Offering self-sampling kits for HPV testing to reach women who do not attend in the regular cervical cancer screening program

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Abstract

In 2016, the Netherlands will switch, as first European country, from cytology-based to HPV-based cervical cancer screening, with cytology triage for those with a positive HPV test. The new Dutch program includes sending self-sampling devices to women who do not respond to an invitation to have a cervical sample taken by their general practitioner. The cost-effectiveness of this additional strategy will depend on its capacity to recruit non-screened women and in particular those at increased risk of cervical (pre)cancer, the possible switch of previous responders to self-sampling, the accuracy and cost of the HPV assay-self sampler combination, and the compliance of women being self-sample HPV-positive with further follow-up. Validated PCR-based assays, detecting high-risk HPV DNA, are as accurate on self-samples as on clinician-collected samples. On the contrary, HPV assays, based on signal-amplification, are less sensitive and specific on self-samples. The introduction of self-sampling strategies should be carefully prepared and evaluated in pilot studies integrated in well-organized settings before general roll-out. Opt-in procedures involving a request for a self-sampler may reduce response rates. Therefore an affordable device that can be included with the invitation to all non-attendees may yield a stronger effect on participation.
In this issue, Rozemeijer et al assess the cost-effectiveness of HPV testing on samples taken by the woman herself (1). There is now substantial evidence that high-risk human papillomavirus (hrHPV)-based screening is more effective in reducing the incidence of cervical precancer and cancer than cytology-based screening (2, 3). Several countries have switched or are in the process of switching to hrHPV testing for primary cervical cancer screening, taking advantage of the greater reassurance a negative hrHPV test than a negative Pap test and permitting longer intervals between screens (2, 3).

Another advantage of using HPV testing is that, contrary to cytology, it can be done using a vaginal sample collected by the woman herself. Offering women a device to self-sample can increase the population coverage by reaching those who are reluctant to participate in the regular screening program that require clinic-based visits and pelvic exams (4).

In 2016, health authorities in the Netherlands plan to switch to HPV-based screening for women aged 30-60 years for 5 screens in a lifetime at ages 30, 35, 40, 50, and 60 years. All women age 30-60 years will be invited to contact their GP to have a cervical Pap specimen collected into liquid-based cytology (LBC) medium, which will be tested for hrHPV DNA. Reflex cytology will be done on hrHPV positives and if negative, a follow-up LBC 6-12 months later will be conducted. Women with an abnormal reflex or follow-up LBC will be referred to colposcopy. Women who do not respond to the invitation will be given the opportunity to request a free self-sampling kit to be sent to their home address, with the self-sample being tested by the same hrHPV test used for clinician-collected specimen (5, 6). In this issue of CEBP, Rozemeijer et al., simulated the potential advantages, costs and harms
associated with including self-sampling as part of the new Dutch organized program over plausible ranges of influencing factors (1). As noted by Rozemeijer et al., approximately 50% of the cervical cancer that occurs in the Netherlands occurs in the ~30% of women who do not attend screening regularly or at all, a similar issue in many high-resource countries (7). Strategies which include offering self-sampling to non-attendees generally are cost-effective, unless hrHPV testing on self-samples would be substantially less accurate and regularly attending women should switch to self-sampling and the response of non-attenders to use self-samplers would be poor (1).

The article by Rozemeijer et al. raises some important considerations with regards to the introduction of self-sampling into cervical cancer screening programs to reach the non-attendees. First, the effectiveness of offering self-samplers will in the first place depend on its capacity to recruit unscreened women and in particular those at increased risk of cervical (pre)cancer. In trials, the response rate among under-screened women who received invitations including self-samplers varied widely between settings ranging from 6% (8) to 31% (9), which was on average 2.1 times higher (95% CI: 1.3-3.5) than in the control groups who received a conventional reminder letter (4). In two trials, conducted in Italy and Sweden, women were sent a self-sampler if they confirmed their wish to receive one (10, 11). The pooled difference in participation rates between the opt-in self-sampling arm and the control arm of conventional reminder letter was not significantly different from zero (1%, 95% CI -4 to 5%) (pooled from 11-12). These findings suggest that opt-in strategies, which may reduce the waste of unused self-samplers, compromise the potential gain in population coverage. It should be underlined that self-sampling strategies will run most efficiently in well-monitored settings with up-to-date registries covering organized and opportunistic screening allowing a
precise targeting of women who did not have a screen test over the last years and avoiding sending self-samplers to women already screened.

A second issue is the performance and acceptability of the device. A recent meta-analysis on accuracy of HPV testing on self-samples did not reveal device effects (12). Very few studies compared the relative accuracy of different devices. Recently, a trial conducted in the Netherlands, showed similar performance of HPV testing with two devices specifically designed for vaginal self-sampling (13). Whether more simple and cheap self-samplers might be as appropriate, acceptable, and accurate as the more expensive specially designed tools is a challenging research question. Such inexpensive, user-friendly devices, which could be included in invitation letters to non-attendees, relieve the economical need for opt-in procedures.

