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Vitamin A – potential anticancer weapon

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ABSTRACT

Introduction:

Vitamin A, one of the most popular vitamins that people usually associate with eye health or beautiful skin, also has many other functions and uses. Recently many scientists conducted studies to determine if vitamin A could be a new weapon against cancers.

Aim of the study:

The aim of the study was to discuss recent findings regarding the impact of Vitamin A and other retinoids on potential applications in anticancer therapy.

Materials and methods:

This review of studies is based on scientific articles available in PubMed and Google Scholar databases. The names of the cancers were juxtaposed with term "Vitamin A" and with term "Retinoids" to gather data regarding the effect of retinoids on cancer treatment and prevention.

Results:

After analyzing the gathered publications, it is possible to conclude that retinoids can have a positive impact on cancer treatment. Some of them can induce apoptosis of cancer cells and others can reduce their proliferation. Moreover, retinoids can also play an important role in preventing cancers, such as ovarian, breast, cervical, or skin cancer. The role of retinoids in the prevention of prostate cancer remains unclear due to conflicting research results.

Conclusion:

The studies have shown promising results which indicate a need for further research into anticancer mechanisms of retinoids. Specifically, more research is needed to explore the positive impact of retinoid use in treating cancer diseases. The significant potential of retinoids may make it possible to include them in clinical practice and develop an effective therapeutic strategy for cancer treatment based on them.

Keywords: vitamin A; all-trans-retinoic acid (ATRA); retinoids; cancer; carotenoids

INTRODUCTION

It has been approximately 111 years since the discovery of vitamin A in the year 1913 [i]. This discovery marked a significant milestone in the field of nutrition and health, as vitamin A is an essential nutrient for human health, playing a vital role in vision, immune function, and growth and development. The discovery of this nutrient opened up new avenues for research and development in the field of nutrition, leading to the discovery of many other essential vitamins and minerals that are crucial for human health. Today, the importance of vitamin A in maintaining good health cannot be overstated, and it continues to be an area of active research and investigation. Vitamin A is a lipid-soluble compound essential for the proper functioning of the human body. It is supplied in the diet as preformed vitamin A (retinol and retinyl esters) which occurs in foods from animal sources, including dairy products, fish, eggs, and meat. The second source is provitamin A carotenoids, plant pigments contained mainly in yellow and orange fruits as well as in red and green vegetables. After consumption and absorption, both forms must be transformed into active metabolites - retinal and retinoic acid. They are formed in the oxidation process. These active metabolites can bind nuclear receptors of the RAR family and regulate gene expression [ii]. Retinoids have been found to have antineoplastic properties which are linked to the RAR inhibition gene transcription of activating proteins. Some studies have shown that retinoids have an effect on genes that control cell death, and vitamin A may have a protective effect against certain types of cancer. Additionally, retinol has been found to play a role in regulating cell growth. ATRA promotes cell differentiation by activating transcription factors, but it also inhibits a set of proteins involved in cell development and triggers cellular apoptosis. The impact of carotenoids on cancer is less clear, although they are well-known antioxidants with potentially positive effects in cardiovascular diseases and type II diabetes mellitus [3].

PURPOSE OF THE STUDY

The purpose of this study is to conduct in-depth research on the potential impact of Vitamin A on the development and occurrence of cancer. We also focus on the importance of Vitamin A, its overall functions, and the consequences of both its deficiency and overdose. The objective of this work is to establish a scientific foundation for further expanding our understanding of the anti-cancer mechanisms of Vitamin A and its derivatives and to explore new potential therapeutic methods for combating cancer through its use.

METHODOLOGY

The purpose of this research was to explore the potential of vitamin A and other retinoids in preventing or treating four types of cancer: prostate, skin, ovarian, and cervical. In pursuit of

our goal, an extensive review of the pertinent literature was conducted. The following are the research questions that have been formulated:

1. What is the anticancer effect of retinoids?
2. If retinoids have an impact on the treatment and prevention of skin cancer?
3. If retinoids have an impact on the treatment and prevention of cervical cancer?
4. If retinoids have an impact on the treatment and prevention of prostate cancer?
5. If retinoids have an impact on the treatment and prevention of ovarian cancer?
6. If retinoids have an impact on the treatment and prevention of breast cancer?

The search process was conducted separately by all researchers. All of them were searching until they gathered sufficient relevant material. After that, all researchers started the review of collected material to determine whether the papers met the inclusion criteria and whether the gathered data was adequate to fulfill the study's objectives. Once the initial search phase was completed, all authors agreed that the compiled material was sufficient.

After that, all researchers reviewed the accumulated material and evaluated the gathered data to determine if it met the study's objectives and inclusion criteria. Subsequently, all researchers carried out the data extraction process by analyzing the materials relevant to each research question. They identified key information and compared their findings. In case there were any discrepancies, they discussed until they reached a consensus.

