Offering self-sampling for human papillomavirus testing to non-attendees of the cervical screening programme: Characteristics of the responders

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ABSTRACT

Background: Self-sampling for high-risk human papillomavirus (hrHPV) testing is accepted by up to 30% of non-attendees to the regular cervical screening programme. Here, the yield of cervical intraepithelial neoplasia (CIN)2 or worse (≥CIN2) and CIN3 or worse (≥CIN3) of 15,274 HPV self-sampling responders amongst non-attendees were compared to that of 176,027 women participating in regular screening in the same period and in the same region. We also analysed which subpopulations amongst non-attendees are targeted by HPV self-sampling, and which characteristics relate to hrHPV prevalence and yield of ≥CIN2/≥CIN3.

Method: Data from two consecutive self-sampling studies were pooled. ≥CIN2/≥CIN3 yields, screening history, age and ethnic status were retrieved from centralised pathology and screening databases, respectively. A logistic regression model was fitted to analyse method of invitation, ethnicity, age group, and screening history as predictors for response rate, hrHPV presence and ≥CIN2/≥CIN3 in non-attendees. For screening history analyses, women <34 years were excluded since it was the first screening round in their life.

Findings: ≥CIN2/≥CIN3 yields of HPV self-sampling responders were higher than those of screening participants (≥CIN2: relative risk (RR) = 1.6, 95% confidence interval = 1.4–1.9; ≥CIN3: RR = 1.8, 95% CI = 1.5–2.1 with relative risk values increasing with age (test of homogeneity: ≥CIN2: p = 0.04; ≥CIN3: p = 0.03).

Native Dutch non-attendees responded better than immigrants (32% versus 22%, p < 0.001) and those screened in the previous round revealed a higher response than underscreened (i.e. previous smear taken >7 years ago) or never screened (34% versus 25%, p < 0.001) women. Strikingly, amongst under- and never screened women aged ≥39 years, never screened women responded better (25% versus 23%, p < 0.001). ≥CIN2 rates were higher amongst responding native Dutch women than immigrants (p < 0.001), and higher in under-/never screened women than in women screened in the previous round (p < 0.001).

Interpretation: Offering hrHPV self-sampling increases the efficacy of the screening programme by targeting a substantial portion of non-attendees of all ethnic groups who have not regularly been screened and are at highest risk of ≥CIN2.

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Key messages

What is known about this topic?

Self-sampling for high-risk human papillomavirus (hrHPV) testing (i.e. HPV self-sampling) is accepted by up to 30% of non-attendees to the regular cervical screening programme. However, the population of non-attendees reached by HPV self-sampling is poorly defined.

What is learned about this topic from this study?

1. Response rate of non-attendees to HPV self-sampling is particularly affected by ethnicity and screening history.
2. Native Dutch non-attendees responded better than immigrant non-attendees. Amongst immigrants, non-attendees from developed countries responded better than immigrants from developing countries.
3. Amongst all ethnic groups of non-attendees, never screened women responded better than underscreened women.
4. Since ≥CIN2/≥CIN3 yields were highest amongst native Dutch non-attendees and those who were under- or never screened offering self-sampling for HPV testing is a meaningful and effective approach for reaching those women who are in the highest need for cervical screening.

1. Introduction

Organised cervical screening programmes have reduced the incidence of and mortality from cervical cancer. Non- or infrequent attendance is one of the main threats to the success of those screening programmes. Targeting non-attendees is important because these women have an increased risk of cervical cancer. Recently, we found that offering self-sampling for high-risk HPV (hrHPV) testing (further referred to as HPV self-sampling) to non-attendees is an effective approach for increasing screening coverage (PROHTECT studies).

Nevertheless, it is still unknown which subpopulations of non-attendees, in terms of age, ethnicity and screening history, are targeted by HPV self-sampling. It is known that screening participation rates vary across ethnic populations. Moreover, not being screened within previous screening intervals has been found to be associated with increased risks of cervical intraepithelial neoplasia (CIN) grades 2 and 3, and cervical cancer.

