www.srjhs.org

Sri Ramachandra Journal of Health Sciences

Review Article

Association between Vitamin A and cancer: A review

B. S. Niranjanaa Vani[1], V. Supriya[1]

[1]Department of clinical Nutrition, Sri Ramachandra Faculty of Allied Health Sciences, Sri Ramachandra Institute of Higher Education and Research (DU), Chennai, Tamil Nadu, India.

ABSTRACT

Vitamin A is a fat-soluble micronutrient vital for the immune system, cellular differentiation, epithelial barrier function, and eyesight; they also play a significant function as a potent antioxidant regulating oxidative stress and the onset of cancer. There are two ways to get it through food: Provitamin A (beta-carotenoid) and preformed Vitamin A (retinol and retinyl ester). Uncontrolled cell proliferation and the development of metastatic features are characteristics of cancer initiated by agents such as aflatoxin, tobacco smoke's carcinogenic compounds, and solar ultraviolet radiation. Vitamin A, an antioxidant vitamin, is hypothesized to exert chemo-preventive effects and reduce the risk of cancer by preventing tissue damage through the capture of organic free radicals, an end-product of numerous metabolic processes. This review is performed to investigate the association between Vitamin A and cancer. From March 2017 to March 2022, relevant articles were searched through PubMed, Science Direct, and Google Scholar databases. All the studies involving Vitamin A and cancer were included in this review. Intake of Vitamin A was significantly inversely associated with improved cancer prognosis. The present review demonstrates that there is an inverse association between Vitamin A and cancer treatment.

Keywords: Vitamin A, Cancer, Review, Retinol, Retinoic acid

INTRODUCTION

Vitamin A includes a variety of fat-soluble compounds, including beta-carotene, retinol, and retinyl palmitate acquired by diet in the following forms: Preformed Vitamin A (retinol and retinyl ester)- meat, dairy products, and fish and Provitamin A (beta-carotenoid) – colorful fruits and vegetables.[1,2] Cancer is characterized by the proliferation of cells that evade central endogenous control mechanisms.[3] Antioxidants such as Vitamin A have been used in the treatment of cancer as they have cytotoxic effects, and decreases cancer risk by preventing tissue damage. Yet the efficacy and safety of using antioxidants while addressing cancer treatment is not familiar. Hence, this study aims to investigate that Vitamin A, with its antioxidant properties, can alleviate the risk of cancer by preventing tissue damage caused by free radicals, which are by-products of various metabolic functions and are implicated in cancer development and summarizes Vitamin A's preventive and therapeutic functions in the management of cancer.

METHODS

A search was performed of the databases: PubMed, ScienceDirect, and Google Scholar using terms related to Vitamin A and cancer with applying time restriction of five years from March 2017 to March 2022. Studies utilizing the terms related to cancer such as neoplasms/prevention and control, chemoprevention, tumor suppressor genes, oncogenes, prostatic neoplasms/genetics, breast neoplasms, leukemia, antineoplastic agents, neoadjuvant chemotherapy (CT), radiotherapy, chemo-radiotherapy, adverse effects, prostatic/cervical/pancreatic neoplasms, leukemia, myeloid, acute, sarcoma, and multiple myeloma and studies involving all forms of Vitamin A and it's terms such as Vitamin A/deficiency, antioxidants/therapeutic use, chemoprevention, retinol/metabolism, retinoic acid receptors (RARs), dietary supplements, treatment outcome, free radicals, Vitamin A absorption, metabolism, deficiency, retinol-binding proteins, drug-related side effects, adverse reactions, safety, and toxicity were searched using AND/OR and included in this review.

The study uses a broad search method, using a variety of terms associated with both Vitamin A and cancer and databases such as PubMed, ScienceDirect, and Google Scholar. The review's thorough and comprehensive search approach, which covers a wide range of Vitamin A and cancer-related phrases, is one of its strong points. This detailed method will yield a wide range of investigations, offering a solid basis for the compilation and evaluation of the data.

