

## Commentary

See related article by Saba et al., p. 283

## Chemoprevention of Squamous Cell Carcinoma of the Head and Neck: No Time to Lose Momentum

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### Abstract

The prospects for chemoprevention to reduce the incidence of squamous cell carcinoma of the head and neck (SCCHN) are great. The tissue at risk for harboring disease is relatively accessible for examination and biopsy. Patients appropriate for study can be easily identified by their risk factors and the presence of premalignant lesions. Our understanding of the pathogenesis of SCCHN is ever increasing, and offers new opportunities to explore strategies for prevention therapies. In this issue of *Cancer Prevention Research*, Saba and colleagues report on a phase Ib trial of celecoxib plus erlotinib to prevent progression to higher-grade dysplasia or invasive carcinoma in patients with oral premalignant lesions. The overall response rate was 57%, though by the time of last analysis, 85% of patients relapsed. In this commentary, challenges to the success of chemoprevention clinical trials for SCCHN, such as pitfalls in using surrogate biomarkers and reversal of histologic premalignant changes as study endpoints, are discussed. In addition, strategies to help ensure further development in the field of head and neck cancer prevention are reviewed. These include focusing efforts on tobacco cessation and human papillomavirus vaccination, targeting key molecular drivers of head and neck carcinogenesis, and focusing on combination strategies that have the potential to eradicate premalignant clones, even if some toxicity is encountered. *Cancer Prev Res*; 7(3); 279–82. ©2014 AACR.

The annual summary of cancer statistics shows a gratifying improvement in squamous cell carcinoma of the head and neck (SCCHN) survival by several percentage points over the past four decades (1). These gains, however, are offset by a slow but steady increase in incidence. The statistics deceive us further, as the gains in survival have not come by virtue of the medical community's improvements in early detection or treatment, but instead seem to result entirely from the emergence of good-risk SCCHNs caused by human papillomavirus (HPV; ref. 2). Despite our best efforts at improving outcomes for SCCHN, advancements in surgery, radiation and systemic therapy have yet to cure more patients. This, plus the fact that we can identify a subset of people at risk for future SCCHN by the presence of premalignant oral leukoplakia lesions, makes a great case for the need to establish effective preventative approaches. What better way to cure more patients with SCCHN could there be than to eliminate some before they ever exist?

In many ways, SCCHN is a perfect model for chemoprevention. Many patients harbor oral premalignant lesions, visible as leukoplakia or erythroplakia, with various degrees of histologic dysplasia on biopsy. Patients at high risk for

malignant transformation can be identified by a history of tobacco use and/or prior SCCHN, as well as the presence of high-risk biomarkers, such as loss of heterozygosity, particularly at chromosomes 3p and/or 9p (3). These premalignant lesions, thought to represent risk for cancer not just at the lesional site but throughout the head and neck mucosa as a result of field cancerization, are accessible for biopsy and can be sampled for evaluation of representative surrogate molecular marker endpoints in clinical trials. Moreover, with recent advances in bioinformatics and whole-exome sequencing, we now know even more about the molecular underpinnings of SCCHN (4, 5). Lastly, should a successful chemoprevention strategy be developed, not only will lives be saved by averting head and neck cancers, but also patients will be spared the hardship of SCCHN and its treatment, which often leads to lifelong impact on some of the most fundamental aspects being alive, such as eating, drinking, speaking, and breathing.

If, indeed, SCCHN is a perfect model for chemoprevention, why is there no established treatment in use? It is certainly not for lack of trying. Since the landmark study of 13-*cis*-retinoic acid, published in 1986 by Hong and colleagues, which showed that high-dose 13-*cis*-retinoic acid works for SCCHN prevention in patients with oral leukoplakia, but tolerability was problematic and lesions recurred shortly after the drug was stopped, numerous studies have been performed (6). Included in agents studied are low-dose retinoids and carotenoids, other antioxidant vitamins, epigallocatechin gallate (EGCG) and Bowman-Birk inhibitor compound and other nutritional organic compounds, and nonsteroidal anti-inflammatory drugs, such as ketorolac and celecoxib (7–15).