THE STATE OF KNOWLEDGE

Chemistry

Vitamin A is a fat-soluble compound necessary for the organism's proper functioning. Carotenes and retinoids possess an activity of vitamin A. All vitamin A forms have a similar structure and may be classified as retinoids. These consist of an isoprenoid tail, a β-ionone ring, and a polar end-group which can be different: a carboxylic group in retinoic acid, a hydroxyl, in retinol, and an aldehyde in retinal. The retinoids belong to the four generations groups, and their common feature is a structure composed of four isoprenoid units. The first one is of natural origin and contains tretinoin (ATRA), retinol, retinal, alitretinoin, and isotretinoin. The second-generation group (acitretin, etretinate), third-generation retinoids (tazarotene, bexarotene, adapalene), and fourth (trifarotene) are synthetic derivatives developed from the first generation.

Retinol is a storage form of vitamin A. It is supplied in the diet in free form or as retinyl esters. Retinal is produced by the oxidation of retinol in the target cell. Retinoic acid is the most active biological form of vitamin A and is formed as a consequence of the oxidation of retinal [iii,iv,v].

Carotenoids are colorful from yellow to orange, liposoluble pigments, synthesized by the merge of two C20 geranylgeranyl diphosphate molecules. Whole of them have a polyisoprenoid structure. Carotenoids divide into non-provitamin and provitamin A including α-carotene, β-carotene, and β-cryptoxanthin [vi,vii]. β-carotene is the most important precursor of vitamin A, during oxidation it forms two retinal molecules [viii].

Sources of Vitamin A

Supplementation of vitamin A with diet is essential because the human body is not able to synthesize it. Lipids can be produced from over 50 dietary carotenoid precursors [ix]. The most common in the diet is β-carotene, which is found mainly in orange and red vegetables (red pepper, tomato, carrot, pumpkins, sweet tomato). Other sources are yellow, orange, or red fruits (apricot, mango, dates, red grapefruit, papaya) as well as green vegetables (spinach, parsley, onion leaf, leek, lettuce, broccoli). β-cryptoxanthin is mostly ingested through omnifarious citruses (tangerines, mandarins, oranges, mineolas, and clementines) [x]. These carotenoids also have been taken from various herbs, plants, vegetable oils, and cereals.

The most important source of vitamin A is retinol and its esters, which are found in animal-origin products: meat, fish, eggs, and milk. The retinol content in milk increases in proportion to its fat content. The high vitamin A levels are noticed in the livers of marine fish [3].

Vitamin A biological functions

Vitamin A is a vital micronutrient that plays a crucial role in maintaining the health of various bodily functions. One of them is the appropriate functioning of the visual system, 11-cis-retinal is associated with a G-coupled protein receptor in the retina. Together, they form the complex known as rhodopsin - a pigment that plays a crucial role in light perception. When light stimulates the eye, 11-cis-retinal is converted to all-trans-retinal which triggers a series of reactions leading to the transmission of optic perceptions to the brain. A lack of retinol can lead to impaired low-light vision due to the insufficient formation of rhodopsin [3,xi,xii,xiii,xiv,xv,xvi].

The second Vitamin A function is maintaining the structural integrity and function of the epithelium in various tissues. It promotes keratinocyte differentiation into mature epidermal cells. When the vitamin A level in the body is adequate some mucus-producing epithelial cells are stimulated. Changes in the balance of retinoids in the body can directly impact skin integrity. In Vitamin A deficiency in many tissues, keratin-producing cells replace cells that secrete mucus. The lack of mucous secretion leads to irritation and subsequent infection as the affected areas experience keratinization and stratification of the epithelium [3,xvii].

Vitamin A also plays a crucial role in gene regulation by interacting with nuclear receptors.

These receptors, after activation by ligands, can directly affect gene expression by interacting with DNA. Retinoids can interact with various nuclear receptor families. In 1987 scientists identified the first receptor that has a high affinity for retinoids. It was the retinoic acid receptor α. Since this breakthrough discovery, scientists have gained a better understanding of the mechanisms of certain retinoids' biological functions. From this time, additional receptors, known as retinoid receptors, have been identified that interact with retinoids. The main families of retinoid receptors are RAR and retinoid X receptor. Scientists also described a third retinoid-interacting nuclear receptor family - RAR-related orphan receptor. [3,xviii]

Vitamin A regulates various immune processes. It helps in the development of T helper cells and B cells, which are essential for adaptive immunity. It also contributes to the regeneration of mucosal epithelial cells and the functioning of neutrophils, macrophages, and natural killer cells, which are important components of innate immunity. A deficiency of vitamin A can impair normal immune function and increase the risk of infectious diseases [xix,3,xx].

Embryogenesis also requires the presence of retinoids to ensure proper growth and development. A low amount of vitamin A during pregnancy can cause birth defects that affect cardiovascular and nervous systems. Also, other tissues can be less developed. This condition is known as vitamin A deficiency syndrome [3,xxi].

Retinoids play a role in the process of meiotic entry. They play a crucial role in this process by interacting with nuclear receptors. Meiotic entry is indispensable for spermatogenesis and in gonadal differentiation during fetal development. Changes in factors involved in the process can have serious health consequences such as infertility, sex development disorders, or even cancer formation [3,xxii,xxiii,xxiv].

