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## INTRODUCTION

Carcinogenesis is a multistep process that transforms normal cells into malignant ones. The various steps involved are: (1) initiation, where DNA damage occurs; (2) promotion, where additional genetic mutations accumulate; and (3) progression to locally invasive or distant metastatic disease. It is believed that carcinogens produce “fields” of mutated cells long before invasive malignant disease develops; this is the fundamental basis for the concept of using medication to ‘prevent’ cancer. The phrase ‘cancer chemoprevention’ was used in the published literature for the first time by Sporn *et al.* in 1976.<sup>[1]</sup> Extensive epidemiological and clinical data support the role of retinoids as chemopreventive agents. Features which favour the use of retinoids for this purpose include the availability of adequate pharmacological data, experience and dose-response data, reasonably good safety profile, and a convenient dosing schedule and route of administration.

## MECHANISM OF RETINOID ACTION

The retinoids are natural and synthetic derivatives of vitamin A. Upon entry into cells, retinoids bind to cytosolic retinoid-binding proteins (retinoic acid-binding proteins and retinol-binding proteins). This complex then translocates to the nucleus where retinoids bind to nuclear retinoid receptors through their DNA-binding domains, thereby resulting in

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altered gene expression. Two classes of nuclear retinoid receptors are known: Retinoic acid receptors (RAR -  $\alpha$ ,  $\beta$ ,  $\gamma$ ) and retinoid X receptors (RXR -  $\alpha$ ,  $\beta$ ,  $\gamma$ ). Retinoic acid receptors (RAR) form heterodimers with retinoid X receptors (RXR); retinoid X receptors can additionally form heterodimers with vitamin D or thyroid hormone receptors, or form homodimers with other retinoid X receptors. Figure 1 provides a diagrammatic representation of the mechanism of action of retinoids.

## CLINICAL ACTIVITY OF RETINIDS AS CHEMOPREVENTIVE AGENTS

The role of retinoids in cancer prevention was first highlighted in 1925 when vitamin A was found to be required for epithelial cell homeostasis.<sup>[2]</sup> Rats rendered vitamin A-deficient developed squamous metaplasia at several epithelial sites. An inverse relationship exists between vitamin A levels and the

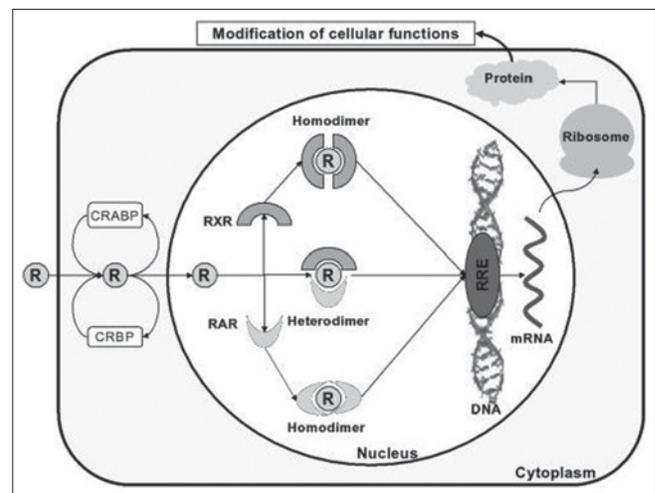


Figure 1: Mechanism of action of retinoids

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**How to cite this article:** Kaur S. Retinoids as chemopreventive agents. Indian J Dermatol Venereol Leprol 2016;82:59-64.

**Received:** January, 2015. **Accepted:** August, 2015.

Access this article online	
<b>Quick Response Code:</b>	<b>Website:</b> www.ijdvl.com
	<b>DOI:</b> 10.4103/0378-6323.168942

incidence of malignancies, which provides additional evidence in favor of this role of retinoids.

Clinical data reveals that retinoids are active in reducing some second primary cancers. For example, 13-cis-retinoic acid reduces second aerodigestive tract tumors in patients with resected head and neck cancers.<sup>[3]</sup> Retinoids are also used to treat overt malignancies, including acute promyelocytic leukemia, juvenile chronic myelogenous leukemia and mycosis fungoides.

Various precancerous and malignant conditions where retinoids have been tried either for prevention or treatment are listed in Table 1.

