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Sustenance and Oral Cancer

Medical Science

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ABSTRACT

Nutrition plays a vital role in cancer along with tobacco. High consumption of foods rich in substances such as fibers, carotenoids, some vitamins & minerals have been associated with reduced risk of oral cancer. Various macronutrients & micronutrients have an inverse relation with oral cancer. Nutritional deficiency causes alteration in the methylation of DNA, increase in the tumor cells & decrease in the normal healthy cells thereby affecting the health of the individual in the form of weight loss, cachexia, leading to death of the individual. This paper provides a review on the metabolic effects of dietary elements in oral cancer.

ORAL CANCER

Oral cancer is the 6th most common cancer. "The disease of our century is cancer". This statement was made by Dalitsch and Vazirami when they examined the increasing incidence of oral cancer(Dalitsch WW et al. 1959). Incidence and mortality rates are higher in men than women. Tobacco use, including smokeless tobacco, and excessive alcohol consumption are estimated to account for about 90% of oral cancers.

In the last 20years the result of epidemiologic studies have provided strong evidence that some factors related to the human diet may have major determining influences on the prabability of the development of cancer by the human. One mechanism through which dietary components have the potential to increase the incidences of cancers is by exposures of individuals to carcinogens that may occur in foods either as natural constituents or as inadvertent contaminants that develop during harvesting, processing or cooking(1).

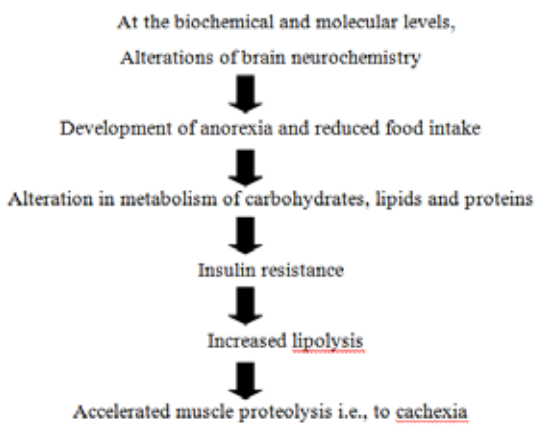
CANCER CACHEXIA

Cancer cachexia is derived from the Greek words "kakos hexis" (meaning bad condition) and is found in any disease that involves the wasting of the host's tissue(2,3). It is a syndrome in which progressive wasting of the body is characterized by the loss of adipose tissue and skeletal muscle mass(4). Increased levels of specific cytokines, or proteins, released during an immune response and directly related to the presence of a malignant tumor, mediate this loss of adipose tissue and skeletal muscle mass(2,4,5).

Cachexia is found in approximately one-half of all patients with cancer, which causes a decrease in survival time and a decrease in response to cancer therapy for these patients when compared to cancer patients who do not experience cachexia(6). In reported cases, the signs and symptoms of cachexia are present before the cancer diagnosis has been determined(7). This decrease in weight has been associated to abnormal, or altered, metabolism of carbohydrates, lipids and proteins(4).

ANOREXIA-CACHEXIA SYNDROME

The anorexia-cachexia syndrome is clinically characterized by a number of signs and symptoms interfering with energy intake i.e., reduced appetite, early satiety, changes in taste/smell and affecting nutritional status (i.e., increased metabolic rate, weight loss, hormonal alterations, muscle and adipose tissue wasting, functional impairment, fatigue)(8,9,10).



PATHOPHYSIOLOGY OF CANCER CACHEXIA

The changes that take place during cachexia are as follows:

