

Vitamin A's derivatives, known as retinoids, are increasingly found today in over-the-counter (OTC) cosmetic products, including sunscreens. Is there any reason they shouldn't be? Some concerned citizens would have you think so.

The omnipresence of retinoids such as Retin-A, retinol, retinyl palmitate and tretinoin in both OTC and prescription items is not surprising, since they have been found to be outstanding topical agents offering innumerable benefits to both the function and appearance of skin. Targeting all key skin cells in the epidermis and dermis, they are variously used to combat photoaging, acne, psoriasis, and even some forms of skin cancer.<sup>1-4</sup> They are the only topicals proven in clinical tests to perform such an array of activities—tightening pores, preventing and reversing ultraviolet (UV) damage, reducing wrinkles, increasing blood flow in skin, fighting acne, increasing cell turnover, boosting collagen and evening out skin tone.<sup>1-4</sup>

And yet, at least one group of vocal critics warns that even trace amounts of these products can be dangerous. The question is whether their alarms have any basis in reality.



## PRECEDENTS FOR RETINOIDS

The earliest account of vitamin A application dates back to ancient Egypt 3,500 years ago. In the US, dermatologists began using tretinoin (retinoic acid) as an acne treatment decades ago.<sup>3</sup> The treated patients were noted to have fewer wrinkles and smoother skin tone. Today, in our practice, new patients are instructed to apply a retinol or another retinoid product as part of their regular skin care regimen.

They are among the great anti-aging tools of the past several decades, yet some critics consider them a threat. What's the reality?

Vitamin A is also essential for healthy eyes, teeth and bones, as well as skin. In addition to being applied topically, it may be acquired through dietary sources such as animal products (e.g., liver and eggs) and plants (e.g., carrots and spinach). Once absorbed, it is converted to retinol, which is transported to the tissues, including the skin, where it is stored as retinyl palmitate until needed. Most of the skin's supply of vitamin A is stored in this form. When needed, it is converted to its metabolically active form, retinoic acid.<sup>1,4</sup>

While vitamin A from our diet serves most of the aforementioned physiological purposes, it is the topical derivatives of the vitamin that serve most of the therapeutic purposes for the skin. Luckily, there are many choices, which differ in potency (e.g., 0.25% vs. 0.5% concentrations), delivery method (e.g., gel or cream), and their ability to act immediately.<sup>1</sup> The OTC preparations, such as the compounds typically found in cosmeceuticals, most commonly

contain retinol, whereas prescription strength retinoids contain retinoic acid, the active form of vitamin A. Because retinol and other precursors of retinoic acid have to be converted in the skin to retinoic acid to become active and have a therapeutic effect, they work less immediately and are much less potent; basically, your skin has to do some work first to oxidize the precursor into retinoic acid. Meanwhile, prescription retinoic acid/tretinoin is active from the start and immediately available for your skin to reap the benefits.<sup>4</sup> [See Table 1 on pg.34]

## RETINYL PALMITATE: TEMPEST IN A TEAPOT?

One particular derivative of vitamin A, retinyl palmitate (RP), has been the eye of the storm of recent sunscreen controversies. It is used in minute amounts as a kind of preservative in sunscreens to help keep their active ingredients from breaking down in the sun.

RP is also naturally occurring in many foods, as well as in our liver and skin, as the main stored form of vitamin A. Given how much of it we already naturally encounter, it came as some surprise a few years back when the Environmental Working Group (EWG), a consumer watchdog, classified the tiny trace amounts of RP in many sunscreens as a potential carcinogen. The EWG claimed—and still claims—that the RP in sunscreens might lead to skin cancers when exposed to ultraviolet light. The furor raised by the EWG on this issue prompted sensational media coverage frightening consumers with questions like, "Is your sunscreen giving you skin cancer?"

