

A Large Population-Based Randomized Controlled Trial to Increase Attendance at Screening for Cervical Cancer

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Abstract

Objective: Although cervical cancer is one of the potentially most preventable malignancies, it is still fairly common. In settings with established screening programs, increased compliance is important for future reduction in cervical cancer incidence, but it is presently unclear how this can be effectively achieved. **Methods:** We conducted a randomized controlled trial including all 12,240 women invited to organized screening in Sweden. To increase compliance, three successive interventions were tested: (a) modified invitation *versus* the standard invitation letter, (b) reminder letter to nonattenders after the first intervention *versus* no reminder letter, and (c) phone reminder to nonattenders after the reminder letter *versus* no phone reminder. We analyzed the proportion of women attending screening after each intervention and the cumulative proportion after the interventions as well as the cumulative proportions of cytologic

abnormalities. **Results:** The modified invitation did not increase attendance compared with the standard invitation letter [difference 1.3%; 95% confidence interval (CI) -0.3 to 2.9]. In contrast, a reminder letter increased the proportion of women attending with 9.2% (95% CI 7.9–10.5) compared with women who did not receive a reminder letter, and a phone reminder increased the proportion of women attending with 31.4% (95% CI 26.9–35.9). Combinations of modified invitation, written reminder, and phone reminder almost doubled attendance within 12 months, and the number of detected cytologic abnormalities was more than tripled. **Conclusion:** Simple reminders by mail and phone can drastically increase women's participation in Papanicolaou smear screening and increase the number of detected precursor lesions and thereby save lives. (Cancer Epidemiol Biomarkers Prev 2004;13(3):346–354)

Introduction

The use of cervical Papanicolaou (Pap) smears can markedly reduce mortality and suffering from cervical cancer (1, 2). In Sweden, the introduction of Pap smear screening about three decades ago resulted in removal of precursor lesions on a large scale, which ultimately reduced the national incidence of invasive cancer by about 50% (3, 4). However, epidemiological studies (5) and mathematical modeling (6) indicate that a much larger reduction would be within reach if compliance with the screening program were improved. In settings where all women have access to cervical cancer screening, one main reason for disease occurrence seems to be noncompliance. Although women usually are favorable to the idea of having a Pap smear, they do not always apply it personally (7).

Despite type of screening and practical differences between screening programs in different settings, reasons for nonattendance seem to be the same, at least in Western countries. A high degree of perceived barriers (8–13), a low degree of perceived benefits (11, 13, 14), poor knowledge about the purpose of the screening (9, 15–17) or the recommended screening interval (9, 17), and lack of a regular gynecologist or other health care source (12, 18, 19) are important predictors of nonattendance. In some studies, nonattendance is also more common among women who are single (12, 16, 20, 21), women who live in rural areas (17, 22), immigrated women (23), or women with low socioeconomic status (24–26).

Several studies have examined strategies to increase attendance at screening for cervical cancer through increasing knowledge or by reminders (27–44). Although some of these studies have used a randomized design (27, 31, 32, 36–38, 42–44), they were often restricted to certain categories of women such as minority or low-income groups (31, 32, 42, 43), women over 40 years (27, 32, 38, 44), or women living in rural areas (27, 37). Several randomized studies were also based on small samples (36, 43, 44). To our knowledge, no prior population-based randomized controlled trial was conducted on a large sample of women of all ages relevant for screening. Therefore, we conducted such a study with

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three successive interventions: (a) a modified invitation *versus* the standard invitation letter, (b) a reminder letter *versus* no reminder letter, and (c) a personal phone reminder *versus* no phone reminder. We then measured the proportion of women attending screening after each intervention and the cumulative proportion of women attending after two and three interventions 12 months after the initial mailing as well as the cumulative proportions of detected cytologic abnormalities. Our main hypothesis was that each one of the interventions would increase attendance at screening for cervical cancer compared with the group not receiving the intervention.

Materials and Methods

Setting. Organized screening for cervical cancer was introduced in Sweden in 1967. In Uppsala County, where the present study was conducted, information on all Pap smears taken in both organized screening (about 20% of all screening) and opportunistic screening (about 80% of all screening; 45) has been compiled in a cytology register since 1969. In this register, each woman is identified through her individually unique national registration number. The register is continuously updated concerning vital status, migration, and deregistration of women who have asked to be excluded from the call-recall system, mainly due to a hysterectomy. Most women in Sweden have, at some point, had a Pap smear. In Uppsala County, all women who have not had a Pap smear during the previous 3 years are invited to have a Pap smear from the calendar year when they turn 25 until age 59. Women who do not attend screening within a year after they have been invited are thereafter invited every year. The invitations are administered by the Cytology Laboratory at the Uppsala University Hospital in collaboration with the 13 maternity wards where the Pap smears are taken, free of charge.