**RETINOID CHEMOPREVENTION MECHANISMS**

Experimental data suggests that retinoids act during the promotion and progression stages of carcinogenesis. Various mechanisms which contribute to their chemoprotective properties are:

- **Retinoid-induced proteolysis:** Retinoids cause cell cycle arrest in G1 phase via retinoid-dependent proteolysis of G1 cyclins D1 and E thus preventing phosphorylation of the retinoblastoma protein or other substrates.<sup>[4]</sup> This G1 cell cycle arrest allows repair of genomic damage caused by carcinogens  
In acute promyelocytic leukemia, retinoic acid induces degradation of the oncogenic protein, promyelocytic leukemia-retinoic acid receptor-α. This protein results from the balanced (15; 17) rearrangement and blocks myeloid differentiation

- **Epidermal growth factor receptor as a retinoid target:** Epidermal growth factor receptor is often over-expressed in malignancies. Epidermal growth factor receptor activation promotes cellular growth and transformation as well as produces other biological effects. Retinoids repress epidermal growth factor receptor expression through a transcriptional mechanism<sup>[5]</sup>
- **Induction of differentiation:** Tretinoin and other retinoids can induce differentiation in certain malignant cell lines in mice and humans, such as acute promyelocytic leukemia, histiocytic lymphoma, neuroblastoma and embryonal carcinoma. The carboxylic acid end group may be critical for this capability of retinoids because it is crucial for binding and activation of retinoic acid receptors<sup>[6]</sup>
- **Inhibition of proliferation:** In addition to differentiation induction, retinoids also have a direct anti-proliferative effect which is also linked to their carboxylic acid end group
- **Inhibition of ornithine decarboxylase:** Ornithine decarboxylase is the rate-limiting enzyme in the synthesis of polyamines (putrescine, spermidine, and spermine). Polyamines play important roles in stabilizing DNA structure and in the DNA double-strand break repair pathway; they also function as antioxidants. Thus, ornithine decarboxylase promotes cell growth and reduces apoptosis. Ornithine decarboxylase is a transcriptional target of the oncogene Myc and is upregulated in a wide variety of cancers.<sup>[7]</sup> Inhibitors of ornithine decarboxylase such as eflornithine have been shown to effectively reduce cancers in animal models.<sup>[8]</sup> Along with their direct effect on DNA

**Table 1: Malignancies where retinoids have been tried**

Various malignant and precancerous lesions where retinoids have been tried			
Cancer prevention		Treatment of precancerous lesions and malignancies	
Skin conditions	Non-cutaneous conditions	Skin conditions	Systemic conditions
Xeroderma pigmentosum	Superficial bladder tumors	Premalignant conditions	Premalignant conditions
Basal cell carcinoma	Second primary tumors in head and neck carcinoma	Actinic keratosis	Dysplasia and papillomatosis of larynx
Squamous cell carcinoma		Keratoderma	Bronchial metaplasia and dysplasia
		Epidermodysplasia verruciformis	Mammary dysplasia
		Oral leukoplakia	Cervical dysplasia
			Vulval dystrophy
			Bladder papillomas
			Myelodysplastic syndrome
Actinic keratoses		Treatment of cancers	Treatment of cancers
Keratoacanthoma		Basal cell carcinoma	Squamous carcinoma of head and neck area
Melanoma of skin		Squamous cell carcinoma	Non-small cell lung cancer
Epidermodysplasia verruciformis		Melanomas	Acute promyelocytic leukemia
		Cutaneous T-cell lymphoma	

stability, polyamines also upregulate gap junction genes and downregulate tight junction genes.<sup>[9]</sup> Gap junction genes are involved in communication between carcinogenic cells and tight junction genes act as tumor suppressors.<sup>[10]</sup> Retinoids block the induction of ornithine decarboxylase by tumor promoters.

- Other possible mechanisms of action may include immunomodulation and induction of apoptosis. Physiologic doses of retinoids also stimulate killer T-cell production and cell-mediated cytotoxicity which may well be crucial in the treatment of cancer.

### EFFICACY OF RETINOIDS AS CHEMOPREVENTIVE AGENTS IN DERMATOLOGY

The role of systemic retinoids in skin cancer prevention was first observed in xeroderma pigmentosum.<sup>[11]</sup> Shuttleworth *et al.* studied the efficacy of etretinate in preventing skin cancer in renal transplant recipients.<sup>[12]</sup> Although systemic retinoids are widely used in organ transplant recipients, only a few randomized controlled trials have been performed, with limitations, including small sample sizes.

