

The role of therapeutic nutrition in the treatment of oral cancer patients

دور التغذية العلاجية في علاج مرضى سرطان الفم

Research

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﴿ يَرْفَعُ اللَّهُ الَّذِينَ ءَامَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا
الْعِلْمَ دَرَجَاتٍ ۗ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴾

سورة المجادلة

صدق الله العظيم

Dedication

To my family,

My late father, my mother, my husband, my children, and my little sister.
For their support, encouragement, love, and trust in me.

Acknowledgement

I extend my sincere thanks and appreciation to *Professor Dr. Hisham Mansour, Owner and General Manager of Master Life Academy*, who illuminated our paths to knowledge and learning by founding and managing this academy.

I would like to extend my sincere thanks and appreciation to *Professor Dr. Mohamed Fawzy*, for his efforts in supervising the preparation of this research and the support and guidance he provided me.

And I thank everyone who helped me and extended a hand to bring this research to light.

Salma Ramadan Ahmed

Introduction to the Study

The term "head and neck cancer" includes malignant tumors located in the upper digestive tract: the oropharynx, larynx, and hypopharynx.

Globally, it is the sixth most common malignant tumor, with a particularly high prevalence in Southeast Asia.⁽²⁾

Oral cancer specifically includes a subset of tumors that arise in the lips, the anterior two-thirds of the tongue, the gums, the hard and soft palates, the oral mucosal surfaces, and the floor of the mouth.⁽³⁾

Among these oral cancers, more than 90% are oral squamous cell carcinomas (OSCC)^{(4), (6), (5)}.

Approximately 355,000 cases of oral cancer and 93,000 cases of pharyngeal cancer are diagnosed annually, representing 2% and 0.5% respectively of the malignant tumors detected worldwide.⁽⁷⁾

It has been established that the incidence rate is higher in men than in women (5.8 and 2.3 per 100,000 individuals, respectively); however, there seems to be an increasing trend among women mainly due to their relatively recent exposure to risk factors such as tobacco or alcohol. The average age at diagnosis is around the sixth decade of life, although an increase in the onset of the disease has been observed in young adults (under 45 years old), which is primarily associated with genetic predisposition and the human papillomavirus (HPV).

The prevalence rate is particularly high in Asia (24% of all diagnosed cases), followed by Europe (17.4%) and North America (7.3%).

This increased prevalence in Asian countries may be linked to exposure to risk factors such as smokeless tobacco, alcohol consumption, and betel quid chewing.⁽⁹⁾

In Europe, since the 1990s, an increase has been reported mainly due to greater exposure to known risk factors such as alcohol and tobacco.⁽¹⁰⁾

The five-year survival rate for oral cancer remains low, despite diagnostic and therapeutic advancements.⁽¹¹⁾

The survival rate varies according to factors such as the anatomical location and the stage of the tumor at diagnosis. If the tumor is diagnosed in its early stages, the survival rate ranges between 80% and 90%, which limits the scope of surgical treatments and the use of adjuvant therapies.⁽¹²⁾

The risk factors for oral cancer are widely known and include tobacco (chewing/smoking), alcohol, betel quid chewing, genetic factors, socioeconomic status, poor oral hygiene, human papillomavirus (HPV), and diet.⁽¹³⁾

On the other hand, we refer to the preventive aspect of a healthy lifestyle and a diet based on natural foods with a known "preventive role," as a preventive philosophical approach toward cancer.

In 1997, the World Cancer Research Fund and the American Institute for Cancer Research published a consensus report providing scientific evidence linking high consumption of fruits and vegetables to a reduced risk of cancers of the mouth, pharynx, esophagus, lung, colon, and rectum⁽¹⁶⁾. This has also been confirmed in numerous studies that reported a protective relationship against the most common head and neck cancers, which is why we prepared this study consisting of an introduction, two chapters, and a conclusion:

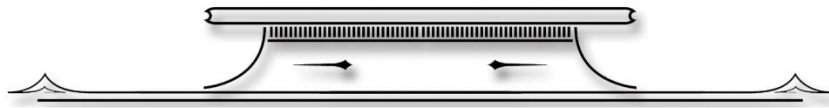
Chapter One: Theoretical Framework of the Study, which includes: Study Problem – Its Importance – Objectives.

Chapter Two: The Role of Therapeutic Nutrition in the Treatment of Oral Cancer, consisting of two sections:

Section One: Oral cancer: It examines the nature of oral cancer, its symptoms, diagnosis, causes, and the factors that increase the risk of developing it.

Section two: It examines how therapeutic nutrition can be used for prevention, assisting in the treatment of oral cancer, or alleviating its symptoms.

The researcher has made sure in her formulation of this study that it is for the general public and not just for the scientific community.



THEORETICAL FRAMEWORK



Chapter (One): Theoretical framework

▪ **Study problem**

The researcher, in her capacity as a dentist, chose the topic of her research on a serious issue, which is oral cancer. Its symptoms cause the patient to be unable to chew, swallow, or taste, and lead to loose and falling teeth, resulting in malnutrition, weight loss, and poor response to treatment. The study problem can be summarized in the following question:

What is oral cancer? And what are its causes and symptoms? And what are the risk factors that cause its occurrence? And what is the role of therapeutic nutrition in the prevention of oral cancer and in aiding its treatment?

