The Effects of Vitamins and Nutrition on Cancer Illnesses

Introduction

Primary Prevention
There are many reasons to consider vitamin supplements in connection to cancer illnesses. Within the framework of a possible prophylaxis, primary prevention can be taken into account; for example, to reduce the oxidants in the metabolism which are regarded as harmful to health. Different researchers have associated the importance of nutrition with different malignancies, following the assessment that was undertaken in 1981 by the British epidemiologists Doll and Petro. Through nutrition, it has been shown that it is possible to lower the cancer mortality rate in the USA, by up to 35%. However, the actual percentage could lie between 10-70%.

Cancer Illness
Eicholzer’s work brings into consideration that up to 50% of cancer patients would be identified with "nutrient absorption disorders, disturbances in food utilization or problems with their metabolism." The reason for this lies in malnutrition brought about through tumor progression (e.g. cachexia, anorexia). Most researcher writers in oncology text books agree on this point. However, also as a consequence of tumor treatment there can be possible nutrient absorption disorders appearing, as well as cases of malnutrition – due to: operations (according to the affected organ; above all, stomach cancer and intestinal cancer), radiotherapy (e.g. nausea, vomiting, diarrhea, fatigue), chemotherapy (e.g. stomatitis, enterocolitis, fatigue syndrome, loss of appetite). Besides the physical consequences of cancer illness and the associated treatment, there are also the diverse psychosocial changes that can indirectly influence the nutritional situation: intra-psychological, relational, familiar and professional. Psychological factors can also lead to other problems such as nausea, vomiting, early satiety, diarrhea and malabsorption. Cancer patients with poor nutritional status (e.g. anorexia and malnutrition) can meet with possible complications in their treatment. Therefore, according to Aapro, there are needs for specific nutritional therapy in conjunction with parenteral treatment. In addition, Aapro recommends that cancer patients should benefit from nutritional advice prior to major surgery, intensive chemotherapy or radiotherapy, in order to better tolerate the applied treatment; even if the final result of the illness is unchangeable.

Tertiary Prevention
An increase in the use of vitamin supplements, e.g. discussed after malignancies with the aim of possibly improving patients’ health, is known as tertiary prevention. Vitamin supplementing is conceivable in several ways: from the natural nutritional source in corresponding nutrient-rich foods, that are rich in vitamins (primarily wholesome food; mostly fruit and vegetables and low processed whole grains) and with possible additional vitamin preparations and/or food.
supplements, such as parenteral (ex., infusion) or artificial enteral nutrition (ex., stomach probe). This paper covers the first two aspects of vitamin intake. Even though not mentioned here, there is also the possibility of local application of vitamin preparations as a medication, along with the artificial nutrition. For example, the use of vitamin A in local applications was used in the 1970s. It was also used in individual pilot studies, for example, on small superficial melanoma dermal metastases\textsuperscript{13, 14} (injection), with respiration metaplasia and dysplasia epithelium\textsuperscript{15, 16} (aerosol) or with Kaposi’s sarcoma\textsuperscript{17} (gel).

**Unfortunately, Only a Few Useable Surveys**

A precise estimation concerning the frequency of using vitamin supplements as a complementary medical measure among cancer patients is not possible at this time, because the corresponding examinations are neither comparable nor representative. In a review of 26 surveys about the prevalence of the use of CAM (Complementary and Alternative Medicine) in 13 countries, Ernst et al. pointed out that the included studies lacked much in agreement and reliability; thus it was not possible to establish a systematic review.\textsuperscript{18}

Based on a summary of 18 surveys of various design and responses, concerning the use of CAM by cancer patients in the USA (8.7-84\%) vitamins were among the three most frequent CAM types. Divided into three categories it could be seen that vitamins were taken in adults in 4 out of 10 studies (n = 11'244), in female patients with breast cancer in 1 out of 4 studies (n = 1295) as well as in children in 2 out of 4 studies (n = 414).\textsuperscript{19} Changes in nutrition were noted with adults in 5 studies, with female patients in 1 study and for children in 2 studies.

In a new review of 14 surveys concerning the use of CAM in children with cancer, from many different countries (8.7-84\%), it was found in 4 more studies next to the 10 previously mentioned (n = 1074), that the use of 2 of the vitamins and of 4 of the food supplements, belonged to the most frequently complementary medical methods used.\textsuperscript{20}

**The Connection Causality Problem**

At this time, data available on the effect of vitamins in relation to cancer prevention or in cancer illnesses is made up of three different types of completed surveys: a. Investigations on the effects of the specific nutritional state within epidemiological studies (case, control and cohort studies), b. Investigations on the effects of specific supplements in intervention studies (clinically non-controlled, controlled or randomized control studies (RCT)), c. Investigations on the results of a. and b. through reviews (systematic reviews) or meta-analyses.

The value of individual study models is due to their respective defined and restricted methodical approach: In order to put an end to the “causality of an observed connection” it must be viewed while considering the respective criteria of a series of studies from which they are drawn (for example, dosage effects, temporal sequencing, strengths of connections, consistency of results, plausibility, etc.). Therefore, it is necessary not only to consider the causality of observed connections “frequently not ‘proven,’ but also from various probabilities.”\textsuperscript{4, 2} Epidemiological studies can only give indications of connections; but ideally, there would have to be more exact examinations in intervention studies (e.g. \(\beta\)-carotene).

When faced with the abundance of publications on the topic of “Vitamin Intake and Cancer Illnesses”, in assembling this present summary, it seemed necessary to give an informative overview which included findings from specific surveys, overview papers\textsuperscript{4, 5, 10, 12} and from selected individual studies; providing of course that they refer to human beings. Selections were also made from other publications, extracts from text books and from bibliographies of the respective articles. This subjective selection can be viewed only as a general one and no systematic review is presented with it.

**Which Vitamins Are Taken Into Consideration?**

The fat-soluble vitamins A, D and E are referred to in this section. Also included is an additional exception, from the carotenoids, meaning \(\beta\)-carotene, a plant precursor of vitamin A, which has been the subject of many studies. The water-soluble vitamins mentioned here are vitamins C, niacin and folic acid. No information is presented with regard to the vitamin B complex vitamins, namely B\(_1\), B\(_2\), B\(_6\), B\(_{12}\), pantothenic acid, and biotin.

These vitamins and plant precursors are briefly described below, listed with their specific names, physiological effects, dosages, their occurrence in foods and their detrimental effects (due to deficiency and/or overdose). There is also a small selection of vitamin study extracts mentioned. However, these are short summaries and are not to be considered full and complete representations.

It is difficult to arrive at a broad consensus with interpretation, as well as to clearly present a practical overview of the scientific data on vitamins, in the form of reference values concerning nutritional supplies.
It became clear that this was important. Reference values were provided by the United Nations Food and Agricultural Sector along with the WHO first in 1985, the Food and Nutrition Board provided values in 1997 and the DACH (German Nutrition Society (DGE), the Austrian Nutrition Organization (ÖGE), as well as the present Swiss Society for Nutrition (SGE)) gave their corresponding reference values in 2000. These references were an overview of those usually in good health, as well as those attempting to preserve good health. Also, these published accounts could sometimes vary; according to the particular country, organization, data conditions and interpretations. However, these reference values give a first indication about nutrition (see tab. 1).

