Research Article

Cancer Epidemiology, Biomarkers & Prevention

Self-sample HPV Tests As an Intervention for Nonattendees of Cervical Cancer Screening in Finland: a Randomized Trial

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Abstract

Background: Attendance in screening is an important determinant of cervical cancer. Previous experience on high-risk human papillomavirus (hrHPV) DNA testing on patient-obtained samples suggests a good effect among nonattendees of screening. We assessed the effects of self-sampling on attendance in the Finnish screening program.

Methods: Nonattendees after the primary invitation in one municipality (Espoo) were randomized to receive either a self-sampling kit (2,397 women) or an extra invitation (6,302 women). One fourth (1,315 women) of reminder letter arm nonattendees also received a self-sampling kit as a third intervention. Main outcomes were increases in screening attendance and coverage.

Results: The adjusted relative risk for participation by self-sampling as a second intervention in comparison to a reminder letter arm was 1.21 (95% CI: 1.13–1.30). Total attendance increased from 65% to 76% by self-sampling and from 65% to 74% with a reminder letter. Combining the interventions (reminder letter and then self-sampling) increased total attendance from 63% to 78%. One fifth of the participants in all three groups increased screening coverage (previous Pap smear $\geq$5 years ago or never). Self-obtained samples were more often HPV positive than provider-obtained ones (participants after primary invitation and reminder letter), 12% to 13% versus 7%.

Conclusions: Self-sampling is a feasible option in enhancing the attendance at organized screening, particularly as an addition to a reminder letter.

Impact: If self-sampling is used as a third intervention after two written invitations, the overall attendance in Finland could most likely reach the desired 80% to 85%. *Cancer Epidemiol Biomarkers Prev; 20(9); 1960–9.* ©2011 AACR.

Introduction

Suboptimal attendance rates limit the effectiveness of the cervical cancer screening program. Higher rates can result from prefixed appointments in invitations and reminder letters to nonattendees, but even as a part of national screening recommendations, they are not used in all municipalities (1–4). In Finland, the overall attendance rate in the organized screening program is 70% and among women aged 30 to 35 only 50% to 60%; the desired 80% to 85% attendance nationwide is not fulfilled (5). Attendance in screening is an important determinant of cervical cancer (6).

A possible new method to activate the current nonattendees of the program are screening tests in which the woman herself takes the sample at home (self-sampling tests). High-risk human papillomavirus (hrHPV) DNA detection–based self-sampling tests are sensitive in finding cervical cancer and its severe precursors (7–15). Experience of previous studies, although limited and restricted by local conditions, also suggests a good effect among nonattendees of screening (16–21). Our study results after 1 year showed self-sampling to be a valid alternative for a reminder letter arm in optimizing attendance rates in Finland as well (21). Abundant recent opportunistic Pap smears among women screened by self-sampling, however, caused the effect of self-sampling on screening coverage (i.e., the coverage of any smear within the screening interval) to remain small.

We present here the results of the 2-year study in the routine screening program of a Finnish municipality, with self-sampling as a second or third intervention for nonattendees. We compared self-sampling with the current recommendation (2 written invitations) in their effect on screening attendance and coverage.

This trial is registered as an International Standard Randomized Controlled Trial (trial number ISRCTN25346540). The ethics committee of the local hospital district (approval number 430/E9/07 HUS) and the city of Espoo gave the trial ethical approval.

