

Review Article

Insight to Role of Nutrition in Carcinogenesis

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ABSTRACT

Cancer is a disease in which body cells divide uncontrollably, with potential to invade and metastasize throughout the body via different routes. According to WHO, Nutrition is a critical part of health and development. Lack of nutrients affects the mind as well as the body. Although each group of nutrients play a vital role and unique function in our body, they all are essential as they work together and contribute to maintaining good health. Nutritional intake and quality can be impacted by poor oral health and might elevate the risk of several systemic pathologies. Since, nutrients are comprised of both defensive as well as carcinogenic factors, henceforth mutagens might develop the risk of carcinogenesis, especially in predisposed individuals having genetic mutations. There are many diseases which can be caused due to lack of nutrition but one of them is cancer in which deficiency of it leads to many different sorts of cancer as well as on the other hand can be the source by which we can prevent it and lower the potential risk of cancer. Cancer prevention diets have some protective elements which help to fight cancer. Henceforth, in depth introspection with the healthcare provider is of utmost importance to perceive the patient's nutritional requirements. This signifies the role of nutritional therapy on relieving symptoms and providing the best possible intervention so as to obtain highly favourable prognosis in cancer patients.

INTRODUCTION

Presently, Cancer is considered to be the foremost causes of mortality throughout the world. It doesn't affect health physically but psychologically too which further leads to many other problems. Nutrition is one the major factors which affects the health of patients suffering from cancer whether it is oral, breast, lung, prostate or any other origin.^[1]

Cancer is a complex or complicated disease which

doesn't have any particular source of origin; it can be from multiple reciprocal origins from genes and environment.^[2] Alterations in the nutritional as well as metabolic and nutritional might affect the recovery and prognosis of the individual suffering from malignancy.^[3] Nutrition has a highly significant role in the health of patient as there are many different metabolic alterations or nutritional deficiency which influence survival of cancer

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patients as well as the recovery rate.

Malnutrition is a situation that occurs as a result of lack of calories or key nutrients like vitamins or minerals, which can be accompanied by malabsorption, defined as a term used for wide range of disorders in which body is unable to absorb nutrients from food further leads to indigestion or malnutrition. Both these conditions further ensue anorexia and consequently, weight loss. Furthermore, malnutrition can alter treatment outcomes as it affects immune system, delay wound healing, loss of muscle mass, fatigue, weakness, pre- or post-operative complications and impair tolerance, response to antineoplastic treatment which extends hospital stay, increased the chance of having hospital acquired diseases, increase risk of treatment complications and possibly reduce recovery as well as survival rate of patient.^[4]

Cachexia or wasting syndrome is a complex syndrome in which a general state of ill health involves marked loss of muscle mass and weight loss. When it is associated with end stage cancer it is called cancer cachexia. It has severe affect on patient's life quality and also associated with poor response to chemotherapy which further lead to decreased survival rate.^[5]

A disease free oral cavity empowers an individual to execute routine daily activities without any limitations. However, any pathology within the oral cavity might disturb regular oral functions. Continuous discomfort and a functionally

deregulated oral cavity might lead to decreased self-confidence and compromising his or her Quality of life.

Oral potentially malignant disorders (OPMDs) depicts the group of pathologies that are clinically manifested with increased chances of developing oral cancer. The malignant transformation might be in a clinically visible precursor pathosis or in clinically normal appearing oral mucosa. Recently, potentially premalignant oral epithelial lesions (PPOEL) has been considered as a newer term to illustrate both histological and clinical pathology with malignant potential. This group comprises of varied oral lesions such as leukoplakia, speckled leukoplakia, OSF and lichen planus.^[6]

Diligent evaluation of such lesions by an experienced specialist is of extreme significance to rule out any malignant transformation in the early stages to decrease the cancer burden. OSMF being an OPMD has affected approximately 5 million people in India and is also highly prevalent in Indian subcontinents. It is a chronic disease and highly progressive in nature. Although the etiology is multifactorial but arecoline within areca nut is the main source of disease initiation. OSF is generally illustrated by an early sign and the symptoms of burning sensation within oral cavity along with vesiculation and ulceration followed by blanching of the oral mucous membrane. This lead to elevated stiffness and marked fibrosis of the tissues resulting in reduced mouth opening.