The skeletal system also needs an adequate level of retinoids to maintain proper functioning. Tesfaye et al. conducted a meta-analysis to investigate the effect of β -carotene on fracture risk. They considered 9 peer-reviewed studies involving 190 545 men and women. They proved that dietary intake of β-carotene at a dose of (1,76-14,3 mg/day) was connected with a 12% reduction in the risk of fractures. They found that higher intake of β -carotene was also associated with a lower risk of hip fracture. A meta-analysis showed an inverse relationship between β -carotene intake and the risk of fractures in case-control studies and prospective cohort studies. In addition, they found a lower risk of fractures in women compared to men in the case of high β -carotene intake. A diet rich in vitamin A can be useful for bone health and prevent fractures [xxv].

Feng et al. conducted a study explaining the effect of β- carotene on bone resorption. For this purpose, they exposed monocytes/macrophages from the bone marrow (BMM) to various

doses of β -carotene. In this study, they established that β-carotene inhibits osteoclastogenesis and resorption by weakening the NF-κB pathway activated by RANKL. At dose 0,4 i 0,6 μM, it increases LDH secretion and reduces BMM survival [xxvi].

Dosage and administration

Vitamin A can be supplemented orally or intramuscularly. Fatty meals increase its absorption [xxvii]. Vitamin A requirement is recommended at approximately 1 mg per day. The range for plasma concertation is from 10 μg/dl to 100 μg/dl [xxviii].

RAE are retinol activity equivalents that enable the conversion of various forms of retinol and carotenoids. 1 μg RAE is equivalent to 24 μg dietary β-cryptoxanthin or α-carotene, 12 μg dietary β-carotene, 2 μg supplemental β-carotene or 1 μg retinol.

Recommended Dietary Allowance (RDA) for Vitamin A is 400 μg/day RAE from birth to 6 months, 500 μg/day RAE from 7 to 12 months, 300 μg/day RAE from 1 to 3 years of age, 400 μg/day RAE from 4 to 8 years of age, 600 μg/day RAE from 9 to 13 years of age, 900 μg/day RAE for male from 14 years of age, 700 μg/day RAE for female from 14 years of age, 750 to 770 μg/day RAE for pregnant women and 1200 to 1300 μg/day RAE for lactating [xxix,xxx].

Hypervitaminosis

Ingesting preformed vitamin A is essential for maintaining good health, but it's important to understand the risks associated with excessive consumption. Hypervitaminosis A, a condition caused by elevated levels of this essential vitamin in the body, can lead to acute and chronic toxicity. Excessive supplementation, rather than consuming large amounts of vitamin A-rich products, may lead to hypervitaminosis A [xxxi].

Acute toxicity is rare and occurs when someone takes more than 100,000 RAE in a short time. The symptoms of acute toxicity can range from nausea, vomiting, irritability, headache, blurred vision, dizziness, and problems with coordination to more severe symptoms such as increased intracranial pressure. Vitamin A toxicity can also cause mucocutaneous effects such as erythema, dry skin, itching, and peeling of the palms [21,xxxii].

Chronic vitamin A toxicity results from excessive ingestion of vitamin A exceeding 8000 RAE per day. The symptoms are dry and cracked skin, yellowing of the skin, photosensitivity, alopecia, subcutaneous swelling, loss of appetite, fatigue, anemia headache, and bone pain [21]. Neil et al. reported in their review study that high vitamin A intake causes reduced bone formation and increases bone resorption. Additionally, it causes bone pain, and radiographic changes and may lead to osteoporosis and fractures [xxxiii].

Chronic ingestion of high doses of vitamin A for 1 to 8 years can result in portal hypertension, ascites, and esophageal varices, even without frank cirrhosis [xxxiv]. Elevated levels of serum

transaminases in the blood are common laboratory abnormalities. Hypertriglyceridemia is another laboratory abnormality that can occur with oral retinoids. Drugs, such as bexarotene, isotretinoin, etretinate, and acitretin, can increase low-density lipoprotein, total cholesterol, and triglyceride levels [31].

Antonio et al. described a clinical case of vitamin A overdose. The patient came to the emergency room with a headache, abdominal pain, and nausea. In the following days, skin peeling became visible. The patient was taking 200,000 IU of retinol and 50 mg of dl-alpha tocopherol acetate daily for acne and skin redness. Due to the interview, it was decided to measure the serum retinol level. In the laboratory test, the retinol level was 435 μg/dL. A complete blood count revealed mild thrombocytopenia and anemia. Biochemical tests showed increased levels of liver enzymes and serum calcium. After Four days of discontinuing retinoids, tests were performed and the retinol level was 78 μg/dL, clinical symptoms except skin peeling disappeared, and the laboratory tests returned to normal [xxxv].

