



The Effects of Dietary Nutrient Intake on Cervical Cancer: A Brief Review

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Ind J Med Paediatr Oncol

Abstract

Cervical cancer (CC) results from a subsequent process, starting from the infection of normal cervical epithelium with oncogenic human papillomavirus and gradually progressing to cervical intraepithelial neoplasia (CIN), before finally developing into invasive cervical cancer (ICC). Over recent decades, dietary micronutrients have gained much attention due to their pivotal role in cancer prevention. We reviewed several relevant literature studies to investigate the protective roles of dietary nutrient intake in CC. Dietary intake of vitamin C, green–yellow vegetables, and provitamin A carotenoids that are rich sources of antioxidants may widely inhibit the process of CC development, whereas vitamins A and D might be more helpful in preventing the early events in the disease development. Vitamin E, lycopene, and folate are more effective for the treatment of high-grade CIN. Fruits exert their protective effects in the late stages of the cancer process, thus playing a vital role in ICC prevention. Polyphenols, flavonoids, and polyunsaturated fatty acids are more often used in cases of CC in combination with chemotherapy and radiotherapy. Thus, as a primary prevention strategy, the health benefits of various nutrients in CC must be clarified by *vitro* and *in vivo* approaches rather than epidemiological studies.

Keywords

- ▶ diet
- ▶ nutrition
- ▶ HPV
- ▶ cervical dysplasia
- ▶ cervical cancer

Introduction

Diet and nutrition not only serve as the source of important physiologically functional components of human beings, but they also play crucial roles in cancer management. Dietary factors approximately contribute to 20 to 60% of all cancers worldwide.^{1,2} Cervical cancer (CC) ranks as the third most commonly diagnosed cancer type and fourth leading cause of cancerous deaths in women worldwide.^{3,4} The Global Cancer Observatory estimates of the incidence rate of CC due to human papillomavirus (HPV) in 2020 were 604,127 and mortality rates were 341,831 globally (95% UI).⁵ Oncogenic HPV is a necessary but insufficient risk

factor for the development of cervical carcinoma, as most HPV infections clear spontaneously without leading to any cervical cytological abnormalities.⁶ However, the persistence of genital HPV infection that might progress to cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC) is influenced by a variety of infectious, behavioral, lifestyle-associated cofactors.^{7,8} Various studies on risk factors have associated the role of the diet with CIN, hypothesizing that women with a relatively high dietary intake of certain nutrients have a reduced risk of developing intraepithelial and invasive cervical lesions. Of particular interest are antioxidants that play major roles in cell survival, proliferation, and differentiation, such as vitamins

DOI <https://doi.org/10.1055/s-0043-1768049>.
ISSN 0971-5851.

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A, D, C, and E,^{1,2,9-11} tea polyphenols (TPPs),¹² flavonoids,^{1,2} tocopherol, and provitamin A carotenoids^{10,13-17}; regulators of DNA synthesis and repair such as folate^{10,18-20}; and inflammatory response relievers such as polyunsaturated fatty acid (PUFA).²¹

Understanding the effects of diet and nutrition on CC development is very important for the management of public health concerns. For these reasons, it is necessary to understand the roles of various dietary nutrients in CC development. This paper reviews the current issues, effects, and possible protective mechanism of these dietary micronutrients in CC in relation to each stage of CC development.

Role of Dietary and Nutrient Intake on Cervical Cancer

In India and other developing nations, cervical cancer (CC) is the second most common cancer among women of reproductive age.²² Infection with HPV is the disease's main underlying cause. It usually takes nearly 10 to 20 years for a precancerous lesion to develop into cancer. CC is also proven to be associated with many factors such as the age at marriage, age at the consummation of marriage, parity, history of promiscuity, smoking habits, and the use of oral contraceptives (OC).²³ But the dietary intake of various nutrients plays a vital role in either the development or prevention of CC.