**Amounts and Peak Values**

If one makes a rough overview on the present day data availability on the complex themes of vitamins and nutrition in cancer illness, one quickly realizes that the question that continuously comes up, "Which amount of certain vitamins must I take on a daily basis in order to prevent getting cancer?" cannot be answered today, based on scientific evidence. It is also noteworthy that the question concerning individual vitamins quantities necessary for intake was never asked by the scientists who reprocessed the available data. For the moment, the most extensive summary of available data to date comes from the findings of the World Cancer Research Fund, and the American Institute for Cancer Research, (WCRF/AICR) completed in 1997. In this work, the question wasn’t usually put forward on specific vitamin quantities, but instead, rather broadly on the influence of foods and complete nutrition concerning certain types of cancer. The answers provide a possible connection between cancer formation and nutrition and are cautiously formulated from a scientific perspective ("Evidence") covering four categories (convincing, probable, possible or insufficient). However, since some cancer patients take certain food supplements, it seemed necessary also to cover the position from this aspect. This is reviewed on page 10 of this paper. During this study, and up until now, there remains the unsolved question, "Which amounts of vitamins are completely harmless?" If vitamins have already been demonstrated as effective, then no attention was paid to the high quantity ratios of vitamins that are used for the nutrient enrichment of foods, nor to the state of discussion on the possible interactions between vitamins and chemotherapy or radiotherapy.

Today, the maximum amount of vitamins for daily nutritional requirements are subdivided into three value ranges; in which the values may vary, according to the particular country and/or organizations:

1. The tolerated upper vitamin intake (UL = Tolerable Upper Intake Level); “even under long term intake no negative influences on the health of a particular population group are expected.”

2. Next to this tolerable upper level intake (UL), that can be meaningful in epidemiological terms, individual values are higher. The value for this, with regard to undesirable side effects, is known as the Lowest Observed Adverse Effect Level (LOAEL). This level is not yet known for all vitamins.

3. The next important value of the high quantity ration of vitamins is the level at which no toxic effects were observed. This is known as No Observed Adverse Effect Level (NOAEL).

The differences among these high quantity vitamin ratios and the reference values that are mentioned below for each of the vitamins, is resulting from the consideration given to further safety factors (also see tab. 1).

We hope this list gives both doctors and patients enough credible information, in order to make decisions at the time of a common discussion. If necessary, such common conversations should also include family members and/or lifetime partners.

**Fat-soluble Vitamins**

**Vitamin A**

**Definition:** Included under this relatively nonspecific term of Vitamin A, are all substances/combinations of Vitamin A with similar biological activity; for example 11-cis-retinol, retinoic acid, all-trans-retinol and the so-called plant precursors of vitamin A; for example β-carotene (beta-carotene), mentioned here but dealt with separately under carotenoids. "The biological activity of the individual Vitamin A derivate is indicated in International Units (IE), in which 1 IE means 0.3 µg retinol."

**Physiological Effects:** Necessary for proper vision (rhodopsin), embryogenesis (for example, development of the skeletal system), neural tube, cell proliferation and differentiation (skin and respiration mucous membrane).

**Dosage within the Framework of Nutritional Recommendations:** The recommended daily amount for healthy adults between the ages of 25 and 51 years old, according to DACH; for women – the equivalent
of 0.8 mg retinol; for men – the equivalent of 1 mg retinol (= 1 mg retinol). There is an insignificant value difference for other age groups; for example, as written in the DACH recommendations to date.

Content in Foods: For many years it was usual to cite information on nutrient content in relation to 100 grams of a particular food. However, in the meantime, some authors now write on how many grams of a food contain the suggested daily quantity of a particular nutrient. In each case, examples are given here with respect to both types of representation:

In 100 grams of each of the following foods, the amounts of Vitamin A (retinol equivalent) that are contained are stated in mg – meat: beef liver 15.3; – plant (vegetable/fruit): carrots (raw) 1.6, honeydew melon 0.78, apricots 0.27. The daily recommended amount of approximately 0.9 mg can be found for example in 10 g of liver (depending upon the type of meat), 100 g of liver sausage, 150 g of butter, 200 g of Camember cheese or tuna fish, 3 l whole milk.

Toxicology: For adults the acute toxic dose is indicated at 2-5 Millions IE per day. Symptoms of toxicity include: headache, vertigo, vomiting and feeling dazed. The chronic toxic dose is close to 100’000 IE per day; with pregnancy, however, due to possible teratogenic; birth defects could occur with the intake of 10’000 IE. This value lies in the order of magnitude of the high quantity vitamin ration (explanation, see p. 3) for the daily dose in mg retinol equivalent: UL: 3 (approx. 9000 IE), LOAEL: 6.5, NOAEL: 3.

Selected Data: In the survey conducted by the World Cancer Research Fund in conjunction with the American Institute for Cancer Research (WCRF/AICR), 1997, none of the 18 designated organs and/or organ systems had a connection between Vitamin A and a reduced or increased risk of falling ill with cancer.

The only meta-analysis with undertaken epidemiological investigations concerned six studies that showed a reduced risk for bladder cancer, as a result of a nutrition high in fruit and vegetable consumption and low in fat consumption. However, it remains unclear as to which food elements this is due to exactly. No increased risk was perceived for nutrition with a low retinol or β-carotene content. The increased risk of falling ill with bladder cancer and low fruit consumption was: relative risk (RR) = 1.4; 95% confidence interval (CI) = 1.08-1.83. Two recent epidemiological studies concerning nutritional habits point in the same direction. A controlled case study of 812 post-menopausal women showed no effect between the intake of Vitamin A or Vitamin E and incidences of breast cancer. A cohort study of 58,279 men between the ages of 55 and 69 years old showed no effect between the intake of Vitamin A and Vitamin C, as well as Vitamin E, and the total risk of becoming ill with prostate cancer.

Intervention studies on Vitamin A and cancer illnesses make reference to, for example, leukemia (acute promyelotich leukaemia), on what the authors call a randomized controlled study (RCT; n = 30 children from the APL 93 Study); using as a first choice of treatment a standard chemotherapy that is combined with an oral dose of 45 mg/m²/per day of all-trans-retinoic acid.

Vitamin D

Definition: The historic conditional name of the Vitamin D₃ is actually incorrect, but has become the custom to employ the name in everyday use. Vitamin D₃ is actually hormonal precursor and in its hormonal working form is 1,25(1α,25)D₃, abbreviated as 1,25(OH)₂D₃, which is a secosteroid hormone. It is also referred to as calcitriol, the Vitamin D hormone, or 1,25-Dihydroxy-Vitamin D₃.

