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# Metabolic Management of Cancer Disease – A Review

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**Abstract:- The US National Cancer Institute (NCI) define cancer as a disease in which some of the body's cells are growing uncontrollably and are also spreading to other parts of the body. Cancer disease is a major cause of deaths worldwide and from the World Health Organization (WHO) report, in year 2020 alone, cancer caused about 10 million deaths globally. Also from a WHO report, cancer disease is responsible for 1 out of every 4 to 5 deaths worldwide. Conventionally, the treatment of cancer is based on three major approaches, viz; chemical therapy, surgery and radiation therapy. But, the outcome and prognosis of the conventional treatment of cancer disease is limited in its effectiveness, so there is an urgent need for more research based therapies that can effectively treat and manage cancer disease. With that, the treatment outcome and the survival rate of cancer will likely increase. Meanwhile, the term tumour was originally applied to the swelling caused by inflammation and there are two types of tumours; benign tumours and malignant tumours. Cancer is the common term for malignant tumours and the normal progression of most malignant tumours can be divided into four phases, which are; malignant change in the target cells, growth of the changed cells, local invasion of the surrounding tissues and organs by the changed cells, and distant metastases of the changed cells to other organs. In the clinical diagnosis of cancer disease, systems have been developed to express the level of differentiation of cancer within a patient (grade) and also the extent of spread of cancer within a patient (stage). The staging of cancers is based on the; size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases. Two major staging systems are quite common and the first was developed by the America Joint Committee (AJC) on Cancer Staging, while the second was by the Union Internationale Contre Cancer (UICC). The UICC employs a classification called the TNM system. Normal cells use the sophisticated process of respiration for their cellular energy production, but cancer cells use the primitive process of fermentation. However, no cell in its right conditions would ever use fermentation when there is enough oxygen, especially considering that fermentation does not produce as much energy as respiration, and it also creates toxic by-products. So, fermentation is primitive and wasteful. But, surprisingly, cancer cells use fermentation even when there is plenty of oxygen around. That very observation is the basis of the explanation for the Warburg effect, which is considered to be the metabolic signature of most cancer cells. From the meta-analysis research done on cancer at the University of Cambridge, UK, it was concluded that cancer is a mitochondrial disease and one of the effective ways of managing it is through diets. So, it was concluded from the meta-analysis that cancer growth and progression can be managed through a whole body transition from fermentable metabolites made up of basically glutamine and glucose, to respiratory metabolites made up of majorly ketone bodies.**

***Keywords:-*** *Cancer Disease, Cancer Management, Metabolic Treatment, Cancer Review.*

## I. INTRODUCTION

The US National Cancer Institute (NCI) define cancer as a disease in which some of the body's cells are growing uncontrollably and are also spreading to other parts of the body.[1] Meanwhile, cancer can start almost anywhere in the human body and normally when cells become damaged for any reason, or when they grow old, they die. But, in the case of cancer cells, they continue to grow after becoming damaged.[1]

Cancer disease is a major cause of deaths worldwide and from the World Health Organization (WHO) report, in the year 2020 alone, cancer caused about 10 million deaths globally.[2] Also from a WHO report, cancer disease is responsible for 1 out of every 4 to 5 deaths worldwide.[2] Meanwhile, the Global Cancer Observatory (GLOBOCAN) and the International Agency for Research on Cancer (IARC) reported that more than 18 million new cases of cancer occur annually.[3] That figure translates to about 1.5 million new cases of the disease every month.[3] Worldwide, cancer disease is on the rise and going by the GLOBOCAN report, the burden of cancer is expected to increase globally by about 50% around year 2040.[3]

According to a WHO data, the most common cancers are cancer of the breast, cancer of the lung, cancer of the colon, cancer of the rectum, and cancer of the prostate. In addition, each year, about 400,000 children develop cancer worldwide.[2] The cost burden of cancer is quite high, especially when compared to other chronic diseases like diabetes, stroke, etc. On average, it costs about $10,000 US Dollars each month to care for cancer disease.[4]

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Conventionally, the treatment of cancer disease is based on three major approaches, viz; chemical therapy, surgery and radiation therapy. But, the outcome and prognosis of the conventional treatment of cancer disease is limited in its effectiveness, so there is an urgent need for more research based therapies that can effectively treat and manage cancer disease. With that, the treatment outcome and the survival rate of cancer patients will likely increase.[5]

