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Review Article

Is Cancer the Overflow of the Adipose Tissue?

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Abstract

In "Cancer- the Pragmatic Switch to Combat Metabolic Syndrome," the concept of cancer being a bidirectional switch that the body can use to combat metabolic syndrome was proposed [1]. The paper "Does Cancer Have a Benefit? - Your Immune System Might Think So" states that cancer has been around for 240 million years. Cancer must have a purpose; otherwise, it would have been deselected [16]. This paper shows how Cancer the Pragmatic Switch is under the control of the Adipose Tissue. When the adipose tissue is overwhelmed for a long period, it can call upon "Cancer the Pragmatic Switch to Combat Metabolic Syndrome," which converts large quantities of glucose into lactate before the organs are damaged. Cancer cells can consume between 10 and 100 times the amount of glucose as normal cells without using toxic oxygen and producing nontoxic lactate. It is hypothesized that Cancer comes from a stem cell that is turned on when the adipose tissue is overwhelmed. Tumorigenesis is supported by adipocytes. Adipose tissue and cancer have many similar qualities: Ignored by the immune system, the ability to encourage angiogenesis [2]. Both cancer and white adipose tissue apoptosis in a low-glucose environment. Undiagnosed prostate, breast, and thyroid cancer are found next to the adipose tissue in autopsies of people who died from something else. This explains the following hallmarks of cancer: early metastasizing and being able to mask the immune system by utilizing CD47 and PDL1 proteins. Cancer's main tumor secretes tumor suppressors to keep secondary cancer tumors from getting out of control, and cancer, for the most part, is not contagious. We humans were designed to live in a calorie-scarce environment. Before industrialized food supplies existed, the cycle of life included frequent starvation, which would cause adipose tissue and cancer to apoptosis and disappear in the wild.

Keywords: cancer; cancer pragmatic switch; cancer adipose tissue; cancer adipose tissue bloom; adipose tissue and cancer tumorigenesis; cancer stem cell and adipose tissue

Introduction

Blooms occur when the organism is ripe for growth. It occurs when nutrients and energy are abundant. Perhaps cancer is to adipose tissue, which is what an algae bloom is to a lake: excessive nutrients and an undesirable outcome. Up until industrial food supplies existed, all humans lived with food scarcity. It was incumbent upon the body to hoard excessive amounts of calories and to store them in the adipose tissue for leaner times. This ancient evolutionary pressure to overeat possibly explains why the adipose tissue has a 20-minute delay in signaling feeling full to the brain, which shows we are designed to overeat. Further, your taste buds are particularly sensitive to sweets, salt, and fat, all scarce in the wild, which contribute to overeating.

Hypothesis:

The road to cancer starts when too many lipids are overflowing for a prolonged period, causing triglyceride levels to rise. The body deals with this by expanding the adipose tissue. If the body cannot expand the adipose tissue any further and the glucose and lipids are overflowing even after being stored in the heart, liver, and any available spot the body can store them. Then, the body has a dysfunctional white adipose tissue known as dyslipidemia. It is hypothesized that the reason it becomes dysfunctional is that the body cannot support the level of adipose tissue, so a hypoxic state exists, which promotes necrosis and attracts the macrophages to prevent a sepsis condition from occurring. This has the benefit of the excessive energy that is stored in these adipocytes being destroyed and cleansed from the body with the macrophage. The cost is inflammation and susceptibility to disease. It is hypothesized that If this inflammation condition goes on too long the body might be forced to make a harsh decision of Cancer the "Pragmatic Switch to Combat Metabolic Syndrome" [1]. As the body gets overwhelmed with Metabolic Syndrome**,** higher-capacity conversion cells are needed to convert toxic glucose and lipids to nontoxic lactate. It is hypothesized that Cancer comes from a stem cell that is turned on when the adipose tissue is overwhelmed. It is hypothesized that Cancer stem cells switch on and off as the body needs these high-capacity cells to process pockets of lipid and glucose spillover. The cancer cells in the chest cavity are located near the adipose tissue and use the white adipose tissue for fuel [22]. As a reminder, cancer cells can consume between 10 and 100 times the amount of glucose as normal cells without using toxic oxygen and producing nontoxic lactate. Further, cancer cells will apoptosis when placed in a low glucose environment. It is hypothesized that the reason for the existence of cancer cells is to consume large amounts of lipids to protect the organs. [2]. The key to an individual's risk for cancer is how the body deals with the excessive lipid overflow and the threshold to start the cancer stem cells concerning the excessive amounts of calories. Further, It is hypothesized the reason certain cancer drugs become ineffective is that the body is modulating the genome to prevent cancer from being ineffective, just like as people take drugs have to increase the dosage to gain the desired effect. The body compensates by

maintaining homeostasis. Further, chemicals, radiation, and genetics all can play a part in starting the process sooner or with a lower threshold.

