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Dietary Aspects in Cancer Prevention — A Mini-Review

Mohamed Abdulla and Sangeeta Shukla

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1. Introduction

Currently, there are more than 12 million new cancer cases each year worldwide, and it constitutes approximately 12% in mortality statistics. The cancer incidence remains high in south East Asia. In recent years, an alarming increase in cancer incidence has been observed in parts of central and Eastern Europe. A number of studies have implicated chronic inflammations as of the factors involved in cancer development, but the specific ways chronic inflammation lead to cancer is not very clear at the moment. It has been estimated that almost 20% of all cancers are associated with chronic inflammation. Many cancers arise from sites of infection, chronic irritation and inflammation. Tumor necrosis factor (TNF alpha) is a pleiotropic cytokine, is known to regulate multiple inflammatory cells (neutrophils and macrophages). The assumption that nutrition is an important factor in the risk of cancer development dates back to ancient times. Wiseman in 1676 suggested that cancer might arise from “an error in diet” and he recommended restriction of salt and meat in the diet as a means of cancer prevention [1]. During the early decades of twentieth century, the idea of diet modification in cancer prevention gained momentum and several recommendations for the increase or decrease of various dietary components have been tried. Shah in 1907 advocated a prudent dietary regime designed to reduce the risk of cancer development, with more food of vegetable origin, less meat, alcohol and tobacco [2]. Along with the scientific advances during the early part of the 20th century, two hypotheses on the environmental cause of cancer were developed. The first one related to occupational exposure of workers to chemical carcinogens and the other one focused on various dietary components. Hoffman in 1931 indicated that increased amounts of fats in diets, sugar and bread as possible contributing factors to some types of cancer development [3]. At the same time, a few epidemiological surveys indicated that a number of dietary components may contribute to the pathogenesis of cancer [4,5]. During the last 50 years, increased attention was focused on the preventive and modifying actions of diet on cancer prevention in general. An early analysis of cancer incidence worldwide indicated that over 50% of cancers is due to external factors and hence theoretically preventable [6-10, 18]. This was further reinforced by a large

number of descriptive, ecological and epidemiological studies. Studies by Doll and Peto indicated the importance of antioxidants, leafy vegetables, fish and several other bioactive micronutrients in cancer prevention [7]. In 1982, The National Academy of Sciences in USA proposed six interim guidelines to reduce the risk of cancer [8]. This included reduction of dietary fat, increased consumption of food rich in fruits and vegetables, salt restriction, decreased intake of smoked food-stuffs and reduced intake of alcohol. This review will discuss some important concepts in cancer prevention by diet modification.

2. Cancer pattern

As mentioned in the introduction, cancer is a major cause of mortality throughout the world. In developed and fast-growing countries, the mortality due to cancer is generally exceeded only by mortality from cardiovascular diseases. According to a report in the Lancet in 1977, the World Health Organization (WHO) identified the 4 of the 10 leading causes of mortality worldwide. They are from Ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease and lung cancer. In an earlier report, the fourth leading cause of death worldwide was due to nutritional disorders. The authors in that report predicted that even in 2020, the fourth leading cause of death would be due to nutritional disorders [11]. The incidence of lung cancer is likely to increase in the coming decades, especially in fast-growing countries like China, India, Brazil, South Africa and Russia (BRICS) due to smoking, environmental pollution and other unknown factors. The incidence of cancer in our ancestors (gather-hunters and pastoral people) living in remote areas of the globe was very low. The average lifespan on the other hand was very low in those days. According to some experts, the dramatic shift away from the eating habits of our ancestors is probably responsible for fostering many of the “diseases of civilization” including cancer [12]. For males and females taken together, the incidence of most of the common cancers are shown in Table 1.

Cancer site	Males(%)	Females (%)
Lung	18.6	6.7
Stomach	11.9	7.6
Colorectal	8.4	8.6
Prostate	7.5	—
Breast	—	18.6
Oro-Pharyngeal	7.3	3.8
Esophagus	6.1	—
Bladder	4.4	—
Liver	7.1	—
Ovary	—	3.9
Others	28.8	17.4

Table 1. Estimated number of new cases in men and women in 1996

Rank	cancer site	New cases	%of all cancers
1	Lung	1608	12.7
2	Breast	1384	10.9
3	Colorectal	1235	09.8
4	Stomach	989	7.8
5	Prostate	899	7.1
6	Liver	750	5.9
7	cervix uteri	530	4.2
8	Esophagus	482	3.8
9	Bladder	383	3.0
10	Non-Hodgkin lymphoma	356	2.8
11	Leukemia	350	2.0
12	Corpus uteri	288	2.3
13	Pancreas	279	2.2
14	Kidney	274	2.4
15	Others	1879	13.8

