The use of antioxidant vitamin supplements among oncological patients

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D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online)

Adv Clin Exp Med. 2018;27(10):1365–1369

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Funding sources

None declared

Conflict of interest

None declared

Received on October 26, 2016

Reviewed on January 19, 2017

Accepted on March 30, 2017

Abstract

Background. Dietary supplementation is becoming more and more common among both healthy and unhealthy people. The use of supplements is often unjustified, though in some groups of patients it is a necessary management for providing the required vitamins and minerals.

Objectives. The aim of the study was to assess the frequency of using antioxidant vitamin supplements (A, C and E) among the patients of the oncology ward.

Material and methods. The study group included 78 patients aged 19–83 years. The dietary intake of vitamins as well as the intake of supplements was assessed based on the data from the Food Frequency Questionnaire (FFQ).

Results. It was observed that 46.2% of patients used some kind of a dietary supplement and 77.8% of them used antioxidant vitamins. Among those taking vitamin A, C or E supplements, 72.2% of women and 80% of men used multivitamins. It was reported that the average fulfillment of the recommended daily intake for vitamin A was $303 \pm 136\%$, for vitamin C it was $282 \pm 166\%$ and for vitamin E it was $199 \pm 80\%$. More than 25% of the patients whose diets contained at least the same level of vitamins as dietary recommendations were using antioxidant vitamin supplements at the same time.

Conclusions. Although the average dietary intake of antioxidant vitamins among the patients was not insufficient, the use of dietary supplements in different forms was common in our study. The results of other studies concerning the safety of using dietary supplements by cancer patients are not conclusive. Dietary supplementation in oncological patients should always be used after a medical consultation with a doctor and a dietician.

Key words: cancer, oxidative stress, antioxidant vitamins, supplementation

DOI

10.17219/acem/70030

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Introduction

A tumor is an abnormal mass of tissue that has the capacity for proliferation and unregulated growth. It can develop anywhere in the body and can spread to other organs. Cancer is the leading cause of death worldwide, accounting for 8.2 million deaths in 2012. The mortality rate of the disease in Poland is 150 deaths per 100,000 people.¹

Although some studies have found that the use of selected supplemental vitamins and minerals decreased the risk of cancer, other studies did not confirm such a relationship or they even demonstrated the opposite effect.^{2–4} It is further noted that the use of β -carotene supplementation was associated with an increased risk of carcinogenesis in heavy smokers.⁵ Thus, the mechanism of action of the individual substances is complex and may depend both on the origin of the dietary component and on other risk factors for cancer.

Antioxidants are compounds that interact with and neutralize reactive oxygen species (ROS). The balance between the production of ROS and the mechanism of action of antioxidant defense is essential to maintaining homeostasis in the body. The most common dietary antioxidants include vitamins A, C and E, and polyphenols. Antioxidant deficiency may contribute to the development of diseases resulting from the action of ROS, such as cancer, cardiovascular diseases, neurodegenerative diseases, and diabetes. Due to the ability of antioxidants to regulate the cell cycle and to limit DNA damage, studies on their potential use in cancer treatment have been carried out.⁶

Supplementation as a form of adjuvant therapy in cancer is common in oncological patients. Boon et al. showed that patients with breast cancer most commonly supplemented vitamin C and vitamin E in the form of pharmaceutical preparations.⁷ Patients used complementary therapy to alleviate the symptoms of the disease and to improve their health. Such activities are often made without their doctor's knowledge, and the recommendations come from forums and untested websites.

The aim of the study was to assess the use of antioxidant vitamin supplements (A, C and E) among the patients of the oncology ward and to discuss the efficacy and safety of using those dietary supplements in cancer therapy.

Material and methods

The study group included 78 patients (48 women and 30 men) from the Department of Clinical Oncology, Wrocław Medical University, Poland, aged 19–83 years (59.6 ± 11.3 years) and diagnosed with cancer. Nearly 1 in 4 participants was hospitalized due to colorectal cancer and in every other woman, breast cancer was diagnosed. Other patients were diagnosed with lymphoma, bladder, ovarian, prostate, kidney, pancreatic, liver, lung, urinary tract, or testicular cancer (Table 1).