1)Metabolic Changes: The metabolic changes found in cachexia are multifactorial and complex. Weight loss of cancer cachexia is due to loss of both skeletal muscle and adipose tissue mass, whereas weight loss is mainly from adipose tissue stores in starvation(11). In cachexia, there is an increase in muscle protein catabolism leading to net loss of muscle mass. The ATP ubiquitin-dependent proteolytic pathway is the greatest contributor to proteolysis in cachexia(12,13). Increased intracellular proteolytic activity usually manifests as loss of body weight. This proteolysis has been shown to occur even in the absence of weight loss in cancer patients. Activation of proteolysis is an early event during tumor growth and it may be present for a long time prior to its clinical manifestation(14). Loss of adipose tissue mass is due to lipolysis(9). This process is driven by lipid mobilizing factor(LMF) and tumor(and host) factor zinc-alpha-2 glycoprotein which has a direct lipolytic effect and sensitizes adipocytes to lipolytic stimuli and shows increased expression in cachexia(15). A further compounding factor is the increased resting energy expenditure due to the dysregulation of energy metabolism. This is due to altered gene expression of mitochondrial membrane uncoupling proteins which uncouple respiration from ATP production resulting in loss of energy as heat(9). The metabolic changes seen in cachexia are a result of the interplay of tumor factors, host factors, and the interaction between the two.

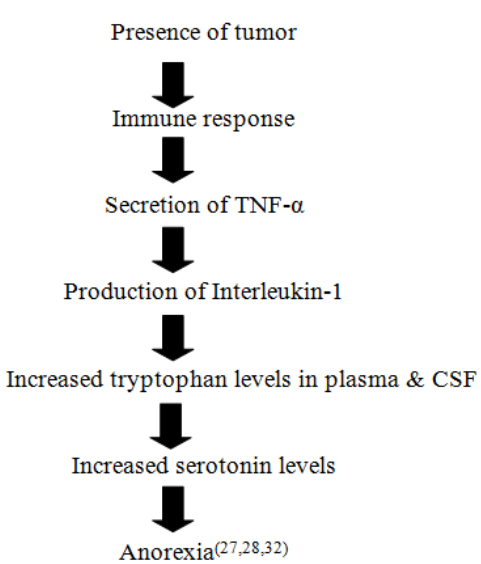
2)Tumor Factors: Tumor cells produce both proinflammatory and procachectic factors, which stimulate a host inflammatory response(16). Tumor produced procachectic factors include pro-

teolysis-inducing[4] and lipid-mobilizing factors[17]. Parathyroid hormone-related peptide (PTHrP), another tumor-derived circulating factor, is associated with higher soluble tumor necrosis factor receptor levels and with lower albumin and transferrin levels[18]. Lipid mobilizing factor has been found in cancer patients losing weight but not in those with stable weight[19]. It is thought that LMF sensitises adipocytes to lipolytic stimuli by increasing cyclic AMP production[20]. LMF may bind to beta adrenergic receptors and causes either increased receptor number or increased G protein expression[21].

3)Host-Tumor Interaction: Inflammatory cytokine production by the tumor microenvironment in response to tumor cells may drive the cachexia process. The murine model of cancer cachexia associated with systemic inflammation suggests that there is an interplay between IL-1β and IL-6 within the tumor microenvironment, which leads to their amplification[22]. Pro-inflammatory cytokines produced include TNF-α, IL-1 and IL-6[16]. It is not certain whether the cytokine production is primarily from tumor or host inflammatory cells. It has been hypothesized that either tumor cell production of pro-inflammatory cytokines or the host inflammatory cell response to tumor cells is the source of the acute phase protein response seen in many malignancies and in cachexia. Tumor tissue concentrations of IL-1β protein correlated with serum CRP concentrations and tumors with diffuse or patchy inflammatory cellular infiltrate were associated with elevated serum CRP[18]. TNF-α and the tumor factor proteolysis-inducing factor are the major contenders for skeletal muscle atrophy in cachectic patient. They both increase protein degradation through the ubiquitin-proteosome pathway and depress protein synthesis through phosphorylation of eukaryotic initiation factor 2α[15]. Only antagonists to proteolysis-inducing factor prevent muscle loss in cancer patients, suggesting that tumor factors are the most important[23].

