Review Article

Chemopreventive Agents; Its Role in Oral Cancer Prevention

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ABSTRACT

Oral cancer is a life-threatening disease, with a high death rate, thus posing a challenge for the clinicians to treat it. Advances in understanding the process of carcinogenesis at the cellular and molecular level and progress in identifying the major causes of human cancer have led to the development of cancer chemoprevention as a promising approach. Prevention of cancer is an ideal way for reducing the risk of cancer. In the past few years, extensive research has revealed that natural fruits and vegetables along with chemical compounds act as cancer prevention agents. The chemopreventive agents have potential to be used as adjuncts to cancer therapies.

Keywords: Antioxidants, Carcinogenesis, Chemoprevention, Chemopreventive agents, Oral cancer

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INTRODUCTION

Cancer has been described by Robbins as an autonomous new growth of tissue or an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persists in the same excessive manner even after cessation of stimuli which evoked the change.[1]

Oral cancer is one of the most prevalent cancers and one of the six major causes of death.[2] Age-standardized incidence rate of oral cancer in India is 12.6 per 1,00,000 population. Oral cancer causes considerable morbidity and is associated with a 5 years survival rate of less than 50%. It can develop *de novo* or from potentially malignant disorders.[3]

One of the major causes of oral cancer in India is the potentially malignant lesions and conditions due to their increased risk of malignant transformation. Some lesions are now definitely considered to carry a potential for malignant changes such as leukoplakia, erythroplakia, smoker's palate. A group of conditions, although not themselves premalignant, are associated with higher than normal incidence of oral cancer like Oral Submucous Fibrosis, Syphilitic Glossitis, Sideropenic Dysphagia, Oral Lichen Planus, Discoid Lupus Erythematosis, and Dyskeratosis Congenita.

Many of these lesions show a high potential to become cancers and are therefore termed "precancerous," even though only a small proportion of "precancers" actually progress to cancer. This development forms the source for over 70% of oral cancers in India.

Carcinogenesis is a multiple step process, which is initiated by carcinogens leading to the formation of cancer. It is a chronic disease process characterized by abnormal cell and tissue differentiation.[4] Different carcinogens may induce neoplasm by different mechanisms and in many tumors more than one mechanism is involved in carcinogenesis.

The various hypotheses of carcinogenesis are:

The genetic theory: This is the most popular theory, which suggests that cells become neoplastic because of alterations in the DNA. The mutated cells transmit their characters to the next progeny of cells. Evidence in support of genetic theory comes from all types of etiologic agents in carcinogenesis.

The epigenetic theory: This theory is less well supported than the genetic theory. According to the epigenetic theory, the carcinogenic agents act on activators or suppressors of genes and not on the genes themselves and result in the abnormal expression of genes.

The multi-step theory: This is the other well accepted and documented theory. According to this theory, carcinogenesis is a multi-step process.[1]

CHEMOPREVENTION

Chemoprevention of cancer is a means of cancer control in which the occurrence of this disease is prevented by administration of one or several compounds either naturally occurring fruits and vegetables or chemical compounds.

Chemoprevention of cancer was first defined in 1976 by Sporn. Chemoprevention is the use of natural, synthetic, or biologic, chemical agents to reverse, suppress, or prevent carcinogenic progression.[5] Incidence of cancer can be controlled and reduced to a certain extent by chemoprevention. Potentially malignant disorders serve as a model for investigating the chemopreventive method of control of cancer. Concepts of multifocal field carcinogenesis and multistep carcinogenesis form the basis for explaining chemoprevention. Chemoprevention asserts that one can intervene at the many steps of carcinogenesis. The chemopreventive agents also have very recently been found to reverse chemoresistance and radio resistance in patients undergoing cancer treatment. Thus, chemopreventive agents have potential to be used as adjuncts to current cancer therapies.

According to studies at present, approximately 400 compounds are being researched as potential chemopreventive agents, in laboratories. Over 40 of these agents are being investigated in clinical trials. Few of these agents are being tested as single agents, and others are being studied as a combination of two drugs.[6] Clinical research regarding chemopreventive agents identify the various methods to prevent occurrence of cancer with interventions that include vitamins, diet, hormone therapy, drugs and other agents. The preclinical development of chemopreventive agents includes an initial assessment of their efficacy using *in vitro* and cell-based mechanistic assays and *in vivo* screens in animal models of carcinogenesis that are representative of human cancers and exhibit precancerous lesions. The most promising agents are characterized more fully in the animal models to evaluate, for example, dose-response curves, dosing regimens, and combinations with other agents tested. Compounds that show high efficacy and low toxicity in animal studies are considered for testing in humans. Potential chemopreventive agents selected for testing in people at high risk of developing cancer must have low toxicities compared with the drugs used to treat existing cancer. The agents showing promise in these studies may be tested further in animals. When a compound shows promise in such research studies, it may then be examined in clinical trials.[7]

MECHANISMS OF ACTION OF CHEMOTHERAPEUTIC AGENTS

Research over the past decade has been able to identify different mechanisms of various chemopreventive agents occurring at molecular levels to inhibit cancer (Figure 1).