The overall coverage of Pap smear screening in Uppsala County at ages 25–59 is around 70% over a period of 3 years. In the year 2000, of the 71,300 female residents aged 25–59 in Uppsala County, 23,000 (32%) women were registered as not having had a Pap smear within the last 3 years and were thus invited to organized screening. Of these women, 6600 (29%) attended within (1 year) the year 2000.

Design and Sample

Eligible Subjects. Participants in our study were all women (12,240) invited to screening for cervical cancer in Uppsala County during 17 weeks in the first half of 2001. These eligible women were aged 25–59, were residents in Uppsala County, had not had a Pap smear during the previous 3 years, and had not asked to be excluded from the call-recall system (<1%/year). All Pap smears taken after invitation were recorded until March 15, 2002. Besides experimental conditions and participation, each woman was categorized according to age, time since the last smear, and whether she had a prior smear or not. Our database includes individual information on screening history, invitations to screening, randomization to intervention, and subsequent Pap smears. This database was linked to a longitudinal database on education, income, and employment (the LOUISE register) at

Statistics Sweden. This linkage enabled us to add individual information about the women's level of education, employment status, disposable income, receiving social welfare, marital status, having children or not, country of birth, and whether they were Swedish citizens. Information on demographic and socioeconomic variables was retrieved from December 31, 1999. The study was approved by the Institutional Review Board of Karolinska Institutet in Stockholm.

Interventions. Three successive interventions to increase attendance at screening for cervical cancer were tested: (a) modified invitation *versus* the standard invitation letter, (b) reminder letter to women who did not attend after the first intervention *versus* no reminder letter, and (c) phone reminder to women who did not attend after the reminder letter *versus* no phone reminder.

1. The modified invitation letter consisted of sending an additional information brochure with the standard invitation. The brochure, entitled "A Small Examination of Great Importance," was designed in collaboration with professionals at the Swedish Cancer Society and is further described in Table 1. The standard invitation letter, printed on ordinary white stationery, contained a brief description of the purpose of the Pap smear, whom it is for, how it is taken, how to schedule an appointment, and that test results are classified and conveyed by mail.
2. The reminder letter was identical to the standard invitation letter, except that it included the information that the woman had received a prior invitation and that this was a reminder. The word "REMINDER" was printed in capitals in the heading.
3. Women who received a phone reminder were called up by one of two professional female research assistants who gave a short description of the Pap smear and offered to schedule an appointment for the women.
4. Women who were not randomized to receive the respective intervention (*i.e.*, they only received the standard invitation to organized screening, no reminder letter, and no phone reminder) composed the comparison group for the respective intervention groups.

Table 1. Description of the contents of the brochure included in the modified invitation

The brochure, entitled "A Small Examination of Great Importance," told the recipients about the following:

- Type of cancer the Pap smear is supposed to protect against
- That the Pap smear is a preventive measure
- Why it is important to have a Pap smear when invited
- At which ages and with what time intervals women are invited to have a Pap smear
- How the Pap smear is taken
- How they receive the test results
- How precursor stages are followed up and that an eventual treatment is simple
- When not to have a Pap smear (during menstruation, etc.)
- That the test is taken free of charge of a midwife
- That the test can be and often is taken in opportunistic screening
- That the test cannot detect sexually transmitted diseases or other types of cancer
- Illustrative pictures and drawings of the female body showing the location of the cervix

From the cytology register, we noted the first time each woman attended after an invitation or reminder. The main outcome measure was the proportion of women attending screening after each intervention. We also measured the cumulative proportion of women attending after two and three interventions 12 months after the initial mailing as well as the cumulative proportions of detected abnormalities.

Randomization. Figure 1 summarizes the randomization of the initial sample of 12,240 women on the three successive interventions. Each woman due for an invitation was on a weekly basis assigned a random number, which allowed us to randomly allocate her to the intervention or control groups.

First Intervention. Firstly, women eligible for invitation to screening were, on a weekly basis, randomly allocated to one of the experimental conditions to receive a modified or a standard invitation letter. Twenty-three women (0.2%) had recently requested to be excluded from the call-recall system, and 60 women (0.5%) had had a Pap smear just before the first intervention. Because these women did not meet our criteria for eligibility, they were excluded from the study (Fig. 1).

Second Intervention. Secondly, all women who did not attend, on average, within 5 months after the first intervention were thereafter randomly allocated to the second intervention (*i.e.*, to receive a reminder letter or not). Due to a break for summer holidays, there was some variation in the time interval between receiving the first invitation and the reminder letter (from 3 to 5 months), depending on the week of the initial random allocation (Fig. 1).

Third Intervention. Women who remained noncompliant 2 months after the reminder letter and who had received their first invitation during the first 8 weeks of the study (starting January 16, 2001) were eligible for the third intervention (*i.e.*, to receive a phone reminder or not). The restriction of the sample to 8 (of the possible 17 weeks) was done to achieve cost-effective use of available resources. Moreover, for practical reasons (distance to the maternity wards for the research assistants), we only included women who lived within Uppsala municipality (6 of 13 maternity wards). This restriction was implemented after the randomization took place (Fig. 1).