Here, we used the pooled data from the two consecutive PROHTECT HPV self-sampling studies comprising a total of 52,447 non-attendees of the regular screening programme recruited from 230,509 women invited for cervical screening in the counties Noord-Holland and Flevoland in 2005 and 2006. First, we compared the yield of CIN2 or worse (≥CIN2) and CIN3 or worse (≥CIN3) of HPV self-sampling responders (n = 15,274) with that of their counterparts participating in primary cytology-based screening (n = 176,027). In addition, we analysed which subpopulations amongst non-attendees are targeted by HPV self-sampling, and how these characteristics relate to hrHPV prevalence and yield of ≥CIN2 and ≥CIN3.

2. Methods

2.1. Study population

2.1.1. Non-attendees of the regular screening programme

All 54,482 women out of 230,509 invitees (aged 30–60 years) in the counties Noord-Holland and Flevoland who did not attend the cervical screening programme after two invitations in 2005 and 2006 were registered as screening non-attendees and were recruited to participate in the PROHTECT studies from December 2006 to March 2008. In these studies, the effect of offering self-sampling for hrHPV DNA testing by Hybrid Capture 2 (HC2) on response rate and cumulative 18-month ≥CIN2/≥CIN3 yield was evaluated. Response rate was compared with women who received a second reminder for conventional cytology (recall control group). Written informed consent was provided by all women. The studies were approved by the Ministry of Public Health (no. 2006/01WBO) and registered as International Standard Randomised Controlled Trial, numbers ISRCTN45527158 (PROHTECT-1) and NTR1851 (PROHTECT-2). In the PROHTECT-1 study (non-attendees in 2005), self-sampling of a (cervico)vaginal specimen by a lavage-based device (Delphi®-Screener, Delphi-bioscience, The Netherlands) was offered to 27,792 women (self-sampling group), and a second recall for conventional cytology was sent to another 281 women (recall control group). In PROHTECT-2 (non-attendees in 2006) a brush-based self-sampling device (VibaBrush®, Rovers Medical Devices, The Netherlands) was offered to 26,145 women, whereas 264 women received a second recall for cytology. Further study details have been described before. Apart from the self-sampling method, both PROHTECT studies were essentially the same in design. Women with a hrHPV-positive self-sample were advised to visit a general practitioner for a cervical smear and referred for colposcopy in case of abnormal cytology (threshold borderline or mild dyskaryosis (BMD), equalling AGC/ASC-US/ASC-H/LSIL). Those with normal cytology received a re-invitation for a cervical scrape after 1 year, and were referred for colposcopy if either hrHPV test result was positive or cytology was abnormal. Women of the recall control groups were managed according to the current cytology guidelines of the national screening programme. For the purpose of this study data from these PROHTECT studies were pooled.

2.1.2. Screening participants

The pooled 18 month yields of ≥CIN2/≥CIN3 in the HPV sampling group were compared with those of all women (n = 176,027) who did participate in the regular screening programme in the same region and the same period. These women were managed according to the current cytology screening guidelines.

Cytology and histology results of both the HPV sampling group and the screening participants were obtained by
querying the nationwide, centralised network and registry of histology and cytology database (PALGA; Bunnik, The Netherlands) as well as record tracking of individual cases of invited non-attendees. We linked patient records based on identity of the encrypted first four letters of the maiden name and date of birth. Groups of records presumably belonging to a single person were ‘eyeballed’ (checking every case manually) to filter out administrative twins by checking domicile, initials and apparent inconsistencies in clinical history.

2.2. Study parameters

Response rate in PROHTECT was operationally defined as the proportion of eligible women of both arms who sent in an informed consent form, combined with submission of a self-sampled specimen for women assigned to the self-sampling group.6,7 hrHPV prevalence was defined as percentage of women with HC2 hrHPV-positive self-sampled specimens.6,7

Yields of ≥CIN2/≥CIN3/cervical carcinoma refer to the 18-month cumulative yields of these lesions in women in the self-sampling group who submitted a self-collected specimen or women who participated in the screening programme.

Ethnic status of non-attendees defined by country of birth was retrieved from the invitational database of the Regional Health Council. In accordance with the method of the Dutch Central Bureau of Statistics, countries of origin (in total, \(n = 188\)) were grouped into three major groups: The Netherlands (native Dutch), Other Developed countries (i.e. Europe, United States of America/Canada). Australia and New-Zealand) and Developing countries (i.e. the major four immigrant populations in the Netherlands (The Netherlands Antilles, Surinam, Turkey and Morocco) and Other Developing countries).