***Corresponding author:** V. Supriya, Associate Professor, Department of Clinical Nutrition, Sri Ramachandra Faculty of Allied Health Sciences, Sri Ramachandra Institute of Higher Education and Research (DU), Chennai, Tamil Nadu, India. supriya.v@sriramachandra.edu.in

Received: 03 April 2023 **Accepted:** 04 December 2023 **Published:** 04 January 2024 **DOI:** 10.25259/SRJHS_13_2023

Inclusion criteria

This review included all forms of Vitamin A and all types of cancer-related research publications, clinical studies, clinical trials, and cohort studies published between March 2017 and March 2022 on PubMed, ScienceDirect, and Google Scholar.

Exclusion criteria

Studies from different timelines involving any other vitamins or nutrients and other disease types are excluded in this review.

RESULTS

Vitamin A is found as a Provitamin like β-carotene in vegetables. The three oxidation states of Vitamin A are retinal, retinol, and retinoic acid. While retinoic acid is important for bone remodeling, reproductive biology, and epithelial tissue homeostasis, the retinal plays a major role in vision. Although retinoic acid is not stored in our bodies, retinol and retinal are stored. Vitamin A is essential for vision, epithelial barrier function, immune function, and differentiation of cells. After being absorbed, ingested forms of Vitamin A must be transformed into retinal and retinoic acid to support biological processes. Esterification of retinol to retinyl esters occurs in the liver and is stored in the stellate cells. Retinol and β-carotene undergo oxidation in tissues to produce retinal and retinoic acid, which are crucial for gene regulation and vision, respectively. Then, to regulate gene expression, nuclear receptors belonging to the RAR family are bound by active metabolites. When needed, retinol, which is a stored Vitamin A, is released into the bloodstream. Retinol is present in the plasma bound to transthyretin and retinol-binding protein. Therefore, the patient's physiological state may be impacted by conditions such as protein shortage, liver disease, acute inflammation, or infection, which may, then, have an impact on the protein balance and Vitamin A status. Absorption and metabolism of Vitamin A can be impacted by gastrointestinal disorders, including but not limited to Crohn's disease, celiac disease, and pancreatic disorders.

Although cancer is the most difficult disease to treat, but due to technological advancements, early detection can dramatically increase the chances of both prevention and a cure. The majority of the time, uncontrolled cell cycle development and the deactivation of apoptotic mechanisms result from oncogenes activation and the deactivation of tumor suppressor genes. Cancers are classified according to the organ or tissue from which they originated as well as the molecular traits of the cancer cells. Since antioxidants such as Vitamin A have cytotoxic effects on cancer cells while sparing healthy cells, they have been utilized to cure cancer and reduce the negative effects of CT treatments. Vitamin A is hypothesized to exert chemo-preventive effects and reduce the risk of cancer by capturing organic free radicals and preventing tissue damage.

Serum Vitamin A levels were found to be reduced immediately after chemo-radiotherapy in cervical carcinoma patients. Decreased nutritional intake and increased oxidative stress cause depletion of serum Vitamin A before chemo-radiotherapy. The efficacy of chemo-radiotherapy causes a decrease in serum antioxidant levels in vitamins such A, C, and E. During follow-up, hike in serum Vitamin A was seen due to supplementation during treatment, absence of emesis, and increased food intake after chemo-radiotherapy.[4] In a study involving α-carotene and β-carotene, α-tocopherol, and γ-tocopherol, β-cryptoxanthin, lutein, lycopene, retinol, and selenium found no significant association with prostate cancer, a higher intake of α-carotene and β-carotene lowers the risk of breast cancer and other chronic diseases.[5,6]

Dose Vitamin A administration was not seen to be toxic but appeared to be safe in post-molar gestational trophoblastic neoplasia (GTN).[7] Anticancer drugs may also create adverse events as they treat cancers. Retinol palmitate expresses mutagenic, cytotoxic, and cell death in neoplastic cells without affecting the normal cells. However, Vitamin A supplementation with neoadjuvant CT causes a significant reduction of tumor size in cervical carcinomas.[8,9]

