Original article

Repeat invitations and participation in cervical screening: A population-based cohort study

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Abstract

Objective: Cervical cancer screening reduces incidence and mortality dependent on participation. To increase participation we investigated the best time to send repeated invitation (RI) letters to those who did not attend screening after the first letter.

Methods: We designed a prospective population-based cohort study featuring 3,352,211 first invitation letters and 2,449,187 RI letters sent between 2012-01-01 and 2023-12-31 to all Swedish screening-eligible women aged 23 to 70. We measured participation rates based on the time between invitation letters and their first RIs, adjusted for age, calendar month/year, screening test (HPV/cytology), and healthcare region.

Results: The strongest RI-to-participation association was observed for RIs sent 8–12 weeks after the invitation letter, with 65% participation and adjusted odds ratio (aOR) 1.42 (1.34–1.50). This was consistent for women below 50, aOR 1.35 (1.28–1.44) / 64% participation; and women above 50, aOR 1.95 (1.63–2.32) / 72% participation. Participation declined with number of RIs sent, with the first RI followed by 49% participation and the seventh followed by 21% participation. Only 10.9% of the screening population required a fourth RI or more.

Conclusion: Sending a RI 8–12 weeks after the original invitation was associated with the highest participation. After sending four RIs other methods of communication should be employed to encourage screening participation.

Keywords

screening, cytology, HPV, cervical cancer, healthcare, public health, quality registry, surveillance

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Introduction

Cervical screening programs reduce mortality.[1] The efficacy of these programs is contingent on achieving high coverage in the target population.[2] Many screening programs employ letters of invitation to screening appointments, and repeat invitation (RI) letters of some variety (SMS/test messages, letters, phone calls, etc.) when an appointment has been missed.[3] Invitation letters lead to increased participation from the screening population,[4,5] with the greatest effect among those with an existing screening history.[6,7] The oldest method for improving participation[8] is that of sending a RI letter to individuals that, for some reason, missed their screening appointment. Considerable uncertainty surrounds RI strategies and how to optimally employ them for maximum screening participation. The effect of a RI letter so far has appeared at best modest and of uncertain size, with a few studies reporting improvements in participation from 2% to 10%.[8,9] The national guidelines for cervical screening in Sweden recommend sending a RI letter to individuals that missed their screening appointment at an arbitrary time point of one year after the fact.[10] RI letters that do not lead to participation result in delays, dependent on time between RI letters, that may increase the risk of cancer developing.

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Furthermore, the size of the non-participating screening-eligible population dictates the cost and effort of interventions applied; a smaller target population offers a greater range of practical intervention options.

The Swedish cervical screening program is based on primary human papillomavirus (HPV) testing since 2015, implemented individually by each of the nation's 21 healthcare regions. All data generated from the program are collated annually into the National Cervical Screening Registry[11] (Swedish abbreviation NKCx). The national guidelines are implemented regionally, leading to varying program models and algorithms. This has led to multiple strategies for re-inviting individuals, with RI letters being sent at different time points after the original invitation.

The national HPV vaccination program started in 2012 in Sweden, providing free vaccinations for all girls at the age of 11, organized through the school system.[12] In Sweden, heavily vaccinated birth cohorts are just starting to enter screening as of 2023. However, globally, it will not be until 2070 that most screening populations will come from vaccinated birth cohorts. Organized screening program coverage will thus remain a key aspect of minimizing cervical cancer incidence for the foreseeable future, and efforts to maximize participation need to continue. In Sweden, cervical screening has typically been performed by trained midwives; as of 2024, self-sampling is also a recommended option.[13]

Through data generated by the regional variation in RI strategies manifest during 2012–2023 in Sweden, which resemble a natural experiment or even a pragmatic randomized trial, we here assess which RI strategies have been associated with the highest screening program participation. Our specific question was to investigate if RIs were associated with higher participation or not, and if so with which time interval they should optimally be issued. Using the longitudinal data available in NKCx, we analysed the various timings employed by different healthcare regions over a period of eleven years and assessed which point in time was the most likely to result in a screening test for the first RI sent. We also compared the participation rates for each RI letter sent after an invitation letter as well as the recipient pool for these letters.

Methods

Data sources

We used data from the National Cervical Screening Registry (NKCx) which comprises all cervical screening data from the nation, including all invitation and RI letters, and all records and results from HPV tests, cytology and biopsies from the female genital tract. The registry is complete for the entire Swedish screening population since 1995 and has recently been updated to include indices for whether a cervical test derives from primary HPV, primary cytology, triage or clinical follow-up. Each invitation letter includes a scheduled time and place for the screening appointment, as per the national guidelines,[14] as well as instructions for how to reschedule said appointment. Self-sampling was introduced recently in Sweden, a practice highly limited before 2022, when a few regions switched to pandemic-related self-sampling strategies. No self-sampling tests or letters for self-sampling were included in this study.

We linked this dataset to matching data from the Swedish Tax Authority on region of residence, by using the personal identification number unique to all Swedish citizens. All data were pseudonymized before analysis.

Aim

We wanted to find out which timing of the RI (measured as time since original invitation) had the best participation rate for screening and what the participation rate for each RI letter was. For the first aim, we defined two subgroups from the population: those that participated in screening after having received a single RI letter, and the complement to this group. For the second aim we defined one subgroup for each number of RI letters sent before resulting in a screening test (ranging from zero to eleven).

