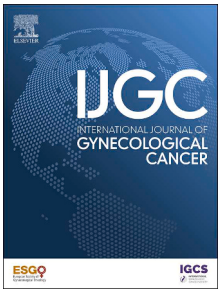
EDITORIAL

Topical treatment for high-risk human papillomavirus: evidence gap persists



Jose Jeronimo*, Maria Demarco

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The systematic review by Pareja and colleagues[1] provides a timely and rigorous examination of an area increasingly marked by enthusiasm among health clinicians, significant commercial interest, and patient demand: topical therapies intended to clear high-risk oncogenic human papillomavirus (HPV) infection and prevent progression to cervical pre-cancer. Despite decades of research and development of candidate agents, the most important finding of Pareja and colleagues[1] is that no randomized controlled trial to date has been adequately designed to demonstrate a reduction in progression to CIN (Cervical Intraepithelial Neoplasia) II+, the clinical threshold that requires treatment. This negative finding is not trivial; rather, it is deeply informative.

The strength of this review lies in its methodological discipline. By restricting eligibility to women with confirmed high-risk HPV infection, histologically verified CIN I or less, appropriate placebo or observation comparators, and progression to CIN II+ as the primary outcome, the authors align their analysis with contemporary risk-based management paradigms.[2] This approach mirrors current international guidelines, which emphasize observation over intervention in low-grade disease because of the high likelihood of spontaneous regression and the low absolute risk of progression to cancer. In doing so, the review exposes a fundamental disconnect between much of the existing literature and real-world clinical decision-making.

Many trials excluded by the authors relied on surrogate outcomes, such as HPV clearance or cytologic regression. Although this may sound biologically appealing, these end points do not necessarily translate into reduced cancer risk. As Pareja and colleagues[1] underscore, HPV clearance alone is not an oncologic outcome. Persistent infection is common, regression is frequent, and only a small fraction of women with CIN I progress to CIN II+.[3] Any intervention proposed for this population must, therefore, demonstrate benefit beyond the natural history of the disease, a bar that none of the reviewed studies were designed or powered to meet.

The review by Pareja and colleagues[1] has immediate implications for clinical practice. In multiple regions, particularly in low- and middle-income countries, topical agents are increasingly marketed as "non-invasive" solutions for HPV infection. This review provides strong evidence that such practices are not evidence-based and carry the risk of diverting attention and resources away from proven strategies such as high-quality screening, appropriate triage, and timely treatment of CIN II+. The absence of serious safety signals in previous studies should not be misconstrued as justification for routine use when efficacy remains unproven.

Equally important are the implications for future research. Future studies must be adequately powered, use standardized diagnostic criteria, include observation or placebo controls, and focus on CIN II+ progression as the primary end point. Without these elements, further research risks perpetuating uncertainty rather than resolving it.

In an era increasingly shaped by risk-based management and implementation science, the work by Pareja and colleagues[1] reminds us that innovation without rigor does not advance care. Until high-quality evidence demonstrates otherwise, topical treatments for high-risk HPV infection should remain investigational; they should not be part of clinical practice, and observation should remain the standard of care.

Author Affiliations

National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA

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* ***Correspondence to*** *Dr Jose Jeronimo, Division of Cancer Epidemiology & Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA; jose.jeronimo@nih.gov (J. Jeronimo)*

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