## II. DISCUSSION

Cancer disease is a cellular disorder of cell behaviours and cell growth. Therefore, its ultimate cause has to be defined at the cellular and also at the subcellular levels. Meanwhile, the study of cancer patterns in populations contribute substantially to the knowledge about the origins of the disease. For example, the concept that chemicals can cause cancer arose from the rigorous observations of Sir Percival Pott, who was able to link the increased incidence of scrotal cancer in chimney sweeps to their chronic and continuous exposure to soot.[6]

### *A. The Pathology of Cancer*

The term tumour was originally applied to the swelling caused by inflammation and there are two types of tumours; benign tumours and malignant tumours. Cancer is the common term used to refer to malignant tumours.[6] Meanwhile, the normal progression of most malignant tumours can be divided into four phases; malignant change in the target cells, growth of the changed cells, local invasion of the surrounding tissues and organs by the changed cells, and distant metastases of the changed cells to other organs.[6]

Almost all benign tumours remain localized to their site of origin and cannot infiltrate, invade, or metastasize to distant sites like a malignant tumour. So, the growth of malignant tumours (cancers) is usually accompanied by the gradual and continuous infiltration, invasion, and destruction of the surrounding tissues. This process is called local invasion.[6] The invasiveness of cancers permits them to penetrate blood vessels, lymphatic vessels, and body cavities. This then provide the opportunity for their spread from the sites of origin to other distant sites and organs. This spreading is called metastases and metastases usually mark a tumour as being malignant, considering that benign tumours do not metastasize.[6]

For most cancers, the more aggressive the cancer is, the more rapidly growing, and the larger the primary tumour will be. This then generally increases the likelihood of such cancers metastasizing to a distant site, or has even already metastasized to a distant site. Unfortunately, the metastatic spread of cancer often reduces the possibility of a patient recovering from, or surviving, the disease.6

### *B. Staging and Grading of Cancer Disease*

In the clinical diagnosis of cancer disease, systems have been developed to express the level of differentiation of cancer within a patient (grade) and also the extent of spread of cancer within a patient (stage), as parameters of the clinical diagnosis of the disease.[6] So, grading of cancer is based on the degree of differentiation of the tumour cells and the number of mitoses within the tumour, since it correlates to the neoplasm's aggressiveness. In grading, cancers are classified as grades I to IV, and that is in accordance with increasing anaplasia. However, the criteria for the individual grades vary from one cancer to another, but the objective is to determine the extent to which the cancer cells resemble or fail to resemble their normal counterparts.[6]

For the staging of cancers, it is based on; the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases. Two major staging systems are quite common and the first was developed by the America Joint Committee (AJC) on Cancer Staging, while the second was by the Union Internationale Contre Cancer (UICC). The UICC employs a classification called the TNM system. The T stands for primary tumour, N stands for regional lymph node involvement, and M stands for metastases.[6] However, it should be noted that staging has proven to be of more clinical value than grading, and in some cases, like lung cancers, staging can been greatly aided by imaging techniques such as Positron Emission Tomography (PET) scan.

### *C. The Immune System and the Conventional Treatment of Cancer*

The immune system functions in such a way that it always keeps a record of virtually all the disease-causing agent it has encountered in the past. And those records are usually kept inside the B-lymphocytes, and the T-lymphocytes. Together, these specialized white blood cells are referred to as the memory immune cells, since they can quickly recognize and destroy disease-causing agents anytime it enters the body again. That way, the attack and destruction of any harmful agent are immediately carried out before the disease-causing agent can be able to multiply inside the body and then cause illness.[7]

So, the major purpose of the immune system is to prevent and limit infections. Meanwhile, the immune system can distinguish between unhealthy cells and healthy ones, by using a system referred to as the Danger Associated Molecular Patterns (DAMPs). However, a cell may become unhealthy due to infections, or from damages to the cells by disease-causing agents like cancer. In addition, the immune system works through a system called Pathogen Associated Molecular Patterns (PAMPs). The PAMPs is the system usually responsible for disease-causing agents like viruses and bacteria.[8] The immune system can attack and (or) inactivate disease-causing agents directly, or indirectly, through both the cellular inflammatory process and the molecular inflammatory process. The importance of the immune system to survival cannot be overemphasized and a demonstration of its importance can be seen in the devastating consequences of the immune system breakdown usually observed in Acquired Immune Deficiency Syndrome (AIDS) patients. Therefore, to survive diseases like cancer, the role of the immune system is very critical.[8]