▪ **Importance of the study:**

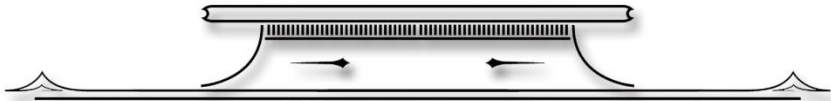
The importance of the study is due to the following:

- 1) Spreading the culture of prevention from the risk of oral cancer by avoiding risk factors that can increase the likelihood of developing oral cancer, which include the following factors:
 - Smoking tobacco
 - Consumption of alcohol
 - Excessive exposure of the lips to sunlight
 - Weakness of the immune system
 - Exposure to the human papillomavirus (HPV): It is a common virus transmitted thru sexual contact, and it does not cause problems for most people and goes away on its own. However, it causes changes in cells in others, which may lead to various types of cancer, including oral cancer.


Chapter (One): Theoretical framework

The researcher advises the necessity and urgency of receiving the vaccines recommended by the specialist doctor.

- 2) In addition to avoiding risk factors, the researcher advises in this study the use of a diet that provides protection against the risk of developing oral cancer. In the event that it occurs – God forbid – a therapeutic nutrition system helps in recovering from this serious disease.

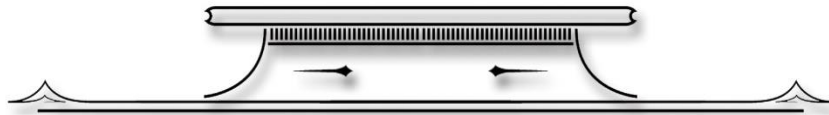


AIM OF THE STUDY



Aim of the Study

This study aims to highlight the vital role of nutritional therapy in improving the health status and clinical outcomes of oral cancer patients, and to study the relationship between oral cancer and diet, in addition to shedding light on factors that may be harmful and those that may be considered preventive due to their properties. Moreover, these potential relationships are important not only for the scientific community but also for the general public.



THERAPEUTIC NUTRITION REVIEW



Section (One): Definition of oral cancer - diagnosis - causes - symptoms - risk factors

▪ **Oral Cancer**

What is oral cancer? And what are its symptoms and causes? And what are the factors that increase the risk of infection? And what are the methods

Prevention of it? And how can therapeutic nutrition be used to prevent it, assist in its treatment, or alleviate its symptoms?

○ **Definition of oral cancer:**

Oral cancer is one of several types of cancers that fall under the category of head and neck cancers. Often, the treatments for oral cancer are similar to those for other types of head and neck cancers.

Oral tumors significantly affect the patient's ability to chew, swallow, and taste, often leading to malnutrition, weight loss, and poor treatment response.

This study analyzes a cohort of patients undergoing nutritional follow-up during different stages of cancer treatment - from diagnosis to post-surgical, radiotherapy, or chemotherapy care.

Oral cancer is the growth of cancerous cells that develops in the mouth. Oral cancer can affect any part of the mouth.

Oral cancer may appear on:

- The lips.
- The gums.
- The tongue.
- The inner lining of the cheeks.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

- The roof of the mouth.
- The floor of the mouth.

The mouth is also called the oral cavity, and therefore, cancer that occurs in the mouth is sometimes called oral cancer or oral cavity cancer.



Cancer of the mouth



A White or red spot on the inside of the mouth

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

○ Symptoms of the disease:

The signs and symptoms of oral cancer may include the following:

- A sore that does not heal on the lips or inside the mouth.
- A white or red spot on the inside of the mouth.
- Loosening of teeth.
- Growth or lump inside the mouth.
- Mouth pain.
- Ear pain.
- Difficulty or pain when swallowing.



Oral cancer – white patches

One of the symptoms of oral cancer is the appearance of white patches in the mouth.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

○ **Causes of the disease:**

The causes of oral cancer syndrome are not always clear, and this cancer begins as a growth of cells in the mouth, often arising in cells called squamous cells; these are flat, thin cells that line the lips and oral cavity. Squamous cell carcinoma is the most common type of oral cancer. Oral cancer develops when the cells of the lips or oral cavity undergo changes in their DNA.

The cell's DNA is responsible for carrying the instructions that guide the cell to perform its function. In the case of healthy cells, DNA directs the cells to grow and reproduce at a specific rate, and it also directs the cells to die at a specific time.

But in cancerous cells, DNA changes give different instructions, directing cancerous cells to grow and multiply rapidly. Cancerous cells may remain alive while healthy cells die, leading to a very large number of cancerous cells.

Cancer cells can form a mass called a tumor, and the tumor can grow and invade healthy body tissues, destroying them. At the same time, cancer cells can detach and spread to other parts of the body. And when cancer spreads, it is called metastatic cancer.

○ **Risk factors**

The factors that can increase the likelihood of developing oral cancer include the following:

✓ ***Tobacco smoking:***

All forms of tobacco increase the risk of oral cancer. They include cigarettes, cigars, pipes, chewing tobacco, and snuff.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Consumption of alcoholic beverages*

Chronic and excessive alcohol consumption is associated with an increased risk of oral cancer. The simultaneous use of alcohol and tobacco leads to an effect that doubles these risks.

✓ *Excessive exposure of the lips to sunlight*

Exposure to ultraviolet rays emitted by the sun and tanning lamps increases the risk of lip cancer.

✓ *Exposure to the human papillomavirus*

Human papillomavirus (HPV) is a common virus transmitted thru sexual contact, and it does not cause problems for most people and clears up on its own. However, it causes changes in cells in others, which can lead to various types of cancer, including oral cancer.

✓ *Weak immune system*

In case the immune system responsible for resisting germs weakens due to medications or illness, the likelihood of developing oral cancer may increase. This is particularly true for individuals with weakened immune systems who take medications to regulate the immune system, such as after organ transplants. Some medical conditions, such as HIV infection, can also weaken the immune system.

