

The Hybrid Causes for the High Cancer Incidences in Cold Climates in Humans

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Abstract

Cancer disease is an evolutionary metabolic disorder that consumes Glucose and Glutamine as the main food and these two biological compounds are the important fuel to produce ATP and Lactic Acid. The main cause of cancer is the high amounts of Reactive Oxygen Species (ROS) and also Reactive Nitrogen Species (RNS), produced by mitochondria, that is a main danger to the living normal human/animal cells and causes mitochondrial damages specifically in their cristae. This research has gone through the epidemiology of the cancer plus the human biochemistry and physiology in the cold weather to find the relation between the high rates of cancer incidences in the cold climates in comparison with the warm and humid climates (specifically the equator). Bohr Effect (BE) and increasing the amount of blood glucose level in the cold weather are the main issues which is discussed in this research that causes hypoxia, increasing the amounts of Reactive Oxygen Species (ROS) and inflammation in the normal cells which explains the high rates of cancer incidences in the cold areas of the earth.

Keywords: Cold Weather; Bohr Effect; ROS; Blood Glucose; Cancer; Butterfly Effect

Abbreviations

ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; ATP: Adenosine Triphosphate; BE: Bohr Effect; EMHC: Evolutionary Metabolic Hypothesis of Cancer; MCT: Medium Chain Triglycerides

Introduction

Evolutionary metabolic hypothesis of cancer (EMHC)

The first living eukaryotic cells on the Earth has been thought to have arisen more than 3.5 billion years ago, when the Earth was not more than about 109 years old. The environment of the earth really was zero amounts of oxygen molecules. However; was presumably rich in geochemically produced organic molecules, and some of the earliest metabolic pathways for creating ATP compound may have resembled the present-day forms of fermentation process which is the same as cancer cells. Processing of fermentation, ATP is produced by a phosphorylation procedure that harnesses the energy released when a hydrogen-rich organic molecule, such as glucose, is partly oxidized. The electrons lost from the oxidized organic molecules are transferred via NADH or NADPH to a different organic molecule or to a different part of the same molecule, which thereby becomes more reduced. At the end of the fermentation process, one or more of the organic molecules produced are excreted into the medium as metabolic waste products such as Lactic Acid. Others, like pyruvate, are retained by the cell for biosynthesis. The excreted end-products are different in disparate organisms, but they likely to be organic acids. Among the most important of such products in bacterial cells are lactic acid which also amasses in anaerobic mammalian glycolysis, and formic, acetic, propionic, butyric, and succinic acids [1].

The first cell on the earth before the entrance of the bacteria did contain nucleus and used the fermentation process to produce ATP for its energy. Then an aerobic proteo-bacterium enters the eukaryote either as a prey or a parasite and manages to avoid digestion. It then became an endosymbiont. As we observe, the fermentation process used the glucose or even glutamine to produce ATP, but the aerobic process used the glucose, fat and protein to produce more ATP than the previous one. The symbiogenesis of the mitochondria is based upon the natural selection which had been presented and introduced by Charles Darwin. Based upon Otto Warburg Hypothesis (OWH),

almost all cancer cells, the mitochondrion is defected and the cancer cell do not need to use its mitochondrion to produce ATP [2]. This process of adaptation in mitochondrion, is based upon Lamarckian Hypothesis of Evolution which shows and proves that the normal cells move back into the primitive era of evolution to protect themselves from apoptosis and uses the fermentation process similar to the first living cells in 3.5 billion years ago. Therefore; cancer is an evolutionary metabolic disease which consumes glucose as the prime food/fuel to produce ATP and Lactic Acid. The main reason behind of cancer incidence in human/animal is the high amounts of Reactive Oxygen Species (ROS) produced by mitochondria that is a main threat to the living normal cells which cause mitochondrial damages mainly in their cristae which has been proven and referenced time and time again by Professor Thomas N Seyfried [3].

Bohr Effect

The Bohr Effect is a physiological phenomenon which was first described in 1904 by the Danish physiologist named Christian Bohr, mentioning that hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide [4]. Since carbon dioxide reacts with water to form carbonic acid, an increase in CO_2 results in a decrease in blood pH [5] resulting in hemoglobin proteins releasing their load of oxygen. Conversely, a decrease in carbon dioxide provokes an increase in pH, which results in hemoglobin picking up more oxygen [6].