In a prospective, open, randomized, cross-over trial, George *et al.* evaluated the efficacy of acitretin on non-melanoma skin cancer development in renal transplant recipients.<sup>[13]</sup> Acitretin (25 mg/day) was administered to 14 patients while nine patients received no therapy. Cross-over was done at 1 year. The number of squamous cell carcinomas observed in patients on acitretin was significantly lower than that in the drug-free period ( $P = 0.002$ ). A similar, yet not significant, trend was observed for basal cell carcinomas. A severe rebound in squamous cell carcinoma development occurred in one patient upon discontinuation of acitretin. Poor drug tolerability resulted in a high withdrawal rate.

In a randomized, controlled, open-label trial, 26 renal transplant recipients were assigned randomly to two different 1-year treatment protocols with acitretin.<sup>[14]</sup> Thirteen patients were treated with acitretin 0.4 mg/kg/day for a year and 13 patients received acitretin 0.4 mg/kg/day during the first 3 months followed by 0.2 mg/kg/day for the remaining 9 months. In both groups, the number of actinic keratoses decreased by nearly 50% but the number of new malignant tumors during the study year was similar to the pre-treatment period. The

frequency of mucocutaneous sideeffects resulted in significant dose reductions.

In a retrospective before-after study, Harwood *et al.* evaluated the efficacy of acitretin in the chemoprevention of squamous cell carcinomas.<sup>[15]</sup> A total of 32 organ transplant recipients received acitretin for 1–16 years. The number of squamous cell carcinomas developing annually during retinoid therapy was compared to the number of squamous cell carcinomas during the 12-month pre-treatment period. A statistically significant reduction in squamous cell carcinomas was noted in the first ( $P = 0.006$ ), second ( $P < 0.001$ ) and third ( $P = 0.02$ ) years after starting retinoids.

A brief summary of various other studies, highlighting the use of retinoids in cancer prevention and treatment is given in Table 2.

### FUTURE PROSPECTS

Non-classical retinoids that bind nuclear retinoid X receptors (also known as rexinoids) are yet to be studied extensively in cancer chemoprevention but have been examined in certain cancer therapeutic settings. Bexarotene, a selective retinoid X receptor agonist, is an active agent in cutaneous T-cell lymphoma and was approved by the Food and Drug Administration for the treatment of this disease.<sup>[54]</sup>

Some retinoids exert their effects through retinoid receptor-independent pathways. One example is N-(4-hydroxyphenyl) retinamide that can induce apoptosis in responsive cells including those resistant to classical retinoids due to retinoid nuclear receptor defects.<sup>[55]</sup> N-(4-hydroxyphenyl) retinamide triggers its biological effects in part through the generation of reactive oxygen species. It has reported activity in the prevention of second breast cancers.

B-Rapidly Accelerated Fibrosarcoma (BRAF) inhibitors have recently been approved by Food and Drug Administration for metastatic melanoma. The main toxicity associated with these agents is the development of hyperkeratotic lesions, in particular, squamous cell carcinomas. The use of acitretin in patients on selective BRAF inhibitors is recent but it seems to be effective in reducing the number of new benign hyperkeratotic lesions as well as malignant lesions such as squamous cell carcinomas.<sup>[56]</sup>

**Table 2: Retinoids in cancer prevention and treatment**

Indication	Patient number	Outcome	References
Actinic keratosis	105	43% showed complete response; 47% had partial resolution; 10% showed no response	[16-18]
Epidermodysplasia verruciformis	12	8% had complete resolution; 92% showed partial response	[19-23]
Keratoacanthoma	3	67% had complete response; 33% showed partial response	[24-26]
Squamous cell carcinoma	4	25%: Complete response; 25%: Partial response; 50%: No response	[16]
Basal cell carcinoma	40	7.5%: Complete response; 70%: Partial response; 22.5%: No response	[27]
Melanoma	20	10%: Partial response; 10%: No response; 75%: Progression	[28]
Cutaneous T-cell lymphoma	29	7%: Complete response; 38%: Partial response; 38%: No response	[29,30]
Oral leucoplakia	49	18%: Complete response; 70%: Incomplete resolution; 10%: Unchanged; 2%: Progression	[31,32]
Larynx dysplasia	42	67%: Complete resolution; 26%: Partial response; 7%: No response	[33]
Bronchial metaplasia	40	75%: Partial to complete response; 5%: No response; 20%: Progression	[34,35]
Bronchial dysplasia	3	All patients showed complete response	[36]
Myelodysplastic syndrome	69	6%: Complete response; 32%: Partial response; 62%: No improvement	[37-42]
Acute promyelocytic leukemia	228	85.5%: Complete response; 5.5%: Partial response; 9%: Progression	[43-53]