Silverio et al. Illustrate in their study case report of a 3-month-old boy admitted to the Department of Pediatrics, 2nd University of Naples. The reason for hospitalization was severe anemia and thrombocytopenia for further diagnostics. Physical examination of the patient revealed pale, itchy skin, hepatosplenomegaly, tachycardia with systolic heart murmurs, and a bulging anterior fontanelle. A medical interview revealed that the infant had been taking an aqueous solution of vitamin A palmitate in too high doses since the 10th day of his life. The total daily intake of vitamin A was about 62,000 IU. Higher levels of unbound retinol resulted in elevated levels of retinyl esters and a raised retinol/retinol-binding protein ratio. Bone marrow biopsies showed that the suspension of vitamin A intake and bone marrow recovery are closely related in time. Siverio et al. study aimed to investigate the association between hypervitaminosis A and anemia/thrombocytopenia by conducting in vitro experiments on cellular models. Their findings indicate that retinol at concertation similar to the dose achieved in vivo during chronic vitamin intoxication hindered the proliferation of a multipotent hematopoietic cell line. It was observed that vitamin A led to the accumulation of two key inhibitors of cyclin-dependent kinases. Based on the findings, it was concluded that the blockage of the cell cycle primarily occurred at the S→G2 phase transition, as evidenced by the observed up-regulation of cyclin A and E contents [xxxvi].

Hypervitaminosis is especially dangerous during pregnancy. As we mentioned before, Vitamin A plays a crucial role in the regulation of gene expression and directing cell differentiation during the development of an embryo. The first trimester of pregnancy, marked by rapid organogenesis, is a particularly vulnerable period for the embryo as excessive

amounts of vitamin A can have teratogenic effects which could be associated with various disabilities that affect the central nervous system, for example microcephaly and hydrocephalus. High doses of Vitamin A during pregnancy could also cause cardiac issues, like transposition of the great vessels. Limb deformities, craniofacial abnormalities, or disorders of the urinary tract are other undesirable effects that may occur. It's important to note that teratogenic effects are not usually associated with dietary sources of vitamin A. Retinoid Medications are most often responsible for this complication [xxxvii,xxxviii].

THE INFLUENCE OF VITAMIN A AND ITS DERIVATIVES ON CANCER:

Vitamin A has been shown to produce cellular and tissue changes similar to those found during neoplastic transformation. Consequently, vitamin A supplementation has been identified as a potential measure for cancer prevention. Specifically, in populations with vitamin A deficiency due to inadequate dietary intake or tobacco use, supplementation programs have been effective in reducing cancer incidence. However, in groups with sufficient dietary or supplemental vitamin A, cancer prevention by added vitamin A may not be particularly effective. This is likely due to feedback mechanisms that increase retinol storage in the liver, thereby limiting retinol plasma levels. Notably, β -carotene, along with other dietary carotenoids, also serves as a metabolic source of retinol and functions as an antioxidant that can prevent carcinogenesis by decreasing levels of free radicals that cause DNA damage [xxxix].

The activity of retinoic acid (RA) is mediated largely by the retinoic acid receptor (RAR) subfamily, comprising RARα, RARβ, and RARγ, which are members of the nuclear receptor (NR) superfamily of transcription factors. RARs form heterodimers with members of the retinoid X receptor (RXR) subfamily and act as ligand-regulated transcription factors by binding to specific RA response elements (RAREs) located in the promoters of target genes. RARs also exert non-genomic effects and activate kinase signaling pathways, which fine-tune the transcription of RA target genes. The disruption of RA signaling pathways is believed to be responsible for the etiology of several hematological and non-hematological malignancies, such as leukemias, skin cancer, head cancer, neck cancer, breast cancer, lung cancer, renal cancer, prostate cancer, ovarian cell carcinoma, pancreatic cancer, liver cancer, neuroblastoma, and glioblastoma. Notably, RA and its derivatives (retinoids) are used as potential chemotherapeutic or chemopreventive agents due to their differentiation, anti-proliferative, pro-apoptotic, and antioxidant effects. In humans, retinoids reverse premalignant epithelial lesions and induce the differentiation of normal and leukemic myeloid cells [xl].

Notably natural retinoids exhibit chemotherapeutic qualities in the treatment of acute

promyelocytic leukemia (APL), which is characterized by the reciprocal translocation of the long arms of chromosomes 15 and 17 [t(15;17)]. One of the primary therapeutic mechanisms for APL cells is the degradation of the fusion product induced by all-trans retinoic acid (ATRA). The post-maturation apoptosis of APL-blasts is triggered by high concentrations of ATRA through the induction of the tumor-selective death ligand TNF-related apoptosis-inducing ligand [xli].

Xiaoyong et al. conducted a meta-analysis of 49 studies, comprising 29 on breast cancer, 10 on ovarian cancer, and 10 on cervical cancer. The studies included 38 case-control studies, with 25,363 cases and 42,281 controls, and 11 cohort studies, which followed up on 1,334,176 individuals, among whom 9496 cancer cases were recorded. Subgroup analyses were conducted based on cancer type, diet or supplements, serum or plasma, study type, and geographic regions. Studies have shown that an increase in dietary consumption of vitamin A or supplements in Asian and North American populations may potentially lower the incidence of three types of cancers in women. The findings suggest that breast and ovarian cancers could be particularly affected by this dietary change. However, high circulating vitamin A concentrations were not significantly associated with the incidence of the three malignancies. The findings suggest that moderate increases in dietary vitamin A intake or supplements may be beneficial in preventing the development of certain cancers among high-risk groups [xlii].