Normal metabolic activities and lifestyle factors such as smoking, exercise, and diet generate reactive oxygen species (ROS). Oxidative stress, induced by the overproduction of ROS, causes oxidative damage to biomolecules such as lipids, proteins, and DNA. Thus oxidative stress has been implicated in the development of several chronic diseases, one of which

is cancer. Antioxidant deficiency might render individuals more vulnerable to oxidative stress, thereby increasing the risk of cancer occurrence. Exogenous antioxidant supplementation has been proven to alleviate oxidative damage by scavenging ROS and reducing the oxidation of cellular biomolecules.²⁴ Thus, dietary patterns have a protective effect against the development of a variety of cancers, particularly those of epithelial origin.²⁵ So the consumption of more antioxidant-containing food such as vegetables, legumes, fruits, and nuts can significantly reduce the risk of any cancer including CC. Barchitta et al reported that a western diet, which includes red and processed meats, salty foods such as pickles and salted/dried fish, dipping sauces, chips, snacks, instant noodles, and low intake of olive oil, is associated with a higher risk of HPV infection.²⁶ Additionally, women who showed low adherence to a Mediterranean diet (MD), which includes vegetables, legumes, fruits, nuts, milk, cereals, fish, and a high ratio of PUFA, were posed to a greater risk of HPV infection.^{26,27} The author demonstrated a direct relationship between the increased intake of MD and the slowdown of progression of hrHPV infection, thus playing a protective role in the onset of neoplasia. As a result, a 60% reduction in CC risk can be attained with high adherence to MD.²⁶

Recently, Yang et al reported that dietary oleic acid commonly found in edible oils exerts a stimulatory effect on cancerous cell growth and metastasis of the cervix.²⁸ Brock et al and Delam et al reported that a diet low in citrus fruits and green-yellow vegetables (green vegetables, carrots, and pumpkins), which are rich sources of antioxidants can elevate the risk of ICC.^{23,29} The roles of dietary and nutrient intake in preventing various stages of CC are discussed below, and **Fig. 1** depicts the pictorial representation of the same.

