Vetting the Internet's Favorite Cancer Cures

Stephan C. Jahn, Ph.D.
Department of Medicinal Chemistry and UF Health Cancer Center, University of Florida, Gainesville, FL
Email: scjahn@ufl.edu

Abstract

Modern medicine has developed many ways of treating cancer but, unfortunately, we are still a long ways from being able to successfully treat every patient. Some cancer patients may feel that their oncologists are not aware of other options while others may prefer a treatment that has not been approved for use in patients. The prevalence of complementary and alternative medicine in cancer treatment is surprisingly large and information regarding these treatments, whether true or false, is spread easily over the internet. In this review I hope to touch on a few of the most "popular" cancer treatments that can be found on the internet. By no means does this review cover even a small portion of those that can be found, and it is not meant to be a comprehensive review on any one of them. It should be viewed as a scientific snapshot of the current laboratory and clinical data that are available for these methods and to serve as a contrast to the hype, insufficient data, and incorrect information that can be found on any number of websites.

Keywords: alternative medicine, cancer, dichloroacetate, diet, fasting, vitamin D

Introduction

Through a meta-analysis of available literature, a recent review determined that up to 93.1% of cancer patients utilize a form of treatment that would be considered complementary or alternative [1]. Many times physicians and scientists view these treatments in a negative light, but with an extremely high usage rate it is clearly important that they be understood. These methods may be used for any number of reasons. Some may seem logical while others may not, but it is important for those studying them to put themselves in the patient's shoes. There is a population that believes the medical community does not want their cancer to be cured and is seeking the treatment that will produce the most profits. While discussing the validity of this sentiment is well beyond the scope of this review, one must remember that patients have a right to these thoughts and they are best approached through science and bettering our current treatment options. Other potential, and seemingly valid, reasons for attempting these methods include financial concerns (i.e. not being able to afford the standard of care) as well as falling to them as a last resort upon failure of the standard of care. Once treatment shifts from curative to palliative, patients may feel as if they have nothing to lose, and that decision is theirs solely. Not only do alternative and complimentary treatments offer them options that oncologists would not endorse, but it allows them to sidestep the Food and Drug Administration approvals and regulations that all treatments must abide by in the clinic, allowing patients to utilize high-risk treatments. Ultimately, these treatments provide these patients with hope, making it the duty of us in the scientific community to understand them, allowing us to harness the benefits they provide, while allowing us to better counsel patients in the use of these treatments, either

singularly or in conjunction with the standard of care.

The wealth of medical information and, unfortunately, misinformation available on the internet has vastly increased the amount of information a patient can acquire regarding the treatment of his or her disease. In this review, I hope to examine the science information that is available for a few of the most popular forms of complementary and alternative forms of cancer treatment. These were determined by internet searches and pared down to a few that I felt were not inherently false at their very premises based on my own personal knowledge, and those that did indeed have data available, many of which unfortunately do not. With this publication, I hope to benefit both the patients in bringing them data and information they may not have previously had, as well as the medical and scientific community in the form of bringing to light that these treatment methods are being used by cancer patients.

Dichloroacetate: The little (but unpatentable) molecule that could.

Dichloroacetate (DCA) is a small molecule that is being investigated for use in cancer [2-5] as well as mitochondrial disorders [6-8] and pulmonary arterial hypertension [9]. It is an inhibitor of pyruvate dehydrogenase kinase [10], which is itself a physiological inhibitor of pyruvate dehydrogenase, a mitochondrial enzyme that is important in carbohydrate metabolism [11]. DCA is then effectively an activator of pyruvate dehydrogenase and mitochondrial metabolism.

This is important in the treatment of cancer two different ways. First, it is able to reverse the Warburg effect. The Warburg effect is a well documented shift of cancer cell metabolism from mitochondrial oxidative phosphorylation to aerobic glycolysis in the cytoplasm (reviewed in [12] and [13]). While a definitive explanation as to why cancer cells would shift their metabolism to the less efficient glycolytic pathway has yet to be found, possible reasons include increased invasive capacity due to the acidified environment [14], the fact that glycolysis produces a number of building blocks that are essential for rapid cell proliferation (reviewed in [15]), or that it is simply a consequence of mitochondrial shutdown as an anti-apoptotic mechanism (discussed below). Second, the mitochondria are critical in the process of apoptosis, and their shutdown leads to apoptotic resistance (reviewed in [16]). DCA therefore reverts cellular metabolism to a normal state and reactivates the apoptotic pathway, either leading directly to death due to intrinsic cellular death signals or sensitization to other therapeutics.