We did not exclude women who could not be reached from the analysis or from subsequent interventions, because there was a difference in the postal tracking system between the modified invitation letter and the standard invitation letter (*i.e.*, women who had moved were not tracked to their new address in the standard call-recall system, while women who were sent modified invitations were tracked), or women who could not be reached for a phone reminder due to no answer or no registered phone number. No difference in the proportion of women attending after randomization to a reminder letter or not as well as after randomization to the phone reminder or not were found between women receiving a modified or a standard invitation letter (data not shown). Because the first intervention had no effect on attendance in subsequent interventions, we collapsed the intervention arms in all subsequent analyses.

End Point of Follow-up. Because the interventions were sequential, the end point of follow-up after the first intervention (on average, 5 months after it was mailed) was the starting point for the second intervention, and the end point of the second intervention (2 months after it was mailed) was the starting point for the third intervention. There was no washout period between the interventions, which means that some women might already have scheduled an appointment that took place during a subsequent intervention period. Because these women would be included in the group eligible for randomization for the next intervention, we expect some displacement in attendance. The final end point of follow-up after the third intervention was 1 month after the last phone reminder was conducted.

Blinding. Collaborators in the study were blinded to the women's group assignment. Because the end point was whether a woman had a Pap smear or not, none of the collaborators, except the research assistants conducting the phone reminder, could influence this decision. The midwives who performed the Pap smears had no information about whether a woman was randomized for intervention or not. In addition, the participants were not aware that the modified invitation, the reminder letter, or the phone reminder were part of a scientific study and that they were randomized to receive these interventions. This design was a necessary condition for valid effect estimation and was approved by the Institutional Review Board of Karolinska Institutet in Stockholm.

Statistical Methods. The analyses were performed according to the intention-to-treat principle. Women randomized a certain week in the first intervention experienced equal follow-up periods, and the statistical analysis was stratified on week of randomization. The results of the interventions were analyzed using a generalized linear regression model with identity link, assuming that the probability of participation after an invitation was binomially distributed. The results are expressed as absolute differences, with 95% confidence intervals (CI) between the proportion of women participating in the intervention group and the control group. We also compared the results from a univariate logistic regression model with that from a multivariate logistic regression model, adjusting for screening history and demographic and socioeconomic factors. The model assumes that the logarithm of the odds of attending is a linear function of the explanatory variables; odds ratios (ORs) with 95% CI were computed from the estimated parameters and SEs. The multivariate model included the following variables: experimental condition, age (24–29, 30–39, 40–49, or 50–59 years), time since last smear (3–4 years ago, ≥ 5 years ago, women aged 24–26 who never had Pap smear, or women aged 27–59 years who never had a Pap smear), education (low, intermediate, or high), employment status (employed/student or other), disposable income (0–100% of the median or >100% of the median), social welfare (yes or no), marital status (married/cohabitant or single), having children (yes or no), country of birth [Sweden, other Nordic or European Community (EC) countries, or all other countries], and citizenship (Swedish or other).