Summary:

The adipocytes and immune cells within the adipose tissue synthesize and secrete proteins known as adipokines. These proteins regulate appetite, energy expenditure, insulin sensitivity, oxidative capacity, and lipid uptake in the non-adipose tissues such as the heart, liver, B-cells, and skeletal muscle [3]. The adipose tissue is the body's storage facility for future energy and is the controlling regulator for the brain to shut off food consumption. Adipose tissue is the controlling endocrine organ for metabolic health. If adipose tissue can absorb the extra glucose, then cancer, "the Pragmatic Switch," is not needed. If pockets of high glucose exist and the adipose tissue is overwhelmed for a long period, it can call upon cancer to convert large quantities of glucose or lipids quickly before they destroy the organ. Then, when lean times occur, the immune system or the low glucose environment will cause the cancer cell to undergo apoptosis or return to a normal cell when exposed to a healthy environment [27,28]. It is, therefore, logical that cancer cells would develop near adipose tissue. Adipocytes support tumorigenesis. Adipose tissue and cancer have many similar qualities: The immune system ignores both cancer and adipose tissue. Both can encourage angiogenesis, and both are reduced in a low-glucose environment. It is hypothesized that adipose tissue and cancer are linked. Researchers are finding undiagnosed prostate, breast, and thyroid cancer in autopsies of people who died from something else. 80% of the people diagnosed with pancreatic cancer have diabetes. Even glioblastoma, the deadliest form of brain cancer, is more aggressive in diabetic rather than nondiabetic patients [25]. In the case of melanoma, obesity, and diabetes are risk factors. [31]. People who cannot expand their subcutaneous adipose tissue are at greater risk in the short term. People who can expand their subcutaneous adipose tissue can eventually overrun their ability of the adipose tissue to deal with the issue [2]. It is further hypothesized that small undiagnosed cancer cells will be found all over the body and are just part of the body's way of dealing with excessive glucose. This explains the following hallmarks of cancer: early metastasizing and being able to mask the immune system by utilizing CD47 and PDL1 proteins [19] [20]. Further, cancer cannot tolerate a low-glucose environment. Cancer's main tumor secretes tumor suppressors to keep secondary cancer tumors from getting out of control, and cancer, for most parts, is not contagious [30]. We humans were designed to live in a calorie-scarce environment. Before industrialized food supplies with year-round food, the cycle of life was as follows: Many calories during the spring and summer, followed by fewer calories in the fall and starvation in winter. As starvation in the winter occurs, white adipose tissue is consumed by brown for thermogenesis. Cancer dies off because it cannot tolerate a low-glucose environment. It all fits together in ways we are just beginning to understand [24][25].

Background:

Characteristics of Adipose Tissue:

Adipose tissue is an important endocrine organ within the body. It is capable of not only providing energy and heat but also regulating metabolic homeostasis. Furthermore, adipocytes appear to be a major component in the tumor microenvironment. Adipose tissue can grow through two mechanisms: hyperplasia and hypertrophy. In hyperplasia, the number of cells increases; in hypertrophy, each cell expands to absorb larger amounts of lipids or energy. The adipocytes and immune cells contained within the adipose tissue synthesize and secrete proteins known as adipokines. These proteins act to regulate appetite, energy expenditure, insulin sensitivity, oxidative capacity, and lipid uptake in the non-adipose tissues such as the heart, liver, B-cells, and skeletal muscle [3]. The adipose tissue is the body's storage facility for future energy and is the controlling regulator to the brain to shut off the consumption of food.