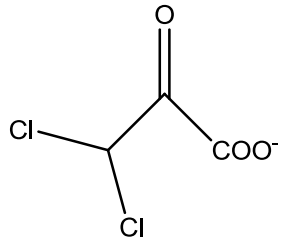

Figure 1. Dichloroacetate The highly bioavailable small molecule DCA is usually administered as the sodium salt.

DCA is different than most other forms of CAM in that it is not viewed as a "natural cure," nor is it simply a lifestyle modification. It is generally thought of as a drug and is being investigated scientifically as such, but is also being used by cancer patients to self-medicate. Grass-roots supporters aim to get the word out about DCA, stating that it is a drug that "big pharma doesn't want you to know about." DCA is a generic

drug, therefore unpatentable. This creates a perfect storm of conspiracy that was initially buoyed by unscientific and sensationalistic interpretation of the small amount of scientific data available at the time. Of course, even if the pharmaceutical industry does not want to investigate DCA for this reason (the validity of this statement is both beyond the scope of and inconsequential to this review), academic researchers may still approach it and it is possible that this online controversy has soured the interest of those in the academe in studying it.

While the early results were overblown, there is in fact plenty of promising data regarding DCA, although there have been limited clinical trials for its use against cancer. DCA induces apoptosis in breast [17], small-cell lung [17], glioblastoma [17], endometrial [18], and prostate [19] cancer cell lines. Animal models have shown that DCA may work as a single agent [3] as well as synergistically with current chemotherapy treatments [3,20]. Interestingly, sensitization to radiotherapy is seen in vitro while a protective effects is observed in a xenograft model due to induction of tumor hypoxiabecause of the switch to oxidative phosphorylation upon treatment [21]. Similarly, DCA induced apoptosis in normoxic colorectal cancer but had the opposite effect, increasing tumor growth, in hypoxic conditions [22], demonstrating that there is much to be learned about the use of DCA.

Clinically, the small size of DCA lends it excellent bioavailability and the ability to cross the blood-brain barrier. It is in the brain, largely due to the dearth of acceptable treatments for brain cancers, that DCA has found its most use. The first clinical trial saw DCA used in five patients after debulking surgery for glioblastoma multiforme [5]. One patient had a very large tumor and died during the clinical trial. The others either showed no growth or survived past the end of the study after having additional debulking surgeries.

An open-label phase II clinical of DCA in non-small cell lung cancer (NSCLC) and breast cancer recently concluded [23]. The study was open to up to 29 advanced NSCLC and 18 metastatic breast cancer patients but was only able to recruit 6 NSCLC and 1 breast cancer patient. The breast cancer patient showed no progression for two months before developing brain metastases. Two patients died soon after beginning treatment, with connections to DCA unknown. To additional patients experienced progression between the first treatment and the first follow-up examination. The final two NSCLC enrollees withdrew their consent due to worsening health conditions. The study was closed due to a lack of clinical benefit and the authors suggest that DCA is likely not a suitable monotherapy for NSCLC.

The results of these limited clinical trials show that while DCA has promise (as in the treatment of brain cancer), it doesn't appear to be the magic bullet it is sometimes perceived as. It is disappointing that the NSCLC/breast cancer trial received such a small enrollment prior to closing. With the noted difficulty in funding clinical trials of DCA, those receive funding are of utmost importance. The breast cancer arm only has one data point and the NSCLC arm only had two patients in which the treatment could be effectively analyzed. DCA may indeed be a useful therapeutic for some cancers, but we are in great need of determining what the biomarkers are that influence treatment outcome.

Vitamin D: Got Milk?

A lack of vitamin D is touted as a reason for cancer development by a number of websites. Vitamin D supplements as well as increased UV exposure through natural sunlight or UV lamps are claimed as effective measure for both preventing and treating cancer. The known science creates a case that is best classified as "inconclusive," with positive results seen in experimental settings but rather lackluster data coming from humans.

Vitamin D is synthesized in the skin as part of a photochemical reaction upon exposure to UVB light. This form of vitamin D, vitamin D_3, is then converted into other active forms of vitamin D once it reaches the liver. While it is well known that these molecules play a major role in calcium and phosphorus absorption [24], their role in cancer formation is not as recognized. The data backing up this role are mixed, with laboratory results showing a strong influence while clinical results do not.

