reconsideration of landmark study by D’Cruz et al4 from 2015 that found a statistically significant survival benefit for patients undergoing an elective neck dissection for early-stage oral cavity carcinoma compared with patients randomized to a watchful-waiting group. The study was performed in India, the world’s largest producer and consumer of betel nut, and it did not assess, nor control for this variable.5 If betel nut consumption is indeed an independent prognosticator, the generalizability of these results to non-betel nut regions may be mitigated.

Conversely, numerous other oral cavity studies from betel nut regions have shown higher proportions of verrucous carcinomas, a remarkably indolent variety of oral cancer with minimal metastatic potential. Over a 10-year period, Vidyasagar et al6 reported 438 institutional oral cancer diagnoses, of which 107 were verrucous carcinomas (24%). Such proportions of verrucous disease have never been reported in non-betel nut regions. When taken in conjunction with conclusions by Yang et al,3 these findings suggest a substantially different spectrum of oral cancer phenotypes in betel regions relative to non-betel nut regions.

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In Reply Our study7 reported that Native Hawaiian and other Pacific Islander individuals were more likely to present with advanced head and neck squamous cell carcinoma and worse survival compared with their Asian and non-Hispanic White counterparts. We conducted a subanalysis of oral cavity cancer cases, given the prevalent use of betel nuts among Native Hawaiian and other Pacific Islander communities and the known association between betel nut consumption and oral cavity cancer.2,3 There were no differences in clinical presentation or survival among Native Hawaiian and other Pacific Islander patients in comparison to non-Hispanic White patients. We thank Dr Moss for the thoughtful comments on the important nuances of betel nut-associated oral cavity cancer, and wish to provide a response.

We agree with Dr Moss that the results of our subanalysis on oral cavity cancer should be interpreted in context. There are several reasons that may explain the lack of significant results. First, our study7 focused on Native Hawaiian and other Pacific Islander individuals diagnosed in the mainland US and Hawaii, whose pattern of betel nut use may differ from that of the population in betel nut endemic regions. To our knowledge, there is currently no study in the literature comparing regional differences and this should be the subject of future research. Second, our subanalysis was inclusive of all oral cavity squamous cell carcinoma cases, including those that were likely unrelated to betel nut use. The Surveillance, Epidemiology, and End Results database does not capture etiological data. Finally, it is also possible that disparities were not found in our study because we combined all subtypes of squamous cell carcinoma into a single group. As Dr Moss points out, there appears to be a spectrum of oral cavity cancer phenotypes among betel nut users.4,5 Therefore, it may be important for a future study to assess for differences by oral cavity squamous cell carcinoma subtype.

We appreciate the important insights and reply to our work from Dr Moss. We look forward to studies that are committed to further illuminating the role of betel nut use in the pathogenesis of oral cavity cancers, as well as studies that highlight the health outcomes that are specific to the Native Hawaiian and other Pacific Islander populations.

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CORRECTION

Errors in Figure 1: The Original Investigation titled “Association of Pretreatment Circulating Tumor-DNA–Modified Viral HPV DNA With Clinicopathologic Factors in HPV-Positive Oropharyngeal Cancer,” published online October 27, 2022, included minor data errors that appeared in Figure 1C. These errors did not affect the results of the study. This article has been corrected.