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Improving Natural Resistance to Cancer: An Overview of Metabolic Pathways in Cancer Cells Integrated with Regional Cancer Incidence Statistics

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Abstract

Context: Cellular metabolism is a set of controlled biochemical reactions known as metabolic pathways that occur in living organisms in order to sustain life. Cells may use different metabolic pathways and alter metabolism to use more effective processes for survival depending on cellular conditions. Alterations in metabolic pathways can lead to the transformation of normal cells into cancerous cells, leading to cancer initiation and development.
Objectives: Proper cellular conditions in terms of pH and the availability of essential nutrients and oxygen are important for the healthy functioning of aerobically respiring human cells. If cells are exposed to stressors such as carcinogens that can induce mutations in the genes involved in metabolic pathways, anaerobic metabolism may be used by cells, turning them into cancerous cells. Cellular conditions that maintain aerobic cellular respiration and mitigate the effects of cellular stressors can improve cells' resistance to neoplastic transformation.
Methods: This paper explores the key metabolic pathways used by cancer cells as a function of their environmental conditions based on the Warburg effect. In addition, some analyses and studies were conducted on global and regional cancer incidence rates, taking into account changes in lifestyle and dietary patterns.
Results and Conclusions: Natural resistance to cancer may be improved when cells grow in healthy conditions at molecular levels, requiring a balanced alkalizing diet and healthy lifestyle, as well as reduced exposure to environmental carcinogens, which are key control factors. In particular, effective nutritional interventions can help normal cells resist metabolic changes underlying cancer development.

Keywords: Cancer Resistance, Metabolic Pathways, Warburg Effect, Cancer Diet

1. Context

All living cells in the modern world, including those that respire aerobic respiration, have retained their characteristics from a common ancestor that lived anaerobically on an ancient oxygen-deficient earth (1-3). In parallel with a significant increase in atmospheric oxygen on earth, living organisms that could adapt to the new condition survived by finding a way to utilize the rich potential of oxygen for respiration (4-6). Oxygen acted as an ideal oxidant for the efficient generation of energy after nutrient breakdown, so aerobic life evolved faster, gradually forming complex and advanced multi-cellular systems, which later gave rise to plants, animals, and modern humans (6-8).

As all living cells in the modern world have their roots in anaerobic life on the ancient earth, where living conditions were harsh and the atmosphere was extremely oxygen deficient, these cells are still able to utilize anaerobic pathways when facing harsh living conditions caused by cell stressors such as exposure to carcinogens. When a stressful situation is experienced by these cells, in order to survive longer, a metabolic switch from aerobic to anaerobic occurs as an evolutionary throwback to apply the survival mechanisms used by ancient cells (3-10).

The metabolic switch to utilize anaerobic cellular respiration, as a consequence of metabolic adaptation, is common in cancer cells, a discovery revealed by Dr. Otto

Heinrich Warburg (1883 – 1970), a German scientist and Nobel Prize winner. Warburg realized that cancer cells could inherently change their metabolism from aerobic to anaerobic and use anaerobic cellular respiration and fermentation processes, which typically consume a greater amount of nutrients and form significant amounts of lactic acid as a byproduct, causing metabolic acidosis (11-19).

According to the Warburg findings, a fundamental cause of cell mutations towards developing cancer tumors is the damage of cellular respiration caused by carcinogens (11, 12, 16). When cellular respiration is damaged, some cells die, which may not be a major problem if there are not too many and as long as they can be replaced with new cells. However, some damaged cells may mutate to resist cellular death and survive by repairing themselves (20). These cellular changes are parts of survival mechanisms during adaptation to stressful conditions, which do not necessarily indicate a defect as they can help cells evolve into survivors by acquiring greater resistance to harsh conditions (21).

In recent years, we have seen the emergence of a major area of research in cancer metabolism. This paper explores the key aspects of the metabolic pathways used by cancer cells as a function of their environmental conditions. In order to address some practical solutions, we took into account dietary, lifestyle, and environmental factors involved in metabolic control and improving cellular resistance to cancer development.

2. Metabolic Pathways in Cancer Cells

Metabolism consists of a series of reactions that occur within the cells of living organisms to sustain life. Metabolic processes involve many interconnected cellular pathways that ultimately provide cells with the energy required to carry out their function. Cells may use different metabolic pathways and alter their metabolism to employ more effective pro-survival processes depending on cellular conditions. Alterations in metabolic pathways are also common when a normal cell is transformed into a cancer cell characterized by the dominance of cancer-initiating mechanisms (22, 23).