The first connection between vitamin D and cancer was drawn in 1980, when Garland and Garland noticed that colon cancer rates were higher in states that had lower sun exposure [25]. Recent meta-analyses have shown that colon cancer risk is inversely related to vitamin D intake [26,27]. In contrast, meta-analyses examining vitamin D intake have shown mixed results in breast [28-30] and prostate cancer [31,32].

Animal studies have shown much clearer results. When mice are fed a diet low in vitamin D and calcium they develop colon cancer spontaneously [33], and APC mutant mice develop colon cancer faster when fed a vitamin D and calcium restricted diet [34]. Vitamin D receptor null mice develop breast cancer quicker than control mice when treated with dimethylbenzanthracene [35] and non-vitamin D agonists of the vitamin D receptor can block the growth of breast tumor xenografts [36]. Similar results have been seen in prostate [37,38] and skin cancers [39,40].

While it is clear that vitamin D has an effect on cancer, the mechanistic connection between them is not as obvious. Through its receptor, vitamin D controls the expression of a vast number of genes and some of these genes impact cancer growth in multiple ways. Most directly, vitamin D shows antiproliferative actions. This appears to be downregulation of Cyclins in addition to upegulation of endogenous Cdk inhibitors such as p27 and p21 [41,42]. Additionally, vitamin D downregulates Myc, Fos, and Jun [43] while inducing expression of TGFβ and its receptors [44].

Vitamin D also increases the rate of apoptosis through increasing pro-apoptotic factors such as Bax while decreasing anti-apoptotic factor Bcl and Bcl-XL [45]. Interestingly, the intracellular calcium influx caused by vitamin D preferentially activates caspases and calpains in cancer cells since normal cells are able to buffer the increased calcium through $CaBP_{28k}$, a protein that is only expressed in low levels in cancer [46]. Other relevant mechanisms that are influenced by vitamin D include an activation of DNA damage repair [47-49], inhibition of prostaglandin synthesis [50], reduced angiogenesis through blockage of VEGF production [51], and inhibition of metastasis through activation of inhibitors of matrix metalloproteinases and cathepsins [52].

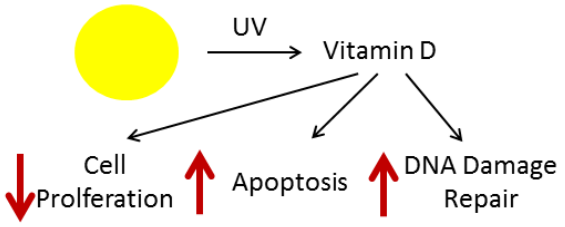

Figure 2. Anticancer effects of vitamin D. Ultraviolet light from the sun results in Vitamin D production in the skin. Through the Vitamin D receptor, this results in decreased cell proliferation, upregulation pro-apoptotic factors, and increased DNA damage repair capacity.

Dietary Changes: Watch what you eat.

In a recent review, Huebner et al. noted that changes in diet are the most common form of CAM used to treat cancer and it was due to the fact that patients often believed their cancer was caused by pollutants or a weakened immune system [53]. They therefore conclude that changing what they eat is the best way to either stop introducing toxins into their bodies or to take in more of the beneficial compounds (i.e. vitamins). As the benefits of these changes as well as their effects on the success of traditional treatments are very poorly understood, here we take a look at two of the most common dietary changes: fasting and the ketogenic diet. Others that have a significant following include the Gershon diet (large amounts of fruit and vegetable juices, high potassium, low sodium, and caffeine enemas) [54], the Gonzales regimen (ingestion of pancreatic proteolytic enzyme) [55,56], and consumptions of large amounts of raw food, among others.

Fasting: Feed a cold starve a tumor?

The American Cancer Society suggests cancer patients undergoing treatment should increase their calorie intake [57]. However, the undocumented health benefits of fasting, which may be done for a variety of reasons, have been touted for thousands of years. A large number of websites promote the practice of fasting as either a single treatment or in combination with traditional treatment. It is of course extremely important for oncologists to be aware of any dietary changes a patient may be implementing and to know what effects it may have on the patient. While there has not been a wealth of studies directly examining the role of fasting in cancer treatment, the physiological changes that the body undergoes during fasting have been extensively studied, allowing potential connections to be drawn. The physiological effects have been described as having three distinct phases: use of glycogen as the primary energy source, a switch to amino acid metabolism, and finally release of fatty acids from adipose tissue and subsequent metabolism (reviewed in [58]).