Inhibitors of the Activated Protein-1 (AP-1) Activation Pathway

AP-1 is a transcription factor. The expression of several genes that are involved in cell differentiation and proliferation is regulated by AP-1. Blockade of AP-1 has been known to cause interference in the transmission of proliferative signals induced by peptide growth factors and steroid growth factors. These results suggest that chemopreventive agents specifically targeting AP-1 or its activating kinases could be promising agents for the treatment of several cancers.

Inhibitors of Cell Proliferation and Initiators of Apoptosis

Numerous studies have shown that cell survival and proliferation have been promoted by activation of nuclear transcription factor-kappa B (NF-kB) and suppression of NF-kB causes cell death and inhibition of proliferation. Chemopreventive agents such as curcumin, green tea, 6-gingerol and resveratrol inhibit the NF-kB or the AP-1 activation pathway. These cause

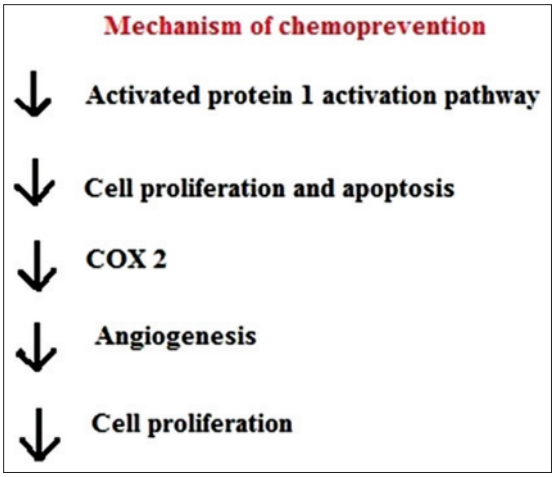

Figure 1: Mechanism of chemoprevention

a significant inhibition of cell proliferation and induce apoptosis in the cells.

Inhibitors of Cyclo-oxygenase-2 (COX-2)

Several studies have demonstrated the importance of regulation of COX-2 expression in the prevention and the treatment of cancers. Over expression of this enzyme has been observed in all pre-malignant and malignant conditions.

Agents like curcumin possess the ability to inhibit COX-2 by the suppression of NF-κB.

Inhibitors of Angiogenesis

Various inhibitors of angiogenesis are under clinical research. Several safe chemopreventive phytochemicals such curcumin, resveratrol and catechins are known to target these pathways leading to inhibition of angiogenesis.

Inhibitors of Cell Cycling

Curcumin, resveratrol and catechins are few of the phytochemicals that have been known to interfere with the regulatory pathways of cell cycle, thus qualifying them as potential therapeutic agents.[4,8]

VARIOUS CHEMOPREVENTIVE AGENTS

Vitamin A

Vitamin A is obtained from the diet. It is present mainly in the form of retinyl esters. These esters are subsequently de-esterified to retinol. Irreversible oxidation of retinol takes place to form retinoic acid.[9] Retinoic acid is a form of vitamin A that has the ability to bind with nuclear receptor sites in the cells. It is essential for the normal growth and differentiation of epithelial cells.[10] Two separate divisions of nuclear receptors are present that regulate the effects of vitamin A on cellular differentiation. They in turn modify the effects of agents such as prostaglandins, vitamin D, and steroid and thyroid hormones.

Derivatives of retinoic acid have been found to have chemopreventive action against epithelial cancer. Various compounds such as Ethyl (E)-9-(2-norbornenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate, (E)-3,7-dimethyl-9-(2-ethyl-6,6-dimethyl-1-cyclohexen-1-yl) nona-2,4,6,8-tetraenoic acid, and 2-(2′-methoxyethoxy) ethyl retinoate have demonstrated an active role in the suppression of tumor promoter-induced mouse epidermal ornithine decarboxylase assay.[11] The chemopreventive action of vitamin A and its derivatives is based on restoring the expression of retinoic acid receptor beta mRNA. It in turn promotes normal tissue growth and differentiation.[12]

