# Low-Dose Systemic Retinoids in Preventing Subsequent Non-Melanoma Skin Cancers (NMSC) in Patients with History of NMSC: A Systematic Review

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## Abstract

**Background:** Non-melanoma skin cancers (NMSC) consists of basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC). Certain populations are predisposed to develop NMSC, including patients with previous history of NMSC. Systemic retinoids have shown promising results in chemoprevention of recurrence of NMSC in other high-risk populations (xeroderma pigmentosum and renal-transplant patients). We assessed the efficacy and safety of low-dose systemic retinoids compared with placebo, as a chemopreventive agent for NMSC in patients with previous NMSC.

**Methodology:** Electronic databases were systematically searched for this study. Participants in the studies selected must have had a biopsy-proven NMSC, over 18 years of age, with no exclusion of other demographic characteristics. All types of systemic retinoids were included with no restriction on dosage. Two authors independently performed standardized eligibility assessment and data-extraction. Differences in opinion were resolved by consensus with the third author. Statistical analysis was done using the Review Manager 5 software.

**Results:** Eleven full-text studies were assessed for eligibility out of 178 studies found. Five studies were excluded because of the different population, while the two articles used topical retinoids. Four articles were included. The interventions were 10.0 mg isotretinoin, 25,000IU retinol and 25.0 mg acitretin, compared with placebo. Meta-analysis produced RR of 0.94 (95% CI, 0.89-1.00), with moderate heterogeneity (34%) due to the difference in interventions used. There are significantly more adverse events in the retinoids group, especially in the incidence of mucocutaneous adverse events, and deranged lipid profile and liver enzymes.

**Conclusion:** There is insufficient evidence to support the use of low-dose systemic retinoids as chemoprevention for patients with previous NMSC. Furthermore, adverse events may limit their use. Topical preparations with less side-effects may be investigated.

**Keywords:** Low-dose systemic retinoids, Non-melanoma skin cancers, NMSC

## Introduction

### Background

Non-melanoma skin cancers (NMSC) are one of the most common malignancies in the human population.[1] These consist of basal cell carcinomas (BCC) and squamous cell carcinoma (SCC). BCC is more common than SCC. In the United States, latest estimates of NMSC were noted to be four million cases diagnosed among 2.5 million people. Exact incidence is difficult to establish because cases are not commonly reported in registries. There is overlap with different subspecialties with regards to the management of these patients. Furthermore, the use of ablative techniques, which are usually done in the outpatient setting, prevents histologic confirmation.[1]

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NMSC develop due to damage to the skin through ultraviolet (UV) radiation. The incidence of NMSC is known to increase as one lives near the equator, because of the direct exposure to the sun.[2] Although NMSCs are more common in fair-skinned individuals because of their tendency to burn easily rather than to tan, these types of cancers are still prevalent even in dark-skinned, pigmented individuals, including Asians.[3]

In the latest available population-based cancer registry database in the Philippines (Department of Health Rizal Cancer Registry and the Philippine Cancer Society Inc.-Manila Cancer Registry), cancers of the skin were estimated at 4.2 per 100,000. The type of skin cancer was not specifically indicated.[4] Among forty patients found to have malignant skin tumors at a local hospital, 22 patients (55%) had BCC, 17 (27.5%) SCC, and seven patients (17.5%) had malignant melanoma (MM). This data approximated skin cancer profile in foreign studies.[5] Furthermore, among 75 patients who underwent Moh's Micrographic Surgery (MMS) in a local hospital, the most common was BCC (76%) followed by SCC

(14%). Majority of the NMSCs were primary, but 18% of BCC and seven percent SCC were recurrent types.[6]

Aside from the fair skin phenotype, other known risk factors include older age, chronic sun exposure, previous pre-cancerous lesion such as actinic keratosis, previous skin cancers, chronic immunosuppression such as organ transplant patients, infection with the human papilloma virus, arsenic exposure, and mycosis fungoides. Other high-risk populations are at higher risk because of UV radiation-induced mutations including xeroderma pigmentosum and basal cell nevoid syndrome. In patients with previous skin cancers, there is a ten-fold increase in incidence of developing subsequent NMSCs, compared with the incidence of a first tumor in the general population. [7]