○ **Methods of preventing oral cancer:**

There is no guaranteed way to prevent oral cancer. However, the risk of developing oral cancer may be reduced by following these tips:

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Avoid smoking tobacco*

If you are not already a tobacco smoker, do not start smoking it. And if you smoke any type of tobacco, consult your healthcare team about strategies that can help you quit.

✓ *Limiting alcohol consumption.*

✓ *Avoid excessive sun exposure on the lip area.*

Protecting the skin of the lips from sun exposure by staying in the shade as much as possible.

By wearing wide-brimmed hats that provide shade for the entire face, especially the mouth, use a lip sunscreen to protect against sun rays.

✓ *Make sure to get the HPV vaccine.*

Receiving the HPV vaccine can reduce the likelihood of contracting the virus, such as oral cancer. Ask your healthcare team if the HPV vaccine is right for you.

✓ *Conducting health and dental check-ups regularly*

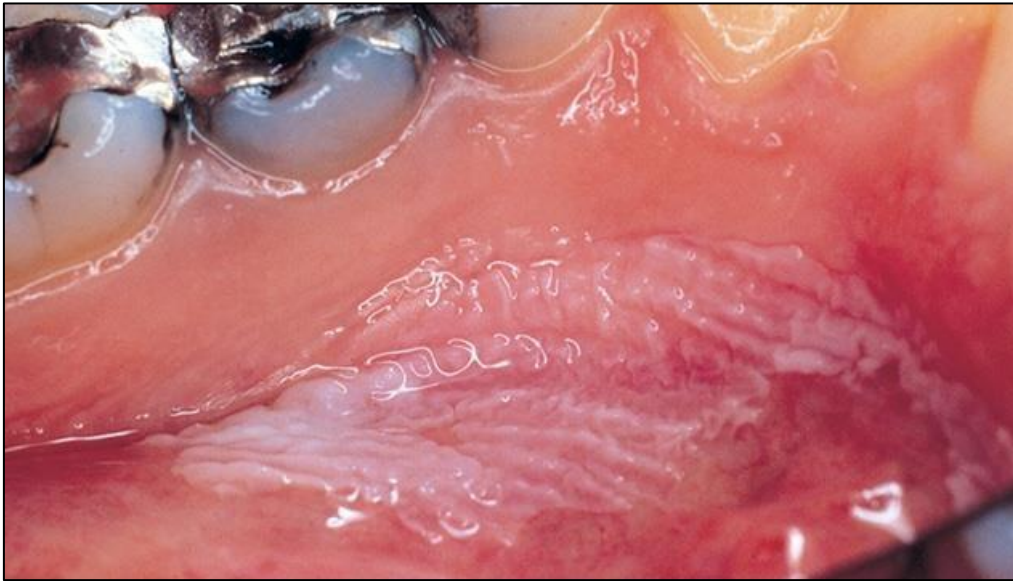
During medical appointments, the mouth can be examined by the dentist, general practitioner, or any other member of the healthcare team to detect any signs of cancer.

○ **Diagnosis**

The diagnosis of oral cancer can begin with an examination of the lips and mouth. The doctor may take a tissue sample for testing to confirm or rule out a diagnosis of oral cancer.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Oral cancer screening*



The doctor examines and palpates the lip and mouth during the physical examination to detect oral cancer. He checks for any lumps or irritated areas in them. White patches in the mouth (leukoplakia) and ulcers may be early signs indicating the onset of cancer.

✓ *Oral cancer biopsy*

If something concerning is found in one of the examinations, the next step may be to take a biopsy for oral cancer. A biopsy is a medical procedure aimed at taking a tissue sample for examination in a laboratory. To take a biopsy of oral cancer, the doctor may use a cutting tool to remove some concerning tissue from the mouth.

In the laboratory, tests can be conducted on tissues to look for indicators of cancer. Other tests may be conducted to look for changes in the DNA within cancer cells. Where the results of these tests can help your healthcare team develop an appropriate treatment plan.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Classification of oral cancer stages*

The healthcare team may need to conduct further tests to determine whether the cancer has spread beyond the mouth.

The healthcare team may use the results of these tests to determine the stage the cancer has reached. Determining the stage helps the healthcare team understand the extent of the disease and know the predictions regarding the course of the disease. And its knowledge also helps in guiding the treatment plan.

Oral cancer staging tests may include:

- **Using a small camera to examine the throat:** The healthcare specialist inserts a thin, flexible tube equipped with a camera thru the throat during the medical procedure known as endoscopy. This medical procedure helps the healthcare specialist detect signs of cancer spread beyond the mouth.
- **Imaging tests:** A variety of imaging tests can help determine whether the cancer has spread beyond the mouth.

Imaging tests may include X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans.

Not everyone needs to undergo all these tests; the healthcare team determines the necessary tests based on the patient's health condition.

○ Stages of oral cancer:

- The stages of oral cancer range from zero to four.
- The earliest stages mean that the cancer is small and has not grown deeply into the tissues inside the mouth. As the cancer grows larger and invades the tissues more deeply, the stages increase.
- Stage four oral cancer may mean that the cancer has grown to a very large size or spread to the lymph nodes.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

Section (Two): The role of therapeutic nutrition in the treatment of oral cancer patients

The relationship between food products and the risk of cancer has recently been evaluated. If studies related to alcohol and tobacco are not included, there seems to be an increased risk concerning certain foods or families, including those rich in inflammatory agents. On the other hand, some nutrients, precise nutrients, and food components can act as protective elements. This protective effect can be obtained from fruits and vegetables, certain vitamins, as well as other common foods and products in our diet. The reduced consumption of fruits and vegetables has been linked to an increased risk of developing oral cancer. Therefore, geographical areas where these foods are difficult to obtain experience a higher prevalence than areas where they are consumed abundantly⁽¹⁴⁾.

