Implications of nutrition on the incidence and treatment of cancer

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Nutrition and the incidence of cancer

Epidemiological data show that at least 30% of all cases of cancer are caused by nutrition *[Doll, 1996; Baena et al., 2014]*. Large regional differences have been observed in the development of cancer depending on the eating habits and nutritional quality, so that the influence of nutrition on the development of cancer can vary between 10% and 70% *[Doll and Peto, 1981]*. There are also strong regional differences in the incidence of individual types of cancer. In some Asian countries, there is a high incidence of stomach and liver cancer. However, the risk of a woman contracting and dying from breast cancer is significantly lower than it is in the US and Europe *[Dagdemir et al., 2013]*. The close link between the lower incidence of breast cancer and nutrition and lifestyle in Asia is revealed, for example, in the increased incidence of breast cancer in Japanese women who have emigrated to the US as well as the increased risk in the following generations.

The influence of nutrition on the occurrence and course of cancer is determined by many factors. The occurrence of tumours is both promoted (mutagenic substances such as aflatoxin) and inhibited (apoptosis-inducing natural products) by food constituents. New studies show that the composition of the diet regarding the proportion and quality of carbohydrates and fats significantly influences the incidence and course of cancer as well as governs the success of treatment.

Carbohydrates that cause a rapid and sharp rise in blood sugar levels, thereby inducing the release of hormones (insulin) and growth factors (insulin-like growth factor-1/IGF-1) are increasingly becoming the focus of cancer research. A study with more than 1.2 million subjects revealed that elevated fasting blood sugar levels increase the incidence of cancer *[Jee et al., 2005]*. A study by Zhou et al. *[2010]* showed that people with elevated blood sugar (pre-diabetes and diabetes) are increasingly contracting cancer and that the death rate from cancer is directly correlated with blood sugar levels. An international study in which the German Cancer Research Centre in Heidelberg was also involved showed that the intake of sugar/carbohydrates is associated with an increased risk of developing breast cancer in menopausal women with receptor status of ER (−) and ER (−)/PR (−) *[Romieu et al., 2012]*. A new study by the German Cancer Research Centre also demonstrated that high IGF-1 levels in the blood are correlated with the occurrence of oestrogen receptor-positive breast tumours in both pre and post menopause *[Kaaks et al., 2014]*. Another recent study, also in cooperation with the German Cancer Research Center, has demonstrated that elevated IGF-1 levels in the blood are correlated with the occurrence of thyroid cancer *[Schmidt et al., 2014]*. These studies demonstrate that the blood glucose level itself as well as the hormones (insulin) and growth factors (IGF-1) induced by it are correlated with the occurrence and course of cancer. In the area of fat intake, it has been demonstrated that the type of fat has a significant impact on the risk of cancer.

An increased intake of omega-3 fatty acids and hence an increase in the ratio of omega-3 to omega-6 fatty acids reduces the risk of breast cancer *[de Lorgeril and Salen, 2014]*.

The role of carbohydrates in the recurrence of cancer

In addition to the increased incidence of the primary disease, nutrition also plays an important role in the recurrence of cancer. It was shown that nutrition is a deciding factor in the recurrence of cancer. A high carbohydrate diet (high glycemic load) leads to a significantly increased rate of recurrence as well as an increase in the death rate for patients with colorectal cancer *[Meyerhardt et al., 2012]*. The role of carbohydrate consumption and the associated levels of IGF-1 was also demonstrated by a recent US study *[Emond et al., 2014]*. It was found that the IGF-1-factor receptor determines whether breast cancer patients experience a recurrence caused by the consumption of carbohydrates. Breast cancer patients experienced a 500% increase in the rate of recurrence of the cancer if carbohydrate consumption was maintained or increased during follow-up – but only if the IGF-1 receptor was present in the primary tumour. Women, in whom the IGF-1 receptor could not be detected in the tumour material, were insensitive to carbohydrate consumption during follow-up. A decisive conclusion can be drawn from this study. There is a subgroup of breast tumours characterised by sugar-associated growth receptors in which the cancer recurs despite surgical removal of the tumour and concomitant therapy if these patients maintain or increase carbohydrate