Being in a state of fasting induces survival mechanisms in normal cells. These include downregulation of the Ras and Tor pathways in yeast [59,60] and an increased d4E-BP in *Drosophila [61]*. Fasting is able to protect mice from oxidative stress induced by the chemotherapeutics etoposide [62] and doxorubicin [63]. Many of these effects are due to a dramatic decrease in the production of the pro-growth factor IGF-1 ([64]and [65] among many others), which may be caused by an increase in the IGF inhibitory protein, IGFBP-1 [66].

With only a prior discussion of these few effects of fasting (for a more in-depth review, see [67]), we can already see a number of ways in which fasting may be detrimental to cancer cells based on their fundamental differences from normal cells, the Hallmarks of Cancer [68]. First, due to the Warburg effect, in which cancer cells metabolize large amounts of glucose through glycolysis [69], the simple metabolic change of switching away from glucose as the primary energy source during fasting will deprive cancer cells of their required glucose intake while normal cells are able to utilize other pathways. As cancer cell growth is often driven by overactive pro-growth pathways, including IGF, Ras, and Tor, if a cancer cell has not become fully independent in its activation of these pathways, a fasting-induced reduction will slow their growth. However, as it is a Hallmark, this independence has generally been achieved in advanced tumors, though this may also lead to a clinical benefit of fasting. While normal cells slow their growth during fasting due to a downregulation of pro-growth factors and upregulation of anti-growth factors, cancer cells may continue their rapid proliferation due to their independence and their insensitivity to anti-growth factors, another Hallmark. This has been shown to lead to better chemotherapeutic and radiotherapeutic outcomes via protection of normal cells, thereby reducing side effects and allowing more aggressive dosing in mice [70] and humans [71]. A more thorough clinical trial is currently underway at the University of Southern California studying the effect of fasting on the side effects and treatment outcome on gemcitabine and cisplatin treatment (clinical trial NCT00936364).

It is important to stress that while there appears to be many ways in which fasting can benefit a cancer patient, much more work needs to be done. It is imperative that an oncologist be involved in any changes in dietary intake. Cancer treatment is notoriously rough on the body, and some patients may not be able to handle an additional insult as a result of fasting. The possibilities are certainly intriguing, however.

The ketogenic diet: Can bacon cure cancer?

The ketogenic diet, one in which individuals eat primarily fats along with the minimum required amount of protein and very few carbohydrates, has many of the same effects on the body as does fasting. The links are easy to make since both have very low consumption of carbohydrates, therefore lowering blood-glucose levels. The fundamental difference, however, is the addition of fats to the diet in the ketogenic regimen. Fats are broken down in the body into fatty acids and ketone bodies, both of which can serve as cellular energy sources. A high level of ketone bodies in the blood is termed ketosis. These ketone bodies may play an additional role in cancer treatment, having a cytostatic effect on cells in vitro through blockage of glucose uptake [72] and providing an energy source for normal cells that cannot be utilized by cancer cells [73].

Studies in mice have shown very interesting results. Initiation of a ketogenic diet prior to tumor implantation significantly reduces the rate of tumor growth [74], while initiation at the time of tumor implantation has no observable effect [74,75]. In more recent studies, higher levels of ketone bodies correlated with improved outcome, but only when the diet had also been restricted sufficiently to induce loss of body-weight [76,77], and the positive effects showed greater

correlation with decreased IGF-1 and blood-glucose levels than with ketone bodies [76].

Clinical trials in humans examining the ketogenic diet have not occurred until very recently. The first simply examined blood parameters and quality of life in advanced stage cancer patients, showing improvements in both [78]. A second treated two astrocytoma patients with a ketogenic diet, with one showing twelve-month progression-free survival [79]. Two clinical trials have shown anticancer activity of a ketogenic diet against glioblastoma [80,81] and a study administering a low carbohydrate diet has shown a correlation with decreased tumor growth and ketosis [82]. Multiple other clinical trials are currently underway.