Ovarian cancer

Ovarian cancer is most commonly diagnosed in women between the ages of 40 and 70 years. The risk of developing ovarian cancer is higher in women who have never given birth and in those who have a family history of ovarian cancer. However, the risk can be decreased in women who have given at least one birth and those who use hormonal contraceptives. The cause of most ovarian cancer is still unknown. Approximately 12% of cases of ovarian cancer are associated with familial congenital ovarian cancer syndrome, breast cancer, and ovarian cancer (due to mutations in the breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2)), or Lynch syndrome. Malignant ovarian tumors are mainly derived from the epithelium covering the ovary, which accounts for about 90% of such tumors. The remaining 10% of malignant ovarian tumors are caused by cancer from germ cells and sexual cords. Epithelial neoplasms are differentiated based on their type, including the most common serous type and others: mucinous, clear cell, endometrioid, mixed, and undifferentiated neoplasms [xliii, xliv, xlv].

In the meta-analysis by Wang et al., the researchers investigated vitamin A intake in the diet and the risk of ovarian cancer. In the study, 15 articles were considered involving 443,179

participants and 4882 cases. Researchers have proven that dietary vitamin A may be associated with a lower incidence of ovarian cancer, mainly in North America [xlvi].

Ko-Hui et al. Investigated the relationship between the consumption of supplements and micronutrients on the risk of ovarian cancer. A case-control study was carried out in Hawaii and Los Angeles. The results showed β -carotene and vitamin A intake was moderately associated with a reduced risk of cancer. An increase in the intake of vitamin A and β -carotene had an inverse gradient with the risk of ovarian cancer, especially among women who did not drink alcohol, smoked, and had the mucinous type of cancer. Additionally, a positive trend of increased β-cryptoxanthin consumption was noticed in terms of the risk of ovarian cancer among postmenopausal women, non-smokers, and those with non-mucinous cancer. The data put forward a position of retinoic acid signaling in oncogenesis [xlvii].

The objective of Stephan et al. was to investigate the early occurrence of loss of vitamin A metabolism in ovarian oncogenesis. To assess this, they examined CRBP1 expression in ovaries prophylactically removed from women with a genetic predisposition to ovarian cancer. Additionally, they examined the ability of normal, immortalized but non-tumorigenic, and tumorigenic human ovarian epithelial cells to synthesize retinoic acid and retinaldehyde when challenged with a physiological dose of retinol. They also determined the expression levels of the retinoid-related genes, RARα, RXRα, CRABP2, CRABP1, RALDH2, and RALDH1 in these cells. It has been disclosed that there is a lack of CRBP1 expression in lesions that have the potential to develop into cancer, during prophylactic oophorectomies. Analysis of vitamin A metabolism showed the production of retinoic acid in four independent, normal human ovarian surface epithelial (HOSE) cell cultures upon exposure to retinol. All of the ovarian carcinoma cell lines failed to produce detectable retinoic acid as a result of the entire loss of RALDH2 function. The impaired conversion of retinol to retinoic acid in ovarian cancer cells, and decreased CRBP1 protein expression in prophylactic oophorectomies suggest a role in ovarian oncogenesis [xlviii].

The study of Dusica et al. aimed to ascertain the clinical relevance of the downregulation of the retinol-binding protein 1 (CRBP1), which is involved in retinol transport and metabolism, to human ovarian cancer. To this end, a cohort of frozen human serous ovarian carcinomas was evaluated for CRBP1 gene expression. The findings revealed that in 35% of ovarian cancer patient samples, CRBP1 was not detectable. The expression of XCRBP1 in microdissected serous ovarian carcinomas did not show any significant correlation with either tumor stage ($P = 0.6839$) or grade ($P = 0.9599$). The results suggest that the loss of CRBP1 expression contributes to the oncogenesis of ovarian cancer through altered vitamin A

metabolism. The frequency of this loss did not show any statistically significant difference between tumor stages and grades, indicating that it is an early event in ovarian carcinogenesis [xlix].

Elena et al. Conducted that expression of Cellular Retinol-Binding Protein-1 (CRBP-1) was significantly reduced or absent in G2 and G3 ovarian carcinomas. Methylation of the CRBP-1 promoter was found to be the cause of CRBP-1 silencing in 60% of G2 and 66.7% of G3 carcinomas. The study demonstrated that CRBP-1-transfected cells exhibited increased retinol-induced apoptosis, reduced clonogenicity in response to retinoids, and down-regulation of proliferation and transcription genes, including AKT3, AKT1, FOS, JUN, EGFR, STAT1, and STAT5A. These findings suggest that the restoration of CRBP-1 expression may be a promising therapeutic approach for ovarian carcinoma [l].

Nooar et al. conducted a study to evaluate the impact of all-trans-retinoic acid (ATRA) treatment at concentrations of 1-5 μM on annexin A2 and S100A10 expression, plasmin activation, and ATRA's ability to impede the survival, motility, and invasion of serous ovarian cancer cells in vitro, as well as ex vivo tissue explant. The study revealed that ATRA treatment at concentrations of 1-5 μM significantly reduced the survival of serous ovarian cancer cells. Furthermore, treatment with 1 μM ATRA demonstrated a significant reduction in proliferation Ki67 positivity ($p = 0.0034$), S100A10 protein levels ($p = 0.0273$). There was also an increase in the number of cells that showed apoptosis cleaved caspase-3 positivity ($p = 0.0024$) in serous ovarian cancer tissues when tested using ex vivo tissue. The findings suggest that ATRA inhibits serous ovarian cancer proliferation and invasion through both S100A10 dependent and independent mechanisms. Moreover, the results of the study indicate ATRA's promising potential as a novel therapy against serous ovarian cancer [li].