**Description of the intervention**

Retinoids include natural and synthetic derivatives of retinol (Vitamin A). Retinol is acquired through diet, absorbed within the intestinal lumen, and stored mainly in the liver. These are transported through the retinol-binding proteins (RBP), that are synthesized in the liver. Other tissues including adipose tissues, kidney, lungs, heart, and skeletal muscles, also express this protein.[8] Retinol is converted to retinoic acid through a two-step oxidation process, first reversibly converted to retinaldehyde, then irreversibly converted to retinoic acid. [9,10]

Retinoids have many important functions in the body including regulation of cell growth and differentiation, immune defense, and tumor suppression. In malignant cell lines, retinoids inhibit cell growth and induce normal differentiation of the cells through their actions in the DNA nuclear receptors, the retinoid acid receptor (RAR) and retinoid x receptor (RXR). Most of these receptors are found in epidermal and hair follicle keratinocytes in the skin.[10,11] Retinoids come in topical and oral preparations. Retinoids are currently used for acne vulgaris, Kaposi's sarcoma, psoriasis, hand eczema, and cutaneous T-cell lymphoma. However, because of their activity on cell differentiation, chemopreventive activity of retinoids has been explored.[12] Other proposed mechanisms of action include influence on growth factors and indirect downregulation of proto-oncogenes.[8,9]

In recent years, there were clinical studies done on high-risk groups prone to acquiring NMSC. These patient groups include xeroderma pigmentosum patients, epidermolysis bullosa, patients with previous history of NMSC, and patients who underwent renal transplant. Only the study on renal transplant patients, comparing acitretin 30.0 mg per day and placebo, showed 78% reduction in the risk of NMSC noted within the first year.[13]

However, the use of retinoids is limited by the known side effects, which was consistent across these studies.[13,14,15] Common side effects of retinoids appear to be dose-related, and are largely attributed to their actions on the RAR and RXR receptors. Most common are mucocutaneous reactions that are due to the decrease in sebum production, reduced stratum corneum, and altered ceramides in the skin. [10] These reactions include cheilitis, dry skin, pruritus, hair thinning, eye irritation, among others. Teratogenicity is also a major concern, especially with the use of actiretin, requiring a contraceptive period of at least three years. Furthermore, due the storage of excess vitamin A in the liver and adipose tissues, elevations in liver enzymes and serum triglycerides were reported.

To achieve optimal benefits, the recommended doses of retinoids vary for different disease conditions and different generation of retinoids. Isotretinoin given for acne is given at 0.5-1mg/kg/day. Acitretin for psoriasis may also be started at this dose, however, in order to decrease side effects, this is initiated at a lower therapeutic dose (0.20-0.25 mg/kg/day), given for at least two to three months.[11] Long-term retinoid therapy should be monitored especially at high doses, since there were reports with skeletal toxicity including tendon and ligament calcifications and hyperostosis of the spine.[12] Thus, long-term follow-up is still needed to reassess benefit and to monitor side effects.[9] Proper patient selection, adequate monitoring, and appropriate dose-adjustments are also emphasized. [10,11]

**Importance of review**

Patients with a previous history of NMSC have a higher risk of developing another NMSC. Changing lifestyles of Fitzpatrick type IV-VI patients in tropical countries may increase the risk for NMSC as well. Although most NMSC are not considered life-threatening due to low risk of metastasis, they may still cause significant physical, psychosocial, emotional and financial burden on the patients. A chemopreventive agent may be useful in decreasing the incidence of NMSC and its sequelae.

Several chemopreventive agents for skin cancers have been explored in clinical studies, which included retinoids, difluoromethylornithine, T4 endonuclease V, lycopene, polyphenolic antioxidants such as green tea and grape seeds, silymarin, curcumin, selenium, beta-carotene, and non-steroidal anti-inflammatory drugs (NSAIDS).[9] For interventions with phase III clinical studies, selenium and beta-carotene were found to be ineffective in decreasing the risk of skin cancers, based from single studies.[16] Retinoids and NSAIDs showed promising results, but are still under further investigation in terms of their efficacy and safety. [9,16] To date, several studies have shown that retinoids decrease the occurrence of new NMSCs in patients with previous NMSC. Aside from close monitoring of these patients, options for prevention should be explored.