Table 1. The incidence of various types of cancers in the study population

Type of cancer	Overall, n = 78		Women, n = 48		Men, n = 30	
	n	%	n	%	n	%
Colorectal cancer	30	38.5	15	31.2	15	50.0
Breast cancer	23	29.5	23	47.9	0	0.0
Other cancers	25	32.0	10	20.9	15	50.0

The dietary intake of antioxidant vitamins (A, C and E) and supplements as well as the period of their use was assessed based on the data from the Food Frequency Questionnaire (FFQ). The questionnaire is a checklist of 154 food items classified into 8 groups: milk and dairy products; fruits; vegetables; meat and eggs; cereal products; mixed dishes; beverages; and snacks. The frequency of consumption was related to the preceding year and was reported as 1 of 9 different categories (0–1/month; 1–3/month; 1/week; 2–4/week; 5–6/week; 1/day; 2–3/day; 4–5/day; >5/day). The portion sizes of the consumed foods were determined by using the “Album of Photographs of Food Products and Dishes” [in Polish].⁸ The food intake in g/day was calculated based on the consumption frequency and the given portion size. The average content of each antioxidant vitamin in daily food rations (DFR) was estimated using the database of the Food and Nutrition Institute from 2008 and was compared to the Polish recommendations from 2012.^{9,10} The analysis of antioxidant vitamin content in DFR was rated at the level of Recommended Dietary Allowances (RDA) or, for vitamin E, at the level of Adequate Intake (AI).

The results of the study were analyzed statistically using STATISTICA v. 12.0 PL software (StatSoft Inc., Tulsa, USA). All statistical analyses were performed using the Shapiro-Wilk test, Student's t-test, the Mann-Whitney U test, and the χ^2 test. The level of statistical significance was set at $\alpha = 0.05$.

The study was approved by the Bioethics Committee of Wrocław Medical University, Poland (No. KB – 362/2014).

Results

The use of dietary supplements was declared by 46.2% (n = 36) of patients, of whom 77.8% were taking antioxidant vitamin supplements. The latter were chosen by oncological patients significantly more often than other vitamin or mineral supplements. Among the patients taking antioxidant vitamin supplements, multivitamins were used by 72.2% of women and 80% of men, while vitamin C supplements were used by 33.3% of women and 50.0% of men. Vitamin E and A supplements were used only by women (11.1% and 5.6%, respectively) (Fig. 1).

Nearly half of the study group using antioxidant vitamins were patients with colorectal cancer. The frequency of the use of supplements containing antioxidant

Fig. 1. The intake of selected antioxidant vitamin supplements in the group of women ($n = 18$) and men ($n = 10$) who declared using antioxidant supplements

vitamins among people with colorectal cancer was similar in the group of women and men. Moreover, there was no statistically significant difference between the intake of vitamin A, C or E supplements or multivitamins and gender and the type of cancer. The percentage of patients taking antioxidant vitamins was comparable in the group of patients using supplements for less than 1 year and those who supplemented their diet for more than 1 year.

Table 2 demonstrates the average daily dietary intake of antioxidant vitamins and the fulfillment of the recommended intake of these components. The estimated daily antioxidant vitamin content in the diet was similar in the group of men and women. The average fulfillment of the recommended daily intake for vitamin A was $303\% \pm 136\%$, for vitamin C it was $282\% \pm 166\%$ and for vitamin E it was $199\% \pm 80\%$. In the group of women, the average fulfillment of the recommendation for vitamin A was significantly higher than in the group of men. It was demonstrated that the intake of vitamins A, C and E was at least at the same level as the recommended level ($\geq 90\%$ of daily requirement) among 97.4% of the patients, 94.9% of the patients and 96.2% of the patients, respectively (Fig. 2).

Overall, antioxidant vitamin supplements were used by 36% ($n = 28$) of the participants. More than 25% of the patients who fulfilled their requirements for vitamins A and E used antioxidant vitamin supplements at the same time. The supplements of vitamin C were used by 1/3 of the respondents who fulfilled their recommended daily intake for this vitamin.