## THE REAL STORY

The EWG based this alleged effect of RP on its own interpretation of research performed by the National Toxicology Program (NTP), a federally funded program that evaluates the human health effects of chemical agents in our environment (<http://ntp.niehs.nih.gov/about/index.html>). The NTP performed tests on laboratory mice, applying various strengths of retinyl palmitate and irradiating the mice with varying doses of artificial ultraviolet radiation. However, it is curious that they particularly targeted retinyl palmitate, since it is the natural way in which vitamin A is stored in the skin, and since it is a natural antioxidant that functions as protection against damaging molecules called free radicals. It normally works alongside other antioxidant vitamins such as C and E, and non-vitamin antioxidants like glutathiones and

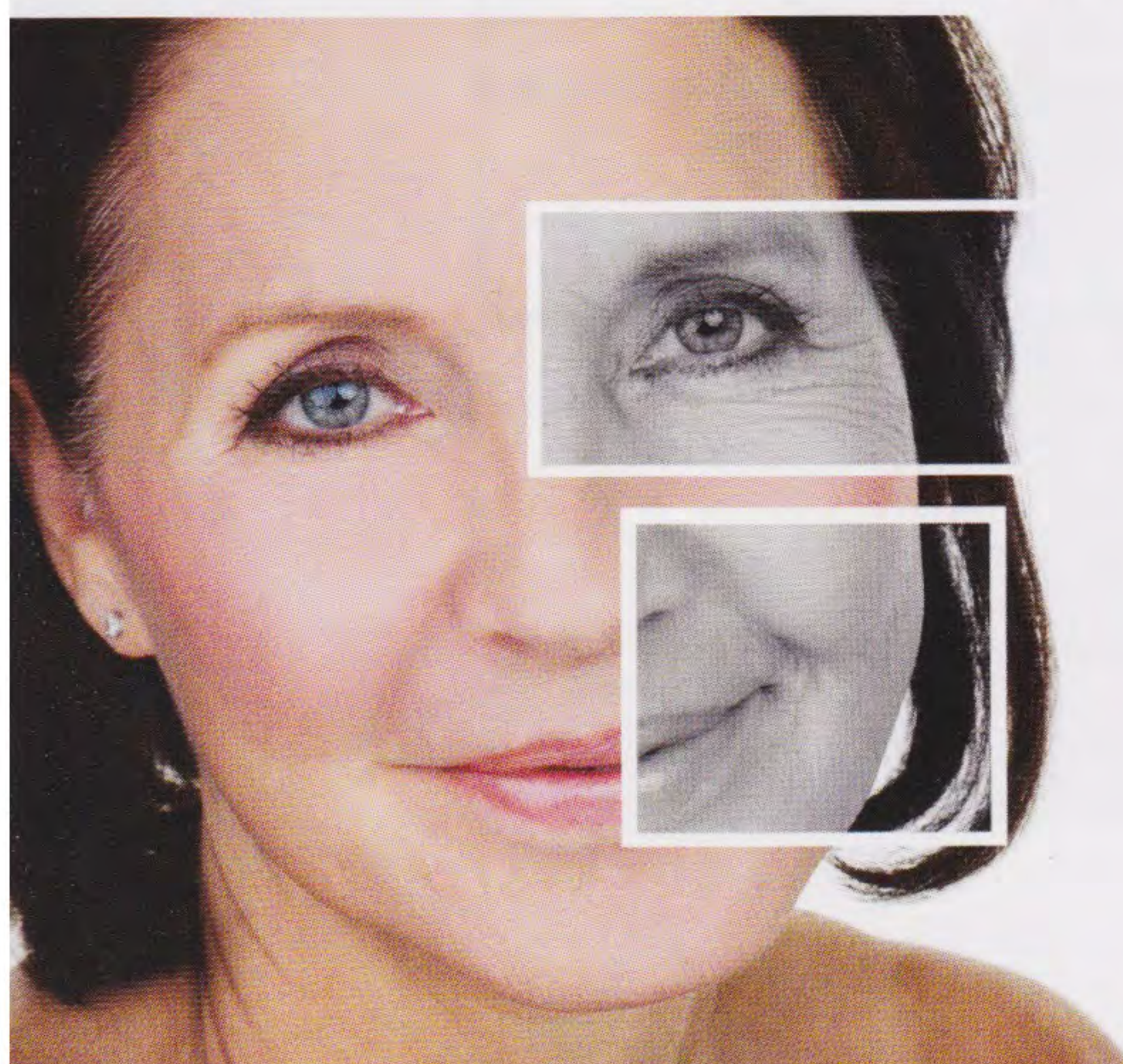
catalases. All these substances work as a team to protect the skin against free radicals. What the NTP studied was not a team of antioxidants, but a lone player. Without the insulation from its counterparts, retinyl palmitate when damaged by ultraviolet radiation might indeed promote the activation of free radicals that can promote carcinogenesis.<sup>5-7</sup> However, that is not the way it works, either in nature or in sunscreens. No study in humans has ever shown that retinyl palmitate is a carcinogen in humans.