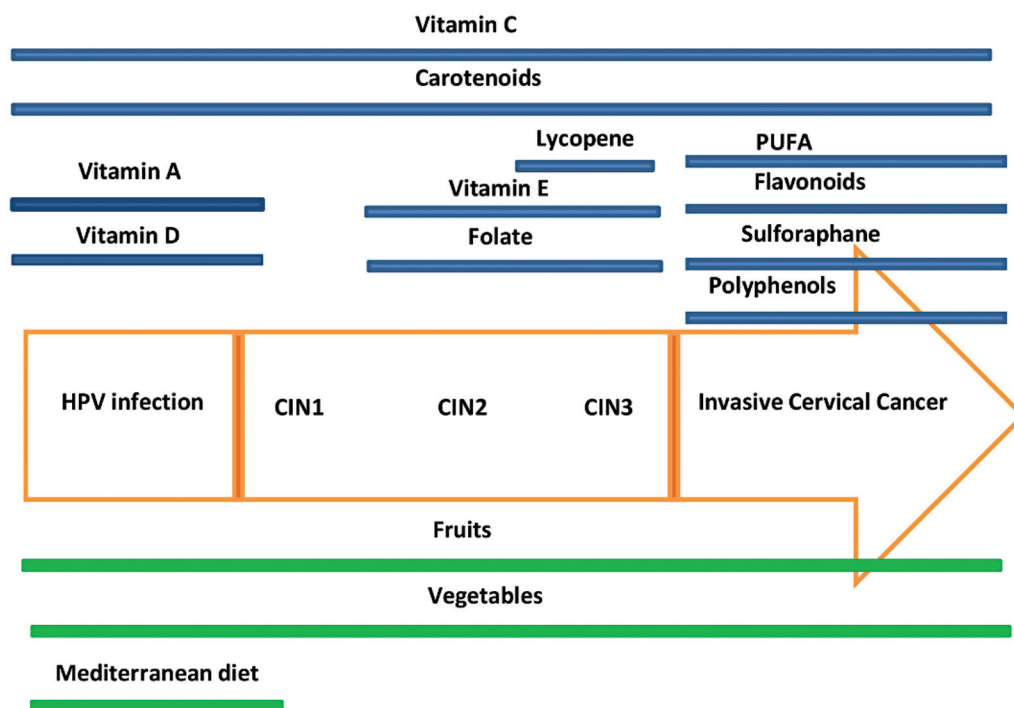


Fig. 1. Role of various nutrients on the development of cervical cancer.

Carotenoids

Carotenoids are pigments that produce the red, orange, and bright yellow colors seen in plants, fruits, and vegetables. There are more than 600 different types of carotenoids. α -carotene, β -carotene, β -cryptoxanthin, lutein, zeaxanthin, and lycopene are among the most common dietary carotenoids. Few of them (e.g., α -carotene, β -carotene, and β -cryptoxanthin) can be converted into vitamin A when released into the body. β -carotene, named provitamin A, is transformed into vitamin A by the liver, according to the body's needs. It is the most powerful precursor of vitamin A, followed by α -carotene, β -cryptoxanthin, and other carotenoids. Vitamin A deficiency stimulates oxidative stress, cellular damage, and inhibition of cell repair function.

Studies indicated inverse associations between dietary and serum antioxidant micronutrients like provitamin A carotenoids (precursor of vitamin A) like α -carotene, β -carotene, lutein/ zeaxanthin, and cryptoxanthin and the risk of CC, especially for squamous-cell carcinoma.^{10,15-17} However, they did not observe any protective effects of dietary retinol (preformed vitamin A) against CC as it might be associated with early events in the HPV infection process and, therefore, may be more effective in preventing low-grade CIN.^{10,15} Blood retinol would not be expected to exert an effect since levels of retinol are under homeostatic control and show little variation except under extreme conditions of over- or undernutrition.³⁰

Two population-based case-control studies analyzing the concentration of a variety of serum carotenoids of ICC patients and controls reported that women possessing low serum levels of total carotenoids (α -carotene, β -carotene, and cryptoxanthin) are significantly more prone to ICC as compared to controls,^{14,31} whereas the supplementation of oral β -carotene has been reported to prevent CC.¹³

However, contradictory results were obtained in a Japanese case-control study (Nagata et al) where it was reported that carotene consumption was not significantly associated with protection against cervical dysplasia. A low serum carotenoid concentration found in cases indicated that it was a result of the disease rather than a cause of its occurrence.¹⁰

Serum concentrations of lycopene carotenoid have also been linked to CC. A low concentration of this micronutrient in serum has the propensity to increase the risk of developing CIN3, whereas medium to high levels were observed to reduce the risk of CIN3 development.¹¹ In summary, lycopene might be more effective for preventing high-grade CIN rather than primary HPV infection. Lycopene is a bright red pigment and phytochemical from tomatoes, red carrots, watermelons, and red papayas. It exerts antioxidant activity and has chemopreventive effects in different types of cancer. Its anticancer property is imparted by its ability to activate cancer preventive enzymes such as phase II detoxification enzymes. It has been found to inhibit human cancer cell proliferation and to suppress insulin-like growth factor-I-stimulated cell growth.¹²

Therefore, it can be concluded that serum carotenoids provide overall protection against CC development. Its pos-

sible mechanism of action is via its antioxidant activity involved in scavenging ROS, thus reducing toxic effects on cell membranes, cellular proteins, and nucleic acids.^{29,32}

Vitamins

In recent decades, dietary antioxidants, such as vitamins, have received much attention in relation to cancer prevention.