Carotene

Carotenoids are found abundantly in fruits and vegetables and belong to the family of conjugated polyene molecules. Carotenoids have high antioxidant property, and some of the carotenoids act as precursors to retinol in human beings.[13] Beta carotene and lycopene have garnered the most attention in the chemoprevention field. According to epidemiological studies intake of beta-carotene intake, has been related to a reduction in the risk of various types of cancer. Epidemiological studies have correlated both high intake and high serum concentrations of lycopene with reduced risk of cancer. Mechanisms of action of lycopene are somewhat obscure.[9]

Vitamin E

Several human intervention trials have examined the ability of vitamin E to prevent carcinogenesis. The chemopreventive mechanisms of vitamin E include stimulation of wild-type p53 tumor suppressor gene, activation of heat shock proteins, down-regulation of mutant p53 and antiangiogenic effect brought about by blockage of transforming growth factor-alpha.[14]

Selenium

Administration of 200 mcg selenium from yeast has been shown to reduce the incidence of several types of cancers in a human trial. These data from the intervention trial confirm prior epidemiological studies that have often shown low selenium status to be associated with increased total cancer incidence.[15] Although there are several proposed mechanisms of action for selenium, including induction of glutathione peroxidase, modulation of cytochrome p450 systems, and immune modulation, the most important mechanism(s) probably remain elusive.[9]

Vitamin C

Vitamin C being a potent water-soluble antioxidant has generated interest in the field of chemoprevention as a potential cancer-preventive agent. Vitamin C is required for the recycling of glutathione, which is an endogenous antioxidant. It has been theorized to protect against the ability of cancer cells to invade tissue, in part by strengthening the cellular matrix.[16]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs have been used for oral cancer chemoprevention. Mode of delivery of the drug is by the topical route through the oral mucosa. According to studies celecoxib, nimesulide and ibuprofen have been known to have high chemopreventive action and remain the agents of choice that target COX-2 in oral epithelial cells.[17]

Head and neck squamous cell carcinomas have found to have great levels of COX-2 expression when compared to the normal oral mucosa. Studies on oral cancer chemoprevention have shown the efficacy of COX-2 inhibition. A significant reduction in incidence oral cancer, the invasiveness of induced cancers, and cancer-associated mortality has been observed with dietary administration of a specific COX-2 inhibitor (celecoxib) and a nonspecific COX-2 inhibitor (piroxicam).[18] The combination oEpidemiological evidence consistently relates low antioxidant intake or low blood levels of antioxidants with increased cancer risk.[16] COX-2 and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors cause simultaneous blockage of EGFR and COX-2 pathways resulting in the inhibition of cell growth. The combination of these plays a great role in the prevention and treatment of head and neck squamous cell carcinomas[19] (Figure 2).

Studies have shown that retinoids inhibit the increased production of COX-2 induced by EGF. However, no effects have been observed on COX-1 and EGFR. Based on these results NSAIDs may be useful as chemoprevention agents in head and neck squamous cell carcinoma.[20]

MISCELLANEOUS

Fruits and Vegetables

Research studies in the field of nutrition have shown that the health benefits of various compounds in plant foods have progressed to a higher stage. Research has shown that thousands of phytochemicals have important physiological effects. These phytochemicals cause blockage of carcinogenesis by prevention of reactive oxygen species attacking the DNA, alteration in the metabolism of procarcinogens in favor of conjugation and excretion of reactive metabolites, inhibition of carcinogen uptake into cells and enhancing DNA repair.[21]

Polyphenols such as ellagic acid present in abundance in various fruits, nuts and vegetables have a high potential in antimutagenesis assays. They lead to inhibition of chemically induced cancer[22] (Figure 3).

Data obtained from various studies have revealed that foods high in phytoestrogens, such as soy (which contains isoflavones), or foods high in precursor compounds that can be metabolized by gut bacteria into active agents, for example some grains and vegetables with woody stems (which contain precursors to lignans), have known to lower cancer risk.[23] Plant derivatives possess various chemopreventive mechanisms. Substances derived from plant foods such as carotenoids, vitamin C, vitamin E, selenium, dietary fiber (and its components), dithiolthiones, isothiocyanates, indoles, phenols, protease inhibitors, allium compounds, plant sterols, and limonene have potentially anticarcinogenic activity. Glucosinolates and indoles, thiocyanates and isothiocyanates, phenols, and coumarins can induce a multiplicity in solubilizing and usually inactivating enzymes. Formation of carcinogens such as nitrosamines is blocked by ascorbate and phenols. Flavonoids and carotenoids act as antioxidants, essentially inhibiting the carcinogenic potential of specific compounds. Lipid-soluble compounds such as carotenoids and sterols may alter cell membrane structure and integrity. Suppression of DNA and protein synthesis is caused by few suFur-containing compounds. Carotenoids can inhibit DNA synthesis and enhance cell differentiation. Phytoestrogens compete with estradiol for estrogen receptors and bring about antiproliferative action. Clinical trials to evaluate the chemoprevention activity in oral leukoplakia patients include vitamin E. Bowman-Birk inhibitor concentrate derived from soybeans, curcumin, and green tea polyphenol epigallocatechin-3-gallate.[24] Studies have also shown