In the Netherlands, women are invited for screening every five years in the year in which they reach the age of 30, 35, 40 etc. till 60 years. Age categorisation was based on the number of prior screening rounds for which women had been invited. As a consequence the following age categories were defined: 29–33 years, 34–38 years, 39–43 years, 44–48 years, 49–53 years, 54–58 years and 59–63 years.

For cytology screening history of non-attendees the time period between the invitation for HPV self-sampling and the last smear taken prior to the PROHTECT test was considered. For this subgroup comparison, only women who had been invited in one or more previous screening rounds (i.e. women aged 34–63 years; \(n = 43,979\)) were included since younger women had no screening history. Since the PALGA database was linked with the invitational database for call and recall not earlier than in 2006, smears made for the invitational screening programme and opportunistic/diagnostic smears were similarly assigned. Based on time since the last smear, women were categorised into one of three subgroups: 1. last smear taken ≤7 years before participating in HPV self-sampling, considered to represent women screened in the previous round, 2. last smear taken >7 years ago (i.e. underscreened women) or 3. no smear in the past (i.e. never screened women). It should be noticed that PALGA has been virtually complete only since 1990 onwards (www.palga.nl). This means that the screening history can be screened only till 1990, and ‘no screening history in the past’ is defined as no screening history in the past approximately 15 years.

2.3. Data analysis

The pooled 18-month cumulative ≥CIN2/≥CIN3 yields in self-sampling responders were compared with those of screening responders using Mantel–Haenszel (M–H) Chi-square testing. For analysing the age stratified data we used the M–H test of homogeneity.

We performed multiple logistic regression analyses models on the potential risk factors as ethnic background, age group and screening history. Outcome measures were response to HPV self-sampling invitation, hrHPV test result and ≥CIN2/≥CIN3/carcinoma. In the analyses for response to self-sampling invitation, the method of invitation (self-sampling or second recall) was also included as a predictor. Significance of the effects was evaluated with the Wald test. For all tests a significance level (\(\alpha\)) of 0.05 was used.

The analyses were performed by using SPSS 15.0 software and STATA 10 package.

3. Results

3.1. HPV self-sampling responders of non-attendees of the regular screening programme

In the PROHTECT studies, a total of 54,482 non-attendees were recruited, of whom 53,937 women were allocated to the self-sampling group and 545 to the recall control group. A total of 1490 women were non-eligible, mainly due to previous hysterectomy, leaving 52,447 women in the self-sampling group. Seven women in the recall control group were non-eligible, leaving 538 women. Finally 15,274 women (29%) submitted a self-sampled specimen. Table 1 provides further details of the self-sampling groups of the individual PROHTECT studies.

3.2. Comparison of ≥CIN2/≥CIN3 yields between self-sampling responders and screening participants

Fig. 1 and Table 2 show the pooled cumulative 18-month ≥CIN2/≥CIN3 yields in PROHTECT self-sampling responders versus screening participants. The ≥CIN2/≥CIN3 yields of self-sampling responders were higher than those of screening participants (≥CIN2: relative risk (RR) = 1.6, 95% confidence interval = 1.4–1.9; ≥CIN3: RR = 1.8, 95% CI = 1.5–2.1). These relative risk values increased with age (test of homogeneity (M–H): ≥CIN2: \(p = 0.04\); ≥CIN3: \(p = 0.03\)). But were also significantly higher than 1 in women aged 29–33 years (≥CIN2: RR = 1.4, 95% CI=1.1–1.8; ≥CIN3: RR = 1.6, 95% CI = 1.2–2.2). When restricting the analysis to women who had abnormal cytology (≥BMD) at baseline similar relative risk values were obtained. In for example women aged 29–33 years with abnormal cytology these relative risks were 1.4 (95% CI = 1.1–1.8) and 1.6 (95% CI = 1.2–2.1) for ≥CIN2 and ≥CIN3, respectively.

Also cervical carcinomas were more frequently found amongst self-sampling responders than regular screening participants (0.09% versus 0.03%, \(p = 0.002\); Table 2). Due to
the low number of carcinomas the effect of age could not be tested.

