Decades of basic scientific studies and initial clinical trials have indicated a potential role for the classical retinoids in cancer chemoprevention (1). Indeed, the concept of cancer chemotherapy is based largely on preclinical and early clinical studies in which retinoids suppressed epithelial carcinogenesis (2–5). However, in a recent randomized phase III intergroup chemoprevention trial, the retinoid isotretinoin did not reduce second primary tumor formation, recurrences, or mortality in patients with stage I non–small-cell lung cancer (6). And in this issue of the Journal, Khuri et al. (7) report results of a rigorously conducted placebo-controlled phase III trial showing that isotretinoin was not effective in mediating chemoprevention in patients with early-stage head and neck squamous cell carcinoma (HNSCC). It is now important to uncover the basis for this paradoxical lack of isotretinoin clinical chemoprevention activity. Answers will likely come from a more complete understanding of the molecular mechanisms and pharmacology of retinoids.

Retinoids comprise natural and synthetic derivatives of vitamin A that regulate many essential biologic functions. Retinoids activate transcription by binding to nuclear receptors. Isotretinoin, also known as 13-cis-retinoic acid, is converted to all-trans-retinoic acid, which activates the classical nuclear retinoic acid receptors (RARs), whereas 9-cis-retinoic acid activates both the RARs and the nonclassical nuclear retinoid X receptors (RXRs). RARs can heterodimerize with RXRs, whereas RXRs heterodimerize with other nuclear receptors, including the thyroid hormone receptor, the vitamin D receptor, and peroxisome proliferator–activated receptors (8). Novel synthetic retinoids, including RXR-selective agonists termed “rexinoids,” have recently shown promising clinical activity in a combination regimen that targets non–small-cell lung cancer (9). Because RXRs form heterodimers with nuclear receptors that affect lipid physiology, their effects are also being investigated in other medical conditions, including the metabolic syndrome, which is characterized by obesity, dyslipidemia, diabetes, and hypercoagulability (8).

The retinoid-signaling pathway was studied in normal and neoplastic tissues to identify why preclinical retinoid activity did not readily translate into clinical success. It was discovered that expression of retinoic acid receptor β (RARβ) is frequently silenced in epithelial carcinogenesis, which has led to the hypothesis that RARβ acts as a tumor suppressor that is partially responsible for the limited clinical activity of classical retinoids (10,11). Restoration of RARβ expression in premalignant oral lesions by isotretinoin treatment was associated with a beneficial clinical response, implying a direct role for RARβ as a mediator of retinoid response and as a biomarker for clinical chemoprevention (12). Clinical strategies to enhance retinoid activity include efforts to reduce toxicity, retain bioavailability, activate specific retinoid receptors, and develop effective combination regimens (1). For example, topical all-trans-retinoic acid (tretinoin) has shown clinical activity in cervical intraepithelial neoplasia, overcoming the systemic toxicity associated with oral retinoid administration (13). Other approaches include the use of nonclassical retinoids that have retinoid receptor–independent properties or that target RXRs that would bypass RARβ repression (1).

The trial reported by Khuri et al. (7) is the largest retinoid chemoprevention study to date in patients with early-stage head and neck cancer. The lack of clinical efficacy in reducing incidence of second primary tumors reported by these investigators is consistent with the findings observed in other trials that used classical retinoids or carotenoids for lung cancer chemoprevention (6,14–16). The clinical benefit of finding an effective, yet tolerable, dosage of a cancer chemopreventive agent should not be underestimated. The dosage of isotretinoin that was used in this trial (30 mg/day) is much lower than that used in a previously reported positive randomized placebo-controlled study (50–100 mg/m²/day) (4). Most patients in that prior study required dose reductions, and more patients in the isotretinoin arm than in the placebo arm did not complete the 12-month course. Therefore, the dosage used in this trial is likely to be the highest dosage that can be tolerated in long-term treatment. In a multivariable analysis, Khuri et al. (7) found that current smokers had statistically significantly higher rates of second primary tumors and mortality than did former and never smokers. This finding confirms the benefit of smoking cessation on clinical outcomes for HNSCC patients.

It is not known whether the lack of isotretinoin activity in this trial was due to inherent tumor resistance or to unfavorable pharmacokinetics. Phase III chemoprevention trials designed to evaluate a treatment by using cancer incidence as an endpoint are costly and time-consuming but essential for definitive assessments of clinical efficacy. Sustained efforts will be required to optimize chemopreventive regimens. One challenge for the future will be to design clinically predictive and mechanistic trials with validated biomarker endpoints to verify drug activity before initiating large phase III trials. For example, when using a classical retinoid it may be necessary to treat only those patients who have an intact retinoic acid–signaling pathway. In a breast cancer chemoprevention trial of the nonclassical retinoid fenretinide, effects on surrogate biomarkers, including circulating insulin-like growth factor I (IGF-I) and mammographic density, are now being analyzed (17). It is interesting that serum levels of IGF-I
and IGF-binding protein have also been reported to predict the risk of second primary tumors in patients with HNSCC (18). Another downstream marker of retinoid receptor activity is the loss of expression of the cell cycle regulator cyclin D1 (19). In a proof-of-principle trial, decreased cyclin D1 protein expression in buccal swabs was used as a biomarker for cellular response in patients with aerodigestive tract cancers treated with the retinoid bexarotene and the epidermal growth factor receptor-tyrosine kinase inhibitor erlotinib (9).

In summary, this definitive randomized placebo-controlled phase III HNSCC trial conducted by Khuri and colleagues revealed that low-dose isotretinoin was not effective in reducing the incidence of second primary tumors or in increasing overall disease-free survival (7). The chemopreventive activities of other classical and nonclassical retinoids and of combination regimens that include retinoids should still be evaluated. Promising treatments include the combination of a retinoid with an epidermal growth factor receptor inhibitor (9) and a synthetic acyclic retinoid that shows activity in preventing second primary hepatocellular carcinomas (20). We do not fully understand why classical retinoids that have shown promise in preclinical studies have not shown clinical activity in the chemoprevention of lung (6) and head and neck (7) cancers. Loss of RARβ isoforms in epithelial carcinogenesis undoubtedly plays a role (10, 11). Proof-of-principle trials are attractive for testing retinoid monotherapy and combination therapy to establish clinical pharmacologic activity. What is also evident is that retinoids are useful tools for identifying critical target genes and pathways that can reduce carcinogenesis (21). Through these ongoing studies, we might even resolve the nature of the retinoic acid paradox in cancer chemoprevention.

REFERENCES