TABLE 1: ROLE OF NUTRITION IN PATHOGENESIS

VITAMIN	ROLE IN CARCINOGENESIS	DEFICIENCY
Vitamin A	<p>It has main role in cellular differentiation, proliferation, growth of bone tissue, immune function and activation of tumour suppressor genes. CRBP-1 expression seen in many tumours.</p> <p>The loss of CRBP-1 expression may compromise retinoic acid metabolism by reducing retinol transport and blocking formation of retinyl esters leading to loss of cellular differentiation and tumour progression.</p> <p>It is crucial for immune defense, maintaining the linings of oral cavities, bone growth, normal cell development, preventing the keratinization of mucous-forming cells, allowing for cell differentiation, stimulating osteoclasts, and enabling normal tooth spacing. [10]</p>	<p>Vitamin A deficiency results in night blindness, epithelial proliferation and maturation defects, hyperkeratotic white patches, xerostomia, gingivitis, periodontitis, tooth morphogenesis defects, decreased odontoblast differentiation, enamel hypoplasia.[11]</p>
Vitamin C	<p>It is an antioxidant thus scavenging free radicals, reduce Vitamin E degradation, inhibits nitrosamine formation, enhance detoxification of cytochrome p450. Scurvy and periodontitis both display gingival bleeding but comprise different diseases.</p> <p>The numerous periodontal illnesses are brought on by oral microbes in tooth plaque, and how the body responds to them is greatly impacted by how well or poorly leucocytes and monocytes function.</p>	<p>Although numerous infections and systemic disorders induce gingival bleeding, avitaminosis C does not cause widely seen periodontal disease, but it will aggravate the previously developed periodontitis. [12]</p>

Vitamin E	Free radical scavenging, maintenance of membrane integrity, inhibits oral cavity carcinogenesis, reduce risk of developing oral cancer, cause reversal of premalignant lesion like leukoplakia, cytotoxicity, inhibits mutagenicity and nitrosamine formation.	Weakened Immunity Muscle Wasting and numbness Eye associated problems as vitamin E protects the eye from free radicals
Vitamin D	Inhibit tumour angiogenesis, stimulate mutual adherence of cells, enhance intercellular communications through gap junctions hence strengthen the inhibition of proliferation that result from tight physical contact with adjacent cells within tissue (contact inhibition). The ability of 1,25-(OH)2D3 to induce apoptosis and to inhibit invasion, cell proliferation, and tumour angiogenesis provides the antitumor activity in a variety of cells. In cancer cells, 1,25-(OH)2D3 activates inhibitors of cyclin-dependent kinases (p21, p27) and mitogenic growth factors (IGF-1, EGF), and promotes the activation of TGF- β , thus exhibiting antiproliferative properties.[13]	Bone and muscle diseases Fatigue
Vitamin K	Inhibition of proliferation, induction of differentiation, inhibition of potential for metastasis, induction for autophagy or apoptosis	Rare but can lead to fat malabsorption syndrome etc.
Iron	Cancer cells shows dysregulated iron homeostasis hence require more iron for metabolism and growth further in cancer cells pool of poorly defined ferrous iron increased further reactions occurs which form reactive oxygen species and which leads to DNA mutations, damage lipids and proteins resulting in either cell death or cell transformation. Iron efflux regulation by the combined action of the regulator hepcidin and the iron efflux pump ferroportin appears to play a significant role in tumorigenesis. A type of iron-dependent cell demise called ferroptosis involves the generation of reactive oxygen species.[14]	Anemia
Copper	Involved in proliferation or angiogenesis which are central	Fatigue, Neurological