3.3. Response rate of non-attendees in relation to invitational method, ethnicity, age, and screening history

The response rate was analysed by fitting a logistic regression model with method of invitation, ethnicity, age group and screening history as predictors.

Women assigned to the self-sampling group responded significantly better than those assigned to the recall control group (29% versus 12%; $\chi^2(1) = 73.9$, $p < 0.001$, Odds Ratio (OR) = 3.2, 95% CI = 2.5–4.2; Table 2). The response rate was also related to ethnicity ($\chi^2(6) = 595.5$, $p < 0.001$), age ($\chi^2(6) = 26.6$, $p < 0.001$), and screening history in women ≥34 years ($\chi^2(2) = 429.4$, $p < 0.001$).

Native Dutch women responded better than immigrant women ($\chi^2(1) = 402.6$, $p < 0.001$, OR = 24, 95% CI = 18–33), and

Table 1 – Characteristics of self-sampling groups of individual PROHTECT studies.

<table>
<thead>
<tr>
<th>Year of non-attendance</th>
<th>Year of recruitment for study</th>
<th>Device</th>
<th>Number of eligible women</th>
<th>Response rate to HPV self-sampling</th>
<th>High-risk human papillomavirus (hrHPV) positivity amongst self-sampling responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROHTECT-1</td>
<td>PROHTECT-2</td>
<td>OR (95% confidence interval)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–007</td>
<td>2007–008</td>
<td>Delphi screener</td>
<td>Viba brush</td>
<td>26,886</td>
<td>7404 (27%)</td>
</tr>
<tr>
<td>757 (10.2%)</td>
<td>652 (8.3%)</td>
<td>1.3 (1.2–1.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 – Yield of ≥ cervical intraepithelial neoplasia (CIN)2 in pooled PROHTECT-1 and PROHTECT-2 studies and amongst women participated the regular cervical screening programme.

* Excluded due to prior hysterectomy or past away during the study.
Table 2 – Response rate and yield of ≥ cervical intraepithelial neoplasia (CIN)2/≥CIN3 and carcinoma in self-sampling responders compared to regular screening participants from the same region in 2005 and 2006.

<table>
<thead>
<tr>
<th>Age</th>
<th>Responders PROHTECT</th>
<th>Participants regular screening programme (RSP)</th>
<th>PROHTECT versus RSP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n %</td>
<td>n %</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>≥CIN2</td>
<td>≥CIN3</td>
<td>Carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative risk (RR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% Confidence interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>29–33 years</td>
<td>2328 27 71 3.1 54 2.3 2 0.09</td>
<td>21,524 61 463 2.2 308 1.4 4 0.02</td>
<td>1.418 (1.1, 1.8)</td>
</tr>
<tr>
<td>34–38 years</td>
<td>3000 30 65 2.2 44 1.5 4 0.1</td>
<td>28,861 64 401 1.4 273 1.0 16 0.06</td>
<td>1.559 (1.2, 2.0)</td>
</tr>
<tr>
<td>39–43 years</td>
<td>2612 30 26 1.0 7 0.1 1 0.04</td>
<td>27,315 71 277 1.0 172 0.6 19 0.07</td>
<td>0.982 (0.7, 1.5)</td>
</tr>
<tr>
<td>44–48 years</td>
<td>2308 30 27 1.2 18 0.8 4 0.2</td>
<td>29,625 72 222 0.8 138 0.5 7 0.02</td>
<td>1.561 (1.0, 2.3)</td>
</tr>
<tr>
<td>49–53 years</td>
<td>1904 30 12 0.6 10 0.5 1 0.05</td>
<td>25,827 72 102 0.4 63 0.2 6 0.02</td>
<td>1.596 (0.9, 2.9)</td>
</tr>
<tr>
<td>54–58 years</td>
<td>1637 28 10 0.6 8 0.5 0 0.00</td>
<td>20,181 69 34 0.2 24 0.1 4 0.02</td>
<td>3.626 (1.8, 7.3)</td>
</tr>
<tr>
<td>59–63 years</td>
<td>1485 27 7 0.5 6 0.4 1 0.07</td>
<td>22,694 59 41 0.2 22 0.1 3 0.01</td>
<td>2.609 (1.2, 5.8)</td>
</tr>
<tr>
<td>Total</td>
<td>15,274 29 218 1.4 157 1.0 13 0.09</td>
<td>176,027 67 1540 0.9 1000 0.6 59 0.03</td>
<td>1.631 (1.4, 1.9)</td>
</tr>
</tbody>
</table>

