Offering Self-Sampling to Non-Attendees of Organized Primary HPV Screening: When Do Harms Outweigh the Benefits?

Kirsten Rozemeijer, Inge M.C.M de Kok, Steffie K. Naber, Folkert J. van Kemenade, Corine Penning, Joost van Rosmalen, and Marjolein van Ballegooijen

Abstract

Background: Human papillomavirus (HPV) self-sampling might be a promising tool to increase effectiveness of primary HPV screening programs when offered to non-attendees. However, effectiveness could decrease if regular attendees “switch” to self-sampling, because self-sampling test characteristics may be inferior. We examined under which conditions the harms would outweigh the benefits.

Methods: The MISCAN-cervix model was used to estimate quality-adjusted life years (QALY) gained and costs of offering HPV self-sampling to non-attendees. We varied the relative CIN2+ sensitivity and specificity (self-sampling vs. regular sampling), extra attendance, risk of extra attendees, and the switching percentage.

Results: Without switching, offering self-sampling is (cost-)effective under every studied condition. If the attendance due to self-sampling increases by ≥6 percentage points, higher primary background risk women (unscreened women who will never attend regular screening) attend and the relative CIN2+ sensitivity and specificity are ≥0.95; it is (cost-)effective to offer self-sampling to non-attendees, even if all regular attendees switch. If the relative sensitivity decreases to 0.90 combined with either a 3 percentage points extra attendance or the absence of higher primary background risk women, QALYs are lost when more than 30% to 20% of the regular attendees switch.

Conclusions: Offering self-sampling will gain health effects if the relative CIN2+ sensitivity is ≥0.95, unscreened attendees are recruited, and the total attendance increases by ≥6 percentage points. Otherwise, switching of regular attendees may decrease the total effectiveness of the program.

Impact: Self-sampling needs to be implemented with great care and advantages of office-based sampling need to be emphasized to prevent switching. Cancer Epidemiol Biomarkers Prev; 24(5); 773–82.

2014 AACR.

See related commentary by Arfyn and Castle, p. 769

Introduction

In the Netherlands, cervical cancer incidence and mortality have decreased in the past decades to 6.5 and 1.3 per 100,000 women-years (age-adjusted to the World Population) in 2012 (1). The introduction and improvements of the screening program played a considerable role in this decrease (2). Since 1996, Dutch women of ages 30 to 60 years are invited to attend cervical cancer screening every 5 years. From 2016 onward, primary cytology will be replaced by primary high-risk human papillomavirus (HPV) testing (3), because the sensitivity for detecting CIN2+ lesions is higher when using HPV testing (4) and HPV testing can be performed on self-samples (5, 6). Although the current screening participation rate ranges from 65% to almost 70% [source: Dutch Network and National Database for Pathology (PALGA); ref. 7], it has been estimated that more than half of the invasive cervical cancers occur in women who did not participate in screening in the previous 6 years. Moreover, some of these women had never been screened at all (8). This shows that addressing non-attendance can increase the effectiveness of the program considerably.

Self-sampling devices, with which women can collect cervical cells themselves, have been developed recently. As self-sampling is more woman-friendly and less time consuming than letting a clinician, general practitioner, or midwife collect cervical cells, it probably increases participation in screening. Indeed, the Dutch PROHTECT study has shown that offering a self-sampling HPV test to non-attendees of the program increased the overall screening participation rate by about 6 percentage points (9, 10). However, the gain in effectiveness of the program [i.e., gain in quality-adjusted life years (QALY)] probably not only depends on the increase in attendance, but also on the test characteristics of HPV self-sampling and on the ability to target higher risk non-attendees. It is likely that unscreened women (who were invited at least once but were never screened) have higher risks on developing cervical cancer than one-time non-attendees (who missed the last screen round, but have been screened in the past). Nevertheless, including any non-attendee will probably increase the effectiveness of the program. However, “switching” of regular attendees from office-based to self-sampling could, given a loss in detection

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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ACKNOWLEDGMENTS: This work has been performed within the Department of Public Health of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands.

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do: 10.1158/1055-9965.EPI-14-0998

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(i.e., more loss to follow-up, possible lower sensitivity), result in a decrease of the effectiveness of the program (i.e., losing QALYs). In other words, the QALYs gained by attracting non-attendees could be annulled by the QALYs lost by switching of regular attendees. It is unclear at which level of switching this will happen.