	<p>for tumorigenesis and cancer development.</p> <p>Copper act on different molecular pathways leading to a proangiogenic response necessary for carcinogenesis process.</p> <p>Also increase the spread of secondary tumors.[15]</p>	<p>problems, muscle weakness, etc.</p>
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All cancers are multifactorial in origin. Cancers usually originate from one atypical cell progressing towards multiplication and thereby producing a profuse tumour tissue. Mutagens are the components that elevates the mutational rate and might also exponential rise of cancer progression. Henceforth, this is suggestive of the fact that all carcinogenesis are mutagens. Some human cancers are result of chemical carcinogens and that might be incorporated within the body via occupation hazards, diet and lifestyle of individuals.^[7]

Benzopyrenes are the most common carcinogen released via cigarettes. Chewing of tobacco chewing is also one of the major causes of oral cancer. Although, Glutathione-S-transferase (GST) is the main detoxicant of various carcinogens, including cigarette smoke but only about 5% of the population are lacking GST. Hence, this solves the mystery that why only some smokers are getting cancer and not all smokers.

Antimutagens are the substance that might interfere with tumour progression. Vitamin A and Carotenoids have the ability to reverse

precancerous conditions. Vitamin E being an antioxidant prevents damage by free radicals and superoxides. Vitamin C when regularly prescribed to persons working with aniline, prevented the occurrence of new cancer cases. Beans and leafy vegetables have proved to interrupt tumour promotion. Curcumin, the yellow component in turmeric, is known to prevent mutagenesis. Phenolic compounds regularly found in fruits such as grapes, strawberries, walnuts, etc. are antimutagenic.^[8] Green tea is depicted to be of high significance against chemically induced mutations. Melatonin being hormone released via pineal gland which is a small organ in vicinity of centre of brain, helps in controlling sleep cycle of the body. Literature suggests that melatonin supplements along with chemotherapy and radiotherapy might be of usefulness and aid in reduction of most of the adverse effects of treatment.

Despite oxygen being the lifeline of the cellular structures of human body, its varied conformational forms like reactive oxygen species could target cellular structures resulting in devastating effects. These free radicals are formed in the inner membrane of mitochondria where O₂ is catalysed to H₂O via cytochrome oxidase. Free radicals can

harm the body in large concentrations and harm all significant cellular components, including DNA, proteins along with cell membranes. Amongst all the free radical damages of cells, DNA damage contributes to the onset of carcinogenesis and other pathologies.^[9] It is formed physiologically or pathologically. It can be degraded by catalytic action of enzymes but if not destroyed, free radicals result to be highly destructive to the same cell since they consist of electron free radicals and thereby bind to almost entire molecules of the cell, which is termed as oxidative stress. Apart from these changes, free radicals can lead to split in single strands of nuclear as well as mitochondrial DNA, resulting in cell injury; which may cause malignant transformation. Antioxidants being endogenous and/or exogenous substances inactivate these radicals and include- Vitamins A, C, E, Sulfhydryl-containing substances such as cysteine and serum proteins like ceruloplasmin, glutathione along with transferrin.^[10]

The primary treatment options for cancer patients are chemotherapy, radiotherapy and the surgical aspect. In this treatment, antineoplastic drugs and radiation are used to kill cells that rapidly divide or by damaging the DNA. The anticancer agents work by either degrading tumour cells or altering their proliferation.^[11] But, the majority of such agents are in reduced quantity and also these are toxic drugs procured during therapies. But on the other side it has some toxic effects on our system which might be seen in oral cavity in the form of lesions or ulcers besides that, there are particular

lesions which are associated with chemotherapy or radiotherapy which is usually neglected by most of the people and also the doctors as they are not seeing this as a major problem from their aspect which further leads to unawareness of the diseases and common findings in oral cavity.^[12]

