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Review Article

Synergistic Effects of Dietary Vitamins on Radiation-Induced Carcinogenesis: Mechanisms and Translational Perspectives

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Abstract

Ionizing radiation is a well-recognized human carcinogen arising from environmental and medical exposures such as diagnostic imaging and radiotherapy. Its carcinogenic potential is mainly mediated through DNA strand breaks, excessive generation of reactive oxygen species (ROS), sustained oxidative stress, and genomic instability that collectively drive malignant transformation. Dietary vitamins have demonstrated potential in modulating these radiation-induced mechanisms through their antioxidant, DNA-repair, and regulatory activities. This review attempts to assess the present knowledge of vitamins A, C, D, E, and B complex in restricting radiation associated carcinogenesis. Vitamins C and E are key antioxidants and prevent the formation of ROS during radiolysis and the peroxidation of cell membrane lipids, respectively. Folate, vitamin B6 and vitamin B12 are responsible for regulating one-carbon metabolism, DNA synthesis and methylation thus ensuring chromosomal integrity. Vitamin D, through its receptor (VDR), promotes DNA repair, regulates apoptosis, and enhances immune defense, while vitamin A derivatives maintain epithelial integrity and exhibit anti-inflammatory effects. Together, these nutrients regulate cell cycle regulation, epigenetic stability, and oxidative damage. As evidence, there appears to be a possible advantage for combined supplementation compared to single agents. However, the clinical results are situation-specific, as illustrated by the chronic increase in risk for lung cancer with excessive intake of the beta-carotene in smokers. Future trials will need to improve dosage, timing, and personalized approaches for safe use of vitamins in cancer prevention.

Keywords: Apoptosis, Cancer, Chemoprevention, Micronutrients, Retinoids, Vitamin D

Introduction

Cancer is one of the most prevalent causes of death in the world, which happens as a result of a complex relationship between genetic vulnerability, exposure to the environment, and lifestyle. DNA strain Breaks, oxidative stress, chronic inflammation, and genomic instability caused by Ionizing radiation make this environmental carcinogen well studied [1]. Radiotherapy is essential in oncology although its application is limited due to collateral damage to normal tissues and secondary malignancies [2]. It is these restrictions that highlight the strong necessity of safe and non-toxic radioprotective measures. Much interest has been on dietary interventions especially on vitamins which control various cellular pathways influenced by radiation. Vitamins A, C, D, E, and B-complex have effects on antioxidant defense, DNA repair, epigenetic stability and apoptosis. Using vitamin D receptor (VDR), vitamin D was reported to maintain intestinal stem cells by inhibiting apoptosis and promoting the repair of DNA [3-5]. Vitamin C, with the ability to scavenge reactive oxygen species (ROS) suppresses oxidative stress and release of inflammatory cytokines, whereas vitamin E strengthens membrane stability and inhibits lipid peroxidation [6]. Collectively, these results indicate the supplementary mechanisms that vitamins have which may hinder radiation-evoked carcinogenesis [3].

Nutrition and Cancer Prevention

Eating habits are closely linked to cancer occurrence, where nutritional factors have been predicted to play a role in causing almost half of all cancer cases worldwide. The lack of micronutrients vital to the body can weaken the immune system and wound healing, hastening the development of cancer. Conversely, fruits, vegetables, and whole grains contain antioxidants, phytochemicals, and anti-inflammatory substances, which prevent tumor-promoting pathways [7-10]. Among all such micronutrients, vitamins are the most important ones: vitamin A ensures the maturation of epithelial cells; vitamin C and vitamin E neutralize ROS; vitamin D, regulates gene transcription; and folate (B9) provides proper DNA methylation and nucleotide synthesis [9,11,12]. The development of nutrigenomics demonstrates that specific human responses to the dietary vitamins depend on the genetic variation, which may imply that an understanding of the interactions between genes and nutrients dictates a personalized approach to vitamin intake in the future [13].

Role of Vitamins in Epithelial Cancer

The percentage of cancer disease incidents that are initiated in the epithelial tissues (both gastrointestinal and respiratory pathways) constitutes about four-fifths of all cancer cases worldwide. These tissues undergo penetration from environmental stressors, so that proper vitamin status is especially important. A deficiency of vitamin A has also been linked to squamous metaplasia and increased contact with epithelial malignancies, and retinoid therapy also has the potential to reverse precancerous lesions through the activation of retinoic acid receptors (RARs) and retinoid X receptors (RXRs) [14,15]. In the same manner, vitamin D works together with the VDR to control apoptosis and immune surveillance, and epidemiological studies suggest that supplemented and sufficient serum vitamin D content may contribute to the lower rates of breast, prostate, and colorectal cancer [11]. Vitamin E enhances the hindrance of epithelial membrane, and regulates inflammatory messaging, while vitamin C reinforces barrier integrity by the synthesis of collagen and the prevention of nitrosamine formation [16,17]. However, the effects are dose-specific *i.e.* beta-carotene supplementation at one high dose has actually resulted in the development of lung cancer in smokers [10].

Mechanistic Overview of Vitamin Action in Carcinogenesis

The anticancer potential of vitamins arises from overlapping molecular mechanisms:

Antioxidant Defense

Vitamins C and E neutralize ROS, protecting DNA, proteins, and lipids from oxidative damage [17,18].

Epigenetic Regulation

B-complex vitamins (folate, B6, and B12) support methylation and nucleotide synthesis essential for genomic stability [19].

Immune Modulation

Vitamins A and D regulate cytokine synthesis and T-cell differentiation, enhancing immune surveillance [9].

Cell Cycle and Apoptosis

Nuclear receptors (RAR, RXR, and VDR), activated by vitamins A and D, influence transcription of genes controlling proliferation and programmed cell death.

These pathways often act cooperatively for instance; vitamin E is regenerated by vitamin C highlighting the potential of combined supplementation for radioprotection.

Objectives of the Study

The review explores the causes of cancer-causing effects of ionizing radiation in terms of DNA breaks, oxidative stress, and genomic instability, as well as the ways in which vitamins can counteract these effects. Emphasis is placed on vitamins A, C, D, E, and the B-complex, along with their antioxidant, DNA repair, epigenetic and immune-modulating effects. Experimental and clinical studies are synthesized with evidence to demonstrate their protective and synergistic capacities. Lastly, the review identifies the gaps in knowledge and the necessity for properly designed clinical trials to determine effective vitamin-based radioprotective measures.