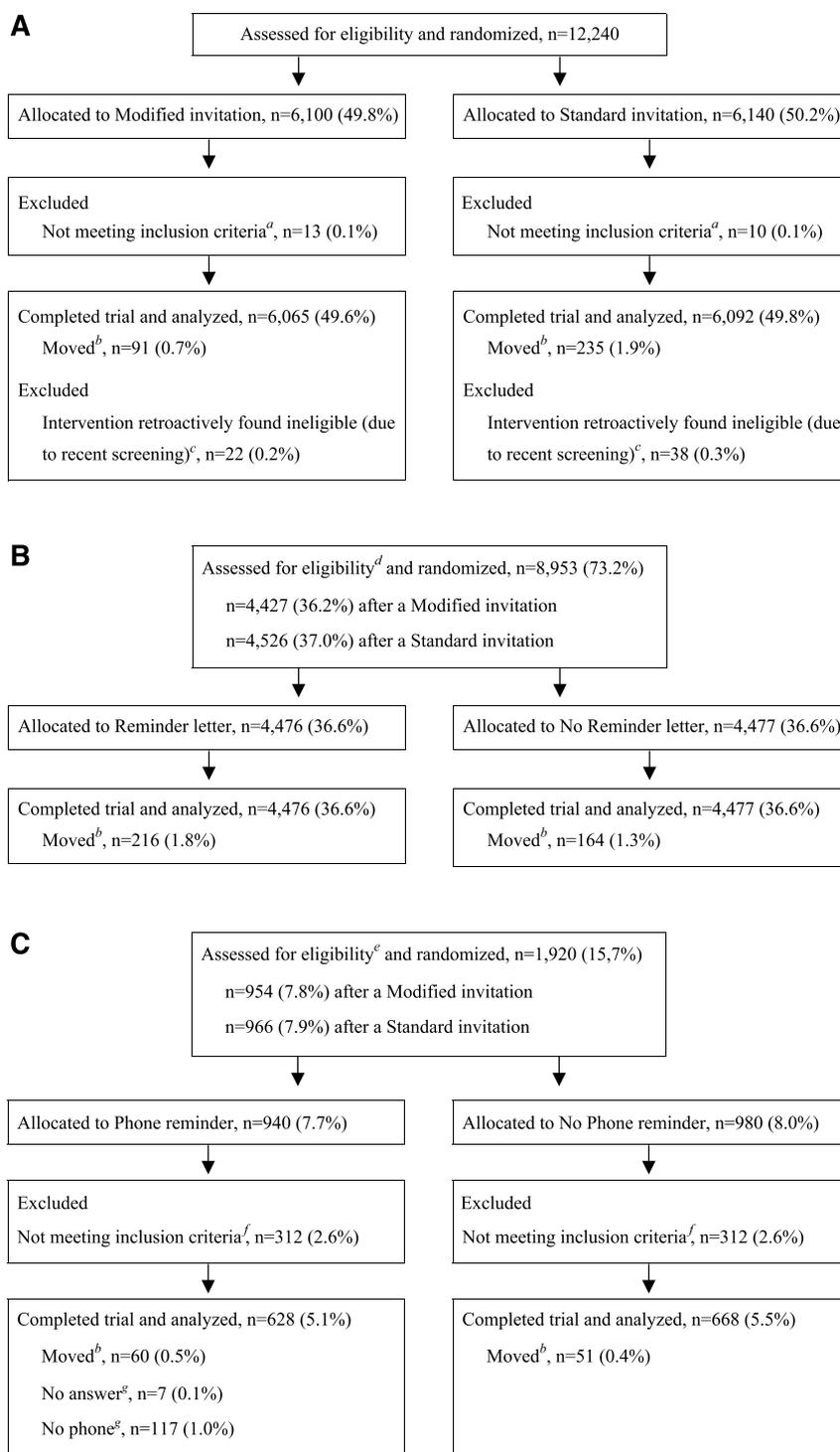


Fig. 1. Randomization of the participants in three successive interventions. **A.** First intervention: modified invitation versus standard invitation. **B.** Second intervention: reminder letter versus no reminder letter. **C.** Third intervention: phone reminder versus no phone reminder. Numbers in parentheses, percentage of the initial sample of 12,240 women. Notes: ^aWomen who recently have personally requested to be excluded from the call-recall system (mainly due to hysterectomy) were excluded after the randomization and from further interventions. ^bWe did not exclude from the analysis the women who had moved due to differences in the postal tracking system between modified and usual invitations and because we did not have the corresponding information for women who did not receive any written reminder or phone reminder. ^cWomen who were invited to screening despite a recorded smear <3 years before the first intervention (mainly due to a time lag between taking a smear and getting it registered in the cytology register) were excluded after the randomization. ^dWomen who had not attended within 5 months after the first intervention were eligible for the second intervention. ^eWomen who had not attended within 2 months after the reminder letter and who were randomized to the first intervention in one of the first 8 weeks during Spring 2001 were eligible for the third intervention. ^fDue to practical reasons, women living outside Uppsala municipality did not receive a phone reminder. ^gWe did not exclude women who did not answer the phone or who had no listed phone number from the analysis because we did not have corresponding information for women who did not receive any phone reminder.

Occurrence of mediating effects of these background factors on the interventions was checked by testing for homogeneity over the categories for these background factors in the multivariate model described above. The categories were collapsed in these analyses.

The fraction attending screening within 12 months in the different intervention groups was estimated from the proportions attending at the times of the different types of interventions. We had information on attendance after 12 months on 9560 women, thus including only these in the analysis. The CIs given are based on the estimated SEs obtained by error propagation using Gauss approximation after a logarithmic transformation of the product of probabilities constituting the 12-month participation rates. Corresponding analyses of the proportions of cytologic abnormalities [cervical intraepithelial neoplasias (CIN) 1+ and 2+] were also performed. Furthermore, the formal statistical tests of differences in proportions of cytologic abnormalities between the different interventions were compared by Fisher's exact test. Due to small number of events, the type of initial invitation (*i.e.*, standard or modified) was disregarded in these analyses. Because only women living in Uppsala municipality were included in the phone reminder intervention, we compared cumulative effects of these women with all women in the country but found attendance only marginally higher (data not shown).

We separately analyzed the effects of screening history and demographic and socioeconomic variables on attendance, regardless of intervention, again using a logistic regression model. The main outcome measure was the proportion of women attending screening within 6 months after the first invitation.

Results

The analysis on the first intervention was based on 6065 (49.7%) women who received a modified invitation and 6092 (50.1%) who received a standard invitation letter (Fig. 1). In the second intervention, the analyses were based on 4476 (36.6%) women who received a reminder letter and 4477 (36.6%) women who did not. In the third intervention, the analysis was based on 628 (5.1%) women received a phone reminder and 668 (5.5%) women who did not.

