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Review Article

Beyond Conventional Therapies: Exploring Nutritional Interventions for Cervical Cancer Patients

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Abstract

All over the world, cervical cancer (CC) is the fourth most common cause of fatalities from cancer in women. This study investigates the critical role of dietary micronutrients in preventing and managing CC, considering the profound impact of malnutrition on cancer patients undergoing chemotherapy and radiation therapy. The study digs the global significance of dietary factors in cancer cases, emphasizing the preventive potential of specific nutrients. Notably, carotenoids, folate, and vitamins C and E emerge as pivotal players due to their functions in regulating DNA synthesis, repair, and cell survival. The study explores the complex landscape of CC, spanning its epidemiology, risk factors, and conventional therapies, highlighting the challenges faced in improving survival rates. The focus then shifts to the potential protective mechanisms of dietary interventions, emphasizing the need for individualized counseling and nutritional strategies. Reactive oxygen species and oxidative stress, linked to lifestyle and dietary choices, are discussed in relation to CC development. The manuscript extensively examines the impact of carotenoids, vitamins C and E, and other nutrients on CC prevention, elucidating their antioxidant properties and potential to mitigate the harmful effects of therapy-induced toxicity. The elucidation encompasses various dietary sources and their role in influencing HPV infection risk. The manuscript concludes with an in-depth analysis of specific nutrients such as carotenoids, vitamins C and E, folic acid, and additional compounds like apigenin, genistein, quercetin, sulforaphane, and tea polyphenols in the context of CC prevention and management. Understanding the intricate interplay between diet, nutrition, and CC development is crucial for devising effective preventive and therapeutic strategies at every stage of the disease.

Key Words: cervical cancer; dietary micronutrients; chemotherapy; radiation therapy; antioxidants; HPV infection

Introduction

After lung cancer, colorectal cancer, and breast cancer, cervical cancer (CC) cause of fatalities from cancer in women all over the world. Women in lower socioeconomic levels and between the ages of 25 and 69 are more common [1]. The primary risk factor for CC (96.6%) is HPV [2]. Only the 16 and 18 HPV variants (70–76%) are linked to CC [3]. There are about 100 HPV variants. The risk of having HPV increases from 2 to 10 times with the initiation of sexual activity. More sexual partners, beginning a sexual relationship before the age of 18, adolescent pregnancy, multiparity, and smoking all make it worse [4]. Cervical cancer is mostly preventable if efficient screening and immunization programs are implemented. Nonetheless, vaccination rates are still low, and few women have access to quality medical care [5]. As a result, there are significant global differences in the number of women diagnosed with cervical cancer each year, over 500,000 of whom die from the disease in low- and middle-income nations [6]. There are essentially two central therapy choices for the treatment of cervical cancer. Surgery is the recommended course of treatment for localized illness when no lymph node metastases have been found or risk factors are present. These therapeutically designed procedures range from radical hysterectomy or total mesometrial resection, which includes significant pelvic and paraaortic lymphadenectomy, to conization that preserves fertility. The mainstay of care for patients with locally advanced cervical cancer is definitive chemoradiotherapy (CRT) followed by brachytherapy (BT) [7]. BT is a key aspect of definitive therapy regimens for individuals with locally advanced cervical cancer [8]. By successfully

