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Review Article

The protective role of carotenoids and polyphenols in patients with head and neck cancer

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Abstract

Head and neck cancer is a critical global health problem and approximately 650,000 patients per year are diagnosed with this type of cancer. In addition, head and neck cancer exhibits a high recurrence rate, readily causing second primary cancers in other locations, often yielding a poor prognosis. Current medical and surgical treatment options result in considerable impairment of speaking and swallowing functions, with side effects such as nausea, vomiting, bone marrow suppression, and renal damage, thereby impairing patients' quality of life. Thus, developing a prevention and therapeutic intervention strategy for head and neck cancer is vital. Phytochemicals have been shown to have a unique ability to protect cells from damage and modulation of cell repair. The chemopreventive activities of phytochemicals have also been demonstrated to be associated with their antioxidant properties and the induction and stimulation of intercellular communication via gap junctions, which play a role in the regulation of cancer cell cycle, differentiation, apoptosis, and stagnate cancer cell growth. Phytochemicals can also regulate cancer cell signaling pathways, reduce the invasion and metastasis of cancer cells, and protect normal cells during treatment, thus reducing the damage caused by chemotherapy and radiotherapy. The most studied of the chemopreventive effects of phytochemicals are the carotenoids and phenolics. In this review, we investigated the multiple mechanisms of carotenoids and polyphenols (PPs) for use in preventing head and neck cancer, reducing the side effects of chemotherapy and radiotherapy, improving patient survival rates, and reducing the occurrence rate of second primary cancers.

Keywords: chemotherapy; head and neck cancer; phytochemicals; radiotherapy; supplementary therapeutic agents

1. Introduction

Head and neck cancer is an umbrella term for cancer that occurs in the paranasal sinuses, nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, and salivary glands. More than 90% of these cancers are head and neck squamous cell carcinomas (HNSCCs).[1] People diagnosed with this type of cancer account for approximately 6% of the cancer population. Every year, approximately 650,000 people are diagnosed with head and neck cancer, and 320,000 people die of the disease.[2] Statistics released by the Health Promotion Administration (HPA) showed that the numbers of Taiwanese people diagnosed with oral or esophageal cancer are the highest among member countries of the Organization for Economic Cooperation and Development. In the Top Ten Deadly Cancers list published by the Ministry of Health and Welfare in 2012, oral cancer was ranked fifth. The recurrence rate is high in patients

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with head and neck cancer, and second primary cancer is likely to occur in locations such as the oral cavity, throat, and esophagus. Studies conducted by the HPA indicated that the risk of male patients with oral cancer developing a second primary cancer was 3.8 times that of other people. Additionally, the risk of patients with oral cancer (of both sexes) of developing second primary cancer was 2.4 times that of the risk of people with other types of cancer. The prognosis of patients with oral and second primary cancers is often poor. Thus, preventing and tracking the development of secondary primary cancer is vital.

The treatments performed on patients with head and neck cancer primarily involve surgical resection, radiotherapy, chemotherapy, or a combination of these methods. The medication used in chemotherapy is often cisplatin or fluorouracil (5-FU). However, resistance occurs frequently during treatment, and previously controlled cancer cells can redevelop. The toxicity of the medication may also result in side effects such as nausea, vomiting, bone marrow suppression, and renal damage, thereby impairing the quality of life of patients. Radiotherapy involves using rapid photons to collide with the basic atomic structure of organisms, causing the electrons traveling on peripheral tracks to leave the tracks. Consequently, oxidative stress occurs, generating large amounts of reactive oxygen species (ROS), damaging the DNA in cells. Thus, the cells lose their ability to divide and proliferate.[3] The side effects of radiotherapy primarily include oral mucositis, dermatitis, xerostomia, dysphagia, osteonecrosis, trismus, and neck muscle fibrosis. These conditions considerably jeopardize the quality of life of patients, thereby decreasing patient willingness to receive treatment. The primary causes of head and neck cancer are unhealthy habits such as betel nut chewing, smoking, and excessive drinking.[4,5] Insufficient vegetable and fruit intake is another contributor to oral cancer.[6] Riboli and Norat[7] analyzed numerous case–control studies and found that low vegetable and fruit intake contributed to an increased risk of oral, pharyngeal, and laryngeal cancer, as well as increasing the risk of recurrent primary cancers (e.g., lung and esophageal cancers) in early-stage head and neck cancer survivors.