Physiological Effects: It is essential in order for the organism to take up calcium: for osteoclasts bone differentiation and in building strong bones, for proper absorption of calcium and phosphorus in the small intestine, for kidney feedback on the phosphate metabolism, and for the parathyroid gland inhibition of parathormone formation.

Within the framework of the cholesterol synthesis for human beings, 7-Dehydrocholesterol is created as a start up molecule for the endogenous Vitamin D synthesis; through the effect of sunlight’s action on the skin, the Vitamin D₃ is produced. This is transformed in the liver to make prohormone 25(OH)-cholecalciferol, and then in the kidney to the actually changed hormone of 1,25-Dehydrocholecalciferol.

Through the sun’s photochemical reaction, Ergosterol that is incorporated in vegetable food is converted into Vitamin D₃.

Dosage within the Framework of Nutritional Recommendations: The recommended daily amount for healthy adults between the ages of 25 and 51 years old, according to DACH; for women and men is 5 µg (1 µg = 40 IE). In spite of this information, "...until now, there has been no general consensus on the
daily recommended amount of Vitamin D (as it exists). Recommendations of consensus conferences and legal opinions published simultaneously have already been brought into question.” Among other reasons, opinions differ due to whole body UV irradiation, below the erythematic dose which can cause the production of 250 µg vitamin D₃.  

Content in Food: The amounts of Vitamin D₃ in µg found in 100 g of each of the following foods is – animal: herring 26, egg 1.75, cream (30% fat) 1.1, milk 0.03; – plant: cep mushrooms 3.1, mushrooms 1.9.  

Toxicology: The highest daily therapeutic dose in µg, is listed at (see p. 3) : UL: 50, LOAEL: 50, NOAEL: 20. 

Selected Data: In the survey of WCRF/AICR, with regard to Vitamin D₃, it is noted that there is not sufficient “Evidence” for a connection to a reduced risk for tumors of the colon and of the rectum. The results of more recent studies remain controversial, as well. Following their overview work in 36 retrospective and 16 prospective studies, Giles and others found in one study on prostate cancer that there was a connection to a high presence of Vitamin D in the serum. However, in a second study the results could not be confirmed. All together, they judge the possibility for a connection between nutrition and prostate cancer to be weak and inconsistent. 

A more recent review, comprised of 37 prospective cohort studies and 4 intervention studies, points in the same direction. In a new control study case, 858 men with prostate cancer and 905 healthy men in a control group surveyed on their nutrition showed apparent and significant effects of protection coming from vegetable intake. In a follow-up analysis from the Nurses’ Health Cohort Study made on a group of 3'482 women, those in post menopause, n = 2'345, who had an intake of dairy products, calcium or Vitamin D, could not be significantly linked to the risk of breast cancer.  

RCTs results were few, with regard to the focus on a connection between Vitamin D alone; however the RCTs done were mostly in combination with calcium. So that, a statement on supplementing, with this sole vitamin, is hardly possible.

Vitamin E

Definition: The most important Vitamin E occurring in nature is α-Tocopherol. Other combinations of Vitamin E are β-Tocopherol, γ-Tocopherol or Tocotrienol. RRR-α-Tocopherol is regarded as a reference substance and its action equivalent is noted as Tocopherol, also indicated as α-Tocopherol-equivalent (α-TE) (1mg = 1.49 IE). 

Physiological Effects: Vitamin E is a component of all biological membranes and probably protects membrane lipids, lipoproteins and depot fat, prior to their reduction through lipid peroxidation (connotation for the oxidases action and radicals onto lipids, as well as unsaturated fats). Vitamin E protects in vitro, in cells and tissues against free radicals and assures the oxidative reduction of polyunsaturated fatty acids; thus, the reason is also called an antioxidant. 

Dosage within the Framework of Nutritional Recommendations: Concerning Vitamin E, DACH has not suggested any reference values for the daily nutrient supply, but has only estimated values (data is not yet sufficiently available for provisional requirements – the estimated values are considered as completely safe) for an adequate vitamin supply per day. For healthy adults between the ages of 25 and 51 years old: For women: 12 mg of α-TE. For men: 14 mg of α-TE. 

Content in Food: For each 100 g of the following foods, the amounts of Vitamin E are given in mg α-TE animal products: butter 2.2, herring 1.5; vegetable: sunflower oil 50, hazelnuts 26.6, sunflower seeds 21.8, peanuts 10.3, olive oil 13.2, paprika 2.5, raspberries 0.9. As with many other vitamins, the content of Vitamin E varies in vegetable foods due to seasonal fluctuations. It is assumed that 20-50% of the Vitamin E amount reabsorbed from foods is α-Tocopherol.

Toxicology: The highest recommended daily limit (see p. 3) in mg is: UL 1000, LOAEL: no information, NOAEL: 800. Biesalski and others considered that orally taken amounts up to 100 mg per day are physiological and also 100-300 mg per day are not supposed to cause any side effects. However, Fairfield sees the possibility of a gastrointestinal trouble already within the range of 200 to 800 mg per day. With simultaneous taking of aspirin, Beutler considers a restriction of 200 mg per day necessary and makes reference to a possible inhibition of the thrombocyte aggregation, with the possibility of bleeding from 800 mg Vitamin E per day. Brown and others recommend a limit of 400 to 800 mg per day. If patients have coagulation problems, they should not take high doses of Vitamin E prior to
operations, nor if they are under treatment with anticoagulants. Over 1200 mg per day can cause nausea, diarrhea, cramps, tiredness, headaches and blurred vision. In contrast, according to Biesalski and others, even the upper most levels of 3200 IE per day should not cause any harm (not described in further detail).  

Selected Data: WCRF and AICR came to the conclusion that a possible connection exists between vitamin E and a reduced risk to those suffering from lung cancer. With regard to a connection between Vitamin E and colorectal cancer illness, the CRF/AICR cites that the existing data is not sufficient. They come to a similar conclusion as the authors of the 1992-Meta-Analysis did; whereby the plasma level of α-Tocopherol in the serum and colorectal cancer is not certain.

An additional result of the Heart Protection Study was that 600 mg of Vitamin E per day (in combination with 250 mg of Vitamin C and 20 mg of beta carotene) didn't have any significant influence on cancer mortality.

In a cohort study published in 1999 that surveyed 2974 healthy men over a 17-year period, it was found that there was a significant increased risk to die of prostate cancer (n = 30), for smokers who had a low Vitamin E in their blood plasma (n = 12).

In the intervention study, the "Alpha-Tocopherol Beta-Carotene Cancer Prevention Study," also known as the ATBC Study, there was a reduced incidence (n = 246) and mortality rate (n = 62) for prostate cancer among smokers, following supplement intakes of α-Tocopherol (50 mg/day), opposite a placebo; on a 6-year average, but not in combination with β-carotene or solely β-carotene (below, under carotenoids). Since the effects of supplement intake on prostate cancer belongs to the secondary study's final results, a confirmation of the results would be necessary through an independent study.

