Nutrition and Cancer
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hnuc20

The Role of Vitamins in Cancer: A Review

Ana Catarina Mamede [a b c], Sónia Dorilde Tavares [a d], Ana Margarida Abrantes [a c], Joana Trindade [a d], Jorge Manuel Maia [e] & Maria Filomena Botelho [a c f]

[a] Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[b] CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal

[c] Centre of Investigation on Environment, Genetics, and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[d] Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal

[e] Faculty of Sciences, University of Beira Interior, Covilhã, Portugal

[f] Institute of Nuclear Sciences Applied to Health, University of Coimbra, Coimbra, Portugal

Available online: 02 May 2011

To cite this article: Ana Catarina Mamede, Sónia Dorilde Tavares, Ana Margarida Abrantes, Joana Trindade, Jorge Manuel Maia & Maria Filomena Botelho (2011): The Role of Vitamins in Cancer: A Review, Nutrition and Cancer, 63:4, 479-494

To link to this article: http://dx.doi.org/10.1080/01635581.2011.539315

Nutrition and Cancer, 63(4), 479–494

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635581.2011.539315

Routledge
Taylor & Francis Group

REVIEW ARTICLE

The Role of Vitamins in Cancer: A Review

Ana Catarina Mamede
Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; CICS-UBI, Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; and Centre of Investigation on Environment, Genetics, and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Sónia Dorilde Tavares
Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal

Ana Margarida Abrantes
Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; and Centre of Investigation on Environment, Genetics, and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Joana Trindade
Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; and Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal

Jorge Manuel Maia
Faculty of Sciences, University of Beira Interior, Covilhã, Portugal

Maria Filomena Botelho
Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Centre of Investigation on Environment, Genetics, and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; and Institute of Nuclear Sciences Applied to Health, University of Coimbra, Coimbra, Portugal

Vitamins are essential nutrients for human metabolism, playing an important role as coenzymes or enzymes in many vital processes for the normal functioning of the body. In recent years, it has become apparent that vitamins are crucial in health and human disease, due to several studies that studied this relationship. Currently, it is known that vitamins can have an important role in the prevention and treatment of cancer, but until now no conclusive results were obtained. In this review, we will present the work and more relevant conclusions obtained in recent years of investigation about the relationship between vitamins and cancer, namely vitamin A, vitamin B complex, vitamin C, vitamin D, vitamin E, and vitamin K.

Submitted 29 June 2010; accepted in final form 1 November 2010.
Address correspondence to Maria Filomena Botelho, Biophysics/Biomathematics Institute, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal. Phone: +351239480240. Fax: +351239480258. E-mail: filomena@ibili.uc.pt

INTRODUCTION

Cancer is a public health problem whose mortality levels have increased every year (1). Until now, scientists have tried to develop numerous strategies to prevent and treat cancer. Pattern antitumoral therapies such as surgery, chemotherapy, and radiotherapy have been subject to some improvements but are still necessary to develop innovative approaches that address the effective treatment of cancer. A promising approach is associated with vitamins, so that in recent years its potential chemopreventive has been considerably analyzed.

Vitamins are a class of organic compounds that are essential for an adequate diet and are required by various biochemical and physiological processes of the body (2). Vitamins are subdivided into fat-soluble (A, D, E, and K) and water-soluble (C and vitamin B complex). Due to the numerous studies about vitamins and their role in cancer that have been published lately, it is necessary to compile all scientific information in a single review article to clarify the state of art of this subject and set new targets for research. To this end, we gather diverse information on more promising vitamins in regard to cancer, i.e., vitamin A, vitamin B complex, vitamin C, vitamin D, vitamin E, and vitamin K.

VITAMIN A AND RETINOIDS

The retinoids are a class of over 4,000 natural and synthetic molecules structurally and/or functionally related to fat-soluble vitamin A (3). These compounds participate in a broad spectrum of biological activities, such as reproduction, embryogenesis, growth, differentiation, proliferation, apoptosis, vision, bone formation, metabolism, hematopoiesis, and immunological processes (4).

Given the great importance of the mechanisms by which vitamin A and retinoids act at the cellular level, their application in the prevention and treatment of cancer early awakened interest. Since the research developed by Wolbach and Howe (5), and later by Lasnitzki (6), several studies were developed to demonstrate the important role of vitamin A and retinoids in the oncogenesis of many tissues (7,8). Lotan (9) demonstrated, through in vitro and in vivo applications, that these compounds can influence malignant cell growth in a number of ways, by producing growth arrest, apoptosis, and redifferentiation in a variety of cell lines. We know now that the homeostasis of vitamin A and retinoids is altered in many types of tumors, including leukemia, breast, skin, oral, prostate, and carcinoma of the cervix (7,10). The impaired conversion of retinol into retinoic acid is found in breast cancer cell lines, and recently Williams et al. observed the same results in ovarian cancer cells (11,12). These results supports the hypothesis that vitamin A metabolism contributes to ovarian oncogenesis.

The effects of vitamin A and retinoids on carcinogenesis are largely mediated through the activity of 2 families of nuclear receptors: the retinoic acid receptors (RAR), which are activated by all-trans-retinoic acid and 9-cis-retinoic acid, and the retinoid X receptors (RXR), only activated by the 9-cis-retinoic acid. There are 3 RARs and 3 RXRs (α, β, and γ) isotypes encoded by different genes (13,14). The action of retinoids at the cellular stage depends on the level of expression of specific receptor isotypes in a specific tissue, as well as the type and concentration of retinoids within the cell. It is thought that the RAR-β, upregulated in vivo by 13-cis-retinoic acid, may have an important role in carcinogenesis, because this receptor is suppressed in premalignant and tumor tissues, as demonstrated in head and neck malignant lesions, preneoplastic oral cavity lesions, and breast and esophageal cancer (15). Several studies have shown that prostate cancer tissue has a lower concentration of retinoic acid than normal prostate tissue and a lower expression of RAR-β and RXR-β (16). Therefore, restoring expression of these receptors through supplementation with vitamin A or treatment with retinoids could, in theory, promote differentiation and regression of premalignant prostate lesions (13).

The natural retinoids have been extensively studied over the past decades, principally 13-cis-retinoic acid and 9-cis-retinoic acid. Hong et al. (17) showed that pharmacologic administration of 13-cis-retinoic acid results in regression of lesions in head and neck, but the lesions reappeared after the therapy was discontinued. This natural retinoid also reduced new skin cancer (nonmelanoma) by 63% in patients with xeroderma pigmentosum and completely eradicated oral premalignant lesions (18). The 9-cis-retinoid-acid induces differentiation and apoptosis in neuroblastoma, as well as decreases the expression of N-myc, a characteristic oncogene present in more aggressive forms of neuroblastoma (19).

All-trans-retinoic acid, a natural retinoid approved by the FDA for the treatment of patients with acute promyelocytic leukemia (4), was shown to reduce the number of lesions due to actinic keratoses with a response rate of about 50%. Topical all-trans-retinoic acid was also able to suppress the development of new skin tumors and reduce the number of existing neoplastic lesions in renal transplant patients (20). Meyskens et al. (21) demonstrated that all-trans-retinoic acid is effective in treatment of patients with Grade 2 cervical intraepithelial neoplasia, suggesting that retinoid therapy can inhibit the progression of early cervical lesions into cancer. In vitro studies demonstrate that all-trans-retinoic acid can be used as a partly redifferentiating agent in follicular carcinoma cell lines and, moreover, the 13-cis-retinoic acid reduces clonogenic survival and increase cellular I-131 uptake of these cells. These agents may become very useful when tumors fail to take up radio-iodine due to loss of differentiation, and can be used as a solution in the treatment of differentiated thyroid metastatic cancer (22,23).

In regard to breast cancer, it has been proven that retinoic acid inhibits mammary carcinogenesis in rodents and inhibits proliferation of human breast cancer cells due to its downregulation of the progesterone receptor expression and the regulation of RARα and γ mRNA by progestins (24). In vitro studies showed that retinoic acid strongly inhibits proliferation of estrogen receptor positive (ER+) human breast cancer cells through RARs but does not inhibit the growth of estrogen receptor negative (ER−) cells. The expression of RARα, increased by estradiol, is markedly greater in ER+ in comparison with ER− breast cancer cells, which suggests that the anticarcinogenic effects of retinoic acid might require estrogens to induce its nuclear receptors (25,26). Retinoic acid was found to decrease the expression of c-erbB, a gene linked to more aggressive forms of breast cancer, suggesting that retinoids may have a role in the treatment of more aggressive forms of breast cancer (27,28). On the other hand, retinoic acid also inhibited growth in human mammary epithelial cells in which the tumor suppressor

p53 was inactivated (29). This is an important finding because many tumors lack functional p53 and drugs that work through a pathway involving this protein are ineffective in these particular tumors.

At high concentrations, natural retinoids have undesirable effects such as teratogenicity or chemical hepatitis. Therefore, in order to minimize toxicity and increase the bioavailability of retinoids, various synthetic retinoids have been produced over the years. Retinoids with subtype receptor selectivity may have better efficacy, fewer side effects, and lower toxicity as demonstrated by a study with RXR-selective retinoid LGD1069 (Targretin) (Table 1). This synthetic retinoid has been shown to prevent breast cancer, induced by N-nitroso-Nmethylurea in an animal model, over 13 wk of treatment without reoccurring signs of retinoid-associated toxicity (30). Fenretinide is a synthetic retinoid that has been applied to treatment of head, neck, breast, lung, bladder, and prostate cancer revealing, in several studies of cell cultures and in animal models, antiproliferative and apoptotic effects with less toxic properties compared to natural retinoids (31,32).

CD437, a synthetic retinoid that acts in a receptor (RAR-γ)-dependent manner, activates and upregulates the transcription factor AP-1, leading to programmed cell death (33). The in vitro and in vivo effects of this potent retinoid in various cancer cells are due to the upregulation of multiple apoptosis-related genes such as Killer/DR5, Bax, and p21WAF1 c-Myc (3). Ren (34) demonstrated that CD437 inhibits proliferation and induces apoptosis and cell cycle arrest in A375 melanoma cell line, thus revealing a potential effect against melanoma. Another recent study revealed that CD437 induces apoptosis in hepatocellular carcinoma via mitochondrial pathways (35).

ALRT1550, a high affinity ligand for all 3 RARs, has shown to have potent antitumor activity against human oral squamous carcinoma xenografts in nude mice (36). Toma et al. (37) evaluated the in vivo effects of the RAR-α selective antagonist Ro 41-5253 in nude mice transplanted with the MCF-7 breast cell line. The applied dosages of 10, 30, and 100 mg/kg/day resulted in an inhibition of cell growth without any toxic effect of the drug. Although it is not able to activate RARs, Ro 41-5253 retains the ability to block cell growth by interfering with AP-1 activity, showing 80% of proliferation inhibition on the MCF-7 line (38). Eckhardt and Schmitt (39) demonstrated in vivo that this RAR-α antagonist is not teratogenic, even at higher doses of 300 mg/kg/day, and it is able to significantly reduce teratogenic effects produced by a preferential RAR-α antagonist.

In recent years, research has shown that vitamin A and retinoids, natural or synthetic, have a promising role in prevention and treatment of many cancers. However, the pathways by which these compounds achieve anticarcinogenic effects are still poorly understood. It is thought that the mechanisms by which vitamin A and retinoids can inhibit cancerous growth are related to increased levels of specific inhibitory signaling pathways, such as the inhibition of the kinase C or reduction of expression of the oncogene H-ras, but it is necessary to develop further studies (40).

Despite the positive results already achieved, several studies have found that retinoids have minimal or no effect on tumor growth or progression in solid tumors. It should also be noted that not all studies have results that point to a potential anticancer role of vitamin A and retinoids, as exemplified by the randomized trial developed by van Zandwijk et al. (41). In this study, the aim of which was to determine the chemopreventive effects of vitamin A and N-acetylcysteine in patients with head and neck cancer or with lung cancer, it can be concluded that after 2 yr of supplementation with these compounds no benefit was observed.