First proposed in 1976 in the USA by National Cancer Institute scholar Michael Sporn,[8] cancer chemoprevention involves using natural or synthetic substances to prevent, block, suppress, or reverse cancer in the initiation, promotion, and progression stages. Chemoprevention consists of Level 1 and Level 2 prevention—that is, treating pathological changes that occur prior to cancer, and preventing post-surgery recurrence and the occurrence of second primary cancer, respectively. This strategy is vital in current cancer prevention and treatment. The substances used to achieve chemoprevention must be safe and the effective doses should be limited to minimal levels to prevent significant toxicity. Additionally, vegetables and fruits have the potential ability to prevent and inhibit cancer[9,10] primarily because these foods contain large amounts of natural chemicals, called phytonutrients or phytochemicals. As determinants of the color, aroma, and taste of plants, phytochemicals are vital for plants to grow healthily. Phytochemicals are defined as bioactive nonnutrient plant compounds in fruits, vegetables, grains, and other plant foods, and can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds.[11] Regarding the mechanism of the effects that phytochemicals have on the human body, Liu[12] argued that phytochemicals can reduce the risks of cardiovascular diseases and cancer possibly because of their antioxidant activity. Lampe[13] indicated that phytochemicals regulate detoxifying enzymes and the immune system, possibly by altering the metabolism of cholesterols and steroid hormones. Phytochemicals can be used to develop novel chemoprevention and chemotherapy methods and function as assistive alternatives for conventional treatments. Although there are no recommended dietary allowances for phytochemicals, higher doses increase the risk of toxicity. Therefore, it is not recommended to take megadoses of purified phytochemicals as dietary supplements before strong supporting scientific evidence confirms its safety.[11] In this review, we primarily focus on exploring the protective effects and mechanisms of carotenoids and polyphenols (PPs) on patients with head and neck cancer.

2. The prevention and treatment effects of phytonutrients on patients with head and neck cancer

2.1. Carotenoids

Carotenoids are fat-soluble pigments; >700 types of carotenoids have been extracted and identified. However, only 24 of these carotenoids have been found in human blood and tissues, and two of them exist in the retina and lens of the human eye. The most extensively researched carotenoids include β-carotene, lycopene, lutein, and zeaxanthin. The carotenoid concentration in blood is an effective indicator of dietary intake. Carughi and Hooper[14] found that healthy people who have been on a 2-week low-carotenoid diet (<0.4 mg/d) exhibited blood carotenoid levels that were <60% of the initial levels observed at the beginning of the experiment. After the participants consumed carotenoid-rich vegetables and fruits for 1 week, the carotenoids in the blood increased to the original value. The human body can absorb large amounts of carotenoids from natural foods (e.g., vegetables and fruits). Specifically, β-carotene, α-carotene, and β-cryptoxanthin in the human body have vitamin A activity, which means that these carotenoids can be converted to retinol. Additionally, carotenoids are superior antioxidants, capable of capturing singlet oxygen and participating in restoring gap junction intercellular communication (GJIC). GJIC abnormalities are significantly related to cancer cell generation.[15] Studies have shown that the levels of β-carotene, lycopene, and vitamin E observed in the blood plasma of patients with HNSCC[16,17] and oral leukoplakia[18] were lower than those of healthy people. Sakhi et al[19] indicated that the levels of lutein, zeaxanthin, α-carotene, β-carotene, lycopene, and total carotenoids observed in the blood of patients with HNSCC were lower than those of healthy people. Because patients with HNSCC consume smaller amounts of vegetables