Many studies indicate that different dietary compounds can alter or modify cancer cells. Therefore, different food products will be effective in preventing and treating certain types of cancer. Specific foods work by producing genetic cellular changes and modifying their genetic material. The term "epigenetics" refers to changes in gene expression and chromatin remodeling independently of the DNA sequence itself⁽¹⁵⁾.

These changes usually occur through DNA methylation, histone modifications, or gene expression by nc-RNA⁽¹⁶⁾. Epigenetic modifications can play an important role in the development of cardiovascular diseases, obesity, type 2 diabetes, and cancer. DNA methylation occurs when a methyl group is added at the carbon 5 (C5) position of cytosine-guanine (CG) dinucleotides, known as CpG dinucleotides, to cytosine. Cytosine methylation involves the transfer of a methyl group from S-adenosyl-L-methionine (SAM), a methyl donor, to the cytosines on CpG dinucleotides. DNA methylation is catalyzed by enzymes known as DNA methyltransferases (DNMTs). Over-methylation of CpG dinucleotides or CpG islands by DNMTs in the transcriptional gene output

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

has been described in some of the aforementioned diseases. The human genome contains four DNMT genes: DNMT1, DNMT2, DNMT3A, and DNMT3B, and changes in the expression and activity of DNMTs have been reported in some of the aforementioned diseases.⁽²²⁾

On the contrary, a deficiency of methyl has also been found in almost all types of human cancers⁽²³⁾. Genetic changes create imbalances in the transcription of genetic material, which may lead to changes in the expression or activation of factors associated with oncogenes or tumor suppressor genes⁽²⁴⁾. Similarly, some diets rich in fruits and vegetables, in addition to being rich in vitamins and minerals, can intervene in the initiation of programmed cell death and suppress tumor genes⁽²⁸⁻²⁷⁻²⁹⁾.

It seems that some bioactive components in the diet have the ability to prevent various types of cancer, including oral cancer. These bioactive compounds are found in precise nutrients in food items such as vegetables, fruits, tea, garlic, grains, and others.⁽³⁰⁾ Various mechanisms have been proposed to regulate cellular DNA.

○ **The inflammation-promoting diet**

Dietary habits have long been associated with the development of several types of cancer. Inflammatory factors in serum, such as C-reactive protein (CRP), interleukin (IL) IL-1 β , IL-4, IL-6, IL-10, and tumor necrosis factor (TNF), have been studied in certain types of diets to determine which foods promote inflammation and which foods reduce this inflammatory condition. The balance between them will determine the extent to which the diet affects inflammation.

An inflammation-promoting diet stimulates chronic inflammation, which enhances the development of cancer in certain parts of the body, including oral cancer.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

The Dietary Inflammatory Index (DII) was developed to establish criteria that help analyze dietary patterns and the risks associated with different types of diets. Current study indicates that the Dietary Inflammatory Index (DII) links diet and serum C-reactive protein to the level of inflammation.

High values of the Dietary Inflammatory Index (DII) indicate pro-inflammatory diets, while low levels of the DII suggest anti-inflammatory diets and consequently a reduced risk of oral cancer.

There are several ways in which an inflammatory diet can increase the risk of oral cancer: first, through the production of biomarkers such as C-reactive protein, interleukin-6, and homocysteine. Thus, the inflammatory process is responsible for providing biologically active molecules to the tumor environment. Additionally, inflammatory transcription factors can also be activated by cytokines and other inflammatory markers.

Inflammatory biomarkers, which interfere with the initiation and progression of cancer. The modification of non-viable oral microbiota has also been proposed as another potential method, demonstrating a possible association with head and neck cancer.

Among the inflammatory factors, the consumption of large amounts of iron has been linked to oral squamous cell carcinoma (OSCC), which is similar in other tumors such as lung, prostate, and breast cancer.

This is attributed to the fact that iron is involved in essential cellular functions, such as cell metabolism, growth, and proliferation, which may lead to the production of nitrogen compounds and the stimulation of free radical formation that cause cell damage.

In addition to iron, natural red meats contain other components, such as nitrates and nitrites, which may contribute to the development of oral cancer.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

Moreover, when cooked, other carcinogenic mechanisms are generated, such as the production of heterocyclic amines and polycyclic hydrocarbons.

The potential carcinogenic effect of nitrates is due to their conversion into nitrites, which produce methemoglobin. This methemoglobin cannot bind to oxygen, and it may cause a deficiency of oxygen in the blood. When stored fresh, the nitrite concentration (as in vegetables) is usually low, but depending on storage conditions, nitrite concentrations may increase either due to bacterial contamination or the internal nitrate reductase enzyme. When storing food in the refrigerator, the nitrate reductase enzyme is inhibited.

These compounds are also found in cruciferous vegetables, at low to moderate concentrations; however, due to their frequent and large consumption, they can become an important source in the daily diet. Although these levels can be reduced depending on the cooking technique to decrease the amount of nitrates consumed, nitrogen fertilizers should be reduced, and proper storage and processing should be ensured to minimize the risk of bacterial contamination.