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

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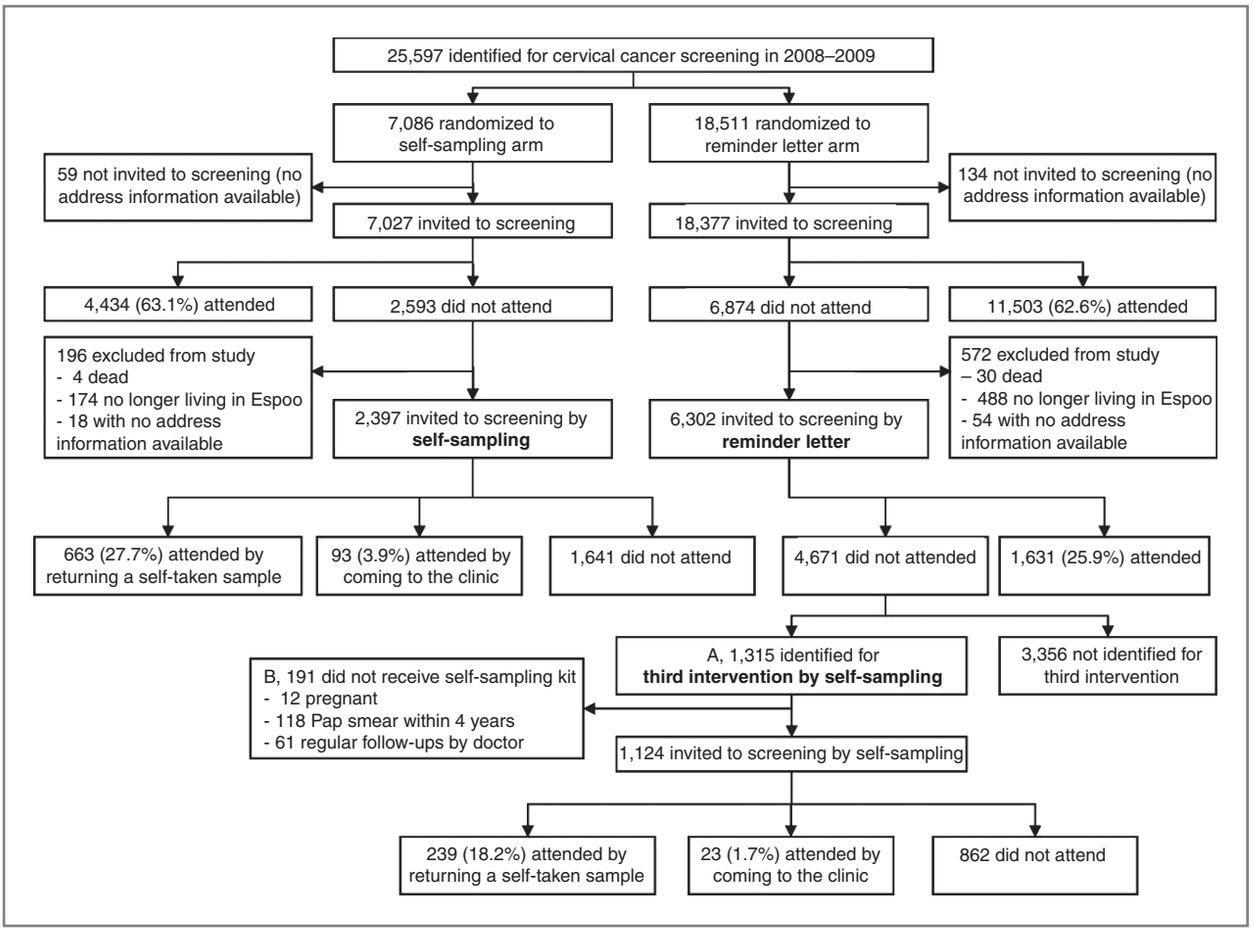

Figure 1. The flow of population to be screened in Espoo in 2008 to 2009. A, nonparticipants with no valid screening appointment 5 months after the first batch of reminder letters and 2 months after the second batch of reminder letters in 2009. B, exclusions made on the basis of the answers given in the questionnaire included in the reminder letter to avoid excess contacts. These women are included in the analysis on participation rates.

Materials and Methods

Setting and study population

The study was conducted as a part of the routine cervical cancer screening program in Espoo, southern Finland, in 2008 and 2009. In the Finnish screening protocol, all women aged 30 to 60 are invited to screening with 5-year intervals unless intensified screening (1-year interval) is required because of previous borderline screening results (ASC-US, AGC-NOS, HPV positivity without cytologic changes). Espoo introduced primary HPV screening from 2004; women are individually randomized to primary hrHPV screening with cytology triage or to cytologic screening (22–25). For our study, all women identified for screening in 2008 or 2009 were individually randomized, irrespective of the previously mentioned randomization, in the Finnish Cancer Registry by a pseudo-number generator into 2 arms. The self-sampling arm was to receive a self-sampling kit and the control arm, a reminder letter, in case they did not participate in organized screening after the primary invitation.

The sampling ratio was based on previous studies on self-sampling among nonresponders to screening (16). We estimated that by using 1,000 self-sampling devices, we could detect a 4% difference in the participation rates of study and control arms (2 sided, $\alpha = 0.05$, power $= 0.8$). In Espoo, approximately 12,000 women are invited to screening yearly and approximately 70% take part, leaving 3,600 nonattendees eligible for interventions. As the primary invitation participation rate in study years became clear, the final randomization ratio came to be close to 1:2.7. The invitees did not know their randomization status at the time of primary invitation.

The flow of the population screened in study years is shown in Figure 1. Invited women without a sampling date or a valid appointment for screening were identified from the screening database, and their address information was updated from the Population Register Centre. Only women still living in Espoo were included in the

study because of the municipally controlled nature of screening in Finland.

The women allocated for self-sampling received by mail a self-sampling device (Delphi ScreenerTM; Delphi Bioscience BV; refs. 19–21, 26) with user instructions, a presentation letter, a brochure on cervical cancer screening and HPV infections available also on screening visits, and a questionnaire including the standard screening form about recent gynecologic health history with some additional questions for study purposes. A few weeks prior to the self-sampling kit, the women received a letter informing them of the upcoming self-sampling kit, and in 2009, this letter included an option for the cancellation of the kit (opt out). The women allocated for a reminder letter arm received a new invitation with a new appointment for screening and the same brochure and questionnaire as did the self-sampling arm (questions about self-sampling excluded).