Fruits (mainly oranges, lemons, strawberries, blackcurrants, and kiwis) and vegetables (mainly tomato, broccoli, and sweet pepper) are rich sources of vitamin C. Vitamin C, also known as ascorbic acid, has several important functions like protecting and maintaining healthy skin, blood vessels, bones, and cartilage while also helping with wound healing.³³ A meta-analysis by Cao et al suggests that there is a significant inverse association between vitamin C intake and the risk of CIN and the association was dose dependent. Notably, increased vitamin C intake by 50 mg/day was significantly correlated with a reduced risk of ICC by 8%.³⁴ The intake of vitamins C and E may widely inhibit the process of CC development. Slattery et al and Kim et al reported that the intake of vitamins C and E significantly lowered CC risk in nonsmokers as well as in smokers. The reason behind their protective function is that both of these vitamins are known to be antagonists to nitrosamines which are predominant in side-stream smoke than in mainstream smoke, thus efficiently reducing the chances of CC in passive smokers.^{9,10} The possible role of vitamin C is the enhancement of cellular immunity, maintenance of the intercellular matrix, and an antioxidative property.¹⁶ Vitamin C is a potent antioxidant that has antineoplastic effects on the cervix. Vitamin C was demonstrated to increase the drug sensitivity of cervical carcinoma cells by stabilizing P53, which was targeted by HPV oncoproteins for degradation and hence causes cell cycle arrest. Antioxidants are able to reduce the toxic effects of ROS, which otherwise lead to changes in the distribution and function of cellular receptors through affecting the fluidity and integrity of the membrane in immunological cells. Free radical is apt to cause extensive damage to DNA, protein, and lipids. Vitamin C could settle this situation by inhibiting DNA adduct formation, thus enhancing mucosal immune response to infection and scavenging the free radicals. Besides, matrix metalloproteinases (MMPs), tumor cells secrete enzymes, that digest the membrane and then allow tumor cells to invade adjacent tissues, eventually resulting in migration of cancer cells. Notably, vitamin C can inhibit MMP production and prevent invasion of cancer cells in vitro, suggesting its potential protective effect on CC development.³⁴

Vitamin E is a fat-soluble antioxidant that exists in many foods including wheat germ oil, sunflower oil, and safflower oils. It represents a family of compounds comprising both tocopherols and tocotrienols, and in particular, α -tocopherol is the most bioactive form of vitamin E that stops the production of ROS when fat undergoes oxidation.¹²

Serum concentrations of vitamin E (α -tocopherol and γ -tocopherol) have been closely associated with CC. A low concentration of this vitamin in serum increases the risk of

developing CIN3, whereas medium to high levels were observed to reduce the risk of CIN3 development.¹¹ In summary, vitamin E might be more effective for preventing high-grade CIN. Some anti-inflammatory mechanisms have been reported for tocopherols, such as inhibitory protein kinase C (PKC) activity, inhibitory activity of enzymes involved in eicosanoid biosynthesis, and inhibiting cyclooxygenase-2-mediated biosynthesis of PGE2 (prostaglandin E2).³²

After exposure to ultraviolet-B light, vertebrates can generate vitamin D in their skins. Light-exposed mushrooms are also an excellent source of vitamin D. Vitamin D promotes calcium absorption in the small intestine and maintains adequate serum calcium needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Vitamin D has other roles, including the modulation of cell growth, neuromuscular and immune functions, and the reduction of inflammation. Stefanska et al reported that vitamin D particularly D3 was associated with PTEN induction as well as p21 up-regulation, thus suppressing tumor formation.^{12,35} Due to its anti-inflammatory activities, vitamin D may be useful for ameliorating clinical symptoms in patients with HPV infection. Schlte-Uebbing et al also reported that treatment with vitamin D vaginal suppositories (12,500 IU, three nights a week, for 6 weeks) resulted in antidyplastic effects in the CIN 1 group, but that it did not affect the CIN 2 group.³⁶ Özgü et al showed that the 25-hydroxy vitamin D level in 22 HPV-positive patients was significantly lower than that in 62 HPV-negative patients.³⁷ These findings may be explained by the assumption that vitamin D deficiency can cause a persistent HPV infection and thus lead to the development of CIN. However, a high intake of vitamin D may therefore suppress persistent HPV infection and prevent the development of CIN 1.^{1,2}