Table 2. Cancer statistics. Cases diagnosed in 2008 (100s). Both sexes

As can be observed, lung cancer is the most common cancer worldwide contributing to nearly 13% of the total number of cases diagnosed in 2008. Breast cancer in women is the second common cause of cancer followed by colorectal cancer. The number of lung cancer in man has decreased a little from 18.6% in 1996 to 16.5% in 2008 [20]. The global cancer burden doubled in the last three decades of the twentieth century and it is estimated that it will triple by 2030. The major increase would be in low and medium resource countries in Asia, Africa and Latin America. At the same time, there is a clear message of hope that some of the cancers can be prevented with advances in sophisticated technology combined with genetic and other screening techniques.

3. Diet and carcinogenesis

Like many other chronic diseases, the major underlying causes of cancers are environmental in nature. Apart from genetic factors, food and nutrition are important modifiers of cancer risk. Studies of immigrants in various parts of the world support the concept that many human cancers arise from interaction between the environment and constituents of the cells and their membranes. In the past, the concept of etiology of cancer has generally focused on four agents: viruses, radiation, chemical carcinogens and environmental pollutants. Currently, it is estimated that environmental factors are primarily responsible for a significant percent of all

human cancers [13]. Some of these factors include exogenous chemicals, tobacco smoke and a number of dietary constituents. During the 1930's and 1940's, a number of studies showed repeatedly that diet modification in experimental animals exposed to chemical carcinogens resulted in a beneficial effect [14]. During this interval, it was shown that dietary constituents such as vitamins and anti-oxidants had a modifying effect in experimental cancers. Humans are continuously exposed to a variety of carcinogens in their immediate environment. These include carcinogens in the smoke, alcoholic beverages, industrial carcinogens such as asbestos and several non-essentials dietary constituents. The compounds found in diet that are known to be carcinogens include aflatoxins, heterocyclic amines, N-nitroso compounds and similar chemicals and polycyclic aromatic hydrocarbons. With the current advances in transportation and export, it is common to find food articles cultivated throughout the world in most parts of the world. In the fast growing countries, many chemicals and fertilizers are extensively used to increase the food production. When such products are exported to industrialized countries, there is additional risk for the intake of dietary components containing carcinogens and toxic residues even in affluent countries. Carcinogens, heavy metals and toxic residues are known to damage DNA in several ways and that detoxification can be a possibility at the early stage in the metabolic pathway. The efficacy of detoxification can be vital in determining the carcinogen potency. Dietary intervention is probably one way of influencing the carcinogen metabolism.

Food-stuffs containing large amounts of plant materials are good sources of a number of bioactive components. Such compounds and their derivatives are shown to inhibit carcinogenesis in a number of experimental systems involving initiation, promotion and progression. The role of diet in the final carcinogenesis is, however, not very clear at present. Recent studies show that many carcinogens and tumor promoters can produce reactive oxygen species (ROS) that can induce DNA damage and consequent chromosomal breakage. Dietary carcinogens mentioned earlier along with the cooking process and spoiled foods can add further to the body's carcinogen load. If diets are rich in fruits and vegetables, some of these carcinogens may be detoxified before they become bioactive. During the second stage of cancer development, restriction of energy intake and increased physical activity may have some additional beneficial effect. In the final stage of tumor development when DNA damage plays a crucial role, the amount of single nutrients such as folate, zinc and selenium are known to play some role in the prevention of chromosomal damage and DNA methylation.

4. Reactive oxygen species, antioxidants and cancer prevention

Carcinogenesis encompasses a prolonged accumulation of injuries at several different biological levels and includes both genetic and biochemical changes in the cells. DNA strand breaks are one such injury. Agents that induce DNA damage, and thereby cause cancer include ionizing radiation, ultraviolet light, tobacco smoke, ozone and oxides of nitrogen in the polluted air. As mentioned earlier, reactive oxygen species (ROS) is known to cause damage to the DNA and it is very likely that the carcinogens mentioned above produce cell damage through the action of reactive oxygen species. It is also known that the