White Adipose Tissue and Brown:

In mammals, white adipose tissue (WAT) stores and releases lipids, whereas brown adipose tissue (BAT) oxidizes lipids to fuel thermogenesis. In obese individuals, WAT undergoes profound changes; it expands, becomes dysfunctional, and develops a low-grade inflammatory state. It is hypothesized that the reason it becomes dysfunctional is the body cannot support the level of adipose tissue, so a hypoxic state exists, which promotes necrosis and, therefore, attracts the macrophages to prevent a sepsis condition from occurring. This has the benefit of the excessive energy that is stored in these adipocytes being destroyed and cleansed from the body. The cost is chronic inflammation and susceptibility to disease and infection. A person is slow to heal and takes a long time to recover from infection because the macrophages are drawn to excessive adipose tissue and are not available to other parts of the body. High-cholesterol mice succumbed to viral infection at higher rates than normal mice with the same viral load. [29] Importantly, BAT content and activity decline in obese subjects, mainly as a result of the conversion of brown adipocytes to white-like unilocular cells. BAT "whitening" is induced by multiple factors, including high ambient temperature, leptin receptor deficiency, β-adrenergic signaling impairment, and lipase deficiency, each of which can induce macrophage infiltration, brown adipocyte death, and crown-like structure formation [15].

Metabolic Syndrome:

When glucose levels are high, the excess acetyl CoA generated by glycolysis can be converted into fatty acids, triglycerides, cholesterol, steroids, and bile salts. The process is called lipogenesis and occurs in the cytoplasm of the adipose tissue and the hepatocytes in the liver. The high-calorie intake eventually causes the blood triglycerides to be elevated as the body becomes insulin-resistant. The body reacts either by an increase in adipocytes adipose tissue (hyperplasia), adipocyte enlargement (hypertrophy), or both to allow safe storage of lipids.[22] [32] High blood pressure occurs because the subcutaneous fat constricts the blood vessels, and the additional load of the adipose tissue requires a larger amount of tissue to be fed from the heart. Increased adipose tissue causes obesity. When the maximum capacity of the adipose tissue's ability for expansion is reached, lipids spill from the adipocyte, which causes an increase in the circulation of free fatty acid levels. Excessive lipid accumulation occurs in the tissues such as the liver, skeletal muscle, B-cells, and the heart, which is harmful. This results in high blood triglycerides, low levels of HDL cholesterol, and insulin resistance "Under chronic calorie excess, energy is converted into fat through de-Novo lipogenesis in the liver and is transported via lipoproteins to adipose tissue for storage. In the absence of sufficient functional subcutaneous adipose tissue, fat accumulates in other adipose deposits and in lean tissues, leading to cellular stress, inflammation, and insulin resistance" [2]. The other danger of this condition is the susceptibility to various types of infection. Lipids are needed for virus reproduction. If excessive lipids are floating around a viral infection becomes more dangerous. Bacterial infections also become more dangerous since the macrophages are drawn to the white adipose tissue to combat sepsis so they are not available in other parts of the body to fight infiltration of bacteria [25].

Current Model for Cancer:

The current model for cancer says that the cell's DNA has mutated, causing uncontrolled growth, angiogenesis, and immunosuppression. Most cells in our body utilize oxidative phosphorylation of glucose in mitochondria to produce energy. However, many cancer cells feature an altered metabolism with dramatically increased uptake of glucose and glycolysis of glucose into lactate, even in the presence of abundant oxygen (Warburg effect). Suggesting that altered cancer metabolism plays a critical role in tumorigenesis [13].

Characteristics of Cancer:

In contrast to normal cells, cancer cells cannot tolerate a low-glucose environment. Cancer cells utilize sophisticated masking mechanisms to evade the immune system. The expression of CD47 protein and PDL1 is common in many cancers. The CD47 blinds the macrophage, and the PDL1 blinds the T-cells to the presence of cancer [19] [20]. Also, cancers have been found in ancient species. Why would the body tolerate this for 240 million years or longer unless there was a benefit? [16]. Cancer cells placed in a healthy environment can revert to normal. For example, studies showed that transplantation of cancer cells into an embryonic tissue environment caused cancer cells to adopt non-cancerous phenotypes and

normal control of proliferation was re-established [27] [28]. If the DNA is damaged, how is it possible for the cell to revert to normal proliferation when placed in a healthy environment? The point of this series of papers is to suggest it's the environment that causes a "Pragmatic Switch" to be turned on and cellular DNA damage increases the sensitivity of the switch. Cancer has the purpose of turning excessive glucose into lactate without oxygen. The cancer cell can convert 10-100 times the amount of toxic glucose to nontoxic lactate as a normal cell. Cancer not counting virus-induced cancers is not contagious [1].

