In the study by Hsu et al. (1), skin lesions, including nonmelanoma skin cancer (NMSC), were used as a marker of arsenic exposure and studied in relation to the risk of subsequent internal malignancy. Compared with those having no skin lesions, participants with NMSC were more than 2 times more likely to be diagnosed with a subsequent internal malignancy; this association was consistent regardless of whether hyperkeratosis was present (relative risk = 2.36, 95% confidence interval: 1.65, 3.37) or absent (relative risk = 2.17, 95% confidence interval: 1.66, 2.85).

In interpreting these findings, the authors inferred that the results were consistent with “...an independent role for these skin lesions in predicting subsequent internal malignancies” (1, p. 210). In fact, considered independently of arsenic level, these results are consistent with a steadily accruing body of evidence indicating that NMSC is a marker of a cancer-prone phenotype. This includes previous findings of ours (2) and many others, as documented in the systematic review and meta-analysis of Wheless et al. (3), that a personal history of NMSC is associated with a significantly elevated risk of other malignancies. This association has been consistently observed for both major histological types of NMSC, squamous cell carcinoma and basal cell carcinoma, and among both men and women (3).

The magnitude of the relative risks observed by Hsu et al. is somewhat stronger than previously observed in the small number of previous prospective cohort studies with individual-level data (3). In addition to the impact of the arsenic exposure, another possible reason for the stronger association than seen in previous studies is that the entire study population was assessed by dermatologists. This is a unique study design feature not seen in most previous studies on this topic that would be expected to substantially reduce misclassification of NMSC status.

In the context of the existing body of evidence on the association between NMSC and risk of other cancers, another notable feature of the study of Hsu et al. is the Asian ethnicity of the study population. Along with the study of Roh et al. (4), it is among the first to document this association in a population of Asian ancestry, implying that this association is not applicable solely to those of European ancestry. NMSC has consistently been observed to be a marker of increased risk of other cancers in many studies carried out in various settings. The fact that NMSC is so common amplifies the importance of research to advance understanding of why NMSC is a marker of increased risk for other cancers. For example, in the United States, the estimated annual number of NMSC diagnoses in 2006 was 2,152,500 (5), 30% greater than the estimated total of all other malignancies combined (6).

In the first hypothesis-driven research to investigate the mechanistic basis for the association between a personal history of NMSC and increased risk of other cancers, null results were observed for variants in hedgehog pathway–related genes (7), but promising findings were observed for DNA repair gene variants (8). These latter findings provide proof-of-principle evidence to document the value of this line of inquiry for uncovering risks of multiple cancers.

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References

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Editor’s note: In accordance with Journal policy, Hsu et al. were asked whether they wished to respond to this letter, but they chose not to do so.