Omega-3 fatty acids have also been linked to patients with oral squamous cell carcinoma. The mechanism of action relies on the metabolism of omega-3 fatty acid, producing arachidonic acid, which generates prostaglandins and lipoxins that cause inflammation thru oxidation.

And the balance between omega-6 and omega-3 fatty acids can reduce the risk, to reduce the risk, to reduce the risk of cancer, cancer and the factors oral cancer.

Fried foods have been directly linked to stomach, rectal, and colon cancer. Research has been conducted to clarify whether this link also exists in oral cancer, and it concluded that there is a moderate increase in the risk of oropharyngeal cancer among men who follow a diet rich in fried foods.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

Other researchers analyzed the relationship between these inflammatory foods and laryngeal cancer, and it was found that this relationship is stronger in individuals who are overweight.

Other food products with high sugar potential, such as soft drinks and sweets, lead to a rapid increase in blood sugar indicators, resulting in elevated plasma insulin levels—a hormone associated with tumor proliferation, although there is no specific data linking these foods to oral cancer.

○ **The preventive diet**

Over the decades, there have been certain trends indicating "green chemical prevention," pointing to the preventive aspect of a healthy lifestyle and a diet based on natural foods with a known preventive role, as a philosophical preventive approach toward cancer.

✓ *The high consumption of vegetables and fruits*

In 1997, the World Cancer Research Fund and the American Institute for Cancer Research published a report providing scientific evidence linking high consumption of fruits and vegetables to a reduced risk of oral cavity, pharynx, esophagus, lung, colon, and rectum cancers⁽¹⁶⁾. This was also confirmed in several studies that reported a protective relationship against the most common head and neck cancer (OSCC). Moreover, a dose-dependent relationship was mentioned, where higher consumption of these foods was associated with a reduced risk of the aforementioned cancers. Some mechanisms have been proposed to explain the potential protective effects, as antioxidants reduce reactive oxygen species.

It is believed that some compounds found in vegetables have anti-tumor properties, such as glycosinolates and indole-3-carbinol (a promoter of phase II enzymes) responsible for eliminating reactive oxygen species and repairing DNA.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

The vitamins found in many food products have antioxidant and anti-proliferative properties, including enhancing the immune system thru DNA synthesis and metabolism.

✓ *Vitamin C*

The consumption of vitamin C, found in citrus fruits, reduces the risk of primary cancers, although there is no clear evidence of its association with secondary cancers.

The recommended dosage has not been determined, but in any case, the risk reduction seems clear.

Vitamin C has a reducing effect in the cell, and there seems to be a synergistic effect between Vitamin C and Vitamin E (which is responsible for eliminating free radicals in the cell membrane).

Vitamin C also protects against the production of nitrosamines and the union of DNA with certain carcinogenic substances. Which leads to chromosome damage, thereby reducing the risk of cancer thru various mechanisms.

Regarding dark yellow fruits (such as oranges, lemons, and apricots), no relationship has been proven.

Between its consumption and the reduced risk of developing oral, pharyngeal, or esophageal cancer, however, in a study conducted in Brazil, researchers observed that banana consumption reduces the risk of head and neck cancer by 77%. 77% of this fruit contains vitamins, phenolic acids, carotenoids, and bioactive amines with antioxidant effects.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Red fruits*

Red fruits, such as blackberries and redberries, in addition to grapes, contain large amounts of polyphenols like resveratrol. This compound is characterized by anti-inflammatory, antioxidant, and anticancer properties.

Resveratrol regulates cell growth, division, migration, adhesion, invasion, as well as programmed cell death and angiogenesis.

✓ *Vegetables*

Vegetables contain high levels of fine nutrients (beta-carotene, alpha-carotene, lycopene, vitamins A, C, E) with anti-cancer properties, and in some cases, a combination of several of these molecules enhances their properties.

Beta-carotene is considered an antioxidant, as it protects against DNA damage. Its conversion to retinol plays a key role, as this molecule is involved in cell adhesion, differentiation, and membrane permeability, including its protective role against cancer.

Lycopene is a natural pigment produced by plants and some microorganisms. Although it is found in fruits like watermelon and grapefruit, ripe tomatoes seem to be the main source of lycopene.

This compound is characterized by excellent antioxidant properties, and its effectiveness in preventing and treating chronic diseases, such as degenerative diseases, bone disorders, and cardiovascular diseases, has been studied. Therefore, it may be useful in treating potential malignant oral conditions and as a preventive agent against oral cancer, thanks to the regulation of lipid peroxides and the reduction of glutathione (GSH).

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Garlic*

Other vegetables like garlic, from the lily family, although used as a spice, are also known for their therapeutic properties, such as antioxidants, anti-cancer agents, anti-inflammatory agents, and antimicrobials.

Garlic is high in organic sulfur compounds and flavonoids that provide flavor, but it also contains non-sulfur components that work synergistically to provide beneficial effects.

Studies investigating the anti-cancer properties of garlic hypothesize that certain phytochemicals can enhance the activity of enzymatic systems by detoxifying carcinogenic substances.

Some authors emphasize the documented evidence regarding the association between garlic consumption and esophageal, prostate, laryngeal, colon, ovarian, kidney, and oral cancers.

This correlation was studied using the available scientific evidence (many methodological shortcomings were observed).

A case study and only one witness showed sufficient methodological quality to claim that high garlic consumption is positively associated with a reduced risk of these cancers. However, it is difficult to analyze the amount of garlic consumption using survey data collection methods. Additionally, there are variables that can affect the data, such as the method of preparation (raw or cooked) and the growing conditions.

