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Top Tips to Optimize Your Mitochondrial Health

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March 27, 2022

STORY AT-A-GLANCE

- Cancer is a metabolic disease, not a genetic one. The genetic mutations observed in some cancers are a downstream effect of defective energy metabolism in the mitochondria (the energy stations inside your cells)
- As long as your mitochondria remain healthy and functional, your chances of developing cancer are slim
- Ketogenic therapy calls for restricting net carbs to 50 grams per day and limiting protein; I recommend a limit of 1 gram of protein per kilogram of lean body mass. Fasting glucose needs to be below 70 mg/dL

This article was previously published December 15, 2019, and has been updated with new information.

If you want to avoid becoming a cancer statistic (and who doesn't?) you'd do well to familiarize yourself with the metabolic theory of cancer. In August 2016, we presented the Mercola.com Game Changer Award to Thomas Seyfried, Ph.D.,[1] a professor of biology at Boston College and a leading expert and researcher in the field of cancer metabolism and nutritional ketosis.

Following is a rerun of this popular and important article and interview with Seyfried, in which we discuss his book, "Cancer as a Metabolic Disease" — an important contribution to the field of how cancer starts and can be treated.

Each day, some 1,600 people die from cancer in the United States alone. Worldwide, we're looking at a death toll of about 21,000 people daily. So many of these deaths are unnecessary — they're preventable and treatable.

Seyfried is one of the pioneers in the application of nutritional ketosis for cancer, a therapy that stems from the work of Dr. Otto Warburg, who was undoubtedly one of the most brilliant biochemists of the 20th century. Warburg received the Nobel Prize in Physiology or Medicine in 1931 for the discovery of metabolism of malignant cells.

Besides being a medical doctor, Warburg held a Ph.D., and was personal friends with Albert Einstein and many of the most prominent scientists of his time. His life's mission was to find a cure for cancer, and he actually did. Unfortunately, few were able to appreciate the importance of his findings.

Seyfried has followed in Warburg's scientific footsteps, and is conducting important research to advance this science. He has in fact exceeded Warburg's initial supposition, shedding important light on the metabolic underpinnings of cancer.

Cancer as a Metabolic Disease

The traditionally held view or dogma is that cancer is a genetic disease, but what Warburg discovered is that cancer is really caused by a defect in the cellular energy metabolism of the cell, primarily related to the function of the mitochondria, which are the little power stations within each cell.

The mitochondria were not well understood in Warburg's time but, today, we have a much better understanding of how they work.

In my view, this information is the game changer that not only treats cancer but virtually every single disease known to man, because at the core of most serious ailments you find mitochondrial dysfunction. As noted by Seyfried:

> *"A dogma is considered irrefutable truth, and that cancer is a genetic disease is, no question, a dogma. The problem with dogma is that sometimes it blinds you*

to alternative views and sets up ideologies that are extremely difficult to change.

All of the major college textbooks talk about cancer as a genetic disease. The National Cancer Institute (NCI) website, the first thing they say is cancer is a genetic disease caused by mutations … [and] if cancer is a genetic disease, everything flows from that concept.

It permeates the pharmaceutical industry, academic industry and textbook industry — the entire knowledge base. There's very little discussion of alternative views to the genetic view. The argument now is that, yes, metabolic problems occur in cancer cells. No one denies that.

But these are all due to the genetic mutations. Therefore we must maintain ourselves on the established track that all of this metabolic stuff could be resolved if we just understood more about the genetic underpinning of the disease.

Now that would be well and good if it were true. But evidence is accumulating that the mutations we see that are the prime focus and the basis for the genetic theory are actually epiphenomenal.

They're downstream effects of this disturbance in the metabolism that Warburg originally defined back in the 1920s and '30s."

How the Metabolic View Alters Cancer Treatment

As Seyfried notes, the problem today is not that scientists and doctors cannot understand the science; it's that they cannot accept that this could be the truth behind the nature of the disease, because it changes how you approach treatment.

If defective mitochondria are responsible for the origin of cancer, and defective energy metabolism is responsible for the majority of the phenotypes, i.e., the observable characteristics of the disease that you see, then how do you treat the disease?