### Objectives

To assess the efficacy and safety of low-dose systemic retinoids, compared with placebo, as a chemopreventive agent for NMSC in patients with previous NMSC.

## Methods

### Eligibility Criteria

**Types of Studies:** The authors included randomized controlled trials (RCT) comparing oral preparations of retinoids with placebo, as chemoprevention for subsequent development of NMSC.

**Types of Participants:** Participants must have had a biopsy-proven NMSC (basal cell carcinoma or squamous cell carcinoma, or both), must be over 18 years of age, whether male or female, with no exclusion of other demographic characteristics.

**Types of Intervention:** The authors included all types of systemic retinoids, with no restriction on the dosage.

### Types of Outcome Measures:

**Primary outcome:** Percentage of participants who developed a new biopsy-proven NMSC within the study duration

**Secondary outcome:** Percentage of participants who developed any adverse event (AE), clinically defined as any new symptoms experienced by the participants during treatment and results also expressed in NNT, RR, CI, p-values.

### Search methods for identification of studies

The authors conducted the electronic literature search in the following databases: the Cochrane Skin Group's Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE (OVID), EMBASE, and Health Research and Development Information Network (HERDIN) database. Reference lists of articles were also used in the search. Search terms used were chemoprevention, prevention, retinoids, skin cancer, NMSC, BCC, SCC. Other relevant journals were hand-searched. The authors also contacted pharmaceutical companies, trial authors, and organizations for potential articles and unpublished studies. No language restrictions were imposed.

### Selection of studies

Two authors (JKG, FMS) checked the titles and abstracts identified from the literature search, and independently assessed the full-text of all the articles that satisfied the inclusion criteria. A pre-tested eligibility form was used. Differences in opinion between reviewers were resolved by consensus with the adviser. Authors of the trials were contacted where ambiguities were noted. The reasons for exclusion of studies were listed.

### Data extraction and management

Two authors performed the data extraction using a pre-tested form, and disagreements were resolved with the adviser. The following details were extracted from each study.

Method: study design and duration
Participants: age range, sex, duration of treatment
Intervention: description of intervention and the comparator, dosage
Outcome: outcome measures and adverse effects

### Assessment of risk of bias in the included studies

The quality of the studies and the risk of bias were assessed independently by the authors, based on the cochrane handbook for systematic reviews of interventions. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting were checked for each study. Based on how the criteria were met, the methodological quality was classified into high (all criteria with low risk of bias), moderate (with one or more than one criteria with unclear risk of bias), and low (with one or more criteria with high risk of bias).

### Data analysis

Results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Statistical analysis was carried out using the Review Manager 5 software. Heterogeneity was tested via $I^2$ statistics, and was interpreted as no heterogeneity ($I^2$ = 0%), low heterogeneity ($I^2$ = 25%), moderate heterogeneity ($I^2$ = 50%), and high heterogeneity.[17] Where subgroup analysis was possible, a calculated treatment effect was calculated using the fixed effects model. Descriptive analysis was performed where meta-analysis was not possible.

## Results

### Results of the search

A total of 169 studies were identified through database search (Figure 1). The search process using reference lists yielded six articles. Excluding duplicates and non-human clinical trials, 11 articles were assessed for eligibility. Five studies were excluded because of the different population - three studies were on renal transplant patients, one on recessive dystrophic epidermolysis bullosa (RDEB), and one

