistic effects demonstrated with anti-cancer & anti-inflammatory drugs to further reduce tumour burden adds clinical and economic significance. Furthermore, placing people with high-risk or survivors of BrCA on this diet has preventive potential, ie, by decreasing the incidence and/or mortality from primary cancer or recurrence. In consideration with the increasing number of survivors and the unaddressed weight issues that are associated with risk of recurrence, this dietary intervention is a very cost-effective strategy for cancer control, prevention and treatment. Although lifestyle modification may pose some cultural hurdles and compliance challenges in adults, with proper implementation plans that take social determinants into account, those barriers can be identified and overcome.

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