

## Antioxidants - Its Preventive Role In Oral Cancer

### Abstract

The prognosis of oral squamous cell carcinoma which accounts more than 95% of the oral cancers is very poor. The main etiology of oral cancers is considered to be the use of tobacco (both smoking and chewing) which increases the production of reactive free radicals as well as eliciting immune suppression. Antioxidant can inhibit reactions of the tobacco specific nitrosamine (carcinogens) which undergo specific activation and detoxification process. Antioxidants such as  $\beta$  carotene, pro-vitamin A, vitamin C, vitamin E, zinc, selenium and spirulina are believed to have a preventive role against oral cancer.

### Key Words

Antioxidants, oral cancer,  $\beta$  carotene, vitamin C, chemo preventive.

### Introduction

Oral cavity cancer is one of the ten most frequent cancers in the world as to 25% of all malignancies are found in the oral cavity<sup>1</sup>. Tobacco is the predominant cause of this cancer. About 48.2% of cancers in men and 20.5% in women are related to tobacco, a major proportion of which is in the oral cavity, pharynx, larynx, oesophagus (74.7%), while lung cancers account only for 15%<sup>2</sup>. Alcohol use is a risk factor that acts synergistically with tobacco. Thus, the major risk factor for oral cancer is the same as that of some other common diseases. eg: emphysema, lung cancer and heart disease. Oral cancers have a poor 5 year survival rate of 50% or less. Consequently, prevention strategies for oral cancer, such as discontinuing tobacco use, can affect many life threatening diseases; other prevention modalities, such as nutritional agents, may similarly be beneficial for several chronic diseases. The successful control of oral cavity cancer will depend on its prevention<sup>2</sup>.

### Role Of Antioxidants In Oral Cancer<sup>3</sup>

The role of antioxidants in cancer chemoprevention can be summarized as:

1. Inhibits oral cavity carcinogenesis
2. Reduces the risk of developing oral cancer.
3. Causes reversal of premalignant lesion like oral leukoplakia.

Oxidative damage is recognized as playing a role in the pathogenesis of cancer which could arise from incorrect nutritional habits and lifestyle practices. This process can cause DNA damage, which is a basic mechanism in cancer induction. Sufficient antioxidative status is crucial in free radical defence. To reduce the risk of oral and pharyngeal cancer, especially oral cell carcinoma, diet must be optimized, primarily to reduce calorie intake, monosaturated fat and red or processed meat.

The important dietary micronutrients that are antioxidant in action include vitamin A,  $\beta$ -carotene, lycopene, Vitamin C, vitamin E (alpha- tocopherol), Zinc and Selenium.

Considerable evidence exists suggesting a role for nutrients, particularly the so-called antioxidants vitamin A,  $\beta$ -carotene, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina in the prevention of this disease<sup>4</sup>. Antioxidants are group of chemical compounds that can deactivate the free radicals and prevent their formation. Free radicals are oxidants which are single unpaired electron that bombard and destroy cells and other molecules in their search for another electron<sup>5</sup>.

A recent study has suggested that these anti-oxidant nutrients act to inhibit the

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development of cancer cells and to destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumor's necessary blood supply or by cellular differentiation<sup>1</sup>. A report has also shown a reduction in adverse effects of chemotherapy when given concurrently with antioxidants<sup>6</sup>.

### A) Role of vitamin A-1

#### Retinoids-

Retinoids are the natural and synthetic derivatives of vitamin A. The retinoids in the body originate from retinyl esters, carotenoids, and retinal in diets. The effects of retinoids are mediated by

retinoid acid receptors (RARs) and retinoid X receptors (RXRs). Three subtypes, designated as  $\alpha$ ,  $\beta$ , and both RARs and RXRs, have been described. Recently, retinoids have been implicated in the induction of cell death in many tumor-derived culture cell systems in both retinoid receptor-dependent and independent manners. The continued development of new synthetic drugs to up-regulate RA receptors and receptor independent drugs would be valuable. It appears that exploiting the apoptotic potential of Oral Squamous Cell Carcinoma would lead to contemporary therapies that might be less toxic to normal cells due to their physiologically controlled survival pathways.

It is suggested that these newer therapies would also be effective in treatment of epithelial dysplasia. Ideally, the root of cancer control lies in instituting chemoprevention. In addition to the chemotherapeutic and chemopreventive agents, a number of dietary components and micronutrients are emerging with considerable potential for the induction of apoptosis. These agents include green tea constituents (EGCG and others), and a number of other phytochemicals, such as carotenoids (lycopene) and retinoids<sup>1</sup>.

#### **Carotinoids: lycopene and others**

There are more than 600 carotenoids in plants, of which approximately 25 are present in human serum and 14 in human tissues. The most common carotenoids in the human diet and plasma are lycopene, lutein,  $\beta$ -carotene,  $\alpha$ -carotene, and  $\beta$ -cryptoxanthin.