Overview of Cancer Biology

The genetic and environmental insults that lead to carcinogenesis are associated with interruptions in cell cycle regulation, preferential DNA mutation, and oxidative stress. Chemical carcinogens and radiation all target these processes, resulting in DNA adducts, strand breaks or base alterations which, when not repaired, facilitate malignant transformation [7,8].

The Cell Cycle and Malignant Transformation

Cell proliferation is orchestrated by a tightly regulated cell cycle, divided into G1, S, G2, and M phases. Normal cells are subject to checkpoints ensuring DNA integrity and controlled progression, with the option of entering quiescence (G0). In contrast, cancer cells frequently bypass these safeguards, enabling continuous division. They exhibit insensitivity to contact inhibition, overexpression of growth factor receptors, and in some cases, autocrine production of mitogenic signals. Furthermore, malignant cells remodel their microenvironment by secreting proteases that degrade extracellular matrix components, facilitating invasion and metastasis [20,21]. Genomic instability further entrenches these phenotypes, as mutations in oncogenes and tumor suppressor genes promote unchecked proliferation and therapeutic resistance [13,19].

Environmental and Chemical Carcinogenesis

This classification of cancer etiology is multifactorial, consisting of intrinsic genetic aberrations, as well as extrinsic to the environment. Majority of the cancers have been attributed to alterations in lifestyle and environmental exposures such as smoking,

diet and exposure to radiation among others [7,8]. Other external causes include ultraviolet (UV) and ionizing radiations, work-related cancerous agents and a few drugs such as oral birth control pills and immunosupperssants [8,10]. Carcinogens exert their effects by causing the creation of mutational damage through repair failures. The unaddressed lesions result in irreversible mutations that stimulate malignant development. Both the ionizing and non-ionizing radiations are established causes of malignancy. Directly depositing energy into DNA ionizing radiation such as X-rays, γ-rays and radioactive decay products or indirectly produces ROS capable of producing base modifications and breaks in double strands. Both ionizing and non-ionizing radiation drive cancer primarily through DNA damage, either by direct strand breaks or ROS formation [8]. The mechanism by which both the ionizing and non-ionizing radiation can trigger cancer is that they lead to damage of DNA.

Cancer Treatments

Cancer has been traditionally managed through surgery, chemotherapy, and radiotherapy; however, these treatment choices have been constrained by toxicity, recurrence, and resistance. These difficulties have aroused interest in complementary measures, such as dietary vitamins, to reduce the damage caused by treatment and enhance patient outcomes. Despite the efficacy of standard modalities of treatment (surgery, chemotherapy, and radiotherapy), a main problem of these treatments is the level of systemic toxicity that the patient is exposed to, the resistance of the tumor and the collateral tissue damage. These side effects have led an increasing interest in the use of vitamin-based adjunctive therapies that can decrease the radiation-induced injury and enhance therapeutic tolerance [9,22].

Chemotherapy

Chemotherapy is the most widely used systemic treatment for malignancies, particularly effective against rapidly proliferating tumor cells. Its key strength, contrary to surgery and radiotherapy is its ability to target micrometastatic or scattered tumor cells at every place of the body. Nevertheless, chemotherapy is not selective therefore it equally induces large number of fast multiplying normal cells such as the gastrointestinal tract, the bone marrow and the hair follicles. This describes a majority of its side effects. Moreover, the developing drug resistance, and multidrug resistance (MDR) is one of the main fields of clinical interest [22]. The MDR is that phenomenon, when cancerous cells under the influence of a certain agent employed in chemotherapeutics receive resistance, however, not to the specified agent, but also of other chemotherapeutical agents of various mechanisms of action. Despite these limitations, chemotherapy has proven effective in treatment of several malignancies especially in hematologic malignancies.

DNA Interactive Compounds

The majority of anticancer drugs kill cancer cells by killing the genetic material or destroying it directly. Other medications work by either binding covalently to the DNA backbone or by intercalating between pairs of bases, which may lead to crosslinking in major or minor grooves of DNA, intra- or intermolecularly [23,24].

Nitrogen Mustards

The discovery of research on the sulfur mustard gas led to the development of nitrogen mustards as the first gas to be explored in reference to the anticancer properties. The first nitrogen-based mustard was produced, which was mechlorethamine (compound 4), which was found to

significantly decrease the cell counts of the white blood cells and was later used to treat some cases of leukemia [23].

Aliphatic Nitrogen Mustards

These are highly reactive and can easily react with any numerous kinds of nucleophiles, the element in their respective toxicities. Under physiological conditions, neutral nitrogen mustards are able to spontaneously rearrange to cyclize, with the anchimeric help of the lone pair of electrons on the nitrogen atom, to provide strained aziridinium ions [23]. These are the potent electrophilic ions and they react with the N-7 position of guanine at the major groove of a DNA. Another reaction that could take place at the junction group of the two chloroethyl groups could be with a second base of guanine on the opposite strand of DNA, which would result in crosslinking that ultimately would prevent DNA copying.

Aromatic Mustards

Examples of aromatic mustards are melphalan (compound 5) and chlorambucil (compound 6). Electron withdrawal properties are also equally effective in inhibiting the alkylation rate of the aromatic ring. Such decreased activity allows absorption and distribution prior to considerable alkylation and this gives the clinical advantage of oral route. Original synthesis Melphalan was first synthesized by the conjugation of phenylalanine with a nitrogen mustard backbone hoping it would increase its targeting of tumor cells. Although this selected incorporation has not been shown to be provided in a healthy manner, melphalan has already demonstrated its usefulness for clinical purposes in multiple myeloma and in breast and ovarian cancer in addition to in macroglobulinemia. Chlorambucil, which is less toxic and slower-acting is usually used in the treatment of chronic lymphocytic leukemia and carcinoma of the breast or ovarian type [23].

Cyclophosphamide

Cyclophosphamide is an example of activating prodrug. Hepatic enzymes convert cyclophosphamide to phosphoramide mustard (cytotoxic) and acrolein (toxic). This drug is an instance of effectiveness as well as side effects [24]. The rationality of the design of cyclophosphamide (compound 7) as a counterpart to the aromatic mustards previously studied was to enhance a more selective activity. It is developed considering that chemoresistant tumors tend to elevate the expression of phosphoramidases. The initial introduction of P=O in the heterocyclic ring was proposed to be used in tuning-out of reactivity, undesired chloroalkylation of mustard. It was imagined the compound could be used as a prodrug since it would not be activated in other body tissues except tumor tissues. Nonetheless, later literature revealed that activation of metabolism in the liver is the initial step, which is encompassed by cytochrome P45O oxidases [24]. Cyclophosphamide is changed to 4-hydroxycyclophosphamide (compound 8) in the liver, which exists in equilibrium with aldophosphamide, a diffusible intermediate transported to peripheral tissues rapidly. Aldophosphamide will subsequently be hydrolyzed and the most active cytotoxic drug and acrolein, the injurious byproduct shall be obtained as phosphoramide mustard. The cytotoxic effects are attributed to phosphoramide mustard; acrolein is the primary agent of resistance with bringing about the adverse effect of the emergence of hemorrhagic cystitis.