All-trans-retinoic acid (ATRA) in combination with oral arsenic trioxide (ATO) and CT is effective in decreasing relapses in newly diagnosed acute promyelocytic leukemia (APL) patients. A study found that ATRA-ATO CT sparing treatment regimen was suitable and cost-effective for treating low-risk pediatric APL patients. Another study found that ATRA along with daratumumab revealed limited activity in daratumumab-refractory multiple myeloma. ATRA, analogous to its effect in APL, improves acute myeloid leukemia (AML). There is a potential inhibition of lysine specific demethylase 1 (LSD1) by tranylcypromine (TCP) with ATRA in patients with relapsed/refractory AML. ATRA-responsive genes are enhanced by the addition of TCP in AML and myeloid dysplasia patients. By functioning as a de-repressor in ATRA-resistant AML cell lines, TCP increases ATRA sensitivity.[10-16]

Lycopene being an antioxidant expresses the protective action in cancer prevention. Several studies reported that there is an inverse correlation between lycopene and tomato intake and several types of cancers, such as stomach, colon, rectal, oral, breast, prostate, cervical, and bladder cancers. Moreover, it is also said that tomato and lycopene consumption decreases intracellular and mitochondrial reactive oxygen species, thereby decreasing cancer mortality.[17,18]

DISCUSSION

This review includes 15 studies totaling 8786 patients that satisfied the inclusion criteria. The results highlight the potential of Vitamin A, including its impact on serum levels during chemo-radiotherapy, its use in neoadjuvant CT, and its effectiveness in leukemia treatment and the studies involving

prostate cancer, α-carotene, β-carotene, lutein, lycopene, retinol, AML and promyelocytic leukemia, cervical cancer, pancreatic cancer, post molar pregnancies, retinol palmitate, sarcoma tumor, and multiple myeloma. Although Vitamin A is hypothesized to exert chemo-preventive effects, one study investigated the relationship between pre-diagnostic antioxidant levels in circulation and the risk of prostate cancer. The results showed no significant correlation between pre-diagnostic antioxidant levels and prostate cancer.

Some studies involving a form of Vitamin A called ATRA reveal that ATRA with a combination of various medications to treat cancer is safe, cost-effective, and feasible regimen to treat AML, APL, and relapsed/refractory myeloid dysplasia. Another study evaluating the blood levels of Vitamins A, E, and C during various stages of concurrent CT and radiation in cervical carcinoma infers that there is an antioxidant depletion that occurs due to the tumor cells' sequestration and scavenging of lipid peroxides; additionally, it shows the effectiveness of the treatment.[4,6,11,13-16]

When the effects of treating advanced cervical carcinoma with neoadjuvant CT and N-acetylcysteine + Vitamin A are compared, it can be seen that Vitamin A is given as tablets at a dose of 8.000 IU every 8 h from the beginning of the patient's first CT cycle to the beginning of their fourth CT cycle (64 weeks) significantly improves the patient's clinical response.[9]

The oral As2O3 induction cohort demonstrated a complete remission (CR) rate of 100% when the efficacy and safety of adding oral As2O3, 1 mg/mL solution at 10 mg/d, to frontline treatment with ATRA, 45 mg/m^2/d (in two divided doses), and CT for newly diagnosed APL were assessed. A median of 37 months passed with no relapses. The non-As2O3 induction cohort, however, had a 100% CR rate. However, following a median of 52 months, 3 relapses (8%) were noted. Due to this, adding oral As2O3 to the induction process for newly diagnosed APL was found to be safe and to reduce relapses.[10]

A study was carried out to assess the additional costs per quality-adjusted life-year gained from the ATO plus ATRA regimen compared with the ATRA plus CT regimen over a 30-year period, adjusting the cost levels based on the Chinese Consumer Price Index. This was done to assess the economic impact of the ATO plus ATRA strategy in treating newly diagnosed APL from the perspective of the Chinese health-care system. Furthermore, compared to the ATRA plus CT strategy, the ATO plus ATRA strategy is more economical for patients with recently diagnosed APL. Consequently, the authors strongly advise China's health authorities to select the earlier course of action for these patients, regardless of age.[12]

An analysis of lycopene's anti-cancerous properties on pancreatic cancer cells revealed that it reduced the levels of ROS within the cells and in the mitochondria and concluded that the supplementation of lycopene reduces the incidence of pancreatic cancer. Furthermore, it was found that higher tomato and lycopene consumption has decreased cancer death rates. In contrast, in another study, it was found that pre-diagnostic antioxidant levels do not protect from prostate cancer.[5,17,18]