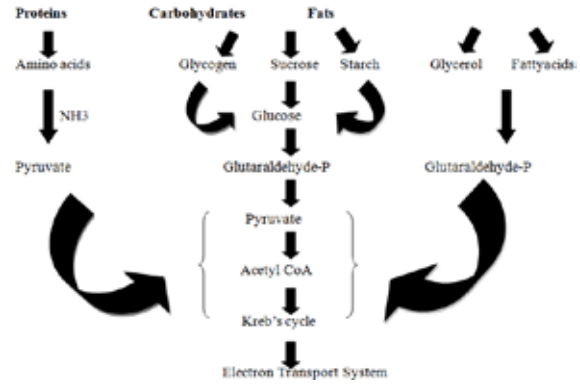
ROLE OF CYTOKINES IN CANCER CACHEXIA

The pathogenesis of cancer-related anorexia is complex and multifactorial, implying a dysruption of the central and peripheral messages that physiologically regulate eating behaviour at the hypothalamic level[8]. In the presence of cancer, the enhancement of cytokine expression in the brain leads to disruption of hypothalamic neurochemistry, interfering with the regulation of satiety, atleast in part via increased serotonin synthesis and release, resulting in reduced food intake. Cytokines may contribute to the long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling[24], but tumor-induced changes in energy metabolism of hypothalamic neurons are also probably involved in the pathogenesis of cancer anorexia[8]. Metabolic abnormalities significantly contribute to cancer-related wasting and involve carbohydrate, lipid and protein metabolism[25,26].



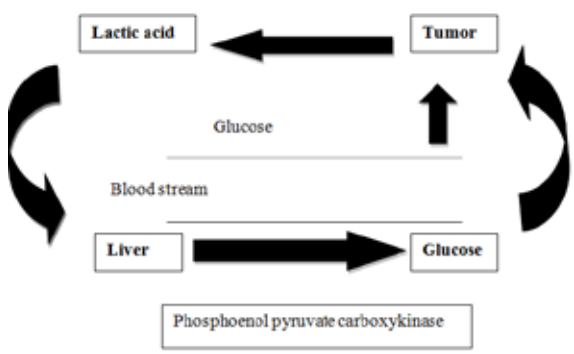
METABOLISM IN NORMAL STATE

The foods ingested are broken down into essential proteins, carbohydrates, and fats, which are metabolized into amino acids, glycogen, sucrose, starch, and glycerol and fatty acids. These building blocks are then used for fuel for respiration and energy via glycolysis, Krebs cycle, and the electron transport system[29,32].



PATHOPHYSIOLOGY OF CARBOHYDRATE METABOLISM IN CANCER CACHEXIA

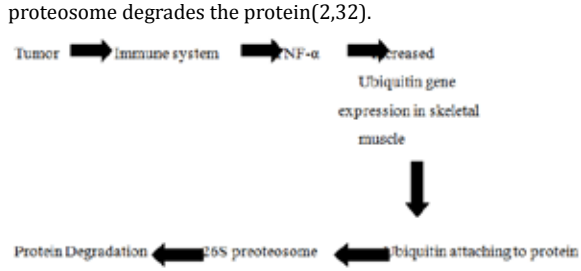
The most important concept to understand about tumor cells is that they require large amounts of glucose (as opposed to oxygen) to grow, usually four to five times the amount of glucose as compared to normal cells[25]. Glucose in the bloodstream is utilized by tumor cells, which, in turn, convert glucose into lactic acid. This lactic acid is then converted into glucose in the liver via the enzyme phosphoenol pyruvate carboxykinase. The glucose produced is then returned to the tumor cell[5,30].



An impaired glucose tolerance is also observed in cancer cachexia. This may be due to an increase in insulin secretion and the increase insulin resistance by TNF-α[30]. It was demonstrated in nontumor-bearing animals that insulin increase inhibits glucose production while stimulating glucose disposal[31,32].