In the same study, when α-Tocopherol was the sole vitamin supplement given, there were no significant effects of incidence and mortality observed in patients with lung cancer. The overall mortality within the study groups where α-Tocopherol was taken, were due to higher hemorrhagic infarcts, even though not significant in number.

Carotenoids

β-Carotene

Definition: Carotenoids are pigments, with a central system of conjugated double bonds, ranging in color from light yellow to red, and can be found in great variety. Carotenoids are lipophils. There are more than 600 known carotenoids (for example, α-carotene, β-carotene, lutein, lycopene and phytoene) and are synthesized from plants and lower organisms. Approximately 30-40 carotenoids are found in food.

Physiological Effects: Carotenoids appear as anti-oxidative in the metabolism and induce intercellular communication that is necessary for regulating cells growth and development processes. Derived from the main serum carotenoids are α-carotene, β-carotene and β-cryptoxanthin which are metabolized by the organism as pro-Vitamin A (Retinol).

Dosage within the Framework of Nutritional Recommendations: There are still not any suggested reference values for β-Carotene, but the DACH organizations give an estimated value range on the daily recommended requirements of 2-4 mg per day.

Content in Food: Carotenoid content can vary according to the type, degree of ripeness and the location conditions of the source plants. For 100 g of a particular food, the following amounts of β-carotene can be found, measured in mg: carrots 1.8-14.7, apricots 0.6-6.4, mangoes 0.1-3.7, broccoli 0.5-1.1, and fresh tomatoes 0.23.

Toxicology: The highest recommended daily limit (see p. 3) in mg is: UL: no information given, LOAEL: no information given, NOAEL: 25.

"No indications are given on the toxic effects of food carotenoids, concerning normal absorbed quantities that occur in food." However, carotenoids taken in high doses through supplements can cause a harmless, yellowing of the skin that is reversible. In the case of "cosmetic skin tinging" that has the carotenoid base of canthaxanthin which represents a dose of 30 mg per day, crystalline deposits were found on the retina. This disturbed the eyes adaptation to the dark, however, it is reversible.

Selected Data: Much of the epidemiological data shows a weak to strong decrease in the risk of lung cancer when a high intake of carotenoids occurs through food. However, through an analysis of case control and prospective study, the situation of evidence in itself has been weakened, with regard to a meta-analysis: the entire fruit and vegetable consumption is shown to be protective. Prior to this knowledge, however, the known facts that nutritional behavior lowers the risk of falling ill to cancer, led to
conducting an experiment on risk groups. Risk groups were given separate individual carotenoids in pharmacological doses. However, two intervention studies later showed contrary effects: I. The four-armed ATBC Intervention Study (1. α-Tocopherol; 2. α-Tocopherol and β-carotene; 3. β-carotene; 4. placebo) among smokers (n = 29'133, median: smokers for 36 years, 20 cigarettes a day) in Finland, resulted in those groups taking the supplements of β-carotene (20 mg/day, over an average of 6 years), having a significant higher incidence for lung cancer. II. The Beta-Carotene and Retinol Efficacy Trial (CARET) was carried out among heavy smokers (currently 20 pack-years or stopping within the last 6 years) and/or workers exposed to asbestos (first exposure, 15 years prior), in the USA. Also in this study, with participants taking the daily supplement (30 mg of β-carotene and 25'000 IE Retinol, on average of about 4 years) a significantly higher incidence appeared for lung cancer (RR = 1.28, p = 0.02); so that the study was abandoned after 4 years. The reasons for this unexpected result have not been clarified until now. The ATBC-study authors noted that the β-carotene was administered perhaps in too short a time period, or that the β-carotene is not the acting cancer preventive substance that was assumed based on epidemiological studies. So the question is whether or not β-carotene is only a marker of a healthy lifestyle. Concerning this possibility, it is to be recalled that even though then, β-carotene was considered a scientific discovery and in fact had capacities for protection against cancer, Peto and others already had pronounced at the beginning of their 1981 controlled studies that in spite of a smaller incidence in observation studies, it still didn’t appear convincing. So that DACH must therefore consider the “safeness” of higher doses of β-carotene (20 and 30 mg) for heavy smokers. WCRF/AICR commented that the information in the epidemiological studies were often roughly estimated and unspecific. So, the entire Vitamin A which was contained in food was subdivided into retinol and β-carotene. Other carotenoids were not paid attention to and Vitamin A was equated partially to β-carotene. Even if these two intervention studies with the mentioned supplements proceeded negatively, it seems that there is a connection in the decrease in cancer risk if carotenoids are given through food (vegetables and fruit).

For the sake of completeness, the third and fourth intervention studies on β-carotene are noted: III. In the four-armed Physicians’ Health Study (PHS) in the USA, doctors took (n = 22'071) 50 mg of β-carotene, every second day over a 12 year period (in another arm of the study, 325 mg aspirin plus a placebo, or β-carotene plus a placebo, or both of the doses, or both of the placebos were given). At the end of the study, neither a significant advantage nor disadvantage was noted in relation to taking β-carotene and effects on neoplasias, cardiovascular illnesses or mortality. IV. In a quite large intervention study conducted in Linxian, China, an area with one of the highest incidence rates of esophageal cancer/intestinal cancer, and a lack of nutrition within the population, 29'584 adults received a daily supplement combination of 15 mg β-carotene, 50 µg selenium and 30 mg of α-tocopherol. The result was a significantly lower rate of mortality in total (RR = 9.1, p = 0.03) after a 5⅓-year period. However, neither of these two studies are comparable to the first two noted above. Neither concerns the study participants, nor are individual statements made on particular conditions.

The SU.Vi.MAX Study (Supplementation in Vitamins and Mineral Antioxidants), a RCT, with 13'017 participating adults, promised further findings. Over a 7.5-year period, adults received further supplements in other proportions: a daily dose of 120 mg Vitamin C, 30 mg Vitamin E, 6 mg β-carotene, 100 µg selenium, 20 mg zinc or a placebo. In the entire collective, no decrease in the cancer incidence was proved. But in a stratified analysis according to sex, a decrease was proved for men. However, it is unclear in as far as this is connected with lowered basal volumes of men, with regard to antioxidants.

There were no details entered into the context of this compilation on the much discussed carotenoids lutein and lycopene.