Regarding oral cancer, with only one valid study, it can be acknowledged that there is very limited evidence supporting the consumption of garlic and its relationship as a protective factor against cancer.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

As mentioned earlier, the combined consumption of fruits and vegetables reduces the risk of developing any type of cancer, with the minimum recommended amount being 400-550 grams per day, although this varies according to the foods and even among different published studies.

Other researchers claim that a cancer-preventive diet should include the consumption of 10 vegetables daily, in their various forms, especially raw, and also included in juices.

The specific nutrients mentioned above have been studied in depth, considering their main source and mechanism of action.

✓ ***Folic acid***

Folic acid or folate, also known as vitamin B9, is found in vegetables, beans, grains, and pasta. Additionally, it can be obtained from plant and animal foods (natural folate) and from dietary supplements also known as folic acid. It is an essential component in DNA methylation, and it has been linked to various tumors such as breast, ovarian, cervical, lung, and colon cancers.

Reports indicate that the consumption of alcohol and tobacco lowers folic acid levels.

The folic acid present in the diet contains side chains of polyglutamate that require oxidation and hydrolysis for absorption. To enhance bioavailability, folic acid can be found in the form of oxidized pteroyl glutamic acid.

Folic acid is essential for DNA synthesis, methylation, cell cycle repair mechanisms, and modulating the risk of oral cancer, as the epithelium is in a state of continuous proliferation and renewal.

This involvement in DNA repair suggests that folic acid deficiency may contribute to the development of certain types of cancer, although this

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

relationship is not entirely clear. Studies have indicated an inverse relationship between high levels of folic acid and the occurrence of oropharyngeal cancer (regardless of the method of consumption/presentation), although this inverse relationship seems stronger in the case of oral cancer. This heightened risk is further increased among alcoholics who have low levels of folic acid.

Similarly, alcohol interferes with the proper transport and metabolism of folic acid, increasing the risk of cancer, as it alters the composition, repair, and methylation of DNA in oral squamous epithelial cells. Moreover, the production of acetaldehyde from ethanol occurs in the oral cavity, which may hinder the potential beneficial effects of folic acid.

✓ *Selenium*

Selenium is a well-known mineral found in walnuts, chicken, beef, and game meats. Selenium is characterized by its antioxidant effects and DNA repair capabilities, in addition to its properties that stimulate programmed cell death, as it affects the methylation of the DNMT enzyme and the histone deacetylase (HDAC) enzyme. Although some studies have indicated an inverse relationship between selenium intake and cancer risk, recent randomized clinical trials have reported that taking supplements of this mineral may increase the risk of cancer.

Regarding oral cancer, high levels of selenium in the serum act as a protective factor when combined with the consumption of large amounts of fruits and fish, along with reducing tobacco and alcohol consumption.

✓ *Zinc and copper*

Zinc is mainly found in proteins of animal origin (beef, pork, and lamb), as well as in food products such as nuts, grains, legumes, and yeast. Zinc interacts with copper in many biological processes, such as eliminating free radicals through the enzymatic system.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

Moreover, zinc is essential in immune response, DNA synthesis, and gene transcription regulation; thus, changes in zinc levels can affect health, and high or low serum copper and zinc levels may be associated with the risk of oral cancer; therefore, these parameters should be controlled in the diet.

✓ *Starch*

Starch is one of the main sources of energy in the diet because it is found in many foods. Different types of starches have been classified as rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS). RDS are processed starches, and their consumption has been linked to an increased risk of oral cancer.

SDS moves slowly in the small intestine, and it is found in legumes and whole grains. Finally, resistant starches are indigestible and non-gelatinous starches.

Depending on the type of starch, different physiological properties can be observed that affect health, especially oral health. However, previous reviews on the impact of starch consumption on oral health did not provide conclusive evidence.

The consumption of certain starchy foods, especially refined grains included in the RDS dietary system, has been associated with an increased risk of oral cancer.

There is some evidence that the consumption of dietary fiber, whole grains, and cereals may reduce the risk of head and neck cancer.

A systematic review was recently published analyzing the effects of total starch intake and the replacement of starchy foods with SDS on oral health. The authors confirmed the data indicating the protective effect of SDS against distress syndrome.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

Respiratory, but they emphasized the insufficiency of evidence due to the limitations of the included studies. In addition to the scarcity of studies, there are biases related to the study category and the amounts of starch consumption. This leads to the belief that the data regarding the relationship between starchy foods and oral cancer is of low quality, and that consistent conclusions cannot be drawn.

✓ *Turmeric*

Curcuma longa (turmeric) is a biological source from the ginger family, native to Southeast Asia. Turmeric resin is used as an orange flavor and food coloring.

Curcumin, a phenolic compound, is used to add flavor and color to many foods, and it has been widely used in traditional medicine (Chinese, Hindu, and Ayurvedic) to alleviate digestive problems. For centuries, it has been known for its anti-inflammatory, antioxidant, anti-angiogenic, and anti-cancer properties, in addition to its significant therapeutic potential.

Turmeric contains three curcuminoid compounds: curcumin (2.8% of the curcuminoids), demethoxycurcumin (1.47%), and bisdemethoxycurcumin (1.3%) with antioxidant properties.