The results from 2008 allowed us to estimate up to 80% participation if self-sampling served as a third intervention after 2 written invitations. To test this hypothesis, in 2009, we conducted a pilot; the women who received a reminder letter in the first 2 mailing batches of 2009 but did not participate were identified to receive a self-sampling kit as a third intervention (1,315 women; 54% of all nonattendees in reminder letter arm in 2009). This intervention had no additional control group. However, the kit was not mailed to 191 of these women that had responded to the questionnaire sent with the reminder letter and reported certain reasons for their nonattendance (pregnancy, recent Pap smear, regular follow-up by a gynecologist) to avoid excess contacts (Fig. 1). These 191 women were still included in the analysis of participation rates. Because there was no allocation to the third intervention before sending screening invitations, the effects of this invitational protocol (reminder letter and then self-sampling) in overall attendance were estimated assuming similar attendance to third intervention among those identified and not identified for the third intervention in reminder letter arm in 2009.

The second and third interventions were mailed within 13 months of the primary invitation (within the screening year).

Outcome

Primary outcomes were increases in total participation rate and in screening coverage achieved by the 3 types of interventions: (i) a self-sampling kit, (ii) a reminder letter, or (iii) a reminder letter and then self-sampling kit. Secondary outcomes were the prevalence of hrHPV test positivity and yield of cervical intraepithelial neoplasias (CIN) among first invitation and second/third intervention attendees.

The coverage of screening was defined by the coverage of any screening test in or outside the program within the 5-year screening interval and was assessed by the self-reported information on previous Pap smears in the questionnaire. In the analysis of participation and coverage, 3 variables were mutually adjusted for each other: invitational mode (5-year interval or intensified screening), mother tongue (Finnish, Swedish, and other), and age (in 5-year age groups). Women in intensified screening were excluded from the analysis on coverage.

Self-sampling device, hrHPV analysis, and further investigations

The self-sampling device, Delphi ScreenerTM, was a lavage device prefilled with saline. The woman inserted the nozzle of the instrument into her vagina and pushed the slide in to release the saline. The saline rinsed the upper vagina and the cervix and was aspirated with the sample cells back into the device. The sample was then sent to Cancer Organization's screening laboratory in a smaller container.

As the sample arrived to the laboratory, it was centrifuged at 1,500 rpm in the test tube it arrived in. The resulting supernatant was discarded and the cell pellet was suspended in 1 mL of standard transport medium (STM; Qiagen, Inc.). A part of the sample was transported into a screen plate for Hybrid Capture analysis (Hybrid Capture Technology HC2; Qiagen) and the rest was frozen in a Digene HC2 tube. Further HC2 analysis was conducted with positive and negative controls according to the manufacturer's guidelines similarly and simultaneously with samples from routine screening obtained by Digene Cytobrushes (22, 27). The used HC2 analysis is a qualitative test that targets 13 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). A sample containing hrHPV DNA equivalent to concentration of 1 pg/mL or above was considered to indicate an hrHPV infection [i.e., cutoff value = 1 relative luciferase units (RLU)].

If the sample contained a visible cell pellet after centrifugation, the sample was considered adequate and the result of the hrHPV analysis reliable. Of the 908 returned samples, 5 (0.6%) did not meet this criterion. In addition, 4 received samples were considered too old for analysis, as they reached the laboratory (taken >50 days prior to arrival). These 9 women were offered new devices or the chance to take part by coming to the clinic, but only 3 participated by sending a new self-obtained sample and were thus included as participants.

Self-sampling participants with a negative (RLU < 1) HPV result were advised to attend cervical cancer screening upon the next invitation in 5 years. Women younger than 40 with a positive (RLU $\geq$ 1) HPV result were invited for a Pap smear at the Cancer Organization's clinic and in the case of positive cytology ($\geq$HSIL) or recurrent HPV positivity, referred to colposcopy in Jorvi Hospital of Helsinki University Central Hospital. HPV-positive women aged 40 or above were referred straight to colposcopy and, when indicated, biopsies. Of the histologic samples obtained within a year of participation date in screening, the more severe one was taken into consideration in the analysis, providing that the samples were taken within 2 months of each other (i.e., most likely, a

diagnostic biopsy and treatment biopsy). Further examinations and treatments after the Pap smear and colposcopy were executed according to current Finnish guidelines (4). HrHPV-positive women with normal cytologic or histologic findings were considered to have reason for intensified screening and were called to a new screening test in 12 months. If the repeated screening test did not give reason (persistent HPV infection and/or cytologic abnormalities) to further examinations by colposcopy, they returned to the normal 5-year screening interval.