The aim of this study is to examine the effectiveness of offering HPV self-sampling to non-attendees of a primary HPV screening program. We modeled effects of parameters such as the relative CIN2+ sensitivity and specificity (self-sampling vs. regular sampling), the extra attendance via self-sampling, and the risk of extra attendees. Given that the percentage of women who will switch from office-based to self-sampling is unknown, we determined the percentage of switching that would result in a decrease of the total effectiveness of the program (i.e., harms outweigh the benefits, QALYs are lost). We also examined the circumstances (i.e., limits) under which it would not be cost-effective to offer HPV self-sampling to non-attendees.

Materials and Methods

We used the MISCAN-cervix model to estimate benefits, harms, and costs of offering a self-sampling HPV test to non-attendees (11). For detailed information on the model specifications, see the Supplementary Data.

Assumptions for screening and triage

The screening policy considered is primary HPV screening with cytology triage, as will be implemented in the Netherlands (Fig. 1; ref. 12). Women will be invited for screening at ages 30, 35, 40, 50, and 60 years. In addition, women will be invited at ages 45, 55, and 65 years, if they do not attend screening or have a positive HPV test in the previous screen round.

Assumptions for attendance

For HPV office-based sampling, we assumed an age-dependent overall 65% attendance rate as currently observed within the Dutch cytological screening program (source: PALGA). On the basis of the findings of the PROHTECT trial (offering self-sampling to non-attendees after an opting-out letter), we assumed that a self-sampling kit was sent to 85% of the non-attendees (13), which resulted in an extra overall attendance of 6 percentage points (9). We assumed that 29% of these extra-attendees are higher primary risk women (i.e., unscreened women who will never attend via office-based sampling and who have a 1.7 times

![Figure 1](image-url)
higher primary background risk for developing cervical cancer than women who are willing to attend office-based sampling), which is equal to the proportion in non-attendees (i.e., 10%/35% = 29%; Fig. 2). In addition to their increased primary background risk, these women also have an increased cervical cancer risk due to never attending regular screening.

We assumed that the loss to follow-up after a positive self-sampling test was higher than after a positive office-based sampling test. On the basis of the observed data (source: PALGA), we assumed that 92% of the women comply with the first triage invitation and 68% with the second. With office-based sampling, the collected material can be used both for primary HPV and direct cytology triage testing (co-collection). Therefore, the collected material can be used both for primary HPV and direct cytology triage testing (co-collection). The first and only triage invitation is 6 months after the positive screen test. This results in a compliance of 100% for immediate cytology triage testing and 92% for triage testing 6 months after the positive office-based sampling test. In case of self-sampling, co-collection is not possible and women receive their first and second triage invitation directly and 6 months after the positive screen test. This results in a compliance of 92% for immediate cytology triage testing and 68% for triage testing 6 months after the positive self-sampling test (Fig. 1).

As no data were available, we considered the two most extreme “switching” scenarios in the base-case analyses: no regular attendees and all regular attendees switch from office-based to self-sampling.

Base-case assumptions for test characteristics

The test characteristics of self-sampling were based on the assumption that a validated PCR test was used, as for instance the GP5+/6+ (4, 14). According to the recent meta-analysis of Arbyn and colleagues (15), the point estimate for the relative sensitivity of CIN2+ when comparing self-sampling with office-based sampling is approximately 0.95, whereas the point estimate for the relative specificity is probably higher than 1.00. Therefore, we assumed a 5 percentage points lower sensitivity for high-risk HPV infections when self-sampling (i.e., 80% vs. 85%), and an equal specificity of 100% (i.e., the true but uncertain value of specificity is probably somewhat lower than 100% due to cross-reactivity with low-risk HPV types and contamination). By including fast-clearing high-risk HPV infections, we were able to model a lack of specificity.

As women in our model can have multiple lesions at the same time, the CIN2+ sensitivity not only depends on the sensitivity for a high-risk HPV infection, but also on the specificity. Therefore, a 5 percentage points lower sensitivity for high-risk HPV infections and an equal specificity corresponds with a 0.95 relative CIN2+ sensitivity. On the other hand, the specificity for a CIN2+ lesion depends on the sensitivity and specificity for a high-risk HPV infection. As the prevalence of high-risk HPV infections in women without CIN2+ is higher in young women and relatively more young women use self-sampling, a 5 percentage points lower sensitivity for high-risk HPV infections and an equal specificity corresponds with a 0.99 relative CIN2+ specificity.