Nor did the NTP data show conclusive evidence that RP exposed to UV light is cancer-causing even in mice. The trace amount of retinyl palmitate used in most sunscreens is a minute fraction of the amount that was used in the study (0.1 grams per oz in the study compared to 0.0000029 grams per oz. in a sample sunscreen), and despite this, only one group of the four RP-treated test mice showed a statistical difference in the formation of skin tumors compared to its counterpart treated



with a placebo cream.<sup>8</sup> Furthermore, the particular strain of mice used for these studies was highly susceptible to forming skin cancers after UV exposure. In fact, many of the study mice treated with the placebo cream also developed both benign and malignant skin tumors.<sup>5</sup> Another deficiency in the study: the researchers did not determine whether a *sunscreen* containing retinyl palmitate applied prior to ultraviolet exposure prevented the development of tumors.

In the end, the data in the study were considered so weak that they were never peer-reviewed and never published. So, in short, the EWG based its alarms to humans on a much-flawed, unpublished rodent study.






## THE BENEFITS STILL PREVAIL

RP, along with its fellow vitamin A derivatives, has been proven to increase collagen content and skin thickness, both classic features of healthy skin. In addition, it helps to regulate immune function in the skin, adding another level of defense against skin cancer. In cosmetic formulations, including sunscreens, this molecule is added in trace amounts as a stabilizer, protecting the product from light-induced breakdown. Dermatologists for decades have prescribed retinoids including RP for the treatment and prevention

of numerous skin conditions, including precancerous skin lesions and skin cancers.

Regular use of a topical retinoid ultimately improves the skin's ability to defend itself from the harmful rays of the sun. It is only during the initial weeks of starting a retinoid product that the skin becomes sun-sensitive, but once it is acclimated, the rejuvenated, more resilient epidermis, with potential precancers cleared away, will actually perform better under stressful environmental conditions including UV radiation.<sup>1-4,9</sup> In other words, the many PROVEN benefits of retinoid use vastly outweigh the

unproven risks suggested by an unpublished rodent study. 

References on pages 105-107.

**LINDA FRANKS, MD**, is Director of Gramercy Park Dermatology and a clinical assistant professor of dermatology, New York University School of Medicine. She is a member of The Skin Cancer Foundation's Medical Council.

**PANTA ROUHANI SCHAFFER, MD, PHD, MPH**, practices medical, cosmetic, and surgical dermatology as well as laser medicine at Gramercy Park Dermatology in New York City. She is a clinical assistant professor at the Ronald O. Perleman Department of Dermatology, New York University.

## The Variations In Retinoids

**Table 1.** Sources of topical retinoids and the conditions they treat.

ACTIVE INGREDIENT	BRAND EXAMPLES	FORMULATION	INDICATION
Retinyl esters - retinyl palmitate - retinyl propionate - retinyl acetate Retinol Retinaldehyde	OTC brands as well as physician office-dispensed products. Common in cosmeceutical products.	Various (0.05%-0.3%)	Photodamage Photoaging/Wrinkling
Tretinoin* (all-transretinoic acid)	Atralin Retin-A Retin-A Micro Renova	Gel, cream, solution (0.1%, 0.05%, 0.04%, 0.025%, 0.02%, 0.01%)	Acne Photoaging/Wrinkling Photodamage
Tazarotene* (synthetic retinoic acid)	Tazorac Avage Zorac Fabior	Gel, cream (0.05%, 0.1%)	Acne Psoriasis Photodamage
Adapalene* (synthetic retinoic acid)	Differin	Gel, cream, lotion (0.1%, 0.3%)	Acne Photoaging

\*Requires a prescription