Statistical methods

Age-, mother tongue-, and invitational mode–adjusted relative risks and 95% CIs for participation in self-sampling arm were estimated by log-binomial regression, using SAS GENMOD procedure with SAS 9.1 software (SAS Institute) with reminder letter arm participants as reference. STATA 10.0 software (StataCorp LP) was used to estimate 95% Wald confidence limits for participation rates, proportions of previous Pap smears among screening participants, and HPV positivity rates, as well as exact confidence limits for the prevalence of CIN findings and positive predictive values (PPV) of colposcopy referrals.

Results

Effects on screening participation and coverage

Of the 2,397 nonattending women who received a self-sampling kit as a second intervention, 756 (31.5%; 95% CI: 29.7–33.4) participated, 663 by returning a self-taken sample and 93 by coming to the clinic for a Pap smear (analyzed by intention to treat in the self-sampling arm; Table 1 and Fig. 1). This was a significantly higher rate than among those ($n = 6{,}302$) who received a reminder letter, of which 1,631 (25.9%; 95% CI: 24.8–27.0) participated. The age, mother tongue, and invitational mode–adjusted relative risk for participation by self-sampling in comparison to a reminder letter arm was 1.13 in 2008 (95% CI: 1.01–1.25) and 1.29 in 2009 (95% CI: 1.17–1.42) and 1.21 in total (95% CI: 1.13–1.30; Table 2).

Total participation in study years among women included in the study increased from 64.9% (95% CI: 63.8–66.0) to 76.0% (95% CI: 75.0–77.0) with self-sampling as second intervention, and from 64.6% (95% CI: 63.9–65.3) to 73.8% (95% CI: 73.1–74.4) with a reminder letter, equating to 17.1% and 14.2% relative increases. In both arms, the additive increase in participation was highest among women aged 35 to 39 (+12.7% and +11.5% by self-sampling and reminder letter, respectively), but the greatest difference in participation between interventions occurred in women aged 55 to 59 with an adjusted relative risk for participation by self-sampling of 1.47 (95% CI: 1.21–1.77).

Among the 1,315 nonattending women in 2009 who received first a reminder letter did not take part and were allocated for self-sampling as a third intervention, 262 (19.9%; 95% CI: 17.8–22.1) participated. Total attendance increased from 63.3% (95% CI: 62.3–64.3) to 72.7% (95% CI: 71.8–73.6) by reminder letter and further to 78.1% (95% CI: 77.3–79.0) by self-sampling (Fig. 2). Best improvement in total participation occurred among women aged 30 to 34 and 35 to 39, 19.3% and 19.8% (relative increases of 37.2% and 35.1%, respectively). Among all initial nonattendees after primary intervention, combining the interventions reached 36% to 45% by age. In different mother tongue groups, attendance by combined interventions was 45% among the Swedish-speaking and 41% among the Finnish-speaking invitees and 33% among those with a mother tongue other than these 2 (i.e., most likely immigrants).

With regard to the effect of interventions on screening coverage, self-sampling seemed to be more attractive than a reminder letter among women who had never had a Pap smear: 25 (3.5%; 95% CI: 2.1–4.8) versus 12 (0.8%; 95% CI: 0.3–1.2) women reported no previous Pap smears (Table 3). Women who received the self-sampling kit as a third intervention had the highest proportion of no previous Pap smears, 16 of 248 (6.5%; 95% CI: 3.4–9.5). In all 3 intervention groups, however, 64% to 75% had had a Pap smear outside the program within the screening interval, and the proportion of all underscreened women (previous Pap smear $\geq$5 years ago) remained the same, approximately one fifth. Adding the third intervention, thus added approximately 4% (0.199×0.22) to the 20% yield of underscreened women by second intervention.

Results of hrHPV analysis and histologic findings

Of the returned self-taken samples considered adequate for analysis, HC2 test was positive in 81 of 663 (12.3%; 95% CI: 9.9–15.0) when self-sampling was used as a second intervention and in 31 of 239 (13.0%; 95% CI: 9.0–17.9) when it was used as a third intervention (Table 4). Among the 466 women screened by primary HPV screening in reminder letter arm and among the 4,801 participants after primary invitation, 33 (7.1%; 95% CI: 4.9–9.8) and 357 (7.4%; 95% CI: 6.7–8.2), respectively, were HPV positive. If women in intensified screening (i.e., invited because of previous abnormalities) are excluded from the population, the HPV positivity rates were 5.6 among primary invitation attendees, 5.8 among reminder letter attendees, and 12.4 among self-sampling attendees (Supplementary Table S1).

The prevalence of detected hrHPV infections among screening participants after primary invitation decreased with age from 16.4% (100 of 611) in women aged 30 to 34 to 3.7% (28 of 763) in women aged 60 to 64. A similar trend from 20.0% (20 of 100) in women aged 30 to 34 to 6.9% (7 of 102) in women aged 55 to 59 was detected among self-sampling participants; but with an unexpected peak, 14.5% (11 of 76) in women aged 60 to 64. HPV test positivity among participants of the reminder letter arm and participants due to self-sampling as a third intervention did not show similar trends with regard to age, most likely due to smaller number of tests (466 and 239).