Assumptions for costs and utilities

Table 1 presents the input for utilities and costs used in the analyses. Utilities were based on (inter)nationally published data (16). The unit costs were estimated from a societal perspective. As compared with office-based sampling, self-sampling was assumed to be less expensive, but the costs of immediate cytology triage were higher. Diagnostic costs of women referred for colposcopy, treatment costs and costs of palliative care were equal between the two tests and were derived from previous cost studies performed in the Netherlands (17).

Cost-effectiveness analysis

We assumed that the evaluated alternative screening policies (i.e., primary HPV screening with and without offering HPV self-sampling to non-attendees) started in 2013 and continued until all women reached the final screening age. The costs and effects of the simulated screening programs were counted from 2013 onward until all simulated women (i.e., born between 1953 and 1992) had died. We also simulated the last three screening rounds before 2013 (i.e., primary cytology screening with cytology triage), because they can influence the effectiveness of the screening program after 2013. We simulated 10 million women for each strategy. Future costs and health effects [life years (LYs) lived and utility losses] were discounted toward the year 2013 at an annual rate of 3%. We computed the net costs and number of QALYs gained by screening as the differences between the simulations with and without screening. The incremental cost-effectiveness ratio (ICER) was defined as the increase in costs per additional (Q)ALY gained when self-sampling would be offered to non-attendees as compared with no such offer. The cost-effectiveness threshold was set to €20,000 per QALY gained, based on decisions of the Dutch government (18), and to €50,000, which is often used in an international perspective (19).

Multivariate sensitivity analyses

The relative CIN2+ sensitivity and specificity can differ from the estimates we used in our base-case analysis, as there is uncertainty about the true value [e.g., the 95% confidence interval (CI) for the pooled relative sensitivity and specificity when using the GP5+/6+ is 0.89 to 1.01 and 0.95 to 1.29, respectively; ref. 15]. In addition,
they depend on the type of HPV DNA test used (15), meaning that the values could be different when another validated HPV DNA test is used. Therefore, we choose to set the sensitivity for a high-risk HPV infection equally, 5 and 10 percentage points lower for self-sampling as compared with office-based sampling. The specificity was set equally, 5 and 15 percentage points lower.

As the CIN2⁺ sensitivity and specificity depend on both the sensitivity and specificity for high-risk HPV infections, the CIN2⁺ sensitivity and specificity varied slightly between different combinations of self-sampling test characteristics for high-risk HPV infections. This resulted in a relative CIN2⁺ sensitivity that varied between 0.89 and 1.02, and a relative CIN2⁺ specificity that varied between 0.84 and 1.00.

The relative CIN2⁺ sensitivity and specificity are expected to have a major influence on the effectiveness of the program, especially when women switch. Therefore, we determined the percentage of women switching (0%, 10%, ... , 90%, 100%) for which offering self-sampling is no longer effective (i.e., QALYs are lost) or cost-effective (i.e., ICER is larger than the cost-effectiveness threshold).

### Table 1. Model input: costs and utilities under base-case assumptions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Costs in €</th>
<th>Fraction</th>
<th>Utility loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invitation</strong></td>
<td>4.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary office-based sampling test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Program</td>
<td>2.68/2.95</td>
<td>0.006</td>
<td>2 wks</td>
</tr>
<tr>
<td>Organization</td>
<td>12.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office-based sampling</td>
<td>12.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>29.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time/travel</td>
<td>6.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>62.55/62.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary self-sampling test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-sampling kit</td>
<td>6.00</td>
<td>0.006</td>
<td>2 wks</td>
</tr>
<tr>
<td>Program</td>
<td>2.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td>12.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>29.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time/travel</td>
<td>6.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>52.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immediate cytology triage test after positive office-based sampling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>30.27</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immediate cytology triage test after positive self-sampling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td>10.00</td>
<td>0.006</td>
<td>2 wks</td>
</tr>
<tr>
<td>Office-based sampling</td>
<td>12.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>32.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time/travel</td>
<td>6.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>60.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytology triage test at 6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td>10.00</td>
<td>0.006</td>
<td>0.5 y</td>
</tr>
<tr>
<td>Office-based sampling</td>
<td>12.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>32.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time/travel</td>
<td>6.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>60.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis and treatment of preinvasive stages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False-positive referral</td>
<td>296</td>
<td>0.005</td>
<td>0.5 y</td>
</tr>
<tr>
<td>CIN grade 1</td>
<td>924</td>
<td>0.03</td>
<td>0.5 y</td>
</tr>
<tr>
<td>CIN grade 2</td>
<td>1,368</td>
<td>0.07</td>
<td>1 y</td>
</tr>
<tr>
<td>CIN grade 3</td>
<td>1,602</td>
<td>0.07</td>
<td>1 y</td>
</tr>
<tr>
<td><strong>Diagnosis and treatment of cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO 1A</td>
<td>5,246</td>
<td>0.062</td>
<td>5 y</td>
</tr>
<tr>
<td>FIGO 1B</td>
<td>12,440</td>
<td>0.062</td>
<td>5 y</td>
</tr>
<tr>
<td>FIGO 2⁺ (screen detected)</td>
<td>12,261</td>
<td>0.28</td>
<td>5 y</td>
</tr>
<tr>
<td>FIGO 2⁺ (clinically detected)</td>
<td>11,451</td>
<td>0.28</td>
<td>5 y</td>
</tr>
<tr>
<td>Terminal care</td>
<td>27,859</td>
<td>0.712</td>
<td>1 mo</td>
</tr>
</tbody>
</table>