consumption following treatment. Based on these results, the authors recommend that breast cancer patients who have the IGF-1 receptor in the primary tumour should reduce their carbohydrate consumption after diagnosis. US cancer researchers and oncologist have also proposed adjusting carbohydrate consumption to the properties of the tumour. This is enabled by biomarkers that indicate an increased intake of carbohydrates in the tumour. This can be performed upon detection of the IGF-1 receptor or other biomarkers (e.g. transketolase like-1 = TKTL1) in tumour tissue obtained by surgery or biopsy. Meanwhile, "liquid biopsies" are more frequently used in order to make a prediction about the properties of the tumour without having to resort to classical biopsy or surgical removal of the entire tumour. In addition to analysing tumour cells that have detached from the tumour and which circulate in the blood, the analysis of macrophages (activated monocytes) that have phagocytosed (eaten) tumour cells has attracted increasing interest in recent years. In this laser-based technique, epitope detection in macrophages (EDIM) is performed, whereby the epitopes represent protein components of the phagocytosed tumour cells within the phagocytes. Using EDIM, it is possible to detect epitopes of the TKTL1 protein of tumour cells phagocytosed in macrophages. The detection of the TKTL1 protein allows the accurate identification of tumours exhibiting increased glucose uptake *[Feyen et al. 2012]*. Because of this, in addition to the detection of the IGF-1 receptor in the primary tumour, the EDIM TKTL1 blood test is also a non-invasive assay for determining glucose metabolism in tumours, which can detect tumours that exhibit carbohydrate-dependent growth. Not only in the follow-up but also before radiotherapy and chemotherapy the tumor can be analyzed in a non-invasive manner regarding activation of sugar metabolism, in order to increase the chances of recovery in acute treatment and after care by means of targeted nutrition.

Phytonutrients in cancer therapy

Our food contain more or less medically active compounds such as the extremely effective, naturally-occurring form of vitamin E, gamma- and delta-tocotrienol or phytochemicals with an anti-cancer effect. Studies have shown that gamma-tocotrienol can effectively fight cancer stem cells, which are resistant to radiation and chemotherapy. This study was published in the International Journal of Cancer, a journal of the German Cancer Research Centre *[Luk et al., 2011]*. Furthermore, it was shown that delta-tocotrienol inhibits hypoxia-induced factor-1 alpha (HIF1-α), which leads to a radiation resistance, and angiogenesis *[Shibata et al. 2008]*. Because of the high-quality data on their anti-cancer effect, tocotrienols were recently proposed for the prevention and treatment of breast cancer *[Sylvester et al., 2014]*.

Over 1,000 studies have demonstrated the therapeutic potential of additional natural products in relation to cancer cells. These include studies on resveratrol, sulforaphane, and quercetin. Agents such as resveratrol and sulforaphane *[Kallifatidis et al., 2009]* can trigger apoptosis in cancer cells, thereby eliminating them. In 2008, a Dutch group demonstrated that Quercetin inhibits the fermentation of glucose to lactic acid (Warburg effect/aerobic glycolysis) in favour of a metabolic shift towards energy release via combustion with the help of oxidative phosphorylation (mitochondria) *[Dihal et al., 2008]*. The possibility of achieving therapeutically effective levels and directly affecting the energy release through consuming such amounts of quercetin has already been demonstrated *[Davis et al., 2009; Davis et al., 2010]*. This demonstrates that the consumption of certain natural products (phytochemicals) can even selectively influence the metabolism of the entire organism.

By modifying nutritional habits (e.g. through the consumption of foods with a low content of phytochemicals), the intake of phytochemicals has been significantly reduced. The use of pesticides and the shielding of the UV component of sunlight caused by growing crops in greenhouses has also drastically reduced the fraction of phytochemicals with an anti-cancer effect. This has also lead to the significantly reduced production of a form of phytochemicals that triggers cell death in tumour cells upon activation by the cytochrome P450 enzyme CYP1B1. These secondary plant compounds which are called salvestrols are a type of phytoalexins and are produced in response to pathogens. This means that the infestation of crops with pathogens such as fungi (e.g. apple scab) lead to the formation of these anti-cancer substances. Because of the predominating mode of crop production and processing, food no longer has the composition with which humankind has co-evolved over hundreds of millennia.