Table 1. Participation in screening by study arms in 2008–2009[a]

	Invited	Participation: primary invitation		Participation: second intervention		Total participation		
	n	*n*	%	*n*	%	%	+% add	+% rel
Self-sampling arm								
Total	6,831	4,434	64.9	756	31.5	76.0	11.1	17.1
Invitational mode								
5-y interval	6,515	4,210	64.6	716	31.1	75.6	11.0	17.0
Intensified screening	316	224	70.9	40	43.5	83.5	12.7	17.9
Mother tongue								
Finnish	5,919	3,881	65.6	593	29.1	75.6	10.0	15.3
Swedish	423	281	66.4	45	31.7	77.1	10.6	16.0
Other	489	272	55.6	58	26.7	67.5	11.9	21.3
Age, y								
30–34	965	552	57.2	110	26.6	68.6	11.4	19.9
35–39	935	554	59.3	119	31.2	72.0	12.7	21.5
40–44	1,051	660	62.8	105	26.9	72.8	10.0	15.9
45–49	1,075	710	66.0	120	32.9	77.2	11.2	16.9
50–54	921	598	64.9	100	31.0	75.8	10.9	16.7
55–59	932	643	69.0	111	38.4	80.9	11.9	17.3
60–64	952	717	75.3	91	38.7	84.9	9.6	12.7
Reminder letter arm								
Total	17,805	11,503	64.6	1,631	25.9	73.8	9.2	14.2
Invitational mode								
5-y interval	16,980	10,908	64.2	1,534	25.3	73.3	9.0	14.1
Intensified screening	825	595	72.1	97	42.2	83.9	11.8	16.3
Mother tongue								
Finnish	15,266	9,982	65.4	1,388	26.3	74.5	9.1	13.9
Swedish	1,234	803	65.1	125	29.0	75.2	10.1	15.6
Other	1,305	718	55.0	118	20.1	64.1	9.0	16.4
Age, y								
30–34	2,525	1,379	54.6	246	21.5	64.4	9.7	17.8
35–39	2,505	1,444	57.6	288	27.1	69.1	11.5	19.9
40–44	2,713	1,709	63.0	269	26.8	72.9	9.9	15.7
45–49	2,779	1,831	65.9	231	24.4	74.2	8.3	12.6
50–54	2,422	1,635	67.5	232	29.5	77.1	9.6	14.2
55–59	2,417	1,724	71.3	180	26.0	78.8	7.4	10.4
60–64	2,444	1,781	72.9	185	27.9	80.4	7.6	10.4

NOTE: Participation after primary invitation and after second intervention (self-sampling test or reminder letter), total participation, and increase in total participation by second interventions among women included in the study.

Abbreviations: %add, additive increase in total participation by intervention; %rel, relative increase in total attendance by intervention.

[a]Only women living in Espoo included, see Figure 1 for exclusions.

Of the 112 women with an HPV-positive self-taken sample, 47 (33 in self-sampling as second intervention and 14 in self-sampling as third intervention) were invited for a Pap smear and 9 (6 and 3, respectively) further to colposcopy (Supplementary Fig. S1). Sixty-five (48 and 17) were referred directly for a colposcopy. The loss in cytologic/histologic follow-up (woman did not follow the referral for a Pap smear or colposcopy after a positive HPV test result) was 15 of 112 (13.4%). The loss was only 10 of 303 (3.3%) among primary invitation attendees and 1 of 31 (3.2%) among reminder letter arm participants.

The yield of mild and more severe (CIN1+) and moderate or more severe CINs (CIN2+) remained small for reliable comparison between groups (Table 4). When used as a second intervention, the used referral protocol for women with positive results had lower PPVs for CIN findings than those samples taken by nurses in screening visits and the routine referral protocol, but the CIs are wide and within each other.

Table 2. Adjusted relative risk (RR) for participation with self-sampling as a second reminder in comparison to a reminder letter (self-sampling, $n = 756$; reminder letter, $n = 1{,}631$) in study years

	RR	95% CI
Total[a]	1.21	1.13–1.30
Invitational mode[b]		
5-y interval	1.23	1.14–1.32
Intensified screening	1.09	0.81–1.42
Mother tongue[c]		
Finnish	1.22	1.13–1.32
Swedish	1.10	0.82–1.44
Other	1.27	0.96–1.67
Age,[d] y		
30–34	1.23	1.01–1.48
35–39	1.15	0.96–1.37
40–44	0.99	0.81–1.20
45–49	1.35	1.12–1.61
50–54	1.07	0.87–1.29
55–59	1.47	1.21–1.77
60–64	1.40	1.14–1.70

[a]Adjusted for invitational mode, mother tongue, and age.
[b]Adjusted for mother tongue and age.
[c]Adjusted for invitational mode and age.
[d]Adjusted for invitational mode and mother tongue.