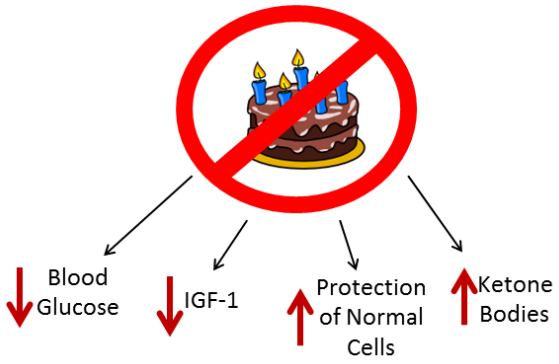

Figure 3. Affects of fasting and a ketogenic diet. Altered diet leads to lower blood glucose levels, a decrease in pro-growth factors including IGF-1, protection of normal cells toward genotoxic insults through growth inhibition, and an increase in circulating ketone bodies, which may have anti-cancer affects.

So far, the benefits of the ketogenic diet have been difficult to distinguish between that of fasting and the majority of its effects may simply be due to an underlying fasting state. However, the anticancer properties of ketone bodies will need to be further studied. While ketone bodies are also produced during the final stage of fasting when metabolism of body fat begins, the ketogenic diet is able to provide them in a more controlled manner and without the associated fatigue that occurs during fasting. This diet may provide a useful alternative to those that cannot handle the physiological stress of a complete fast.

Perspective

Cancer is an extremely complicated condition. It is foolish to believe that it can be "cured" through simple means, however, it is equally as foolish to ignore evidence pointing to the fact that these tactics may be able to provide some anticancer benefits when used along other, more traditional methods. While the promotion and use of complementary and alternative medicines has been occurring since long before the invention of the internet, computers now allow a much wider distribution of both medical knowledge and quackery. With the immense stress that cancer patients and their families must endure, these treatment methods, legitimate or illegitimate, will be used by a portion of the population. Therefore, it is imperative that we understand them, both those that work and those that don't. We owe it to our friends and families to do whatever possible to increase the chances of survival of every single person that is diagnosed with cancer and we, as scientists, must take that responsibility to heart.

References

1. Truant TL, Porcino AJ, Ross BC, Wong ME, Hilario CT (2013) Complementary and alternative medicine (CAM) use in advanced cancer: a systematic review. J Support Oncol 11: 105-113.

2. Vella S, Conti M, Tasso R, Cancedda R, Pagano A (2012) Dichloroacetate inhibits neuroblastoma growth by specifically acting against malignant undifferentiated cells. Int J Cancer 130: 1484-1493.
3. Sun RC, Fadia M, Dahlstrom JE, Parish CR, Board PG, et al. (2010) Reversal of the glycolytic phenotype by dichloroacetate inhibits metastatic breast cancer cell growth in vitro and in vivo. Breast Cancer Res Treat 120: 253-260.
4. Papandreou I, Goliasova T, Denko NC (2011) Anticancer drugs that target metabolism: Is dichloroacetate the new paradigm? Int J Cancer 128: 1001-1008.
5. Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, et al. (2010) Metabolic modulation of glioblastoma with dichloroacetate. Sci Transl Med 2: 31ra34.
6. Abdelmalak M, Lew A, Ramezani R, Shroads AL, Coats BS, et al. (2013) Long-term safety of dichloroacetate in congenital lactic acidosis. Mol Genet Metab 109: 139-143.
7. Stacpoole PW, Gilbert LR, Neiberger RE, Carney PR, Valenstein E, et al. (2008) Evaluation of long-term treatment of children with congenital lactic acidosis with dichloroacetate. Pediatrics 121: e1223-1228.
8. Stacpoole PW, Kerr DS, Barnes C, Bunch ST, Carney PR, et al. (2006) Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. Pediatrics 117: 1519-1531.
9. Michelakis ED, McMurtry MS, Wu XC, Dyck JR, Moudgil R, et al. (2002) Dichloroacetate, a metabolic modulator, prevents and reverses chronic hypoxic pulmonary hypertension in rats: role of increased expression and activity of voltage-gated potassium channels. Circulation 105: 244-250.
10. Stacpoole PW (1989) The pharmacology of dichloroacetate. Metabolism 38: 1124-1144.
11. Patel MS, Korotchkina LG (2006) Regulation of the pyruvate dehydrogenase complex. Biochem Soc Trans 34: 217-222.
12. Palsson-McDermott EM, O'Neill LA (2013) The Warburg effect then and now: from cancer to inflammatory diseases. Bioessays 35: 965-973.
13. Upadhyay M, Samal J, Kandpal M, Singh OV, Vivekanandan P (2013) The Warburg effect: insights from the past decade. Pharmacology and Therapeutics 137: 318-330.
14. Matsubara T, Diresta GR, Kakunaga S, Li D, Healey JH (2013) Additive Influence of Extracellular pH, Oxygen Tension, and Pressure on Invasiveness and Survival of Human Osteosarcoma Cells. Front Oncol 3: 199.
15. Deberardinis RJ, Sayed N, Ditsworth D, Thompson CB (2008) Brick by brick: metabolism and tumor cell growth. Current Opinion in Genetics and Development 18: 54-61.
16. Gillies LA, Kuwana T (2014) Apoptosis regulation at the mitochondrial outer membrane. J Cell Biochem 115: 632-640.
17. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, et al. (2007) A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer Cell 11: 37-51.
18. Wong JY, Huggins GS, Debidda M, Munshi NC, De Vivo I (2008) Dichloroacetate induces apoptosis in