Table 3 – High-risk human papillomavirus (hrHPV) prevalence and ≥ CIN2/≥CIN3/carcinoma yield in self-sampling group, and response rate in both self-sampling and recall control group, stratified by country of birth.

<table>
<thead>
<tr>
<th>Country of birth</th>
<th>Recall control group</th>
<th>Self-sampling group</th>
<th>Total</th>
<th>Self-sampling group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Invited</td>
<td>Response (%)</td>
<td>Participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n %</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>45 382</td>
<td>11.8</td>
<td>11,705</td>
<td>36,072</td>
</tr>
<tr>
<td>Other developed countries</td>
<td>5 40</td>
<td>12.5</td>
<td>969</td>
<td>4036</td>
</tr>
<tr>
<td>Developing countries (subtotal)</td>
<td>13 116</td>
<td>11.2</td>
<td>2600</td>
<td>12,339</td>
</tr>
<tr>
<td>Surinam</td>
<td>2 25</td>
<td>8.0</td>
<td>574</td>
<td>2930</td>
</tr>
<tr>
<td>Netherlands Antilles</td>
<td>0 4</td>
<td>0.0</td>
<td>143</td>
<td>614</td>
</tr>
<tr>
<td>Morocco</td>
<td>1 22</td>
<td>4.5</td>
<td>512</td>
<td>2451</td>
</tr>
<tr>
<td>Turkey</td>
<td>3 13</td>
<td>23</td>
<td>378</td>
<td>1613</td>
</tr>
<tr>
<td>Other developing countries</td>
<td>7 52</td>
<td>13.5</td>
<td>993</td>
<td>4731</td>
</tr>
<tr>
<td>Total</td>
<td>63 538</td>
<td>11.7</td>
<td>15,274</td>
<td>52,447</td>
</tr>
</tbody>
</table>

* The values in this row are the cumulative values summed over countries that are listed below in the shaded rows.
Table 4 – Response rate and high-risk human papillomavirus (hrHPV) prevalence in self-sampling responders stratified by age.

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>Total invited</th>
<th>Response rate</th>
<th>HPV-positive</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>29–33 years</td>
<td>8468</td>
<td>2328 (28%)</td>
<td>364 (16%)</td>
<td>14.2–7.1%</td>
</tr>
<tr>
<td>34–38 years</td>
<td>9937</td>
<td>3000 (30%)</td>
<td>350 (11.7%)</td>
<td>10.5–12.8%</td>
</tr>
<tr>
<td>39–43 years</td>
<td>8576</td>
<td>2612 (31%)</td>
<td>211 (8.1%)</td>
<td>7.0–9.1%</td>
</tr>
<tr>
<td>44–48 years</td>
<td>7796</td>
<td>2308 (30%)</td>
<td>152 (6.6%)</td>
<td>5.6–7.6%</td>
</tr>
<tr>
<td>49–53 years</td>
<td>6435</td>
<td>1904 (30%)</td>
<td>132 (6.9%)</td>
<td>5.8–8.1%</td>
</tr>
<tr>
<td>54–58 years</td>
<td>5806</td>
<td>1637 (27%)</td>
<td>113 (6.9%)</td>
<td>5.7–8.1%</td>
</tr>
<tr>
<td>59–63 years</td>
<td>5429</td>
<td>1485 (27%)</td>
<td>87 (5.9%)</td>
<td>4.7–7.1%</td>
</tr>
<tr>
<td>Total (29–63 years)</td>
<td>5247</td>
<td>15,274 (29%)</td>
<td>1409 (9.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* These percentages are based on the response rate as denominator.