Aziridines

Not only is the structure of this type of agent group structurally related to nitrogen mustards, but the action is the same; this again

involves the production of aziridinium intermediates. Some examples in this include mitomycin C and thiotepa. There is a close similarity between their modes of action. Thiotepa has the 1,3-dimethylaziridine group, while the mitomycin C, a bioreductive antibiotic of Streptomyces is the prototype of this group. Mitomycin C has carbamate, aziridine and quinone groups that are significant to its activity. It takes place via a one-electron reduction quinone ring reaction with an enzyme reaction to semiquinone radical which has the ability to form both mitomycin C and hydroquinone equivalent. The former erupts into a bifunctional alkylating species while the latter loses the methanol to release another more alkylating species along with opening the ring to release yet another alkylating species. Recent reports also show that the mitomycin is mostly alkylated on two doses of guanine N2 functionality of every line, creating a crosslink between strands in the minor groove. The process in which mitomycin attaches itself to the DNA is also a peculiar attribute of this drug as it must first undergo the bioreduction process before it can bind to itself [25]. It was identified that this bioreductive property gives relative selectivity of mitomycin concerning hypoxic neoplastic cells (typical of the cores of the tumors that are very poorly vascularized). Mitomycin is therefore used as a follow-up treatment for solid type cancers including colorectal, lung and breast malignancies. Although these agents still play a key role in therapy, their side effects and restrictions underline the importance of complementary approaches, such as micronutrient-based treatment, to reduce their side effects and enhance their effectiveness.

Vitamins - Functions and Classification

Introduction to Vitamins

Vitamins are small micronutrients which are essential for maintaining metabolism, growth, and cellular homeostasis. They are enzyme cofactors, antioxidants, precursors of hormones, and gene regulators. The vitamins can be broadly divided into water-soluble (the B-complex and vitamin C) and fat-soluble (A, D, E, and K). Their specific biochemical functions and localization lead to their physiological significance as well as their consequences in carcinogenesis [26].

Water-Soluble Vitamins

Water-soluble vitamins are not extensively stored in the body and must be obtained regularly from diet.

Vitamin B1 (Thiamine)

This B-vitamin is vital in the synthesis of nucleotides so that ATP, DNA, ribose, and NAD can be created, all of which serve to power cells. Thiamine is also used as a cofactor in the subsets of enzymes that facilitate the transfer of electrons within mitochondria in the course of metabolizing energy and amino - acids. Lastly, thiamine is used to build the aromatic deoxyribose rings, which are required to assist in the synthesis of nucleotides [27].

Vitamin B2 (Riboflavin)

Riboflavin also appears as a cofactor in proteins engaged in oxidizing fatty acids, fueling electron-transfer chains that generate ATP, maintaining replication and mending DNA, regulating-redox reactions, metabolizing neurotransmitters, cell-methylation and assisting immune system. After absorption in the body, the riboflavin converts itself to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which provide energy equivalency equivalence in the mitochondrial TCA cycle. Riboflavin is also abundant in red meat [27].

Vitamin B3 (Niacin)

Central to nicotinamide adenine dinucleotide/phosphate (NAD/NADP) biosynthesis, facilitating electron transfer in energy metabolism and anabolic pathways. Niacin plays an important role as a precursor to crucial redox cofactors in this cellular metabolism. Nicotinamide adenine dinucleotide (NAD) participates in more biochemical reactions than any other vitamin-derived compound. The products of its conversion to reduced form NADH, together with NAD are, NADH+, represent the major energy equivalents of all anabolic pathways. Similarly, nicotinamide adenine dinucleotide phosphate (NADP) and its reduced form, NADPH, act as critical cofactors in catabolic processes [27].

Vitamin B5 (Pantothenic Acid)

Precursor of coenzyme A, crucial for fatty acid metabolism and acetyl-CoA synthesis. Pantothenic acid is an essential vitamin that serves as the precursor of coenzyme A (CoA), a cofactor central to numerous metabolic pathways. CoA forms acetyl-CoA in the reaction with acetic acid, one of the key products in carbohydrate and fat metabolism. In addition, pantothenic acid contributes to the formation of the acyl carrier protein (ACP), which plays a crucial role in fatty acid synthesis [27].

Vitamin B6 (Pyridoxine)

Participates in amino acid metabolism, neurotransmitter synthesis, and homocysteine regulation; deficiency is linked to genomic instability. Sources of vitamin B6 in diet include cereals, grains, vegetables, meat products, poultry, fish, and seeds. It exists in three forms: pyridoxine (plant-derived, usually as a glucoside), pyridoxal, and pyridoxamine (both derived from animal sources and more bioavailable). The active form is pyridoxal phosphate which is used as a coenzyme in amino acid processes, including transamination and decarboxylation. It also participates in homocysteine catabolism, heme biosynthesis, and the metabolism of lipids and carbohydrates [27]. Red meat, particularly beef, pork, lamb, and veal are especially good sources of vitamin B6.

Folate (B9)

A key donor of methyl groups for DNA synthesis and methylation, maintaining genomic integrity [19, 27].

Vitamin B12 (Cobalamin)

Vitamin B12 is virtually vital in human physiology; without it, it is imperative to turn to cow, eggs, and meat since it can be found exclusively in animal products. When food is being digested, the vitamin B12 attaches to the dietary proteins in a binding reaction that is broken by gastric pepsin. The soluble product interacts briefly with R proteins in saliva before degrading in the small intestine by pancreatic proteases. After loss of salivary binding, B12 is ligated in the lumen of the bowel by the intrinsic factor (IF), which is secreted following the action of gastric parietal cells. This involves the major absorptive route that employs cubilin receptors that are located in the polarized distal ileal enterocytes due to the amnionless protein. The binding and internalization of the IF-B12 complex by cubilin trigger receptor-mediated endocytosis and the ensuing stepwise intracellular breakdown of the complex, ultimately leading to the release of free B12 in the cytoplasm to permit delivery to the portal circulation. Vitamin B12 bioavailability is thus dependent on the availability of precursors in the diet as well as the ability of absorptive mechanisms to operate [27,28]. Academically, it is beneficial to note that vitamin B12 is utilized as an essential cofactor by two mammalian