Discussion

An hrHPV self-sample test sent home to women was somewhat more effective than the current recommendation, a reminder letter, as a second intervention for the nonattendees after the initial invitation in the cervical cancer screening program in Espoo, Finland. If the loss in cytologic follow-up is taken into account, the compliance in the self-sampling arm still reached 31.1% versus the 25.9% in the reminder letter arm. By combining the two interventions (reminder letter and then self-sampling), 40.4% of nonattendees after primary invitations were reached. With regard to total attendance rate in study years, self-sampling and reminder letter arm both increased compliance approximately by 10% and combining the interventions by up to 15%.

Youngest age groups (women aged 30–34 and 35–39) and women with a mother tongue other than Finnish or Swedish, that is, most likely immigrants, had lowest attendance rates in screening (21). The young age groups also have a higher than expected cancer incidence (5). If only 1 intervention for nonattendees would be used in these inadequately participating subgroups, results imply that self-sampling might be slightly more effective than a reminder letter. Among immigrants, the difference between interventions was as much as 27%. Using both interventions combined, the young age groups could reach 70% to 80% attendance rates, as they showed gratifying 35% to 37% relative increases in participation, and immigrants could also be reached better than nowadays.

The 31% compliance to self-sampling as a second intervention was slightly lower than that in a Swedish study conducted in a nonrandomized setting (18), 39%, but higher than in an Italian one in a randomized setting, 9% to 20% depending on the exact protocol (20). In the Italian study, the compliance to a reminder letter was also notably lower than ours, 14%. Among women offered self-sampling as a third intervention, 2 recent randomized studies in the Netherlands with a similar invitational protocol of nonattendees achieved participation rates of 34% and 27% faintly exceeding the 20% in our

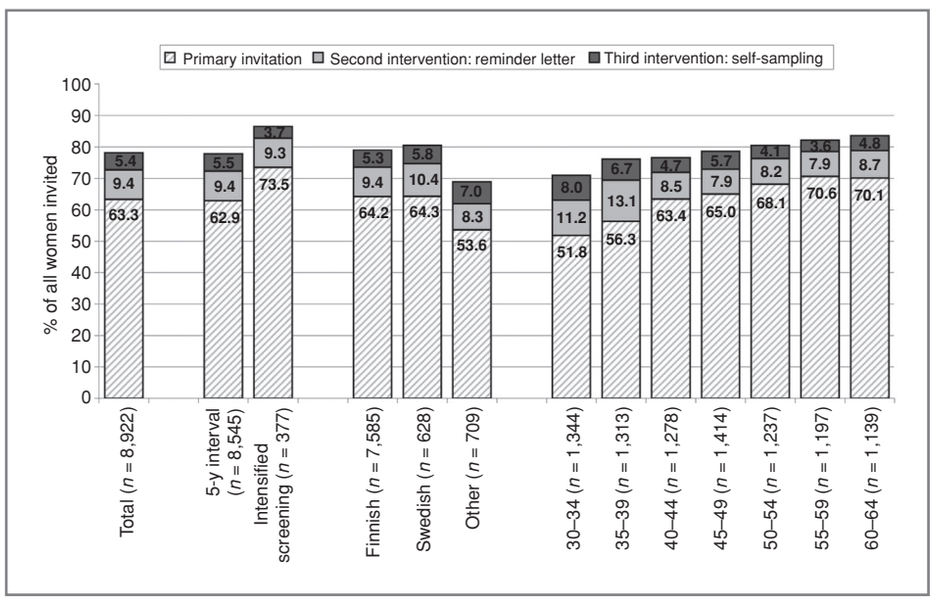

Figure 2. Self-sampling after 2 written invitations: participation in screening in 2009 (total and by invitational mode, mother tongue, and age): reminder letter as second intervention for nonattendees, $n = 3{,}272$; self-sampling as third intervention, $n = 1{,}315$ (assuming similar attendance among those identified and not identified for the third intervention in reminder letter arm in 2009).

Table 3. Effect on screening coverage

	Self-sampling arm			Reminder letter arm			Self-sampling as third intervention		
Previous Pap smear	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**
<5 y ago	497	69.4	66.0–72.8	1,153	75.2	73.0–77.3	159	64.1	58.1–70.1
5–9 y ago	107	14.9	12.3–17.6	292	19.0	17.1–21.0	20	8.1	4.7–11.5
≥10 y ago	15	2.1	1.0–3.1	26	1.7	1.0–2.3	18	7.3	4.0–10.5
Never[a]	25	3.5	2.1–4.8	12	0.8	0.3–1.2	16	6.5	3.4–9.5
Answer missing[b]	72	10.1		51	3.3		35	14.1	
Total	716	100.0		1,534	100.0		248	100.0	

NOTE: Time from previous Pap smear among participants after second interventions (self-sampling or reminder letter) and after third intervention (self-sampling after reminder letter). Women in intensified screening excluded.