targeting the residual amount of disease and optimally sparing neighboring organs at threat, it provides a highly uniform exposure and dispersion of radiation, maximizes local control, and minimizes toxicities [9]. When compared to radiation therapy alone, concomitant chemotherapy has greatly increased the persistence level of patients with cervical cancer. Therefore, platinum-based chemotherapy regimens are typically the first choice for patients who qualify for them [10]. Additionally, a mix of bevacizumab, an inhibitor of vascular endothelial growth factor, with cisplatin, paclitaxel, or topotecan showed a significantly higher likelihood of survival but was also linked to increased toxicity [11]. The treatment of many solid tumors has changed recently thanks to immunotherapies, which are always developing. Pembrolizumab, a programmed death 1 (PD-1) inhibitor, has been approved by the FDA for use in patients with cervical cancer who have met treatment goals and recurrence following chemotherapy. These patients' tumors must exhibit PD-L1 (combined positive score (CPS) ≥1). Immune checkpoint inhibitors are being studied in multiple settings, including the CALLA (durvalumab), NCT02635360 (pembrolizumab), and NRG-GY017 (atezolizumab) trials, for CC treatment, pending additional data. Moreover, therapeutic vaccination techniques (e.g., NCT02853604) and adoptive cell therapies (e.g., NCT03108495) are currently being studied [12]. Accordingly, tisotumab vedotin, an antibody-drug conjugate (ADC), has been approved against tissue factor and monomethyl auristatin E (MMAE) for the treatment of CC. This approval was granted following the completion of the NCT03438396 multicenter, open-label, single arm, phase 2 trial (innovaTV 204/GOG-3023/ENGOT-cx6), which demonstrated efficacy and safety [13]. In spite of these developments, survival rates have not increased dramatically in the last 20 years, and the prospects for women who have dogged, recurring, or metastatic illness in particular is still not good. Toxicology is the unifying denominator of all treatment plans. Finding palliative therapies for the toxicity brought on by chemotherapy is therefore critically important. It's interesting to note that numerous research point to the ability of nutrient-rich plant-based resources to shield animals against the toxicity of a common chemotherapy drug (methotrexate) [14-16]. Between 20 and 60 percent of cancer cases worldwide are thought to be caused by dietary variables [17]. Individualized counseling and nutritional intervention, which combine dietary prescription with nutritional therapy, have been shown to be highly effective in the treatment of a number of disorders, including rheumatoid arthritis [18], diabetes mellitus [22], HIV infection [20, 21], and cervical cancer [22]. In this case of cervical cancer, the stage of the malignancy is crucial [23].

It is well recognized that eating a balanced diet can help lower the risk of cervical cancer and increase resistance to HPV infection. Carotenoids (both vitamin A and non-vitamin A precursors), folate, and vitamins C and E are among the micronutrients that have been shown to have a suppressive effect on HPV infection [24-27]. Therefore, the advantages of different nutrients in CC must be investigated and taken into consideration in CC pharmacology research as a primary preventative and enhanced treatment strategy.

Effect of Dietary Nutrient Intake on Management and Prevention of Cervical Cancer

HPV infection is the main root cause of the illness. A precancerous lesion typically takes 10 to 20 years to progress to malignancy. Additionally, it has been demonstrated that CC is associated with a number of traits, more sexual partners, beginning a sexual relationship before the age of 18, adolescent pregnancy, multiparity, smoking, and contraceptive pills (OC) [4]. Furthermore, the consumption of different nutrients in the food is a major factor in the development or avoidance of CC. Reactive oxygen species are produced by normal metabolic processes as well as lifestyle choices like food, exercise, and smoking (ROS). Overproduction of reactive oxygen species (ROS) causes oxidative stress. Macromolecules such as lipids, proteins, and DNA are harmed by this [28-31]. Numerous chronic diseases like diabetes mellitus [32-38], cardiovascular conditions [39-441, and cancer [45-47] have been linked to oxidative stress. On the other hand, ROS levels can be adjusted by intracellular antioxidants such as glutathione [48, 49].

A lack of antioxidants may make people more susceptible to oxidative stress, which raises the possibility of developing cancer. It has been demonstrated that exogenous antioxidant supplementation reduces oxidative damage by scavenging reactive oxygen species and preventing the oxidation of intracellular macromolecules. It is noteworthy that exogenous antioxidants can be found in good amounts in fruits, vegetables, nuts, and legumes [50-54]. Consuming fruits, vegetables, nuts, and legumes may therefore have a preventive effect on the occurrence of cervical malignancies. Researchers have documented the protective properties of plant-based materials against a range of cancer risks [45-47].

Red and processed meats, pickles, salted or dried fish, dipping sauces, chips, snacks, instant noodles (which are categorized as part of the western diet), and a low consumption of olive oil are all linked to an increased risk of HPV infection, according to Barchitta et al. Furthermore, there was an increased risk of HPV infection for women who did not adhere to the Mediterranean diet (MD), which consists of fish, vegetables, legumes, fruits, nuts, milk, cereals, and a high proportion of polyunsaturated fats. In summary, strong adherence to MD can result in a 60% decrease in CC risk. In a similar vein, dietary oleic acid, which is frequently present in edible oils, has been shown by Yang et al. [55] to stimulate the proliferation of malignant cells and their spread to the cervix. Delam and colleagues [4] observed that a diet deficient in citrus fruits and vegetables can enhance the risk of ICC. It has been discovered that several micronutrients, including carotenoids, folate, polyunsaturated fatty acids (PUFA), and vitamins C and E, decrease the development of HPV and the risk of cancer.