Discussion

According to the American Institute for Cancer Research (AICR), there is no sufficient evidence to assess the safety of using dietary supplements in cancer. Particular caution is advised when using dietary supplements with antioxidant properties. Recommendations of AICR allow the use of moderate amounts of multivitamins, at a dose which does exceed the recommended Dietary Reference Intakes in order to complement the daily intake of these nutrients.¹¹

Despite this, the use of dietary supplements by patients who have been diagnosed with cancer is common. In a systematic review of 32 studies, Velicer and Ulrich reported that 64–81% of the patients used vitamin or mineral supplements, and 26–77% used multivitamins.¹² There were statistically significant differences in the frequency of dietary supplement use depending on the type of cancer, gender and education level of the participants.

The majority of the diets of the study participants were not insufficient in the analyzed nutrients. Despite the fact that the dietary intake of antioxidant vitamins A, C and E fulfilled the RDA, this group of supplements was the most frequently used by the subjects. Taking antioxidant supplements cannot be explained by a lack of the adequate dietary intake of those vitamins.

Vitamin A is a group of chemical compounds called retinoids. The most common retinoid in animal food sources is retinol, whereas in plant-based foods it is β -carotene.

Fig. 2. The percentage of diet with antioxidant vitamin intake below (<90%), at (90–110%) and above (>110%) the dietary recommendation

Table 2. Mean dietary intake of antioxidant vitamins in the study population and the fulfillment of the recommended intake [%] of these compounds

Nutrient	Women, $n = 48$	Fulfillment of the recommended intake [%] (A)	Men, $n = 30$	Fulfillment of the recommended intake [%] (B)	A vs B p-value
	$\bar{x} \pm SD$		$\bar{x} \pm SD$		
Vitamin A [μg]	2301.6 ± 1050.8	328.8 ± 150.1	2359.4 ± 901.9	262.2 ± 100.2	0.03
Vitamin C [mg]	230.9 ± 140.3	307.8 ± 187.0	217.1 ± 103.8	241.2 ± 15.4	ns
Vitamin E [mg]	16.8 ± 6.4	209.7 ± 79.9	18.2 ± 7.9	181.7 ± 79.4	ns

$\bar{x} \pm SD$ – mean $\pm$ standard deviation (SD); ns – no statistically significant differences in the fulfillment of the recommendation between gender groups.

Dietary supplements may contain different forms of vitamin A, such as retinol, retinyl palmitate, retinyl acetate, and β -carotene.¹³

Koay et al. revealed that retinoids in conjunction with trastuzumab or tamoxifen, drugs used in the treatment of breast cancer, inhibited cell growth and induced apoptosis.¹⁴ However, Jiménez-Lara et al. showed that 9-cis-retinoic acid inhibited the apoptosis of breast cancer cells in the presence of anticancer drugs, such as doxorubicin, etoposide and camptothecin.¹⁵ The probable mechanism of action of retinoids was the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), an anti-apoptotic agent.

Vitamin E is common in a variety of food products, like plant oils and margarines, nuts, milk, whole-grain foods, and leafy vegetables.⁹ In dietary supplements, vitamin E may occur in a few chemical forms, but the most common of them are d- α -tocopherol, d- α -tocopheryl acetate and d- α -tocopheryl succinate.¹³

The results of the study conducted by Li et al. showed that the potential anticancer properties of vitamin E varied depending on its chemical form.¹⁶ The authors observed a very weak ability of α -tocopherol to inhibit the promotion of lung cancer in comparison to δ -tocopherol.

In an experimental animal study, Takahashi et al. showed that δ -tocopherol inhibited the promotion of prostate cancer in proportion to the dose.¹⁷ The observed mechanism of action of vitamin E was the modulation of the activity of caspase-3 and caspase-7 – enzymes controlling apoptosis.

Vitamin C, or L-ascorbic acid, is a water-soluble vitamin. Its antioxidant properties are used to prevent the oxidation of food. Chemical forms of vitamin C used in dietary supplements are L-ascorbic acid, L-ascorbyl 6-palmitate, and sodium, magnesium, calcium, and zinc L-ascorbate.¹³

An intravenous infusion of high doses of vitamin C may cause the apoptosis of cancer cells. Uetaki et al. observed important changes in the metabolism of human MCF7 breast cancer and HT29 colon cancer cells after treatment with vitamin C.¹⁸ The vitamin concentration required to eliminate 50% of MCF-7 cells amounted to 2.3 mM, whereas for HT29 it was more than 10 mM. The cytotoxicity of vitamin C toward MCF-7 cells was inhibited in the presence of antioxidants – N-acetylcysteine and glutathione.