endometrial cancer cells. Gynecol Oncol 109: 394-402.

19. Cao W, Yacoub S, Shiverick KT, Namiki K, Sakai Y, et al. (2008) Dichloroacetate (DCA) sensitizes both wild-type and over expressing Bcl-2 prostate cancer cells in vitro to radiation. Prostate 68: 1223-1231.
20. Xuan Y, Hur H, Ham IH, Yun J, Lee JY, et al. (2014) Dichloroacetate attenuates hypoxia-induced resistance to 5-fluorouracil in gastric cancer through the regulation of glucose metabolism. Exp Cell Res 321: 219-230.
21. Zwicker F, Kirsner A, Peschke P, Roeder F, Debus J, et al. (2013) Dichloroacetate induces tumor-specific radiosensitivity in vitro but attenuates radiation-induced tumor growth delay in vivo. Strahlenther Onkol 189: 684-692.
22. Shahrzad S, Lacombe K, Adamcic U, Minhas K, Coomber BL (2010) Sodium dichloroacetate (DCA) reduces apoptosis in colorectal tumor hypoxia. Cancer Lett 297: 75-83.
23. Garon EB, Christofk HR, Hosmer W, Britten CD, Bahng A, et al. (2014) Dichloroacetate should be considered with platinum-based chemotherapy in hypoxic tumors rather than as a single agent in advanced non-small cell lung cancer. J Cancer Res Clin Oncol 140: 443-452.
24. Zhang R, Naughton DP (2010) Vitamin D in health and disease: current perspectives. Nutr J 9: 65.
25. Garland CF, Garland FC (1980) Do sunlight and vitamin D reduce the likelihood of colon cancer? International Journal of Epidemiology 9: 227-231.
26. Ma Y, Zhang P, Wang F, Yang J, Liu Z, et al. (2011) Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. Journal of Clinical Oncology 29: 3775-3782.
27. Yin L, Grandi N, Raum E, Haug U, Arndt V, et al. (2011) Meta-analysis: Serum vitamin D and colorectal adenoma risk. Preventive Medicine 53: 10-16.
28. Rossi M, McLaughlin JK, Lagiou P, Bosetti C, Talamini R, et al. (2009) Vitamin D intake and breast cancer risk: a case-control study in Italy. Ann Oncol 20: 374-378.
29. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, et al. (2002) Intake of dairy products, calcium, and vitamin d and risk of breast cancer. J Natl Cancer Inst 94: 1301-1311.
30. Lin J, Manson JE, Lee IM, Cook NR, Buring JE, et al. (2007) Intakes of calcium and vitamin D and breast cancer risk in women. Arch Intern Med 167: 1050-1059.
31. Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, et al. (2008) Serum vitamin D concentration and prostate cancer risk: a nested case-control study. J Natl Cancer Inst 100: 796-804.
32. Gilbert R, Martin RM, Beynon R, Harris R, Savovic J, et al. (2011) Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. Cancer Causes Control 22: 319-340.
33. Newmark HL, Yang K, Kurihara N, Fan K, Augenlicht LH, et al. (2009) Western-style diet-induced colonic tumors and their modulation by calcium and vitamin D in C57Bl/6 mice: a preclinical model for human sporadic colon cancer. Carcinogenesis 30: 88-92.
34. Xu H, Posner GH, Stevenson M, Campbell FC (2010) Apc(MIN) modulation of vitamin D secosteroid

growth control. Carcinogenesis 31: 1434-1441.