In my view, one of Seyfried's most magnificent contributions to this science was his compilation of research from independent and well-respected scientists within various disciplines, who conducted valuable experiments but had no clue how to interpret the results.

Seyfried put all of their work together, forming a strong scientific foundation for the theory that cancer is indeed a metabolic disease, not a genetic one, and that genetic mutations are a downstream effect of defective energy metabolism in the mitochondria.

> *"Those nuclear transfer experiments were always present in the literature. They were considered anomalies. They were not consistent with the view that cancer is a nuclear genetic disease … but the observation was not interpreted in light of [being] the origin of cancer.*
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> *I bundled all those observations together in a new light, looking at the conclusions of those experiments in light of whether the results would support a nuclear gene-based theory versus a mitochondrial metabolic theory …*
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> *It was just interpreting a series of experiments in light of the origin of the disease, and then asking what conclusion would these experiments support. Would it support the nuclear genetic theory of cancer, or would it support the mitochondrial metabolic theory of cancer?*
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> *In each of these cases, the results more strongly supported the metabolic theory of cancer than the nuclear genetic theory,"* Seyfried says.

What the Nuclear Transfer Experiments Showed

The nuclear transfer experiments in question basically involved transplanting the nuclei of a tumor cell into a healthy and normal cytoplasm (the material within a cell, excluding the cell nucleus), which include the mitochondria, the energy-generating organelle of the cell.

The hypothesis is that if cancer is nuclear-gene driven and the phenotype of cancer is dysregulated cell growth, meaning if genetic mutations are responsible for the observable characteristics of the disease, then those abnormal genes should be expressed in the new cytoplasm. But that's not what happened.

Again and again, what was observed was that when the nuclei of a cancer cell were transferred into a healthy cytoplasm, the new cytoplasm did NOT form cancer. It remained healthy and normal.

> *"What was interesting is that in many of these nuclear transfer experiments, the organisms aborted at certain periods of development. That abortion seems to be related to how many mutations were in the nucleus that was transferred,"* Seyfried says.
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> *"It was true that these cancer nuclei did contain mutations, but those mutations were not causing the hallmark feature of the disease, that is proliferation. Rather, they were causing abortion at some developmental point of the organism that had those nuclei … On the other hand, when the normal nucleus was transferred back into a cancer cytoplasm [which had defective mitochondria], either the cell died or it formed tumor cells."*

Additional evidence has been produced by Benny Kaipparettu, Ph.D., and colleagues at Baylor University. When they transplanted normal mitochondria (with its nuclei intact) into cancer cell cytoplasm, it caused the cells to stop growing abnormally. It downregulated the oncogenes that were alleged to be driving the tumor and made the cells grow normally again.

On the other hand, when they took the mitochondria from a tumor cell and moved it into a very slow-growing type of cancer cell, the cancer cells began growing very rapidly. As noted by Seyfried, "When you bundle all these experiments together, you come to the conclusion that nuclear mutations cannot be the drivers of the disease."

What About BRCA1 and Other Inherited Cancer Genes?

A common argument for the genetic theory is that cancer can be inherited; therefore it must have genetic underpinnings. Li-Fraumeni syndrome,[2] which raises your risk of developing cancer at a very young age, and BRCA1, which raises your breast cancer risk, are two examples.

> *"The answer is, yes, on the surface, that would appear to be true,"* Seyfried says. *"But as Warburg said, there are many secondary causes of cancer but there is only one primary cause, and that's damage to the respiration. So inherited mutations through the germ lines that cause cancer to affect the mitochondria, it is [still] the mitochondria that is the origin of cancer.*
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> *It just so happens that the defect is coming from an inherited gene rather than a chemical carcinogen, radiation, viral infection or an infection of some parasite or whatever, all of which damage respiration; all of which can cause cancer.*
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> *Clearly the origin of the disease is a disturbance of the respiratory capacity of that cell which then, if the cell is to survive, must upregulate genes necessary for fermentation. Many of those genes are the so-called oncogenes. The oncogenes are simply fulfilling a rescue event of that cell to function in a fermentation metabolism rather than an oxidative metabolism. We can downregulate oncogenes simply by putting in new respiration."*

If genetic mutations are not the primary cause of cancer but rather a secondary, downstream effect of dysfunctional cell respiration, why and how do mutations occur? As explained by Seyfried, once the cells' respiration is damaged, that damage then leads to a compensatory fermentation, which requires the upregulation of oncogenes (cancer genes).

