Vetting the Internet’s Favorite Cancer Cures
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Abstract
Modern medicine has developed many ways of treating cancer but, unfortunately, we are still a long way 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
singly 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.

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

![Figure 1. Dichloroacetate](image)
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 hypoxia because 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 D₃, 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 upregulation 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 CaBP₂₈k, 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.

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**


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