The Bohr effect increases the efficiency of oxygen transportation through the blood [7]. After hemoglobin binds to oxygen in the lungs due to the high oxygen concentrations, the Bohr effect facilitates its release in the tissues, particularly those tissues in most need of oxygen. When the metabolic rate of the tissues increase, so does their carbon dioxide waste production [8].

Carbon dioxide When released into the bloodstream, forms bicarbonate and protons through the following reaction: Although this reaction is usually very slow, but the enzyme carbonic anhydrase which is present in red blood cells, drastically speeds up the conversion into bicarbonate and protons [9]. This causes the pH of the blood to decrease, which promotes the dissociation of oxygen from hemoglobin, and allows the surrounding tissues to obtain enough oxygen to meet their demands. In areas where oxygen concentration is high, such as the lungs, binding of oxygen causes hemoglobin to release protons, which recombine with bicarbonate to eliminate carbon dioxide during exhalation [10]. These opposing protonation and deprotonation reactions occur at an equal rate, resulting in little overall change in blood PH [11].

The Bohr effect enables the body to adapt to changing conditions and makes it possible to supply extra oxygen to tissues that need it the most. For example, when muscles are undergoing strenuous activity, they require large amounts of oxygen to conduct cellular respiration, which generates CO_2 and therefore HCO_3^- and H^+ as byproducts [12]. These waste products lower the pH of the blood, which increases oxygen delivery to the active muscles. Carbon dioxide is not the only molecule that can trigger the Bohr effect. If muscle cells aren't receiving enough oxygen for cellular respiration, they resort to lactic acid fermentation, which releases lactic acid as a byproduct. This increases the acidity of the blood far more than CO_2 alone, which reflects the cells' even greater need for oxygen. In fact, under anaerobic conditions, muscles generate lactic acid so quickly that pH of the blood passing through the muscles will drop to around 7.2, which causes hemoglobin to begin releasing roughly 10% more oxygen [13].

The Bohr effect hinges around allosteric interactions between the hemes of the hemoglobin tetramer, a mechanism first proposed by Max Perutz in 1970 [14]. Hemoglobin exists in two conformations: a high-affinity R state and a low-affinity T state. When oxygen concentration levels are high, as in the lungs, the R state is favored, enabling the maximum amount of oxygen to be bound to the hemes. In the capillaries, where oxygen concentration levels are lower, the T state is favored, in order to facilitate the delivery of oxygen to the tissues. The Bohr effect is dependent on this allosteric, as increases in CO_2 and H^+ help stabilize the T state and ensure greater oxygen delivery to muscles during periods of elevated cellular respiration. This is evidenced by the fact that myoglobin, a monomer with no allosteric, does not exhibit the Bohr effect [15].

Hemoglobin mutants with weaker allosteric may exhibit a reduced Bohr effect. For example, in Hiroshima variant hemoglobinopathy, allosteric in hemoglobin is reduced, and the Bohr effect is diminished. As a result, during periods of exercise, the mutant hemoglobin has a higher affinity for oxygen and tissue may suffer minor oxygen starvation [16]. As blood nears the lungs, the carbon dioxide concentration decreases, causing an increase in PH. This increase in pH increases hemoglobin's affinity for oxygen through the Bohr effect, causing hemoglobin to pick up oxygen entering your blood from your lungs so it can transport it to your tissues.

Materials and Methods

One study in 2017 by Dr. Somayeh Zaminpira and Dr. Soroush Niknamian has shown the co-relation between the cancer incidence and multiple sclerosis in cold climates. Increasing ROS/RNS in neuronal areas of the brain is the dominant cause of Multiple Sclerosis and

many types of cancer. Parasites like certain viruses, bacteria or parasitic micro-organisms increase the ROS/RNS which causes the damage to the mitochondria, myelin and mitochondrial DNA. The role of the environment and the distance from the equator is apparent in the incidence of MS. Cold weather is detrimental to the health of nervous system, since in lower temperature below 37°C degrees causes hypoxia in the brain and increases the MS incidence. In multiple sclerosis the amounts of glucose consumption by the neurons decreases. Therefore; glucose as the main source of energy is not useful. The epidemiology of cancer shows that the incidence of this disease is very low in the native American Indians, African Massai populations, Eskimos and Alaska populations which consume native diets, mainly saturated fats, MCTs and medium protein by hunting and very low carbohydrates. Multiple Sclerosis and Cancer Are Evolutionary Metabolic diseases which can be treated by specific Keto-Diet Plus Intravenous Ozone Therapy (IOT). Therefore; we suggest living in the equator line of the earth, using ketogenic diet (80% saturated fat, 15% protein with the lowest glutamine and 5% complex carbohydrates) as the main diet, would be the best way in the prevention of Multiple Sclerosis and cancer disease [S. Zaminpira, S. Niknamian, ECRONICON, 2017].