#### **B) $\beta$ -carotene**

$\beta$ -carotene is a vitamin A precursor commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. Main actions of beta-carotene include;

- Anti-oxidant and free radical scavenging
- Immunomodulation, stimulation of increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors
- Inhibition of mutagenesis
- Inhibition of cancer cell growth

$\beta$ -carotene is especially used for scavenging free radicals in areas of low oxygen concentration. Results from a recent study has demonstrated that one

third of patients (15 out of 46) that used 360 mg  $\beta$  carotene per week during 12 months presented a complete resolution of oral leukoplakia (OL).<sup>7</sup>

#### **C) Lycopene**

The prominent carotenoid in serum is the antioxidant red pigment called lycopene. This is a fat-soluble red pigment found in some fruit and vegetables. The primary sources of lycopene include tomatoes, apricots, papaya and other yellow fruits. In particular, lycopene and other carotenoids rich foods also are inversely related to upper digestive tract neoplasms including oral cancer<sup>1</sup>.

Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Lycopene has the uncommon feature of getting bound to chemical species that react to oxygen, thus being the most efficient biological antioxidant agent<sup>8</sup>.

#### **Reversal Of Leukoplakia-**

The reversal or regression of premalignant lesions such as leukoplakia is an important strategy for cancer prevention. Any agent selected for trial in premalignant lesion, the ultimate goal of which is application for cancer prevention, should have minimal or preferably no toxicity because many subjects whose lesions are unlikely to progress to cancer will be exposed to the intervention. If the object is to develop agents for use by general population to reduce the incidence of oral cancer, then agents preferred are antioxidants such as  $\beta$ -carotene and vitamin E. Intervention trails on betel, quid-tobacco chewers show that administration of Vitamin A cause complete remission of leukoplakia. The most commonly used synthetic retinol, 13 cis- retinoic acid, is toxic even when given at very low dose. There is an increasing emphasis on the use of relatively non-toxic antioxidants such as beta-carotene and Vit.E<sup>3,4</sup>.

A study showing Lycopene effect on oral cancer has proved that high doses of Lycopene (8 mg/ day) are useful in improvement of oral Health<sup>9</sup>.

#### **Green tea Catechins/ Polyphenols**

One of the richest source for polyphenols is from the tea leaves of *Camellia sinensis*. The tea leaves contain

approximately 40% polyphenols by dry weight. The majority of the tea consumed in the world is black tea (78%) while green tea consumption comprises 20%<sup>10</sup>. In vitro studies showed that green tea causes reversible G1 arrest of the cell cycle by inhibition of Rb phosphorylation in oral leukoplakia.<sup>11</sup> EGCG alone or green tea polyphenols were able to induce apoptosis in oral squamous carcinoma cells, while normal human epidermal keratinocytes survived<sup>12</sup>. EGCG or a mixture of green tea polyphenols (GTPP) induced TNF- $\alpha$  gene expression and TNF- $\alpha$  release from cells<sup>13</sup>. The evidence from these studies attests to the feasibility that EGCG is a potential candidate for prevention of human oral cancer.

#### **D) L-Ascorbic Acid (Vitamin C)<sup>3</sup>**

L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrus fruits such as kiwi, strawberries, papaya, and mango. It has been suggested that a daily intake of at least 140mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes.

L-AA has antioxidant properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. L-AA apart from being antioxidant also has following actions:

- Enhances chemotaxis, phagocytosis, collagen synthesis
- Inhibits nitrosamine formation
- Enhances detoxification via cytochrome P450
- Blocks formation of fecal mutagens
- Reduces oncogene expression

#### **E) Tocopherol (Vitamin E)<sup>3</sup>**

Tocopherol (AT) is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves. Tocopherol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation. Main actions of AT includes;

- Free radical scavenging
- Maintenance of membrane integrity, immune function
- Inhibition of cancer cell growth/differentiation
- Cytotoxicity
- Inhibits mutagenicity and

nitrosamine formation

- Inhibition of DNA and RNA, protein synthesis in cancer cells

Recent studies by Balwant Rai et al (2008)<sup>14</sup> have proved that antioxidants such as Vitamin C and Vitamin E may be utilized in oral Lichen planus patients to counteract free radical mediated cell disturbances.

#### F) Zinc and Selenium

Selenium is a trace element. It forms the active site of several antioxidant enzymes including glutathione peroxidase. Similar to selenium, the minerals manganese and zinc are trace elements that form an essential part of various antioxidant enzymes. These trace elements are considered to be helpful in prevention of premalignant lesions.

#### Conclusion

The root of cancer control lies in early diagnosis and treatment. The knowledge of antioxidants is useful in reducing the incidence of oral cancers at initial stages though non invasive techniques. Recent clinical studies have shown the beneficial effects of these antioxidants in oral leukoplakia, a characteristic oral precancerous lesion. Hence, natural products like fruits and vegetables helps in preventing oral cancers at an early stage. Nutrients will be widely utilized and will play an important role in preventing cancers once their

effectiveness is conclusively demonstrated by prospective clinical studies, and when their mechanisms of actions are more clearly understood.

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