To improve the effectiveness of retinoids in the treatment and prevention of cancer, several strategies should be developed. Identification of new effective receptor-specific retinoids with few or no side effects and with lower toxicity is one possibility. The development of selective inhibitors of retinoid metabolism or the combination of retinoids and other agents in order to increase or maintain the effectiveness of retinoids and reduce their toxicity should be a strategy considered.

VITAMIN B COMPLEX

The vitamin B complex consists in several water-soluble vitamins: B1 (thiamin), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid), and B12 (cobalamin). These vitamins can be found in brewer's yeast, liver, whole-grain cereals, rice, nuts, milk, eggs, meat, fish, fruits, leafy green vegetables, and many other foods. The B vitamins maintain and increase the metabolic rate, preserve muscle tone, guarantee the good condition of the skin, improve the functions of the nervous and immune system and promote growth and cell division. The role of B vitamins in the prevention and treatment of cancer is unclear, as the result of scarce and contradictory results published so far.

Vitamin B6, B9, and B12 have been the subject of studies seeking to clarify its potential role in oncology. Although some authors suggest that diminished vitamin B6, B9, and B12 status predisposes to the development of several common cancers, the evidence arising from epidemiologic, animal models and clinical intervention studies still do not explain clearly the role of these nutrients in development and progression of cancer. With regard to folate, Glynn and Albanes (42) were among the first authors to draw up a review on its role in cancer.

Vitamin B6, B9, and B12 have a number of interrelated biological roles that make them potentially important agents in cancer. First, they function as coenzymes in the synthesis of purines and thymidylate for DNA synthesis. When these nutrients levels are insufficient, the initiation of cancer is facilitated by reduction of thymidylate synthesis, resulting in an increased incorporation of uracil in DNA and consequent chromosome breaks, disruption of DNA repair, and neoplastic transformation (43,44). The increased chromosome breakage associated with low intake of folate, vitamin B12, or homocysteine has been demonstrated (45). Folate and vitamin B12 are critical in methylation reactions in the human body. Methionine synthase, a vitamin B12-

TABLE 1
Application of synthetic retinoids to oncologic disease

Synthetic Retinoids	Authors	Outcomes
LGD1069 (Targretin)	Gottardis et al. (30)	Prevents breast cancer (animal model)
Fenretinide	Webber et al. (31) Sharp et al. (32)	Treatment of head, neck, breast, lung, bladder, and prostate cancer Reveals in vitro and in vivo antiproliferative and apoptotic effects with less toxic properties compared to natural retinoids
CD437	Ren (34) Webber et al. (31 Smith (3) Gonda et al. (35)	Inhibition of proliferation, induction of apoptosis, and cell cycle arrest in A375 melanoma cell line. Activates and upregulates the transcription factor AP-1, leading to programmed cell death. Upregulation of multiple apoptosis-related genes such as Killer/DR5, Bax, and p21WAF1 c-Myc. Induction of apoptosis in hepatocellular carcinoma via mitochondrial pathways
ALRT1550	Shalinsky et al. (36)	Potent antitumor activity against human oral squamous carcinoma xenografts in nude mice
Ro 41-5253	Toma et al. (37–38) Eckhardt and Schmitt (39)	Inhibition of cell growth without any toxic effect of the drug in nude-mice transplanted with MCF-7 breast cell line. Blocks the cell growth by interfering with AP-1 activity Is not teratogenic

dependent enzyme, catalyzes the transfer of a methyl group from methyltetrahydrofolate to homocysteine to form methionine, thereby ensuring the provision of S-adenosylmethionine (SAM), the primary methyl group donor for most biological methylation reactions, including that of DNA (46). Low levels of folate and vitamin B12 may reduce the availability of SAM and prevent DNA methylation. Consequently, gene expression and conformation of DNA are influenced, as well as normal controls in the expression of protooncogenes (47–49). Vitamin B6 plays an important role in conversion of homocysteine to cysteine. Homocysteine is converted to cystathionine to form cysteine via the transsulfuration pathway, which is facilitated by 2 pyridoxal 5′-phosphate-dependent enzymes. When levels of folate, vitamin B6, and B12 are inadequate, high levels of homocysteine in the blood may be compromised (50). High intracellular levels of pyridoxal 5′-phosphate (the main active form of vitamin B6) can lead to decreased steroid hormone-induced gene expression (51).

Several epidemiologic studies have suggested that adequate folate, vitamin B6, and B12 intake may be important in the prevention of breast cancer (52–55). In a prospective case-control study with a large number of patient cases of Nurses' Health Study, Zhang et al. (55) examined the relationship between folate, vitamin B6, and vitamin B12 intake and risk of breast cancer, also taking into account the consumption of alcohol because it alters the normal metabolism of folate in a number of ways. The authors concluded that high plasma levels of folate, and possibly vitamin B6, may reduce the risk of developing this pathology, especially in women at higher risk of developing breast cancer because of higher alcohol consumption. Another study conducted by Lajous et al. (56) concluded that high intake of folate and vitamin B12 were independently associated with decreased breast cancer risk, particularly among postmenopausal women.

Hultdin et al. (57) cast doubt on the protective effects of these nutrients when they published a study that concluded that the factors contributing to folate status are not protective against prostate cancer, and vitamin B12 and folate were able to stimulate the development of this type of cancer. These results seem to have been corroborated by Johansson et al. (58), which analyzed circulating concentrations of folate and vitamin B12 in 869 cases and 1,174 controls. The authors concluded that the study did not produce sufficient results that could involve the risk of prostate cancer and circulating levels of folate and vitamin B12, although they believe that high concentrations of vitamin B12 may be associated with an increased risk or advanced stage prostate cancer. Figueiredo et al. (59) demonstrated in a clinical trial that daily supplementation with 1 mg of folic acid was associated with an increased risk of prostate cancer. With respect to vitamin B6, a case-control study of diet and cancer has shown that vitamin B6 intake was inversely associated with prostate cancer (60).

In colorectal cancer, some studies deny the potential therapeutic effects of folate, vitamin B6, and vitamin B12 in cancer. In the study of Cole et al. (61), which aimed to evaluate the safety and efficacy of 1 mg/day supplementation of folic

acid, the authors concluded that there was no reduction in the risk of developing colorectal adenoma after treatment. In contrast, many researchers argue that colorectal cancer incidence is inversely associated with folate concentration in human body, suggesting that this may be a protective agent against this type of cancer (62–66). Giovanucci et al. (67), who wanted to evaluate the relationship between folate intake and incidence of colorectal cancer, concluded that the long-term use of multivitamins containing folic acid substantially reduce the risk of developing colorectal cancer by about 75%. The levels of folic acid, vitamin B12, and homocysteine in patients suffering from colorectal cancer was assessed by Chandy (68), who found that folate and homocysteine levels did not differ significantly between the two groups (controls and cases), while vitamin B12 levels were significantly higher among the patients. Dahlin et al. (69) concluded that increased plasma levels of vitamin B12, alone or together with other factors involved in 1-carbon metabolism, may reduce the risk of rectal cancer, whereas the association appears to be less clear for colon cancer.

Low folate has also been associated with an increased risk for a number of gastrointestinal cancers, including esophageal (70,71) and stomach cancers (72–74). Krumdieck (75) studied the hypothesis of epithelial cancers, such as the cervix, lung, bladder and oropharyngeal region, could be due to localized deficiencies in folic acid and vitamin B12. In the study of Nacci et al. (76), in which the objective was to determine plasma levels of homocysteine, folate, and vitamin B12 in patients suffering from laryngeal cancer, metabolic alterations of this nutrients levels, especially hypofolatemia, could be associated with laryngeal cancer. In regard to bladder cancer, a clinical trial with 121 patients developed by Byar et al. (77) showed that when patients who were followed for less than 10 mo were excluded, pyridoxine provided better activity than placebo and was as efficacious as thiotepa in reducing recurrence. However, these results were not reproduced in other studies (78,79).

The study designed by Pais et al. (80) was performed to determine if an abnormal vitamin B6 status exists in children with newly diagnosed untreated leukemia, the most common type of pediatric malignancy. The study was divided into 2 parts, with the aim of measuring plasma levels of pyridoxal 5′-phosphate by radioenzymatic assay and high-performance liquid chromatography assay in children with leukemia. The authors found that children with leukemia had significantly lower pyridoxal 5′-phosphate levels than the controls and that these differences were significant for acute lymphoblastic leukemia and for acute nonlymphoblastic leukemia. Finally, it is noteworthy that recent studies indicate the possibility that folate possesses dual modulatory effects that depend on the timing and dose of folate administered (81,82). Thus, the administration of this nutrient before the existence of preneoplastic lesions may prevent tumor development, while the increase of folate in the presence of lesions may increase tumorigenesis, a fact explained by the important role that this nutrient plays in the synthesis of nucleotides (83,84).

Vitamin B1 is metabolized to thiamine pyrophosphate, the cofactor of transketolase, which is involved in the synthesis of ribose, required for cell proliferation. Despite the fact that vitamin B1 deficiency has already been identified in patients in advanced cancer, it becomes important to determine the benefits of thiamine supplementation and consider the need for its use despite the possible increase in tumor proliferation (85–87). Comin-Anduix et al. (88) demonstrated, through the use of oxythiamine (an irreversible inhibitor of transketolase) and the measurement of tumor growth in mice with Ehrlich's ascites tumor, that the administration of thiamine strongly stimulates ascites tumor growth depending on the dose and state of thiamine deficiency of tumor cells. On the other hand, the authors found that overdoses of thiamine inhibit tumor proliferation. Another study, developed by Liu et al. (89) established unexpected relationships between thiamine metabolism and genes that may be involved in the oncogenesis of breast cancer.

Vitamin B2 deficiency was also implicated as a risk factor for cancer but the literature relating riboflavin with cancer is complex. Some studies indicate that riboflavin deficiency increases the risk of cancer at certain sites, whereas others point to a possible attenuating effect of riboflavin in the presence of some carcinogens (90). Rao et al. (91) conducted a study that evaluated plasma levels of riboflavin carrier protein (RCP), an estrogen-inducible protein, in patients suffering from breast adenocarcinoma. This study is the result of the observation that other vitamin carrier proteins are overexpressed in patients suffering from malignant disease. Breast cancer is estrogen-related, and because other vitamin-binding protein-like folate-binding protein (92) and retinol-binding protein 4 have been shown to be overexpressed in malignant breast tissue, it was of interest to evaluate RCP dynamics in women with breast cancer. The authors analyzed the serum levels of RCP in patients with breast cancer and with benign breast disease and in healthy controls by RIA and found that levels of RCP were significantly higher in women with breast cancer. A serum RCP level of >1.0 ng/ml was highly predictive of the presence of breast cancer, demonstrating that the levels of RCP may be useful as new markers for breast cancer, even in early stages.

Studies in various animal species have shown that riboflavin deficiency can lead to disruption of the integrity of the epithelium of the esophagus (93), and some epidemiologic studies have identified a relation between esophageal cancer and diets low in riboflavin (94). Nevertheless, not all studies support this relation (95). Recent investigations have shown that riboflavin deficiency in rats exposed to hepatocarcinogens leads to increased DNA strand breakage. Also supportive of a protective role of riboflavin in carcinogenesis is the observation that carcinogen binding to DNA is increased in riboflavin-deficient rats (96). Poor riboflavin status has also been implicated as a risk factor for cervical dysplasia, a precursor condition for invasive cervical cancer (97). Vitamin B2 has been recognized as an important factor in breast cancer, as evidenced by a significant decrease in vitamin B serum levels and elevation of its plasma

carrier protein (91,98). Tsao et al. (99) carried out a study in which the aim was to examine the oxidative stress and B vitamins status in non-small-cell lung cancer patients at different stages. The reduced levels of vitamin B2 and B6 in red cells, inversely correlated with plasma ghrelin, leave us a clue about the importance of these vitamins in patients with lung cancer.