enzymes, the cytosolic methionine synthase and the mitochondrial methylmalonyl-CoA mutase. Methionine synthase is a large, metalloprotein and is associated with zinc and plays a synergistic role with vitamin B6 and folic acid known to act as demethylating enzyme of the homocysteine and one to synthesise a methionine therefore. A dearth in any of these B-vitamins of B6, folate, or B12 would produce the effect that homocysteine accumulates in the system in the formation of a state of oxidative radicals, and the destruction of blood vessels. MethylmalonylCoA mutase, which catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA, a by-product of odd-chain fatty acid oxidation in addition to the metabolism of isoleucine, valine, methionine, and threonine, is also a cofactor of vitamin B12. The product can subsequently serve as the ATP source, or as heme synthesis. Additionally, the optimal vitamin B12 status avoids the development of megaloblastic anemia and hyperhomocysteinemia and can prevent the synthesis of nitrous oxide, thereby weakening hydroxyl radicals and their oxidative consequences [27,28].

Vitamin C (Ascorbic Acid)

A potent antioxidant that scavenges ROS, enhances collagen synthesis, modulates immune function, and protects against nitrosamine formation [17].

Fat-Soluble Vitamins

Fat-soluble vitamins are absorbed with dietary lipids and stored in liver and adipose tissue.

Vitamin A (Retinoids and Carotenoids)

Vitamin A has various forms including retinol, retinal, retinoic acid, and carotenoids such as provitamin A and β-carotene. As a fat-soluble micronutrient, it is acquired from animal-derived foods (preformed vitamin A) and plant-based sources (carotenoids). Vitamin A is essential for vision, immune competence, epithelial integrity and cellular growth. Its metabolite, retinoic acid, regulates gene expression by binding to nuclear RARs and RXRs, thereby influencing pathways involved in cell growth and differentiation—functions critical for preventing epithelial cancers [14,15]. Deficiency leads to suppressed immunity, epithelial barrier malfunction and may potentially induce the premalignant state of squamous metaplasia. On the other hand, overdose results in increased hepatotoxicity and teratogenicity; thus, care should be taken to maintain a balanced dosage. Although carotenoids such as β-carotene exhibit antioxidant activity, high-dose supplementation in smokers has been linked to elevated lung cancer risk, illustrating the dual, dose-dependent nature of vitamin A and its derivatives [15]. It regulates epithelial differentiation, immune function, and vision. Retinoic acid acts via RARs and RXRs to influence gene expression. Both deficiency and excess are linked to carcinogenesis [14,15].

Vitamin D

Vitamin D circulates in several forms: an endogenous form, and a dietary consumed form. The epidermal precursor is a 7-dehydrocholesterol, which results from the photon energy of the ultraviolet radiations in a dramatic case. The conversion to vitamin D3 is later attained through thermal isomerization in physiologic temperatures after conversion of pre-vitamin D3. Following intestinal absorption, vitamin D3 (cholecalciferol) from nutritional sources or natural synthesis and vitamin D2 (ergocalciferol) from aquatic plants travel through the bloodstream to the liver, where 25-hydroxyvitamin D3 is created. The parathyroid gland which is a major regulator of plasma calcium and phosphorus also controls the hepatic expression of the enzyme

catalyzing the hydroxylation to 1,25-dihydroxyvitamin D3. The binding of this vitamer to vitamin D receptors in the rest of the body to down-regulates the transcription of some genes so as to enable the production of calcium and to have its incorporation into the bones. Synthesized endogenously via UVB exposure or obtained from the diet, vitamin D undergoes hydroxylation to form calcitriol, the active metabolite. Through the VDR, it regulates calcium balance, apoptosis, immune function, and cancer-related gene expression [29].

Vitamin E (Tocopherols and Tocotrienols)

A lipid-soluble antioxidant that prevents lipid peroxidation, stabilizes membranes, and modulates redox-sensitive signaling pathways [16]. Vitamin E is composed of eight naturally occurring compounds which are four tocopherols and four tocotrienols. The products of normal metabolism produce reactive species: superoxide, lipid alkoxyl and peroxyl radicals. Out of all the vitamin derivatives, (alpha)-tocopherol is the most bioactive as it can act as a potent antioxidant by readily donating a phenolic hydrogen atom to quench lipid peroxyl radicals. The oxidized tocopherol may be recycled by catechol like ascorbic acid. Here, vitamin E blocks the peroxidation of polyunsaturated lipids localized to cellular membranes. Being lipid-soluble, it is distributed widely in red blood cells, plasma, and tissues, with significant storage in adipose tissue [29].

Vitamin K (Phylloquinone and Menaquinones)

Vitamin K is a fat-soluble vitamin available mainly as vitamin K1 (phylloquinone) from leafy green vegetables and vitamin K2 (menaquinones) from fermented foods and gut microbial synthesis. Traditionally associated with coagulation, it also plays roles in bone health and cellular regulation through vitamin K-dependent proteins (VKDPs). Recent investigations emphasize the anticancer activities of vitamin K, especially K2, by regulating proliferation, apoptosis, and angiogenesis, in which pathways involve protein kinase A and Bcl-2 family proteins. Stepwise apoptosis and autophagy in hepatocellular carcinoma, leukemia, and prostate cancer cells appear to be initiated by vitamin K2 to varying degrees. Additionally, VKDPs such as Gas6 and protein S are increasingly implicated in oncogenic signaling, positioning vitamin K as a promising candidate for cancer modulation [26]. Beyond its role in coagulation, vitamin K influences bone health and apoptosis. Emerging evidence suggests anticancer activities, particularly in hepatocellular and prostate cancers.

Vitamins and Carcinogenesis

Most vitamins share overlapping anticarcinogenic pathways including antioxidant activity, DNA repair facilitation, and immune regulation. Specific mechanistic highlights are discussed under each vitamin below to avoid redundancy:

1) Minimize oxidative stress through ROS scavenging (C and E).

2) Maintain genomic stability through nucleotide synthesis and methylation (B6, B9, and B12).

3) Modulate immune responses and inflammation (A and D).

4) Control apoptosis and cell cycle through nuclear receptor signaling (A and D).

Due to the overlapping of these pathways, vitamins tend to work synergistically. As an illustration, vitamin C replenishes oxidized vitamin E, maintaining redox homeostasis, and folate-B12 relations maintain the capacities of methylation. This interdependence reveals the reasoning behind combined supplementation in radioprotection. The following sections synthesize mechanistic and clinical evidence for individual vitamins implicated in radioprotection and cancer prevention.