Folate

Folate (vitamin B9) plays an important role in red blood cells, DNA synthesis, DNA repair, DNA methylation, and cell proliferation.³⁸ Many vegetables and pulses are rich sources of folate, with folate concentrations up to 600 pg/100 g in some beans and chickpeas and around 200 pg/100 g in leafy vegetables. A sort of general rule is that the lower the water content in the vegetable, the higher the folate concentration, and therefore leafy vegetables are good folate sources (folium means leaf). Folate concentrations in fruits and berries are usually one-tenth those of vegetables, ranging from a few pg to approximately 50 pg/100 g.³⁹

The dietary effect of folic acid on CC has been quite controversial. The intake of folate may prevent or inhibit HPV infection from progressing to various grades of CIN. The studies of Butterworth et al and Kim et al suggested that low plasma folate levels can be associated with an increased risk of cervical dysplasia and dietary supplementation could lead to regression of dysplastic lesions, thus supporting the protective effects of folic acid on CC.^{10,18} Similar results were observed by Kwanbunjan et al in a case-control study. The author reported an association between low serum folate levels and high risk of developing both CIN1 and CIN2/3.¹⁹ However, a medium serum folate concentration was associated with a high risk of developing CIN1 but not

CIN2/3. Thus, dose-responsive serum folate levels might be useful for the prevention of CIN2/3.²⁰

However, Brock et al, Verreault et al, and Palan et al failed to observe a relation between dietary intake of folic acid and the risk of ICC.^{16,29,40} A study by Rampersaud et al (2002) mitigated the controversy related to the role of folate on CC, by supporting the latter studies that there is no inverse association between serum folate and the risk of CC.⁴¹ However, the authors reported a sevenfold increase in CIN and CC when lower serum folate concentration coexisted with HPV infection. This suggests that along with low blood folate, some concurrent factors must be present that will predispose to carcinogenesis. ► **Fig. 2** represents the effects of the availability of folate in body and the risk of CC development.

Folate's possible protection against CC is based on its roles in DNA synthesis and repairing damaged DNA. Folate is involved in DNA methylation, through which it may influence gene expression. If an adequate amount of folate is present, then DNA methylation will occur and proto-oncogenes can be turned off, thus preventing uncontrolled cell growth. However, if there is low folate in the blood, then DNA hypomethylation occurs and genes are turned "on," which increases the risk of uncontrolled cell growth causing cancer.⁴¹

Vegetables and Fruits

Fruits and vegetables are good sources of antioxidant phytochemicals that mitigate the damaging effect of oxidative stress. Carotenoids are a group of phytochemicals that are responsible for different colors of foods. A wide variety of fruits and vegetables provide a range of nutrients and different bioactive compounds including phytochemicals, vitamins, minerals, and fibers.⁴² A large prospective study conducted by the European Prospective Investigation into Cancer and Nutrition involving 299,649 women observed a statistically significant inverse association of ISC (invasive squamous carcinoma) with a 100 g increase in the daily total fruit intake. Their findings revealed that the protective effects of fruits might play a major role in ICC but not in CIN. This suggested that if there was any