Considering the variety of phytochemicals with potent anti-cancer properties, it is not surprising that over 60% of all currently used cancer drugs consist of natural products or derivatives thereof *[Newman and Cragg, 2007]*. With respect to plant based anti-cancer agents, those with negative and positive side effects must be differentiated. Quercetin belongs to a group of phytochemicals with positive side effects because it activates mitochondrial energy metabolism in brain and muscle cells via a biogenesis of mitochondria, which even leads to increased performance (VO2max) *[Davis et al, 2009; Davis et al., 2010]*. In contrast, phytonutrients from the yew (Taxus) and periwinkle (Vinca) lead to considerable adverse side effects. These natural products have been slightly modified so that they could

be patented by pharmaceutical companies and the "new" substances are commercialised as chemotherapeutic agents. However, many oncologists and patients are not aware that (modified) phytochemicals still represent a large number of chemotherapies. Even chemotherapy with vinorelbine or similar preparations is based on an ingredient from the rosy periwinkle. In addition to the decades-long use of natural chemotherapeutic agents such as Taxol, which leads to adverse side effects, phytonutrients such as polyphenols and tocotrienols, which lead to positive side effects, are gaining major importance in cancer treatment.

Ketogenic diets are increasingly becoming the focus of current discussions

Especially in the US, the ketogenic diet, a form of nutrition developed over more than one hundred years, has been established as a clinical treatment of epilepsy when treatment with drugs fails. Severely limiting the intake of carbohydrates and protein results in the formation of the three ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone). The resulting metabolites can cover a substantial part of the energy demand in sugar-dependant organs such as the brain in the absence of glucose as an engergy supplier. Because ketone bodies can only be converted into energy via oxidative phosphorylation, their metabolites cannot be used for fermentation. Fasting or diet induced ketosis was first described by Hans Krebs as "physiological ketosis" with ketone values up to approx. 8 mmol/l *[Paoli et al., 2014]* in order to distinguish this from diabetic ketoacidosis with values up to more than 20 mmol/l. In the case a carbohydrate consumption of 1 g/kg of body weight/day accompanied by a protein consumption of 1.5–2 g/kg of body weight/day, enough glucose in the form of carbohydrates and glucogenic amino acids is taken up so that only mild ketosis occurs, if at all. This form of carbohydrate restriction, which is accompanied by a moderately elevated protein intake, leads to both a significant reduction in glycemic load as well as in the glycemic index. Although a further dietary reduction of carbohydrates and protein and a concomitant increase in the fat content leads to a significant increase in the production of ketone bodies, this is accompanied by a massive reduction in eating pleasure and quality of life. In follow-up care, carbohydrate consumption should be increased to 2 or more g/kg of body weight/day. The amount of carbohydrate should always be adapted to the individual situation in terms of the activation/non-activation of glucose metabolism in the tumour as well as physical activity and cognitive performance.

In the case of increased physical activity and sport as well as stress and performance induced increase in brain metabolism, it is necessary to further increase the amount of carbohydrate in order to enable sufficient protective sugar fermentation metabolism in healthy cells. In addition to the amount of carbohydrate (glycemic load), a low glycemic index of the food and the overall meal should be considered because these are not only determined by the glycemic index of the individual ingredients but also by their combination and preparation.

In the long term, this diet can be maintained without problems because it does not greatly restrict eating pleasure and ultimately enables a generally healthy diet. Because some cancer researchers and book authors have oversimplified the matter and claimed that cancer cells can be starved by sugar withdrawal and an increased consumption of fat, many cancer patients have been led to believe that their cancer problems can be solved simply by adhering to a ketogenic diet. Many oncologists have justifiably responded to this oversimplification with a great deal of criticism. In order to discuss the opportunities and risks of a ketogenic diet as an option for improving cancer treatment, an essential question must be resolved.

From theory to clinical practice

Can the composition of the diet influence therapeutic success in the case of cancer? Yes, because the metabolism of cancer cells can be addressed by changes to the individual diet i.e. a reduction of the carbohydrate and protein fractions. This has been proven in a study conduced by oncologists at the Lübeck University Hospital *[Schroeder et al., 2013]*. This study examined whether reducing the carbohydrate and protein fraction of the diet (ketogenic diet) in patients with head and neck tumours leads to a change in the metabolism of tumours. Using micro-probes, the metabolism of tumours was directly analysed in vivo. It could be proven that a ketogenic diet inhibits the production of lactic acid in tumours *[Schroeder et al., 2013]*. This demonstrates that tumour metabolism and the form of energy release in the tumour can change depending on the composition of the diet. By strictly limiting of carbohydrates and protein (glucogenic amino acids) i.e. the substrates that can be used for fermentation, the tumour can be forced to use oxidative phosphorylation (mitochondria assisted combustion) to release energy.