Anti-Cancer Role of Specific Vitamins

Vitamin A (retinol), its hydrophobic metabolites (retinoic acids) and carotenoid provitamin A are fat-soluble micronutrients with pleiotropic effects on epithelial maintenance, immune function, and gene regulation. The major pathway of retinoid action involves nuclear receptor regulation, where retinoic acid combines with RXRs, and their complexes bind retinoic acid response elements (RAREs) to control genes regulating differentiation, cell-cycle checkpoints, and apoptosis [14,15]. At the cellular level, retinoid signaling enhances cyclin-dependent kinase inhibitor (notably p21^WAF1/CIP1^) expression, down-regulates anti-apoptotic mediators (Bcl-2), pro-apoptotic effectors (Bax), and inhibits pro-tumorigenic transcription programs (AP-1 and NF-kB), restoring growth regulation in dysplastic epithelia. Retinoids also suppress environmental procarcinogens by down-regulating cytochrome P450 isoforms, reducing DNA-reactive metabolite formation and mutational load [13,18,19].

Chemoprevention has been validated in preclinical models. Vitamin A deficiency in animals increases susceptibility to chemically induced neoplasia (lung, bladder, and colon), while retinoid treatment reverses squamous metaplasia and inhibits preneoplastic lesion development. These findings justify clinical interest in retinoids for cancer prevention and early epithelial cancer treatment. Synthetic retinoids have shown potential in preventing recurrence of head and neck premalignancy and inducing remission in acute promyelocytic leukemia (APL), supporting receptor-targeted analog development. However, bioavailability, systemic toxicity (notably hepatic and teratogenic), and interindividual response variability limit therapeutic use, prompting rational analog design and targeted delivery (liposomal and polymeric nanocarriers) to improve tumor selectivity and reduce off-target toxicity [10]. Epidemiological evidence indicates an inverse relationship between dietary retinol/carotenoid intake and epithelial cancer risk (lung, cervical, and gastrointestinal), especially in high-risk groups. Recent studies reported about 30% lower risk of non-small-cell lung cancer among individuals with higher plasma retinol after adjusting for confounders [16,17]. However, excessive β-carotene supplementation paradoxically increases lung cancer risk in smokers, underscoring the need for cautious, evidence-based dosing [10,18]. These findings highlight the importance of stratified preventive interventions considering exposure (*e.g.,* smoking), baseline nutrient status, and genetic variables. As can be seen, in terms of mechanistic-clinical integration, three points work to the practical. retinoid Signaling First, differentiation programs are re-initiated, and cell-cycle checkpoints are enforced, especially in epithelial tissues in which disturbed differentiation is an initial carcinogenic event. Second, synthetic analogues and targeted delivery platform could increase the therapeutic index through the decoupling of antineoplastic signaling and calamitous dose-related toxicities; a number of next-generation retinoids analogues and nanoparticles regimens are associated with encouraging preclinical pharmacokinetics as well as safety profiles that require clinical evaluation [10]. Third, the implementation process should always be accuracy-based: the benefit-risk balance is dependent on monitoring vitamin A/retinol levels, the profile of exposure (smoking, occupational carcinogens), and timeline (chemoprevention or using retinol as adjuvant). Concisely, vitamin A biology, offers a solid mechanistic underpinning of epithelial cancer prevention; though most of translating such medicines into clinical care routines requires smart design, biomarker-driven trials to specify indications, dosing territories and lab programs. The key molecular

processes of retinoids on gene expression, apoptosis, inflammation and DNA stability are shown in Figure 1.

Vitamin D

Vitamin D is synthesized cutaneously (UVB) as well as obtained by diet; the intravascular metabolite of vitamin D 25-hydroxyvitamin D (25(OH)D) is a measure of status but the locally produced active hormone is calcitriol (1,25-hydroxyvitamin D) which binds the VDR to act as a transcriptional effector. VDR is a vitamin D receptor heterodimer of a common plasmid acceptor, which recognizes vitamin D response elements (VDREs) that regulate a large initial network of genes, identified as over 60 different target proteins, that generatively control cell proliferation, differentiation, apoptosis and immunology [30,31]. Extra-renal calcitriol-primarily mediated conversion of various tissues allows the growth and repair pathways to be autocrine/paracrine regulated, and thus the biology of vitamin D is directly connected to cancer-relevant processes. Radiobiology research also supports that VDR activation suppresses apoptosis of intestinal stem cells caused by radiation and enhances restoration of the mucosal position visibly, and that it provides tissue resilience to genotoxic stress [4,5]. Vitamin D and B have anticancer effects that are mediated through a number of convergent pathways which are inherently mechanistic. They regulate cell-cycle checkpoints (at least the modulation of cyclin- dependent kinases), differentiation and apoptosis of rogue cells. Significant to colorectal cancer initiation, calcitriol represses Wnt/β-catenin signaling, an initial colonic carcinoma driving, thereby lowering proliferative signaling and stem-like cellular phenotypes in colonocytes [32,33].

