REVIEW CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS, INTERNATIONAL
EDITION 36(1): 5-10 (2022)
PUBLISHED BY PHARMAKON-Press

Dietary supplements: Innocent or potentially carcinogenic?

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Key words: dietary supplements, cancer, β-carotene, folic acid, PUFA.

Citation: E. Roumelioti, P. Karkalousos, M. Trapali. Dietary supplements: Innocent or potentially carcinogenic? Review Clin. Pharmacol. Pharmacokinet. 2022, 36,1, 5-10.

https://doi.org/10.5281/zenodo.10014142

Received: 02 April 2022
Accepted: 17 May 2022
Republished:17 October 2023

Publisher's Note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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SUMMARY: *Consumption of dietary supplements has increased in recent decades. Below, it is analyzed the conditions under which the dietary supplements and their ingredients have been associated with a possible increase in cancer risk and poor prognosis of the disease. The need for careful use of supplements and their safe administration, with a view to ensuring health by recognizing potential risks, is the ultimate goal of this work.*

INTRODUCTION

Dietary supplements, depending on their ingredients, can be categorized as: vitamins, trace elements, plant origins, amino acids and nutrients that increase the daily dietary intake such as enzymes and other extracts (6).

VITAMIN SUPPLEMENTS

Regarding vitamin supplements, *beta-carotene* supplements have not been found to support any protective effect against various types of cancer (15,26,37). On the contrary, their long-term intake has been linked to lung cancer, prostate cancer, while some findings also indicate a link with bladder cancer, which is still under investigation (1,15,26). The risk of lung cancer due to consumption of β-carotene supplements increases more in male smokers (8), especially for cell lung cancer (1). Long term daily consumption of β-carotene in doses of 20-30 mg increases the risk of lung cancer in male smokers. It is recommended that the daily doses should not exceed 7 mg (15). The form of β-carotene contained in supplements acts pro-

oxidizing in male smokers, increases oxidate stress levels and promotes development of toxic substances in tissues (26). High doses of β-carotene can affect pre-cancerous lesions and affect cell apoptosis (8).

Long -term administration of *vitamins B6 and B12* increases the risk of lung cancer in people who smoke or have been smokers (1,9). B12 supplements, also, increases the risk of adenocarcinoma and small cell lung cancer (17) and inhibit chemotherapy, especially for breast cancer patients (3). High doses of B6 and B12 are able to promote faster cell growth and ultimately lead to carcinogenesis (9). In general, it is stipulated that B6 should not exceed 20 mg while B12, 55 mg per day (1).

Supplements that contain *vitamin E* have not been found to provide protection against cancer (34,37,46). In contrast, intake of vitamin E is likely to increase the risk of prostate cancer (31,33,46) and lung cancer, especially to women. Long term administration for more than ten years, at doses that exceed 215 mg per day, increases the risk of lung cancer (1). In addition, their use is not indicated during chemotherapy and radiotherapy as it could restore cellular oxidative damage to cancer cells (46). When it is consumed simultaneously with other supplements, such as vitamins A, C, β-carotene and coenzyme Q10, it could increase the risk of cancer recurrence (3).

Consumption of *folic acid* supplements increases the risk for any type of cancer (4), especially in cases with pre-existing cancer (30,37). Overdose of folic acid is able to deteriorate the progression of pre-existing cancers that may not yet be diagnosed (4,7,53). The most commonly associated cancers are prostate cancer (18,37,53), especially for men over the age of 57 years and with pre-cancerous lesions in the prostate. In the case of prostate cancer, the risk increases even more when daily long-term consumption of folic acid supplements ranging from 0.4-1 mg (53).

In addition, there is evidence that folic acid supplements can increase the risk of breast cancer in menopausal women who have taken very high doses of this supplement for a long period (37). Long-term doses higher than 400 μg per day showed an increase of risk for breast cancer (47). Moreover, folic acid supplements have not been observed that to offer any form of protection on colon cancer (37,47). On the contrary, in high concentration it may increase the risk of the disease (4,19,29,30). Consumption during chemotherapy treatment has been shown to possibly inhibit the effect of antiplatelet drugs and reduce the function of cytotoxic cells (19,21,30,47).