35. Zinser GM, Welsh J (2004) Effect of Vitamin D3 receptor ablation on murine mammary gland development and tumorigenesis. J Steroid Biochem Mol Biol 89-90: 433-436.
36. VanWeelden K, Flanagan L, Binderup L, Tenniswood M, Welsh J (1998) Apoptotic regression of MCF-7 xenografts in nude mice treated with the vitamin D3 analog, EB1089. Endocrinology 139: 2102-2110.
37. Bhatia V, Saini MK, Shen X, Bi LX, Qiu S, et al. (2009) EB1089 inhibits the parathyroid hormone-related protein-enhanced bone metastasis and xenograft growth of human prostate cancer cells. Mol Cancer Ther 8: 1787-1798.
38. Mordan-McCombs S, Brown T, Wang WL, Gaupel AC, Welsh J, et al. (2010) Tumor progression in the LPB-Tag transgenic model of prostate cancer is altered by vitamin D receptor and serum testosterone status. J Steroid Biochem Mol Biol 121: 368-371.
39. Zinser GM, Sundberg JP, Welsh J (2002) Vitamin D(3) receptor ablation sensitizes skin to chemically induced tumorigenesis. Carcinogenesis 23: 2103-2109.
40. Ellison TI, Smith MK, Gilliam AC, MacDonald PN (2008) Inactivation of the vitamin D receptor enhances susceptibility of murine skin to UV-induced tumorigenesis. J Invest Dermatol 128: 2508-2517.
41. Hager G, Formanek M, Gedlicka C, Thurnher D, Knerer B, et al. (2001) 1,25(OH)2 vitamin D3 induces elevated expression of the cell cycle-regulating genes P21 and P27 in squamous carcinoma cell lines of the head and neck. Acta Otolaryngol 121: 103-109.
42. Palmer HG, Sanchez-Carbayo M, Ordonez-Moran P, Larriba MJ, Cordon-Cardo C, et al. (2003) Genetic signatures of differentiation induced by 1alpha,25-dihydroxyvitamin D3 in human colon cancer cells. Cancer Research 63: 7799-7806.
43. Meyer MB, Goetsch PD, Pike JW (2012) VDR/RXR and TCF4/beta-catenin cistromes in colonic cells of colorectal tumor origin: impact on c-FOS and c-MYC gene expression. Mol Endocrinol 26: 37-51.
44. Peehl DM, Shinghal R, Nonn L, Seto E, Krishnan AV, et al. (2004) Molecular activity of 1,25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray analysis. J Steroid Biochem Mol Biol 92: 131-141.
45. Kizildag S, Ates H (2010) Treatment of K562 cells with 1,25-dihydroxyvitamin D3 induces distinct alterations in the expression of apoptosis-related genes BCL2, BAX, BCLXL, and p21. Ann Hematol 89: 1-7.
46. Mathiasen IS, Sergeev IN, Bastholm L, Elling F, Norman AW, et al. (2002) Calcium and calpain as key mediators of apoptosis-like death induced by vitamin D compounds in breast cancer cells. J Biol Chem 277: 30738-30745.
47. Moll PR, Sander V, Frischauf AM, Richter K (2007) Expression profiling of vitamin D treated primary human keratinocytes. J Cell Biochem 100: 574-592.
48. Akutsu N, Lin R, Bastien Y, Bestawros A, Enepekides DJ, et al. (2001) Regulation of gene Expression by 1alpha,25-dihydroxyvitamin D3 and Its analog EB1089 under growth-inhibitory

conditions in squamous carcinoma Cells. Mol Endocrinol 15: 1127-1139.