...of the immigrants, those from Other Developed countries revealed a higher response rate than those from Developing countries ($\chi^2 = 8.6$, $p < 0.01$, OR = 2.0, 95% CI = 1.3–3.1). No differences in response rate between subgroups of immigrants from Developing countries (i.e. Netherlands Antilles, Surinam, Turkey and Morocco versus Other Developing countries) were found (Table 3).

There was no age trend in the response rate amongst PROH-women (Table 4).

Amongst women of $\geq 34$ years, those who were screened at the previous screening round revealed a higher response rate ($\chi^2 = 218$, $p < 0.001$) and underscreened or never screened women ($\chi^2 = 389.4$, $p < 0.001$, OR = 1.5, 95% CI = 1.5–1.6). This difference was also evident when the analysis was restricted to women $\geq 39$ years, who had been invited at least to two prior screening rounds ($\chi^2 = 420.9$, $p < 0.001$, OR = 2.7, 95% CI = 2.5–3.0). Strikingly, amongst women $\geq 39$ years, never screened women revealed a higher response rate ($\chi^2 = 2270/9151$, 25%) than underscreened women ($\chi^2 = 33.3$, $p < 0.001$, OR = 1.2, 95% CI = 1.2–1.3). This was evident for women of all ethnic groups, although for immigrant women from Other Developing countries this difference did not reach significance (Fig. 2).

3.4. HPV prevalence in relation to ethnicity, age, and screening history

Of the 15,274 women who submitted a self-sampled specimen, 1409 (9.2%) were hrHPV-positive. Neither ethnicity ($\chi^2 = 7.4$, $p = 0.3$) nor screening history (women $\geq 34$ years: $\chi^2 = 0.2$, $p = 0.9$) were found to be related to hrHPV prevalence. The proportion of hrHPV-positive women decreased with age till the age category 39–43 years (29–33 years: 15% ($\chi^2 = 129.8$, $p < 0.001$), 34–38 years: 11.7% ($\chi^2 = 70.8$, $p < 0.001$), 39–43 years: 8.1% ($\chi^2 = 7.0$, $p < 0.01$, OR = 1.3, 95% CI = 1.1–1.5), and remained stable in older women (Table 4).

3.5. $\geq$ CIN2/$\geq$ CIN3 yield in relation to ethnicity, age, and screening history

Sixty one (0.4%) of the self-sampling responders had CIN2, 144 (0.9%) CIN3 and 13 (0.09%) had cervical carcinoma. The overall $\geq$ CIN2 and $\geq$ CIN3 yields were 1.4% ($n = 218$) and 1.0% ($n = 157$), respectively (Table 3).

Both the $\geq$ CIN2 and $\geq$ CIN3 rates were related to ethnicity ($\geq$ CIN2: $\chi^2 = 14.6$, $p < 0.001$; $\geq$ CIN3: $\chi^2 = 9.2$, $p < 0.01$). The $\geq$ CIN2/$\geq$ CIN3 rates were higher amongst native Dutch women than amongst immigrants ($\geq$ CIN2: $\chi^2 = 13.0$, $p < 0.01$, OR = 2.4, 95% CI = 1.5–3.8; $\geq$ CIN3: $\chi^2 = 8.7$, $p < 0.01$, OR = 2.6, 95% CI = 1.4–4.9). No significant difference was found between immigrant women from Developing countries and those from Developing countries. Due to the low frequencies of $\geq$ CIN2 no further subdivision was made amongst women from Developing countries.

The $\geq$ CIN2/$\geq$ CIN3 yields were significantly related to age ($\geq$ CIN2: $\chi^2 = 52.3$, $p < 0.001$; $\geq$ CIN3: $\chi^2 = 38.4$, $p < 0.001$) and were relatively high in young women. Of all $\geq$ CIN2 lesions, 32% were in the group of 29–33 years and only 3.2% were in the group of 59–63 years; likewise 34% of all $\geq$ CIN3 were in the group of 29–33 years and 3.8% in women of 59–63 years.