In addition, Sharma A. *et al* in a research in 2015 have shown that, many risk factors such as smoking and change of life style have been shown to promote genetic and adaptive epigenetic changes responsible for tumorigenesis. This study brings environmental temperature as a cancer causing factor to light. The cancer mortality rate (CMR) of a country was correlated with 17 different variables. Multi-variate analysis of 188 countries found that the average annual temperature (AAT) of a country might have a significant contribution to cancer death when compared with other factors such as alcohol and meat consumption. Univariate analysis found a negative correlation between AAT and CMR.

All these countries were categorized into three temperature zones (zone I, -2 to 11.5°C; number of countries, 38; zone II, 11.6 to 18.6°C; number of countries, 32; and zone III, 18.7 to 30°C; number of countries, 118). Out of the top-most 50 countries having the highest CMR, 26 (68.42%), 10 (31.25%) and 14 (11.66%) belong to zone I, zone II, and zone III, respectively. Out of the least 50 countries having the lowest CMR, 1 (2.63%), 4 (12.5%) and 45 (37.5 %) belong to zone I, zone II, and zone III, respectively. CMR is low in those countries situated near to the Torrid zone (33(°) N to 23.5(°) S), but it is high for those countries situated away from these two latitudes. These data indicate that cold temperature may have a contribution in increasing tumorigenesis. High metabolic stress, which is the result of maintaining our body temperature against a cold environment, could be the possible cause for the higher cancer mortality [17].

In another study done by Guy R in 1970 showed that Age-adjusted death-rates from several types of cancer were correlated for nine census divisions of the United States with the temperature index (mean annual temperature range). Mortalities from many types of cancer were negatively correlated with temperature index and positively correlated with both per-caput income and physician/population ratio. It is suggested that geographical differences in cancer mortality could be associated with both artefacts and indirect causative factors, rather than reflecting a direct environmental effect on cancer risk, and that such differences require careful interpretation [18].

Figure 1 and 2 shows the cancer epidemic is higher in the north and south of the earth where the temperature is low. Cancer incidence in the equator line a lot fewer than the other places in the earth.