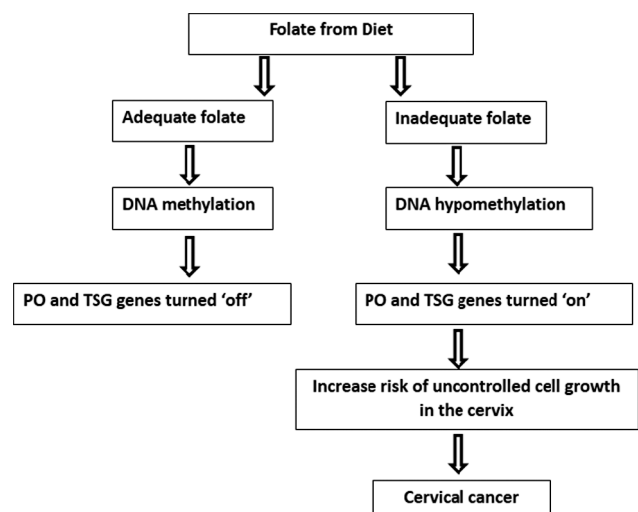


Fig. 2. Availability of folate and the risk of CC development (PO: Protooncogenes; TSG: Tumor Suppressor Genes).

true protective effect, it would be observed in the late stages of the cancer process (ISC > CIN2/3 > CIN1).⁴³ However, Giuliano et al found a reduced risk of HPV persistence among those with a high consumption frequency of papaya and orange. In their study, intake of fatty foods rich in saturated fatty acid was positively associated with HPV infection probably reflecting participants' lifestyle as these food groups were inversely correlated with fruit intake.⁴⁴

The consumption of green–yellow vegetables rich in beta-carotene (carrot, pumpkin, and green vegetables) showed a reduced risk for CC among all age groups, while that of light-green vegetables (cabbage and lettuce) did not appear to influence the risk.²⁷ Increased dietary intake of dark green and deep yellow vegetables and fruits, which are important dietary sources of α -carotene, β -carotene, β -cryptoxanthin, and lutein, were negatively associated with CIN3. However, there are growing pieces of evidence that a high intake of foods rich in β -carotene and lutein has an important role in immune response possibly acting against the persistence of HPV infection.³² All these pieces of evidence suggest that fruits and vegetables provide overall protection against all stages of CC.

Antioxidants present in a variety of vegetables and fruits can act as efficient scavengers of free radicals thereby preventing damage to macromolecules. Free radicals and oxidants if not neutralized by antioxidant molecules, then the inflammatory processes induced by HPV infection would lead to extensive damage to DNA and proteins. Additionally, oxidative stress decreases immune function and increases viral replication. It has been proposed that antioxidants present in fruits and vegetables like vitamin A (retinoic acid), C (ascorbic acid), and E (tocopherol) can prevent HPV persistence and inhibit DNA adduct formation thereby preventing cervical carcinogenesis and proliferation of cancer cells by inducing apoptosis, stabilizing the p53 protein, and reducing immunosuppression.^{1,2,10}

Others

There are many other nutrients that play a critical role in CC development like apigenin, genistein, quercetin, sulforaphane, TPPs, PUFA, etc. Apigenin is a flavone present in vegetables such as parsley, celery, chamomile, and Egyptian plant *Moringa peregrina*. Apigenin can sensitize HeLa cells to paclitaxel-induced apoptosis through the accumulation of excess intracellular ROS. It is considered a mediator for chemoprevention in the cancerous process and induces autophagia by which it exerts its protective role.¹²

Genistein is an isoflavone originating from a number of plants such as lupine, fava beans, soybeans, kudzu, *Psoralea*, *Flemingia vestita*, and coffee. Genistein inhibits the enzymes like tyrosine kinase and DNA topoisomerase II that regulate cell division and cell survival.¹² It also decreases cellular viability by induction of apoptosis due to the generation of ROS.^{1,2} Additionally, genistein has been found to have anti-angiogenic effects, thereby blocking the uncontrolled cell growth associated with cancer.

Quercetin is a flavonoid ubiquitously present in vegetables and fruits, and its antioxidant effect is implied to be helpful for human health. Sundaram et al reported an antiproliferative,

proapoptotic, and antimigratory effect of quercetin on HeLa cells by modulating various signaling pathways.⁴⁵ Quercetin induces apoptosis in CC cells mainly by extrinsic pathway. Quercetin was found to alter the expression of several genes involved in PI3K, WNT, mitogen-activated protein kinases (MAPK), JAK/STAT pathways, effectively causing inhibition of cell proliferation, cell cycle arrest, and apoptosis in CC (HeLa) cells. A promising alternate route to cancer chemoprevention and treatment strategies appears to be the use of dietary polyphenols such as quercetin.