Biochemical investigations have revealed that under appropriate stress-free conditions, normal cells employ aerobic respiration, in which glucose is consumed as the preferred source of energy, and water and carbon dioxide are produced as byproducts. However, under conditions of stress such as hypoxia and exposure to acidic environments and/or carcinogens, cells switch metabolism toward anaerobic respiration, leading to the production of lactic acid as the main byproduct. In the case of chronic anaerobic respiration under inappropriate cellular conditions, numerous mutations and epigenetic changes may occur, likely due to tautomerization reactions, which may cause cancer formation and progression (15, 16, 20-22).

Hypoxia is a common cellular stressor that triggers anaerobic cellular respiration and consequent lactic acidosis. Anaerobic respiration is often observed in the hypoxic tissues of the body where oxygenation is chronically poor (18), which, according to the Warburg effect, gradually leads to the transformation of normal cells into cancerous cells (19). Numerous studies have proved that hypoxia-inducible factor (HIF-1) plays a key role in the body's reaction to oxygen deprivation and may be a common mediator in the initiation and development of various cancers (24). On the other hand, reversing metabolic pathways by providing an oxygen-rich environment with optimum alkalinity can preserve healthy cells and inhibit the progression of hypoxia-induced cancer (15, 16).

Many epidemiological and laboratory studies show that cancers can also be caused by other physical and chemical factors such as smoking, alcohol and addictive drugs, cosmetics, synthetic supplements, viruses, infections, stress, toxins, and radiation (25). Among these cellular stressors, the cells that are chronically exposed to carcinogens may use anaerobic cellular respiration, which acidifies the cellular environment even in the presence of sufficient oxygen. So, the main trigger of cancer development in this condition seems to be exposure to carcinogens rather than hypoxia (22, 25).

Numerous studies show that exposure to cellular stressors such as carcinogens can transform normal cells into cancer cells (17-19). However, damaged cells can repair themselves, gain resistance to stressors, and survive where appropriate cellular conditions are met in terms of the availability of suitable sources of energy, essential minerals, vitamins, enzymes, and co-enzymes, as well as optimal alkaline pH and sufficient oxygenation. Appropriate cellular conditions are essential for the healthy functioning of aerobically respiring human cells, as well as the expression of essential genes and regulation of cellular metabolism, differentiation, and maturation (14, 19). The cell growing in inappropriate conditions, such as in case of deficiencies in key nutrients, poor oxygenation, dehydration, and undesirable pH at the cellular level, may eventually transform into tumors (14, 15, 23).

3. Nutritional Interventions for Cancer

A key controlling factor of genetic mutations may be the diet, as it can have a great impact on cellular conditions. Hence, dietary modifications providing a cellular condition that maintains aerobic cellular respiration may improve cellular resistance to cancer development (16).

Epidemiological and experimental studies have shown that the higher intake of fruits and vegetables reduces the risk of different cancers (25). However, synthetic nutrients such as those in vitamin/mineral supplements show no anti-carcinogenic values, and their frequent consumption may even increase the risk of cancer (16).

Epidemiological studies and meta-analyses performed on different ethnic groups indicate that the excessive consumption of animal proteins that form toxic and acidic metabolic waste, such as hydrogen sulfide and lactic acid, respectively, may be significantly associated with human cancers (26). In particular, breast cancer (the most common cancer in women), prostate cancer (the most common cancer in men), and colorectal cancers may significantly be linked to the excessive intake of animal proteins such as processed red meat and commercial dairy products (16, 25).

Chemical food contaminants are known to increase the risk of cancer (15). A high nitrate intake from chemical fertilizers may shift cells towards using anaerobic respiration, which is a risk factor for cancer. In the cases where agricultural soil or groundwater is contaminated, food may contain carcinogenic content, including toxic heavy metals such as lead, arsenic, fluoride, and cadmium. Also, pesticides and herbicides, particularly glyphosate, which is widely used in the production of genetically modified crops (GMO) such as corn and soybeans, are linked to cancer. Hence, foods that contain significant amounts of carcinogenic contaminants, even if they are labeled as plant food, may not be helpful in preventing cancers (15, 16). Stomach cancer is also associated with dietary factors, such as the frequent consumption of salt-preserved foods and pickled vegetables, which may increase the risk of damage to gastric mucosal cells (16, 24).