Breast cancer

Breast cancer is the most prevalent form of cancer that affects women. Usually, the exact cause of this cancer is unknown. However, some risk factors increase the chances of developing breast cancer like age, genetics, family history of this cancer, use of exogenous sex hormones, early onset of menstruation and late menopause, alcohol abuse, and exposure to ionizing radiation.

Breast cancer is typically asymptomatic in its early stages. There are two main types of non-invasive breast cancers, which are called lobular in situ and intraductal. In addition, there are also infiltrating breast cancers, which are further divided into infiltrating cancers with no special type and infiltrating cancers with special characteristics [lii, liii, liv].

The study conducted by Sowmya et al. aimed to assess the anti-cancer mechanism of β-carotene on human breast cancer cells at a concentration of 1 μM. The results showed that β-carotene inhibited the cell viability in a dose-dependent manner. The cells treated with β-carotene (1 μM) showed an increased number of apoptotic cells, which was associated with the activation of caspase-3. Moreover, β-carotene at a concentration of 1 μM effectively reduced the expression of anti-apoptotic and survival proteins, Bcl-2 and PARP, respectively, along with the inhibition of activation of intracellular growth signaling proteins, Akt and ERK1/2. Additionally, β-carotene down-regulated the endoplasmic reticulum (ER) stress marker, XBP-1 as well as the expression of the antioxidant enzyme, SOD-2, and its transactivation factor (Nrf-2) [lv].

A study was conducted by Eliassen et al. to examine the impact of carotenoid exposure timing on breast tumor subtypes. The study was conducted on a large group of women who donated blood samples between 1989 and 1990. In 2000-2002, a second blood sample was taken from these women. Between the first blood sample collection and 2010, 2188 cases of breast cancer were diagnosed and matched with control subjects. The study found that higher concentrations of α-carotene, lycopene, β-carotene, and total carotenoids were associated with a lower risk of breast cancer by 18-28%. The associations were found for total carotenoids measured both more than and less than 10 years before diagnosis. The study also found that carotenoid concentrations were inversely associated with breast cancer recurrence and death, compared with not recurrent and non-lethal disease [lvi].

Adriana Zanetti et al. found that all-trans-retinoic acid (ATRA) possesses antimetastatic properties by acting on the TGFβ and NOTCH pathways, which regulate the epithelial-to-mesenchymal transition in breast cancer cells [lvii].

A study conducted by Ana Carla Castro-Guijarro and her team revealed that resistance to retinoid acid (RA) could indicate the malfunctioning of RA-targeted genes, including those that encode components of the Src-FAK pathway. The study also demonstrated that RA plays a crucial role in inhibiting the growth and spreading of breast cancer tumors both in vitro and in vivo by controlling focal adhesion kinase (FAK) expression and localization. Additionally, the combination of RA and focal adhesion kinase inhibitors (FAKi) further enhances the effects, indicating that the sensitivity to RA therapies could be improved by co-administering FAKi in breast cancer tumors [lviii].

Kevin Cohen et al. Conducted a study whose purpose was to investigate the link between plasma carotenoids, micronutrients found in vegetables and fruits, and the risk of premalignant breast disease among younger women. In this case-control study of mainly

premenopausal women, they found a possible association between higher plasma β-cryptoxanthin and a lower risk of premalignant breast disease. Specifically, the risk of premalignant breast disease was 38% lower in the highest tertile compared to the lowest [lix].

Formelli et al. conducted a prospective study to investigate the long-term prognostic significance of retinol levels in plasma in a cohort of women who had undergone menopause and had been diagnosed with breast cancer. They discovered that patients with breast cancer with low retinol levels in plasma had a lower overall survival rate than those with higher levels [lx].

Retinoids and cervical cancer

Based on current data cervical cancer is the fourth most common cancer in women globally. The most common cause of this cancer, detected in about 95 percent of cases, is HPV infection [lxi]. It is important to note that most HPV infections are transient and mainly do not lead to long-term health problems. However, persistent oncogenic infections can increase the risk of developing cervical dysplasia and cancer. It is important to note that infection by itself is not enough to cause a disease. Some Cofactors like nutritional factors are required for viral progression to cancer [lxii].

Rebecca L. Sedjo et al. compared women with persistent and intermittent HPV infections to study the role of carotenoids and Vitamin A on HPV persistence. They found that Consuming higher levels of vegetables, which are the major dietary sources of carotenoids, can significantly decrease the risk of HPV persistence by 54% and that women with the highest plasma cis-lycopene (one of the carotenoids) concentrations had a 56% lower risk of HPV persistence as compared to women with the lowest plasma cis-lycopene concentrations. These results suggest that more vitamin A sources in your diet and circulating cis-lycopene may help protect against HPV persistence, which is a major risk factor for cervical cancer [62].