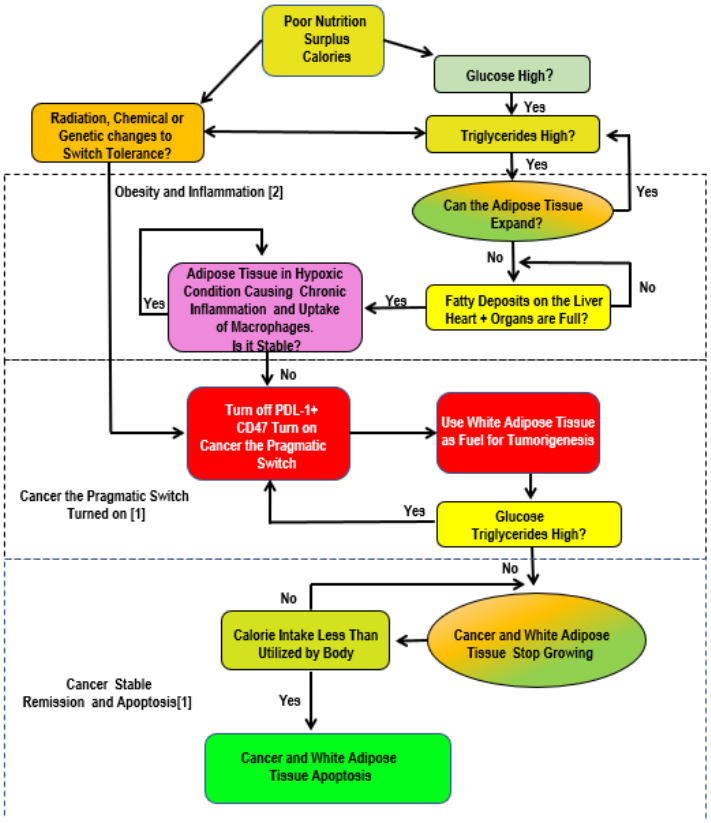

Figure 1: The switch theory of cancer is defined as a logic diagram. Obesity and associated insulin resistance causing hyperglycemia and hyperlipidemia or damage from Genetics, Infection, Chemicals, and radiation initiate a forward switch that leads to chronic inflammation. This inflammation promotes cancer growth. Dietary improvements in metabolic health will trigger a reverse switch, reducing or resolving chronic inflammation and stunting cancer growth and/or lead to tumor regression. [1] [2] See footnotes.

Problems with the Existing Cancer Model:

1. Uncontrolled growth, angiogenesis, and immunosuppression seem to occur simultaneously. This is inconsistent with a random hit on the DNA. If it was random the 1st hit would be uncontrolled growth because the tumor suppressor gene was turned off. Three key random events would have to occur simultaneously for it to pass the body's defense. The development of cancer seems to be well organized for a single stem cell located near adipose tissue. Perhaps the DNA damage enables the "Pragmatic Switch" to be turned on earlier.
2. Cancer's main tumor secretes tumor suppressor hormones. This is evident when surgeons attempt to remove the main tumor and other secondary tumors sprout up. Why would this occur unless the body is trying to limit cancer from getting out of control?
3. Non-viral-induced Cancer is not contagious.
4. A cancer cell that is placed in a healthy environment can revert to a normal cell [27,28].
5. Cancer found in the chest cavity always chooses a metabolism that is adapted to hypoxic conditions by utilizing glycolysis, and not oxidative phosphorylation, to produce energy. If cancer were a random occurrence, there would be some distribution in different types of metabolism.
6. Cancer cannot survive in a low-glucose environment. This again is too logical for a cell that is special to consume large quantities of glucose and produce lactate. The body would want cancer cells to die off when the emergency was passed.
7. Cancer has been in the genome for 240 million years in various species. One would think it would have been deselected by now unless it had the purpose of being the "Pragmatic Switch" [17].