Hirakawa et al. (100) defined the effects of vitamin B3, a vitamin with moderate radical scavenging activity, on the proliferation and invasion of hepatoma cells. The effects of niacin and trigonelline on the proliferation of AH109A cells were examined by measuring the incorporation of (methyl-3H) thymidine into the acid-insoluble fraction of cells for 4 h. The authors found that niacin, trigonelline, and trigonelline-loaded rat serum inhibited the invasion of AH109A cells and suppressed the reactive oxygen species (ROS)-potentiated invasive capacity of hepatoma cells. The mechanisms by which niacin and trigonelline inhibit invasion remain to be elucidated.

VITAMIN C

Vitamin C is a water-soluble antioxidant and enzyme cofactor present in plants and some animals. Unlike most mammals, humans do not have the ability to synthesize this nutrient endogenously and, therefore, must obtain vitamin C through diet. There are 2 chemical forms of vitamin C: the reduced form (ascorbic acid; AA) and the oxidized form (dehydroascorbic acid; DHA). The reduced form is the more predominant chemical structure in the human body, appearing as an essential micronutrient involved in many biochemical and biological functions. The maintenance of necessary concentrations of vitamin C to normal cellular metabolism involves 2 families of vitamin C transporters: glucose transporters (GLUTs) and sodium-coupled transporters (SVCTs). The transport of DHA is done through the GLUTs, mainly GLUT1, 3, and 4, while the intake of AA is achieved through SVCT1 and 2 (Table 2). Most tumor cells cannot transport AA directly to his interior, which is why these cells obtain vitamin C in its oxidized form (101,102).

AA is a potent reducing agent (antioxidant) that efficiently quenches potentially damaging free radicals produced through biological processes in many extracellular and intracellular reactions (101,103). Vitamin C also acts as a prooxidant, promoting the formation of ROS, such as hydrogen peroxide, hydroxyl radicals, and many others. ROS, generated in response to high concentration of vitamin C, interacts with critical cellular molecules and organelles and results in oxidative degradation of these compounds in cancer cells, impairing their viability. Vitamin C acts selectively on tumor cells because they show a decrease of several antioxidant enzymes compared to normal ones, so there is an increased production of ROS when exposed to vitamin C (101,104). On the other hand, in the presence of transition metals and due to the increased oxidation of AA to DHA, this selective cytotoxic effect is enhanced in tumor cells (105–107).

TABLE 2
Forms and types of transport of vitamin C

Vitamin C		Principal Transporters
Reduced form	Ascorbic acid (AA)	Sodium-coupled transporters 1 and 2 (SVCT1 and 2)
Oxidized form	Dehydroascorbic acid (DHA)	Glucose transporters 1, 3 and 4 (GLUT1, 3, and 4)

Taking into account these important characteristics of vitamin C, several studies have been carried out showing the benefit of vitamin C employment in prevention and treatment of cancer. The use of AA in clinical practice is controversial, although studies have shown that supplementation of vitamin C in terminal cancer patients improve their symptoms and prolong their life. The use of vitamin C in clinical practice began in the 1970s when Ewan Cameron, Linus Pauling, and Allan Campbell used high doses of vitamin C as a supplement for cancer patients. Their results were very promising for vitamin use in cancer treatment (108,109).

In vitro studies showed the selectivity of vitamin C, since it killed some cancer cells but not normal cells. Chen et al. (107) showed that AA in pharmacologic concentrations may act as a prodrug leading to the formation of ascorbate radical ($Asc^{\bullet -}$) and hydrogen peroxide in extracellular space (Table 3). The authors tested this hypothesis in vivo using rats, which they injected with vitamin C in human pharmacologic doses (0.25–0.5 mg per g of body weight). The concentration of ascorbate in blood and in extracellular fluid was measured by electron paramagnetic resonance (EPR). In the same study, the differences between the various ways of administration (intravenous, intraperitoneal, or oral) of AA were found. Hoffer et al. (110) demonstrated the antitumor activity of AA alone or together with other agents in patients with advanced cancer or hematologic malignancy who were assigned to sequential groups infused with 0.4, 0.6, 0.9, and 1.5 g AA/kg body weight 3 times weekly. Rozanova et al. (111) conducted a study where they conjugated vitamin C with extracts of medical herbs for treatment of cancer cell lines. This study showed that this conjugation stimulated apoptosis and disrupted cell cycle. In addition, 20–40% of cells underwent apoptosis within 24 h of completing treatment. These results suggested that vitamin C can act as a catalyst in the treatment of cancer.

Recent in vivo studies have shown that DHA can act as an antitumor agent, and it can react with homocysteine thiolactone, a compound present in normal cells in large quantities, converting it to the toxic compound 3-mercaptopropionaldehyde. The same effect has been observed in tumor cells (112). Heaney et al. (113) used 2 cancer cell lines (leukemia and lymphoma), with and without pretreatment with DHA to study the antagonized effect in reactive species formed by antineoplastic drugs. They determined the viability, clonogenicity, apoptosis, P-glycoprotein,

TABLE 3
Application of vitamin C to oncologic disease

Authors and Type of Study		Outcomes
Chen et al. (107)	In vivo	AA in pharmacologic concentrations may act as a prodrug leading to the formation of ascorbate radical and hydrogen peroxide in extracellular space.
Hoffer et al. (110)	Clinical trial	AA alone or together with other agents has antitumor activity in patients with advanced cancer or hematologic malignancy.
Rozanova et al. (111)	In vitro	The conjugation of vitamin C with extracts of medical herbs stimulates apoptosis and disrupts cell cycle in several cancer cell lines.
Toohey (112)	In vitro	DHA can act as an antitumor agent and can react with homocysteine thiolactone, converting it to the toxic compound 3-mercaptopropionaldehyde in normal and tumor cells.
Heaney et al. (113)	In vitro	DHA causes a dose-dependent attenuation of cytotoxicity after treatment with all antineoplastic agents tested in 2 cancer cell lines (leukemia and lymphoma).
Chen et al. (114)	In vitro	Ascorbate at pharmacologic concentrations was prooxidant, generating hydrogen peroxide-dependent cytotoxicity towards a variety of cancer cells without adversely affecting normal cells.
Kuroiwa et al. (115)	In vivo and in vitro	Combination of vitamin C with sodium nitrite induce genotoxicity due to oxidative DNA damage and elevate 8-OHdG levels in the forestomach epithelium, but fail to initiate activity in the 2-stage carcinogenesis rat model.
Verrax and Calderon (116)	In vivo and in vitro	Pharmacological concentrations of AA killed tumor cell lines with high efficiency (EC50 ranging from 3 to 7 mM).
Yeom et al. (117)	In vivo	High concentration of AA can inhibit the angiogenesis in mice with sarcoma cells.

ROS, and mitochondrial membrane potential of the cells. They concluded that the pretreatment with vitamin C caused a dose-dependent attenuation of cytotoxicity, after treatment with all antineoplastic agents tested.

Chen et al. (114) carried out a study that showed that ascorbate at pharmacologic concentrations was prooxidant, generating hydrogen peroxide-dependent cytotoxicity toward a variety of cancer cells in vitro without adversely affecting normal cells. These studies suggested that ascorbate as a prodrug may have benefits in cancers with poor prognosis and limited therapeutic options. Kuroiwa et al. (115) investigated the combination of vitamin C with sodium nitrite in promotion of stomach carcinogenesis in rats and enhanced esophageal carcinogenesis under acid reflux conditions. The purpose of this study was to investigate whether oxidative DNA damage-associated genotoxicity and tumor-initiating potential are involved in the carcinogenesis. The results indicate that these combinations induce genotoxicity due to oxidative DNA damage in vitro and elevate 8-OHdG levels in the forestomach epithelium but fail to initiate activity in the two-stage carcinogenesis rat model.

Verrax and Calderon (116) proposed that high doses of AA possess anticancer effects. This therapeutic potential has been studied for high doses, both in vitro and in vivo. They used several lines of cancer cells, which were exposed to AA for 2 h. They observed that the pharmacological concentrations of AA killed these tumor cell lines with high efficiency (EC50 ranging from 3 to 7 mM). An in vivo study has carried out by Yeom et al. (117) to test the carcinostatic effects of AA in mice with sarcoma cells. The survival rate was increased by 20% in the group that received high-dose concentrations of AA, compared to the control. These results suggested that the high concentrations of AA can inhibit the angiogenesis in cancer cells.

VITAMIN D

After exposure to UV radiation, 7-dehydrocholesterol is converted into vitamin D in the skin. Vitamin D, also obtained from diet and supplements, is a fat-soluble compound with antiproliferative effects involved in bone development and immune system (118). In the liver, vitamin D is hydroxylated to 25-hydroxyvitamin D [25(OH)D], which is then converted to 1α,25-dihydroxy vitamin D [1,25(OH)2D] in the kidneys by 1-α-hydroxylase (119). 1-α-hydroxylase is expressed by a variety of extrarenal tissues, suggesting that it has an important role for autocrine/paracrine metabolism in the activity of vitamin D in local tissues (120). 1,25(OH)2D, or calcitrol, is the active form

of vitamin D, and its effects are mediated through vitamin D receptors (VDRs) (118).

VDRs have been postulated to have a protective effect against tumor proliferation (121,122), controlling serum levels of calcium and phosphorus (123). Only a small percentage of 25(OH)D is hydroxylated to 1,25(OH)2D. Its levels are tightly regulated by serum calcium and phosphate and are limited by poor renal function (124). Because of its lipophilicity, 1,25(OH)2D enters the cell, binds to the intracellular receptor and translocates to the nucleus, where it controls the transcription of a group of genes (124). Activities of 1,25(OH)2D with relevance to cancer include the activation of macrophages and affects on more than 200 genes that influence cellular proliferation, apoptosis, angiogenesis, and terminal differentiation of normal and cancer cells. Their activation requires the presence of a vitamin D-binding protein (Gc protein) (125). A large number polymorphisms at the 3′ end of the VDR gene occur in strong linkage disequilibrium and are linked with a poly(A) microsatellite repeat, including Bsm1, Taq1, and Apa1. Results from in vitro evaluations suggest that these polymorphisms and the poly(A) are involved in the regulation of gene expression and the stability of messenger RNA (mRNA) (126). Lundin et al. (127) found that patients without a particular VDR polymorphism (Taq1) had an increased risk of lymph node metastases, in contrast with and improved survival in patients who were homozygous for this polymorphism. Other research has shown that there was an increased risk of breast cancer in patients homozygous for other VDR polymorphism (bb BSMI VDR genotype) compared with patients who were heterozygous Bb or homozygous for the BB genotype (128).

Grant (129) demonstrated that cancer mortality rates for 13 types of cancer are inversely correlated with local solar UV-B doses. Decreased proliferation of cells from prostate carcinoma (130), colon carcinoma (131), melanoma (132), non-Hodgkin lymphoma (133), ovarian carcinoma (134), and renal carcinoma (135) was observed when vitamin D was added, which also induced differentiation in other cell types, such as colonic HT cells (136) and endometrial carcinoma cell lines (137). Zhou et al. (138) investigated the association of surgery season and vitamin D intake with lung cancer survival and found that patients who had surgery in summer and patients who had a higher vitamin D intake improved lung cancer survival.

Robsahm et al. (139) also found that the season of diagnosis may influence the prognosis of breast, colon, and prostate cancer, with studies diagnosed in the fall having a 15% lower fatality rate compared to cases diagnosed during winter. It has been recently found that, in contrast with normal prostate cells, prostate cancer cells have reduced 1-α-hydroxylase activity, responding to 1,25(OH)2D but not to 25(OH)D treatment (140,141). Giovannucci (142) showed that higher 25(OH)D has a protective effect in the development of colorectal cancer and adenoma. Feskanich et al. (143) examined the risk of colorectal cancer in relation to plasma concentration of vitamin D metabolites. A significant inverse linear association between plasma 25(OH)D and risk of colorectal cancer was found. The association was strong for women >60 yr at blood collection but was not apparent for younger women. A beneficial relation was observed for cancers at the distal colon and rectum but not for those at the proximal colon. For 1,25(OH)2D, there was no evidence of an association with cancer risk at any colorectal site. Tworoger et al. (144) examined weather plasma concentrations of 25(OH)D and 1,25(OH)2D were associated with risk of epithelial ovarian cancer. No significant association between 25(OH)D and 1,25(OH)2D levels and ovarian cancer risk was found. When cases diagnosed within 2 yr of blood collection were excluded, women with adequate 25(OH)D levels had a slightly decreased risk of ovarian cancer.