In a 2012 pilot study, Fine et al. demonstrated the therapeutic success of a ketogenic diet. In tumours with a high intake of sugar, a ketogenic diet stabilised the cancer or even led to a partial remission of the tumour *[Fine et al., 2012]*.

However, in order to adapt to altered levels of substrates resulting from a ketogenic diet, tumour cells require oxygen, which is essential for oxidative phos-

phorylation. A metabolic change back to the combustion is not possible; tumour areas that have a lack of oxygen (hypoxia) thus become necrotic and die. A ketogenic diet can therefore significantly contribute to the death of these hypoxic areas. At the same time, the ketogenic diet inhibits production of lactic acid of the tumour, whereby lactic acid-based matrix degradation of the surrounding healthy tissue is inhibited, thereby counteracting the invasiveness and metastasis of the tumour. The partial necrosis and minimal invasiveness of the tumour significantly contribute to stabilising the disease. This explains the successes shown in the ketogenic diet studies regarding stabilisation of the cancer and partial remission of the tumour *[Fine et al., 2012]*.

However, these results should not be misinterpreted by giving the impression that all tumours can be starved by a ketogenic diet. Fine et al. only investigated tumours that exhibited a strong glucose uptake. Thus, there is a risk of cancer patients perceiving a ketogenic diet as an alternative to chemotherapy or radiotherapy.

The ketogenic diet should not be used as an isolated measure but rather as a supportive measure in patients who have tumours with high sugar intake in order to make these more sensitive to radiotherapy and chemotherapy.

Because the oxygen-containing and oxygen deficient areas of tumours alternate, entire tumours cannot be starved through a ketogenic diet. The use of a permanent ketogenic diet would not even lead to a therapeutic success in tumors with a high glucose uptake in oxygenated areas because the tumour metabolism adapts to the substrate limitation (glucose restriction), thereby leading to a reactivation of oxidative phosphorylation. Metabolic reversal to combustion enables both tumour survival in the presence of oxygen as well as the continued growth of the tumour because fats and ketone bodies can also be used as a source of energy. This metabolic reversal to the mitochondrial release of energy is not a failure but rather the basis of leading the tumour to apoptosis with the release of free radicals or cytotoxic therapies (e.g. chemotherapy). The ketogenic diet thus sensitises a tumour for treatment with radicals and cytotoxic drugs. It is precisely this metabolic change triggered by a ketogenic diet that can be used to increase the success of radiotherapy and chemotherapy.
In order for ketogenic diet to significantly contribute to successful treatment, it is important to combine a ketogenic diet with a treatment that triggers radicals and/or apoptosis e.g. by means of radiotherapy and/or chemotherapy.

This has already been demonstrated in small-scale studies involving fasting or a ketogenic diet prior to radiotherapy/chemotherapy *[Raffaghello et al., 2010; Longo et al, 2010]*.

In practice, ketogenic metabolism can be achieved within three days by using ketogenic sip feeds. Such an application of the ketogenic diet as a short-term measure for metabolic sensitization of tumours to radiotherapy and chemotherapy is crucial and differs from attempts to achieve permanent ketosis lasting for weeks or months – even in phases in which radiotherapy and chemotherapy are not used. Studies have shown that the (pharmacological) inhibition of fermentation has re-sensitised resistant cancer cells for a release of free radicals and apoptosis, thus once again making radiotherapies and chemotherapies (e.g. taxol and cisplatin) effective *[Le et al., 2010; Zhou M et al., 2010; Ihrlund et al., 2008]*.

Studies performed at the University Hospital of Mannheim have also demonstrated that fermentation metabolism in tumours leads to resistance towards radiotherapy and chemotherapy. Schwaab et al. demonstrated that by detecting TKTL1 gene activity in tumours, it is possible to identify patients who would not benefit from the use of radiation and chemotherapy *[Schwaab et al., 2011]*. In these patients, the activation of the TKTL1 gene and the associated sugar metabolism leads to a resistance towards these therapies. However, these patients would benefit from a ketogenic diet prior to radiotherapy and chemotherapy; the treatments would otherwise be ineffective.