**Note:** Costs are in 2012 prices.

**Abbreviation:** N.A., not applicable.

*As the total program costs were fixed, the costs per test were dependent on the number of women participating in the screening program. As this number was higher with the inclusion of the self-sampling test, the costs per test were lower in the situation with versus without self-sampling.

*We assumed that 85% of the non-attendees received the self-sampling kit of €6.00 at home, irrespective of whether they used it or not. This price was estimated on the basis of personal communication with multiple developers of brush and lavage HPV self-sampling kits. The remaining costs (e.g., laboratory, organization, etc.) were only taken into account among women who actually attended via self-sampling.

*Given that it was not required to go to the general practitioner’s office, we assumed that women who attended via self-sampling spent half of the time to screening (€2.76 instead of €5.52) as compared with women who attended via office-based sampling, while travel costs (€0.76) were absent.

*Co-collection–based analysis was possible after positive office-based sampling and, therefore, women did not have to go to the general practitioner’s office for the immediate cytology triage test.

*We assumed that part of the material costs (€2.00) was already included in the price of the office-based sampling test. Therefore, laboratory costs of immediate cytology triage after a positive office-based sampling test were lower than after a positive self-sampling test.
Utility loss associated with cytology triage. True estimates of the utility loss due to having cytology triage are unavailable. Especially if self-sampling is associated with a lower specificity, this may influence the effectiveness of offering self-sampling. Therefore, we studied the effect of assuming no utility loss to 0.012 per cervical cancer (base-case: “higher primary risk” women have a 1.7 times higher background risk as compared with regular attendees), although “higher primary risk” women still have an increased cervical cancer risk due to never attending regular screening.

Results

Base-case scenario

Table 2 presents the undiscounted effects and costs per 100,000 simulated women when offering HPV self-sampling to non-attendees of a primary HPV screening program. Without switching, offering self-sampling increased the number of triage tests and false-positive referrals for colposcopy (+7.5% and +5.7%, respectively) and decreased the number of cervical cancer cases and deaths by 7.0% and 9.2%, respectively. Because the costs increased by only 5.5%, it was not only effective (+12.1% QALYs gained) but also cost-effective (ICER of €2,115 per QALY gained) to add self-sampling to the program (Table 3).

As the sensitivity of self-sampling was lower than that of office-based sampling and because the probability of being lost to follow-up after a positive self-sampling test was higher than after a positive office-based sampling test, switching resulted in a decrease of the number of triage tests and subsequently false-positive referrals, an increase of the number of cervical cancers, and a decrease in the number of cervical cancer deaths prevented and QALYs gained. Still, when all women switched it was effective and cost-saving to offer self-sampling (Tables 2 and 3).
Multivariate sensitivity analyses