In a study conducted by R. W. Harris et al. on 32 women with invasive cervical cancer and 81 with pre-invasive disease, the concentrations of retinol and β -carotene were measured in serum samples and then compared with samples from 226 age-matched control women. The findings of the study revealed that there was no significant difference in retinol levels between patients with cervical cancer and the control group. Concentrations of serum β -carotene were also found to be similar between patients with invasive cervical cancer and the control group. However, a noticeable decrease in β -carotene levels was observed in women diagnosed with pre-invasive disease in comparison with the control group. This decrease was more prominent in women with carcinoma-in-situ than in patients with severe dysplasia. There is an inversely proportional relationship between β -carotene levels and the risk of pre-invasive disease. This

trend has borderline significance [lxiii].

A study by Rodolfo et al. investigated the effect of vitamin A deficiency (VAD) on cervical carcinogenesis in the presence of HR-HPV oncoproteins. To evaluate the potential role of VAD in the development of malignant cervical lesions, transgenic mice expressing E6 or E7 oncoproteins were used. The survival of mice in a VAD condition was studied by detecting molecular cancer markers such as the tumor suppressor retinoic acid receptor beta (RARβ), proliferating cell nuclear antigen (PCNA), cleaved caspase 3, and the tumor suppressor protein (inhibitor of CDK4). The findings showed that VAD mice with expression of the E6 oncoprotein exhibited moderate cervical dysplasia; however, those with E7 expression in VAD mice developed severe cervical dysplasia and cervical in situ carcinoma at an early age [lxiv].

Skin Cancer

According to the World Health Organization (WHO), skin cancers are the most common group of cancers diagnosed worldwide [lxv]. It is a serious condition that occurs when abnormal cells in the outermost layer of the skin (epidermis) grow uncontrollably due to DNA damage. This damage leads to mutations, which cause the skin cells to multiply rapidly and form malignant tumors. The domain of skin cancer is characterized by four principal types, namely basal cell carcinoma, squamous cell carcinoma, melanoma, and Merkel cell carcinoma [lxvi,lxvii].

In the 1990s Thomas E. Moon et al. conducted two randomized clinical trials. They studied the effect of retinoids on skin cancer prevention. In one of these trials, participants had a history of 10 or more actinic keratoses and two or fewer previous skin cancers. High-risk patients who had four or more skin cancers in the past took part in the second trial. In both studies, participants received retinoids or a placebo each day. The results of the trials show that retinol can help lower the risk of developing a first squamous cell skin cancer, but it doesn't appear to have any effect on the development of first basal cell skin cancers. Additionally, the use of retinoids doesn't seem to be significantly beneficial in preventing basal or squamous cell skin cancers in high-risk groups of patients. To sum up, daily use of retinol has been found to be effective in preventing the development of squamous cell cancers in individuals with moderate risk [lxviii]. Recently, in 2019, other researchers decided to address this issue again. Jongwoo Kim et al. studied the association between Vitamin A intake and reduced risk of cutaneous squamous cell carcinoma. In this study of 75,170 women and 48,400 men in the US, they found that a higher total intake of vitamin A was linked to a reduced risk of cSCC. The follow-up period was longer than 26 years [lxix].

Ehsan et al. conducted a case-control study wherein they categorized the patients into a group with newly diagnosed basal cell carcinoma of the skin and a control group. Their findings demonstrated a significant decrease in the concentrations of retinol and α-tocopherol in subcutaneous tissue, as well as a reduction in retinol levels in serum among patients with newly diagnosed basal cell carcinoma [lxx].

Researchers are also looking for the possibility of using retinoids in the treatment of cancer. According to study by So et al., tazarotene shows promise in preventing basal cell carcinoma (BCC). The researchers found that applying a topical tazarotene gel effectively reduced the size and number of BCCs formed in mice exposed to UV or ionizing radiation. The study also tested the drug on a mouse model representative of NBCCS, where tazarotene was effective at reducing BCC formation even five months after stopping the treatment. In addition, So et al. revealed that topical 0.1% tazarotene was able to promote tumor regression in murine models of BCC, indicating some possible therapeutic benefits in humans [lxxi, lxxii].

Efrata and colleagues conducted a retrospective study on a cohort of 34 organ transplant patients who had a history of at least one keratinocyte skin cancer. They compared the number of new cases of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) before and after treatment with a low dose of acitretin (10 mg/day) for 2 years. The study revealed a significant reduction in the average number of new keratinocyte tumors during the treatment period compared to the pre-treatment period with acitretin [lxxiii].

Prostate cancer

Prostate cancer is a type of cancer that is becoming increasingly common in men, particularly in most developed nations. This rise in incidence is mainly caused by the spread of serum prostate-specific antigen testing in asymptomatic men, as well as greater health awareness among people. It's worth mentioning that the cancer rarely affects men younger than 40 years old, and the age of onset is typically above 70 years [lxxiv, lxxv, lxxvi].

Jeannette M. Schenk et al. Conducted a nested case-control study to investigate the potential link between serum retinol concentrations and prostate cancer risk. In their analysis, the researchers found that higher levels of serum retinol were associated with a reduced risk of aggressive prostate cancer, especially in cases of high-grade disease. It is worth emphasizing that this association was only observed in cases of aggressive disease [lxxvii].