A recently published review article from a research group at the MD Anderson Cancer Centre describes the importance of metabolism, especially sugar metabolism (pentose phosphate pathway and TKTL1) for the success of cancer therapies *[Phan et al., 2014]*. The ketogenic diet leads to an inhibition of glucose metabolism, thus allowing an increase in apoptosis and free radical formation because glucose metabolism via the pentose phosphate pathway and the enzyme TKTL1 are inhibited because of a "lack of fuel" (substrate limitation). Because humans are unable to metabolise fatty acids into sugar, which is necessary for pentose phosphate metabolism and the TKTL1 enzyme, increasing dietary fat is one option for inhibiting the pentose phosphate pathway and the TKTL1 enzyme, thereby facilitating the death of cancer cells.

The two sides of fermentative sugar metabolism

The ketogenic diet and the consequent inhibition of the pentose phosphate pathway are not a healthy approach to nutrition. This has been demonstrated by

studies on the importance of the pentose phospate pathway in protecting cancer cells as well as nerve cells *[Vaughn and Deshmukh, 2008; Newington et al., 2011]*. Diseases leading to inhibition of the pentose phosphate pathway and the TKTL1 enzyme results in the increased production of free radicals, which in turn results in DNA damage and ultimately in rapid ageing and early death *[Werner syndrome: Li et al., 2013]*. The protective function of the pentose phosphate pathway and the TKTL1 enzyme in healthy cells is also demonstrated in this way. By means of a ketogenic diet, the protective function of the pentose phosphate pathway and the TKTL1 enzyme phase can gradually be switched off in cancer cells, thereby facilitating the release of radicals and triggering apoptosis in cancer cells. However, in healthy cells (e.g. nerve cells) this protective function should be enabled by ensuring the adequate functioning of the pentose phosphate pathway and the TKTL1 enzyme so that these cells are not damaged and do not die prematurely. Also for this reason, a strict ketogenic diet should not be prescribed over the long term because the pressure to use the mitochondria leads to the increased formation of free radicals and DNA damage in healthy cells, thereby advancing the ageing process of these cells. A strict ketogenic diet should therefore be limited to the period before radiotherapy or chemotherapy. The importance of fermentative glucose metabolism for the survival of neurons has also been demonstrated by the fact that neurons containing β-amyloid plaques survived if they were able to ferment sugar *[Newington et al., 2011]*. Because of this enormously important protective function of fermentative sugar metabolism, the brain rewards the consumption of sufficient amounts of sugar and carbohydrates with the release of certain messengers so that adequate sugar is consumed. The consumption of sugar/carbohydrates is thus an innate and important mechanism for maintaining the function and integrity of our brain, which has been significantly enhanced as vertebrates have developed.

At the same time, the establishment of agriculture and the resulting use of starch as a source of sugar has increased the availability of sugar so much that agricultural region experiences increases in cognitive ability, which manifested in the first advanced civilisation (Mesopotamia, Egypt, Central America). It is therefore not surprising that the TKTL1 gene is among the five human genes deemed the most essential for the development of cognitive neural abilities *[Prüfer et al., 2014; Pääbo, 2014]*. A ketogenic diet should therefore be implemented as a measure to switch off the protective function of the pentose phosphate pathway and the TKTL1 enzyme prior to chemotherapy or radiotherapy so as to ensure therapeutic success. In periods in which no radiotherpay and chemotherapy treatments are performed, a moderate diet can once again be adopted. However, blood sugar and the levels of insulin and IGF-1 should continue to be normalised. This is possible by reducing the dietary intake of glucose, sucrose, and consuming carbohydrates with a low glycemic index, which enables the uniform and reliable supply of sugar to the nerves and brain, thereby positively influencing cognitive performance.

Galactose is of particular importance for ensuring fermentative sugar metabolism in nerves as demonstrated by its neuroprotective effect *[Salkovic-Petrisic et al, 2014]*. Galactose also does not promote undesirable fermentation in cancer cells *[Warburg et al., 1924]*.