PROTEIN METABOLISM IN CANCER CACHEXIA

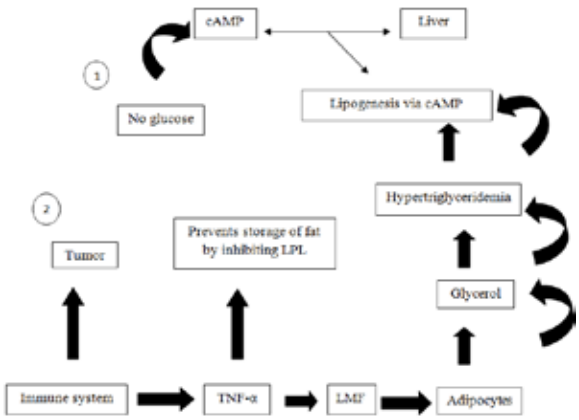
Tumor necrosis factor-α(TNF- α) has shown to increase gene expressions of ubiquitin in skeletal muscle. This increase in gene expression stimulates protein degradation by ubiquitin attaching to a protein and, through an unknown mechanism, 26S proteosome degrades the protein(2,32).



LIPID METABOLISM IN CANCER CACHEXIA VIA THE cAMP PATHWAY

In the absence of glucose, levels of cAMP rise. Tumor necrosis

factor- α(TNF-α) prevents the storage of fat by the enzyme, inhibiting lipoprotein lipase (LPL). TNF-a also stimulates lipid-mobilizing factors (LMF), which induce adipocytes to release glycerol, causing hypertriglyceridemia. High levels of glycerol in the blood have shown to cause lipogenesis via cAMP in the liver[2,6,32].



MUTAGENESIS & CARCINOGENESIS

The specific linear arrangement of the purine & pyrimidine bases in the cellular DNA, through coding for RNAs & subsequently for proteins, determines the potentialities of a cell. Chemical carcinogens, either directly or, more often, as a result of metabolism by the cell, are strong electrophilic reactants, & these electrophilic reactants can react with cellular DNA to cause mutations. Some mutations cause an apparently irreversible change of a normal cell to one that is predisposed toward becoming a tumor cell(i.e an initiated cell)[1].

When exposed at some later time to an appropriate further series of stimuli(by agents collectively called tumor promoters), the initiated cells, through poorly defined steps, give rise to gross tumors. Tumor promotion is generally considered to involve both further modification of the initiated cells & hyperplasia of the initiated cells & their progeny. Whereas tumor initiation occurs rapidly & is largely irreversible, tumor promotion requires repetitive stimuli & appears to be atleast partially reversible. Mutations at specific sites of genes, collectively called proto-oncogenes, is now known to predispose appropriate cells to malignant transformation[1].

EFFECT OF VITAMINS ON CANCER

Vitamin A

Does vitamin A lower cancer risk?

Vitamin A(retinol) is obtained from foods in two ways: preformed from animal food sources, and derived from beta-carotene in plant-based foods. Vitamin A is needed to maintain healthy tissues.Vitamin A supplements, whether in the form of beta-carotene or retinol, have not been shown to lower cancer risk, and high-dose supplements may, in fact, increase the risk for lung cancer(33,34).

What is Beta carotene and does beta-carotene reduce cancer risk?

Beta Carotene, a substance which gives some vegetables their color like carrots and peppers, and which the body converts into vitamin A. It improves the immune responses in the body by stimulating a molecule that helps the immune system target and destroy cancer cells. Because eating vegetables and fruits is associated with a reduced risk of cancer, it seemed plausible that taking high doses of beta-carotene supplements might reduce cancer risk. In three major clinical trials, people were given high doses of synthetic betacarotene in an attempt to prevent lung cancer and other cancers. Two studies found betacarotene supplements to be associated with a higher risk of lung cancer in cigarette smokers, and a third found neither benefit nor harm from beta-carotene supplements. Therefore, consuming vegetables and fruits that contain beta-carotene may be helpful, but high-dose beta-carotene supplements may be harmful, especially for cigarette smokers(33,34,35).

Vitamin C

Does vitamin C lower cancer risk?

Vitamin C is found in many vegetables and fruits. Many studies have linked consumption of vitamin C rich foods with a reduced risk for cancer. The few studies in which vitamin C has been given as a supplement, however, have not shown a reduced risk for cancer(36,37).