Third, the success of a self-sampling strategy depends on the clinical performance of the hrHPV testing of the self-sample. The aforementioned meta-analysis demonstrated that the sensitivity and specificity of HPV testing are similar on self- as on clinician-taken samples when validated PCR tests are used but not when signal amplification-based HPV assays are applied (12). The conclusions of this meta-analysis remain unchanged after addition of recently published studies (12, 14-16). The pooled relative sensitivity and specificity of 20 studies using HC2 (Qiagen) in self- versus clinician-collected samples was 0.86 (95% CI: 0.82-0.91) and 0.95 (95% CI: 0.93-0.98), respectively (see Figure 1). In one study using Cervista (Hologic), the relative accuracy values were: 0.76 (95% CI .70-.83) for sensitivity and 0.95 (95% CI 0.94-0.96) for specificity. On the contrary, in nine studies using validated PCR-based HPV DNA assays, the relative sensitivity and specificity was 0.98 (95% CI 0.96-1.02) and 1.02 (0.94-1.09), respectively (see Figure 2). Rozemeijer et al (1) showed that the use of an HPV-assay with lower sensitivity and specificity on self-samples would make the
new Dutch screening programme less effective, less cost-effective and more vulnerable to a possible switch of previous responders to self-sampling.

A forth issue is the management of hrHPV positive results since most hrHPV-positive women will not have cervical precancer and cancer. Cytology, as reflex test on hrHPV-positive specimens, is rather inaccurate on self-samples. Therefore, women with a hrHPV-positive self-sample will need to contact a clinician to have a Pap smear taken to identify the women who have to be referred for further diagnostic work-up. This step might be particularly problematic for this hard-to-reach target population. Compliance with further follow-up among self-sample hrHPV-positive women varied in trials between 41% (17) and 100% (11, 18). Having a molecular method allowing accurate reflex triage on the same self-sample would offer a major advantage avoiding an additional visit and reducing the burden for further follow-up. Candidate triage methods are the currently available genotyping for HPV16/18 (19), which account for ~70% of the cancer risk, and, in the future maybe also methylation markers of certain viral or human genes (20) which both are associated with progressing infections.

In conclusion, with the adoption of hrHPV testing for primary cervical cancer screening, self-sampling could be used to increase participation of high-risk, non-attendees in the cervical cancer screening program and thereby increase the effectiveness of the overall cervical cancer program. However, its introduction is not without important programmatic caveats and considerations. Only validated PCR-based HPV assays should be chosen. Before rolling out strategies involving HPV testing on self-samples, thorough planning is needed, and pilot studies should be conducted assess the feasibility, costs, logistics and population compliance
in a given setting. Importantly, excellent follow-up of the screen-positives will be necessary in order to make this intervention for the non-attendees effective and cost-effective.

References


Figure 1. Relative sensitivity (left) and specificity (right) of high-risk HPV DNA testing, using validated signal amplification assays on self- versus clinician-collected samples to detect underlying cervical intraepithelial neoplasia of grade 2 or worse.

Figure 2. Relative sensitivity (left) and specificity (right) of high-risk HPV DNA testing, using validated PCRs on self- versus clinician-collected samples to detect underlying cervical intraepithelial neoplasia of grade 2 or worse.
<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
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<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>PCR GP5+/6+</td>
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<tr>
<td>Nobbenhuis, 2002</td>
<td>0.89 (0.72, 1.10)</td>
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<td>Brink, 2006</td>
<td>0.97 (0.86, 1.10)</td>
<td>Dijkstra, 2012</td>
<td>1.03 (0.90, 1.16)</td>
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<tr>
<td>van Baars, 2012</td>
<td>0.91 (0.68, 1.21)</td>
<td>van Baars, 2012</td>
<td>1.00 (0.75, 1.33)</td>
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<tr>
<td>Geraets, 2013</td>
<td>0.90 (0.80, 1.00)</td>
<td>Geraets, 2013</td>
<td>1.00 (0.75, 1.33)</td>
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<tr>
<td>Subtotal (I² = 0.0%, p = 0.540)</td>
<td>0.95 (0.89, 1.01)</td>
<td>Subtotal (I² = 31.3%, p = 0.213)</td>
<td>1.11 (0.95, 1.29)</td>
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<td>MALDI-TOF</td>
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<td>Belinson, 2012</td>
<td>1.00 (0.95, 1.05)</td>
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<td>Abbott RT PCR</td>
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<td>Jentschke, 2013b</td>
<td>1.00 (0.75, 1.34)</td>
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<td>qPCR targeting E6-E7</td>
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<tr>
<td>Hesselink, 2014</td>
<td>1.03 (0.88, 1.21)</td>
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<td>Modified GP5/6 PCR-lum</td>
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<tr>
<td>Darlin, 2013</td>
<td>0.96 (0.75, 1.24)</td>
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<tr>
<td>Overall (I² = 0.0%, p = 0.744)</td>
<td>0.98 (0.95, 1.02)</td>
<td>Overall (I² = 18.2%, p = 0.281)</td>
<td>1.02 (0.94, 1.09)</td>
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Relative sensitivity

Relative specificity
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