The combination of sugars with low glycemic index such as galactose, trehalose, isomaltulose and tagatose is therefore particularly suitable for securing protective sugar metabolism in healthy cells, while insulin/IGF-1-associated growth signals are reduced in cancer cells. While trehalose is an excellent source for a uniform and prolonged release of glucose, galactose is especially well suited for supplying the brain with sugar. Importance of a uniform supply of sugar to the brain is clearly demonstrated by insulin-resistance-related sugar-uptake disorders of the brain and the consequent increase in free radicals and DNA damage, which eventually leads to the death of neurons and the manifestation of Alzheimer's disease *[Willette et al., 2014]*. For this reason, leading scientists often refer to Alzheimer's disease as type 3 diabetes. Because galactose is taken up by the brain even in the case of insulin resistance, uniformly supplying the brain with galactose enables energy release via the pentose phosphate pathway and TKTL1, thereby suppressing the release of free radicals and apoptosis and preventing the premature death of brain cells. Neurodegenerative diseases and cancer therefore represent two sides of the same coin. While activation of TKTL1 glucose metabolism in tumour cells leads to radiotherapy- and chemotherapy-resistant cancer cells, the de-activation of TKTL1 glucose metabolism in nerve cells leads to the increased induction of free radicals and apoptosis in nerves and ultimately to neurodegneration (e.g. via an insulin resistance related lack of substrate). This also explains why the "Framingham Heart Study" revealed that cancer patients had a lower risk of Alzeimer's disease and vice versa.

By selectively influencing the pentose phosphate pathway and the TKTL1 enzyme through nutrition, both the death of unwanted cells (cancer cells) and the protection of vital cells (nerve) can be directly influenced. A strict ketogenic diet limited to a few days prior to radiotherapy and chemotherapy is an untapped and easy-to-implement option for enhancing the effect of radiation and chemotherapy without inducing long-term negative effects.

Summary

Diet can directly influence the influence and progression of cancer through various mechanisms. In addition to the already known factors such as the quality of the food and the presence of tumour-initiating ingredients in the food, the metabolism of tumor cells and the control of it by natural products as well as the by the carbohydrate/fat amount in the food has become a focus of research. Both the amount of carbohydrate and their effect on blood sugar levels alter the growth and death of tumour cells via the associated hormones and growth factors. Thus, blood sugar levels and increased insulin and IGF-1 values in the blood correlate with the incidence and progression of cancer. By limiting dietary carbohydrates and protein while increasing dietary fat intake, it is possible to directly influence the metabolism of tumours, thereby inhibiting sugar fermentation and increasing oxidative phosphorylation. This so-called ketogenic diet offers the possibility of inhibiting fermentative sugar metabolism in tumours in order to (re)sensitise them towards subsequent radiotherapy and chemotherapy, thereby increasing the chances of recovery. Because long-term ketosis leads to negative effects in terms of ageing and cognitive performance, strict ketogenic diets cannot be recommended for cancer prevention and after care.

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Literature

Baena RR et al.: Diet and cancer: risk factors and epidemiological evidence. 2014 Mar;77(3):202–8

Dagdemir A et al.: Breast cancer: mechanisms involved in action of phytoestrogens and epigenetic changes. In Vivo. 2013 Jan-Feb;27(1):1–9

Davis JM et al.: Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol. 2009 Apr;296(4):R1071–7

Davis JM et al.: The dietary flavonoid quercetin increases VO(2max) and endurance capacity. Int J Sport Nutr Exerc Metab. 2010 Feb;20(1):56–62

de Lorgeril M, Salen P et al.: Helping women to good health: breast cancer, omega-3/omega-6 lipids, and related lifestyle factors. BMC Medicine 2014 12:54

Dihal AA et al.: Transcriptome and proteome profiling of colon mucosa from quercetin fed F344 rats point to tumor preventive mechanisms, increased mitochondrial fatty acid degradation and decreased glycolysis. Proteomics 2008, 8, 45–61

Doll R (Ed.), Epidemiology of Cancer, Oxford University Press, Oxford, (1996)

Doll R, Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst, 66 (1981), pp. 1191–1308

Emond JA et al.: Risk of Breast Cancer Recurrence Associated with Carbohydrate Intake and Tissue Expression of IGF-1 Receptor. Cancer Epidemiol Biomarkers Prev. 2014 Jul;23(7):1273–9

Feyen O et al.: EDIM blood test: a non-invasive method to detect up-regulated glucose metabolism in patients with malignancies. Future Oncology, ISSN 1479-6694, october 2012 Vol. 8 No.10

Fine EJ et al.: Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients. Nutrition 2012, 28:1028–35