Without switching, a decrease in the CIN²⁺ sensitivity of self-sampling mainly resulted in fewer QALYs gained (Fig. 3A), whereas a decrease in the CIN²⁺ specificity mainly resulted in increased costs (Fig. 3B). Both resulted in a higher ICER (Fig. 3C). However, even when the relative sensitivity and specificity were inferior to that of office-based sampling (i.e., 0.89–0.91 and 0.84–0.85, respectively), QALYs were gained and the ICER increased (Fig. 3C). The effect of switching on the number of QALYs gained (A), extra costs (B), and ICER (C). Results are given per 100,000 simulated women (3% discounting for costs and effects). The relative CIN²⁺ sensitivity and specificity (self-sampling vs. office-based sampling) are indicated by the sensitivity and specificity in the legend. C, the combined effect of sensitivity, specificity, and switching on the ICER is only shown when adding a self-sampling test resulted in a gain of QALYs as compared with primary HPV screening alone. Therefore, a negative ICER (i.e., cost-saving) is also dominating (i.e., primary HPV screening with offering a self-sampling test to non-attendees was both more effective and less costly than primary HPV screening alone). * = Beyond this level of switching, offering a self-sampling test resulted in a loss of QALYs as compared with primary HPV screening alone. Black dashed line = primary HPV-screening without offering self-sampling to non-attendees.
was below the threshold of €20,000 per QALY gained, if no women switched.

In all scenarios, switching resulted in fewer QALYs gained (Fig. 3A). This effect was larger in case the relative sensitivity was lower than 1.00. However, even when the test characteristics of self-sampling were inferior to that of office-based sampling, QALYs were only lost when more than 60% of the women switched (Table 4). When they were slightly inferior (i.e., 0.95–0.97 relative sensitivity and 0.94–0.95 relative specificity) or similar (i.e., 1.01–1.02 relative sensitivity and 0.99–1.00 relative specificity), it was effective under every switching scenario. If self-sampling specificity was inferior, the costs of offering HPV self-sampling increased with increasing percentages of switching (Fig. 3B). Considering a cost-effectiveness threshold of 20,000 per QALY gained, the switching limit was up to 30 percentage points lower (Table 5). Therefore, offering self-sampling was not effective or cost-effective when more than 40% of the women switch and test characteristics of self-sampling were inferior to those of office-based sampling.

The effect of the level of utility loss associated with cytology triage was negligible (Table 4). Varying the extra attendance or

### Table 4. For what switching percentage does offering self-sampling to non-attendees lead to a loss in QALYs?

<table>
<thead>
<tr>
<th>Relative CIN2 sensitivity and specificity (self vs. office-based sampling)</th>
<th>Base case</th>
<th>Utility loss due to cytology triage</th>
<th>Extra attendance (percentage points)</th>
<th>Background risk of higher primary risk women</th>
<th>% Extra attendees consisting of higher primary risk women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Specitivity</td>
<td>Base case</td>
<td>0.003</td>
<td>0.0012</td>
<td>10</td>
</tr>
<tr>
<td>0.97</td>
<td>0.95</td>
<td>Ind.</td>
<td>Ind.</td>
<td>Ind.</td>
<td>Ind.</td>
</tr>
<tr>
<td>0.91</td>
<td>0.85</td>
<td>&gt;80</td>
<td>&gt;70</td>
<td>&gt;70</td>
<td>&gt;70</td>
</tr>
<tr>
<td>0.90</td>
<td>0.95</td>
<td>&gt;70</td>
<td>&gt;70</td>
<td>&gt;70</td>
<td>&gt;70</td>
</tr>
<tr>
<td>0.91</td>
<td>0.85</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

NOTE: For every scenario, the minimum switching percentage is given under which it is no longer effective (i.e., QALYs are lost) to offer self-sampling to non-attendees. The switching percentage varies between 0 (i.e., even when no women switch it is not effective to offer self-sampling), >90 (i.e., when more than 90% of the women switch it is not effective to offer self-sampling), to independent (ind.; i.e., independent of how many women switch, it is always effective to offer self-sampling).

Base-case assumptions: Utility loss due to cytology triage ¼ 0.008 per week, extra attendance ¼ 6 percentage points, background risk of higher primary risk women as compared with the rest of the screen population ¼ 17 times higher. % of higher primary risk women in extra attendees ¼ 29%. These variables, if not varied, were held constant at their base-case level.