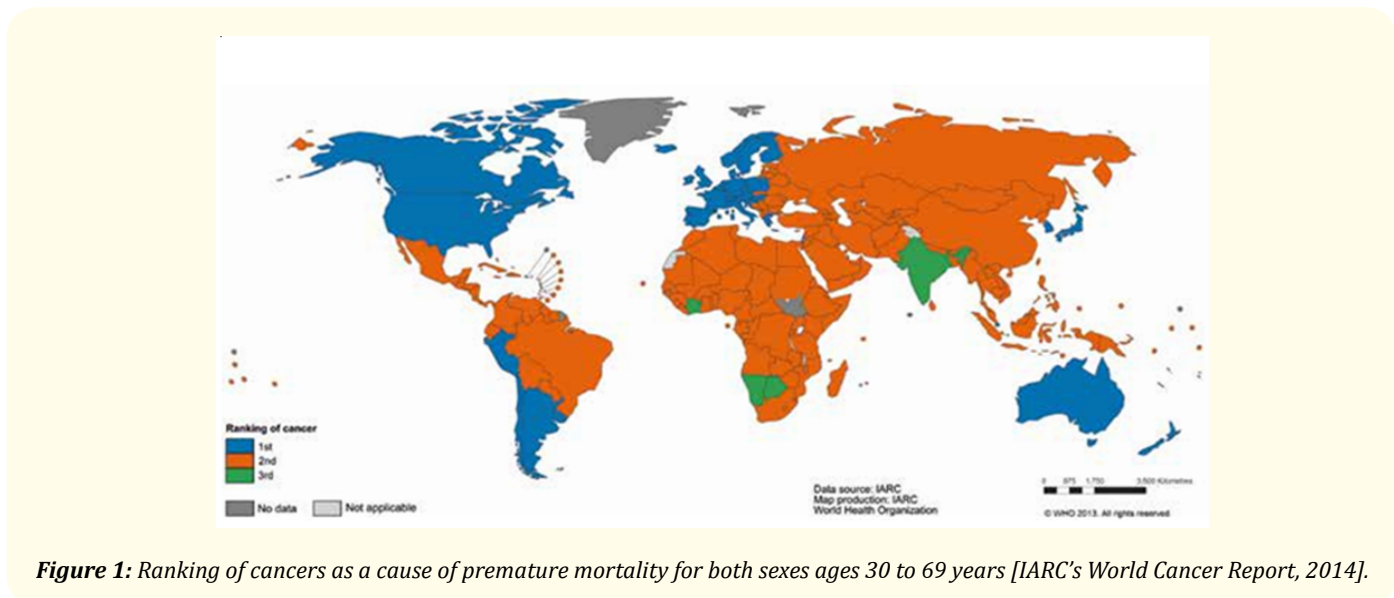


Figure 1: Ranking of cancers as a cause of premature mortality for both sexes ages 30 to 69 years [IARC’s World Cancer Report, 2014].

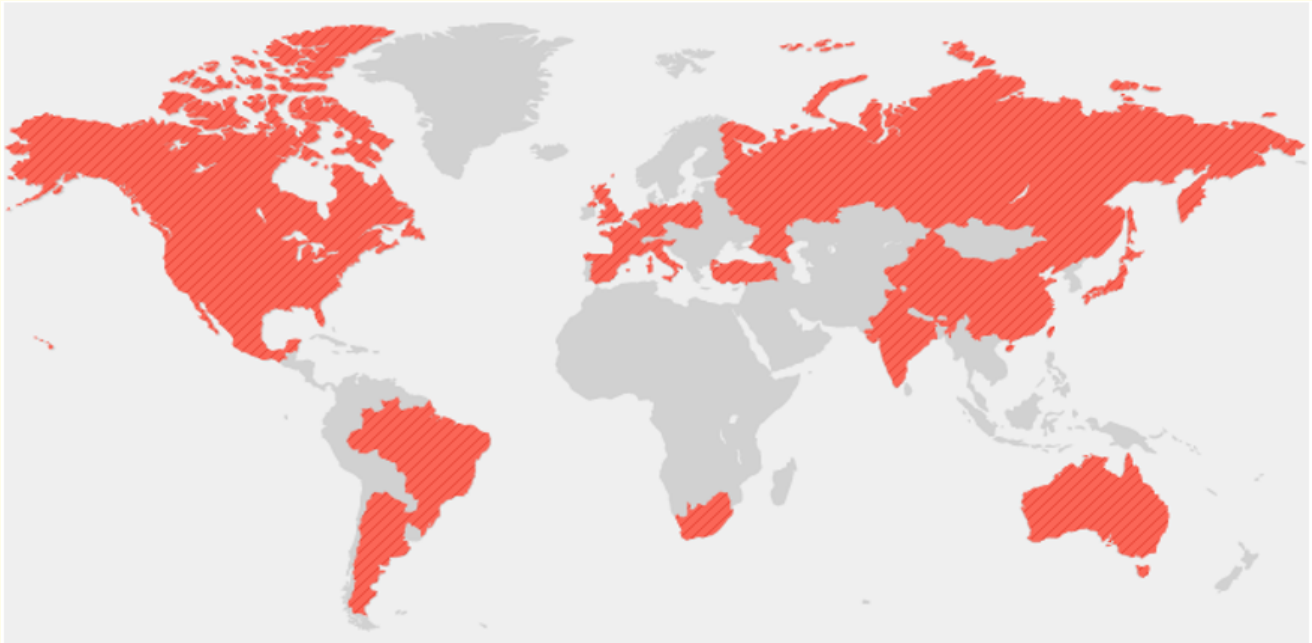


Figure 2: High rates of cancer incidences [World Health Organization, 2015].

In another study in December 6, 2017 by Konstantinos Voskarides showed that Populations living in very low temperatures, like in Denmark and Norway, had among the highest incidences of cancer in the world. This shows there is an evolutionary relationship that exists between adaptation to extreme environmental conditions, like cold and high altitude, and increased cancer risk in humans [23].

Analysis of data from the GLOBOCAN-2012 survey of worldwide cancer incidence shows that evolutionary adaptation to environments of extreme or prolonged cold produces genetic variants that interfere with tumor suppression and increase vulnerability to almost all cancers [24].