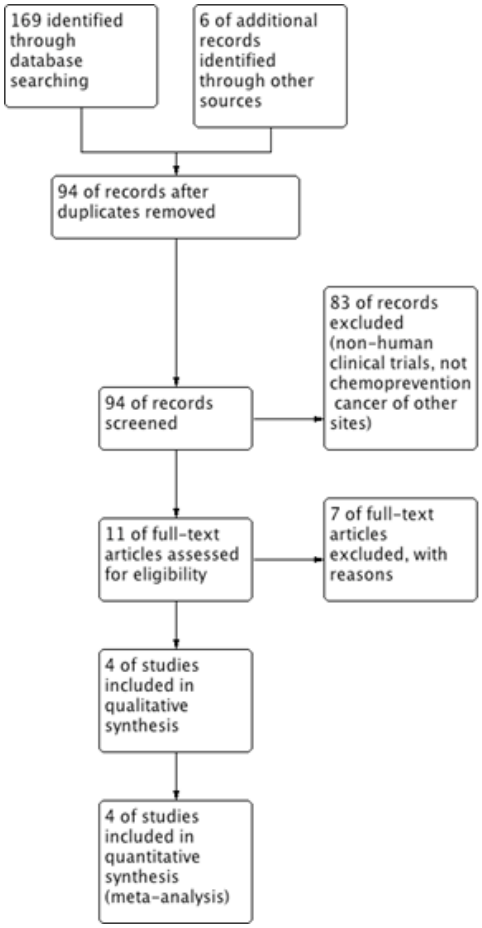


**Figure 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram**

on xeroderma pigmentosum (XP). Two studies were excluded because the interventions used were topical retinoids. At the end of the literature search using the strategy indicated above, a total of four studies were included in this review.

### Risk of bias in the included studies

All of the studies had moderate methodological quality (Table I). Blinding and patients and personnel were reported in all of the trials.

### Results of Individual Studies

In the study by Tangrea et al[18], 10.0 mg isotretinoin (~0.14 mg/kg/day) was used as chemoprevention for BCC. Nine-hundred eighty one (981) participants were randomized to receive isotretinoin or placebo daily for three years. About eight percent of this population were lost to follow-up, and was not detailed in the study. Participants were monitored initially at two weeks, then three months, six months, and every six months thereafter. There was no significant difference in the development of at least one NMSC for both groups (RR = 1.00, (95% CI, 0.89-1.13)). For this study, there

**Table I. Risk Bias Assessment in the Included Studies**

| | Tangrea 1992 | Moon 1997 | Levine 1997 | Kadakia 2012 |
|---|---|---|---|---|
| Selection Bias: Random sequence generation | Unclear | Unclear | Low | Low |
| Selection Bias: Allocation Concealment | Unclear | Low | Low | Unclear |
| Performance Bias: Blinding of patients and personnel | Low | Low | Low | Low |
| Detection Bias: Blinding of assessor outcome | Unclear | Low | Unclear | Low |
| Attrition Bias: Incomplete outcome data | Unclear | Low | Unclear | Low |
| Reporting Bias | Unclear | Unclear | Low | Low |
| Overall | Moderate | Moderate | Moderate | Moderate |

were significantly more mucocutaneous reactions (RR = 0.19, (95% CI, 0.24-1.50), p = 0.005), elevations in triglycerides and/or liver function tests (RR = 3.39, (CI 95%, 1.99-5.80), p = 0.001), and musculoskeletal pain (RR = 1.73, (95% CI, 1.18-2.55), p = 0.005). Dizziness, anxiety, and fatigue were also reported in the isotretinoin group (RR = 1.76, (CI 95%, 1.11-2.18), p = 0.02). Reporting of adverse events were self-reports, and the severity was not detailed.

The study by Moon et al [20] utilized retinol 25,000 IU daily for fivw years for SCC and BCC. A total of 2297 participants were randomized. Follow-up data was complete, and emphasized in the study, with most of the dropout occurring in the fourth and fifth year of the study. There was no statistical difference in the development of subsequent NMSC (RR = 0.83, (CI 95%, 0.66-1.06)). Adverse events were classified as mild, moderate and severe. For this study, there were noted significant differences on the incidence of adverse events.