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Treating cancer is usually a highly complex process, and the conventional treatment approaches which is made up of surgery, chemotherapy and radiotherapy is commonly used. Meanwhile, significant advances are being made in recent times, which includes; targeted therapy, stem cell therapy, nanoparticles, ablation therapy, radionics, natural antioxidants, chemodynamic therapy, sonodynamic therapy, etc. Also, the current systems of oncology focus on the development of efficient and safe cancer nanomedicines. Meanwhile, stem cell therapy has provided some promising efficacy in regenerating and repairing damaged or diseased tissues. That is usually achieved by targeting both the metastatic and primary cancer foci. Also, the use of nanoparticles has brought new therapeutic and diagnostic options to cancer treatment.[9]

In addition, some targeted therapies have good breakthrough potentials for inhibiting the spread and growth of specific cancer cells, thereby reducing the damages to healthy cells. An example of that is the ablation therapy which has emerged as a minimally invasive procedure that can freeze or burn cancers, without the need for an open surgery. Generally, the most commonly recommended conventional treatment of cancer is the surgical resection of the tumors, which is then followed by radiotherapy using x-rays, and (or) chemotherapy. Out of all the treatment options at an early stage of cancer progression, surgery is the most effective method. Usually, the concern with radiation therapy is that it can damage healthy cells, organs, and tissues. For chemotherapy, although it is generally associated with reduced morbidity and mortality of cancer, but almost all the chemotherapeutic agents damage healthy cells because they usually attack rapidly growing and dividing cells. Meanwhile, the efficiency of conventional cancer treatments are usually reduced due to the unique pathology of tumours and also the architectural abnormality of most tumour blood vessels.[9]

*D. Metabolic Treatment of Cancer and the Warburg Effect*

Normal cells use the sophisticated process of respiration for energy production, while cancer cells use the primitive process of fermentation.[10] However, no cell in its right condition would ever choose to use fermentation when there is enough oxygen, considering that fermentation does not produce nearly as much energy and it also creates toxic by-products. So, fermentation is primitive and wasteful. But, that notwithstanding, cancer cells use fermentation even when there is plenty of oxygen around and that observation is the basis of explanation for the Warburg effect, which is considered to be the metabolic signature of most cancer cells.[11]

After the early findings of the metabolic differences between cancer cells and normal cells, Warburg and his co-workers also showed that cancer cells metabolize about 10-fold more glucose (sugar) into lactate at any given time than normal cells. So, that led their Research Team to conclude that the cellular respiration chain in cancer cells are damaged.[7] Meanwhile, apart from the the high dependence of cancer cells on sugar, the observation that proliferating cancer cells are also very dependent on glutamine was firstly reported by Eagle in 1955. Eagle and his team observed that the glutamine consumption rate in many cancer cells was greater than the consumption of any other amino acid by 10-fold.[11] Emerging evidences have therefore proven that cancer is primarily a metabolic disease involving disturbances in the cellular energy production. So, the genomic instability that is usually observed in most cancer cells and all the other recognized hallmarks of cancer cells are actually a downstream epiphenomena of the initial disturbances of cellular energy metabolism.[8] Cancer growth and progression can therefore be managed through a whole body transition from fermentable metabolites made up of basically glucose and glutamine, to respiratory metabolites made up of majorly ketone bodies.[12]

As previously stated above, virtually all cancer cells depend heavily on glucose for their survival and that is how PET scans are able to find many tumours hiding within normal tissues. The PET scans functions by following radioactive glucose as it travels through the bloodstream.[10] That is, because radio-labeled glucose accumulates in tumour tissue more than in the normal tissues surrounding it, it usually lights up the tumour tissues on the PET scan. Meanwhile, a strong link has been established between high blood sugar (hyperglycemia), which is usually present in diabetes, and the incidence of cancer disease in diabetic patients.[10] Also, hyperglycemia has been directly associated with poor prognosis in those with malignant brain cancer. And it has also been linked to the fast growth of most malignant cancers. Moreover, research has shown that hyperglycemia usually raises insulin levels and eventually the raised insulin end up stimulating cancer cells to take in and use more glucose.[10]

So, if food consumption is restricted or controlled in a way that it will lower the blood glucose, then the use of fermentation process by tumour cells, instead of respiration process, will become difficult. It will also become difficult for the tumour cells to recruit new blood vessels and that will eventually slow down the growth of the tumour. Generally, glucose restriction stresses cancer cells. For healthy cells, they prefer to use ketones and fatty acids for their energy production.[13] That is, glucose restriction is good for healthy cells and bad for cancer cells. Therefore, considering the limitations of conventional cancer treatments and the usually poor prognosis of such treatments, it has become necessary for medical researchers to find other effective treatments for managing cancer and thereby increase the chances of surviving the disease. Such treatments will be more promising if it is under the direct control of cancer patients. And an example of that is the type of food and diets which cancer patients consume.