Seven hundred and thirty-four patients were administered with an increased-dose Vitamin A 200,000 IU/daily following the first normal serum human chorionic gonadotropin (hCG) value (<5 IU/L) to the point at which serum hCG levels plateaued in patients with low and plateauing (L and P) serum hCG levels during post-molar follow-up found that high-dose vitamin-A treatment for post-molar patients with low and plateauing serum hCG levels appears to be safe and effective, and it has been reported to reduce the development of post-molar GTN in this population. The population under study tolerated Vitamin A use well, and the few side effects that did occur were temporary, like dry skin, which went away when the medication was stopped.[7]

Retinol palmitate was evaluated for the counteracting effects on toxicogenic damage caused by some medications such as cyclophosphamide and doxorubicin,where the results suggested that retinol palmitate reduced the action of anti-neoplastics in non-tumor cells and mutagenic, cytotoxic, and apoptosis in neoplastic cells.[8]

Therefore, this review sheds light on the therapeutic and preventive functions of Vitamin A in the management of cancer, as well as the effectiveness and safety of using antioxidants during cancer treatment. Since this review revolves around a particular time frame, further systematic reviews can be done as the research progresses.

Data collected only from PubMed, ScienceDirect, and Google Scholar databases and the choice of the five-year timeframe may introduce bias, as it excludes relevant studies conducted before March 2017. Given that the development of scientific knowledge is an ongoing process, future reviews can include studies from other databases and in different timelines.

CONCLUSION

When taken in pharmacological doses, Vitamin A reduces the risk of tumor development. It has been demonstrated that retinoids, both natural and synthetic, can inhibit the growth and development of various tumor types, including cancers of the skin, breast, mouth, lung, hepatic, gastrointestinal tract, prostatic, and bladder. They can also act as chemotherapeutic agents for these tumor types.

Cancer is a major global health concern, and understanding potential preventive measures are crucial. Research revealed a negative relationship between Vitamin A intake and the development of cancer. When taken in pharmacological doses, Vitamin A reduces the risk of tumor development. It has been demonstrated that retinoids, both natural and synthetic, can inhibit the growth and development of various tumor types, including cancers of the skin, breast,

mouth, lung, hepatic, gastrointestinal tract, prostatic, and bladder. They can also act as chemotherapeutic agents for these tumor types. The review establishes a clear association between Vitamin A and a decreased risk of cancer, its substantial implications for public health strategies, dietary recommendations, and cancer prevention initiatives.

Understanding the impact of Vitamin A on cancer treatment, as discussed in the review, is crucial for managing potential side effects and optimizing treatment outcomes. This information can be valuable for oncologists and healthcare professionals in tailoring treatment plans for better patient outcomes. The study briefly touches on economic considerations, indicating the potential cost-effectiveness of certain treatment strategies involving Vitamin A. This aspect is important for healthcare systems and policymakers in allocating resources and designing cancer management protocols. The findings of this study could inform clinical practice, particularly in the realm of cancer treatment. If Vitamin A is demonstrated to be effective in reducing the incidence or improving the prognosis of certain cancers, it may influence treatment protocols and contribute to the development of complementary therapeutic approaches. The study's outcomes may provide valuable information for individuals seeking guidance on dietary choices and supplements to reduce their cancer risk. This can empower patients to make informed decisions about their lifestyle and potentially contribute to cancer prevention strategies.