Vitamin E

This vitamin(particularly α-tocopherol) & its derivatives are lipid-soluble antioxidants, & thus it protects against "oxidative stress" & acts

a) as an antioxidant & a scavenger of free radicals
b) as an inducer of differentiation & growth inhibition of cancer cells
c) synergistically with selenium & vitamin C, which both potentiate its effects
d) as an inhibitor of DNA, RNA & protein synthesis &
e) as a stimulator of the immune system[38]

Vitamin D

Vitamin D in its biologically active form, 1α, 25$(OH)_2D_3$, exerts its anticarcinogenic activity via specific intracellular receptors(VDR), which are found in almost 60% of both normal & cancer cells[38].

Vitamin K

Vitamins K1, K2 & K3 may act on cancer cells by

a) Inhibiting cell growth & proliferation
b) Inhibiting DNA synthesis & cell cycle
c) Acting on apoptosis through expression of c-myc & c-fos protooncogenes
d) Folic acid & folates exert anticarcinogenic effects by influencing methylation of DNA, leading to loss of the normal control of protooncogene expression[38].

ANTIOXIDANTS IN ORAL HEALTH

What are antioxidants and what do they have to do with cancer?

Certain nutrients in vegetables and fruits appear to protect the body against the damage to tissues that occurs constantly as a result of normal metabolism. Because such damage is associated with increased cancer risk, the so-called "antioxidant nutrients" are thought to protect against cancer[39]. Antioxidants include vitamin C, vitamin E, selenium, carotenoids, and many other phytochemicals. Studies suggest that people who eat more vegetables and fruits, which are rich sources of antioxidants, have a lower risk for some types of cancer. Clinical studies of antioxidant supplements are currently underway, but studies have not yet demonstrated a reduction in cancer risk from vitamin supplements. To reduce cancer risk, the best advice presently is to consume antioxidants through food sources rather than supplements.

Phytonutrients are other anti-oxidants, which are not vitamins, are also found in fruits and vegetables and appear to have powerful cancer-fighting properties but lack evidence[40].

Carotenoids are coloured compounds found in the photosynthetic pigments of fruits & vegetables which provide them their bright colours & benefit human health by playing an important role in cell function. More recently, lycopene has attracted substantial interest among researchers due to its antioxidant properties[41].

Lycopene has various benefits on human health such as:

1. Antioxidant activity
2. Inhibition of cancer cell proliferation
3. Interference with growth factor stimulation of cancer cell

proliferation
4. Cancer prevention by inducing phase II enzymes
5. Regulation of transcription
6. Restoration of gap junctions[42]

Will lycopene reduce cancer risk?
Lycopene is the red-orange carotenoid antioxidant found at high levels in tomatoes and tomato-based foods. Several studies have reported that consumption of tomato products reduces the risk of some cancers. Absorption of lycopene is increased when lycopene-rich vegetables are cooked and are consumed together with fat, although only very small amounts of fat are needed for absorption. Even if lycopene in foods is associated with lower risk for cancer, it does not follow that high doses taken as supplements would be either more effective or safe[43].

ROLE OF LYCOPENE IN ORAL HEALTH
Lycopene is a red coloured fat soluble carotenoid, discovered by Ernest et al in 1959, which gives tomatoes & several other fruits their deep red colour[42,44].

Oral Leukoplakia:
Gupta PC et al[45], in their population based case control study observed a protective effect of tomato consumption in oral leukoplakia. A study conducted at Belgaum, Karnataka showed lycopene to be efficacious in the treatment of oral leukoplakia. They also reported that daily dose of 8mg of lycopene was more efficacious than 4mg a day. This efficacy of lycopene was associated to its antioxidant properties[46].

Oral Cancer:
In Hebrew University, Jerusalem, researchers discovered lycopene to kill oral cancer cells when added to culture. They believed it to be due to its ability to restore gap junction communication, which is believed to be destroyed in oral malignancies, suggesting its possible role in oral cancer management as an adjuvant therapy(47,48).

Oral Lichen Planus(OLP):
Though the exact role of free radicals in the pathogenesis of OLP is not established, various studies have suggested oxidative stress to play a vital role in the same[49,50,51]. Nagao et al[52], reported significantly lower levels of serum lycopene in the patients with atrophic & erosive lichen planus as compared to healthy controls. Lycopene supplementation may be used as a therapeutic modality for treatment of atrophic/erosive OLP patients.