There are two interventions in the study by Levine et al. [19], which compared isotretinoin 10.0 mg daily and retinol 25,000 IU daily with placebo for prevention of NMSC. A total of 790 participants were randomized to receive isotretinoin, retinol, or placebo. There was no significant difference in decreasing the number of new NMSC compared with placebo, for both isotretinoin and retinol. Moderate to severe mucocutaneous adverse events were noted both in the retinol (RR = 3.55, (CI 95%, 1.20-10.5), p = 0.02) and isotretinoin group (RR = 6.96, (CI 95%, 2.51-19.3), p = 0.002). Abnormalities in blood chemistry parameters (cholesterol, triglyceride, hemoglobin, liver function tests) were highest in the isotretinoin group (RR = 10.2, (95% CI, 1.33-78.1), p = 0.02).

In the study by Kadakia et al. [21], 73 participants were enrolled but only 53 participants completed the study

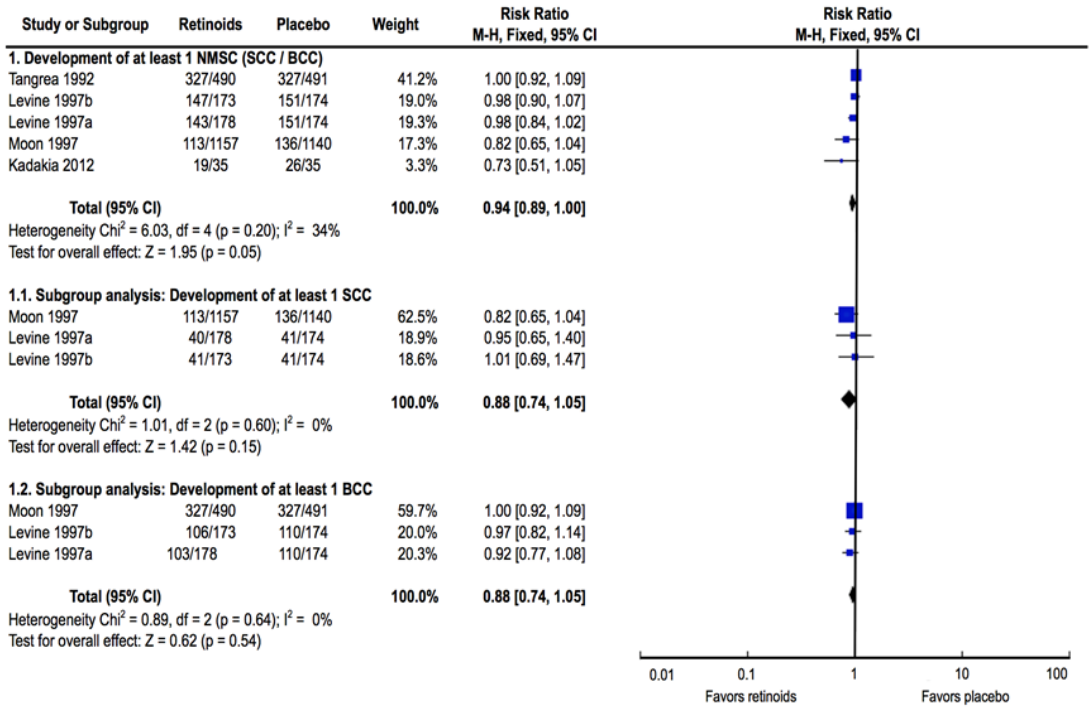


**Figure 2. Forest plot of primary outcome of development of at least 1 NMSC (SCC/BCC), and subgroup analysis for development of SCC and BCC**

according to the protocol. High attrition rate was similar in both groups. There was no significant difference in the development of subsequent NMSC (RR = 0.83, (CI 95%, 0.52-1.31)). Incidence of mucocutaneous adverse events was significantly higher in the treatment group (RR = 2.69 (CI 95%, 1.34-5.24), p = 0.004). On further analysis, among all the studies, this study showed the least number of patients to treat. From the findings in the study, it may be deduced that for every 13 patients given the intervention, one patient will not develop a new NMSC. Summary table of incidence of adverse events may be found in Appendix C.

In summary, all four studies did not show statistical difference in preventing the occurrence of subsequent development of NMSC. However, adverse events were noted to be higher in the retinoid group.