Water-soluble Vitamins

Folate

Definition: Folic acid was isolated for the first time from several tons of spinach leaves in 1941; folium (Latin) = leaf. The biologically active form is 5,6,7,8-tetrahydrofolic acid. 1 µg folic acid equivalent (FE) = 1 µg of food folate = 0.5 µg synthetic folic acid (Pteroylmonoglutamate = PGA). what the different bioavailability and/or absorption of synthetic and food folate shows. Approximately 100 substances of similar structure are understood to fall under the term of folic acid or folate.1

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1 20 pack/year = 1 pack of cigarettes during 20 years
Physiological Effects: Is regarded as an anti-anemic factor; folates (co-enzyme forms) function in many metabolic pathways (for example, amino acids, or DNA and RNA synthesis) as carriers and acceptors of different groups of substances.58

Dosage within the Framework of Nutritional Recommendations: The recommended daily amount for healthy adults between the ages of 25 and 51 years old is, according to DACH: for women and men – 400 μg (1 μg = 40 IE).27

Content in Food: For each of the 100 g of the following vegetable and animal foods, the amount of folic acid that it contains in μg is noted – animal: yogurt 13 (3.5% of fat), plaice 11, veal 5, eggs 67; vegetable: spinach (raw) 145, red beets 83, sour cherries 75, potatoes 20. Folic acid is light sensitive, oxidation sensitive and heat sensitive.31 p. 49

Toxicology: The highest recommended daily limit (see p. 3) in μg is: UL: 1000 (for synthetic folates)30, p. 128, LOAEL: no information given, NOAEL: 1000.27

Selected Data: According the WCRF and AICR survey, there is inadequate data existing in order to make a connection between folic acid and types of colorectal cancer in terms of a reduced risk.5 Due to a part of new studies, Baerlocher and others view more favorably the results, in a sense of a possible 40% reduction of risk in study participants who have a high folate intake.59 Due to contradictory effects in the animal model, questions concerning correct data and the dosage for a safe and effective chemoprevention are unresolved for human beings.60 Therefore, to make recommendations within the framework of folic acid supplements for the purpose of cancer-prophylactic effects is not possible.61

Vitamin C

Definition: Vitamin C is the name, “for L-Threo-hex-2-enono-Lacton, L-Xylo-Ascorbic Acid, as well as L-(+)-Ascorbic Acid, and any of their derivatives.”62

Physiological Effects: Anti-oxidation protection, hydroxylation reactions in the metabolism, involvement with the biosynthesis of neurotransmitters (dopamine to noradrenaline), improvement of iron re-absorption and detoxification reactions within the liver microsomes.62, 63

Dosage within the Framework of Nutritional Recommendations: The recommended daily amount for healthy adults between the ages of 25 and 51 years old is, according to DACH: for women and men: 100 mg; for smokers: 150 mg.27

Content in Food: For each of the 100 g of the following foods, the amount of Vitamin C that it contains in mg is noted. Animal: beef liver 31, cow’s milk 2 (3.5% fat)31, p. 54; vegetable: sand thorn juice 266, black currants 189, kiwi 100, raw paprika 140, steamed paprika 105, raw broccoli 110, lemon juice 51, oranges 50, cooked potato 14.62 “Through inappropriate storage and cooking techniques used in preparing fruits and vegetables, a large portion of Vitamin C content can be lost; in very unfavorable cases, even up to 100%.”36, p. 143

Toxicology: The highest recommended daily amount (s. S. 3) in mg is: UL: 2000, LOAEL: no information given, NOAEL: 1000.27

Selected Data: According the WCRF and AICR survey, on the basis of data available, there is a probable connection that exists between Vitamin C and intestinal cancer for reduced risk, as well as for reduced risk in mouth cancer/pharynx cancer, or esophageal cancer, lung cancer, larynx cancer, breast cancer and bladder cancer.5, p. 405

The epidemiological connection between Vitamin C and a lowered rate of cancer is distorted; in that fruits and vegetables which are a source of Vitamin C, are also rich in other substances, that can work in a protective manner.64 A meta-analysis that examined the influence of nutrition on breast cancer came to the conclusion that a high intake of fruits and vegetables can lower the risk of this illness.55 Four further studies show no connection.33, 53, 66, 67

Until now, an autonomous intervention study with Vitamin C as the sole substance has not been implemented.50, 61 In a prospective investigation, the total mortality of adults sank in each by around 20%, in relation to the increase of the ascorbic acid levels at 20 micromoles/l (20 micromoles/l corresponding to about 40 mg Vitamin C or 50 g of fruit or vegetables per day). However, it is to be noted as confounding (a disturbance factor), that people with existing illnesses often have lower Vitamin C levels and that high fruit consumption can be associated with a generally healthy life-style.68

In a prospective cohort study it was noted that adults who had taken Vitamin C for less than 10 years rarely had cases of intestinal cancer.59 Within a high risk group, lesions in the intestinal lining sank to a
A high consumption of foods rich in Vitamin C could have a protective effect in relation to breast cancer. Patients with advanced cancer illness did not have any benefit from highly proportioned doses of Vitamin C. Several studies proved the anti-coagulation effects of Vitamin C. Therefore, patients with coagulation difficulties or patients who are to be operated on, should avoid high doses of Vitamin C (approximately 2g/d).  

**Vitamin Intake and Cancer Illnesses**  
**For Prevention**  
**Nutrition and Vitamins:**  
At the moment, the most comprehensive summary of WCRF/AICR epidemiological and clinical data available on the topic of nutrition and cancer doses with the recommendation of eating primarily a diet based on vegetable food, which includes many fruits, vegetables and whole grain products, in order to maintain good health over a long period of time. The “American Cancer Society,” also describes in their guidelines a reduced risk in falling ill to various types of cancer is possible with a wholesome nutrition based on vegetable foods. That means a diet that is rich in vegetables, fruit and whole grain products, but low in animal fat, meat and calories. These clear, generally acknowledged nutritional recommendations are made based on epidemiological data. In the case of objective scientific conclusions, RCTs are regarded as “gold standards;” but presently they are unavailable for most food factors, and may well be never available. In the meantime, we are also professing the slogan, to eat five or more portions of fruit and vegetables per day. This is based of the following assumption: “The combined effect of nutrients, contained in compositions that are generally referred to as real food ("whole foods") appears to be most effective in lowering cancer risk, than nutrients found in supplements.” Nevertheless, it remains in question, within the framework of cancer illness prevention whether a vitamin supplement is reasonable. The American Cancer Society states that at this time, there isn’t any scientific discovery that claims supplements could lower cancer risk. “To reduce cancer risk, the best advice presently is to consume antioxidants through food sources rather than supplements.” The few intervention/clinical trials done in human populations designed to test whether supplements can reduce cancer risk have yielded disappointing results. However, if supplements are taken “the best choice is a balanced multivitamin/mineral supplement containing no more than 100% of the ‘Daily Value’ of most nutrients, since high doses of some nutrients can have adverse effects.” Before going into depth on the background of this question as to why supplement use in cancer prevention is generally viewed with some reservations, it’s worthwhile to note the interesting aspects founded by Grune; how for instance, the “necessity to take up a complex antioxidant mix for the normal and effective functioning of the antioxidative protective system.” In this case, it is “extremely difficult (and unlikely), to assign cancer hindering effects to individual antioxidants. Due to the complex interaction of antioxidants among each other, different substances usually are necessary in order to achieve the desired effect.” Independent of cancer illness, there are comments on the toxicology aspects that no study is available concerning symptoms or illnesses due to the “pure overdosing of antioxidants.” However, investigations showed “that massive application of antioxidants can cease normal cellular functions.” So that the free radicals neutralized by the antioxidants, are also ascribed cellular functions; for example, antimicrobial defense. This function could be influenced through “extensive use of some of the antioxidants.” Besides the focused view on nutrition and vitamins given here, a quick reminder should be given on the diverse causes of cancer formation which are also found in the American Cancer Society’s guidelines. Other key aspects in supporting cancer prevention are increased physical activity, maintaining normal weight and only small amounts of alcohol consumption. (see also 73, 74).