Damaged respiration also produces large amounts of reactive oxygen species (ROS) and secondary free radicals that damage DNA proteins and lipids (fats inside your cellular membranes). The ROS also cause mutations in the nuclear genome. So the mutations are the result of defective respiration and subsequent exaggerated ROS production.

Why the War on Cancer Has Not Yet Been Won

At present, the cancer industry is focusing on the downstream effects of the problem, which is why the "war on cancer" has been such a miserable failure.

> *"Personalized medicines, checkpoint inhibitors, all of these kinds of therapies are basically looking at downstream effects of the disease,"* Seyfried says. *"Unfortunately, most of the cells in the tumor are all different from each other genetically.*
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> *You're not going to be able to target all of the different cells using these kinds of approaches. Even though you may get success for a few months, or even a year in some people, the majority of people will not respond effectively to these kinds of therapies for the most part."*

Why Being an Efficient Fat Burner Is so Important

The ROS also target the actual mitochondria themselves, where respiration occurs, which brings us to a very important point. ROS are mostly generated through the co-enzyme Q couple in the electron transport chain. Both glucose and fatty acids produce FADH2, which can generate ROS.

In contrast, fat-derived ketone bodies produce only NADH, which increases the redox span of the co-enzyme Q couple and reduces production of ROS. Hence, ketone bodies are considered a more "clean" fuel than is either glucose or fatty acids Today, most people are burning glucose as their primary fuel, thanks to an overabundance of sugar and processed grains in the diet and a deficiency in healthy fats.

If you have less ROS being generated in the mitochondria, you end up with less mitochondrial damage and less DNA damage. So not only is switching the fuel you're feeding your body the key component of cancer treatment, but in my view it's the primary way that you prevent cancer from occurring in the first place.

"I think that's an important point. One of the things that trigger cancer is inflammation. We have inflammation. Chronic high levels of blood sugar create inflammation. This you see in a lot of situations. Glucose itself is not carcinogenic, but elevated dysregulated glucose metabolism can lead to inflammation, and can cause a number of other disturbances in the overall metabolism of the body," Seyfried says.

"If you fast, if you stop eating, your blood sugar goes down. Your insulin levels go down. The body starts to metabolize fat for energy. But the fatty acids themselves are only one component. The major components of course are the ketone bodies … They are water-soluble fat products. They readily enter cells and they're metabolized to acetyl-CoA through a series of steps.

These steps generate nicotinamide adenine dinucleotide (NADH), which is a reducing equivalent. But they also keep the coenzyme Q couple in an oxidized state. This is very important because it's that coenzyme Q couple where ROS are in fact generated in the first place …

Ketones are clean fuel only in the sense that they suppress the formation of ROS, especially when blood sugar levels are low, because if you have very high ketones AND high blood sugar, you have ketoacidosis, which is a life-threatening event."

Do Not Confuse Nutritional Ketosis With Ketoacidosis

Nutritional ketosis should NOT be confused with diabetic ketoacidosis (DKA), which is not a concern unless you have Type 1 diabetes. It's rare for a person with normal physiology to elevate their ketones above 7 or 8 millimole (mmol). If you have DKA, your ketones will be about 20 mmol. Additionally, your blood sugars will be very high, while in nutritional ketosis blood sugars are very low. These are clearly two entirely different states.

And whereas ketoacidosis can be life threatening, nutritional ketosis is a healthy state that helps you maintain maximum energy efficiency and reduces ROS production in your body. As noted by Seyfried, "Mitochondria actually get very healthy when ketones are metabolized as opposed to some of the other fuels, especially glucose."

For the last few decades, most natural health enthusiasts would attempt to circumvent the ROS challenge by taking antioxidants, either through foods high in polyphenols and other natural antioxidants, or supplements. I now believe this is a fatally flawed strategy that has significant drawbacks.