Adipose Tissue and Cancer Tumorigenesis:

In Neiman's brilliant paper "Adipose Tissue and Adipocytes Supports Tumorigenesis and Metastasis" [22] the following is stated: "Many tumor types (gastric, breast, colon, renal, and ovarian) grow in the anatomical vicinity of adipose tissue. During their interaction with cancer cells, adipocytes dedifferentiate into pre-adipocytes or are reprogrammed into cancer-associated adipocytes (CAA)". The abundant availability of lipids from adipocytes in the tumor microenvironment supports tumor genesis [22]. The evidence supports a model in which cancer cells switch on near adipocytes, seizing metabolites such as ketone bodies, fatty acids, pyruvate, and lactate from stromal adipocytes [7]. This means the cancer cell is using adipocytes for energy, and there is intelligence and coordination. This article confirms the "Pragmatic Switch Theory of Cancer". It is not reprogramming. It's turning on a switch. The switch already existed, and it was signaled to turn on by the overflow from the adipose tissue. To summarize, cancer grows near adipose tissue. Tumorigenesis is supported by adipocytes. Adipose tissue and cancer have many similar qualities: The immune system ignores both cancer and adipose tissue. Both are capable of encouraging angiogenesis, and both are reduced in a low-glucose environment.[21] Pyruvate is a 2-oxo monocarboxylic acid anion that is the conjugate base of pyruvic acid, which is an important metabolic product for energy-producing biochemical pathways. Pyruvate is the final product of glycolysis and, when hypoxic conditions arise, can be metabolized anaerobically to form lactate. Lactate is non-toxic, unlike glucose [23].

When glucose levels are high, healthy stem cell production and angiogenesis go down, and the immune system is degraded. Why would the immune system be degraded when there is abundant energy unless a degraded immune system is required for cancer to grow? Cancer blooms with its angiogenesis and cancer uses the CD47 and PDL1 to mask its existence from the immune system [19] [20]. Systems working in concert are rarely random. It is proposed that a new cancer-related cycle of life. In the spring and summer, there are abundant calories. The number of calories available in the fall drops. Cancer cannot survive in a low-calorie, low-glucose environment; it will apoptosis or turn back to normal. In a calorie-limited, low-glucose environment, the normal cell can go into starvation mode. Interestingly, people who try to lose weight through starvation frequently gain more weight as the body adjusts to the low-calorie environment. [18]. It is hypothesized that It would be logical for Cancers to occur in areas of high glucose concentrations. Cancer found in the chest cavity always chooses a metabolism that is adapted to hypoxic conditions by utilizing glycolysis. The hypoxic conditions imply poor blood flow, causing toxic glucose to exist in an organ. This would explain how a thin person like Audry Hepburn would die of intestinal cancer. She may have had HNF4A a precursor to diabetes brought on because of starvation during the war. Or Steve Jobs would die of pancreatic cancer and have a form of child diabetes. Poor circulation would result in pockets of high blood glucose and therefore could be the cause of cancer in the organs. This explains the paradox of an obese person who does not get cancer and a lean person who does. Adipose tissue is our energy storage facility for the winter or lean periods [2].

Cancer Appears in Many People:

Undiagnosed cancers were found in the Thyroid, Breast, and Prostate glands of people who died of something else [9][10][11]. These cancers were found near the adipose tissue. This is consistent with the above hypothesis that cancer is a “Pragmatic Switch” that is turned on and off as the body needs to deal with excessive glucose/triglycerides and lipids. As we age, we tend to fall into metabolic syndrome. Age-related changes in mitochondria are associated with a decline in mitochondrial function. With advanced age, mitochondrial DNA volume, integrity, and functionality decrease due to the accumulation of oxidative damage [12]. Individuals who are of normal weight can be at high risk of metabolic syndrome if they accumulate fat in normally lean tissues such as the liver, heart, and skeletal muscle. On the other hand, an obese individual can be at lower risk of metabolic syndrome if they can expand their subcutaneous adipose tissue, especially in the gluteal-femoral area, and therefore protect the organs. This explains the paradox of an obese person who does not get cancer and a lean person who does [2]. “Cancer is a Pragmatic Switch” to deal with excessive glucose and lipids that spill over that the adipose tissue cannot deal with effectively [1]. It is hypothesized that when the adipose tissue is overwhelmed, the cancer switch is turned on to prevent the organs from being damaged. It is further hypothesized that when surplus glucose is not present the adipose tissue signals to the cancer cell to either apoptosis or revert to normal. These two hypotheses explain why the immune system is degraded in a high glucose environment and why people with metabolic syndrome are so susceptible to cancer and viral diseases such as COVID.