The effect of screening history of women $\geq 34$ years on $\geq$ CIN2/$\geq$ CIN3/carcinoma yields, stratified by ethnicity and age, is shown in Table 5. There was a significant effect of screening history on both $\geq$ CIN2 ($\chi^2 = 11.1$, $p < 0.01$) and $\geq$ CIN3 ($\chi^2 = 6.6$, $p < 0.05$). Women who were under- or never
screened revealed significantly higher ≥CIN2/≥CIN3 yields than women screened within the last 7 years (≥CIN2: $\chi^2(1) = 7.8$, $p < 0.01$, OR = 2.7, 95% CI = 1.3–5.3) and ≥CIN3: $\chi^2(1) = 4.6$, $p < 0.05$, OR = 2.5, 95% CI = 1.1–5.5). A similar effect was seen after restricting the analyses to women ≥39 years (≥CIN2: $\chi^2(2) = 14.2$, $p < 0.001$); ≥CIN3: $\chi^2(2) = 11.4$, $p < 0.01$). The ≥CIN2/≥CIN3 yields were highest in never screened women (Fig. 3).

Both in women of ≥34 and those of ≥39 years there was no significant effect of screening history on carcinoma yield. This reflects the fact that two carcinomas were diagnosed in women ≥33 years and the number of carcinomas in the older age groups was apparently too low to reach significance.

4. Discussion

In the screening region of the Netherlands investigated here the attendance rate was 67%, which is in agreement with the overall attendance in the Netherlands after one year (65%). Together with opportunistic smears the coverage of the population after 5 years is about 77%, which leaves...
23% invited women unprotected. We showed that the yields of \( \geq \text{CIN2/}\geq \text{CIN3} \) were higher in the HPV self-sampling group of the non-attendees than in the regular attendees of the screening programme. Moreover, the relative \( \geq \text{CIN2/}\geq \text{CIN3} \) risk values increased with age.

In addition, we found that Dutch non-attendees responded better and also revealed significantly higher \( \geq \text{CIN2/}\geq \text{CIN3} \) yields than their immigrant counterparts. Amongst women invited at earlier screening rounds, never screened women responded better to HPV self-sampling than underscreened women, independent from ethnicity. These underscreened and never screened women displayed the highest risk of \( \geq \text{CIN2/}\geq \text{CIN3/carcinoma} \). These are the women who health programme managers particularly like to target to improve cervical cancer prevention strategies, supporting the notion that offering HPV self-sampling is a meaningful and effective approach for reaching those women who are in the highest need for cervical screening. Since non-attendees harbour more than 50% of cervical cancers,\(^9,12\) targeting of approximately 30% of these women by HPV self-sampling is likely to result in earlier detection of at least 15% of the cervical carcinomas.

For this study, we pooled data from two large self-sampling studies. Independent from ethnicity, age, and screening history, we measured different response rates between the individual PROTECT studies. In PROTECT-1 slightly fewer women responded than in PROTECT-2 (27% versus 31%). This small difference may partly reflect a higher acceptability of the brush device used in PROTECT-2 compared to the lavage-device used in PROTECT-1. Alternatively, since PROTECT-1 was performed prior to PROTECT-2, the difference might be attributable to more awareness, and therefore less uncertainty, due to the earlier publicity around the PROTECT-1 study.

Most interesting is the finding that never screened women were more likely to respond than underscreened women, independent from the ethnic background. Although it is still unclear why never screened women responded better than underscreened women, a plausible explanation might be that these women consistently refuse to visit the physician for making a preventive smear because of cultural, religious and/or organisational reasons. HPV self-sampling may help to overcome this barrier.

It should be realised that increased \( \geq \text{CIN2/}\geq \text{CIN3} \) yield in self-sampling responders might be the result of a more sensitive screening test (hrHPV test used in self-sampling compared to the cytology test used for screening participants). However, similar relative risk values were obtained after restricting the analysis to women with abnormal cytology at baseline. Therefore, the increased relative risk of self-sampling responders cannot solely be attributed to a more sensitive screening test.

An unexpected observation was that an increased relative risk of \( \geq \text{CIN2/}\geq \text{CIN3} \) was also found amongst self-sampling responders for whom it was their first screening round. A likely explanation for this finding is that women at risk because of their lifestyle (e.g. in terms of sexual behaviour and smoking habits) are better targeted by offering HPV self-sampling than by invitation for a physician-collected cervical scrape. The increased relative risks by age most likely reflect an overall poorer screening history of older self-sampling responders.