Rather than trying to quell the ROS after they're produced, it's far more effective to address the ROS generation at its source, which is the fuel your body is primarily burning for energy. Change the fuel, from sugar to fat, and you will generate fewer ROS.

Ketones Prevent Dysregulated ROS Production

It's not that ketones don't generate any ROS; they do, just not as much. And this brings us to yet another crucial point. ROS are not merely agents of destruction; they're also powerful signaling molecules. If you suppress them indiscriminately, you'll create biological dysfunction.

So you do not want to eliminate them. You just want to control them to optimal levels so all the signaling can occur without damage. That's what happens with ketones. When your body is burning ketones as its primary fuel, you more or less ensure that you're in an ideal therapeutic window with regard to ROS generation, so you have neither too much nor too little ROS.

> *"There's no question about that. It's what we call a homeostatic state,"* Seyfried notes.*"Ketones prevent dysregulated ROS production … You're allowing your body to remain healthier for a longer period of time. That's basically what we're doing here … Cancer is accelerated entropy. It's a total disorganization of the homeostatic parameters within cells and outside the cells in the morphogenetic field and in the entire body itself.*

Cancer patients have all kinds of disturbances in systemic homeostasis. It's not just in the cells … When the body has cancer there are a number of ramifications that take place throughout the body.

We're producing more acidity. There are a lot of responses in the part of hormones and signaling cascades throughout the body as a result of this disease. One has to treat cancer as a systemic [disease]. The whole body has to be treated but in a nontoxic way."

Indeed, toxicity is one of the biggest failures of current treatment protocols for cancer. The majority of treatments for cancer are extremely toxic, which further exacerbates the problem. Many cancer recurrences are likely due to the initial treatment.

On the other hand, when you view cancer as a metabolic disease, you can target and manage the disease without creating systemic toxicity. As explained by Seyfried, you do this by targeting the fuels the cancer cells are using, primarily glucose and glutamine.

"What we have to recognize … is that if cancer is a mitochondrial metabolic disease and you get cancer because of mitochondrial failure in certain populations of cells and certain tissues, if you prevent your mitochondria from entering into this dysfunctional state … [then] the probability of getting cancer is going to be significantly reduced.

To what percent? I would say a minimum of 80%. Cancer is probably, as I said in my book, one of the most manageable diseases that we know of …

The problem is that many people don't want [to take the preventive steps to avoid cancer]. They're like, 'I have to therapeutically fast for a week? Oh, I'm not going to. Give me a break' … An effective prevention is to eat less and move more. A lot of people don't want to do that … Once you realize what cancer is, that it's a metabolic disease, you can take charge of those kinds of things. In other words, getting cancer is not God's will. It's not bad luck."

Most Disease Is Rooted in Mitochondrial Dysfunction

Cancer is not the only outcome when mitochondrial respiration goes awry. This kind of dysfunction also plays a role in neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS).

It's also at play in seizure disorders and in diabetes, obesity, hypertension and hypercholesterolemia. Most of the major diseases we're currently treating with harsh and toxic drugs can potentially be solved with proper nutritional intervention that addresses your choice of cellular fuels.

How exactly do you do that? According to Seyfried, in order to achieve nutritional ketosis, you need to reduce net carbohydrates (total carbs minus fiber) to less than 100 grams, probably less than 50 grams. I have a slightly different view on this, which I'll expound on in the next section.

You also need to reduce your amino acid content. Glutamine is the most common amino acid in proteins, and besides glucose, cancer cells can use glutamine for energy and growth as well. The combination of both glucose and glutamine creates a really "supercharged system," Seyfried notes.

In order to lower glutamine, you have to eat less protein. Also, there's a threshold for amino acids, above which you will simply stimulate the mTOR pathway, which in conjunction with insulin may wield a more powerful influence on mitochondrial dysfunction and mitochondrial biogenesis than insulin alone.

How to Assess the Health of Your Mitochondria

How can you assess the health of your mitochondria? There are a couple of ways of doing this. Seyfried has published a paper on the glucose ketone index calculator[3] (GKIC) in an open access journal, which can be accessed by anyone. You can use that calculator to assess the health and vitality of your mitochondria.