49. Bao BY, Ting HJ, Hsu JW, Lee YF (2008) Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int J Cancer 122: 2699-2706.
50. Krishnan AV, Trump DL, Johnson CS, Feldman D (2010) The role of vitamin D in cancer prevention and treatment. Endocrinol Metab Clin North Am 39: 401-418, table of contents.
51. Ben-Shoshan M, Amir S, Dang DT, Dang LH, Weisman Y, et al. (2007) 1alpha,25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. Mol Cancer Ther 6: 1433-1439.
52. Bao BY, Yao J, Lee YF (2006) 1alpha, 25-dihydroxyvitamin D3 suppresses interleukin-8-mediated prostate cancer cell angiogenesis. Carcinogenesis 27: 1883-1893.
53. Huebner J, Marienfeld S, Abbenhardt C, Ulrich C, Muenstedt K, et al. (2014) Counseling patients on cancer diets: a review of the literature and recommendations for clinical practice. Anticancer Res 34: 39-48.
54. Gerson M (1978) The cure of advanced cancer by diet therapy: a summary of 30 years of clinical experimentation. Physiol Chem Phys 10: 449-464.
55. Chabot JA, Tsai WY, Fine RL, Chen C, Kumah CK, et al. (2010) Pancreatic proteolytic enzyme therapy compared with gemcitabine-based chemotherapy for the treatment of pancreatic cancer. J Clin Oncol 28: 2058-2063.
56. Gonzalez NJ, Isaacs LL (1999) Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. Nutr Cancer 33: 117-124.
57. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, et al. (2006) Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 56: 323-353.
58. Wang T, Hung CC, Randall DJ (2006) The comparative physiology of food deprivation: from feast to famine. Annu Rev Physiol 68: 223-251.
59. Thevelein JM, de Winde JH (1999) Novel sensing mechanisms and targets for the cAMP-protein kinase A pathway in the yeast Saccharomyces cerevisiae. Mol Microbiol 33: 904-918.
60. Wei M, Fabrizio P, Hu J, Ge H, Cheng C, et al. (2008) Life span extension by calorie restriction depends on Rim15 and transcription factors downstream of Ras/PKA, Tor, and Sch9. PLoS Genet 4: e13.
61. Tettweiler G, Miron M, Jenkins M, Sonenberg N, Lasko PF (2005) Starvation and oxidative stress resistance in Drosophila are mediated through the eIF4E-binding protein, d4E-BP. Genes Dev 19: 1840-1843.
62. Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, et al. (2008) Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci U S A 105: 8215-8220.
63. Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, et al. (2010) Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer Res 70: 1564-1572.

64. Moller N, Jorgensen JO (2009) Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 30: 152-177.
65. Norrelund H (2005) The metabolic role of growth hormone in humans with particular reference to fasting. Growth Horm IGF Res 15: 95-122.
66. Conover CA (1996) Regulation and physiological role of insulin-like growth factor binding proteins. Endocr J 43 Suppl: S43-48.
67. Lee C, Longo VD (2011) Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. Oncogene 30: 3305-3316.
68. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.
69. Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 324: 1029-1033.
70. Safdie F, Brandhorst S, Wei M, Wang W, Lee C, et al. (2012) Fasting enhances the response of glioma to chemo- and radiotherapy. PLoS One 7: e44603.
71. Chen KW, Turner FD (2004) A case study of simultaneous recovery from multiple physical symptoms with medical qigong therapy. J Altern Complement Med 10: 159-162.
72. Magee BA, Potezny N, Rofe AM, Conyers RA (1979) The inhibition of malignant cell growth by ketone bodies. Aust J Exp Biol Med Sci 57: 529-539.
73. Maurer GD, Brucker DP, Bahr O, Harter PN, Hattingen E, et al. (2011) Differential utilization of ketone bodies by neurons and glioma cell lines: a rationale for ketogenic diet as experimental glioma therapy. BMC Cancer 11: 315.
74. Van Alstyne EV, Beebe SP (1913) Diet Studies in transplantable Tumors : I. The Effect of non-carbohydrate Diet upon the Growth of transplantable Sarcoma in Rats. J Med Res 29: 217-232.
75. Fearon KC, Tisdale MJ, Preston T, Plumb JA, Calman KC (1985) Failure of systemic ketosis to control cachexia and the growth rate of the Walker 256 carcinosarcoma in rats. Br J Cancer 52: 87-92.
76. Seyfried TN, Sanderson TM, El-Abbadi MM, McGowan R, Mukherjee P (2003) Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. Br J Cancer 89: 1375-1382.
77. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, et al. (2007) The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutr Metab (Lond) 4: 5.
78. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kammerer U (2011) Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. Nutr Metab (Lond) 8: 54.
79. Nebeling LC, Miraldi F, Shurin SB, Lerner E (1995) Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. J Am Coll Nutr 14: 202-208.
80. Zuccoli G, Marcello N, Pisanello A, Servadei F, Vaccaro S, et al. (2010) Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report. Nutr Metab (Lond) 7: 33.
81. Rieger J BO, Hattingen E, Maurer G, Coy J, Weller M, Steinbach J. (2010) The

ERGO trial: A pilot study of a ketogenic diet in patients with recurrent glioblastoma. J Clin Oncol (Meting Abstracts) 28: e12532.

82. Fine EJ S-IC, Feinman RD, Herszkopf S, Romano M, Tomuta N,, Bontempo A SJ (2011) A pilot safety and feasibility trial of a reduced

carbohydrate diet in patients with advanced cancer. J Clin Oncol (Meting Abstracts) 29: e13573.