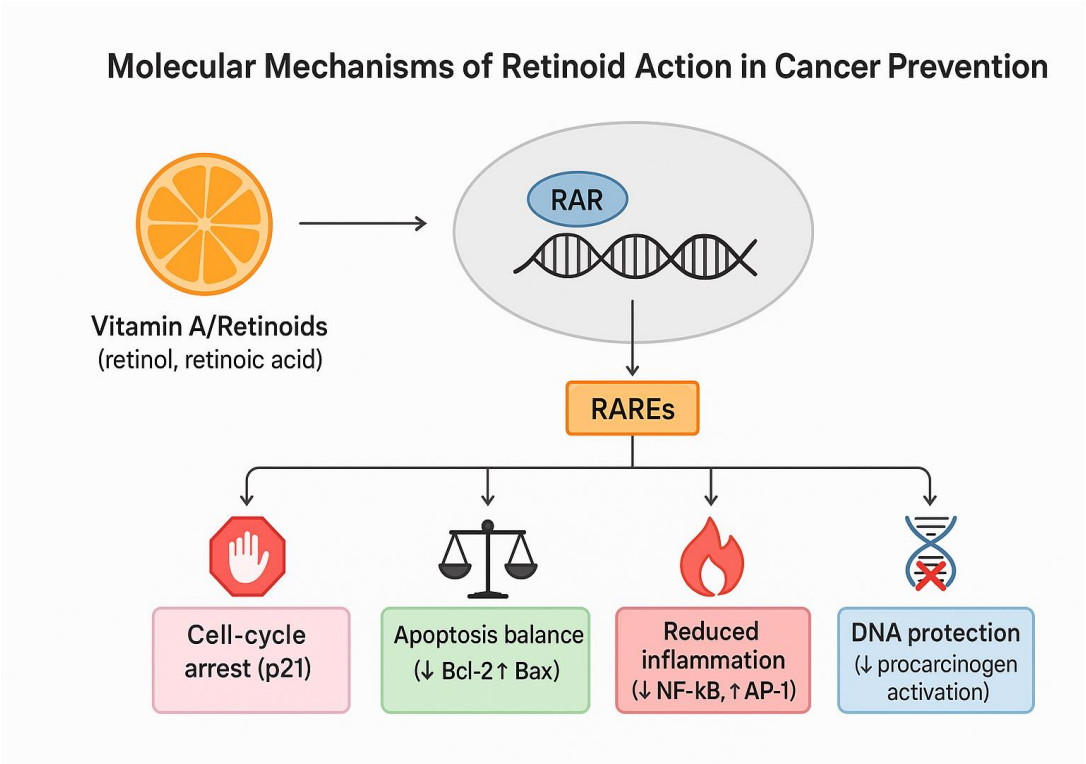

Figure 1. Mechanistic representation of retinoid (vitamin A) actions in regulating gene expression, apoptosis, inflammation, and DNA repair pathways contributing to epithelial cancer prevention

Vitamin D has a similar effect as pro-angiogenic and pro-inflammatory cytokines, suppressing microenvironmental nurturing of tumors; such immunomodulatory and anti-

angiogenic effects offer a mechanistic basis of preventive and adjuvant therapy. Evidence from epidemiology and cancer-site shows that massive meta-analyses consistently demonstrate an inverse correlation between observable levels of 25(OH)D and cancer incidence/mortality in various types of cancers, most predominantly colorectal, breast, and prostate cancer [30,32,33]. In case of colorectal neoplasia, those with serum 25(OH)D below 30 ng/mL have proven to have higher adenoma and carcinoma rates and after confounding variability measurement, some places of meta-analyses show a near-doubling of risk at exceedingly low levels (<20 ng/mL) [12,19]. *Mechanistic coherence*: Numerous mechanisms may contribute to reduced colorectal tumorigenesis as vitamin D deficiency suppressing the Wnt pathway stimulating differentiation enhancing anti-inflammatory actions in specific areas of the gut [33].

There is a reflection in the observational data on breast cancer between geographic and exposure gradients: high exposure to sunlight and vitamin D status are associated with reduced incidence and better outcomes in most cohorts. In experimental models, it has been reported that calcitriol inhibits mammary epithelial growth and angiogenesis in favor of mammary differentiation and that low levels of circulating 1, 25(OH) 2D are correlated with phenotypes of aggression and adverse prognosis especially in estrogen receptor-negative disease [15]. In the case of prostate cancer, the evidence is more heterogeneous: there are studies indicating protective effects and others that have negative effects- as such heterogeneity is probably due to differences in study design, timing of vitamin D measurement, and interaction with androgen signaling [30,32].

Translational and Therapeutic Issues

Although there is strong mechanistic and epidemiologic evidence, randomized trials of vitamin D supplementation to prevent cancer have had variable results- results are critically dependent on baseline vitamin D status, dose, sourcing, and duration. Non-calcemic calcitriol analogs are deployed to minimize the risk of hypercalcemia and make use of anticancer signaling: in early development or initial testing, they are commonly used with chemotherapy or radiotherapy, and in which the additive advantage is reported in cells and mice to date [9,33]. The most promising avenue for clinical impact is biomarker-directed approaches (usually including the incorporation of Wnt activity, integrating VDR expression profiling, and using mixtures of drugs that alter Wnt or inflammatory signaling) to achieve clinical effectiveness in these areas. Moreover, there are radioprotective results (VDR-managed stem cell protection, amplified DNA repair) that indicate that vitamin D status might be a modulation factor in normal tissue resistance to genotoxic treatments and should be explored in the future as an adjunctive to radiotherapy [4,5]. Summary of research and research priorities. To clinicians and researchers, priority is (1) to screen and manage diagrammatically the Vitamin D deficiency in the at-risk populations, (2) to develop stratified trials that would recruit participants with established insufficiency to test meaningful clinical outcomes, and (3) test targeted Vitamin D analogs and rational combinations (*e.g.,* include calcium, immune modulators or WNT pathway inhibitors) with close attention in regard to safety. The trial design should consider molecular stratification such as VDR expression, polymorphisms influencing the metabolism of Vitamin D, and pathway activation pilot. pathway in the tumor to maximize signal interception and achieve the most biologically anchored interventions. This type of program will bring in the promise of mechanistic advancements to evidence-based nodal prevention and adjunctive therapeutic interventions. The diagram and Figure 2

outline vitamin D metabolism and summarize its anticancer and radioprotective activity.

Vitamin E

Vitamin E is linked to eight substances (tocopherols and tocotrienols), the most effective of which is α-tocopherol. The lipid soluble vitamin E as an antioxidant is able to defend the membranes of the cells by removing lipid peroxyl radicals and by stabilizing the redox equilibrium [16,29]. The fat-soluble vitamin like vitamin E is crucial in the process of stabilizing the cell structures against oxidative attacks. It is absorbed into the proximal small intestine with the bile acids and pancreatic enzymes into the chylomicron, to the liver via the lymphatic system. At that site a-tocopherol is preferentially taken into circulation based on its high affinity with the hepatic a-tocopherol transfer protein (α-TTP). Vitamin E is present in eight isoforms, which include four tocopherols and four tocotrienols (α, β, γ, and δ). These are the 2-S-3-R 2,3disubstituted 2-methyl-3-hydroxy-5-trimethyl-hex-6- enoyl groups system that happen to be the most biologically active and the only variant of the 2-S-3-R α-tocopherol 2,3-disubstituted system that is preferentially maintained in human plasma: 2-methyl-3hydroxy-5-trimethyl-hex-6- enoyl.