At this point, since research has shown the favourite source of energy metabolite for cancer cells to be sugar,[7] it would therefore be beneficial for cancer patients to reduce their intake of foods and diets which are high in sugar contents. Meanwhile, sugar comes in different types and forms, such as; sucrose, glucose, fructose, etc. Also, sugar can be categorized into either natural (the unrefined and unprocessed sugar) or artificial (the refined and processed sugar).[14] So, the sugar to be avoided as part of the metabolic management of cancer disease, using diets, is the artificial

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sugar. By nature, and also by molecular design, sugar is not found in a free and unbounded state. That is, in its natural form, sugar (such as glucose, sucrose, fructose) come bounded with; enzymes, vitamins, minerals, fibres, nutrients, etc. So, it is the bounded sugar that is good and healthy for consumption, especially by cancer patients.[14] But, the artificial sugar usually found in processed food and drinks, have been stripped of; enzymes, vitamins, minerals, fibres, and nutrients; and must therefore be avoided or reduced as much as possible. The reason for that is that since artificial sugars have been stripped in such a way that they have become free and unbounded, during digestion they usually cause spikes in blood glucose level, hyperglycemia, and research have shown that hyperglycemia promotes cancer growth and aggressiveness.[15]

Therefore, cancer patients who control their diets, by avoiding or reducing the consumption of processed foods, processed drinks, refined sugar, table sugar, etc. stands a higher chance of surviving the disease. And the reason is because they will be able to systematically starve the cancer cells in their body to death.[11,15] So, instead of consuming food and diets made up of artificial or refined sugar, cancer patients will benefit greatly from the consumption of food from natural and unprocessed sources, like; whole grains, raw organic nuts and seeds, whole-wheat flour, unprocessed tubers, unprocessed fruits, etc.

## III. CONCLUSION AND SUGGESTION

The meta-analysis carried out by two Cellular and Molecular Biologists at the University of Cambridge, UK, on the outcome of various cancer researches, has showed that cancer is actually a mitochondrial disease and one of the effective ways of managing it is through diets. Infact, from the meta-analysis, nearly all the cancer researches from the year 1934 to 2016 recorded some forms of mitochondrial damages and abnormal deformations in most cancer cells. The damages occurred mostly in the mitochondrial cristae.[10] Also, according to the analysis, one of the best ways to prevent cancer disease is by reducing the consumption of simple carbohydrate and protein, and by increasing the amount of ketones in body.[10] Although genetic inheritance influences the risk of cancer, but it has been shown that most of the variations in cancer risk across populations and among individuals are due to lifestyle and environmental factors.[11] Also, data from experimental and epidemiological studies indicate that excessive adiposity, due to excessive energy intake and minimal physical activity, increase the risk of developing cancer.[11]

In addition, research has shown that calorie restriction and protein restriction, without malnutrition, can help in preventing and managing cancer disease. The calorie restriction acts by; reducing the activity of pro-aging pathways, reducing cancerous growth, reducing inflammation in pre-cancerous or normal cells, and increasing apoptosis in damaged cells. Furthermore, calorie restriction also modulates the growth and invasiveness potentials of most cancerous cells. Therefore, understanding the role of calorie restriction and of other dietary manipulations in cancer management has the potential for the formulation of drugs and (or) therapies which can provide a broad spectrum prevention and treatment of cancer.[11]

In conclusion, various emerging evidences have indicated that cancer is primarily a metabolic disease involving the disturbances of cellular energy production. Meanwhile, the genomic instability usually observed in tumor cells and all the other recognized hallmarks of cancer are actually downstream epiphenomena of the initial disturbances of cellular energy metabolism. Meanwhile, the disturbances in tumor cells energy metabolism has been linked to the abnormalities in structure and function of the mitochondria. But, when viewed as a mitochondrial metabolic disease, the evolutionary theory of Lamarck can better explain cancer progression, as against the evolutionary theory of Darwin. So, cancer growth and progression can be managed through a whole body transition from fermentable metabolites basically made up of glucose and glutamine, to respiratory metabolites majorly composed of ketone bodies.[12]

## ACKNOWLEDGMENT

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