Carotenoids

Carotenoids are pigments that give plants, fruits, and vegetables their characteristic red, orange, and bright yellow hues. Carotenoids come in over 600 different varieties. The most prevalent dietary carotenoids are lutein, zeaxanthin, β-carotene, β-carotene, β-cryptoxanthin, and lycopene.

A small number of them, including beta-cryptoxanthin, alpha-carotene, and beta-carotene, can be released into the body and transformed into vitamin A. When the body needs vitamin A, beta-carotene, also known as provitamin A, is converted by the liver. A lack of vitamin A increases cellular damage, oxidative stress, and the suppression of cell repair mechanisms. Surprisingly, there are plenty of carotenoids in fruits, vegetables, and nuts [56-60]. Research revealed inverse relationships between the risk of colorectal CC, particularly squamous-cell carcinoma, and blood antioxidant micronutrients [25].

Lycopene is a vivid red colorant and plant chemical from tomatoes, papayas, carrots, watermelons. In several cancer forms, it exhibits chemopreventive properties in addition to antioxidant action. Its capacity to activate cancer-preventive enzymes, such as phase II detoxifying enzymes, confers anticancer properties. It has been discovered to reduce insulin-like growth factor-I induced cell growth and to limit the proliferation of human cancer cells. According to Nath et al. [61] the risk of developing CC is more likely to occur at low serum concentrations of this micronutrient, while the risk is lower at medium to high concentrations. Consequently, it may be said that

serum carotenoids offer general defense against the development of CC. Its potential mode of action is through its antioxidant activity, which scavenges ROS and minimizes their harmful effects on nucleic acids, cellular proteins, and cell membranes [25].

Vitamins

Vitamin C is abundant in fruits (oranges, lemons, strawberries, blackcurrants, and kiwis) and vegetables (mostly broccoli, tomato, and sweet pepper). Vitamin C also called ascorbic acid, is a vital nutrient that protects and maintains healthy skin, blood vessels, bones, and cartilage. It also aids in the healing of wounds [62, 63]. Cao et al. [64] found a significant correlation between a 50 mg daily increase in vitamin C intake and an 8% reduced risk of CC in their meta-analysis. Consuming vitamins C and E may significantly slow down the development of CC. Vitamin C has antioxidant properties, improves cellular immunity, and maintains the intercellular matrix [65, 66].

Antioxidants vitamins (A, C, and E) can lessen the harmful effects of reactive oxygen species (ROS). ROS can alter the fluidity and integrity of immune cells' membranes, which can alter the distribution and function of cellular receptors. ROS seriously harm lipids, proteins, and DNA. By preventing the development of DNA adducts, vitamin C can improve the mucosal immune system's ability to fight off infections and scavenge excess reactive oxygen species (ROS). Additionally, tumor cells that secrete matrix metalloproteases (MMPs) release enzymes that break down the membrane, enabling the tumor cells to infect nearby tissues and ultimately cause cancer cells to migrate. Notably, vitamin C has the ability to stop the formation of MMP and stop cancer cells from invading in vitro, indicating that it may have a preventive effect on the development of CC [64].

Vitamin E is an antioxidant that is fat-soluble and found in numerous foods such as sunflower oil, safflower oil, and wheat germ oil. It is a class of chemicals encompassing both tocopherols and tocotrienols, and in particular, alpha-tocopherol is the most bioactive form of vitamin E that stops the creation of ROS when fat experiences oxidation [67]. Vitamin E (α- and γ-tocopherol) concentrations in serum have been strongly linked to cancer. The chance of having CC is higher in those with low serum concentrations of this vitamin, while the risk is lower in those with medium to high concentrations [25]. Thus, vitamin E could attenuate CC. Tocopherols have been linked to several anti-inflammatory processes, including the inhibition of PKC activity, the inhibition of eicosanoid biosynthesis-related enzymes, and the inhibition of cyclooxygenase-2-mediated PGE2 (prostaglandin E2) formation.