EFFECT OF MINERALS, TOBACCO, ALCOHOL & SMOKING ON CANCER
Selenium, copper & cadmium are antitumorigenic but high levels of selenium might be toxic to humans. Iron, zinc, iodine & molybdenum deficiency are carcinogenic. High concentrations of arsenic & lead are carcinogenic. Betel nut alone or in combination with tobacco & lime is carcinogenic & that there is a direct relationship between the frequency of chewing & induction of carcinogenesis. Alcohol & smoking cause enhanced activation & hydroxylation of nitrosamines i.e., N-nitrosopyrrolidine & N-nitroso-nornicotine(NNN) which enhance the mutagenicity & induce head & neck cancers[40].

FLAVANOIDS
Flavanoids are super antioxidants which have antiviral, anti-allergic, anti-inflammatory, anti-thrombogenic & anti-carcinogenic effects. They scavenge for free radicals & inhibit oxidative enzymes. Sources of flavanoids are fruits, vegetables, flowers, roots, tea, wine etc[40].

TIPS FOR ANTI-CANCER DIET
Tip 1: Focus on fruits & vegetables

Tip 2: Bulk up on fiber

Tip 3: Cut down on meat

Tip 4: Choose your fats wisely

Tip 5: Choose cancer-fighting foods

Tip 6: Prepare your food in healthy ways(53)

GENERAL DENTISTRY MISSION:
CORRECT & PREVENT DISEASE
"Our mission as General Dentists is no longer merely to wipe out dental decay but to correct diseases in the mouth so that the patient's overall health also benefits. This can be achieved with the help of certain medications especially ANTIOXIDANTS" (54).