Adipose Tissue and Cancer:

People tolerate excessive glucose differently**.** Some morbidly obese individuals maintain normal glucose tolerance, whereas some mildly overweight individuals become severely insulin resistant. When the maximum capacity of adipose tissue is reached, the spillover occurs in the circulation of fatty acids that accumulate in non-adipose tissue [2]. Organs such as the heart, liver, and skeletal muscles try to take up these fatty acids [3]. When the body is overwhelmed by calories to such an extent that the adipose system can no longer effectively deal with the issues, the body must turn on “Cancer the Pragmatic Switch” to protect the organs, limit viral and bacterial infections, and avoid a septic condition. [1]. Cancer-associated adipocytes use the ketone bodies, fatty acids, pyruvate, and lactate from the stroma adipocytes [29]. The design of the body was for a calorie-scarce environment. The body wants to store as many calories as possible for the future because calories are uncertain in the wild. With excessive triglycerides, lipids, and glucose, the body is facing many threats. The viruses use lipids to reproduce, adipose tissue has overwhelmed the circulatory system, and sepsis condition can occur. Macrophages are drawn to the adipose tissue to prevent sepsis and are not available to other parts. Excessive calories create an immediate threat to the body, which is organ failure, infection, or sepsis. At this point, the body has no choice but to call upon “Cancer the Pragmatic Switch” to combat its dire situation with the assumption that calories will become scarce and Cancer will apoptosis.

Conclusion:

Adipose tissue and Cancer have a close relationship. Both can create angiogenesis, block the immune response and apoptosis in a low-glucose environment. Adipose tissue is capable of not only providing energy and heat but also regulating metabolic homeostasis. Further, adipocytes appear to be a major component in the tumor microenvironment. The adipocytes and immune cells within the adipose tissue synthesize and secrete proteins known as adipokines. These proteins regulate appetite, energy expenditure, insulin sensitivity, oxidative capacity, and lipid uptake in the non-adipose tissues such as the heart, liver, B-cells, and skeletal muscle [3]. The body's impressive logic has the storage facility for future energy, which is the adipose tissue, which is also the controlling regulator to the brain to shut off food consumption.

High-calorie intake eventually causes the blood triglycerides to be elevated as the body becomes insulin-resistant. The body reacts by increasing adipose tissue to allow safe storage of lipids.[22] [32] The expansion of the adipose tissue leads to high blood pressure because the subcutaneous fat constricts the blood vessels, and the additional load of the adipose tissue requires a larger amount of tissue to be fed from the heart. When the maximum capacity of the adipose tissue's ability for expansion is reached, lipids spill from the adipocyte, which causes an increase in the circulation of free fatty acid levels. Excessive lipid accumulation occurs in the organs, which is harmful [2]. The other danger of this condition is the susceptibility to various types of infection. Lipids are needed for viral reproduction. If excessive lipids are floating around, a viral infection becomes more dangerous [29]. It is hypothesized that the reason adipose tissue becomes dysfunctional is the body cannot support the level of adipose tissue, so a hypoxic state exists, which promotes necrosis and attracts the macrophages to the adipose tissue to prevent a sepsis condition from occurring. This can be a stable but undesirable condition for the body. Bacterial infections become more dangerous since the macrophages are drawn to the white adipose tissue to combat sepsis and are not available in other parts of the body to fight the infiltration of bacteria [25]. The body is inflamed, has frequent viral and bacterial infections, and is overwhelmed with lipids with a chronic septic condition. When the body can no longer tolerate the above condition, it may turn on “Cancer the Pragmatic Switch” [1]. Cancer-associated adipocytes (CAA) use the stroma adipocytes' ketone bodies, fatty acids, pyruvate, and lactate. These CAA secrete inflammatory factors that modify the behavior of cancer cells. Cancer is a ‘Pragmatic Switch’ for excessive glucose intake [1]. Cancer can consume 10-100 times glucose and apoptosis in a low-glucose environment. When treating cancer, perhaps we should consider diet as part of the treatment of cancer and its strong ties to Metabolic Syndrome.

Author:

John Claras Independent Researcher Sunnyvale, CA The original concept of “the Pragmatic Switch” was proposed in 2011 at a youth soccer game. The blog describing the initial concept appeared in 2016. This is the 3rd in a series of papers to define the cancer model.

Author Contributions he did all the following:

1. Conceptualization
2. Format analysis
3. Funding
4. Investigation
5. Methodology
6. Project Administration

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