**Nutrition and Vitamins during Cancer Illness**  
**Nutrition Prior to Cancer Treatment:**  
Cody and Selvin point out the importance of food in maintaining a good state of nutrition, general health and well-being. A poor nutritional status (for example, anorexia and malnutrition) can lead to complications in the treatment of patients with cancer. Therefore, patients require specific nutritional advice and therapy; if necessary, also with parenteral nutrition. The positive influence of a wholesome
nutrition (see above) covers the general conditions of health and the quality of life that most authors emphasize today. In the same way, cancer patients should receive sound nutritional advice prior to major surgery, chemotherapy or radiotherapy, in order to better tolerate the recommended treatment. On the other hand, Cody and Selvin comment that there were not any findings on the fact that a far-reaching change in nutritional habits would alter the course of the cancer illness itself. Therefore, they see no basis for this, possibly in the hope, of what healing potential this could have. Also, according to Kolb, an influence of diet, vitamins and/or trace elements on tumor growth could not be verified in large-scale studies. 

Not Generally Necessary, but Presumably Frequently Applied: A supplement of nutrients with the possibility of a complete, wholesome nutrition doesn’t seem to be a necessity with the good nutritional status of today and the benefit is not evident. However, for risk groups with vitamin deficiencies, to which some authors\textsuperscript{44} count on among other things, that quite generally, ill people suppose that vitamin supplementing taken within a safe field of dosage, is in accordance with the reference values that are recommended,\textsuperscript{9, 12, 44} and in fact, with vitamin combinations instead of high doses of individual vitamins. However, it is emphasized that vitamin supplements can in no way replace a balanced, wholesome nutrition that is made up of many fruits, vegetables and whole grain products. In spite of this scientific directive, some patients would like to take nutrient supplements in higher doses, even if no influence on their cancer illness is itself proven. After considering the possible undesirable effects based on the DACH reference values and the international high dosage recommendations, it appears that this supplementing situation of doubling the daily recommended amount for a period of several months is harmless (Tab. 1). In theory, it is possible to consider that for individual nutrients, a higher possible dosage would indeed be measured according to the high dosage recommendation. However, for us, it is still a question of finding clear, pragmatic evidence for all recommended or valued nutrient amounts. There is only one exception to this: the doubling of the reference amount for calcium amounts to 2000 mg, and this would exceed the upper most quantity recommendations. Based on this, until now there were some individually observed undesirable effects; NOAEL states 500 mg. 

Besides dosage analysis, it was also previously discussed up until which time prior to treatment is nutritional supplementing relatively risk-free. With regard to chemotherapy, concerning chemotherapeutics from the substance group of alkylating substances (Tab. 3) that works, above all, on pro-oxidative oxygen compounds, the hypothesis was formulated that the long term effect of tissue bound fat-soluble vitamins in dosages which were higher than the reference values, would be considered especially critical. This is because interactions between pro-oxidative working chemotherapeutics and antioxidative working nutrients are theoretically possible. The authors of this warning also point out that until now, there were not any reports issued on the corresponding interactions. However, this could be due to underreporting with the present system of reporting.\textsuperscript{76}

Taking these considerations into account, it would be advisable to observe a safety interval between the last intake of antioxidants and the start up of chemotherapy. Until now, hardly any definitive information can be found on this matter. One recommendation made is to maintain a safety interval of 2 weeks before and after the chemotherapy.\textsuperscript{77} This consideration seems sufficient; with respect to the relatively short half-life of vitamins in serum, in the range of hours for water-soluble vitamins (for example, for Vitamin C, 10 hours) or a few days for fat-soluble vitamins (for example, for Vitamin E, 3.5 days).\textsuperscript{79} Uncertainty still exists on the question of accumulation of fat-soluble vitamins in the tissue, as well as to their relevant concentrations and on their long term presence in the organism, since there are only publications on animal experiments that reference can be made to.\textsuperscript{79} Here, a 3-week safety interval appears advisable to us. Concerning multivitamin preparations with a high level of β-carotene, with a long half-life of 5 to 11 days,\textsuperscript{78, 80} clearly longer time intervals would be necessary, according to our assessment.

Nutrition and Vitamin Supplementing during Treatment (Surgery, Chemotherapy, Radiotherapy): During cancer treatment, it is recommended to continue with good, wholesome nutrition. This is usually possible in the framework of surgical treatment, with the exception on the day of the operation and possible interventions to the digestive organs. However, under chemotherapy and radiotherapy, it could be different, for example, due to loss of appetite, diarrhea, and/or mouth mucosa inflammation.

Example: Admittedly, there are indeed some small studies that have been done on the nutritional status of patients during chemotherapy, but the question of possibly supplementing diets with nutrients during chemotherapy has in no way been definitively conclusive. Atukorala reports on the nutritional status of 14 patients with metastases of malignant testicular teratoma. In this dated longitudinal study with every cycle (vinblastine and bleomycin and partially additional cisplatin), during chemotherapy, patients lost weight and didn’t make up the weight loss again between the cycles. Levels of the vitamins retinol, E, B\textsubscript{1} and B\textsubscript{5} also sank during these cycles.\textsuperscript{81} Henquin and others, reported on the nutritional status of patients
(n = 19) who followed a 2-month advised nutritional plan and who were under a 1-year chemotherapy treatment due to cancer or metastases in the gastrointestinal tract: Most patients who followed the good nutritional plan benefited from the highly correct nutritional intake, those with an average nutritional intake could have improved and those with poor nutritional intakes deteriorated further. Therefore, the researchers saw a possible advantage to the nutritional advice given, even though the informative strength of their study was somewhat restricted due to the small number of patients surveyed. With regard to the individually examined nutrients, carotene remained unchanged, retinol had a slight change, and Vitamin B12 sank at the 2nd to 5th cycle, but then again went up. This was similar for Vitamin B2 and iron, but for Vitamin B5 the values were low, for more than 50% of the patients at the beginning and end of the treatment. Based on this result and in comparison to other studies, Vitamin B5 should be considered to be given as a supplement.82