POLYUNSATURATED FATTY ACIDS

Dietary polyunsaturated fatty acids (PUFAs) are associated with increased risk of prostate cancer and higher mortality rate is observed after consumption of supplements containing *omega-3 fatty acids* than these with *omega-6-fatty acids* (10, 22). It has been found, also, that they are associated with other types of cancer, such as breast cancer, as well as to increase cancer mortality in general (22).

INORGANIC INGREDIENTS

Studies have found that some trace elements supplements, such as *selenium*, are not recommended for use as a chemoprotective factor against cancer (51) because, when administrated in high doses, they can act as pro-carcinogens in the body. The most commonly observed type of cancer that has been linked with trace elements supplements is prostate cancer (36). There is evidence that trace elements supplements increase the risk of high-grade malignancies, as they have been found to increase the risk of DNA damage, especially, in the prostate tissue (33).

Recent findings highlight the negative effect of *iron* supplementation during chemotherapy as regards to the outcome of the treatment. Iron supplements are able to both increase cancer mortality and possible recurrence of the disease, as iron is thought to play a very important role in tumor progression due to its effect on the microenvironment (3).

HERBAL SUPPLEMENTS

The most widely used herbal supplements with a link to cancer that have been identified as genotoxic carcinogens are those containing: pyrrolizidine alkaloids, alkenylbenzenes and aristolochic acids (44). *Supplements containing alkaloids* have been implicated in liver cell necrosis and liver cancer (40,41,50,52).

Alkenylbenzene supplements have also been associated with an increase in liver cancer (2,12,16,45,50). Supplements containing aristolochic acids are associated with the development of primary or secondary cancer (25,35,50). In particular, they increase the risk of urinary cancer (13) and renal cell carcinoma (5,11, 42). It causes a rare type of cancer with malignant lesions occurring in both the renal pelvis and upper ureter (39) while the International Agency for Research on Cancer (IARC) has placed aristolochic acids in the category of carcinogens (35,50).

Researches have shown that *coumarin supplement* consumption can increase the incidence of cancer in humans, but more research is needed due to their majority being conducted only to mice and not on human population (23). Coumarin supplements significantly increase the incidence of tumors in experimental animals. These tumors were detected, mainly, in cancer of kidneys, liver and cholangiocarcinoma in both male and female mice, while tumors in the lung and squamous cell carcinoma were found mainly in male rats (24). Although coumarin, under normal conditions, inhibits cell proliferation and causes apoptosis, in some cases it links to cell proliferation (23). That's why the German Federal Institute recommends that coumarin supplements should not exceed 0.1 mg per body weight (24).

It is argued by many scientists that *soy supplements* have benefits only in Asian population, in whom soy has already been introduced into their diet from a very early age, while women in the Western world may have a negative effect (28). Soy supplements have been linked to increased breast cancer risk (14,38,55). Isoflavones in soy supplements can affect the way breast mammalian epithelial cells proliferate in premenopausal women (55). Blood tests have shown that soy supplementation can affect premenopausal women, because the Ki-67 proliferation index, which is used to detect breast cancer, has been found to increase (28). Soy supplements may further elevate the risk of breast cancer in women with pre-existing history of breast cancer (49). In addition, soy supplements can affect chemotherapy, due to the diverse biological action of isoflavones (43), and how they associate with the risk of prostate cancer. So far, it has been found that soy supplements do not have a protective effect against prostate cancer (38).

Green tea supplements may interfere with cancer treatment when drugs with active substance bortezomib are used (20,27,54). French epigallocatechin-3(EGCG) contained in tea can reduce or even completely inhibit bortezomib protease (27,54). In particular, consumption of even 10 μM was able to inhibit the action of the active substance bortezomib (27). Also, green tea supplements are recommended to be avoided during radiotherapy as it can affect cell apoptosis, offering protection to cancer cells from ionizing radiation (48).

Conflicts of Interest: The authors declare no conflicts of interest.

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