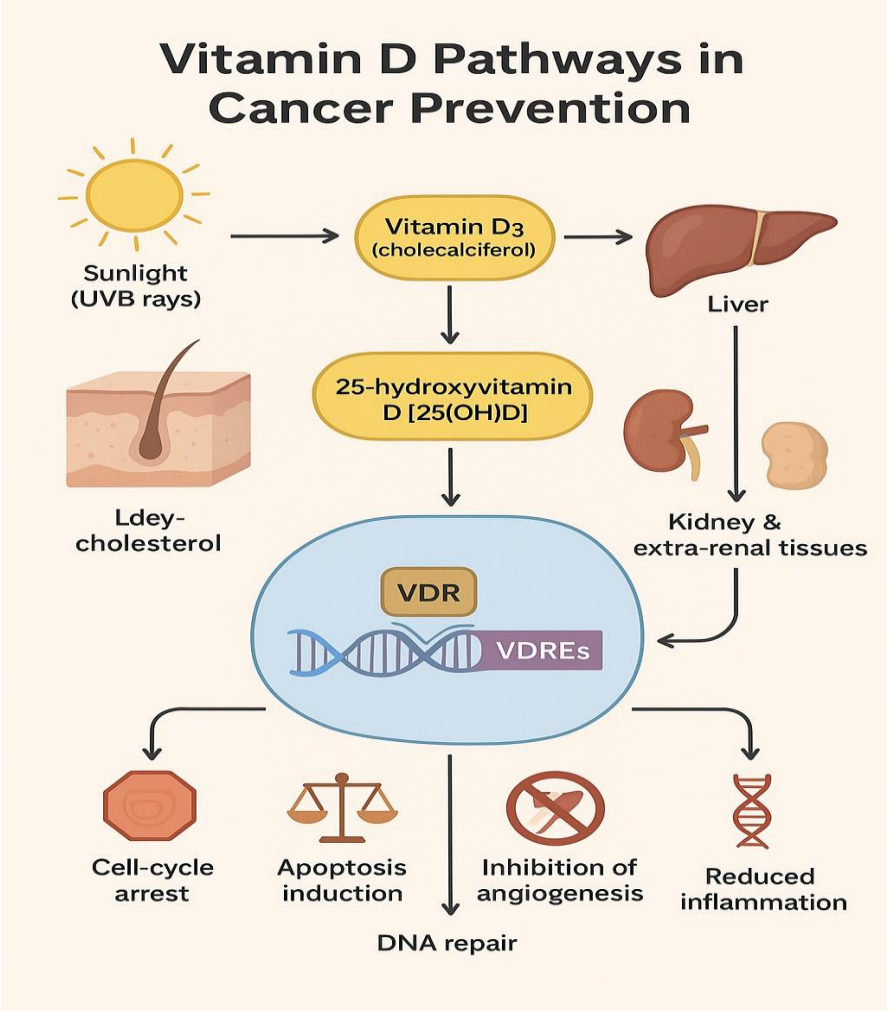

Figure 2. Overview of vitamin D metabolism and its anticancer mechanisms, including VDR-mediated gene regulation, apoptosis induction, anti-angiogenesis, and immune modulation

The vitamin E possesses the ability to regulate various physiological resonances including membrane stability, gene expression, signaling as well as apoptosis. Visibility to antioxidant activity, vitamin E regulates the manner in which signaling pathways such as protein kinase C (PKC) and NF-kB control cell proliferation, apoptosis, and inflammatory reactions. Vitamin C helps to regenerate it and represents synergistic relationships among antioxidants [34,35]. It it known to inhibit protein kinase C (PKC) activity by antioxidant-mediated binding with the kinase domain hence repressed tumor cell proliferation angiogenesis [34]. Besides, α-tocopherol can bind with nuclear receptors pregnancy X receptor (PXR) and peroxisome proliferator-activated receptors (PPARs) which regulate lipid metabolism, xenobiotic detoxication and pro-inflammatory expression. Deficiency in vitamin E which is typically inherited abnormalities of a-TTP or even abnormal weigh in the stomach will involve neural symptoms, budget surpassing erythrocytes, and the abnormalities in lipoprotein. These effects appear to be linked with heightened lipid peroxidation and oxidative stress plays a role in the development and advancement of cancer. Interestingly, at the physiological level, vitamin E is generally a known antioxidant but when in high dosage as a pharmacological dose, it is possible that it provides pro-oxidant effects which can produce α-tocopheroxyl radical to promote the production of ROS. Some of its anticancer effects may be implicated in this paradoxical nature, though this can also disrupt homeostasis of antioxidants by replacing other fat-soluble antioxidants including γ-tocopherol. Moreover, it has been demonstrated that vitamin E can inhibit some of the glutathione S-transferase forms, especially the carbon-4 isoforms, which involve toxicity of the carcinogenic factors, thus altering the cancer vulnerability. The study on multigrain milk enriched with cinnamon extract provided additional evidence for combined antioxidant and nutritional matrices influencing free radical scavenging in complex food systems. Vitamin E and alpha-tocopherol, moreover, are cell membrane protectors as well as redox sensitive signaling pathway modulators and all these may have contributed to their hypothesized cancer-preventing properties. Pre-treatment with selenium and vitamin E (as single treatment or synergistically with 6 MV X-rays) in human lymphocytes also reduced the DNA damage significantly. This joint action resulted in a maximum of 50% decrease in the frequency of micronuclei relative to untreated controls, supporting the radioprotective efficacy of combined micronutrients [36]. The benefit of vitamin E dietary consumption on oxidative stress and DNA damage is preclinically shown in post-radiation exposure. For instance, when the radiation was treated with a combination of selenium and vitamin E, chromosomal damage caused to the lymphocytes decreased by the fifty percent [36]. There is an epidemiological correlation that increased vitamin E consumption diminishes risk of certain epithelial malignancies, but there is no invite overlapping epidemiological evidence among populations [11]. High concentrations of vitamin E may be pro-oxidant and also produce radicals, altering other antioxidants, showcasing the impression of narrow dividing lines between toxic and protective drug doses [37,38].

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble antioxidant present in flora and vegetables as a product. It has a direct scavenging effect on ROS, increases collagen production and controls immune responses [17]. Beverages containing ascorbic acid or vitamin C are water-soluble vitamins found naturally in citrus fruits, leafy vegetables, and other foods. It is a strong antioxidant because it can work