### Synthesis of results

Pooling of data was done for studies in which results can be grouped and combined. Meta-analysis on all studies (3,873 participants) produced a risk ratio of 0.94 (95% CI, 0.89-1.00) with noted moderate heterogeneity at 34%. Heterogeneity may be attributed to the difference in the interventions used (Figure 2). Further subdividing studies with available data for SCC, similar trends favoring retinoids was noted (RR = 0.88, (CI 95%, 0.74-1.05)) but not statistically significant. For BCC, similar trends were also noted although not statistically significant (RR = 0.98, (CI 95%, 0.91-1.05)). There was no evidence of heterogeneity for both subgroup (Figure 2).

### Incidence of adverse events

Meta-analysis was done on all the studies to check the incidence of adverse events (Figure 3). Incidence of mucocutaneous adverse events was noted to be statistically significant in the retinoid group (RR 2.11, 95% CI, 1.86-2.39). There was high heterogeneity in the studies, which may be attributed to the differences in reporting of adverse events. Meta-analysis in the incidence of the musculoskeletal adverse events was not statistically significant (RR=1.18 (CI 95%, 0.87-1.59)), with low heterogeneity. There is a trend favoring the control group in the incidence of abnormalities in blood chemistry (RR = 1.52, (CI 95%, 1.26-1.83)), with noted moderate heterogeneity. Meta-analysis on the incidence of CNS adverse events showed no statistical difference (RR = 1.08, (CI 95%, 0.77-1.51)) with moderate heterogeneity.

## Discussion

The studies on the use of retinoids for chemoprevention in patients with previous history of NMSC, when assessed individually, did not show statistically significant results. However, this meta-analysis highlighted positive trends, favoring the use of retinoids in chemoprevention of