Baseline Characteristics. Reflecting our large sample size, the baseline characteristics were evenly distributed within each intervention group (data not shown). During the process of three subsequent randomizations, there was a gradual increase in the proportion of women who were younger, more highly educated, single, nulliparous, and immigrants (Table 2). Furthermore, women aged 24–29 years, with no prior Pap smear, on social welfare, and who were single, nulliparous, and born outside Sweden were overrepresented among women not reached by the phone reminders (data not shown). The impact of the background characteristics on attendance rate is further analyzed and quantified in Table 3. In general, the effect was statistically significant but small, with ORs of 1.5 or lower.

Primary Outcomes. We found only a minor effect, of borderline significance, of the modified intervention compared with the standard invitation (Table 4). The

Table 2. Baseline demographic and socioeconomic characteristics of women included in the analysis in each intervention group

	First intervention		Second intervention		Third intervention	
	No.	%	No.	%	No.	%
Total	12,157		8953		1296	
Age distribution (yr)						
24–29	2941	24.2	2271	25.4	445	34.3
30–39	3542	29.1	2589	28.9	363	28.0
40–49	2895	23.8	2077	23.2	244	18.8
50–59	2779	22.9	2016	22.5	244	18.8
Years since last smear						
3–4	5475	45.0	3206	35.8	442	34.1
5–32	3654	30.1	3246	36.3	390	30.1
0 prior smear, 24–26 years	1535	12.6	1179	13.2	268	20.7
0 prior smear, 27–59 years	1493	12.3	1322	14.8	196	15.1
Education ^a						
Low	1950	16.3	1505	17.1	143	11.3
Intermediate	5185	43.3	3733	42.5	494	39.1
High	4842	40.4	3555	40.4	625	49.5
Employment status ^a						
Employed/student	9344	76.9	6761	75.5	980	75.6
Other	2807	23.1	2189	24.5	316	24.4
Disposable income ^{a,b}						
0–100% of median	6084	50.1	4560	51.0	653	50.4
>100% of median	6067	49.9	4390	49.1	643	49.6
Social welfare						
Yes	929	7.6	742	8.3	133	10.3
No	11,228	92.4	8211	91.7	1163	89.7
Marital status ^a						
Married/cohabitant	6430	52.9	4537	50.7	533	41.1
Single	5721	47.1	4413	49.3	763	58.9
Having children ^a						
Yes	6284	51.7	4477	50.0	555	42.8
No	5867	48.3	4473	50.0	741	57.2
Country of birth ^a						
Sweden	10,370	85.3	7579	84.7	1055	81.4
Other Nordic and EC countries	603	5.0	441	4.9	57	4.4
Rest of the world	1183	9.7	932	10.4	184	14.2
Citizenship ^a						
Swedish	11,322	93.2	8291	92.7	1167	90.1
Other	828	6.8	658	7.4	129	10.0

^aWhen the numbers do not add up to 12,157 for the first intervention, 8953 for the second intervention, or 1296 for the third intervention, it is due to missing observations (from 1 to 180) in the LOUISE database.

^bThe median disposable income is 99,300 SKR. The disposable income equals the sum of all family members' disposable income (total income minus tax, repaid study loan, alimony, and cost deduction) multiplied by the individual consumption weight divided by the family's total consumption weight and the basic amount for current year.

proportion of women attending within 5 months increased from 25.7% with standard invitation to 27.0% with modified invitation (difference 1.3%; 95% CI –0.3 to 2.9). In contrast, the reminder letter increased the proportion of women attending from 6.3% to 15.5% (difference 9.2%; 95% CI 7.9–10.5). Lastly, the phone reminder had the greatest relative and absolute impact; the proportion of women attending increased from 10.0% to 41.4% (difference 31.4%; 95% CI 26.9–35.9). The multivariate analyses, which adjusted for potential confounders, changed our effect measure only marginally (Table 4).

Table 3. Proportion of women participating within 6 months after the first randomization, regardless of intervention, by screening history and socioeconomic and demographic factors