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REFERENCE

1. Elizabeth C, Miller, James A.Miller, Carcinogens & Mutagens that may occur in Foods, Cancer 1986, 58:1795-1803. | 2. Tisdale M. Biology of cachexia. J Natl Cancer Inst. 1997;89;1763-1773. | 3. Tisdale MJ. Cancer Cachexia: metabolic alterations and clinical manifestarions. Nutr. 1997;13:l-7. | 4. P. Todorov, P. Cariuk, T. McDevitt, B. Coles, K. Fearon, and M. Tisdale, "Characterization of a cancer cachectic factor," Nature, vol. 379, no. 6567, pp. 739–742, 1996. | 5. Albrecht JT, Canada TW. Cachexia and anorexia in malignancy. Hema/Oncol Clitj N Amer. 1996;10:791-800. | 6. McDevitt TM, Todorov PT, Beck SA, et al. Purification and characterization of a lipid-mobilizing factor associated with cachexia-inducing tumors in mice and humans. Cancer Research. 1995;55:1458-1463. | 7. Yeh S-S, Schuster MW. Geriatric cachexia: The role of cytokines. Am J Clin Nutr. 1999;70:183-197. | 8. Laviano A, Meguid MM, Rossi Fanelli F, Cancer anorexia: clinical implications, pathogenesis and therapeutic strategies. Lancet Oncol 2003; 4:686-94. | 9. M. J. Tisdale, "Cachexia in cancer patients," Nature Reviews Cancer 2002; 2(11): 862–871. | 10. Alessandro Laviano, Akio Inui, Daniel L. Marks, Michael M. Meguid, Claude Pichard, Filippo Rossi Fanelli, Marilia Seelaender, Neural Control Of The Anorexia-Cachexia Syndrome, Am J Physiol Endocrinol Metab August 19, 2008. | 11. J. F. Moley, R. Aamodt, and W. Rumble, "Body cell mass in cancer-bearing and anorexic patients," Journal of Parenteral and Enteral Nutrition, vol. 11, no. 3, pp. 219–222, 1987. | 12. J. Khal, A. V. Hine, K. C. H. Fearon, C. H. C. Dejong, and M. J. Tisdale, "Increased expression of proteasome subunits in skeletal muscle of cancer patients with weight loss," International Journal of Biochemistry and Cell Biology, vol. 37, no. 10, pp. 2196–2206, 2005. | 13. C. H. DeJong, S. Busquets, A. G. Moses et al., "Systemic inflammation correlates with increased expression of skeletal muscle ubiquitin but not uncoupling proteins in cancer cachexia," Oncology Reports, vol. 14, no. 1, pp. 257–263, 2005. | 14. D.C.McMillan,T. Preston,K.C.H. Fearon, H. J. G. Burns, C. Slater, and A. Shenkin, "Protein synthesis in cancer patients with inflammatory response: Investigations with [N]glycine," Nutrition, vol. 10, no. 3, pp. 232–240, 1994. | 15. M. J. Tisdale, "Cancer cachexia," Current Opinion in Gastroenterology, vol. 26, no. 2, pp. 146–151, 2010. | 16. M. J. Tisdale, "Mechanisms of cancer cachexia," Physiological Reviews, vol. 89, no. 2, pp. 381–410, 2009. | 17. K. Hirai, H. J. Hussey, M. D. Barber, S. A. Price, and M. J. Tisdale, "Biological evaluation of a lipid-mobilizing factor isolated from the urine of cancer patients," Cancer Research, 1998, 58(11): 2359–2365. | 18. C. Deans, S. Wigmore, S. Paterson-Brown, J. Black, J. Ross, and K. C. H. Fearon, "Serum parathyroid hormone-related peptide is associated with systemic inflammation and adverse prognosis in gastroesophageal carcinoma," Cancer, vol. 103, no. 9, pp. 1810–1818, 2005. | 19. P. T. Todorov, T. M. McDevitt, D. J. Meyer, H. Ueyama, I. Ohkubo, and M. J. Tisdale, "Purification and characterization of a tumor lipid-mobilizing factor," Cancer Research, vol. 58, no. 11, pp. 2353–2358, 1998. | 20. S. Khan and M. J. Tisdale, "Catabolism of adipose tissue by a tumour-produced lipid-mobilizing factor," International Journal of Cancer, vol. 80, no. 3, pp. 444–447, 1999. | 21. B. Islam-Ali, S. Khan, S. A. Price, and M. J. Tisdale, "Modulation of adipocyte G-protein expression in cancer cachexia by a lipid-mobilizing factor (LMF)," British Journal of Cancer, vol. 85, no. 5, pp. 758–763, 2001. | 22. K. Yasumoto, N. Mukaida, A. Harada et al., "Molecular analysis of the cytokine network involved in cachexia in colon 26 adenocarcinoma-bearing mice," Cancer Research, 1995; 55(4): 921–927. | 23. Claire L. Donohoe, Aoife M. Ryan, and John V. Reynolds, Cancer Cachexia:Mechanisms and Clinical Implications, Gastroenterology Research and Practice, Volume 2011;1-13. | 24. Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? Cancer Res. 1999;59:4493-4501. | 25. Mathupala SP, Rempel A, Pederson PL. Glucose metabolism in cancer cells.; BioChem. 