Vertebrates can produce vitamin D in their skin after being exposed to UVB rays. Light-exposed mushrooms are also a good source of vitamin D. The small intestine benefits from vitamin D's promotion of calcium absorption, which also keeps serum calcium levels sufficient for osteoblasts and osteoclasts to develop and remodel bone. In addition, vitamin D modulates immunological, neuromuscular, and cell proliferation in addition to reducing inflammation. Vitamin D may help individuals with HPV infection by reducing clinical symptoms because of its anti-inflammatory properties. D vaginal suppositories resulted in antidysplastic effects in the CC treatment [68]. Comparatively to HPV-negative patients, Özgü et al. [69] showed a decrease in vitamin D levels in patients with HPV infection. These results could be explained by the theory that a chronic HPV infection brought on by a vitamin D deficit can eventually result in the development of CC. Nonetheless, an upsurge vitamin D consumption may hence inhibit the formation of CC and reduce persistent HPV infection [17].

Additional nutrients

Folic acid (folate, or vitamin B9) plays a crucial function in red blood cells, DNA synthesis, DNA repair, DNA methylation, and cell proliferation. Leafy vegetables are rich sources of folate. The impact of folic acid on CC through food has generated significant debate. Consuming folate may stop or slow the progression of HPV infection to different CC grades. Folate's involvement in DNA synthesis and DNA damage repair suggest that it may offer protection against CC. Because it participates in DNA methylation, folate has the potential to affect how genes are expressed. Proto-oncogenes can be inhibited and DNA methylation will take place if there is sufficient folate, which will stop unchecked cell proliferation. On the other hand, DNA hypomethylation and genes become "on" in low folate blood, raising the possibility of unchecked cell development leading to cancer [61].

The following nutrients are essential for the development of CC: apigenin, genistein, quercetin, sulforaphane, tea polyphenols (TPPs), and polyunsaturated fatty acids.

Apigenin, a flavone contained in vegetables such as parsley, celery, chamomile, and moringa. Apigenin triggers apoptosis, which has a protective effect, and is thought to act as a mediator for chemotherapy prevention in the malignant process.

One isoflavone found in plants including coffee, soybeans, fava beans, and lupine is called genistein. Enzymes that control cell division and survival, such as tyrosine kinase and DNA topoisomerase II, are inhibited by genistein. Additionally, it reduces cellular viability by causing apoptosis as a result of ROS formation [17]. Furthermore, genistein has been shown to have antiangiogenic properties, which prevent the unchecked cell proliferation linked to cancer.

Vegetables and fruits are rich sources of quercetin, a flavonoid whose antioxidant properties may be beneficial to human health. Quercetin was shown by Kedhari et al. [70] to have antiproliferative, proapoptotic, and antimigratory effects in CC cells, making it a potentially useful tool for cancer chemoprevention and treatment approaches.

Broccoli, Brussels sprouts, and cabbages are examples of cruciferous vegetables that contain the organosulfur chemical sulforaphane. By stopping cell growth in the G2/M phase and causing apoptosis by upregulating proapoptotic genes, sulforaphane delays the development of cancer [17].

The most prevalent catechin component in green tea is epigallocateocatechin-3-gallate (EGCG), a type of polyphenol found in tea. A growing body of research indicates that EGCG may be helpful in the treatment of CCs.

The antiapoptotic protein Bcl-xl, which is implicated in the survival of cancer cells, is bound by EGCG and inhibited.

Saturated fat-rich diets increase the risk of cancer [27]. According to a clinical experiment by Wuryanti et al. [71] individuals with advanced cancer may see a decrease in inflammation while using PUFA-enriched dietary supplements. PUFA lowers serum PGE2 levels, which in turn decreases the viability of cancer cells. As a result, PUFA supplementation plus radiation therapy improves CC cells' responsiveness to radiation.

Conclusion

This manuscript underscores the pivotal role of dietary micronutrients, such as carotenoids, folate, and vitamins C and E, in the prevention and management of cervical cancer. Recognizing the significant impact of

malnutrition on cancer patients undergoing conventional therapies, the study advocates for individualized nutritional interventions. The complex interplay between diet, oxidative stress, and HPV infection is thoroughly explored, emphasizing the potential of specific nutrients to mitigate therapy-induced toxicity and enhance overall treatment outcomes. As cervical cancer continues to pose a global health challenge, understanding and incorporating dietary strategies into comprehensive care approaches could prove instrumental in improving patient outcomes at various stages of the disease.

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