### Table 5. For what switching percentage is offering self-sampling to non-attendees not (cost-)effective?

<table>
<thead>
<tr>
<th>Relative CIN2 sensitivity and specificity (self vs. office-based sampling)</th>
<th>Base case</th>
<th>Utility loss due to cytology triage</th>
<th>Costs of self-sampling kit in €</th>
<th>Extra attendance (percentage points)</th>
<th>Background risk of higher primary risk women</th>
<th>% Extra attendees consisting of higher primary risk women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Specitivity</td>
<td>Base case</td>
<td>0.003</td>
<td>0.012</td>
<td>10</td>
<td>3</td>
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<tr>
<td>1.01</td>
<td>0.99</td>
<td>Ind.</td>
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<tr>
<td>1.02</td>
<td>0.84</td>
<td>&gt;80</td>
<td>&gt;60</td>
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<tr>
<td>0.95</td>
<td>0.99</td>
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<tr>
<td>0.96</td>
<td>0.95</td>
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NOTE: For every scenario the minimum switching percentage is given under which it is no longer effective (i.e., QALYs are lost) and/or cost-effective (i.e., €20,000 per QALY gained) to offer self-sampling to non-attendees. The switching percentage varies between 0 (i.e., even when no women switch it is not effective and/or cost-effective to offer self-sampling), >90 (i.e., when more than 90% of the women switch it is not effective and/or cost-effective to offer self-sampling), to independent (ind.; i.e., independent of how many women switch, it is always effective and cost-effective to offer self-sampling).

Base-case assumptions: Utility loss due to cytology triage ¼ 0.008 per week, extra attendance ¼ 6 percentage points, background risk of higher primary risk women as compared with the rest of the screen population ¼ 17 times higher. % of higher primary risk women in extra attendees ¼ 29%. These variables, if not varied, were held constant at their base-case level.

*Because a higher utility loss for primary than triage testing does not seem realistic we also assume no utility loss for primary testing.

*Average ¼ equal to the rest of the screen population.
background risk of higher primary risk women had more influence. When the extra attendance was halved (from 6 to 3 percentage points) or if higher primary risk women did not have an elevated background risk, QALYs were lost when more than 50% of the women switched and test characteristics were slightly inferior. When they were inferior, it was no longer effective if more than 30% of the women switched. The most influential parameter was the attendance of higher primary risk women. When they did not attend, it was not effective to offer self-sampling when more than 60% of the women switched and test characteristics were equal. In case they were inferior, this threshold decreased to 10%. For offering self-sampling to be cost-effective, these switching thresholds were even lower (Table 5).

Discussion

The number of QALYs gained by offering HPV self-sampling to non-attendees was influenced by self-sampling test characteristics, the extra attendance via self-sampling, and the risk of extra attendees. When none of the regular attendees switched to self-sampling, it was always effective to offer HPV self-sampling. Switching resulted in fewer QALYs gained because the probability of being lost to follow-up after a positive self-sampling test was higher than after a positive office-based sampling test. If in addition the sensitivity of self-sampling was lower than that of office-based sampling, the number of QALYs gained decreased even more. However, when test characteristics were inferior, up to 60% of the regularly attended could switch before the QALYs gained by the 6 percentage points extra attendance were annulled by the QALYs lost by switching. This percentage dropped to 30% when the extra attendance halved from 6 to 3 percentage points or when higher primary risk women did not have an elevated background risk. It dropped to 10% if higher primary risk women did not attend self-sampling. When also considering a cost-effectiveness threshold of €20,000 per QALY gained, these switching thresholds were 10 to 20 percentage points lower.

Our base-case assumption of 6 percentage points extra attendance was based on the Dutch PROHTECT trial in which a self-sampling kit was sent to 85% of all non-attendees (i.e., the remaining 15% opted-out via a letter; ref. 9). Using another strategy will probably result in another extra attendance rate. If this rate will be lower than 3 percentage points (almost) no women can switch before more QALYs are lost than gained.

We assumed that a subset of the unscreened women have a 1.7 times higher background risk on cervical cancer (i.e., higher primary risk women) than the rest of the screening population, which was based on model calibration. Dugue and colleagues' (20) results have shown that non-attendees of cervical cancer screening (i.e., no cervical smear taken in the past 8 years) had a 3.8-fold increased risk of dying from non-cervical (i.e., non-screened) HPV-associated cancers, which seems to confirm our assumption that at least part of the non-attendees have an increased background risk. Although the PROHTECT study showed that unscreened women (i.e., invited for screening at least once but never attended) attended via self-sampling (21), it is uncertain whether this is the subset with an increased background risk. If these higher primary risk women do not attend via self-sampling, 10% to 60% of the women can switch before QALYs are lost by offering HPV self-sampling to non-attendees.

