Comment on: Effect of Pap Smear Cytology, HPV Genotyping On the Concordance of Colposcopy and Conization Results

Sir,

We appreciated the opportunity to read the recent article by Saglam *et al.* examining the concordance between cervical cancer screening modalities.[1] While the study provided useful data, we would like to highlight some limitations regarding the study population and human papillomavirus (HPV) genotyping methodology that should be addressed in future research.

First of all, regarding the study population, only 17% of the 517 patients included were postmenopausal, with the large majority aged 30-45 years. However, the epidemiology and natural history of cervical precancers differ significantly before and after menopause. After menopause, the prevalence of cervical abnormalities decreases substantially, driven by declining HPV infection with age.[2] Cervical cancer rates also show a marked decrease after menopause, with a low risk of progression from precancer in older women, especially those over 50 years.[3] As such, management guidelines recommend less aggressive approaches for abnormalities in perimenopausal and postmenopausal women. Therefore, results from this predominately younger cohort may not be applicable to the majority of older women undergoing routine cervical cancer screening.

We would also like to highlight that key cervical cancer screening technologies such as HPV testing perform differently in older women compared to those aged 30-45 years. The clinical accuracy of HPV testing for detecting carcinoma *in situ* (CIN) 2+ decreases with age, with lower positive predictive value and higher false positive rates in older women.[4] The proportion of positive HPV tests due to transient infections also declines with age. Age-specific HPV genotype distribution also varies, which can influence the performance of partial genotyping assays. Therefore, to improve generalisability to real-world screening populations, the inclusion of a greater proportion of perimenopausal and postmenopausal women with age over 45 years is imperative.

We also noticed that the authors did not provide any details regarding the specific HPV genotyping assay used. It is known that analytical sensitivity, specificity, genotype detection, clinical accuracy, and concordance with cytology can vary greatly between different HPV tests.[5] For example, assays only detecting 14 high-risk types would misclassify HPV 66-related abnormalities. Some tests are more prone to cross-reactivity between types than others. Knowing precise test details is imperative to judge the validity of HPV results and their relation to cytology / histology outcomes. At a minimum, the authors should have clearly specified the HPV test used, as performance differences across assays directly impact measured concordance with other modalities such as cytology and colposcopy.

In a nutshell, a study population more representative of routine cervical cancer screening and detailed reporting of the specific HPV test methodology would significantly strengthen this study examining multimodal algorithms. We believe that addressing these limitations will produce higher-quality evidence to guide clinical management, especially for perimenopausal and postmenopausal women.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HNKA: Conception, data Collection, and writing of the draft.
AP: Editing of the draft, proofreading, and final approval of the project.
Both authors approved the final version of the manuscript to be published.

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AUTHOR'S REPLY:

We are honoured that you evaluated our article. As you suggest, classifying the characteristics into premenopausal, perimenopausal, and postmenopausal and conducting a study in this way will make a better contribution to the literature. However, due to data limitations, there were not enough postmenopausal patients. The HPV test is included in the national cervical cancer screening programme in our country. Our hospital is an oncology hospital and a reference hospital, and since this study was conducted with HPV tests examined in many regions of the country and different laboratories, unfortunately, we did not specify test method as it was not examined with a single method. It was one of the limitations of our study.

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