Frömberg et al. observed an improved sensibility of cancer cells treated with vitamin C toward anticancer drugs: docetaxel, epirubicin, irinotecan, and fluorouracil.¹⁹ However, Heaney et al. reported that vitamin C reduced the cytotoxicity of doxorubicin, cisplatin, methotrexate, and imatinib, through suppressing the depolarization of the cell membrane.²⁰

Padayatty et al. concluded that the results of studies concerning the effectiveness of vitamin C therapy in cancer treatment are not conclusive.²¹ What is more, their methodology varied depending on the route of administration

of the preparations. Vitamin C plasma concentration, after the administration of its maximum safe oral doses (3 g every 4 h), was dozens of times lower than after an intravenous injection of 50 g of ascorbate. Only the parenteral administration increased the concentration of vitamin C in the blood high enough to result in a possible anticancer action of this substance.

The reason for the rising interest in the possibility of using antioxidants in the treatment of cancer is the evidence-based role of ROS in carcinogenesis. Chronic oxidative stress may induce mutations in genetic material and is involved in the development of cancer. Increased ROS levels in cancer cells are thought to be the reason for tumor progression and for resistance to treatment with anticancer drugs.²² At the same time, it was shown that excessive amounts of ROS inhibited tumor growth and promoted apoptosis.²³ So if the mechanism of action of antioxidative agents is linked to ROS depletion, their use in cancer patients is highly questionable.

The safety of antioxidant vitamins in the form of dietary supplements remains highly controversial during radiotherapy and chemotherapy. Daily supplementation with 400 IU of α -tocopherol and 30 mg of β -carotene reduced the side effects of radiotherapy in head and neck cancer patients. However, the applied treatment has been found to be less effective, including an increase in mortality, among participants who received vitamin E.^{24,25} The results of the study conducted by Meyer et al. showed that taking antioxidant supplements is particularly unfavorable in smokers during radiotherapy.²⁶ The authors reported more than a 2-fold increased risk of all-cause mortality or recurrence as well as more than a 3-fold increased risk of death from cancer of the head or neck in smokers compared to nonsmokers.

On the other hand, Suhail et al. observed that oral supplementation of 500 mg of vitamin C and 400 mg of vitamin E was associated with lower levels of DNA damage in breast cancer patients during chemotherapy.²⁷ It may indicate the usefulness of these vitamins in reducing the side effects of treatment.

Moreover, Poole et al. reported a 16% reduced risk of death linked to the intake of multivitamins, vitamin E or vitamin C in a group of women who had completed breast cancer treatment.²⁸

The use of antioxidant vitamins might be beneficial in terminal patients for improving their quality of life. In the study conducted by Fuchs-Tarlovsky et al., the supplementation of antioxidant vitamins in patients with cervical cancer increased quality of life measured by the Quality of Life (QoL) scale.²⁹ It also decreased protein damage caused by oxidative stress. However, it had no effect on the increase in food intake by the participants of the study.

Summing up the possibility of the use of oral antioxidants as part of cancer treatment, Yasueda et al. reported that so far there has been no sufficient evidence

of the harmful effects of antioxidants on oncological patients.³⁰ The authors emphasized that the exception was tobacco smokers during radiotherapy. Based on scientific research, it is not possible to determine whether supplements influence the effectiveness of the applied cancer therapy or decrease the side effects of the treatment.

Conclusions

Patients participating in the study were hospitalized in the oncology ward during anticancer therapy or shortly before or after its termination. Although the diet of most patients contained adequate amounts of vitamins A, C and E, the use of antioxidant supplements was common. According to the current knowledge, antioxidant vitamin supplementation during anticancer treatment not only increases the effectiveness of therapy, but may even reduce it. Making the decision to use a complementary therapy alongside conventional medical treatment should always be supported by evidence in medicine, pharmacology and dietetics.

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