Alison M. Mondul et al. also examined the correlation between serum retinol levels and the risk of prostate cancer, but their conclusions were completely different. Their study suggests that there is a positive correlation between higher serum retinol levels and an increased risk of prostate cancer. This correlation was observed for both aggressive and total prostate cancer.

Moreover, they claimed that individuals with sustained high exposure to retinol are at the greatest risk [lxxviii].

Wei Qi Loh et al. conducted in their study that higher concentrations of retinol and carotenoids were positively merged with prostate cancer risk [lxxix].

The exact biological mechanism by which higher levels of retinol in the body might increase prostate cancer risk is still unknown. However, some laboratory experiments have suggested that retinol may cause increased cell de-differentiation and proliferation, which could potentially contribute to the development of tumors. Another hypothesis says that retinol may affect the risk of prostate cancer by sex steroids or other cell-signaling changes [78].

Jianjun et al conducted a study to investigate the effect of vitamin A and vitamin D on the proliferation ratio of prostate cancer cells. The results showed that the inhibition of cell growth was both time and concentration dependent. Further analysis revealed that the treatment of vitamin A and vitamin D increased the proportion of apoptotic cells, which induced prostate cancer cell apoptosis. In addition, it is worth noting that the concomitant administration of vitamin A and vitamin D has been found to significantly enhance the expression of Bax, a protein involved in programmed cell death, and reduce the expression of Cyclin D1, a protein involved in cell cycle regulation. To conclude, the study suggests that vitamin D and vitamin A can work together to effectively induce apoptosis in prostate cancer cells [lxxx].

A study conducted by Jessica Ray et al. has reported higher miR-191 expression in tumor tissues compared to normal tissues, with increased expression in higher Gleason scores. Further in vitro and in vivo experiments have demonstrated that miR-191 overexpression contributes to a more aggressive phenotype, promoting radiation survival. A novel target of miR-191 has been found to be retinoid X receptor alpha (RXRA). Furthermore, research has shown that treatment with 9-cis-retinoic acid, an RXRA agonist, can restore the radiosensitivity of prostate cancer cells. Patients with high miR-191 and low RXRA abundance experienced a quicker biochemical recurrence, while reduced RXRA translated to a higher risk of distant failure after radiotherapy. These findings are significant and may aid in the development of new therapeutic approaches for prostate cancer [lxxxi].

Guoyu et al. showed that activation of RAR by agonists, including all trans retinoic acid (ATRA), targets the molecular basis of abnormal bone formation induced by metastatic prostate cancer. ATRA is a promising therapeutic agent for treating prostate cancer bone metastases [lxxxii].

The study conducted by Zhiwei et al. sheds light on a novel effect of all-trans retinoic acid

(ATRA) in inhibiting the growth of androgen receptor (AR−) resistant human prostate cancer cells. This is achieved through the alteration of HOXB13 expression, which results from epigenetic modifications. The findings suggest that ATRA has the potential to be a therapeutic agent for AR− resistant prostate cancer [lxxxiii].

CONCLUSION

It seems that vitamin A and β -carotene, when consumed in the diet, can reduce the risk of ovarian cancer, especially in women who do not smoke or drink and have a mucinous type of tumor. Several studies have also shown that a decrease in CRBP1 expression and impaired conversion of retinol to retinoic acid are important in the early development of cancer. ATRA has been shown to inhibit carcinogenesis in ovarian serous cancer and may be a promising novel therapy for ovarian cancer.

Research suggests that a diet rich in vitamin A and carotenoids can protect against HPV infection, which is the primary risk factor for cervical cancer. People with pre-invasive cancer generally have low β -carotene concentrations. Additionally, low levels of vitamin A can lead to the earlier development of carcinoma in situ during HPV infection.

Research studies have shown that individuals with higher concentrations of carotenoids have a lower risk of developing breast cancer. β -carotene has been found to induce apoptosis of breast cancer cells and inhibit proteins that signal tumor growth. Postmenopausal women diagnosed with breast cancer and having higher serum retinol concentrations have a better prognosis. Additionally, evidence suggests that ATRA has the potential to inhibit the growth and metastasis of breast cancer.

Studies have shown that regular use of retinoids can reduce the incidence of squamous cell skin cancer, as well as basal cell skin cancer. Research has also found that tazarotene can decrease the size of basal cell skin cancer in mice, which could potentially be applied to humans. In people who take oral acitretin, there is a lower risk of developing basal cell and squamous cell skin cancer.

Studies on the effect of serum concentrations of retinol and carotenoids on the risk of developing prostate cancer show conflicting data. Treatment of prostate cancer cells with RXRA agonist, 9-cis-retinoic acid, may restore sensitivity to radiation. ATRA is a promising therapy for prostate cancer especially with bone metastases and AR (-) prostate cancer.

There exists a pressing need to undertake further research and expand our understanding of the impact of carotenoids and retinoids on the development, treatment, and prevention of cancer. Notably, retinoids hold great therapeutic promise for the prevention and treatment of

cancer. It is therefore imperative that we delve deeper into the applications of retinoids to ascertain their role in the fight against cancer.

DISCLOSURE

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