It has been reported that curcumin modulates enzymatic activity in target organs, reducing the levels of metalloproteinases (MMP-2 and MMP-9), thereby inhibiting cancer invasion. Curcumin also modulates the expression of epithelial-mesenchymal transition (EMT) markers and stimulates the expression of the p53 gene. Various publications have reported that consuming curcumin for 3 months (100 mg/kg) reduced the presence of various carcinogenic substances, which are induced by 4-nitroquinoline 1 oxide (4 NQO) used in cancer research to produce tumors in laboratory animals. It also reduced cytological dysplasia and the expression of genes associated with EMT, along with reducing other processes related to the presence of human papillomavirus 1t, the prevention of squamous cell carcinoma, and dysplastic lesions.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

✓ *Green tea*

Tea is one of the most consumed beverages in the world. It is extracted from the *Camellia sinensis* plant, and the black and green types are the most common varieties.

An hour after consuming green tea, high concentrations of catechins and flavins can be detected in the saliva, which enhances the slow release of these compounds in the oral cavity. As a result, it can be effective in preventing tooth decay and gum diseases.

A reverse relationship has been noted between tea consumption, especially green tea, and oral cancer. Several mechanisms have been proposed to explain this relationship: green tea induces apoptosis in oral cancer cells, and epigallocatechin-3-gallate (EGCG) inhibits the growth and invasion of cancer cells.

It has been reported that EGCG, a derivative of epigallocatechin and gallic acid, possesses antioxidant, anti-inflammatory, anti-angiogenic, anti-proliferative, pro-apoptotic, and anti-metastatic properties. These properties may explain its effect on the development and progression of different types of tumors.

Laboratory studies have indicated that green tea is a natural inhibitor of DNMT, preventing DNA hypermethylation. Epigallocatechin-3-gallate reverses hypermethylation of RECK (a cysteine-rich reversion protein with Kazal-like domains), a gene known for its tumor-suppressing properties, and regulates the levels of MMP-2 and MMP-9.

These laboratory results were not reported in other studies conducted on living organisms, indicating individual differences. It seems that some individuals develop a protective role from green tea against oral cancer. Some studies have investigated the role of individual oral microbes as a potential distinguishing factor. Catechins affect bacteria, leading to changes in oral microbiota (*Clostridium* bacteria reduce their regulation, while *Bifidobacterium* and *Lactobacillus* bacteria enhance their regulation).

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

According to each individual, oral microbes can metabolize polyphenols into functional metabolites.

Oral microbes have emerged as a modulating factor for the concentration of nutrients and vitamins, and they may contribute to regulating the formation of carcinogenic metabolites.

✓ *The Mediterranean diet*

The Mediterranean diet is popular in the southern European countries bordering the Mediterranean Sea: France, Portugal, Italy, Spain, Greece, Malta, and Cyprus. These locations are also characterized by a special climate.

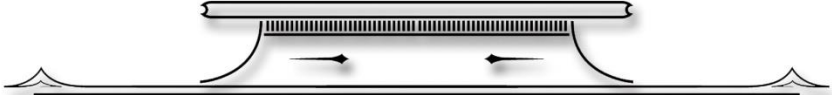
This diet was first described by **Trichopoulou and Ligiou in 1997**, and it is based on the consumption of olive oil, in addition to regularly eating fish, seafood, vegetables, fruits, and grains.

Other recommendations include moderate alcohol consumption, eating small amounts of meat and dairy products, and the Mediterranean food pyramid promotes the consumption of seasonal local products, which is environmentally friendly. According to the literature, individuals who adhere to the Mediterranean diet (MediD) have a lower cancer incidence rate, although the literature supporting this statement is scarce.


Filomeno et al. analyzed data from a case-control study conducted between 1997 and 2009 in Italy and Switzerland, which included 378 patients with histologically confirmed cancer cases and 2078 hospital control cases. Three indices were used for evaluation: the Mediterranean Diet Score (MDS), the Mediterranean Diet Adherence Index (MDI), and the Mediterranean Adequacy Index (MAI). The researchers found a strong inverse correlation between the risk of oral cancer and adherence to the Mediterranean diet, indicating a strong positive role of the MediD system in the prevention of oral cancer.

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

The results of this study are consistent with those previously published by **Bosetti et al. and Samoli et al. Mentella et al.** conducted a comprehensive narrative review in 2019, highlighting the benefits of the Mediterranean diet in reducing oxidative and inflammatory cellular processes, avoiding DNA damage, cell proliferation, and metastasis, and thus lowering the cancer incidence rate.



DISCUSSION



○ Study boundaries

The vast majority of the studies analyzed in this review point to a series of limitations. We consider the lack of quality studies to be the main obstacle to analyzing the relationship between diet and oral cancer in a detailed and specific manner. In most of them, oropharyngeal cancer was mentioned, but the difference regarding oral cancer was not clarified. It is also worth noting the epidemiological limitations. The majority of studies use questionnaires or one-time interviews, avoiding the use of prospective data collection methods, such as dietary diaries, as reported by some researchers. Some bias can be detected, resulting from the inaccuracy of past food consumption memory. Moreover, it is very difficult to determine the amounts of various specific nutrients consumed thru a retrospective survey. In addition to this limitation, foods themselves may contain multiple types of precise nutrients, and it may be difficult to scrutinize their combined effects due to the numerous input variables.

The quantity of food, its freshness, type, cooking time, and shelf life affect the number of precise nutrients consumed, leading to inaccurate results. Even the same precise nutrients can be consumed naturally or as dietary supplements, complicating the process of determining quantities and bioavailability. Other studies indicate limitations in sample size and self-selection bias among participants particularly interested in nutrition issues, who are more likely to participate. Additionally, patients diagnosed with head and neck cancer will remember their diet more accurately, as in some cases, due to medical treatment (radiation therapy, chemotherapy, or even surgery), certain foods may cause discomfort: either mucositis or even difficulty in chewing.