Experience with Children: In a recent prospective 6-month observation study on children (n = 103) with acute lymphoblastic leukemia (ALL), Kennedy and others examined the relationship among nutrients from the moment of intake, plasma concentration and the incidences of side effects from chemotherapy. The analysis of the nutritional supply concerning food and supplements of Vitamins A, C, E and carotenoids showed, when comparing the data from the first with the last visit 6 months later, a significantly lowered absorption of Vitamin A (overall) and of Vitamin E (from food), as well as a constant absorption of β-carotene and no significant differences for Vitamin C. The comparison of plasma samples from the first to the last examination showed a significant increase for Vitamin A and carotenoids, for Vitamin C there was first a significant increase and then decrease and for Vitamin E there was a significant decrease. A greater nutrient absorption was associated with a much lower incidence of side effects (significantly for Vitamin C and β-carotene with reference to hematological and non-hematological toxicity) and in the regression analysis concerning all 3 investigations, Vitamin C stayed significant. An explanation for these observations could not be given. The nutrient supply comparison and the response to the treatment showed the higher the Vitamin A supply at the time of the diagnosis position was accompanied by a slower response rate and the higher Vitamin E supply was accompanied by a quicker response rate. Vitamins furnished through supplements between the first and last examination dates were 4% and 1% below the expected frequency and were not associated with any side effects. With the exception of Vitamin C, the amount of all other measured nutrients was below the daily recommended values. Due to debate on possibly undesirable interactions between chemotherapeutics and the doses of antioxidants, the authors don't recommend giving any supplements during chemotherapy, but advise to give nutritional advice at that time.83

Examples of Radiotherapy and Chemotherapy: The following sentence clarifies the condition of the theoretical considerations on the benefits or possible risk of vitamins as antioxidants: “This is how radiotherapy functions... just as chemotherapeutics generates free radicals; so that the enrichment of tumor tissue with free radical neutralizers such as Vitamin C, E or carotenoids would be undesirable.” On the other hand, such enrichment would be important to have in the healthy tissue; in order to protect it against the therapeutically induced damages.86

The question of which direction "could vitamins and trace elements cause a modification of the cellular sensitivity to radiation," has not been clarified.84 It is currently safely viewed that during cancer treatment (therapy) the amounts of nutrients, including vitamins, to be taken should correspond to the amounts noted in the nutritional guidelines given for daily nutrient requirements.10 Higher amounts that are discussed remain generally controversial. Only folic acid is warned against being used in high supplemental amounts or in enriched food supplements during chemotherapy with methotrexate, since this chemotherapeutical works through it; it intervenes in folic acid metabolism and its effect could be reduced by a high presence of folic acid.10

Questions on the Effects of Antioxidants during Chemotherapy: With regard to chemotherapeutics that form reactive oxygen compounds which cause oxidative damage to the tumor tissue, Labriola and others have cited theoretical considerations concerning the changes in the antioxidants' effectiveness. (Tab. 2). The authors see an accompanying danger in the reduction of the effectiveness with regard to short term achievements; such as improving the compatibility of chemotherapeutics through antioxidants. With reduced effectiveness, the authors view a possibility of undesirable long term effects, such as tumor relapses through the survival of micrometastases.76 Therefore, the authors warn against dosage of supplements during the chemotherapy in quantities that are higher than the basic reference values (Tab.1), which were adopted by the American Cancer Society in their guidelines.10 Bagley criticizes the hypothesis of Labriola and others, in that the assumption of a reduction in the concentration of free radicals formed through chemotherapy could have the same effect as a reduction in the dosage of the chemotherapeutics cannot be justified without having the supporting data as reference.85 Nevertheless,
there was a method described in the study with which an interaction between reactive oxygen compounds that originated through alkylating chemotherapeutics and antioxidants in the plasma is supposed to be possible (TRAP = Trapping Antioxidant Parameters – total peroxyl radical). It will still have to be proven whether this procedure can be established as an instrument.

Reilly criticizes that some in-vitro experiments showed that some antioxidants could improve the antitumor effect of chemotherapeutics; for example, in human melanoma cells. However, he doesn’t comment on how this distant experimental data can be made transferable to human beings. Ratain warns of chemotherapeutical inhibition of the metabolism through flavonoids and therefore also recommends renouncing the use of supplements during chemotherapy. Kelly recommends delaying the use of supplements until after chemotherapy since antioxidants in the blood analyses of cancer patients did not prove to be adequately beneficial.

Kong and others put forth a radical hypothesis. They consider that the use of inhibitors could improve the effectiveness of the tumor treatment against antioxidants. Opposing this is the hypothesis proposed by Prasad and others on what could be the growth inhibiting effect of radiotherapy, chemotherapy or hyperthermia of the tumor tissue, when reinforced by antioxidants in vitro. Furthermore, the toxicity towards healthy cells due to standard tumor treatment can be reduced through the use of antioxidants. Lamson and others are of a similar opinion and cite some case reports to this effect. However, Weiger cites individual studies in cases of antioxidants’ contradictory effects during chemotherapy, which were observed: Concerning one study in patients with ovarian carcinoma, Vitamin B6 indeed lowered the neurotoxic side effects significantly, but because of an inexplicable contrary effect on the response rate, the authors rejected its simultaneous usage.

It is thus advised to be against the use of high dosages of antioxidants during chemotherapy. This advice is based on the contradictory opinions and experimental data results which are available at present and which is shared by other authors. Nevertheless, attempts should be made, but, only upon agreement and coordination of the treating doctor/oncologist.

The discussion on advantages and disadvantages of supplementing with antioxidants becomes more complex because besides vitamins being antioxidants, there are also certain medicines that are known as antioxidants (Tab.3). The medicine, Mesna, as an anti-oxidizing agent, was examined in clinical studies for its effectiveness in the reduction of side effects of the chemotherapeutical cyclophosphamide. It is possible that the Women’s Healthy Eating and Living (WHEL) Study which was completed in 2004 will also provide new findings. In this study, the effects of vegetables, fruit, fiber and low-fat nutrition in the diet of women with early stage breast cancer has been examined.

Nutrition and Vitamin Supplementing after Treatment (Chemotherapy, Radiotherapy): Since chemotherapy causes the desired and necessary inhibition of cell metabolism that is much stronger in the tumor tissue, which is distinctive from healthy tissue, a diminished metabolism for protein synthesis could partly explain the reason for patients’ exhaustion. Therefore, also after treatment it is important for patients to have a proper intake of adequate amounts of calories and nutrients. At this point, complete, wholesome nutrition would be recommended. For many patients, it is important to once again enjoy a feeling of wellbeing as soon as possible and no longer feel continuously ill. It is necessary for some patients to sense again the normal functioning of their body and to be able to determine the course of their lives and their general welfare. Subjective feelings are a part of this; so that improvement through the patient’s own active participation of support measures can be influenced (conscious relaxation, forms of psychotherapy, therapeutic agents and remedies). Here, too, arises the question of nutrition and supplements. Wholesome food is also recommended at this point and if necessary, additional food supplements in a simple dosage with respect to the reference values (Tab. 1) are safe. Following therapy, the wishes of some patients can be matched to contribute to the recovery of their organisms through an increase in the amounts of nutrients and in accordance with maximum recommendations, up to the doubling of reference values. However, until now scientific evidence for such an effect is still missing, according to the known criterions of “evidence based medicine,” in relation to controlled studies. During patients’ recovery after treatment, the American Cancer Society views the intake of a well-balanced multivitamin and a multi-mineral preparation once or twice a day as a sensible recommendation.