An epidemiological study done by Ahonen et al. (145) found an association between an increased risk for subsequent earlier appearance and more aggressive development of prostate cancer and low levels of 25(OH)D, especially before andropause, which suggests that the development of prostate cancer is dependent on a relatively high circulating serum androgen level. A nonsignificant declining trend in risk of breast cancer with increasing vitamin D intake was demonstrated by Gissel et al. (146). A trend toward fewer cases of breast cancer in woman with intakes of vitamin D above 400 IU (10 μg)/day was found, associated with an 8% reduction in the risk of breast cancer. Shin et al. (147) found that vitamin D intake of 500 IU or more per day was associated with a significant 28% lower risk of breast cancer in premenopausal women.

When considering multiple determinants of vitamin D exposure to estimate sunlight exposure (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure-time physical activity) in relation to cancer risk, Giovannucci et al. (148) found that a 25(OH)D increment of 25 nmol/L was associated with 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, and a 43% and 45% reduction in incidence and mortality, respectively, of digestive-system cancers.

The most investigated VDR polymorphisms for their association with various cancers are Fok1 and Bsm1. Fok1 has been shown to be functionally relevant, resulting in an altered translation start site (149), whereas Bsm1 seems to be associated with different diseases (150,151). In a meta-analysis, Gandini et al. (116) determined that the f allele at the Fok1 restriction site was associated with a significant increase risk for cutaneous malignant melanoma, with a risk increase attributable to the ff genotype estimated at 21% more than the FF genotype. For nonmelanoma skin cancer, the increased risk for the f allele was significant, and the risk increase attributable to the ff genotype was estimated at 30%. At the Bsm1 restriction site, the B allele was associated with a significant decrease of cutaneous malignant melanoma, with a risk decrease attributable to the BB genotype estimated at 25% less than the bb genotype. Polymorphisms in the 3′end (intron 8 and exon 9), the middle (exon 2), and the 5′upstream regulatory region of the gene may influence the expression and/or function of the VDR protein (119).

Taylor at al. (152) and Ingles et al. (153) reported a three- to fourfold increased risk of prostate cancer associated with 3′ polymorphisms. Subsequent studies assessing 3′ polymorphisms, Taq1, Bsm1, Apa1, and poly-A, or the exon 2 polymorphism, Fok1, produced reports of significant (154,155) and nonsignificant (156,157) associations as well as no association (158–160). John et al. (117) found significant risk reductions of advanced prostate cancer with the high activity alleles Fok1 FF or Ff, Taq1 tt, and BglI BB genotypes and a nonsignificant reduction with Cdx-2 AG or AA genotype in the presence of high sun exposure. When compared to men with low sun exposure and lack of protective genotypes, men with both high sun exposure and protective VDR genotypes had a 33% to 54% risk reduction. Slattery (161) also studied the role of VDR polymorphisms in relation to colorectal cancer. It was demonstrated that the polyA (short), Bsm1 (BB), and Taq1 (tt) variants of the VDR gene were associated with reduced risk of colon cancer. Fok1 was not associated with colon cancer risk. Other studies found that VDR Fok1 polymorphism influences development of colorectal adenomas and that its effect may be modified by calcium and vitamin D status. It is also known that vitamin D plays a role in reducing the risk of colorectal cancer through interactions with calcium (162,163).

It has been shown that vitamin D has a role in the prevention of various types of cancer. Evidence for a role of dietary vitamin D in endometrial cancer is still too scarce, and additional studies of vitamin D levels are necessary (164). No clear association of plasma vitamin D levels and ovarian cancer risk were observed by Tworoger et al. (144). An increase of vitamin D intake above 400 IU/day may help prevent the development of breast cancer (146). The data for breast cancer suggest a benefit from vitamin D, but data are limited and inconclusive (142). Much about the relationship between vitamin D and breast cancer is still unknown (165).

VITAMIN E

Vitamin E, a fat-soluble antioxidant nutrient, is taken up in the proximal part of the intestine, bile and pancreatic esterase and enters the circulation via lymphatic system. It is absorbed together with lipids, packed into chylomicrons, and transported to the liver. Vitamin E, an essential compound in cell membranes, has specific biological activities: regulation of gene expression, signaling, cell proliferation, and reproduction. There are different forms of vitamin E: 4 tocopherols (α, β, γ, and δ) and 4 tocotrienols (α, β, γ, and δ). The α-tocopherol is the only form that is maintained in human plasma and is the more abundant form found in nature and in human tissues. After passing to the liver, only α-tocopherol appears in the plasma due to its specific selection by the hepatic α-tocopherol transfer protein (α-TTP). Non-α-tocopherols are poorly recognized by α-TTP. The α-TTP and plasma phospholipid transfer protein have a well-characterized importance in cytosol because they are responsible for the homeostasis of vitamin E levels in the body (166–168).

There are several stereoisomers of α-tocopherol (RRR, RSS, RSR, SSS, SRR, SSR, and SRS), but the most commonly found in food is the RRR-α-tocopherol (also called *natural* or *d-α-tocopherol*). The synthetic α-tocopherol (all-rac-α-tocopherol) is found in food enriched with vitamin E, has a half-biological activity compared to natural α-tocopherol and is 3 to 4 times more digestible. Scavenger receptor class B Type 1 (SR-BI) is also involved in vitamin E transport, due to its wide tissue distribution and expression on the apical membrane under certain conditions. It's believed that α-tocopherol might also have the function to control pathways based on hypothetical nuclear receptor binding. There are 2 nuclear receptor classes that respond to modulation by vitamin E: pregnane X receptor (PXR, which regulates a variety of xenobiotic pathways and responds to a wide range of potentially toxic foreign compounds) and the peroxisome proliferator-activated receptors (PPARs; which have the ability to bind a variety of ligands). The specific vitamin E α-tocopherol binds to PXR. The PPARs have an action like a lipid sensor that translates changes in fatty acid concentrations into metabolic activity (169,170). Vitamin E deficiency might be due to the deficiency in the human TTP, which can lead to an increase of peroxidation of erythrocytes and fatty acids, some neurological symptomatic symptoms, such as difficulty in walking and severe progression of speech, lipoprotein abnormalities, and, subsequently, poor fat absorption syndrome (169,171,172). Therefore, the α-tocopherol is a powerful soluble antioxidant that inhibits the destruction of lipid chain through the detoxification of free radicals by acting as a protective agent against several chronic diseases, such as cardiovascular disease or cancer.

Cell proliferation and differentiation, along with apoptosis, are important cellular regulatory mechanisms that must be closely controlled, being the protein kinase C (PKC) an important signaling molecule that is involved in this process. However, α-tocopherol has been described as an inhibitor of PKC in various cell types due to its antioxidant effects. It reacts with the catalytic domain, inhibiting PKC activity and tumor promotion (168,173). Several studies have clarified the prooxidant effect of vitamin E and related this as a potential anticancer agent at high doses (174). These potential effects are due to the production of α-tocopheroxyl radical, which promotes oxidative stress. However, the prooxidant effect of vitamin E is inhibited in the presence of other coantioxidants such as AA and ubiquinol. High doses of vitamin E may displace other fat-soluble antioxidants (e.g., γ-tocopherol), disrupting the natural balance of antioxidant systems and increasing vulnerability to oxidative damage, being the ROS involved in the process of cancer initiation and promotion. Vitamin E may also inhibit human cytosolic glutathione S-transferases, which help to detoxify drugs and endogenous toxins that promote oxidative stress (175,176).

During the last two decades, scientists have been focused in the role of vitamin E in cancer, and many studies have been carried out (177,178). However, many of these studies are

contradictory. Vitamin E could be an important protective agent against lung cancer, as demonstrated by Quin et al. (172). These scientists showed that vitamin E and succinate (VES) reduce cell proliferation in vitro and in vivo. The human A549 cell line was exposed to VES for 24 h and, as a result, cell proliferation was inhibited in a concentration-dependent manner with an IC_{50} of approximately 18 μg/mL. In vivo studies were carried out using 25 female athymic nude mice. Tumor inoculation was performed, and, after 7 days, the scientists calculated tumor volume. One group of mice received a daily dose of 150 mg/kg of VES during 5 days, followed by 2 days of rest, for 20 days. Twenty days after initiation of treatment, volume tumor was calculated and mice were sacrificed. This study confirmed inhibition of cellular proliferation of human A549 cells to in vitro study of VES, and an in vivo study demonstrated that tumor growth in VES mice was significantly decreased relative to control mice ($P < 0.001$).

Bermudez et al. (179) studied the effect of vitamin E in suppression of telomerase activity in ovarian cancer cells. They used 2 cell lines of ovarian cancer that were cultured with and without D-alpha-tocopheryl acetate (vitamin E). In this study, it is suggested that, by suppressing telomerase activity, vitamin E may be an important protective agent against ovarian cancer cell growth, as well as a potentially effective therapeutic adjuvant. On the other hand, Mitchel and McCann (177) made an in vivo study using mice (female SENCAR mice 6–8 wk old) to study the possibility of vitamin E as a promoter of skin tumor. They applied vitamin E (8 or 80 μmol) twice per week in the dorsal skin region where a single topical of DMB (7,12-dimethylbenz(a)anthracene) was previously applied. At the end of the course of twice-weekly treatments with the tumor promoting agent (vitamin E), the total number of visible tumors on each mouse was recorded along with the number of live animals in the group. They concluded that vitamin E has a tumor-promoting activity at high concentrations. However, when vitamin E was applied in low concentrations, no tumor was observed. Scientist believes that vitamin E selectively reacts with the regulatory domain of PKC, stimulating its activity and signaling for tumor promotion.

In the last 2 decades, many studies demonstrated the potential anticancer effects of vitamin E in prostate cancer, alone or combined with other nutrients. In 2005, it was believed that vitamin E, alone or combined with selenium, has protective effects against prostate cancer due to both antioxidant and anticancer properties that inhibit specific cellular processes in the development of this cancer. Lippman et al. (180) concluded that selenium, vitamin E, or selenium plus vitamin E did not prevent prostate cancer in the generally healthy, heterogeneous population of men. These findings also compel the medical research community to continue the search for new, effective agents for prostate cancer prevention.

VITAMIN K

Vitamin K exists in 3 natural and synthetic different forms (Table 4). Vitamin K1 (phylloquinone) is a natural form of the vitamin K and is mostly found in green leafy vegetables. Vitamin K2 (menaquinone) is also a natural form and is synthesized by the intestinal flora. Vitamin K3 (menadione) is a synthetic analogue, a derivative of vitamin K1 and K2, and a provitamin (181). Physiologically, natural vitamin K works as a cofactor of g-glutamylcarboxylase, which, in turn, catalyzes the carboxylation of glutamate residues into g-carboxyglutamate in prothrombin and the vitamin K-dependent coagulation factors VII, IX, and X, and protein C and S, as well as other proteins.