damaging effect of free radicals (ROS) are encountered by enzymes and small molecules such as glutathione, acetylcysteine and uric acid. Certain vitamins like carotene derivatives, minerals and certain trace elements may also counteract the action of free radicals [23]. Under normal circumstances, the defense systems in the body work efficiently and balance the oxidants produced in the cells during various metabolic activities. When oxidant stress is increased, additional antioxidants may be required. The most important antioxidant enzymes are superoxide dismutase, catalase and peroxidases. Among the micronutrient antioxidants, the important ones are vitamin C, Vitamin E, beta-carotene and the essential trace element selenium. The richest source of these nutrients is fresh fruits, vegetable oils, nuts and grain. Most plants contain phytochemicals such as flavanoids and polyphenols. A number of experimental studies have shown that they have antioxidant activities. Flavanoids are water soluble pigments found in exotic fruits, seeds, leaves and bark. These pigments can scavenge reactive oxygen species and thus can prevent breaking lipid peroxide chain reactions. According to Carmia, experimental studies show that the phytochemicals can protect cells from ionizing radiation, inhibit mutations and block prostaglandin synthesis and thus prevent multistage carcinogenesis [16]. Polyphenols found in green tea and grapes have greater antioxidant potential than that exerted by vitamin C and E [17]. Ellagic acid is a phenol found in grapes, various berries and it has been found to protect liver toxicity leading to cancer. Garlic, onions, shallots and leeks also contain several natural antioxidants including flavanoids, vitamin C, selenium and sulfur compounds that increase the metabolic disposal of chemical carcinogens. In recent years, it has been reported that dark chocolate and red wine also contains phytochemicals and may scavenge reactive oxygen species [18]. With the increased pollution of the environment, it is likely that many of these useful components in plant materials may decrease, especially in fast-growing countries.

Until recently, scientists engaged in the study of aging thought that the ROS played a crucial role in aging process. Now, the theory of aging due to oxidative damage is being replaced by other factors. Over the course of past few years, many experiments designed to further support the idea that the ROS and other reactants drive aging have shown very challenging and controversial results. What these results show is that under certain situations, the high energy ROS may not be dangerous but useful and healthy. A final proof, however, for the beneficial effect of free radicals is currently lacking. It is hard to imagine that antioxidants will ever fall out of favor completely. As mentioned earlier, the amounts of natural antioxidants found in plant material, fruits and nuts ought to have a beneficial effect from an evolutionary point of view. There are millions of people in countries like India who survive mainly on food-stuffs of vegetable origin. So are many other species thriving in the forests. Nature must have designed its own mechanisms to deal with environmental factors that influence health and disease.

Table 3 shows a list of various dietary components that have shown to have some beneficial against detoxification of chemical carcinogens.

Nutrient	Active component	Known function
Tea	phytochemicals	Antioxidant
Chocolate	Polyphenols	Antioxidant
Plants	Phytochemicals	Hydroxyl scavenger
Grapes	Catechin	Antioxidant
Olives	Polyphenols	Antioxidant
Soybean	Isoflavones	estrogen-like action
Garlic and Onions	Flavanoids, sulfur	disposal of carcinogens
Vegetables	flavanoids, Indoles	DNA damage protection
Selenium	Antioxidant enzymes	Antioxidant
Vitamin C	Vitamin C	Scavenger of ROS
Vitamin E	Vitamin E	Lipid peroxidation protection
Beta-Carotene	provitamin A	Antioxidant
Tomatoes, salmon	Lycopene	Antioxidant
Red wine	Phenols	Antioxidant

Table 3. List of selected nutrients that have antioxidant potential

As can be seen from table 3, a large number of constituents in fruits, vegetables, green tea, grapes, pepper, red wine and salmon possess substances that have anticancer potential. Apart from the carcinogen exposure from the immediate environment, a number of substances in cooked, grilled and smoked meat can contribute to the carcinogenic load of the cells in the body. The extents to which such carcinogens induce cancer development depend on the quality and quantity of the food consumed regularly and the concentration of scavengers available during the metabolism of cells. During the intermediate stage of cancer development, the restricted energy intake and increased physical activity can have significant additive effect on cancer development through the action of hormones and growth factors.

