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Letter to the Editor

Cancer Prevention Research

Role of *SFRP1* in NPC Metastasis—Letter

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We have read the findings reported by Ren and colleagues with interest. They have investigated the expression of secreted frizzled-related protein 1 (SFRP1) in nasopharyngeal carcinoma and its relationship to clinical outcome (1) and have concluded that SFRP1 expression does predict the prognosis of NPC patients.

Nasopharyngeal carcinoma is a lethal malignancy, and distant metastasis is the main reason for treatment failure in this condition. Thus, the identification of prognostic markers that may predict distant metastasis and perhaps response to therapy are warranted. Therefore, the findings reported by Ren and colleagues (1) are of great significance. Nevertheless, in our opinion, some aspects of the study need to be discussed in further detail.

Nasopharyngeal carcinoma tissues are characterized by cellular heterogeneity, representing a mixture of normal tissue, stroma, or *in situ* tumor cells and influx of immune cells in nasopharyngeal carcinoma lesions (2). This heterogeneity within the same clinical subgroups of patients prevents the reliable ascertainment of its biologic properties, including its responsiveness to treatment. The isolation of a relatively pure population of tumor cells by laser capture microdissection may allow the identification of tumor-specific molecular alterations (2). Moreover, evaluation of tumor heterogeneity and possible evolution of cancer cells after tumor relapse should be documented within multiple samples of a single tumor and repeated biopsies to decrease the risk of avoidable errors.

Ren and colleagues (1) have normalized the expression of SFRP1 by using a housekeeping gene (HKG), *GAPDH*, in RT-PCR. It has documented that HKG expression, despite being occasionally constant in a cell type or experimental condition, can vary considerably (3). Accurate normalization of the data should be based on the geometric means of multiple internal control genes, and determination of the gene stability is required to avoid single control normalization error and to identify proper tissue-specific HKG for gene expression analysis (3). Moreover, a Bonferroni correction may be warranted as a consequence of the number of variables/clinical features of the population with respect to SFRP1 expression to avoid false-positive associations.

Finally, IHC is an imprecise and empirical method, and outcomes depend on the antibody used and pathologist's expertise. Moreover, traditional scorings methods, for example, based on tumor size, nodal involvement, are relatively poor in predicting the chance of developing metastases, and tailored treatments based on expression profiles are challenging and are still far from being useful in the management of NPC patients (4). This can be explained by several factors, including the bias of a single-factor analysis, compared with several key determinants of drug activity and characteristics of cancer cell, which could influence the prognosis. Thus, validation of the results and reevaluation of the slides by at least two independent pathologists may decrease the risk of mistakes and avoid interlaboratory variation in results from IHC assessment (5).

We thank Ren and colleagues for their report but believe that additional analysis with the incorporation of a more refined methodologic approach is required to validate the prognostic value of SFRP1 in an independent cohort, preferably multicenter settings, to establish its value beyond the already available clinical factors.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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