The investigation of the antitumor action of vitamin K started in 1947. Vitamin K1 has been found to exhibit anticancer activity against a number of cell lines, including liver, colon, lung, stomach, nasopharynx, breast, oral epidermoid cancer, and leukemia (182). Oztopcu et al. (183) found no activity from K1 on the proliferation of C6 (rat glioma) and low passage human glioma cell proliferation. In a study conducted by Carr (184), a 20% tumor response rate was achieved in 40 hepatocellular carcinoma patients receiving 40 mg of oral K1 daily. Five patients

TABLE 4
Different forms of vitamin K and its suspected anticancer activity

Forms of Vitamin K		Suspected Anticancer Activity
K1 (phylloquinone)	Natural form	Anticancer activity against liver, colon, lung, brain, stomach, nasopharynx, breast, oral epidermoid cancer, and leukemia
K2 (menaquinone)	Natural form	Anticancer activity against liver, colon, leukemia, lung, stomach, lymphocyte, head, nasopharynx, breast, and oral epidermoid cancer
K3 (menadione	Synthetic form	Anticancer activity against liver, cervix, nasopharynx, colon, lung, stomach, and breast cancer, as well as leukemia and lymphoma. Some results have suggested that co-administration of vitamin C and K can increase the potential toxicity of these vitamins. Vitamin K3 administered in combination with chemotherapeutic agents, enhances their antitumoral abilities.

survived longer than 1 yr on the treatment. In another study conducted by the same team, 30 patients with hepatocellular carcinoma received 40 mg of oral K1 daily. Out of the 30 patients, 6 had disease stabilization, and 7 had a partial response. In 15 patients, the undercarboxylated prothrombin normalized, and in 7 other patients, liver function improved with no resulting coagulopathy.

Vitamin K2 has also been proved to have anticancer effects, which was shown by both in vitro and in vivo studies. Liver, colon, leukemia, lung, stomach, lymphocyte, nasopharynx, breast, and oral epidermoid cell lines have been screened (182). Sun et al. (185) showed that vitamin K2 induced growth inhibition in a dose-dependent manner for glioma cells in both rat and human cell types via cell cycle arrest and apoptosis. In a study conducted by Takami et al. (186), an 80-yr-old woman with myelodysplastic syndrome received an oral dose of 45 mg/day of vitamin K2. After 14 mo, an improvement in her pancytopenia was seen, and transfusions were no longer needed. Vitamin K2 induced apoptosis in a dose-dependent manner in glioma, hepatoma, and leukemia cell lines, as well as induced cell cycle arrest in the G0G1 transition (185,187). Yaguchi et al. (188) tested MK-4, a naturally occurring vitamin K2 analogue, with leukemic blast cells and was found to induce apoptosis in 90% of leukemic blast cells.

Due to its inability to employ 1-electron redox cycling, vitamin K2, and presumably vitamin K1, must initiate apoptosis through a nonoxidative mechanism, which appears to involve transcription factors (189). The first mechanism consists of the production of ROS, via the 1-electron cycling of the quinone. The oxidative capacity of the cell is surpassed by the increased redox-cycling of menadione and the production of ROS, which results in its death. The second mechanism focuses on cell cycle arrest and apoptosis induced by modulation of transcription factors (190).

Vitamin K3 may act by 2 different mechanisms. At higher levels, it initiates an oxidative action and necrosis or autochizis. At lower levels, it acts by a nonoxidative mechanism, inducing apoptosis (191). Vitamin K3 has been found to exhibit antitumor activity against the liver, cervix, nasopharynx, colon, lung, stomach, breast, leukemia, and lymphoma cell lines (192,193). Vitamin K3 acts as a radiosensitizing agent that was discovered to increase the survival time in inoperable bronchial carcinoma patients (194). Some results have suggested that coadministration of vitamin C and K can increase the potential toxicity of these vitamins. Vitamin C and K3 activate apoptosis or cause cell necrosis, depending on the dose, duration of exposure, and the subsequent amount of oxidative stress (195).

When the two vitamins are combined, their interaction stimulates the reduction of vitamin K3 via 1-electron reduction and increases the rate of redox cycling of the quinone (196). Noto et al. (197) combined vitamin C and vitamin K3 in a ratio of 100:1. The combination exhibited specific antitumor activity against human oral epidermoid, breast, and endometrial tumor cell lines at lower doses than when either vitamin was administered alone. In another study, Taper et al. (198) showed that the combination between vitamins C and K3 is an effective chemosensitizer and radiosensitizer that induces little systemic or major organ pathology. Jamison et al. (199) demonstrated vitamin C and K synergistic antitumor activity against 2 androgen-independent human prostate cancer cell lines and other urologic tumor cell lines.

Venugopal et al. (200) reported, more recently, that the growth rate of solid tumors in nude mice could be significantly reduced by administration of clinical doses of oral vitamins. As verified by Noto et al. (185), vitamin K3 (13.8 μg/mL) produced a 50% inhibition of breast cancer cell lines and, when combined with vitamin C (99.01 μg/mL), K3 (1.38 μg/mL) increased inhibition by 74%. When both vitamin C and K3 concentrations were increased (104 μmol/L and 105 nmol/L, respectively), a 93% inhibition was produced. Venugopal et al. (188) found that the co-administration of vitamins K3 and C enhanced the cytotoxic antitumor effect by five- to 20-fold over either single agent in human prostate carcinoma cell lines. What characterizes the cytotoxic action of the combination of vitamin C and K3 is a cell death process called *autoschizis*, in which cytoplasm is extruded, leaving an intact nucleus (201). Taper (202) found that vitamin K3 selectively reactivated alkaline DNAse in malignant tumor cells, whereas vitamin C exclusively reactivated acid DNase, both of which have been demonstrated to have their activity inhibited in non-necrotic cells of malignant tumors in men and in experimental animals, as well as during the early stages of experimental carcinogenesis (203–204). It was also found that these 2 vitamins potentiated the effects of chemotherapy induced by 6 different cytotoxic drugs (198).

Many studies have demonstrated that vitamin K3 administered in combination with chemotherapeutic agents enhances their antitumoral abilities (190). In vivo and in vitro studies conducted by Waxman and Bruckner (205) showed a synergistic effect when vitamin K3 was combined with 5-fluorouracil, a conventional chemotherapeutic agent. This combination enhanced the action against hepatoma cells. Gold (206) demonstrated a 99% inhibition of tumor growth when combining methotrexate (0.75 mg/kg/day) with menadione (250 mg/kg/day). Nutter et al. (207) has also shown that vitamin K3 can enhance the cytotoxic effect of some clinically useful anticancer agents, having an action against multidrug resistant human cancer cell lines, and was thought to have less serious toxic effects (207,208). Ni et al. (181) found that Cpd5, a synthetic vitamin analog, is a more potent growth inhibitor and apoptosis inducer than vitamin K for HepB cells. Various studies demonstrated that cell death induced by vitamin K3 is associated with apoptosis and overexpression of c-myc gene, which is considered to be related to apoptosis (190). It has also been shown that vitamins K1 and K2 have cell growth inhibitory effects in vitro, although these effects are weaker than those of vitamin K3 (190).

Vitamin K is a good option for cancer treatment that can be easily introduced into the classical protocols of clinical cancer therapy without any risk for patients (209). Another benefit is

its antitumoral activity on multidrug resistant human cancer cell lines and the fact it has less serious toxic side effects (207,208).

CONCLUSION

The vitamins and other micronutrients have attracted the attention of the scientific community in recent decades, and it has become clear that they play an important role in the etiology of many diseases, including cancer. With respect to cancer, the results obtained so far are not conclusive but are optimistic. To understand if vitamins and other micronutrients may play a role in the prevention and treatment of cancer, more studies are needed to clarify the mechanism of action.

REFERENCES

1. Lee KW, Lee HJ, Surh YJ, and Lee CY: Vitamin C and cancer chemoprevention: reappraisal. *Am J Clin Nutr* **78,** 1074–1078, 2003.
2. Young VR and Newberne PM: Vitamins and cancer prevention: issues and dilemmas. *Cancer* **47**(Suppl)**,** 1226–1240, 1981.
3. Smith W and Saba N: Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Critical Rev Oncol Hematol* **55,** 143–152, 2005.
4. Sun SY and Lotan R: Retinoids and their receptors in cancer development and chemoprevention. *Critical Rev Oncol Hematol* **41,** 41–55, 2002.
5. Wolbach SB and Howe PR: Tissue changes following deprivation of fat-soluble A vitamin. *J Experimental Med* **42,** 753–777, 1925.
6. Lasnitzki I: The influence of A hypervitaminosis on the effect of 20-methylcholanthrene on mouse prostate glands grown in vitro. *Br J Cancer* **9,** 434–441, 1955.
7. Zhang D, Holmes WF, Wu S, Soprano DR, and Soprano KJ: Retinoids and ovarian cancer. *J Cell Physiol* **185,** 1–20, 2000.
8. Trump DL: Retinoids in bladder, testis and prostate cancer: epidemiologic, pre-clinical and clinical observations. *Leukemia* **8**(Suppl 3)**,** S50–S54, 1994.
9. Lotan R: Retinoids and apoptosis: implications for cancer chemoprevention and therapy. *J Natl Cancer Inst* **87**, 1655–1657, 1995.
10. Fontana JA and Rishi AK: Classical and novel retinoids: their targets in cancer therapy. *Leukemia* **16,** 463–472, 2002.
11. Mira YLR, Zheng WL, Kuppumbatti YS, Rexer B, Jing Y, et al.: Retinol conversion to retinoic acid is impaired in breast cancer cell lines relative to normal cells. *J Cell Physiol* **185,** 302–309, 2000.
12. Williams SJ, Cvetkovic D, and Hamilton TC: Vitamin A metabolism is impaired in human ovarian cancer. *Gynecol Oncol* **112,** 637–645, 2009.
13. Kristal AR: Vitamin A, retinoids and carotenoids as chemopreventive agents for prostate cancer. *J Urol* **171**(Pt. 2)**,** S54–S58; discussion S58, 2004.
14. Poulain S, Evenou F, Carre MC, Corbel S, Vignaud JM, et al.: Vitamin A/retinoids signalling in the human lung. *Lung Cancer* **66,** 1–7, 2009.
15. Lotan R, Xu XC, Lippman SM, Ro JY, Lee JS, et al.: Suppression of retinoic acid receptor-beta in premalignant oral lesions and its up-regulation by isotretinoin. *N Engl J Med* **332,** 1405–1410, 1995.
16. Lotan Y, Xu XC, Shalev M, Lotan R, Williams R, et al.: Differential expression of nuclear retinoid receptors in normal and malignant prostates. *J Clin Oncol* **18,** 116–121, 2000.
17. Hong WK, Endicott J, Itri LM, Doos W, Batsakis JG, et al.: 13-cis-retinoic acid in the treatment of oral leukoplakia. *N Engl J Med* **315,** 1501–1505, 1986.
18. Beenken SW, Huang P, Sellers M, Peters G, Listinsky C, et al.: Retinoid modulation of biomarkers in oral leukoplakia/dysplasia. *J Cell Biochem Suppl* **19,** 270–277, 1994.
19. Wada RK, Pai DS, Huang J, Yamashiro JM, and Sidell N: Interferon-gamma and retinoic acid down-regulate N-myc in neuroblastoma through complementary mechanisms of action. *Cancer Lett* **121,** 181–188, 1997.
20. Rook AH, Jaworsky C, Nguyen T, Grossman RA, Wolfe JT, et al.: Beneficial effect of low-dose systemic retinoid in combination with topical tretinoin for the treatment and prophylaxis of premalignant and malignant skin lesions in renal transplant recipients. *Transplantation* **59,** 714–719, 1995.
21. Meyskens FL, Jr., and Manetta A: Prevention of cervical intraepithelial neoplasia and cervical cancer. *Am J Clin Nutr* **62**(Suppl)**,** 1417S–1419S, 1995.
22. Bassi V, Vitale M, Feliciello A, De Riu S, Rossi G, et al.: Retinoic acid induces intercellular adhesion molecule-1 hyperexpression in human thyroid carcinoma cell lines. *J Clin Endocrinol Metab* **80,** 1129–1135, 1995.
23. Van Herle AJ, Agatep ML, Padua DN III, Totanes TL, Canlapan DV, et al.: Effects of 13 cis-retinoic acid on growth and differentiation of human follicular carcinoma cells (UCLA R0 82 W-1) in vitro. *J Clin Endocrinol Metab* **71,** 755–763, 1990.
24. Roman SD, Clarke CL, Hall RE, Alexander IE, and Sutherland RL: Expression and regulation of retinoic acid receptors in human breast cancer cells. *Cancer Res* **52,** 2236–2242, 1992.
25. Roman SD, Ormandy CJ, Manning DL, Blamey RW, Nicholson RI, et al.: Estradiol induction of retinoic acid receptors in human breast-cancer cells. *Cancer Res* **53,** 5940–5945, 1993.
26. Vanderburg B, Vanderleede BJM, Kwakkenbosisbrucker L, Salverda S, Delaat SW, et al.: Retinoic acid resistance of estradiol-independent breast-cancer cells coincides with diminished retinoic acid receptor function. *Mol Cellular Endocrinol* **91,** 149–157, 1993.
27. Paik SM: Clinical-significance of Erbb-2 (Her-2/Neu) protein. *Cancer Investigation* **10,** 575–579, 1992.
28. Offterdinger M, Schneider SM, Huber H, and Grunt TW: Expression of c-erbB-4/HER4 is regulated in T47D breast carcinoma cells by retinoids and vitamin D-3. *Biochem Biophys Res Comm* **258,** 559–564, 1999.
29. Seewaldt VL, Dietze EC, Johnson BS, Collins SJ, and Parker MB: Retinoic acid-mediated G1-S-phase arrest of normal human mammary epithelial cells is independent of the level of p53 protein expression. *Cell Growth Differ* **10,** 49–59, 1999.
30. Gottardis MM, Bischoff ED, Shirley MA, Wagoner MA, Lamph WW, et al.: Chemoprevention of mammary carcinoma by LGD1069 (Targretin): an RXR-selective ligand. *Cancer Res* **56,** 5566–5570, 1996.
31. Webber MM, Bello-DeOcampo D, Quader S, Deocampo ND, Metcalfe WS, et al.: Modulation of the malignant phenotype of human prostate cancer cells by N-(4-hydroxyphenyl)retinamide (4-HPR). *Clin Exp Metastasis* **17,** 255–263, 1999.
32. Sharp RM, Bello-DeOcampo D, Quader ST, and Webber MM: N-(4-hydroxyphenyl)retinamide (4-HPR) decreases neoplastic properties of human prostate cells: an agent for prevention. *Mutat Res* **496,** 163–170, 2001.
33. Sun SY, Yue P, Mao L, Dawson MI, Shroot B, et al.: Identification of receptor-selective retinoids that are potent inhibitors of the growth of human head and neck squamous cell carcinoma cells. *Clin Cancer Res* **6,** 1563–1573, 2000.
34. Ren J: Comparison between synthetic retinoid CD437 and acitretin inhibiting melanoma A375 cell in vitro. *J Nanjing Med Univ* **22,** 87–91, 2008.
35. Gonda K, Tsuchiya H, Sakabe T, Akechi Y, Ikeda R, et al.: Synthetic retinoid CD437 induces mitochondria-mediated apoptosis in hepatocellular carcinoma cells. *Biochem Biophys Res Commun* **370,** 629–633, 2008.
36. Shalinsky DR, Bischoff ED, Lamph WW, Zhang L, Boehm MF, et al.: A novel retinoic acid receptor-selective retinoid, ALRT1550, has potent antitumor activity against human oral squamous carcinoma xenografts in nude mice. *Cancer Res* **57,** 162–168, 1997.
37. Toma S, Emionite L, Scaramuccia A, Ravera G, and Scarabelli L: Retinoids and human breast cancer: in vivo effects of an antagonist for RAR-alpha. *Cancer Lett* **219,** 27–31, 2005.