[a]Including 6 women aged 30 in the self-sampling arm, 3 in the reminder letter arm, and 8 among those with self-sampling as third intervention.

[b]Including 3 women aged 30 in the self-sampling arm, 10 in the reminder letter arm, and 6 among those with self-sampling as third intervention.

study; but the 5% increase in overall participation rate by self-sampling was similar to ours (16, 19). With a similar protocol in a randomized setting in the United Kingdom; however, the response in the self-sampling arm was lower, 10% (28).

Self-obtained samples had a higher proportion of positive hrHPV results with an HC2 assay than did samples taken by nurses at screening visits (primary invitation and reminder letter participants). This phenomenon is observable also in other studies on self-obtained samples (18–20, 29–31). In principle, this can be due to a truly higher prevalence of HPV infections in this group of women, or to the difference in the sample-taking procedure and the sample itself.

A true higher prevalence of HPV infections could result from overall more risky health behavior among nonattendees of the program. It could, however, also be due to an interest in self-sampling and HPV testing because of previous abnormal Pap smear results, as most women screened by self-sampling had had a Pap smear outside the program within 5 years. Only 20% (208 of 1,018) of all participants and 20% (22 of 112) of HPV-positive participants, however, reported ever having cervical lesions or abnormal smear results (no report from 13%). Participants in the reminder letter arm had higher proportions of previous abnormal smear results, 29% among all participants (467 of 1,631) and 52% (17 of 33) among HPV-positive ones (no report from 34%). Thus, participation in self-sampling screening because of curiosity does not seem an adequate explanation for the higher proportion of positive HPV results.

A more probable reason for the differences in detected HPV positivity rates is still the fact that self-taken samples more likely also include cells of vaginal or even vulvar origin than provider-obtained (cervical) samples, and the analysis can thus detect HPV infections not affecting the cervix (15, 32, 33). Furthermore, vaginal infections are more often of low-risk types (15, 34, 35), and there is a possibility of cross-reaction in the HC2 analysis that has been reported to result in 8% to 10% false-positive rate of hrHPV (33–41). The detected HPV positivity rate may thus partly result from vaginal infections not affecting the cervix, also of low-risk genotypes. In this study, the lower PPV of a self-taken sample with a positive HPV result for CIN2+ findings (4.3 with self-sampling as a second intervention and 7.4 as third; vs. 8.0 and 12.1 after primary invitation and reminder letter, respectively) support the interpretation that vaginal infections and cross-reactivity might have affected.

A common hypothesis is that nonattending women of the screening program have more cervical lesions than the attending ones. They do have a higher risk for cervical cancer (6) and previous studies on the use of self-sampling among nonattendees also support this hypothesis (18, 19, 42). Even though our study was not empowered for the comparison of precursor yields, there was a tendency toward a higher CIN2+ prevalence among initially nonattending women that attended only after 2 interventions compared with those attending after the initial invitation or 1 reminder. Still, 20% of all invitees did not take part even after 2 interventions, and at this point, we are unaware of the true load of precursors in this nonattending population. The results nonetheless allow us to estimate the increase in the yield of detected severe precursors achieved by these extra interventions. As a sole second intervention, self-sampling would increase the yield of detected CIN2+ lesions by 17% from 70 to 81 ($70 + 0.32 \times 8699 \times 3/756$). A reminder letter would increase the yield by 20% and the use of a self-sampling after a reminder letter by 34%.

We found that only 20% of attendees after second interventions were truly underscreened and adding a

Table 4. HPV test positivity and yield of CINs grade 1 and more severe (≥CIN1; not including mild HPV changes without dysplasia) and CINs grade 2 and more severe (≥CIN2) among screening participants after primary invitation, after second interventions (self-sampling or reminder letter), and after third intervention (self-sampling after 2 written invitations); positive predictive value for ≥CIN1 and for ≥CIN2 of a referral for colposcopy

	HPV+			≥CIN 1					≥CIN 2				
							PPV/referral[a]					PPV/referral[a]	
	n	%	95% CI	*n*	%	95% CI	%	95% CI	*n*	%	95% CI	%	95% CI
Primary invitation													
Cytology screening ($n = 11,136$)	–			52	0.47	0.35–0.61	35.9	28.1–44.2	42	0.38	0.27–0.51	29.0	21.7–37.1
Primary HPV screening[b] ($n = 4,801$)	357	7.44	6.69–8.18	45	0.94	0.68–1.25	30.4	23.1–38.5	28	0.58	0.39–0.84	18.9	13.0–26.2
Second intervention													
Self-sampling arm													
Primary HPV screening[c] ($n = 663$)	81	12.2	9.72–14.7	5	0.75	0.25–1.75	10.2	3.4–22.2	3	0.45	0.09–1.32	6.12	1.3–16.9
Reminder letter arm													
Cytology screening ($n = 1,165$)	–			8	0.69	0.30–1.35	42.1	20.3–66.5	6	0.52	0.19–1.12	31.6	12.6–56.6
Primary HPV screening[b] ($n = 466$)	33	7.08	4.75–9.41	5	1.07	0.35–2.49	45.5	16.7–76.6	4	0.86	0.23–2.18	36.4	10.9–69.2
Third intervention													
Self-sampling after 2 letters													
Primary HPV screening[c] ($n = 239$)	31	13.0	8.71–17.2	4	1.67	0.46–4.23	21.1	6.1–45.6	2	0.84	0.10–2.99	10.5	1.3–33.1