As an effective alternative/complementary solution to hypothetically utilize the reversed Warburg effect in favor of normal cells, it is proposed to sufficiently consume certain foods and drinks that have alkalizing effects in human body (except for alkaline water or baking soda). Based on the alkalizing diet theory and related food charts, adequate consumption of certain nutrient-rich plant-based foods that form alkaline metabolic waste, including natural and raw/fresh vegetables such as garlic, red onion, celery, carrot, onion, and on-tree sun-ripened fruits such as dates, lemons, sweet apples, oranges, figs, mangos, and raw almonds, can help maintain the acid-base balance and improve health (16). On the other side, the excessive consumption of foods that form acidic metabolic waste, such as processed red meat, commercial dairy products, confectioneries, coffee, sugary drinks, and nutrient-depleted foods such as factory-processed products, which are common in typical Western diets, is linked to some cancers (25). A balanced, alkalizing diet may help maintain optimal blood pH and improve oxygen saturation, which, according to the Warburg effect, may be potentially helpful in resolving hypoxia and acidosis and reducing the risk of cancer (15, 16).

Studies show that, in addition to following a healthy diet, autophagy (an intracellular degradative and self-digesting process) can play a key role in maintaining cellular homeostasis by regulating oncogenes and tumor suppressor genes, contributing to the maintenance of normal cell functioning under different stressful conditions. Particularly during the early stages of tumor development, autophagy can eliminate damaged organelles, cells, and old proteins, preventing the damage triggered by carcinogens. In addition, molecular studies have shown that nutrient deprivation with a suitable fasting method that can maintain blood glucose levels within the normal range, can trigger autophagy and improve cell survival by providing an alternative source of energy from recycled cellular materials, bearing in mind that the relationship between autophagy and cancer may be stage-dependent (27-29).

4. Regional Studies on Natural Cancer Resistance

Global statistics on the age-standardized incidence rate (ASR) of cancer published by the International Agency for Research on Cancer (IARC) for the age groups of 0-60 and 60+ years have been shown in Figure 1, providing age-adjusted data that allow for meaningful comparisons of cancer incidence rates between different countries. Particularly, for the age group of 0-60 years, the global trends of cancer incidence are totally independent of the median age or life expectancy (25, 30).

Cancer incidence ASRs indicate a great areal variation and different global trends for each type of cancer. Based on cancer rate statistics in different age groups, the ASR of cancer is significantly lower in African, Mediterranean, Arabian, Persian Gulf, and South Asian countries, where people often live and eat according to healthy traditional cultural rules. However, in Western industrialized countries, such as the United States of America, Denmark, and Australia, the ASR of cancer is significantly higher,