Ihrlund LS et al.: 3-Bromopyruvate as inhibitor of tumour cell energy metabolism and chemopotentiator of platinum drugs. Mol Oncol. 2008 Jun;2(1):94–101

Jee SH et al.: Fasting Serum Glucose Level and Cancer Risk in Korean Men and Women. JAMA, January 12, 2005, Vol 293, No. 2

Kaaks R et al.: Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status-A prospective study within the EPIC cohort. Int J Cancer. 2014 Jun 1;134(11):2683–90

Kallifatidis G et al.: Sulforaphane targets pancreatic tumour-initiating cells by NF-kappaB-induced antiapoptotic signalling. Gut 2009 58: 949–963

Le A et al.: Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. Proc Natl Acad Sci U S A. 2010 Feb 2;107(5):2037–42

Li B et al.: Downregulation of the Werner syndrome protein induces a metabolic shift that compromises redox homeostasis and limits proliferation of cancer cells. Aging Cell (2013) pp1–12

Longo VD et al.: Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci. 2010 February; 31(2): 89–98

Luk Su et al.: Gamma-tocotrienol as an effective agent in targeting prostate cancer stem cell-like population. Int. J. Cancer: 128, 2182–2191 (2011)

Meyerhardt et al.: Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Natl Cancer Inst. 2012 Nov 21;104(22):1702–11

Newington JT et al.: Amyloid Beta Resistance in Nerve Cell Lines Is Mediated by the Warburg Effect. PLoS One. 2011 Apr 26;6(4)

Newman DJ and Cragg GM: Natural products as sources of new drugs over the last 25 years. J Nat Prod. 2007 Mar;70(3):461–77

Pääbo S: The Human Condition-A Molecular Approach. Cell. 2014 Mar 27;157(1):216–226

Paoli et al.: Ketogenic Diet in Neuromuscular and Neurodegenerative Diseases. BioMed Research International vol. 2014, Article ID 474296, 10 pages, 2014

Phan LM et al.: Cancer metabolic reprogramming: importance, main features, and potentials for precise targeted anti-cancer therapies. Cancer Biol Med 2014;11:1–19

Prüfer K et al.: The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505, 43–49 (02 January 2014)

Raffaghello L et al.: Fasting and differential chemotherapy protection in patients. Cell Cycle 2010, 9:22, 4474–4476

Romieu, I et al.: Dietary glycemic index and glycemic load and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2012;96:345–55

Salkovic-Petrisic M et al.: Long-term oral galactose treatment prevents cognitive deficits in male Wistar rats treated intracerebroventricularly with streptozotocin. Neuropharmacology. 2014 Feb;77:68–80

Schmidt et al.: Insulin-like growth factor-I and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev. 2014 Mar 19. (Epub ahead of print)

Schroeder U e al.: Decline of Lactate in Tumor Tissue After Ketogenic Diet: In Vivo Microdialysis Study in Patients with Head and Neck Cancer. Nutr Cancer. 2013;65(6):843–9

Schwaab J et al.: Expression of Transketolase like gene 1 (TKTL1) predicts disease-free survival in patients with locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy. BMC Cancer. 2011 Aug 19;11:363

Shibata A et al.: Tocotrienol inhibits secretion of angiogenic factors from human colorectal adenocarcinoma cells by suppressing hypoxia-inducible factor-1alpha. J Nutr. 2008 Nov;138(11):2136–42

Sylvester PW et al.: Potential role of tocotrienols in the treatment and prevention of breast cancer. Biofactors. 2014 Jan-Feb;40(1):49–58

Vaughn AE und Deshmukh M.: Glucose Metabolism Inhibits Apoptosis in Neurons and Cancer Cells by Redox Inactivation of Cytochrome c. Nat Cell Biol. Dec 2008; 10(12): 1477–1483

Warburg O et al.: Über den Stoffwechsel der Carcinomzelle. Biochem Z 152: 309–344(1924)

Willette et al.: Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimers Dement. 2014 Jul 17. pii: S1552-5260(14)02420–0

Zhou M et al.: Warburg effect in chemosensitivity: Targeting lactate dehydrogenase-A re-sensitizes Taxol-resistant cancer cells to Taxol. Molecular Cancer 2010, 9:33

Zhou XH et al.: Diabetes, prediabetes and cancer mortality. Diabetologia (2010) 53:1867–1876