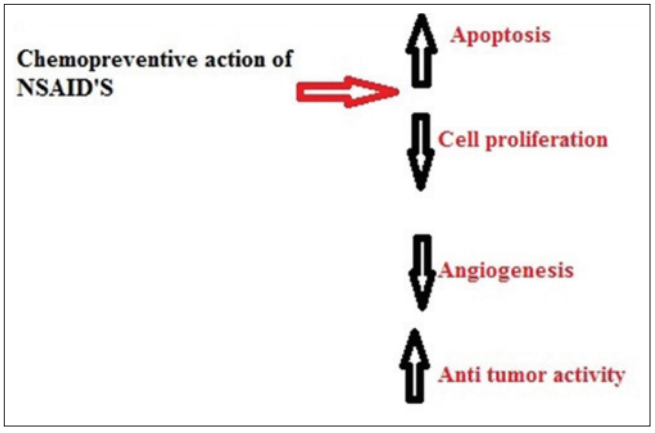

Figure 2: Chemopreventive actions of nonsteroidal anti-inflammatory drug

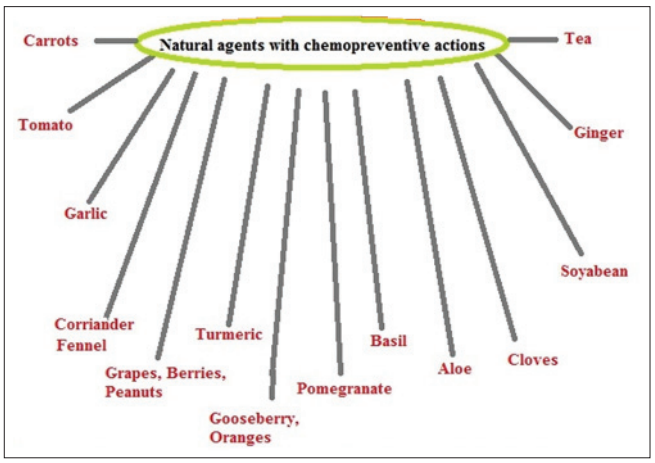

Figure 3: Chemopreventive agents

that Black Raspberries are capable of inhibiting tumor formation.[25]

Decreased intake of plant food in the diet results in a reduction of a variety of substances that can possibly lower cancer risk. In individuals with a modern lifestyle and diet which high in potential carcinogens and its promoters overall risk of cancer at epithelial sites is increased. Plant foods are known to reduce the risk of malignancy; however the site specific risk of cancer varies depending on the exposure to initiators and promoters of carcinogenesis and also the genetic susceptibility.

Green Tea

One of the most widely consumed beverages across the world is tea. Green tea, black tea, or oolong is the various forms of tea available. Black tea comprises around 80% of tea products. Epicatechin (EC), epigallocatechin (EGC), EC-3-gallate, and EGC-3-gallate (EGCG) are the four main polyphenols present in green tea. EGCG, is the most active phenolic compound in green tea. Experimental studies conducted in chemically induced rodent carcinogenesis models and in different cancer cells in culture have demonstrated EGCG to have potential antitumor activity and chemopreventive action.[22,26]

Spirulina Fusiformis (SF)

The blue-green microalgae Spirulina are used in daily diets of natives in Africa and America. They have been found to be a rich natural source of proteins, carotenoids, and other micronutrients. Research studies in animal models have shown that Spirulina algae cause inhibition of oral carcinogenesis. In India, various studies among preschool children have shown SF to be an effective source of dietary vitamin A.[27]

CONCLUSION

This brief review presents evidence that chemopreventive agents can be used not just to prevent cancer but also to treat cancer. Cancer cells survive and multiply by several cell survival mechanisms. Therefore agents that can suppress these mechanisms have great potential in prevention and cure of cancer. Many promising preclinical studies have been performed on the efficacy of various chemopreventive agents for cancer prevention. Although this approach needs refinement, it allows doctors to develop an individual risk profile for cancer that may help guide and motivate patients.

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