Besides the dosage, the timing on the start-up of giving supplements is unclear here and is not taken into account by some authors. A safe interval distance of 2 weeks, or as well as in our opinion, 3 weeks after treatment (therapy) would be recommendable.

After a certain time of elevated amounts intake, supplements should be taken again, but only in the range of the recommended reference values. At the 15th Hohenheimer Consensus Meeting, no “Evidence” was presented on any side effects that patients would have, following long-term use of the simple dosage in addition to complete, wholesome nutrition.
These recommendations also refer to the aspects of adjuvant (support) therapy. They can be changed differently and on an individual basis under the conditions of palliative (systematic care) therapy.

Conclusion

From a purely nutritional-medical viewpoint at this moment, for example, founded on the opinion of the WCRF/AICR, the American Cancer Society or DACH, a complete wholesome nutrition that is based on vegetable foods – meaning rich in vegetables, fruit and whole grain products, is one of the preventive lifestyle factors, with respect to cancer illnesses (for other aspects see also: "European Codex for Cancer Prevention")

This same type of nutrition is valid and recommended also in the case of cancer illness or during the time of treatment. In a broad sense, and for the record, findings on vitamin amounts within food taken during cancer illness have not been definitely clarified. Some uncertainties remain.

Nevertheless, for all those who are concerned by this, a statement should be made. Therefore, if due to the disease or treatment nourishment is limited, the nutrient supply can be supported by supplementing. According to our judgment on this and being based on the discussion above, as well as to our level of knowledge, the justifiable dosage is at the level of the simple reference values for daily nutrient intake (Tab. 1), while covering the time periods of 3 weeks before, until 3 weeks after chemotherapy or radiotherapy.

After this time span (safety interval), the dosage can be increased, following chemotherapy from the convalescence point of view; also up to the doubling of the reference values. This assessment makes reference to the safety considerations as well as to the risk considerations, since an actual benefit from this higher dosage has not been proven in randomized studies up until now.

We encourage patients to inform their treating physician about their intake of nutrient supplements or to discuss this matter so that a comprehensive therapy concept can be jointly taken into consideration; based on the ideas of both patient and doctor, in partnership.

***

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Table 1: International Upper Reference Levels of Nutrients, Reference Value for Suggested Amounts of Nutrients and Percentages in Selected Supplements (a selection)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Suggested / Estimated Daily Nutrient Intake</th>
<th>Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin</td>
<td>For Healthy Adults 21-50 years old</td>
<td>allisan Multi-Vitamin ABC 25 (1 Tablet) Burgerstein Multi-Vitamin-Mineral ABC 14 (1 Tablet) careimmun (1 Capsule) Hermes Multivitamin (1 Tablet) Orthomol immum (1 ampoule, to drink)</td>
</tr>
<tr>
<td>Highest Recommended Daily Nutritional Amount</td>
<td>NOAEL NOAEL</td>
<td>100 % RDA 100 % RDA 100 % RDA 100 % RDA</td>
</tr>
<tr>
<td>3 mg</td>
<td>6.5 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td>2000 mg</td>
<td>1000 mg</td>
<td>200 mg / Smokers 150 mg</td>
</tr>
<tr>
<td>1000 mg</td>
<td>800 mg</td>
<td>(12-14 mg α-TA)</td>
</tr>
<tr>
<td>-</td>
<td>50 mg</td>
<td>B₁</td>
</tr>
<tr>
<td>-</td>
<td>200 mg</td>
<td>B₂</td>
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<tr>
<td>35 mg</td>
<td>1500 mg</td>
<td>500 mg</td>
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<tr>
<td>-</td>
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<td>100 mg</td>
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<td>-</td>
<td>3000 µg</td>
<td>B₁₂</td>
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<tr>
<td>50 µg</td>
<td>50 µg</td>
<td>20 µg</td>
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<tr>
<td>1000 µg</td>
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<tr>
<td>Vitaminoids</td>
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<tr>
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</tr>
<tr>
<td>Trace Elements</td>
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<td>45 mg</td>
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<tr>
<td>-</td>
<td>-</td>
<td>1000 µg</td>
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<tr>
<td>10 mg</td>
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<tr>
<td>11 mg</td>
<td>-</td>
<td>10 mg</td>
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<tr>
<td>2 mg</td>
<td>-</td>
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<td>910 µg</td>
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<td>60 mg</td>
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<td>Secondary Plant Substances</td>
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appendix
Table 2: Antioxidants as Nutritional Supplements that Can Change the Effects of Chemotherapeuticals

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Chemotherapeuticals</th>
<th>Active Ingredients</th>
<th>Effect Mechanism / Effect Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Substances, whose effect is based on oxygen compounds</td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Busulfan, Chlorambucil, Ifosfamide</td>
<td>Reactive oxygen compounds formed; which could be transformed by antioxidants</td>
<td></td>
</tr>
<tr>
<td>Q Enzyme 10, α-Tocopherol</td>
<td>Anthracycline (Antibiotics)</td>
<td>Doxorubicin, Daunorubicin, Idarubicin Epirubicin</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Mitomycin, Bleomycin, Streptozocin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant Alkaloids</td>
<td>Epipodophyllotoxin</td>
<td>Etoposide, Teniposide</td>
<td></td>
</tr>
</tbody>
</table>

| A, B6, C, β-Carotene | Antimetabolite | Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine |
| Plant Alkaloids | Vincristine, Vinblastine, Vindesin |
| Plant Alkaloids | Taxane | Paclitaxel, Docetaxel |

Other Nutrients

| Folic Acid | Methotrexate | Methotrexate works by intervening in the folic acid alteration. Supplementing of folic acid or food that is enriched with folic acid and thus exceeding the reference level, could lead to contrary effects |

Table 3: Antioxidants Used as Medicine to Diminish the (Organ Specific) Side Effects of Chemotherapy

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Chemotherapeuticals</th>
<th>Active Ingredients</th>
<th>Effect Mechanism/Effect Hypothesis of Antioxidants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna</td>
<td>Alkylating Agents</td>
<td>Ifosfamide, Cyclophosphamide</td>
<td>Mesna in the body metabolizes to Mesna-Disulfide, this interacts with Metabolite Acrolein, and through it reduces the toxicity of alkylating substances; fast renal elimination without reducing effects</td>
</tr>
<tr>
<td>Amifostine</td>
<td>Cisplatin</td>
<td>Protection against Cisplatin's induced renal damage Also approved for use in the prevention of secondary xerostomia through radiation of tumors in the head and neck</td>
<td></td>
</tr>
</tbody>
</table>

appendix