38. Toma S, Isnardi L, Raffo P, Riccardi L, Dastoli G, et al.: RARalpha antagonist Ro 41-5253 inhibits proliferation and induces apoptosis in breast-cancer cell lines. *Int J Cancer* **78,** 86–94, 1998.
39. Eckhardt K and Schmitt G: A retinoic acid receptor alpha antagonist counteracts retinoid teratogenicity in vitro and reduced incidence and/or severity of malformations in vivo. *Toxicol Lett* **70,** 299–308, 1994.
40. Prasad KN, Cole WC, Kumar B, and Prasad KC: Scientific rationale for using high-dose multiple micronutrients as an adjunct to standard and experimental cancer therapies. *J Am Coll Nutr* **20**(Suppl)**,** 450S–463S; discussion 473S–475S, 2001.
41. van Zandwijk N, Dalesio O, Pastorino U, de Vries N, and van Tinteren H: EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. For the European Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. *J Natl Cancer Inst* **92,** 977–986, 2000.
42. Glynn SA and Albanes D: Folate and cancer: a review of the literature. *Nutr Cancer* **22,** 101–119, 1994.
43. Ames BN: DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. *Mutat Res* **475,** 7–20, 2001.
44. van Poppel G and Van Den Berg H: Vitamins and cancer. *Cancer Lett* **114,** 195–202, 1997.
45. Fenech M: Micronucleus frequency in human lymphocytes is related to plasma vitamin B12 and homocysteine. *Mutat Res* **428,** 299–304, 1999.
46. Kim YI: Nutritional epigenetics: impact of folate deficiency on DNA methylation and colon cancer susceptibility. *J Nutr* **135,** 2703–2709, 2005.
47. Mason JB and Levesque T: Folate: effects on carcinogenesis and the potential for cancer chemoprevention. *Oncology (Williston Park)* **10,** 1727–1736, 1742–1723; discussion 1743–1724, 1996.
48. Kim YI: Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr* **80,** 1123–1128, 2004.
49. Rogers AE: Methyl donors in the diet and responses to chemical carcinogens. *Am J Clin Nutr* **61,** S659–S665, 1995.
50. Selhub J, Jacques PF, Wilson PWF, Rush D, and Rosenberg IH: Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA* **270,** 2693–2698, 1993.
51. Tully DB, Allgood VE, and Cidlowski JA: Modulation of steroid receptor-mediated gene-expression by vitamin-B-6. *FASEB J* **8,** 343–349, 1994.
52. Sellers TA, Kushi LH, Cerhan JR, Vierkant RA, Gapstur SM, et al.: Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. *Epidemiology* **12,** 420–428, 2001.
53. Negri E, La Vecchia C, and Franceschi S: Re: dietary folate consumption and breast cancer risk. *J Nat Cancer Inst* **92,** 1270–1271, 2000.
54. Levi F, Pasche C, Lucchini F, and La Vecchia C: Dietary intake of selected micronutrients and breast-cancer risk. *Int J Cancer* **91,** 260–263, 2001.
55. Zhang SM, Willett WC, Selhub J, Hunter DJ, Giovannucci EL, et al.: Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. *J Natl Cancer Inst* **95,** 373–380, 2003.
56. Lajous M, Lazcano-Ponce E, Hernandez-Avila M, Willett W, and Romieu I: Folate, vitamin B-6, and vitamin B-12 intake and the risk of breast cancer among Mexican women. *Cancer Epidemiol Biomarkers Prev* **15,** 443–448, 2006.
57. Hultdin J, Van Guelpen B, Bergh A, Hallmans G, and Stattin M: Plasma folate, vitamin B12, and homocysteine and prostate cancer risk: a prospective study. *Int J Cancer* **113,** 819–824, 2005.
58. Johansson M, Appleby PN, Allen NE, Travis RC, Roddam AW, et al.: Circulating concentrations of folate and vitamin B-12 in relation to prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition study. *Cancer Epidemiol Biomarkers Prev* **17,** 279–285, 2008.
59. Figueiredo JC, Grau MV, Haile RW, Sandler RS, Summers RW, et al.: Folic acid and risk of prostate cancer: results from a randomized clinical trial. *J Natl Cancer Inst* **101,** 432–435, 2009.
60. Key TJA, Silcocks PB, Davey GK, Appleby PN, and Bishop DT: A case-control study of diet and prostate cancer. *Br J Cancer* **76,** 678–687, 1997.
61. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, et al.: Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* **297,** 2351–2359, 2007.
62. Kim Y and Mason JB: Folate, epithelial dysplasia and colon cancer. *Proc Assoc Am Physicians* **107,** 218–227, 1995.
63. Giovannucci E: Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* **31,** 925–943, 2002.
64. Glynn SA, Albanes D, Pietinen P, Brown CC, Rautalahti M, et al.: Colorectal cancer and folate status: a nested case-control study among male smokers. *Cancer Epidemiol Biomarkers Prev* **5,** 487–494, 1996.
65. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, et al.: Alcohol, low-methionine low-folate diets, and risk of colon-cancer in men. *J Nat Cancer Inst* **87,** 265–273, 1995.
66. Glynn SA and Albanes D: Folate and cancer: a review of the literature. *Nutr Cancer* **22,** 101–119, 1994.
67. Giovannucci E, Stampfer MJ, Colditz GA, Hunter DJ, Fuchs C, et al.: Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Internal Med* **129,** 517–524, 1998.
68. Chandy S: Effect of vitamin B12 and folate on homocysteine levels in colorectal cancer. *Indian J Clin Biochem* **23,** 258–261, 2008.
69. Dahlin AM, Van Guelpen B, Hultdin J, Johansson I, Hallmans G, et al.: Plasma vitamin B12 concentrations and the risk of colorectal cancer: A nested case-referent study. *Int J Cancer* **122,** 2057–2061, 2008.
70. Zhang ZF, Kurtz RC, Yu GP, Sun M, Gargon N, et al.: Adenocarcinomas of the esophagus and gastric cardia: The role of diet. *Nutr Cancer* **27,** 298–309, 1997.
71. Heimburger DC: Localized deficiencies of folic-acid in aerodigestive tissues. *Ann NY Acad Sci* **669,** 87–96, 1992.
72. Mayne ST, Risch HA, Dubrow R, Chow WH, Gammon MD, et al.: Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* **10**,1055–1062, 2001.
73. Lavecchia C, Ferraroni M, Davanzo B, Decarli A, and Franceschi S: Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Biomarkers Prev* **3,** 393–398, 1994.
74. Harrison LE, Zhang ZF, Karpeh MS, Sun M, and Kurtz RC: The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* **80,** 1021–1028, 1997.
75. Krumdieck CL: Localized folate-deficiency and cancer. *Vit Cancer Prev* **14,** 39–49, 1991.
76. Nacci A, Dallan I, Bruschini L, Traino AC, Panicucci E, et al.: Plasma homocysteine, folate, and vitamin B12 levels in patients with laryngeal cancer. *Arch Otolaryngol Head Neck Surg* **134,** 1328–1333, 2008.
77. Byar D and Blackard C: Comparisons of placebo, pyridoxine, and topical thiotepa in preventing recurrence of stage I bladder cancer. *Urology* **10,** 556–561, 1977.
78. Newling DW, Robinson MR, Smith PH, Byar D, Lockwood R, et al.: Tryptophan metabolites, pyridoxine (vitamin B6) and their influence on the recurrence rate of superficial bladder cancer. Results of a prospective, randomised phase III study performed by the EORTC GU Group. EORTC Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol* **27,** 110–116, 1995.
79. Lattouf JB: Chemoprevention in bladder cancer: what's new? *Can Urol Assoc J* **3**(Suppl 4)**,** S184–S187, 2009.
80. Pais RC, Vanous E, Hollins B, Faraj BA, Davis R, et al.: Abnormal vitamin B6 status in childhood leukemia. *Cancer* **66,** 2421–2428, 1990.
81. Kim YI: Folate: a magic bullet or a double edged sword for colorectal cancer prevention? *Gut* **55,** 1387–1389, 2006.
82. Ulrich CM and Potter JD: Folate supplementation: too much of a good thing? *Cancer Epidemiol Biomarkers Prev* **15,** 189–193, 2006.
83. Ulrich CM and Potter JD: Folate and cancer—timing is everything. *JAMA* **297,** 2408–2409, 2007.
84. Kim YI: Folate and colorectal cancer: an evidence-based critical review. *Mol Nutr Food Res* **51,** 267–292, 2007.