Reactive oxygen species are also known to be associated with aging process in a number of species, including humans. It is a common observation that the prevalence of many human cancers is high in aging populations. Average life-span in most developed countries as well as in many fast-growing developing countries in Asia, Africa and Latin America has increased tremendously during the last few decades. According to several research groups, cellular damage caused by oxidation is one of the main mechanisms of aging. According to this theory, rampant oxidation in the cells mangles more and more lipids, proteins, and snippets of DNA and other key components of cells over time, eventually compromising tissues and organs and thus resulting in organ failure. Recent studies, however, showed that increase in certain free radicals in mice and worms correlate larger life span. Indeed, in some circumstances, reactive oxygen species seem to signal cellular repair methods. Experimental studies by several groups in the United States of America

show that rather than causing aging, some ROS may prove beneficial. One possibility is that certain number of ROS stimulates an organism's internal repair mechanism to get to work. In genetically modified roundworms which produced high levels of certain ROS, it was observed that these worms lived much longer than the normal worms. And further, when these worms were fed with antioxidants, their longevity advantage disappeared. In the February issue of *The Scientific American* this year, Melinda Moyer has summarized the results of recent studies and her title of her article is "The Myth of Antioxidants" [25].

It appears that the final verdict about the role of ROS in aging and cancer and the beneficial effect, if any, of antioxidants is yet to come. In most developed countries, the consumption of antioxidants as OTC products is very high. These antioxidants include Vitamin E, beta-carotene and Vitamin C. As mentioned earlier, epidemiological studies show that people who eat lots of fruits and vegetables, which are rich in these antioxidants, tend to live longer and are less likely to develop cancer compared to those who eat normal diets. So, it seemed obvious that supplementing daily diets with antioxidants should lead to a better life. But the results of the most rigorously designed studies do not support that hypothesis. Indeed, the evidence shows that some people who take certain vitamin supplements are actually more likely to develop life-threatening illnesses such as lung cancer and heart disease [18]. The influence of mass media is one reason for the high consumptions vitamins and antioxidants. We need more studies and further proof to establish the relation between ROS and antioxidants. Until that time, we have to cope with controversy about ROS, aging, and cancer.

5. Minerals and trace elements

Many of the minerals and trace elements are nutrients that cannot be synthesized by the body. They are involved in all phases of cellular metabolism in one way or another. Trace elements are integral parts of very many enzymes including the ones that scavenge ROS. The minerals and trace elements that are of interest include calcium (together with vitamin D), magnesium, iodine, iron, selenium and zinc. Evidence suggesting the relationship of other minerals and toxic heavy metals with cancer is not substantial and as such, they are not described in this review. The dietary intake of minerals and trace elements in various parts of the world vary significantly due to varied eating habits, culture and tradition, climatic conditions and the amount present in the soil. Studies by the current authors indicate that the intake of a number of important trace elements and minerals is below the current recommended levels [18]. The intake levels are especially low in the elderly [18]. The richest source of calcium is dairy products and fish. Selenium levels in the soil vary greatly in different regions of the world. Australia, New Zealand and Scandinavian countries have low selenium levels in the soil. Selenium is mainly found in meat, fish and certain cereals [18]. Hem iron is mainly found in foods of animal origin. Non-hem iron is found in plant foods and legumes. Zinc is rich in seafood, meat and unprocessed vegetable material. Oysters are one of the richest sources of zinc. Modern food processing destroys significant amounts of trace elements than found in the natural material. For iodine, the best sources are sea food and seaweed.

Evidence on the relationship between calcium and cancer was considered by the 1982 and 1989 reports of the national Academy of Science [19, 20]. According to the report, there are some epidemiological evidence linking high calcium intake and the cancers of colon and rectum. High calcium intake together with vitamin D has also been documented to have some effect in the risk of developing colorectal cancer. Data for other cancer sites linking calcium intake is inconclusive.

With regards to iron and cancer, there is some evidence that diets high in iron may possibly increase the risk of liver and colorectal cancers in humans. In humans, the dietary iron overload is rare except in some ethnic groups in Africa where iron utensils are widely used for cooking. Data from case-control studies are, however, inconsistent. Iodine in the body is related to thyroid function and it has been proposed that a high intake of iodine may induce thyroid cancer. Ecological and experimental studies support the association between high dietary intake and the risk of developing thyroid cancer.

Selenium has attracted considerable interest in cancer research during the middle part of twentieth century. During the early 1960's, it was shown that selenium is an integral part of the antioxidant enzyme, glutathione peroxidase [19]. Currently, selenium is also recognized as an essential component of iodothyronine 5'-deiodinases as well as a few other proteins without any known functions. During the last few decades, a number of experimental studies have indicated the importance of this trace element for cancer prevention. A few epidemiological studies have confirmed such an association even in humans. Several selenium compounds have been found to inhibit or retard carcinogenesis in a variety of experimental animal models using chemical, viral and transplanted tumor models. A prospective case control study in Finland showed a link between selenium status and cancer development. Studies of humans have tended to show selenium status and cancer mortality to be inversely correlated. The soil in Finland was enriched by selenium due to low levels in the environment and studies afterwards did not show any specific pattern on the relationship between selenium and cancer. Other epidemiological studies in low soil areas have failed to show the protective effect of selenium on cancer development. Any potential anticarcinogenic influence of this trace element may relate to its antioxidant properties. This, however, is controversial at present. In some studies, selenium has been shown to suppress cell proliferation, to enhance immune response, and to alter the metabolism of carcinogens to less toxic compounds [21]. The overall interest in selenium as a protective trace element against cancer, however, has faded during the last two decades.

