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Enhancing cervical cancer screening: the promise and future of self-sampling HPV testing

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INTRODUCTION

Self-sampling human papillomavirus (HPV) testing is a promising approach for cervical cancer screening, particularly in underserved regions. Despite the availability of HPV vaccines, primary cervical cancer screening remains crucial for prevention. The transition from cervical cytology to HPV detection has been one of the significant public health advancements in recent decades.[1] HPV testing is more sensitive and allows for longer screening intervals due to the low risk of cervical cancer with negative HPV results.[2] Importantly, molecular testing provides women with the opportunity to sample themselves. In 2020, the WHO announced a goal to eliminate cervical cancer, with a target to screen 70% of women aged 35–45 years by 2030.[2] However, the burden of cervical cancer remains high, especially in disadvantaged populations, highlighting the need for alternative screening methods such as self-sampling for HPV.[3]

EXISTING LIMITATIONS

Despite the advantages, there are several limitations to the current cervical cancer screening methods. Even in the USA, cervical cancer screening is suboptimal for 20% to 30% of the eligible populations due to operational, geographic or sociocultural barriers, such as income level, medical insurance, race and ethnicity.[4] Additionally, over half (56%) of all new cervical cancers diagnosed in the USA were among women who were not screened during the period 4–36 months prior to diagnosis.[5] These barriers necessitate alternative approaches like self-sampling for HPV testing, which can potentially overcome these challenges.[6]

CURRENT INSIGHTS AND METHODOLOGIES

Sampling devices and detection methods

The first report on self-sampling using cervicovaginal lavage samples for HPV analysis was in 1992.[7] Since then, various collection devices such as brushes, swabs and tampons have been evaluated. In 1999, Hillemanns *et al*[8] first evaluated self-collected vaginal HPV tests for cervical cancer screening, finding it a reliable method with a sensitivity of 93% for detecting CIN2+. Different detection methods also affect the accuracy of self-sampling,[9] and it is now acknowledged that HPV DNA assays based on clinically validated PCR testing on self-samples are as accurate as those on clinician-obtained samples.[6] However, for HPV mRNA detection, further research is needed as it has not yet been proven for primary screening, although it shows promise in high-risk populations.[2]

Acceptability, accuracy and screening efficacy

Evidence from both high-income and low-income areas suggests that self-sampling HPV testing can effectively increase cervical cancer screening uptake and operational feasibility compared with conventional clinician sampling.[10] Self-sampling offers advantages such as privacy, convenience and reduced discomfort.[11] Studies have shown that self-sampling has comparable performance with clinician-collected samples for detecting high-risk HPV infection, with high sensitivity, specificity and negative predictive value.[12] A meta-analysis of test concordance between self-collected and clinician-obtained samples for HPV testing in 26 studies with 10 071 participants showed pooled overall agreement of 88.7% (95% CI: 86.3% to 90.9%). The positive and negative agreements were 84.6% (95% CI: 79.9% to 88.7%) and 91.7% (95% CI: 89.1% to 94.0%), respectively, with a kappa value of 0.72 (95% CI: 0.66 to 0.78).[6] Subgroup analyses indicated that target amplification-based DNA assays (ie, PCR) (90.4%) had the highest overall concordance at 90.4% compared with other assays, which ranged from 82.3% to 86.7%.

In women screened for HPV, self-sampling was non-inferior to clinician sampling for detecting cervical intraepithelial neoplasia grade 2 or worse, with sensitivity ranging from 74% to 92%, specificity from 87% to 94% and negative predictive value greater than 98% across multiple assays.[13 14] Five-year follow-up data from the PaVDaG study showed that the relative sensitivity for CIN3+ and specificity for ≤CIN1 of high-risk HPV testing on self-taken specimens were only slightly lower compared with clinician-collected samples: 0.95 (95% CI: 0.90 to 0.99; PMcN=0.0625) and 0.98 (95% CI: 0.95 to 1.00; PMcN≤0.0000), respectively.[15] Thus, self-sampling showed a similar prevalence of HPV infection and excellent detection rates of CIN2+ and CIN3+ in histology compared with clinical cervical sampling.[14] Accumulated evidence supports the accuracy and effectiveness of self-sampling to increase coverage, especially in developing countries where health resources are limited.[9] This is further supported by the effectiveness of HPV self-sampling to increase coverage among target populations, particularly in developing countries where lack of resources and existing psychological and cultural barriers are significant.[10 16]

FUTURE DIRECTIONS

The application of self-sampling HPV testing is expanding globally. As of February 2021, 48 out of 194 WHO member states have adopted primary HPV-based programmes, with 17 incorporating self-sampling in their national programmes, including 2 low-, 5 lower-middle-, 4 upper-middle- and 6 high-income countries.[17] The proportion of self-sampling usage is higher in high-income countries compared with low- and middle-income countries.[17] The WHO recommends self-sampling as part of cervical cancer screening, and the FDA approved self-collected vaginal specimens for cervical cancer screening in May 2024.[18]

Looking forward, urine collection as a non-invasive self-sampling method also shows promise for similar sensitivity in detecting CIN2+ compared with cervical samples.[19] This method could provide an even more accessible option for reaching women who are under-screened for cervical cancer. Advances in molecular screening techniques, such as HPV extended genotyping, HPV viral load, E6/E7 mRNA and methylation, may further enhance screening efficacy. These techniques can potentially refine the screening process by identifying specific high-risk populations. Although promising, many of these methods require clinical validation to ensure their accuracy and reliability in primary screening settings. For instance, HPV extended genotyping can differentiate between various high-risk HPV types, which may have different risks of progression to cervical cancer.[20] Assessing HPV viral load in HPV-positive self-collected samples may show increased sensitivity and specificity for detecting CIN2+ lesions, thereby enhancing the effectiveness of the screening process. Similarly, E6/E7 mRNA detection can indicate active viral oncogene expression, which is closely linked to the development of high-grade cervical lesions.