	Sample size (no.)	Participated within 6 months regardless of intervention			
		No.	%	OR	95% CI
All women	12,157	3594	29.6		
Age distribution (yr)					
24–29	2941	772	26.3	1.0	(Reference)
30–39	3542	1084	30.6	1.2	1.1–1.4
40–49	2895	922	31.9	1.3	1.2–1.5
50–59	2779	816	29.4	1.2	1.0–1.3
Years since last smear					
3–4	5475	2,512	45.9	5.7	5.1–6.7
5–32	3654	475	13.0	1.0	0.8–1.2
0 prior smear, 24–26 years	1535	413	26.9	2.5	2.0–3.0
0 prior smear, 27–59 years	1493	194	13.0	1.0	(Reference)
Education ^a					
Low	1950	494	25.3	1.0	(Reference)
Intermediate	5185	1631	31.5	1.4	1.2–1.5
High	4842	1447	29.9	1.3	1.1–1.4
Employment status ^a					
Employed/student	9344	2899	31.0	1.4	1.3–1.5
Other	2807	691	24.6	1.0	(Reference)
Disposable income ^{a,b}					
0–100% of median	6084	1718	28.2	1.0	(Reference)
>100% of median	6067	1872	30.9	1.1	1.1–1.2
Social welfare					
Yes	929	207	22.3	1.0	(Reference)
No	11,228	3387	30.2	1.5	1.3–1.8
Marital status ^a					
Married/cohabitant	6430	2116	32.9	1.4	1.3–1.5
Single	5721	1474	25.8	1.0	(Reference)
Having children ^a					
Yes	6284	2030	32.3	1.3	1.2–1.4
No	5867	1560	26.6	1.0	(Reference)
Country of birth ^a					
Sweden	10,370	3135	30.2	1.4	1.2–1.6
Other Nordic and EC countries	603	178	29.5	1.3	1.1–1.7
Rest of the world	281	281	23.8	1.0	(Reference)
Citizenship ^a					
Swedish	11,322	3402	30.1	1.5	1.2–1.7
Other	828	188	22.7	1.0	(Reference)

^aWhen the numbers do not add up to the 12,157 women studied, it is due missing observations (from 1 to 180) in the LOUISE database.

^bThe median disposable income is 99,300 SKR.

Of the 628 women randomized to receive a phone reminder, 444 (70.7%) were actually reached, and of those, 250 (56.3%) women attended (data not shown). Of the 194 women who were reached but did not attend, 66 (34.0%) had scheduled for a Pap smear but did not show up, whereas 128 (66.0%) declined, chiefly because they had a temporary impediment, preferred a private midwife or gynecologist, or experienced fear or anxiety.

Stratified Analysis. We also analyzed the effect of the three interventions among subgroups of women stratified by age, having had a prior smear, education, employment status, income, social welfare, marital status, having children, country of birth, and citizenship. Only one factor did significantly modify effects of the first intervention (*i.e.*, age). Women aged 30–44 years were slightly more sensitive to a modified invitation than the youngest women. Only in the former age group were women more likely to attend after a modified invitation than after a standard invitation (difference 3.2%; 95% CI 0.7–5.6; Table 5). The effect of the second intervention was significantly modified by having had prior smear, education, social welfare, and marital status; women who had had a prior smear were more sensitive to a reminder letter than those who had not had a prior smear, as were women with intermediate education, women who were not on social welfare, and women who were married/cohabitant (Table 5). Lastly, four variables modified the effect of the third intervention: age (≥ 30 years), prior Pap smear (yes), social welfare (no), and having children (yes; Table 5).

Cumulative Effects. The cumulative effects of different combinations of sequential interventions on attendance and on the number of detected cytologic abnormalities were estimated 12 months after the first randomization (Fig. 2).

The attendance rate after 12 months was 33% (95% CI 33–34) for a standard invitation letter only and 36% (95% CI 35–38) for a modified invitation only. The modified invitation thus shows a long-term effect of around 3% (Fig. 2A). However, there was no evidence of a significant difference caused by the modified invitation for women who received the phone reminders. The combination of modified invitations and reminder letters gave a cumulative attendance of 44% (95% CI 42–45; *i.e.*, an 11% higher attendance rate compared with that

Table 4. ORs and 95% CIs of participating in screening after randomized intervention

	Sample size (no.)	Participated in screening		95% CI for proportion		Univariate modeling		Multivariate modeling ^a	
		No.	%	Difference ^b	95% CI	OR	95% CI	OR	95% CI
First intervention									
Modified invitation	6065	1638	27.0	1.3	–0.3 to 2.9	1.1	1.0–1.2	1.0	0.9–1.1
Usual invitation	6092	1566	25.7	0.0	(Reference)	1.0	(Reference)	1.0	(Reference)
Second intervention ^c									
Written reminder	4476	693	15.5	9.2	7.9–10.5	2.7	2.4–3.2	2.9	2.5–3.3
No written reminder	4477	282	6.3	0.0	(Reference)	1.0	(Reference)	1.0	(Reference)
Third intervention ^c									
Phone reminder	628	260	41.4	31.4	26.9–35.9	6.3	4.7–8.5	6.9	5.0–9.4
No phone reminder	668	67	10.0	0.0	(Reference)	1.0	(Reference)	1.0	(Reference)

^aControlling for experimental condition and for all background factors included in Tables 1 and 2.

^bDifference in proportion of attenders in comparison with reference categories.

^cBecause no washout period existed between the interventions, displacement in attendance might be expected.