as a free radical scavenger circle, and an electron donor, to neutralize ROS and prevent the oxidation of DNA, lipids, and proteins [39]. Vitamin C contains some mechanisms, that support its anticancer activities of vitamin C. It suppresses production of nitrosamine by reducing nitrites to nitric oxide, which suppresses carcinogen formation of the stomach and intestinal track [40]. It enhances the integrity of extracellular matrix by synthesis of collagen which limits the invasiveness and metastasis of tumors. It also regulates proteins in the process of apoptosis (Bax/Bcl-2) and also regulates the pathways of liver detoxification [41,42]. It inhibits the formation of carcinogenic N-nitroso compounds in the stomach during the process of converting nitrite to nitric oxide, thereby inhibiting the nitrosation of amines. This response is especially necessary considering that nitrates and nitrites are common components of processed meat, which are known to be precursors to mutagenic agents [40]. Vitamin C also helps combat cancer because it improves the performance of the immune system, boosting the activity of natural killer cells, and regulating cytokines. It influences liver enzymes involved in the xenobiotic metabolism and enhances its ability to remove toxins, which could decrease the carcinogenicity of environmental toxins [41]. Vitamin C also contributes to the integrity of the extracellular matrix because it is involved in collagen synthesis, its activity prevents the activity of hyaluronidase, an enzyme that leads to the breakdown of the matrix. These responses decrease the invasive and spreading nature of the tumors. Ascorbic acid also aids in healing tissues and regulating inflammatory reactions in tumor growth. Studies on epidemiology have continuously shown a reduced occurrence of numerous types of cancers due to increased intake of vitamin C, particularly non-hormone related such as lung and gastric cancer. Blood based research is limited because serum vitamin C decreases with time hence dietary consumption studies have shown significant protective benefits in a statistically significant manner [43]. The preclinical models show that, vitamin C pre-treatment reduces the hepatic damage and the radiation-exposed mice experience the hepatic apoptosis [42]. Its radioactivity with vitamin E causes even radioprotection by stabilizing the proteins and cell membranes [35]. Vitamin C, which is one of the various antioxidants that are found in fruits and vegetables, food, may also work synergistically with the other antioxidants in such a way that in cancer prevention, the vitamin C does not act per se according to a certain nutritional pattern. Vitamin C and vitamin E exhibit synergism in the antioxidative capacity under radiation conditions. They both have complementary protective properties on gamma-irradiated bovine serum albumin: they better hindered structural protein damage compared to their respective vitamin stable counterparts. Vitamin C pre-treatment lowered hepatic injury in a murine electron-beam irradiation model. It maintained liver structure, restored normal serum transaminase levels (ALT and AST) and regulated apoptosis indices (*e.g.,* Bax/Bcl-2), establishing its role in radiation tissue protection [42]. Consistent evidence of clinical medication with high dose vitamin C is immature which might be fluctuating chiefly in bioavailability and metabolic particularity. The existing data support the use of dietary intake and integration of therapies as opposed to pharmacological monotherapy. Recent analyses highlight that dietary antioxidant, including vitamins C and E, exhibit potent radioprotective and anticancer activities through modulation of oxidative stress, inflammation, and apoptotic signaling.

B-Complex Vitamins

One-carbon metabolism, nucleotide biosynthesis and reactions related to methylation are maintained by the B-complex

vitamins, in particular, B6, B12 and folate (B9) and contribute to genomic fidelity. Methyl groups to synthesize and for synthesis and modification at DNA ends are supplied by folate and B12, while a lack of B6, B9 or B12 increases hyperhomocysteinemia and oxidative stress damaging the vascular and genomic integrity [12,19,27]. Vitamin B6 also promotes transamination and heme biosynthesis and has postulates with regard to cellular redox equilibrium and DNA demand. Epidemiologic reports show that both adequate folate status and folate supplementation are linked to a lower risk of colorectal cancer and in high-risk populations, the incidence of adenoma recurrence can also be diminished by adopting folate supplements [12]. Deficits in the B-complex are associated with a lack of DNA repair ability, chromosomal instability and poor prognoses in a variety of malignancies [27,28]. The B-vitamins as radioprotective factors enhance the supply of nucleotides to promote repair processes as well as to aid the methylating processes to stabilize the chromatin; while acting in concert with the antioxidant vitamins, they create an overall response that diminishes effects of radiations on genome.

Research Gaps and Future Directions

Despite the existence of the clear mechanistic and epidemiologic data, certain important research gaps exist:

Standardization of Consumption and Bioavailability

The use of different formulations for vitamin containing drugs and the variability in metabolism make outcome comparisons difficult [9].

Biomarker Guided Trials

It has been suggested that clinical trials could be improved by stratifying for serum levels of vitamin D/D25, VDR/RXR expression, and genetic polymorphisms [33].

Combinations of Vitamins C, E and D with Radiotherapy or Chemotherapy

Synergistic interactions in controlled studies need to be verified [35,36].

Long-Term Safety Profiling

Excess intake of b-carotene and fat-soluble vitamins increases the risk of cardiovascular cancer for susceptible populations 10.

Nutrigenomic Implication of Nutrigenomics

Personalized vitamin therapy based on genetic and metabolic profiling deserves to be studied in future translational studies [13].

These recommendations may be used in the design of large-scale, randomized, and individualized clinical trials of vitamin administration as radioprotectants that pose no toxicity.

Conclusion

Among the health effects of radiation carcinogenesis induced through radiation intervention is radiogenic carcinogenesis that is precipitated by presence of DNA damage, presence of oxidative stress and prolonged inflammation. The current treatments show the side effects of toxicity, and the second malignancies. The evidence provided in the review indicates that vitamins, in particular, A, C, D, E, and B-complex, possess an enormous protective potential due to their influence on key processes of carcinogenesis. They involve the deactivation of ROS, conservation of the integrity of the genome, the regulation of the immune response, and the regulation of the checkpoints on apoptosis and cell division. The aggregate findings have upheld the principle of synergism radioprotection; in this way, mixed nutritional supplementation of vitamins is more effective radioprotection compared to pure vitamins. The B12 in methylation interacts with the folate, and B12, and folate, the vitamin D and retinoids, while

the regeneration of the vitamin A including vitamin E, is facilitated by the common receptor pathways, respectively. These interrelations emphasize the biological mutualism of micronutrients that determines homeostasis of the cell. The challenges are there, notwithstanding the positive outcomes. The effects are specific to given dosage, bioavailability, genetic variations and the exposure an individual has had to the environment. It is worth noting that a large amount of beta-carotene in smokers promotes the escalation of cancer risk, and that is why a personalized approach should be supported. Besides, the clinical evidence and preclinical evidence have a gap where there are small randomized controlled trials regarding the correct dosing or the window of treatment. Nutrigenomics, systems biology and precision medicine will need to be integrated in the future so as to become better acquainted with individual genetic and metabolic situation and their impacts on vitamin efficacy. Only carefully designed clinical trials can help to develop evidence-based guidelines to support the use of supplementation in cases of exposure to radiation throughout the span of radiation across the populace. An interesting use of this type of approach to non-toxic, complementary methods of cancer prevention and radioprotection could be made with the use of dietary vitamins to take advantage of the synergistic potential of the method.

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Conflict of Interest

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