Comment

HPV testing of self-samples: Influence of collection and sample handling procedures on clinical accuracy to detect cervical precancer

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We applaud Inturrisi et al. for their report describing the first findings of the pioneering HPV-based Dutch cervical cancer screening programme.1 Since 2018, women living in the Netherlands who are due to screening receive an invitation to contact their general physician for the collection of a liquid cervical specimen. Non-responders receive a second invitation to request a vaginal self-sampling device and those who confirm this option, receive an Evalyn-Brush (Rovers Medical Devices, Oss, the Netherlands) at their home address (opt-in procedure). Used vaginal brushes are sent to one of the five HPV screening laboratories where they are transferred into 20 mL of PreservCyt liquid (Hologic Inc, Bedford, MA, USA). Eight percent of women not responding to the primary invitation requested and performed self-sampling. The proportion of women with a hrHPV positive result was 7.4% and 9.3%, in the cohorts with a self-sample (SS cohort) and a clinician-collected specimen (CS cohort), respectively (ratio of 0.79). The Dutch study revealed obvious differences between self- and clinician-samples with respect to the used Cobas-4800 PCR test (Roche, Pleasanton, CA, USA) signal strength expressed in Ct values, which reflect differences in viral load (known to be lower in the vaginal environment than in scraped cervical cells) yielding lower analytical sensitivity. Using the default cut-off predefined by the manufacturer for both type of specimens, the estimated relative clinical sensitivity and relative specificity, accounting for confounding factors, for CIN3+ were 0.94 and 1.02, respectively.

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We compared the Dutch findings with the results of our systematic reviews (which we keep continuously updated)2−3 and findings from our ongoing VALHUDES study that compares HPV test accuracy in SS with matched CS.4 The rather low response to the offer of a self-sample (8%) among primary non-responders in the Dutch programme is not surprising and corresponds with the average response observed in the opt-in arms of the participation trials included in our meta-analysis (average of 8%, 95%CI 5−11%), which was not significantly higher compared to control interventions (reminder letter proposing a clinical visit for collection of a cervical specimen).5 Participation was substantially higher when women directly received the SS device without opting in Arbyn et al.3 We therefore agree with the Dutch programme managers to abandon the initial opt-in procedure and to offer women the option of self-sampling at the level of the first invitation which is not conditioned any more by the two-step opt-in procedure.

The observed relative sensitivity and specificity of validated PCR-based HPV assays (SC/CS) pooled in our meta-analysis was 0.99 (CI including unity) and 0.98 (CI excluding unity), respectively, for both outcomes CIN2+ and CIN3+. The recent Dutch IMPROVE trial, where the Evalyn self-sample was suspended in only 1.5 mL of PreservCyt and tested with the GP5+/6+ PCR, showed a relative sensitivity and specificity for CIN3+ of 0.99 and 1.00, respectively.1 In one of our VALHUDES studies, we observed a loss in sensitivity when vaginal self-samples were transferred into 20 mL of PreservCyt and not when they were transferred in only 2.5 mL.6 These findings support the Dutch proposal to reduce the transport volume for self-samples.

Other issues in collection, transport and laboratory handling, and choice of cut-offs specific for HPV testing on self-samples may also influence the accuracy. Our previous systematic reviews could not reveal significant effects of the self-sample devices on the relative accuracy of HPV testing on self- versus clinician-collected...
samples, by lack of direct comparisons. However, newer studies including VALHUDES comparing multiple self-sampling devices could demonstrate such effects.\(^6,7\)

The choice of the transport medium, in which the used self-sampler is submerged immediately after collection or in the laboratory in case of dry collections may also influence accuracy. In many studies, liquid-based cytology media containing alcohol (for instance PreservCyt, SurePath [BD]) were used for transport of self-samples. However, since cytology on self-samples is poorly accurate,\(^3\) cell preservation is not needed. A recent Australian study demonstrated good analytical sensitivity of certain non-volatile media that lyse cells but conserve nucleic acids and could be used as transport medium for self-collections.\(^8\) To extend our meta-analysis to address the impact of important elements of the whole logistical chain from collection to testing.

Today, laboratories performing HPV tests on self-samples must develop their own procedures, which require further optimisation and standardisation. This is now understood by certain manufacturers of HPV assays who are elaborating on-label protocols for self-samples. Excellent guidelines exist for validation of HPV tests on clinical samples: a meta-analysis\(^9\) and request more detailed information on sample handling procedures. We also propose to developers of HPV tests and devices for self-sampling to conduct careful piloting addressing the impact of important elements of the whole logistical chain from collection to testing.

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Declaration of interests
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Contributors
MA drafted original manuscript. All authors critically revised and approved the final manuscript.

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