Table 5. Difference in proportion of women participating in screening after receiving intervention by screening history and socioeconomic and demographic factors

	First intervention			Second intervention			Third intervention		
	Difference ^a	95% CI	^b	Difference ^a	95% CI	^b	Difference ^a	95% CI	^b
All women	1.3	-0.3 to 2.9		9.2	7.9-10.5		31.4	26.9-35.9	
Age									
24-29	-2.0	-5.0 to 1.0		7.9	5.4-10.4		21.7	14.7-28.7	
30-44	3.2	0.7-5.6	*	9.8	7.7-11.9		34.5	27.1-42.1	**
45-59	1.5	-1.2 to 4.3		9.5	7.5-11.6		38.4	29.8-47.0	
Have had prior smear									
Yes	1.8	-0.0 to 3.7		10.6	9.1-12.2		36.5	30.8-42.3	
No	-0.8	-3.5 to 1.9		5.6	3.6-7.7	***	20.5	13.9-27.1	***
Education ^c									
Low	3.7	-0.1 to 7.4		8.1	5.3-10.8		24.7	12.3-37.2	
Intermediate	1.4	-1.0 to 3.9		11.5	9.4-13.5	*	30.9	23.8-38.1	
High	0.1	-2.4 to 2.6		7.2	5.1-9.3		32.9	26.3-39.5	
Employment status ^c									
Employed/student	1.7	-0.1 to 3.5		9.5	8.0-11.1		32.6	27.3-37.8	
Other	-0.4	-3.5 to 2.7		8.0	5.7-10.2		27.0	18.8-35.2	
Disposable income ^c									
0-199	1.9	-0.3 to 4.1		9.1	7.3-10.9		29.8	23.8-36.0	
≥200	0.7	-1.5 to 3.0		9.2	7.4-11.0		32.7	26.1-39.2	
Social welfare									
Yes	1.7	-3.4 to 6.9		4.2	0.6-7.9		17.3	5.2-29.5	
No	1.2	-0.4 to 2.9		9.7	8.3-11.0	**	33.1	28.3-37.9	*
Marital status ^c									
Married/cohabitant	1.5	-0.7 to 3.8		11.4	9.5-13.3		35.3	28.0-42.6	
Single	0.8	-1.4 to 3.0		7.0	5.2-8.6	***	28.2	22.5-33.7	
Have children ^c									
Yes	1.7	-0.5 to 4.0		9.9	8.0-11.8		36.2	29.2-43.3	
No	0.7	-1.5 to 2.8		8.5	6.8-10.1		27.0	21.3-32.7	*
Country of birth ^c									
Sweden	1.5	-0.2 to 3.2		9.1	7.6-10.5		32.2	27.1-37.2	
Other	0.3	-3.6 to 4.3		10.0	6.9-12.9		28.0	18.6-37.3	
Citizenship ^c									
Swedish	1.6	-0.0 to 3.2		9.0	7.7-10.4		32.4	27.7-37.2	
Other	-3.5	-9.0 to 2.0		10.4	6.5-14.4		20.6	8.7-32.6	

^aDifference in proportion of attenders in comparison with reference categories.

^bTest for homogeneity: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

^cWhen the numbers do not add up to the 12,157 women studied, it is due missing observations (from 1 to 180) in the LOUISE database.

observed with a standard invitation letter only). By combining modified invitations, reminder letters, and telephone reminders, a cumulative attendance of 64% (95% CI 61-68) was reached (*i.e.*, the attendance rate was almost doubled compared with that observed with a standard invitation letter only).

The cumulative number of women diagnosed with CIN1+ was tripled by using the combination modified invitation, reminder letter, and phone reminder (227/10,000 women) compared with the standard invitation only (67/10,000 women), corresponding to a 239% (95% CI 103-464) increase in the number of detected cytologic abnormalities (Fig. 2B). Women who received a reminder letter only and women who received a reminder letter in combination with a phone reminder yielded significantly higher numbers of CIN1+ diagnoses compared with those receiving the initial invitation only ($P < 0.0012$ and 0.0001 , respectively). Corresponding differences were also demonstrated for the number of CIN2+ diagnoses ($P = 0.03$ and 0.004 , respectively).

Discussion

Our large randomized trial demonstrates that relatively simple modifications of the call-recall system can

drastically increase women's motivation to attend Pap smear screening. Overall, we almost doubled the number of women participating in Pap smear screening and more than tripled the number of detected cytologic abnormalities. Whereas reminders by letter and by phone both strongly increased the proportion of women attending, the modified invitation had only a small short-term impact, while it seemed to entail a somewhat higher long-term increase. The proportion of women attending screening increased by almost 10% after a reminder letter and by another 30% after the phone reminder. An additional effect of the interventions was to increase the proportion of detected cytological abnormalities. Hence, efforts to increase attendance seem to reach those in greatest need for screening.