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The article by Saba and colleagues in this issue of *Cancer Prevention Research* adds combined celecoxib plus erlotinib to the list (16). Unfortunately, no clear winner has been declared, but several themes have emerged. First, agents taken for prevention in a premalignant, otherwise healthy patient population that result in significant side effects are not feasible. Toxicity may be acceptable if a drug is effective, but if this is the case, transient benefit is not enough; the benefit must be long-lasting. In addition, modulation of tissue biomarkers in a favorable direction is no guarantee of success. Moreover, even regression of clinical oral premalignant lesions and reversal of histologic dysplasia does not correlate well with cancer risk reduction.

With this track record in mind, how do we adapt and continue moving forward? The problem can be broken down into the following components: the patient, the malignancy, the drugs, and the endpoints.

Considering the patient, two thoughts come to mind. One, we know that tobacco use is the leading cause of preventable disease worldwide. Despite the increase of HPV-associated oropharyngeal squamous cell carcinomas (OPSCC) in our population, tobacco remains the leading cause of SCCHN. We also know that tobacco cessation results in durable regression of oral premalignant lesions and decreases the risk of second primary cancers in SCCHN survivors (17, 18). Any SCCHN prevention effort, therefore, must include a focus on tobacco cessation. Tobacco cessation in study participants could, of course, confound results, but would simply need to be addressed in study design. Second, the relatively high prevalence of oral HPV infection present in our population and dramatic increase in HPV-associated OPSCC cannot be ignored when thinking about prevention (2, 19). The two U.S. Food and Drug Administration (FDA)-approved vaccines, HPV bivalent (types 16 and 18) vaccine and HPV quadrivalent (types 6, 11, 16, and 18) vaccine, have both been shown in randomized phase III study to be highly effective at preventing HPV-related neoplasia, and hold great promise in reducing the burden of HPV-associated SCCHN (20–23). Yet, at the present time, vaccination coverage is low. For example, in 2012, only 53.8% of girls and 6.8% of boys 13 to 17 years old had received all three doses of the HPV vaccine, falling well short of the Healthy People 2020 target of 80% for girls (24). The Healthy People 2020 campaign did not establish a goal for HPV vaccination in boys, but when vaccine coverage for girls is low, the incremental benefit for vaccination of boys can help achieve herd immunity (25). Effective vaccination programs will curb the growing burden of HPV-associated malignancy, and quite simply, should be funded and executed without delay.

About the malignancy, focus can be placed on the role of biomarkers. Prevention studies carried out not just in patients who harbor leukoplakia or erythroplakia, but in patients with oral premalignancy at greatest risk for future cancer can have the power to show benefit in smaller sample sizes. Markers that predict progression to invasive carcinoma have been described. Loss of heterozygosity of chromo-

somes 3p and/or 9p is one such predictor (3). Another analysis demonstrated that gene signatures found by gene expression profiling can accurately predict future cancer in patients with oral premalignancy (26). These markers are not, however, the key drivers of carcinogenesis, in and of themselves. Ideally, a predictive marker used to select participants appropriate for a given study would also be a molecular driver of carcinogenesis and serve as the target for intervention. As whole-exome sequencing has shown, mutations in *TP53* occur in 47% to 62% of SCCHN (4, 5). Mutations in *TP53* are common in premalignant lesions and predict future SCCHN, as well (27). Although exploiting this abnormality that results in tumor suppressor gene loss of function remains an unmet therapeutic challenge, strategies with potential, such as targeting the MDM2-p53 interaction with MDM2 inhibitors, are emerging (28). Other tumor markers worth future consideration for patient selection and preventative targeting include the phosphoinositide 3-kinase pathway, which is the most frequently mutated oncogenic pathway in SCCHN, and the key cell cycle regulatory protein, cyclin D1, found in premalignancy and established SCCHN (27, 29–32). Yet another risk factor crying out for targeting in prevention is HPV. Carriers of oral HPV can now be identified, and although the current prophylactic HPV vaccines to not have any effect in pre-existing HPV infection and cannot prevent progression to malignancy, several therapeutic vaccines aimed at eradicate HPV-infected tissues at risk for malignancy are in development. Beyond directly targeting HPV, targeting the PD-1: PD-L1 interaction that facilitates adaptive immune resistance may also have a future role in SCCHN prevention (23, 33, 34).