NOTE: Number of referrals to colposcopy and missing final diagnoses due to noncompliance (cytology screening/primary HPV screening): after primary invitation referrals 150/153, diagnoses missing 5/5; among self-sampling attendees referrals 0/54, missing diagnoses 0/5; among reminder letter arm referrals 11 of 20, diagnoses missing 0 of 1; and among self-sampling as third intervention attendees referrals 0/20, diagnoses missing 0/1. Ninety-three women (self-sampling arm) and 23 women (self-sampling after 2 letters) who chose cytology screening in the clinic after receiving the self-sampling kit all had normal screen results, i.e., no referrals for colposcopy.

[a]Referral algorithm in routine screening (here primary invitation and reminder letter attendees, and women who chose cytology screening in the clinic after receiving a self-sampling kit): in cytologic screening referral for colposcopy and histology, if cytology ≥HSIL or recurrent ASC-US; in primary HPV screening, if HPV positive and triage cytology ≥HSIL or recurrent HPV positivity with normal or borderline (ASC-US) cytology in triage. Referral algorithm in screening with self-taken samples: referral if HPV-positive and age ≥40, or among women <40 if HPV-positive and cytology triage ≥HSIL or recurrent HPV positivity with normal or borderline (ASC-US) cytology in triage.

[b]Women randomized for primary HPV screening and cytology triage in the routine screening program of the city of Espoo.

[c]Women who took part in screening with a self-taken sample.

third one increased this to 24%. As Finland does not have a record of opportunistic Pap smears, we do not know how many underscreened women remained in the population. We previously calculated that 17 self-sampling devices were needed to include an underscreened woman into the program (21) and similar numbers were calculated in Italy and United Kingdom as well, 13 and 16 (20, 28). Still, surprisingly, in our study, only a minority (1 of 5 in self-sampling participants and 2 of 10 in reminder letter participants) of the detected severe precursors among initial nonattendees were found in truly underscreened women (previous Pap smear ≥5 years ago or never).

In the Finnish population, cervical cancer is rare due to effective screening. As the prevalence of abnormal histology remained small among those women with HPV-positive results by HC2 from self-taken samples, the protocol of further investigations should be considered carefully to avoid unnecessary colposcopies and possible psychologic harm. The referral policy for positive self-taken samples used in this study resulted in a very low PPV for CIN2+. It is, however, even more important

not to lose these possibly high-risk nonattending women from follow-up as might happen if all women were directed to cytologic triage and an extra invitation for a Pap smear. The original nonattendance to screening and higher loss in follow-up (12%–13% vs. 3%) suggests that self-sampling participants may be more prone to abandon follow-up. Personal contact by telephone instead of written test results may possibly reduce the loss. Results from more years will clarify the yield of detected precursors by self-sampling which will help in defining the protocol.

Samples with current self-sampling methods are at least as sensitive as a traditional Pap smear in detecting high-grade CIN lesions (8–14, 18, 26). Still, their lower specificity and PPVs compared with cytologic screening and provider-obtained samples for HPV analysis (7, 10–14, 43–45) make traditional participation in organized screening the current primary option.

Strengths and limitations

As the study was conducted as a part of routine screening, the results are well applicable when considering the feasibility of self-sampling in cancer screening. However, rather extensive screening outside the organized program, not yet registered systematically, limits the setting and results of this study to some extent. Another limitation of this study was the urban nature of the municipality studied; the results are well applicable for similar municipalities, but the effects of self-sampling still have to be assessed in different regions to determine the effects on a national scale. As this study was not empowered to study the differences in yield of precursors by the interventions, more research is needed especially with regard to cancer prevention and cost-effectiveness analysis.

Conclusions

In an individual level, attendance in screening is an important determinant of cervical cancer. A high attendance rate is also a major factor in the effect of the whole screening program. We offered hrHPV self-sampling as a screening option for nonattendees of the program in an urban setting, in which opportunistic smears are abundant, and screening invitations are independent of these. The effect on screening coverage remained small and did not differ from that of a reminder letter, not even when self-sampling was offered as a third intervention. In enhancing the attendance at organized screening, however, self-sampling is still a feasible option for or addition to a reminder letter. If self-sampling is used as a third intervention after 2 written invitations, the overall attendance in Finland could most likely reach the desired 80% or even exceed this.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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