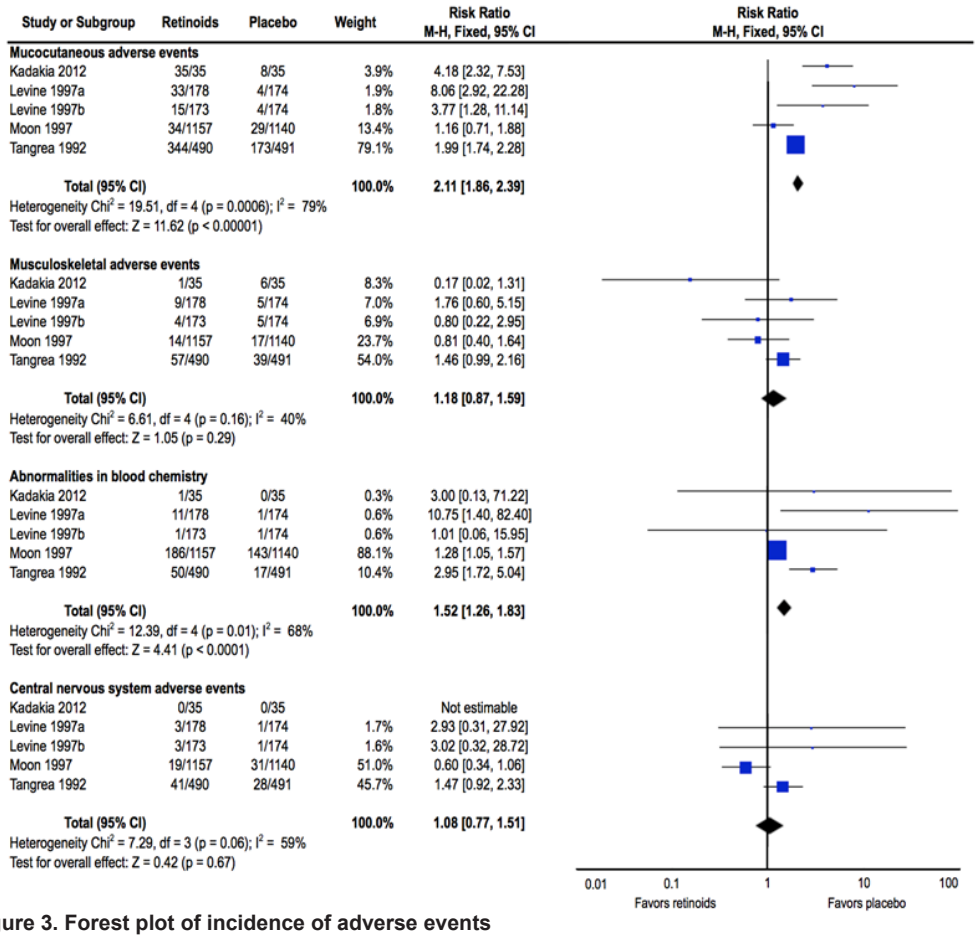


**Figure 3. Forest plot of incidence of adverse events**

subsequent NMSC in patients with a prior history of BCC and SCC. The studies included in this review have well-executed methodology. Based from the studies, the selected interventions were relatively well-tolerated, and showed dose-related and reversible toxicities.

Retinoids are usually given at a high dose (0.5-1mg/kg/day) to achieve the optimal effects on the skin. However, low-dose systemic retinoids (0.20-0.25mg/kg/day) are recommended for disorders needing lifelong maintenance such as in keratinizing disorders.[22] Adverse events have been observed in the studies of Kadakia et al.[21] and Tangrea et al.,[18] despite the use of the lower dose, and were considered to be the factors that led to the high attrition rate. However, it is important to note that the participants were informed of the possible toxicities at the start of the trial, hence the possible increase in reports of adverse events in both the treatment and control groups.

In this review, the adverse events were grouped according to the involvement of mucocutaneous, musculoskeletal, abnormalities in blood chemistry, and central nervous system, with the mucocutaneous adverse events still the most common, especially noted in the isotretinoin group. Mucocutaneous adverse events included cheilitis, dry oral mucosa and dry skin not relieved by emollients. The next common adverse events were the abnormalities in blood chemistry, particularly elevations in liver enzymes and lipid profile, which are typically seen in patients on retinoid therapy. Transient increase in liver enzymes are seen in approximately 20% of patients treated with acitretin and less with isotretinoin. These are usually mild, developing between two to eight weeks of therapy, and returns to normal even after a month of continued therapy.[10,11] Hypercholesterolemia and elevated triglycerides, on the other hand, are seen in 50% and 30%, respectively, of patients on isotretinoin and acitretin therapy. In this study, elevations in liver enzymes were noted to be significant with the treatment of isotretinoin in Levine et al.[19] and Tangrea et al.[18] Other less reported, but still relevant adverse events include musculoskeletal and symptoms pertaining to the central nervous system. Musculoskeletal adverse events included moderate to severe reporting of myalgias, arthalgias and arthritis, while the central nervous system adverse events involved intolerable dizziness, nausea, and headache.

It is important to note that for all studies, except for the hematologic adverse events, severity of the symptoms noted was based on the self-reports by the patients. The

most common side effects remain to be the dryness of the mucous membranes and the skin, and this is mainly due to the mechanism of action of the retinoids. Transient elevations of the liver enzymes and lipid profile are also seen, hence monitoring of these parameters are recommended monthly. These are mild, reversible upon dose-adjustment and cessation of the drug.

Results of this study suggest that there is currently not enough evidence on the use of low-dose oral retinoids for patients with prior history of NMSC. Retinol, acitretin and isotretinoin are all available in the country at less than 100 pesos (roughly two dollars) per tablet. Risk and benefit should always be assessed for each patient. Close monitoring and follow-up are warranted.

## Conclusions

Results of this study suggest that there is not enough evidence on the use of low-dose systemic retinoids as chemoprevention for patients with prior NMSC. Furthermore, adverse events, although mild, limit their use. Hence, the risks and benefits of the retinoid use should be assessed for each patient. Close monitoring and follow-up are warranted.

At the time of this study, the study on acitretin as chemoprevention for non-transplant patients was still considered as a pilot study, with noted limited sample size. Additional future studies and systematic review for acitretin in NMSC may be helpful in strengthening evidence for its chemopreventive use. Moreover, topical preparations for retinoids may have less side effects compared with oral retinoids, and these may be further investigated and reviewed for preventing NMSC.

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