### CONCERNS REGARDING USE OF RETINOIDS AS CHEMOPREVENTIVE AGENTS

Concerns relating to the achievement of sufficient, non-toxic levels of retinoids in target tissues are justified because of their high affinity for multiple binding sites during absorption and their self-induced metabolism enroute to target sites. Several potential strategies have been suggested to address these issues. One is the use of retinoic acid metabolism-blocking agents and a second is using locally effective formulations (e.g. aerosol formulations for the lung) of the retinoid.<sup>[57]</sup>

Despite numerous studies dealing with retinoids in chemoprevention of non-melanoma skin cancer, precise details regarding the type of retinoid to use, dosage, duration and management of side effects have not been standardized. Moreover, the use of retinoids for chemoprevention is not approved by the Food and Drug Administration (FDA), USA and hence, no guidelines exist to regulate the same.<sup>[58]</sup>

However, Hardin and Mydlarski have suggested the use of low starting doses of acitretin (i.e., 10 mg/day) for the chemoprevention of secondary malignancies in organ transplant recipients. The dose of acitretin may be increased to 30 mg/day, depending on clinical response and drug tolerability. According to them, chemoprevention should be viewed as a lifelong therapy in organ transplant recipients as rebound flare occurs upon discontinuation of retinoids.<sup>[59]</sup>

### SIDE EFFECTS OF RETINOIDS

Since retinoids need to be used for long durations for prevention or treatment of skin or systemic cancers, it is important to be aware of their potential side effects. The various possible side effects are summarized in Table 3.

### MONITORING

- Baseline: History and examination to rule out any contraindication for the use of retinoids, serum pregnancy test, complete blood count with platelets, liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, bilirubin), fasting lipid profile (triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein cholesterol), renal function tests (blood urea nitrogen, creatinine), urinalysis (optional)
- Follow-up: Complete blood count with platelets, liver function tests, fasting lipid profile, renal function tests should be done monthly for first 3–6 months and then every 3 monthly. Serum or urine pregnancy test should be done monthly for women of childbearing potential (and at the end of treatment).

### CONCLUSIONS

The development of new, more effective and less toxic retinoids, alone or in combination with other drugs, may provide additional avenues for cancer chemoprevention and therapy.

**Table 3: Side effects of retinoids**

Organ system/ tissue	Side effects
Teratogenicity	Retinoic acid embryopathy: Defects in cranium and face, cardiovascular defects, thymic abnormalities, central nervous system malformations. Spontaneous abortions
Ocular	Night blindness Dry eyes Photophobia <i>Staphylococcus aureus</i> infections Blepharoconjunctivitis
Mucocutaneous	Cheilitis Cutaneous staphylococcal infections Exuberant granulation tissue formation: pyogenic granuloma Acne fulminans Xerosis Palmoplantar digital desquamation Photosensitivity
Hair	Telogen effluvium Abnormal hair texture, dryness
Nail	Fragility with nail softening Paronychia Onycholysis
Bone	Diffuse skeletal hyperostosis Osteophyte formation Premature epiphyseal closure
Lipids	Hypercholesterolemia Hypertriglyceridemia
Gastrointestinal	Nausea, diarrhea, abdominal pain Inflammatory bowel disease flare Pancreatitis due to hypertriglyceridemia
Hepatic	Transaminase elevations Toxic hepatitis (rarely)
Hematologic	Leucopenia Agranulocytosis
Neurologic	Pseudo-tumor cerebri Depression, suicidal ideation
Musculoskeletal	Myopathy Myalgias Arthralgias Tendinitis

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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