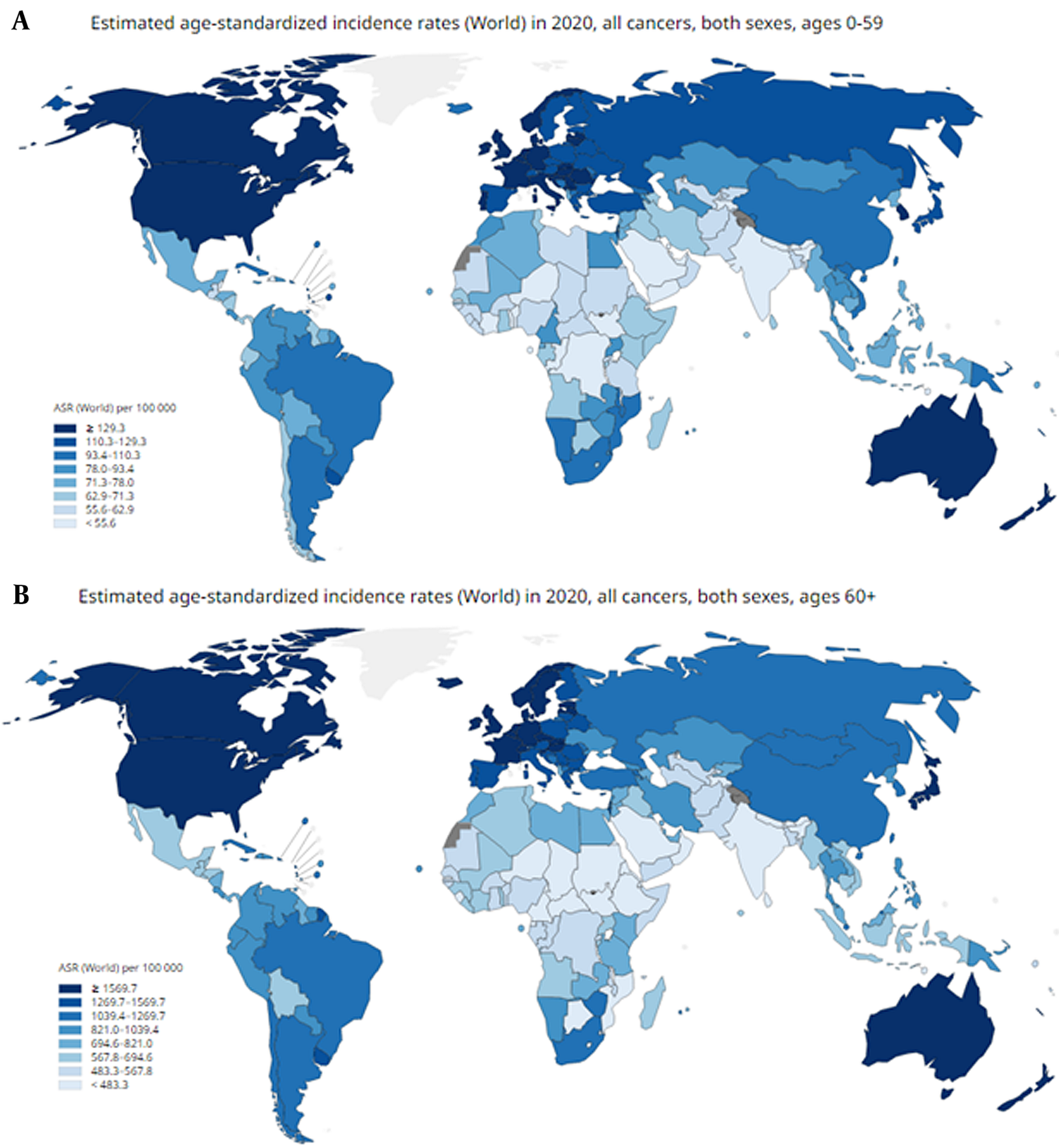

Figure 1. Worldwide cancer statistics for all cancers in the age groups of 0 - 59 and 60+ years (IARC, 2020).

which may be due to people frequently following Western dietary habits and consuming acidogenic diets (16, 25, 30).

For more detailed evaluations, cancer statistics and natural resistance to cancer can be studied in separate regions. For instance, Ramsar, a green city in the north of Iran, is known to have the highest natural background radioactivity on earth, where local/original residents of the city have developed a natural resistance against radiation. In this city, some people live in houses made of radium-contaminated bricks, emitting high levels of radioactive radon gas indoors. Nevertheless, the incidence of lung cancer among Ramsar's residents is even lower than the world's average. In contrast, immigrants who have moved from other cities to Ramsar show much higher rates of cancer and related mortality. As a result of the unique characteristics of cells in the bodies of Ramsar's natives and their successful adaptation to a highly radioactive environment, they were once listed as NASA's preferred human beings for traveling to Mars (31-34).

The improved resistance of body cells to cancerous transformation in the natives of Ramsar may have been achieved over several hundreds to thousands of years. Our interviews with these people indicated that over generations, they could promote alkalizing diets and healthy lifestyles as a habit. Typical diets in Ramsar mostly contain regionally-grown fresh vegetables and sun-ripened fruits, and natural local garlic (either raw or cooked) is often consumed in most of their meals. People from Ramsar often eat locally grown raw garlic in almost every meal and use garlic, onion, tomato, eggplants, olives, and other alkalizing foods when cooking and preparing their daily meals. These foods are generally rich in anti-cancer substances and have strong alkalizing properties. In addition, original people from Ramsar normally avoid processed or fast foods; instead, they often prepare their meals by themselves using natural local ingredients. Furthermore, they consume local animal products in moderation and balanced meals containing plenty of fresh or dried vegetables. Such healthy and balanced eating habits may have helped them to naturally adapt to the radioactive environment by creating suitable cellular conditions in their bodies. According to the Warburg effect, these cells are less likely to mutate and have increased resistance to radioactivity. Some studies also confirm that the frequent consumption of raw garlic can significantly reduce the risk of lung cancer (35).