Our study is unique, because of its large size and performance within the setting of the regular cervical screening programme. Moreover characteristics of non-attendees of the screening programme who responded to self-sampling for HPV testing has not been described before. A limitation is that we pooled two studies in which different collection devices were used. As reported earlier,\(^7\) hrHPV-positivity rates slightly differed between samples collected by both devices, but the concordance between hrHPV-positivity rates in both types of self-collected samples and corresponding physician-collected cervical samples was very high (over 90%) in women with \( \geq \text{CIN2} \).\(^5,20\) Furthermore, \( \geq \text{CIN2} \) yield was comparable in both studies\(^7\) indicating that it is unlikely that pooling the PROTECT studies would influence the interpretation of the results.

Another limitation is that we did not test the prevalence of \( \geq \text{CIN2} \) in women with hrHPV-negative self-sample test. The medical ethics committee considered follow-up of these women in light of the very high negative predictive value of the hrHPV test for \( \geq \text{CIN2} \) an unnecessary burden.\(^21\)

Finally we defined ethnic status based on the country of birth. Thus some women from ethnic minorities who were born in the Netherlands might have been classified as ‘native Dutch’, even though culturally they may to some degree resemble paternal immigrant communities. Although this might play a role predominantly amongst younger women we think that the number of women concerned is limited. Most women who united with their husband by immigration in The Netherlands did so in the late 1970s and beginning of 1980s. The number of women born from these immigrated women and invited for screening (30–60 years) constitutes in our opinion therefore a small minority.

Finally, it is important to note that in order to make HPV self-sampling a successful alternative to physician-sampling, the whole organisation should be well controlled. This involves the sequence of sending the invitation with the self-sampling kit, return sending by surface mail, hrHPV testing with a clinically validated test that is compatible with the self-sampling device, follow-up of hrHPV-positive women by triage cytology by a physician and follow-up of hrHPV-positive women with normal cytology after 6 months to 1 year. We showed earlier that compliance to direct cytology triage is high (>90%) but that there is poor adherence to follow-up testing after 1 year (~60%), which needs careful attention.\(^6,7\) Still, these results strongly argue to implement hrHPV testing on self-sampled material as an alternative for hrHPV testing on a physician taken scrape.

5. Conclusion

Amongst women who had not been screened in the previous screening round, those who were never screened before were preferentially attained when offering HPV self-sampling. This likely contributed to higher \( \geq \text{CIN2/}\geq \text{CIN3} \) yields than found in regular screening participants, which is highly relevant for the success of the screening programme. Although native Dutch women responded better than immigrants, the response rates amongst immigrants from different countries hardly differed, making the method successful independent of the country of birth.
Contributors

CJLM Meijer was the project leader, designed the study with D.A.M. Heideman, F.J. van Kemenade, P.J.F. Snijders, had full access to all data. M. Gök and C.J.L.M. Meijer drafted the first version of the manuscript and A.L.M. de Vries, F.J. van Kemenade, D.A.M. Heideman, J. Berkhof, L. Rozendaal, F. Voorhorst, and P.J.F. Snijders, commented on the next versions. M. Gök, A.L.M. de Vries and J. Berkhof did the data analyses; J. Berkhof was responsible for the data analyses. L. Rozendaal and J.A.M. Beliën were responsible for database management. D.A.M. Heideman, P.J.F. Snijders and C.J.L.M. Meijer were responsible for HPV DNA testing. M. Babovic was responsible for the screening register of the Regional Screening Organisation Database. J. Spruyt was responsible for communication with gynaecologists. F.J. van Kemenade was responsible for coordination of cytological testing at the individual laboratories. All authors critically reviewed the manuscript and approved the final version.

Conflict of interest statement

CJLM Meijer has relationships with Qiagen (Gaithersburg, USA) and GSK; P.J.F. Snijders has occasionally been advisory board member of Gen-Probe (San Diego, USA), Roche (Pleasanton, USA), and GSK (Rixensart, Belgium); DAM Heideman has occasionally been invited speaker by Roche (Pleasanton, USA). CJLM Meijer, P.J.F. Snijders, and DAM Heideman are shareholders of Self-screen, a recent spin-off company of VU University medical center. The sources of funding did not have any influence on the design and the analysis of the results.

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R E F E R E N C E S