The oral microbiome and its role in the development of oral cancer have recently been studied, including some mechanisms that describe the relationship between specific microorganisms and oral cancer. These mechanisms include promoting chronic inflammation, attacking the epithelial barrier, causing genetic

Chapter (Two): The role of therapeutic nutrition in the treatment of oral cancer

changes, and producing carcinogenic metabolites. Oral microbes can also weaken the role of certain micronutrients in preventing or promoting oral cancer. Several differences have been reported between laboratory studies and live studies.

Social desirability bias was also reported among individuals who chose their answers to please study members where anonymous or online surveys were not conducted.

The methodological constraints related to environmental studies and the possibility of an environmental fallacy in this type of research cannot be ruled out. Additionally, the reduced construct validity is another possibility that cannot be excluded, as not all variables explaining the results may be included in the methodology.

Research related to race, gender, or body size is rare. And we believe that these studies may have implications for public health programs in different countries.

Despite the progress made in the past thirty years regarding the impact of diet on the development of oral cancer, we need more well-designed studies to reduce the methodological limitations mentioned in our review.



RECOMMENDATIONS



Many epidemiological studies link diet to the prevention of various types of cancer. The effect of different types of foods on body cells is influenced by genetic mechanisms that alter their genetic material. And these same mechanisms can affect cancer cells, altering or modifying them, and they are effective in preventing and treating cancer.

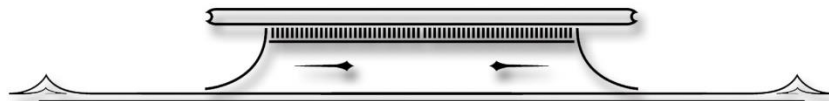
The beneficial effect of a diet rich in vegetables and fruits is attributed to their content of various precise nutrients, such as polyphenols, lycopene, catechins, flavonoids, curcuminoids, slow-digesting starches, minerals (selenium, zinc, copper), carotenoids, vitamins (A, B, C, E), folic acid, and omega-3 fatty acids. However, some of these are also found in fish and animal products. The mechanisms of action of these compounds vary, and when combined, they may have synergistic properties that are antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative.

Regarding oral cancer, research is scarce. Most published studies refer to oropharyngeal cancer or upper gastrointestinal cancer without clearly distinguishing it from oral cancer. There are very few studies with sufficient detail and quality that define the relationship between diet and oral cancer. More studies are needed to investigate the specific relationship between oral cancer and diet.

Oral cancer, classified as a type of head and neck cancer, is the sixth most common malignant tumor in the world. The main causative factors are tobacco and alcohol, although diet is currently considered an important factor in its development. Many nutrients have specific mechanisms of action that contribute to protection against cancer and increase the risk of its development, growth, and spread. Foods such as fruits, vegetables, curcumin, and green tea can reduce the risk of developing oral cancer, while a diet known as the pro-inflammatory diet, rich in red meats and fried foods, can increase the risk.

Nutritional factors with protective effects demonstrate various mechanisms that complement and interact with the effects of antioxidants, inflammation, angiogenesis, and proliferation. The main limitation of bio-studies lies in the complexity of isolating the effects related to each nutrient and its relationship with other potential causative mechanisms.

On the contrary, bio-studies allow for the identification of specific mechanisms of action for certain dietary compounds. In conclusion, despite the limited research, the health benefits of a diet rich in vegetables and fruits are attributed to various specific nutrients that are also found in fish and animal products. These compounds are characterized by antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative properties, which contribute to the prevention of oral cancer and other types of cancer.



SUMMARY



This study addresses a key aspect of oral cancer–related problems, focusing on the therapeutic and supportive role of nutrition in improving treatment outcomes and reducing disease-related complications, particularly in light of the increasing incidence of oral cancer and its negative impact on patients’ health and quality of life. The research aims to clarify the relationship between the nutritional status of patients with oral cancer and their response to various treatment modalities, emphasizing the importance of early nutritional assessment as an essential component of a comprehensive treatment plan.

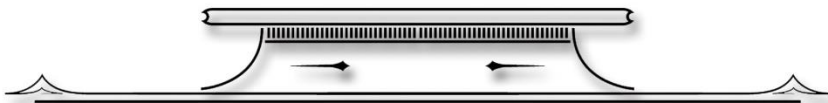
The study adopted an applied analytical scientific methodology, including a systematic and comprehensive review of previous research and studies related to oral cancer and therapeutic nutrition, in addition to an analysis of clinical data associated with patients’ general and nutritional status.

It examined the impact of deficiencies in essential nutrients and malnutrition on disease progression, patients’ tolerance of surgical, radiotherapeutic, and chemotherapeutic treatments, the incidence of complications, and delayed tissue healing.

The study reviewed the positive role of appropriate nutritional interventions in supporting immune function, enhancing wound healing, reducing weight loss and general weakness, and improving oral functional capacity, thereby positively affecting patients’ quality of life. The results demonstrated a clear association between improved nutritional status and better therapeutic response, as well as a reduction in the severity of treatment-related side effects, confirming that therapeutic nutrition is a complementary and essential component in the management of oral cancer rather than a secondary measure.

This research highlights the importance of integrating medical treatment with nutritional intervention and supports the inclusion of nutritional assessment within standard treatment protocols for patients with oral cancer in clinical

practice. Finally the study concludes by emphasizing the importance of health and nutritional education for patients with oral cancer and their caregivers, and calls for further large-scale future studies to support the current findings and to develop more effective therapeutic nutritional strategies



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