In Ikaria (a Greek island), people are exposed to radioactivity and Radon gas (36), but not only cancer incidence is generally lower in this region than in other European countries, but also the residents of this island live nearly a decade longer on average, and many of them pass 100 years of age without developing odd non-communicable diseases (37). The reason might be due to their balanced alkalizing dietary habits such as regular consumption of legumes, wild greens, potatoes, olive, olive oil, local vegetables, sun-ripened fruits, and sea foods (36, 37). Such traditional diets are mostly balanced in terms of alkalizing effects on the human body (16).

In Hungary, the ASR of lung cancer and colon cancer incidence is the highest (No.#1) in the world (30). In this country, building materials in some areas have elevated natural radiation, some of which greatly exceeds the world's average. Also, across the country, there are several hot-water springs containing toxic metals and radioactive elements, leading to the natural radioactivity of drinking waters in some regions of Hungary beyond the worldwide average (38). In addition, Hungarians often follow an unhealthy diet and have a low intake of fruits and vegetables (39), causing Hungarian dishes to have acidifying features. These unhealthy dietary habits, together with exposure to high concentrations of heavy toxic metals and radioactivity, maybe the possible reasons explaining the substantially high risk of lung cancer and colon cancer in this country.

According to the data published by the International Agency for Research on Cancer in 2020, Bhutan, a country in the north of India, has the lowest ASR of cancer worldwide in all age groups, including the elderly, younger people, and children (30). Bhutanese have a strong connection with nature, and their foods are mainly locally grown and naturally produced; plant-based foods are frequent in their diet, and their intake of animal-based products is very limited due to religious interests in vegetarianism. Bhutanese normally follow their traditional dietary habits and lifestyle in a way that most visitors to the country report that they have not seen such a lifestyle elsewhere (40, 41). In addition, food safety regulations in Bhutan control all procedures in the entire food chain with a focus on following traditional farming and avoiding food production industrialization as much as possible to ensure the production of natural, healthy, and safe foods. For instance, in 2013, Bhutan became the first country in the world to turn its agriculture completely organic, banning the sales of chemical pesticides and herbicides and relying on its own animals and farm waste as fertilizers (42). In addition, the cultivation and import of GMO products are banned in Bhutan (43). Interestingly, in Bhutan, the average incidence rates of breast and prostate cancers are significantly lower than in Western populations (30). In general, for the most common cancers in the world, ASRs of cancer incidence are relatively low in Bhutanese, except for limited types of cancers, such as stomach cancer and cervical cancer, whose incidence rates in Bhutan are relatively high (30), while these specific cancers are preventable by some specific lifestyle modifications (25). For instance, consuming salt-preserved vegetables, generally a common eating habit of Bhutanese, is a risk factor for stomach cancer (44), so by reducing/eliminating salt-vinegar-preserved vegetables from their diet, the risk of stomach cancer, the most common type of cancer in Bhutanese (30), can be significantly reduced in this country.

"African Mediterranean countries, in general, have relatively lower cancer incidence rates than Western countries, which could be related to their dietary habits and lifestyle. The Mediterranean diet consists primarily of vegetables, legumes, whole grains, potatoes, fruits, fish, and extra virgin olive oil, which may reduce the risk of diet-associated cancers (45-47). In a study on the effects of dietary habits on the risk of cancer among African Americans, those who followed fatty meat-rich diets (a typical Western diet) had a significantly higher risk of colorectal cancer than those consuming African foods rich in beans and vegetables grown in rural regions (48).

The findings of our study suggest that the risk of cancer may substantially be lowered by adhering to healthy, balanced, alkalizing natural diets that can boost the resistance of cells against cancerous transformation.

5. Conclusions

Complex systems and mechanisms, such as those involved in the survival of cancer cells and tumor growth, may be misunderstood when our analytical framework for dealing with these phenomena is not fully integrated. Understanding the root causes of cancer and the signaling pathways controlling the metabolism of cancer cells bring new insights to treating cancer as a metabolic disease and developing some complementary or alternative solutions accordingly. Our review of the literature suggests that controlling the cellular environment, particularly in terms of oxygen content and pH, may be helpful in preventing and treating cancer. According to regional cancer statistics, environmental factors and dietary habits (i.e., the quality and type of foods) seem to be among the key factors governing cancer development. Under specific conditions, the effects of dietary factors on the risk of cancer may even be more significant than environmental factors. In general, dietary habits can be important regulators of cancer development because they can potentially render cells resistant to spontaneous and forced mutations. Hence, effective nutritional interventions for cancer prevention should be combined with healthy lifestyles and avoiding exposure to environmental carcinogens to be effective in preventing this disease.

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Footnotes

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