Results and Discussions

Decreasing temperature leads to the decrease in core body temperature as well, which leads to the decrease in blood flow throughout the body. Hypocapnia is the outcome of the cold temperature in humans which leads to the lack of oxygen absorption by the blood vessels from the lungs. This phenomenon leads to the poor oxygen absorption by the tissues as well through the Bohr Effect and causes hypoxia in tissues. Raynaud's phenomenon is the result of the cold weather and stress which explains why tissues would gain hypoxia. Raynaud's phenomenon Brought on by cold weather and stress, symptoms of this condition include numbness and coldness in the fingers and toes. This usually occurs when blood vessels constrict in the hands and feet [19].

The Bohr effect increases the efficiency of oxygen transportation through the blood [G Hüfner, *et al.* 1890]. After hemoglobin binds to oxygen in the lungs due to the high oxygen concentrations, the Bohr effect facilitates its release in the tissues, particularly those tissues in most need of oxygen. When a tissue's metabolic rate increases, so does its carbon dioxide waste production [8].

Hypoxia as mentioned by Otto Warburg in the 1930s which is called Warburg Hypothesis leads to mitochondrial damage and cancer in normal cells [25].

Hypoxia in tissues leads to the incline in the amounts of Reactive Oxygen Species (ROS) in the cells which leads to the change of normal cells into cancer cells through the Butterfly Effect [20].

Chaos theory is a branch of mathematics which is focused on the behavior of dynamic systems that are highly sensitive to initial conditions. Chaos is an inter-disciplinary theory stating that within the apparent randomness of chaotic complex systems, there are underlying patterns, constant feedback loops, self-similarity, repetition, fractals, self-organization, and reliance on programming at the initial point known as sensitive dependence on initial conditions. The butterfly effect (BE) describes how a small change in one state of a deterministic non-linear system can result in large differences in a later state [Boeing (2015). "Chaos Theory and the Logistic Map". Retrieved 2015-07-16]. Decreasing the body temperature leads to the incline in body glucose as well which increases the rates of hypoxia in tissues and decrease in blood PH as well which has been studied by Sanchez-Alvarez., *et al.* in 2009 [21].

The in-effective respiratory pattern or heavy breathing in increasing the blood glucose, causes Systemic Hypocapnia which means Carbon Dioxide deficiency in the alveoli, arterial blood and other cells. Hypocapnia leads to vasoconstriction and the suppressed Bohr effect. As a result, hypocapnia reduces body and cell oxygenation. It can decrease insulin production due to insufficient perfusion and oxygen supply to pancreas, or it can lead to chronic pancreatic inflammation. Furthermore, those patients who have more severe forms of hyperventilation that is less than 10 s for the body Oxygen (O₂) test, will experience more problems [22].

Decreasing blood PH also is a factor in reducing the oxygen absorption by the tissues as well [S. Zaminpira, S. Niknamian, ECRONICON, 2017].

Conclusion

This research has gone through many factors including the epidemiology of cancer, reviews, biochemistry and physiology of the human body and cells in the cold weather/climates to find out the prime reason for the high cancer incidences in low temperatures. The cancer epidemic shows that the rate increases as we go far from the equator line. Number of cancer patients in cold weather areas of the earth is much higher than the other places. There are many important factors are included in the cause of cancer including lifestyle, nutrition, lack of exercise and stress. But the main cause of cancer is increasing the amounts of Reactive Oxygen Species and inflammation which leads to the Butterfly Effect (BE) in the normal cells. In conclusion, we would like to mention that the cold weather/climates decreases the core body temperature, hypocapnia, increasing the blood glucose level, lowering the blood PH which through the Bohr Effect (BE) results in the hypoxia in body tissues and leads to the increase in the amounts of ROS, stress and inflammation in the normal cells. Therefore; as the temperature decreases, the rates and the possibility of changing the normal cells into cancer cells increases. Mentioning the lines above, we have proved that one of the prime cause of cancer incidences in the Northern Area of the Earth is the cold climate based on Bohr Effect. This paper also warns about the migration of people living in Middle-East, Asia, Africa and warm climates into the Northern Europe/Northern America that increases the possibility of this disease epidemically in these migrants as well.

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Conflicts of Interests

There are no conflicts of interest between the authors of this research.

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