The relative sensitivity and specificity of self-sampling as compared with office-based sampling will depend on the type of HPV DNA test used (15, 22). However, even when a validated PCR is used (e.g., GP5+/6+ or the real-time hrHPV test), it is possible that the sensitivity and specificity of self-sampling are both inferior to that of office-based sampling. In fact, relative test characteristics of self-sampling might even be worse than we assumed in our sensitivity analyses (15). In that case, the maximum percentage of women that can switch before QALYs are lost is also lower.

Studies in Sweden (23), Finland (24), the United Kingdom (25), and Italy (26) have also shown that offering self-sampling to non-attendees increased screening participation rates. We expect that our conclusions to a large extent apply to other countries and regions with well-organized invitational screening programs with a high compliance and an optimal age range and screening frequency. Even if this would mean that HPV self-sampling would be offered to non-attendees of a primary cytology instead of a primary HPV program. For countries and regions with a lower background risk and/or a more intensive screening program as compared with the Netherlands, benefits of increased participation due to self-sampling are probably lower. In countries without a highly organized invitational program, it may not be feasible to offer a self-sampling test to unscreened women. Instead, it could be offered to the general population by selling it over the counter. When screening is not reimbursed by the government, it is questionable to what extent unscreened women will use self-sampling. Indeed, a discrete choice experiment in the United States showed that vulnerable adults valued costs higher than the kind of screening offered, which are important and uncertain parameters for the effectiveness of offering self-sampling.

A limitation of our study is that we only focused on unvaccinated women. Screening programs will probably be adapted when vaccinated cohorts reach the start age of screening. A separate analysis for this future situation is beyond the scope of the present analysis. However, we expect that offering self-sampling to non-attendees will be less (cost-)effective, because we expect that fewer health effects can be gained by increasing attendance because of a lower background risk. Another drawback is the limited transposability to other health systems. We expect lower benefits of increased participation due to self-sampling in screening programs that are more intensive than the Dutch future program will be (i.e., 5 lifetime screens at ages 30, 35, 40, 50, and 60 years). Moreover, we might have overestimated the colposcopy compliance after a positive self-sampling test, because this may be lower than after a positive office-based sampling test. This may have resulted in a slight overestimation of the effectiveness of self-sampling. In addition, the relative CIN2+ specificity as described in our study will be somewhat higher when regular attendees...
switch, as the prevalence of high-risk HPV infections in women without a CIN2+ is slightly lower in regular attendees as compared with non-attendants attending self-sampling. Furthermore, we did not account for other healthcare that women may get while attending clinic-based screening. This may have underestimated health losses in regular attendees switching to self-sampling, as well as health gains in the small group of extra attendees with a positive self-sampling test complying with their triage invitation.

Offering self-sampling to non-attendants clearly offers an opportunity to increase health benefits in cervical cancer screening if health providers make sure that (i) the relative CIN2+ sensitivity is at least 0.95, (ii) unscreened attendees are recruited with self-sampling, and (iii) the total attendance increases by at least 6 percentage points. Otherwise, switching of regular attendees to self-sampling may annul the benefits of self-sampling and even decrease the effectiveness of a primary HPV screening program.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

Because the Dutch National Institute for Public Health and the Environment is a nonprofit organization, the funding source had no involvement in the study design, data collection, data analysis, interpretation of the data, writing of the report or in the decision to submit the article for publication.

When Is It Effective to Offer Self-Sampling to Non-Attendees?

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Acknowledgments

Data sharing: Model inputs, technical details, and more extensive or intermediate results are available from the corresponding author at k.rozemeijer@erasmusmc.nl. Extra material supplied by the author is also available as Supplementary Material.

Grant Support

This study was funded by the Dutch National Institute for Public Health and the Environment (007/12 Vidi & NvO/vEM).

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Received August 26, 2014; revised November 19, 2014; accepted November 23, 2014; published OnlineFirst November 28, 2014.

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www.aacjournals.org Cancer Epidemiol Biomarkers Prev; 24(5) May 2015 781

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Cancer Epidemiology, Biomarkers & Prevention

Offering Self-Sampling to Non-Attendees of Organized Primary HPV Screening: When Do Harms Outweigh the Benefits?

Kirsten Rozemeijer, Inge M.C.M de Kok, Steffie K. Naber, et al.


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