Cytotoxic drugs have some general toxicity as most of the time the cytotoxic drugs target profusely dividing cells, as the main classical target of such drugs are the precursors of nucleic acid synthesis. Rapid nucleic acid synthesis takes place during cellular multiplication. Suppression of bone marrow leads to certain systemic conditions such as thrombocytopenia, granulocytopenia, aplastic anaemia and agranulocytosis. The other complications of these drugs are infection and bleeding.^[13]

Lymphocytopenia and inhibition of functional activity of lymphocytes leads to immune suppression including both cell mediated and humoral immunity. As a result of this there is serious damage to epithelial surfaces, host specific systems are broken down and further increase susceptibility to all infections. Henceforth, it has been found that as a result of elevated turnover rate of epithelial cells with oral mucous membrane, oral cavity is highly susceptible to such drugs.^[9]

Chemotherapeutic drugs including methotrexate, doxorubicin and fluorouracil can produce stomatitis as an initial manifestation of toxic effect of drug. Stomatitis is a condition which causes painful sores

in the mouth in which patients are uncomfortable to eat. Also, the gingiva and oral mucosa are continuously subjected to mild trauma and ulcerations are common during chewing.^[14] Oral flora which normally present in our normal cavity can become a source of infection due to increased pathogenicity as there is decrease in the host response. Immunity depression and neutropenia caused by drugs alternatively increases chance of oral infections. Thrombocytopenia might further lead to bleeding from gingiva. Xerostomia (Dry mouth) resulting as a result of continuous drug intake may lead to rapid progression of dental caries. It is not the disease but a symptom that produces serious effects on a patient's quality of life.

Therapeutic radiation for head and neck tumours is the foremost causes of xerostomia. The irradiated side of the gland majorly affected. The glandular atrophy after the radiation therapy could be attributed either to downfall in the glandular vascularity or to the immediate effect of radiation on highly sensitive and specialized epithelial cells of secretory nature. Dentition is also affected from reduced salivary secretion. Cytotoxic drugs also lead to nausea and vomiting. Vomiting causes erosion of enamel, chronic sore throat, redness of mouth and tongue.^[15]

Patients exhibit immunosuppression as a result of the host defensive system being compromised by the use of anticancer medications. Also, chemotherapy leads to bone marrow cytotoxicity, destruction of red and white blood cells and

platelets leads to thrombocytopenia, anaemia, and leukopenia. These patients are at high risk for developing infections such that even a minor pathology like periodontal infections might turn out to be life-threatening. Bacterial, viral, fungal infections are very common seen intraorally in such patients. One should always evaluate the patient before chemotherapy, because some of the systemic infections can be seen intraorally in the form of ulcers, erythema etc. Hence, teeth with a poor prognosis should be extracted. On the other hand, clinicians must emphasize to the patient the importance of good oral hygiene. During giving any sort of dental treatment coordination of oncologist and dental clinician is of utmost importance. Dental treatment should only be started when the white blood cell count is $> 2000/\text{mm}^3$ of blood.

The use of radiotherapy synergised along with surgical resection is routinely done not only in cases of head or neck tumours specifically but also in other sorts of tumours such as breast, prostate. The adverse effects of ionising radiations cause dramatic perioral changes i.e. mucositis, xerostomia, dysphagia, radiation caries etc. Patients in need for head and neck radiation therapy must be introduced to dental consultation in the initial days only in order to decrease the morbidity of well-known perioral problems.

CONCLUSION

Hence, it becomes a well-established fact that there is a synergism between the genetic as well as environmental factors such as nutritional factors in controlling the malignant transformation of certain

pre-malignancies. Also, our body acts as a reservoir of extremely complicated system of cellular division which establishes the development of new cells and the cellular senescence. Most of the cancer patients prefer special diets in order to improve their prognostication. Henceforth, in depth introspection with the healthcare provider is of utmost importance to perceive the patient's nutritional requirements. This signifies the role of nutritional therapy on relieving symptoms and providing the best possible intervention so as to obtain highly favourable prognosis in cancer patients.

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