Strengths of our study include the strictly randomized study design, the large study sample, a population-based setting, reliable information on prior screening history, and the ability to include women who were due for a Pap smear over a period of almost 4 months. This design enabled statistically powerful analyses of both intervention effects and heterogeneity among subgroups of women. Because all women randomized to the study contributed with information, whether they attended screening or not, selection bias due to dropouts after the randomization was not a problem. We were unable

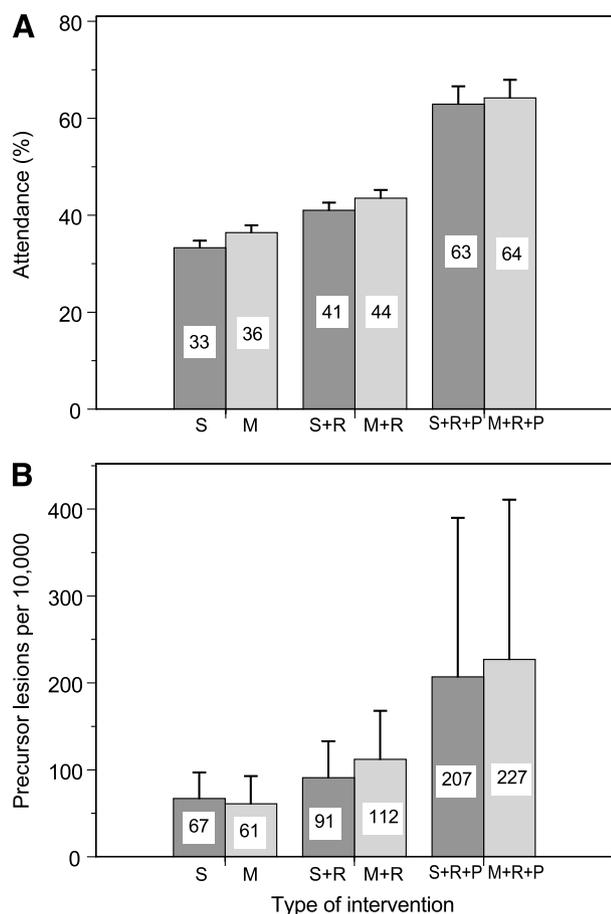


Fig. 2. Proportion of women participating at Pap smear screening (A) and rate of precursor lesions (CIN1+; B), within 12 months from first randomization, by selected combinations of interventions and reference point (no intervention). S, standard invitation (reference); M, modified invitation; S + R, standard invitation + reminder letter; M + R, modified invitation + reminder letter; S + R + P, standard invitation + reminder letter + phone reminder; M + R + P, modified invitation + reminder letter + phone reminder.

to exclude from the analysis women who had moved from their address, which might cause a slight underestimation of the absolute effects. Likewise, if a larger proportion of women had been reached in the third intervention, the total benefit of a phone reminder would likely increase, as would the cumulative effect.

We pondered why a substantially modified invitation letter did not improve participation in our study. Although women over a certain age are more attentive to written information, specific information likely is needed for women who are invited to screening for the first time. In previous studies, higher attendance was achieved by increasing knowledge through mail-outs (34, 43, 44), direct contact (29, 30, 35, 38, 43), or educational programs (27, 33, 40, 41). Most studies were, however, performed on subgroups of women with low attendance to screening, such as ethnic minorities (29, 30, 33, 35, 40, 41, 43), low-income women (34, 40, 41), or women attending appointments at a certain clinic/hospital (38). This precludes direct comparisons with the present study as well as generalization to other settings.

However, despite differences in prior studies, an overall estimate of them is that increased knowledge can be a powerful tool in efforts to increase attendance, perhaps especially so in settings where the initiative to have a Pap smear mainly lies with the woman.

A reminder letter increased attendance at screening for cervical cancer substantially, most strongly in women who had had a prior smear and among women who had not received social welfare. Overall, the effect seemed to be stronger among women from higher socioeconomic groups. This agrees with one previous study (46). A reminder letter is cost-effective, because it adds relatively little cost in an existing call-recall system and definitely improves the overall attendance rate.

The strong relative and absolute effect of a phone reminder agrees with one earlier study on attendance at mammography (47) and a study on the combination of a physician reminder letter and a phone contact (32). The phone reminder showed a somewhat lower effect on women aged 24–29 years, who had not had a prior smear, who were on social welfare, or who were nulliparous. However, the effect may have been underestimated in these groups, because they were over-represented among women who could not be reached by a phone reminder. In our experience, women perceived the phone reminder favorably because an appointment could be scheduled directly and questions could be answered. A positive effect has also been shown in studies among minority groups by offering on-site screening when visiting a clinic or a hospital (28–30, 38). A personal contact might also be important, especially for women who feel anxious about the examination or the Pap smear. The possibility to have the Pap smear taken by the person who the women talked to might further increase motivation.

To conclude, relatively simple measures may drastically influence compliance with Pap smear screening. These measures may affect in particular women at high risk of cervical cancer because the number of detected cytologic abnormalities increased more than the participation rate. Because our interventions were nonspecific and the effects are fairly robust over strata of numerous background factors, we believe that our findings are generalizable to other settings with high-quality screening programs.

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