Zinc is another trace element that has attracted considerable interest in human health and disease. Zinc was recognized as an essential nutrient for human growth and development several decades ago. Marginal deficiency of zinc is widespread throughout the world. The prevalence of nutritional zinc deficiency is high in populations consuming large amounts of cereal proteins which contain organic phosphate compounds, such as phytate. Even in affluent countries; it has been observed that mild deficiency of zinc occur in vulnerable groups such as the elderly [18]. Hormonal effects of zinc deficiency include decreased testosterone level in serum of males, increased serum prolactin levels, and decreased activity of serum thymulin, a zinc-dependent thymic hormone. This trace element has attracted much interest in cancer

research since Cristo in 1922 showed high amounts in cancer tissues [22]. Many research groups in the past have shown that patients with cancer in general have low plasma zinc levels. It is assumed that this decrease is due to the high demand of the tumor tissue, especially when they have a high rate of DNA synthesis. As mentioned earlier, zinc is essential for growth and development of normal tissues and as such it may be needed even more in cancer tissues. Opinion, however, differs regarding the role of zinc in the induction and proliferation of malignant cells. A high zinc intake has been associated with lower incidence of gastric and esophageal cancers in certain parts of the world. Our own studies have shown that low dietary zinc inhibit the growth of oral cancer in experimental animals [22]. Once the tumor starts growing, the requirement becomes high and plasma levels go down. Many essential trace elements like zinc have dual functions: in low concentrations, they show signs of specific disease and at high concentrations, signs of toxicity. Iron is a trace element that shows such a pattern: when the intake is low, it produces anemia and at higher concentrations, it shows toxicity symptoms such as hemochromatosis and liver injury. In general, only little is known about the role of trace elements in carcinogenesis.

6. Summary

Cancer is a major killer throughout human history. In 2008, there were an estimated 12.7 million cancer cases throughout the world. This number is expected to increase to 21 million by 2030. Cancer changed its grasp as humans advanced industrially and technologically. Although the risk of a few cancers has declined significantly in affluent countries during the last few decades, the incidence of other cancers at sites of lung, breast and prostate has increased. Lung cancer is the most common cancer worldwide contributing nearly 13% of the cases diagnosed in 2008. Breast cancer (in women) is the second followed by colorectal cancer. Carcinogenesis encompasses a prolonged accumulation of injuries at several different biological levels and includes both genetic, biochemical and environmental changes in the cells. At each of these levels, there are several possibilities of intervention in order to prevent, slow down or even halt the gradual march of healthy cells to malignancy. Diet modification is one such possibility. A number of natural foodstuffs, especially fruits and vegetables contain significant quantities of molecules that have chemoprotective potential against cancer development. Such molecules include vitamins, certain mineral and trace elements and a variety of other substances with antioxidant properties. Carotenoids, flavanoid polyphenols, osoflavones, catechins, and several other compounds found in cruciferous vegetables are molecules that are thought to protect against the deleterious effect of reactive oxygen species (ROS). A number of epidemiological and experimental studies have shown that some of the above-mentioned antioxidants can reduce the risk of cancer. Consistent observations during the last few decades that cancer risk can be reduced by diets rich in fruits and vegetables, legumes, grains, nuts, green tea and red wine have encouraged research to identify several plant components, especially phytochemicals that protect against DNA damage. Many of these substances are known to block specific carcinogen pathways. Very recent studies have, however, questioned the role of ROS, aging and cancer development. Certain reactive oxygen

species have been found to be useful as part of the defense mechanism. Other studies have shown that high doses of anti-oxidant supplements may not provide protection against ROS as it was originally thought. We need a lot more proof about the role of ROS in health and disease. The debate on the role of antioxidants as protective agents against cancer is likely to continue. Only little is known about the role of trace elements in cancer.

Author details

Mohamed Abdulla¹ and Sangeeta Shukla²

1 Department of Primary care, Swedish Medical Board, Olofström, Sweden

2 Department of Zoology, Jiwaji University, Gwalior, India

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