85. Lee WN, Boros LG, Puigjaner J, Bassilian S, Lim S, et al.: Mass isotopomer study of the nonoxidative pathways of the pentose cycle with [1,2–13C2]glucose. *Am J Physiol* **274**(Pt. 1)**,** E843–E851, 1998.
86. Boros LG, Puigjaner J, Cascante M, Lee WN, Brandes JL, et al.: Oxythiamine and dehydroepiandrosterone inhibit the nonoxidative synthesis of ribose and tumor cell proliferation. *Cancer Res* **57,** 4242–4248, 1997.
87. Cascante M, Centelles JJ, Veech RL, Lee WN, and Boros LG: Role of thiamin (vitamin B-1) and transketolase in tumor cell proliferation. *Nutr Cancer* **36,** 150–154, 2000.
88. Comin-Anduix B, Boren J, Martinez S, Moro C, Centelles JJ, et al.: The effect of thiamine supplementation on tumour proliferation. A metabolic control analysis study. *Eur J Biochem* **268,** 4177–4182, 2001.
89. Liu S, Stromberg A, Tai HH, and Moscow JA: Thiamine transporter gene expression and exogenous thiamine modulate the expression of genes involved in drug and prostaglandin metabolism in breast cancer cells. *Mol Cancer Res* **2,** 477–487, 2004.
90. Rivlin RS: Riboflavin and cancer: a review. *Cancer Res* **33,** 1977–1986, 1973.
91. Rao PN, Levine E, Myers MO, Prakash V, Watson J, et al.: Elevation of serum riboflavin carrier protein in breast cancer. *Cancer Epidemiol Biomarkers Prev* **8,** 985–990, 1999.
92. Holm J, Hansen SI, Sondergaard K, and Hoier-Madsen M: The high-affinity folate binding protein in normal and malignant mammary gland tissue. *Adv Exp Med Biol* **338,** 757–760, 1993.
93. Foy H, Kondi A, and Verjee ZH: Relation of riboflavin deficiency to corticosteroid metabolism and red cell hypoplasia in baboons. *J Nutr* **102,** 571–582, 1972.
94. Foy H and Kondi A: The vulnerable esophagus: riboflavin deficiency and squamous cell dysplasia of the skin and the esophagus. *J Natl Cancer Inst* **72,** 941–948, 1984.
95. Siassi F, Pouransari Z, and Ghadirian P: Nutrient intake and esophageal cancer in the Caspian littoral of Iran: a case-control study. *Cancer Detect Prev* **24,** 295–303, 2000.
96. Pangrekar J, Krishnaswamy K, and Jagadeesan V: Effects of riboflavin deficiency and riboflavin administration on carcinogen-DNA binding. *Food Chem Toxicol* **31,** 745–750, 1993.
97. Liu T, Soong SJ, Wilson NP, Craig CB, Cole P, et al.: A case control study of nutritional factors and cervical dysplasia. *Cancer Epidemiol Biomarkers Prev* **2,** 525–530, 1993.
98. Vaidya SM, Kamlakar PL, and Kamble SM: Molybdenum, xanthine oxidase and riboflavin levels in tamoxifen treated postmenopausal women with breast cancer. *Indian J Med Sci* **52,** 244–247, 1998.
99. Tsao SM, Yin MC, and Liu WH: Oxidant stress and B vitamins status in patients with non-small cell lung cancer. *Nutr Cancer* **59,** 8–13, 2007.
100. Hirakawa N, Okauchi R, Miura Y, and Yagasaki K: Anti-invasive activity of niacin and trigonelline against cancer cells. *Biosci Biotechnol Biochem* **69,** 653–658, 2005.
101. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, et al.: Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res* **68,** 8031–8038, 2008.
102. Rivas CI, Zuniga FA, Salas-Burgos A, Mardones L, Ormazabal V, et al.: Vitamin C transporters. *J Physiol Biochem* **64,** 357–375, 2008.
103. Verrax J and Calderon PB: The controversial place of vitamin C in cancer treatment. *Biochem Pharmacol* **76,** 1644–1652, 2008.
104. Fruehauf JP and Meyskens FL: Reactive oxygen species: a breath of life or death? *Clin Cancer Res* **13,** 789–794, 2007.
105. Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, et al.: Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice: editorial comment. *J Urol* **181,** 2384–2385, 2009.
106. Rozanova N, Zhang JZ, and Heck DE: Catalytic Therapy of cancer with ascorbate and extracts of medicinal herbs. *Evide-Based Complement Alternative Med* **7,** 203–212, 2010.
107. Chen Q, Espey MG, Sun AY, Lee JH, Krishna MC, et al.: Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. *Proc Nat Acad Sciences USA* **104,** 8749–8754, 2007.
108. Cameron E and Pauling L: The orthomolecular treatment of cancer: I. The role of ascorbic acid in host resistance. *Chem Biol Interact* **9,** 273–283, 1974.
109. Cameron E and Campbell A: The orthomolecular treatment of cancer: II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. *Chem Biol Interact* **9,** 285–315, 1974.
110. Hoffer LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, et al.: Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol* **19,** 1969–1974, 2008.
111. Rozanova N, Zhang JZ, and Heck DE: Catalytic therapy of cancer with ascorbate and extracts of medicinal herbs. *Evid Based Complement Alternat Med* **7,** 203–212, 2007.
112. Toohey JI: Dehydroascorbic acid as an anti-cancer agent. *Cancer Lett* **263,** 164–169, 2008.
113. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, et al.: Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res* **68,** 8031–8038, 2008.
114. Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, et al.: Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc Nat Acad Sci USA* **105,** 11105–11109, 2008.
115. Kuroiwa Y, Yamada M, Matsui K, Okamura T, Ishii Y, et al.: Combined ascorbic acid and sodium nitrite treatment induces oxidative DNA damage-associated mutagenicity in vitro, but lacks initiation activity in rat forestomach epithelium. *Toxicol Sci* **104,** 274–282, 2008.
116. Verrax J and Calderon PB: Pharmacologic concentrations of ascorbate are achieved by parenteral administration and exhibit antitumoral effects. *Free Radic Biol Med* **47,** 32–40, 2009.
117. Yeom CH, Lee G, Park JH, Yu J, Park S, et al.: High dose concentration administration of ascorbic acid inhibits tumor growth in BALB/C mice implanted with sarcoma 180 cancer cells via the restriction of angiogenesis. *J Transl Med* **7,** 70, 2009.
118. Gandini S, Raimondi S, Gnagnarella P, Dore JF, Maisonneuve P, et al.: Vitamin D and skin cancer: a meta-analysis. *Eur J Cancer* **45,** 634–641, 2009.
119. John EM, Schwartz GG, Koo J, Van Den Berg D, and Ingles SA: Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res* **65,** 5470–5479, 2005.
120. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, et al.: Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psych* **65,** 508–512, 2008.
121. Pendas-Franco N, Gonzalez-Sancho JM, Suarez Y, Aguilera O, Steinmeyer A, et al.: Vitamin D regulates the phenotype of human breast cancer cells. *Differentiation* **75,** 193–207, 2007.
122. Roy D, Calaf G, and Hei TK: Role of vitamin D receptor gene in radiation–induced neoplastic transformation of human breast epithelial cell. *Steroids* **68,** 621–627, 2003.
123. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Set al.: Extrarenal expression of 25-hydroxyvitamin D-3–1 alpha-hydroxylase. *J Clin Endocrinol Metabolism* **86,** 888–894, 2001.
124. Corder EH, Guess HA, Hulka BS, Friedman GD, Sadler M, et al.: Vitamin-D and prostate-cancer: a prediagnostic study with stored sera. *Cancer Epidemiol Biomarkers Prev* **2,** 467–472, 1993.
125. Holick MF: Vitamin D deficiency. *New Eng J Med* **357,** 266–281, 2007.
126. Uitterlinden AG, Fang Y, van Meurs JBJ, Pols HAP, and van Leeuwen JPTM: Genetics and biology of vitamin D receptor polymorphisms. *Gene* **338,** 143–156, 2004.

127. Lundin AC, Soderkvist P, Eriksson B, Bergman-Jungestrom M, Wingren S, et al.: Association of breast cancer progression with a vitamin D receptor gene polymorphism. *Cancer Res* **59,** 2332–2334, 1999.
128. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, et al.: Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype, and breast cancer risk in a UK Caucasian population. *Eur Jo Cancer* **41,** 1164–1169, 2005.
129. Grant WB: An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* **94,** 1867–1875, 2002.
130. Zhao XY, Peehl DM, Navone NM, and Feldman D: 1 alpha,25-dihydroxyvitamin D-3 inhibits prostate cancer cell growth by androgen-dependent and androgen-independent mechanisms. *Endocrinology* **141,** 2548–2556, 2000.
131. Corder EH, Friedman GD, Vogelman JH, and Orentreich N: Seasonal-variation in vitamin-D, vitamin-D-binding protein, and dehydroepiandrosterone: risk of prostate-cancer in black and white men. *Cancer Epidemiol Biomarkers Prev* **4,** 655–659, 1995.
132. DeLuca HF and Ostrem V: The relationship between the vitamin D system and cancer. *Adv Exp Med Biol* **206,** 413–429, 1986.
133. Hickish T, Cunningham D, Colston K, Millar BC, Sandle J, et al.: The effect of 1,25-dihydroxyvitamin D3 on lymphoma cell lines and expression of vitamin D receptor in lymphoma. *Br J Cancer* **68,** 668–672, 1993.
134. Ahonen MH, Zhuang YH, Aine R, Ylikomi T, and Tuohimaa P: Androgen receptor and vitamin D receptor in human ovarian cancer: growth stimulation and inhibition by ligands. *Int J Cancer* **86,** 40–46, 2000.
135. Fujioka T, Hasegawa M, Ishikura K, Matsushita Y, Sato M, et al.: Inhibition of tumor growth and angiogenesis by vitamin D3 agents in murine renal cell carcinoma. *J Urol* **160,** 247–251, 1998.
136. Vandewalle B, Wattez N, and Lefebvre J: Effects of vitamin D3 derivatives on growth, differentiation and apoptosis in tumoral colonic HT 29 cells: possible implication of intracellular calcium. *Cancer Lett* **97,** 99–106, 1995.
137. Yabushita H, Hirata M, Noguchi M, and Nakanishi M: Vitamin D receptor in endometrial carcinoma and the differentiation-inducing effect of 1,25-dihydroxyvitamin D3 on endometrial carcinoma cell lines. *J Obstet Gynaecol Res* **22,** 529–539, 1996.
138. Zhou W, Suk R, Liu G, Park S, Neuberg DS, et al.: Vitamin D is associated with improved survival in early-stage non-small-cell lung cancer patients. *Cancer Epidemiol Biomarkers Prev* **14,** 2303–2309, 2005.
139. Robsahm TE, Tretli S, Dahlback A, and Moan J: Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control* **15,** 149–158, 2004.
140. Hsu JY, Feldman D, McNeal JE, and Peehl DM: Reduced 1alpha-hydroxylase activity in human prostate cancer cells correlates with decreased susceptibility to 25-hydroxyvitamin D3-induced growth inhibition. *Cancer Res* **61,** 2852–2856, 2001.
141. Whitlatch LW, Young MV, Schwartz GG, Flanagan JN, Burnstein KL, et al.: 25-Hydroxyvitamin D-1alpha-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer. *J Steroid Biochem Mol Biol* **81**,135–140, 2002.
142. Giovannucci E: The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* **16,** 83–95, 2005.
143. Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, et al.: Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* **13,** 1502–1508, 2004.
144. Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, et al.: Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **16,** 783–788, 2007.
145. Ahonen MH, Tenkanen L, Teppo L, Hakama M, and Tuohimaa P: Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* **11,** 847–852, 2000.
146. Gissel T, Rejnmark L, Mosekilde L, and Vestergaard P: Intake of vitamin D and risk of breast cancer—a meta-analysis. *J Steroid Biochem Mol Biol* **111,** 195–199, 2008.
147. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, et al.: Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* **94,** 1301–1311, 2002.
148. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, et al.: Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* **98,** 451–459, 2006.
149. Haussler MR, Haussler CA, Jurutka PW, Thompson PD, Hsieh JC, et al.: The vitamin D hormone and its nuclear receptor: molecular actions and disease states. *J Endocrinol* **154**(Suppl)**,** S57–S73, 1997.
150. Uitterlinden AG, Fang Y, van Meurs JB, van Leeuwen H, and Pols HA: Vitamin D receptor gene polymorphisms in relation to Vitamin D related disease states. *J Steroid Biochem Mol Biol* **89–90,** 187–193, 2004.
151. Sillanpaa P, Hirvonen A, Kataja V, Eskelinen M, Kosma VM, et al.: Vitamin D receptor gene polymorphism as an important modifier of positive family history related breast cancer risk. *Pharmacogenetics* **14,** 239–245, 2004.
152. Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, et al.: Association of prostate cancer with vitamin D receptor gene polymorphism. *Cancer Res* **56,** 4108–4110, 1996.
153. Ingles SA, Coetzee GA, Ross RK, Henderson BE, Kolonel LN, et al.: Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. *Cancer Res* **58,** 1620–1623, 1998.
154. Huang SP, Chou YH, Chang WSW, Wu MT, Chen YY, et al.: Association between vitamin D receptor polymorphisms and prostate cancer risk in a Taiwanese population. *Cancer Letters* **207,** 69–77, 2004.
155. Oakley-Girvan I, Feldman D, Eccleshall TR, Gallagher RP, Wu AH, et al.: Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor. *Cancer Epidemiol Biomarkers Prev* **13,** 1325–1330, 2004.
156. Luscombe CJ, Fryer AA, French ME, Liu S, Saxby MF, et al.: Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *Lancet* **358,** 641–642, 2001.
157. Gsur A, Madersbacher S, Haidinger G, Schatzl G, Marberger M, et al.: Vitamin D receptor gene polymorphism and prostate cancer risk. *Prostate* **51,** 30–34, 2002.
158. Tayeb MT, Clark C, Haites NE, Sharp L, Murray GI, et al.: Vitamin D receptor, HER-2 polymorphisms, and risk of prostate cancer in men with benign prostate hyperplasia. *Saudi Med J* **25,** 447–451, 2004.
159. Suzuki K, Matsui H, Ohtake N, Nakata S, Takei T, et al.: Vitamin D receptor gene polymorphism in familial prostate cancer in a Japanese population. *Int J Urol* **10,** 261–266, 2003.
160. Cheteri MB, Stanford JL, Friedrichsen DM, Peters MA, Iwasaki L, et al.: Vitamin D receptor gene polymorphisms and prostate cancer risk. *Prostate* **59,** 409–418, 2004.
161. Slattery M: Variants of the VDR gene and risk of colon cancer (United States). *Cancer Causes Control* **12,** 359–364, 2001.
162. Lamprecht SA and Lipkin M: Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann NY Acad Sci* **952,** 73–87, 2001.
163. Lamprecht SA and Lipkin M: Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer* **3,** 601–614, 2003.
164. McCullough ML, Bandera EV, Moore DF, and Kushi LH: Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature. *Prev Med* **46,** 298–302, 2008.
165. Bertone-Johnson ER: Vitamin D and breast cancer. *Ann Epidemiol* **19,** 462–467, 2009.
166. Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, et al.: SELECT: the Selenium and Vitamin E Cancer Prevention Trial: rationale and design. *Prostate Cancer Prostatic Dis* **3,** 145–151, 2000.
167. Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, et al.: SELECT: the Selenium and vitamin E Cancer Prevention Trial. *Urol Oncol Seminars Original Investigations* **21,** 59–65, 2003.

168. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, et al.: Effects of long-term supplementation on and cancer vitamin E cardiovascular events: a randomized controlled trial. *JAMA* **293,** 1338–1347, 2005.
169. Traber MG and Atkinson J: Vitamin E, antioxidant, and nothing more. *Free Radical Biol Med* **43,** 4–15, 2007.
170. Azzi A and Stocker A: Vitamin E: non-antioxidant roles. *Progress Lipid Res* **39,** 231–255, 2000.
171. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM, et al.: Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Nat Cancer Inst* **97,** 94–102, 2005.
172. Quin J, Engle D, Litwiller A, Peralta E, Grasch A, et al.: Vitamin E succinate decreases lung cancer tumor growth in mice. *J Surg Res* **127,** 139–143, 2005.
173. Traber MG: Vitamin E regulatory mechanisms. *Ann Rev Nutr* **27,** 347–362, 2007.
174. Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, et al.: Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Nat Cancer Inst* **90,** 440–446, 1998.
175. Brigelius-Flohe R and Traber MG: Vitamin E: function and metabolism. *FASEB J* **13,** 1145–1155, 1999.
176. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, et al.: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Internal Med* **142,** 37–46, 2005.
177. Mitchel RE and McCann RA: Skin tumor promotion by vitamin E in mice: amplification by ionizing radiation and vitamin C. *Cancer Detect Prev* **27,** 102–108, 2003.
178. Bermudez Y, Ahmadi S, Lowell NE, and Kruk PA: Vitamin E suppresses telomerase activity in ovarian cancer cells. *Cancer Detect Prev* **31,** 119–128, 2007.
179. Bermudez Y, Ahmadi S, Lowell NE, and Kruk PA: Vitamin E suppresses telomerase activity in ovarian cancer cells. *Cancer Detect Prev* **31,** 119–128, 2007.
180. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, et al.: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* **301,** 39–51, 2009.
181. Ni R, Nishikawa Y, and Carr BI: Cell growth inhibition by a novel vitamin K is associated with induction of protein tyrosine phosphorylation. *J Biol Chem* **273,** 9906–9911, 1998.
182. Wu FY, Liao WC, and Chang HM: Comparison of antitumor activity of vitamins K1, K2, and K3 on human tumor cells by two (MTT and SRB) cell viability assays. *Life Sci* **52,** 1797–1804, 1993.
183. Oztopcu P, Kabadere S, Mercangoz A, and Uyar R: Comparison of vitamins K1, K2 and K3 effects on growth of rat glioma and human glioblastoma multiforme cells in vitro. *Acta Neurol Belg* **104,** 106–110, 2004.
184. Carr BI: Suppression of DCP/PIVKA-2 and alpha-fetoprotein levels in human hepatocellular carcinoma (HCC) by high doses of vitamin K1 (VK1). *Hepatology* **24,** 887–887, 1996.
185. Sun L, Yoshii Y, Miyagi K, and Ishida A: Proliferation inhibition of glioma cells by vitamin K2. *No Shinkei Geka* **27,** 119–125, 1999.
186. Takami A, Nakao S, Ontachi Y, Yamauchi H, and Matsuda T: Successful therapy of myelodysplastic syndrome with menatetrenone, a vitamin K2 analog. *Int J Hematol* **69,** 24–26, 1999.
187. Miyazawa K, Yaguchi M, Funato K, Gotoh A, Kawanishi Y, et al.: Apoptosis/differentiation-inducing effects of vitamin K2 on HL-60 cells: dichotomous nature of vitamin K2 in leukemia cells. *Leukemia* **15,** 1111–1117, 2001.
188. Yaguchi M, Miyazawa K, Katagiri T, Nishimaki J, Kizaki M, et al.: Vitamin K2 and its derivatives induce apoptosis in leukemia cells and enhance the effect of all-trans retinoic acid. *Leukemia* **11,** 779–787, 1997.
189. Cantoni O, Fiorani M, Cattabeni F, and Bellomo G: DNA Breakage caused by hydrogen-peroxide produced during the metabolism of 2-methyl-1,4-naphthoquinone (menadione) does not contribute to the cytotoxic action of the quinone. *Biochem Pharmacol* **42,** S220–S222, 1991.
190. Lamson DW and Plaza SM: The anticancer effects of vitamin K. *Altern Med Rev* **8,** 303–318, 2003.
191. Sata N, KlonowskiStumpe H, Han B, Haussinger D, and Niederau C: Menadione induces both necrosis and apoptosis in rat pancreatic acinar AR4–2J cells. *Free Radical Biol Med* **23,** 844–850, 1997.
192. Nutter LM, Cheng AL, Hung HL, Hsieh RK, Ngo EO, et al.: Menadione-Spectrum of anticancer activity and effects on nucleotide-metabolism in human neoplastic cell-lines. *Biochemical Pharmacology* **41,** 1283–1292, 1991.
193. Wu FYH, Chang NT, Chen WJ, and Juan CC: Vitamin-K3-induced cell-cycle arrest and apoptotic cell-death are accompanied by altered expression of c-fos and c-myc in nasopharyngeal carcinoma cells. *Oncogene* **8,** 2237–2244, 1993.
194. Mitchell JS, Brinkley D, and Haybittle JL: Clinical trial of radiosensitizers, including synkavit and oxygen inhaled at atmospheric pressure. *Acta Radiol Ther Phys Biol* **3,** 329–341, 1965.
195. Juan CC and Wu FY: Vitamin K3 inhibits growth of human hepatoma HepG2 cells by decreasing activities of both p34cdc2 kinase and phosphatase. *Biochem Biophys Res Commun* **190,** 907–913, 1993.
196. Jarabak R and Jarabak J: Effect of Ascorbate on the dt-diaphorase-mediated redox cycling of 2-methyl-1,4-naphthoquinone. *Arch Biochem Biophysics* **318,** 418–423, 1995.
197. Noto V, Taper HS, Jiang YH, Janssens J, Bonte J, et al.: Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. I. Synergism of combined vitamin C and K3 action. *Cancer* **63,** 901–906, 1989.
198. Taper HS, de Gerlache J, Lans M, and Roberfroid M: Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pretreatment. *Int J Cancer* **40,** 575–579, 1987.
199. Jamison JM, Gilloteaux J, Taper HS, and Summers JL: Evaluation of the in vitro and in vivo antitumor activities of vitamin C and K-3 combinations against human prostate cancer. *J Nutr* **131,** 158S–160S, 2001.
200. Venugopal M, Jamison JM, Gilloteaux J, Koch JA, Summers M, et al.: Synergistic antitumour activity of vitamins C and K3 against human prostate carcinoma cell lines. *Cell Biol Int* **20,** 787–797, 1996.
201. Gilloteaux J, Jamison JM, Ervin E, Arnold D, and Summers JL: Scanning electron microscopy and transmission electron microscopy aspects of the synergistic antitumor activity of vitamin C/vitamin K3 combinations against human T24 bladder carcinoma: another kind of cell death? *Scanning* **20,** 208–209, 1998.
202. Taper HS: Reversibility of acid and alkaline deoxyribonuclease deficiency in malignant tumor cells. *J Histochem Cytochem* **29,** 1053–1060, 1981.
203. Fort L, Taper HS, and Brucher JM: Gastric carcinogenesis in rat induced by methylnitrosourea (MNU). Morphology and histochemistry of nucleases. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol* **81,** 51–62, 1974.
204. Taper HS and Bannasch P: Histochemical correlation between glycogen, nucleic acids and nucleases in pre-neoplastic and neoplastic lesions of rat liver after short-term administration of N-nitrosomorpholine. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol* **87,** 53–65, 1976.
205. Waxman S and Bruckner H: The enhancement of 5-fluorouracil antimetabolic activity by leucovorin, menadione and alpha-tocopherol. *Eur J Cancer Clin Oncol* **18,** 685–692, 1982.
206. Gold J: In vivo synergy of vitamin K3 and methotrexate in tumor-bearing animals. *Cancer Treat Rep* **70,** 1433–1435, 1986.
207. Nutter LM, Cheng AL, Hung HL, Hsieh RK, Ngo EO, et al.: Menadione: spectrum of anticancer activity and effects on nucleotide metabolism in human neoplastic cell lines. *Biochem Pharmacol* **41,** 1283–1292, 1991.
208. Wang Z, Wang M, Finn F, and Carr BI: The growth inhibitory effects of vitamins K and their actions on gene expression. *Hepatology* **22,** 876–882, 1995.
209. Taper HS, Jamison JM, Gilloteaux J, Gwin CA, Gordon T, et al.: In vivo reactivation of DNases in implanted human prostate tumors after administration of a vitamin C/K-3 combination. *J Histochem Cytochem* **49,** 109–119, 2001.