The GKIC looks at your glucose to ketone ratio. Ketones must be measured by blood, not urine, and your glucose must be entered in mmol, not in milligrams per deciliter

(mg/dL). "When you have a glucose ratio of 1.0 or below, you know your mitochondria are in a very healthy zone," Seyfried says.

Now, getting down to a 1.0 is quite difficult. I'm typically between 2 and 3, and my diet is about 80% healthy fats with minimal net carbs. You may need to do a complete fast in order to get that low. However, you don't need to remain in that ultralow zone for very long. On the other hand, if you have cancer, you'll want to hit that mark as much as possible.

> *"You do a water fast for about three to four days, then you can take some exogenous ketones, and you can get your blood sugars way down,"* Seyfried says. *"To prevent cancer, you don't have to stay there [longer than] four or five days every six months or something like this. It's just a guide,"* Seyfried says.
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> *"Some people can get into these zones very quickly and very easily. Other people really struggle. All of this is a biomarker gauge. We've done some interesting linear regression analysis on survivability of mice with cancer using the GKIs, the independent variable, the glucose-ketone index.*
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> *There definitely is statistical relationship on how long you can keep your GKI [and] how long you can survive with a very aggressive cancer. Clearly, it's just one biomarker system that allows individuals to help battle their own cancer."*

Therapeutic Ketosis Made Simpler With a Nutrient Tracker

That strategy will likely be too extreme for most folks, unless you're faced with death or otherwise highly motivated. Rather than doing lengthy water fasting, I believe a more user-friendly strategy would be to restrict your net carbs below 50 grams per day and your protein to below 1 gram per kilogram of lean body mass. Most people eat a lot more net carbs and protein than that.

To make sure you're actually meeting these targets you need an analytical tool to do a detailed nutritional analysis of what you're eating. Otherwise, you really don't know how much fat, carbs and protein you're getting. This was my motivation for working with the

developer of www.Cronometer.com/mercola, an online nutrient tracker, to create a Mercola version of the software programmed specifically for nutritional ketosis.

You can sign up and use Cronometer.com/Mercola for free. This software will make all the calculations for you, based on the parameters you enter, such as your height, weight, body fat percentage and waist circumference. You can also enter and track various biomarkers, such as fasting glucose, which is an essential measurement.

You really must keep tabs on your fasting blood sugar. Ideally, you would measure it twice a day; first thing in the morning and right before you go to bed. You want to get your blood sugar below 70 mg/dL, ideally somewhere around 60.

If your fasting blood sugar is significantly higher in the morning than in the afternoon, it's likely due to glucogenesis, which is a sign you're not getting enough protein. You need a certain amount of amino acids or else your body will start to metabolize lean body tissue to generate them. In that process, the excess gets shuttled to your liver, which is what generates the extra glucose (hence the elevated reading in the absence of food).

More Information

If you really want to dig deep into the details of therapeutic ketosis, read Seyfried's book, "Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer." If you want to start with a shorter treatise, you can read through his paper, "Cancer as a Metabolic Disease: Implications for Novel Therapeutics," published in the journal Carcinogenesis in 2014,[4] or his 2015 paper in the journal Frontiers.

Hopefully, we've inspired you to consider the nutritional roots of cancer and other chronic disease. I can promise you will hear a lot more about this in the months and years to come, as I am convinced addressing mitochondrial dysfunction is the real key to solving most of our current health problems.

The good news is that optimizing mitochondrial function can be effectively accomplished through diet and lifestyle strategies like exercise. No costly drugs or

invasive procedures required.

And, while we still have a long way to go, more doctors are starting to pay attention. "This is the tipping point," Seyfried says. "Many physicians are coming on board. I think things are going to start changing for the best and for the success of people."

Too many people have died and continue to die needlessly. It's time to get back on the right track. It's going to require a lot of education, but the effort is absolutely worth it. The information about how to prevent cancer and other chronic illness already exists. It's just a matter of applying it.

Sources and References

- [1] Thomas Seyfried Bio
- [2] NIH.gov Li-Fraumeni Syndrome
- [3] Nutrition and Metabolism 2015;12:12
- [4] Carcinogenesis. 2014 Mar; 35(3): 515–527