This study contributes to the existing body of scientific knowledge by synthesizing and analyzing evidence from multiple studies. The review identifies areas where further research is warranted. This creates a roadmap for future investigations, allowing researchers to address gaps in knowledge, refine methodologies, and explore new avenues in understanding the relationship between Vitamin A and cancer.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Chea EP, Lopez MJ, Milstein H. Vitamin A. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
2. Kim JA, Jang JH, Lee SY. An updated comprehensive review on vitamin A and carotenoids in breast cancer: Mechanisms, Genetics, assessment, current evidence, and future clinical implications. Nutrients 2021;13:3162.
3. Sarkar S, Horn G, Moulton K, Oza A, Byler S, Kokolus S, *et al*. Cancer development, progression, and therapy: An epigenetic overview. Int J Mol Sci 2013;14:21087-113.
4. Shrivastava A, Pradhan S, Mishra SP, Asthana AK, Choudhary S, Zahra K, *et al*. Serum vitamin A, E and C status in cervical cancer patients undergoing Concurrent Chemo-Radiotherapy, an institutional study. J Nutr Intermed Metab 2019;18:100107.
5. Graff RE, Judson G, Ahearn TU, Fiorentino M, Loda M, Giovannucci EL, *et al*. Circulating antioxidant levels and risk of prostate cancer by TMPRSS2:ERG. Prostate 2017;77:647-53.
6. Prentice RL, Pettinger M, Neuhouser ML, Tinker LF, Huang Y, Zheng C, *et al*. Application of blood concentration biomarkers in nutritional epidemiology: Example of carotenoid and tocopherol intake in relation to chronic disease risk. Am J Clin Nutr 2019;109:1189-96.
7. Uberti EM, Diaz RK, Cardoso RB, Braga A. Evaluation of high-dose vitamin A treatment in post molar patients with low and plateauing serum human chorionic gonadotropin levels. Rev Bras Ginecol Obstet 2020;42:240-7.
8. de Carvalho RM, de Alencar MV, da Mata AM, de Lima RM, de Aguiar RP, Teixeira JS, *et al*. Retinol palmitate against toxicogenic damages of antineoplastic drugs on normal and tumour cells. Chem Biol Interact 2020;330:109219.
9. Sanusi RS. Outcome of combined neoadjuvant chemotherapy and vitamin A in advanced cervical carcinoma: A randomized double-blind clinical trial. Asian Pac J Cancer Prev 2019;20:2213-8.
10. Gill H, Kumana CR, Yim R, Hwang YY, Chan TS, Yip SF, *et al*. Oral arsenic trioxide incorporation into frontline treatment with all-trans retinoic acid and chemotherapy in newly diagnosed acute promyelocytic leukemia: A 5-year prospective study. Cancer 2019;125:3001-12.
11. Zhang L, Zou Y, Chen Y, Guo Y, Yang W, Chen X, *et al*. Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: A randomized controlled trial. BMC Cancer 2018;18:374.
12. Chen X, Hong Y, Zheng P, You X, Feng J, Huang Z, *et al*. The economic research of arsenic trioxide for the treatment of newly diagnosed acute promyelocytic leukemia in China. Cancer 2020;126:311-21.
13. Frerichs KA, Minnema MC, Levin MD, Broijil A, Bos GM, Kersten MJ, *et al*. Efficacy and safety of daratumumab combined with all-trans retinoic acid in relapsed/refractory multiple myeloma. Blood Adv 2021;5:5128-39.
14. Redner RL, Beumer JH, Kropf P, Agha M, Boyiadzis M, Dorritie K, *et al*. A Phase 1 study of dasatinib plus all-trans retinoic acid in acute myeloid leukemia. Leuk Lymphoma 2018;59:2595-601.
15. Wass M, Gollner S, Besenbeck B, Schlenk RF, Mundmann P, Gothert JR, *et al*. A proof of concept phase I/II pilot trial of LSD1 inhibition by tranylcypromine combined with ATRA in refractory/relapsed AML patients not eligible for intensive therapy. Leukemia 2021;35:701-11.
16. Tayari MM, Santos HG, Kwon D, Bradley TJ, Thomassen A, Chen C, *et al*. Clinical responsiveness to All-trans Retinoic Acid is potentiated by LSD1 inhibition and associated with a quiescent transcriptome in myeloid malignancies. Clin Cancer Res 2021;27:1893-903.
17. Mazidi M, Ferns GA, Banach M. A high consumption of tomato and lycopene is associated with a lower risk of cancer mortality: Results from a multi-ethnic cohort. Public Health Nutr 2020;23:1569-75.
18. Jeong Y, Lim JW, Kim H. Lycopene inhibits reactive oxygen species-mediated NF-κB signaling and induces apoptosis in pancreatic cancer cells. Nutrients 2019;11:762.

How to cite this article: Niranjanaa VBS, Supriya V. Association between Vitamin A and cancer: A review. Sri Ramachandra J Health Sci. 2023;3:42-5. doi: 10.25259/SRJHS_13_2023