1995;270:16918-16925. | 26. M Muscaritoli, P Costelli, Z Aversa, A Bonetto, FM Baccino and FR Fanelli, New strategies to overcome cancer cachexia: from molecular mechanisms to the 'Parallel Pathway', Asia Pac J Clin Nutr 2008;17 (S1):387-390. | 27. Laviano A, Meguid MM, Yang Z-J, et al. Cracking the riddle of cancer anorexia. Nutr. 1996;12:706-710. | 28. Picton SV. Aspects of altered metabolism in children with cancer. Intj Cancer. 1998;S11:62-64 | 29. Campbell NA. Biology, 4th ed. Menlo Park, Calif: Benjamin/Cummings Publishing Company, Inc; 1996:177. | 30. De Blaauw 1, Deutz NEP, Von Mcyenfcldt MR Metabolic changes in cancer cachexia-first of two parts. Clin Nutr. 1997;16: l69-176. | 31. Tayek JA, Manglik S, Abemayor E. Insulin secretion, glucose production and insulin sensitivity in underweigbt and normalweight volunteers, and in underweight and normal-weight cancer patients: A clinical research center study. Metabolism 1997;46:140-145. | 32. Amanda J. Tijerina, MS, The Biochemical Basis of Metabolism in Cancer Cachexia, Dimens Crit Care Nurs 2004;23(6):237-243. | 33. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group.The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-1035. | 34. Omenn G, Goodman G,Thornquist M, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150-1155. | 35. Henneken SC, Buring J, Manson J, et al. Lack of effect of long term supplementation with betacarotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996;334:1145-1149. | 36. Block G.Vitamin C and cancer prevention: The epidemiologic evidence. Am J Clin Nutr 1991;53:270-282. | 37. Byers T, Perry G. Dietary carotenes, vitamin C and vitamin E as protective antioxidants in human cancers. Annu Rev Nutr 1992;12:139-159. | 38. Lupulescu AP, Hormones, Vitamins & Growth factors in cancer treatment & prevention. A critical appraisal, Cancer 1996;78(11), 2264-2280. | 39. Willett WC. Micronutrients and cancer risk. Am J Clin Nutr 1994;59:1162-1165. | 40. Tim Byers, Marion Nestle, Anne McTiernan, Colleen Doyle, Alexis Currie-Williams, Ted Gansler, Michael Thun, American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer with Healthy Food Choices and Physical Activity, CA Cancer J Clin 2002;52:92-119. | 41. Nisheeth A, Shashikanth MC, Shambulingappa P, Deepak U, Lycopene: A Promising Antioxidant, JIAOMR 2007;19(4): 458-463. | 42. Levy J, Sharoni Y, The functions of tomato lycopene and its role in human health. Herbalgram 2004;62:49-56. | 43. Giovannucci E. Tomatoes, tomato-based products, lycopene and cancer: Review of the epidemiologic literature. J Natl Cancer Inst 1999;91:317-331. | 44. Stahl W, Sies H, Lycopene a biologically important carotenoid for humans? Arch Biochem Biophys 1996;336(1):1-9. | 45. Gupta PC, Hebert JR, Bhonsle RB, Sinor PN, Mehta H, Mehta FS, Dietary factors in oral leukoplakia and submucous fibrosis in a population based case-control study in Gujarat, India, Oral Dis 1998;4(3):200-6. | 46. Singh M, Krishanappa R, Bagewadi A, Kefuskar V Efficacy of oral lycopene in the treatmentof oral leukoplakia. Oral Oncol 2004;40:591-6. | 47. Schwartz B, Can tomatoes fight oral cancer? JADA 2001;132:154-156. | 48. Livny O, Kaplan I, Reifen R, Charcon SP, Madar Z, Schwartz B, Lycopene inhibits proliferation and enhances gap junction communication of KB-1 human oral tumor cells, J Nutr 2002;132:3754-9. | 49. Winbrow VR, Winyard PG, Morris CJ, Blake DR, Free radicals in inflammation: second messengers and mediators of tissue destruction, Br Med Bull 1993;49(3):506-22. | 50. Sander CS, Cooper SM, Ali I, Dean D, Thiele JJ, Wojanarowska F, Decreased antioxidant enzyme expression and increased oxidative damage in erosive lichen planus of the vulva, BJOG 2005;112:1572-5. | 51. Brennan PA, Umar T, Callender MP, Spedding AV, Mellor TK, Buckley J, A study to assess inducible nitric oxide synthase expression in oral lichen planus, J Oral Pathol Med 2000,29:249-54. | 52. Nagao T, Warnakulasuriya S, Ikeda N, Fukano H, Yamamoto S, Yano M, Serum antioxidant micronutrient levels in oral lichen planus, J Oral Pathol Med 2001;30: 264-7. | 53. Maya W. Paul, Melinda Smith, M.A, The Anti-Cancer Diet, Cancer Prevention Nutrition Tips and Cancer-Fighting Foods, April 2010. | 54. General Dentistry, Correct and Prevent Disease, 50(6), Nov-Dec 2002. |