In conclusion, self-sampling is poised to become a primary method for cervical cancer screening. By incorporating advanced molecular techniques, self-sampling can offer a more precise and effective screening strategy as well as controlling costs. This approach has the potential to overcome existing barriers, improve screening acceptability and significantly contribute to the global effort to eliminate cervical cancer.

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REFERENCES

1 Wentzensen N, Arbyn M, Berkhof J, *et al*. Eurogin 2016 Roadmap: how HPV knowledge is changing screening practice. *Int J Cancer* 2017;140:2192–200.
2 Arbyn M, Simon M, de Sanjosé S, *et al*. Accuracy and effectiveness of HPV mRNA testing in cervical cancer screening: a systematic review and meta-analysis. *Lancet Oncol* 2022;23:950–60.
3 Singh D, Vignat J, Lorenzoni V, *et al*. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *Lancet Glob Health* 2023;11:e197–206.
4 Medicaid and CHIP Payment and Access Commission. Access in brief: use of cervical, breast, and colon cancer tests among adult medicaid enrollees. MACPAC. Available: https://www.macpac.gov/publication/access-in-brief-use-of-cervical-breast-and-colon-cancer-tests-among-adult-medicaid-enrollees [Accessed 3 Jun 2024].
5 Leyden WA, Manos MM, Geiger AM, *et al*. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst* 2005;97:675–83.
6 Arbyn M, Smith SB, Temin S, *et al*. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ* 2018;363:k4823.
7 Morrison EA, Goldberg GL, Hagan RJ, *et al*. Self-administered home cervicovaginal lavage: a novel tool for the clinical-epidemiologic investigation of genital human papillomavirus infections. *Am J Obstet Gynecol* 1992;167:104–7.
8 Hillemanns P, Kimmig R, Hüttemann U, *et al*. Screening for cervical neoplasia by self-assessment for human papillomavirus DNA. *Lancet* 1999;354:1970.
9 Belinson JL, Du H, Yang B, *et al*. Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing. *Int J Cancer* 2012;130:1855–60.

10 Yeh PT, Kennedy CE, de Vuyst H, *et al*. Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. *BMJ Glob Health* 2019;4:e001351.
11 Arbyn M, Castle PE, Schiffman M, *et al*. Meta-analysis of agreement/concordance statistics in studies comparing self- vs clinician-collected samples for HPV testing in cervical cancer screening. *Int J Cancer* 2022;151:308–12.
12 Arbyn M, Verdoodt F, Snijders PJF, *et al*. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15:172–83.
13 Toliman PJ, Kaldor JM, Badman SG, *et al*. Evaluation of self-collected vaginal specimens for the detection of high-risk human papillomavirus infection and the prediction of high-grade cervical intraepithelial lesions in a high-burden, low-resource setting. *Clin Microbiol Infect* 2019;25:496–503.
14 Tatara T, Wnuk K, Miazga W, *et al*. The Influence of Vaginal HPV Self-Sampling on the Efficacy of Populational Screening for Cervical Cancer-An Umbrella Review. *Cancers (Basel)* 2022;14:5913.
15 Stanczuk GA, Currie H, Forson W, *et al*. Self-sampling as the principal modality for population based cervical screening: five-year follow-up of the PaVDaG study. *Int J Cancer* 2022;150:1350–6.
16 Untiet S, Vassilakos P, McCarey C, *et al*. HPV self-sampling as primary screening test in sub-Saharan Africa: implication for a triaging strategy. *Int J Cancer* 2014;135:1911–7.
17 Serrano B, Ibáñez R, Robles C, *et al*. Worldwide use of HPV self-sampling for cervical cancer screening. *Prev Med* 2022;154:106900.
18 U.S. Food & Drug Administration. FDA roundup: May 17, 2024. FDA; 2024. Available: https://www.fda.gov/news-events/press-announcements/fda-roundup-may-17-2024 [Accessed 3 Jun 2024].
19 Van Keer S, Latsuzbaia A, Vanden Broeck D, *et al*. Analytical and clinical performance of extended HPV genotyping with BD Onclarity HPV Assay in home-collected first-void urine: a diagnostic test accuracy study. *J Clin Virol* 2022;155:105271.
20 Li X, Rao X, Wei M-J, *et al*. Extended HPV Genotyping for Risk Assessment of Cervical Intraepithelial Neoplasia Grade 2/3 or Worse in a Cohort Study. *J Natl Compr Canc Netw* 2022;20:906–14.