Getting the drug right is, of course, the holy grail of chemoprevention. It has long been presumed that a chemopreventive agent must have a quite tolerable side effect profile to be feasible for use in an otherwise healthy premalignant population. The phase Ib study of combined celecoxib and erlotinib by Saba and colleagues, in which the maximum tolerated dose of erlotinib with celecoxib in oral premalignant patients was one third of that used to treat lung cancer, confirms that drug tolerance is critical in prevention studies (16). But perhaps suppressing carcinogenesis with minimally toxic agents is not an effective strategy after all. Perhaps we need the preventative equivalent of cytotoxic therapeutics that will eliminate premalignant clones, rather than temporarily suppress carcinogenesis with agents that allow for regrowth upon discontinuation. Two strategies, both aimed at improving the therapeutic ratio, may enable the study of more potent compounds. First, nanoparticle engineering to direct drugs into premalignant cells while sparing normal tissues, may allow for the delivery of more toxic drugs without the cost of greater side effects (35). Another appealing strategy could be to take advantage of the phenomenon recently illustrated by BRAF inhibition in melanoma, in which vertical inhibition in the same pathway, i.e., combined BRAF and MAP-ERK kinase inhibition, may lead to not only more effective therapeutic targeting, but can also abrogate the

consequences of negative feedback and thus improve the side effect profile of treatment (36). Improving targeting strategies for chemopreventative agents to premalignant tissues may facilitate more effective combination therapy, which is likely necessary if the goal is to truly eradicate, rather than suppress, premalignancy.

Feasible endpoints have long been an issue in chemoprevention clinical trials. A surrogate primary endpoint that can provide a more rapid read out than the development of cancer itself, as well as accurately predict prevention of future cancers, would be ideal. We now know that regression of clinical premalignant lesions, or even change in histologic dysplasia, are not good markers of efficacy for SCCHN prevention (37). Although reduced cancer risk will ultimately be required for a new chemopreventative approach to become standard of care, a good surrogate marker can be used to select new drugs for definitive study and shorten the duration of development. Ideal surrogate endpoints would not only relate to the participant's risk, but also reflect drug activity at the level of the target. Unfortunately, we are not there yet. Some studies to date have shown a pharmacodynamic effect in biomarker studies (12–15, 38). Markers of proliferation, such as Ki-67 by immunohistochemistry, are doable and appealing as surrogate endpoints, but showing a decline in premalignant proliferation does not equal eradication of cancer risk. What we need are accurate molecular determinants of carcino-

genesis that are measurable in premalignant tissues, can be targeted and change with therapy, and represent risk of future cancer. Early-phase prevention trials that use stringent surrogate endpoints to select compounds for definitive phase III study may eliminate all but the most promising agents from development, and optimize the utilization of our limited resources (37).

Two and a half decades of work have yet to lead to a new standard of care for SCCHN prevention and highlight the stubborn challenges of chemoprevention in this setting. The rapidly evolving understanding of the molecular drivers of SCCHN, coupled with advances in honing the therapeutic index of targeted cancer therapies, offers new promise for innovation in SCCHN prevention. There is no time like now to capitalize on prevention strategies already poised for execution, such as HPV targeting. And we cannot forget about the critical importance of tobacco cessation. In addition, it is time to redouble efforts to leverage recent gains in our understanding of the molecular biology of SCCHN and keep the momentum going in the study of SCCHN prevention.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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