Sulforaphane is an organosulfur compound obtained from cruciferous vegetables such as broccoli, brussels sprouts, and cabbages. Sulforaphane acts by delaying the development of CC by arresting cell growth in the G2/M phase^{1,2} and inducing apoptosis by upregulation of proapoptotic genes. Sharma et al analyzed the effect of sulforaphane on the expression of Bcl-2, COX-2, and IL-1 β by RT-PCR on HeLa cell and reported that sulforaphane was found to induce dose-dependent selective cytotoxicity in HeLa cells in comparison to normal cells pointing to its safe cytotoxicity profile.⁴⁶ Also, the expression analysis of genes involved in apoptosis and inflammation revealed significant downregulation of Bcl-2, COX-2, and IL-1 β upon treatment with sulforaphane, and it proves that sulforaphane uses its anticancer activities via apoptosis induction and anti-inflammatory properties, which may be useful for the treatment of CC.

EGCG (epigallocatecatechin-3-gallate), a TPP, is the most abundant catechin compound in green tea. Increasing pieces of evidence show that EGCG can be beneficial in treating CCs. Among numerous mechanism studies, EGCG binds and inhibits the antiapoptotic protein Bcl-xl, a protein involved in cancer cell survival. EGCG has shown to inhibit MAPK, cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 and NF- κ B, topoisomerase I, and matrix metalloproteinases.¹² TPPs can act in synergy with bleomycin (BLM), thus enhancing its therapeutic properties. TPP-BLM synergistically inhibits CC cell viability by reduced proliferation through apoptosis. Singh et al reported that TPPs such as EGCG and theaflavins (TF) can chemosensitize CC cells (HeLa, SiHa) to cisplatin-induced growth inhibition and apoptosis by excessive ROS generation.⁴⁷

A recent clinical trial by Wuryanti et al concluded that dietary supplementation enriched with PUFA can reduce the inflammatory response in patients with advanced CC. PUFA reduces serum PGE2 levels thereby lowering cancer cell viability. Thus, PUFA supplementation together with radiotherapy enhances the response of CC cells to radiations.²¹

Conclusion

Regarding dietary nutrients, various antioxidants have varying capacities to affect the natural history of HPV-mediated CC. Particularly, each vitamin may have various suppressive effects at various phases of the development of CC (from HPV infection to the development of CIN and CC). The intake of vitamins A and D may prevent the early events in CC development (from HPV infection to CIN 1). Vitamin C and carotenoids have the potency to inhibit the events from HPV infection to the development of

various grades of CIN. However, lycopene carotenoid has been observed to inhibit CIN 3 development. The reason behind such multiple mechanisms of action of carotenoids is unclear. The intake of vitamin E and folate might be more effective for preventing high-grade CIN. Consumption of fruits and vegetables rich in multivitamins may significantly reduce the risk of the overall disease. Polyphenols, flavonoids, and PUFA are often used in CC treatment in combination with chemotherapy and radiotherapy for obtaining better results. Therefore, health care professionals should counsel women with HPV preinfection or infection to boost their intake of dietary antioxidants and to bring changes in their lifestyles like in sexual activity, parity, OC use, and quit smoking, in order to stop CC from developing. There is a further need to take up research on this important aspect of diet as a useful primary prevention strategy.

Contributions

All the authors contributed in literature survey, collection of data, and manuscript writing.

Funding

This research received funding from ICMR.

Conflicts of Interest

None declared.

Acknowledgments

The authors would like to thank the Indian Council of Medical Research (ICMR) for sponsoring this research work and to Vice chancellor, Raiganj University for providing all the facilities to conduct the present research.

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