Public involvement

The public was not included in the design or conduct of this study. Dissemination of the study results will come from public authorities and sources through uptake in guidelines on patient care and screening strategy recommendations.

Definition of exposure: invitations versus repeat invitations

All letters recorded in NKCx to women in the 21 regions were categorized as either an invitation to participate, or a subsequent RI related to a missed earlier invitation. An invitation was defined as the first letter sent to an individual of 22–23 years (i.e., at entry to screening) or, if no such letter was available due to the woman entering the screening population at a later age, the first letter sent to the woman after a recorded primary screening test. We removed letters prior to the first test to ensure that the woman was registered in the system so that all subsequent events would be captured in the data. The recorded primary tests were used as a starting point as the Swedish screening recall system uses the date of the last primary screening test to determine when to schedule the next invitation. Opportunistic tests (such as those deriving from clinically indicated testing rather than the organized screening program) were included in the assessment, as per national guidelines on screening recall scheduling, which state that the date of the latest

test (whether organized or opportunistic) shall govern the date of issuing the next invitation to organized screening. Only primary tests were used for this process; biopsy tests, colposcopies and/or clinically indicated follow-up tests were not used. This was done as these test types are only used for follow-up of earlier tests and are not indicative of baseline screening participation, nor are they considered for screening recall scheduling. In the case of co-testing or reflex (triage) testing, we used the first reported test to represent the primary test type (HPV or cytology) when multiple tests were recorded following the same source sample. Consequently, we defined a RI as any letter sent after an invitation letter but before any subsequent primary test for the woman in question.

Definition of outcome: participation in screening versus no participation

Participation was defined as a woman having received any letter chain consisting of an invitation and a single RI resulting in a record of subsequent screening tests for that woman. Comparisons were defined as letter chains with an invitation and more than one RI, with or without a subsequent screening test on record, or a letter chain with an invitation and one RI but no recorded test.

Statistics

We studied participation as an outcome in relation to i) number of RIs between invitation letter and subsequent test, ii) time interval of first RI after the original invitation, iii) age group of the woman at the time of invitation (<50 versus >=50 years) and iv) calendar month of invitation (which we explored due to potential seasonality of participation since summers are typically low-intensity in the screening venues).

We calculated the odds ratios (ORs) of participation (yes/no) for time between the RI and the original invitation, using a baseline of RIs sent 48 to 56 weeks after the original invitation. This corresponds to the national guidelines in Sweden. For this calculation, we used intervals of four weeks (RIs sent 28–56 days compared to RIs sent 336–392 days after the original invitation, etc). The ORs were calculated as a logistic regression with robust standard errors and adjusted for age at the time of the invitation, registered healthcare region of the individual at the time of invitation, month the invitation was sent, year the invitation was sent, and the type of test (HPV or cytology) that was used. Age, year and type of test were included to account for potential bias arising from changes to the national guidelines over time. Regressions and ORs were computed in R[15] 4.3.1, and the robust standard errors were computed using lmtest[16] and sandwich[17] packages. No matching was used as the study population was comprehensive for the entire country. The impact of interactions was tested as a sensitivity analysis compared to the main results.

Results

Study population

We collected the identification numbers from all letters sent to individuals between the ages of 22 and 70 from 2012 to 2023 from NKCx. For these individuals, we collected all letters in the registry, resulting in 18,335,887 letters, from 1993-05-25 until 2023-12-29. From these, 9 were removed for incompatible personal identification numbers, and 239,259 were removed as duplicated records. Mapping the remaining letters to invitation or RI types according to our algorithm (see Definition of exposure for details), we removed 10,055,474 letters sent prior to the first screening test recorded in the registry. Once letter types (invitation or RI) had been determined, we removed all letters sent prior to 2012-01-01 as well as invitation letters sent out 2023-01-01 or after to avoid skewing the data towards early RIs in the final year. This removed an additional 1,442,099 letters. We then removed 2276 letters sent to an individual above or below the age limit. The final study population consisted of 5,801,398 letters: 3,352,211 invitation letters and 2,449,187 RI letters (Table 1). For the invitation letters, 1,589,402 were mapped to HPV tests, 1,394,293 were mapped to cytological tests, and 368,516 had no associated test. Single repeat (SR) chains were defined as letter chains consisting of an invitation and one RI with subsequent screening test, and the comparison chains as letters with more than one RI or a letter chain with one RI but no recorded test. The study population contained 428,673 SRs and 450,708 comparisons (Table 1), with invitations sent out between 2012-01-02 and 2023-12-29. This population was followed for exploring the likelihood of participation based on the time between the original invitation and the first RI, and screening program participation based on the number of RIs received.

Timing of first repeat invitation

The cohort consisted of 879,381 invitation letters, of which 428,673 were SRs and 450,708 were comparisons. Compared to the reference level of issuing a RI at 48–56 weeks after the initial invitation, a RI recorded within 8–12 weeks was associated with a 65% (8386 / 12,854) participation rate and an adjusted OR (aOR) of 1.42 (1.34–1.5). RIs sent within 4–8 weeks showed a 62% (9188/14,731) participation rate with aOR 1.28 (1.22–1.35). In contrast, RIs issued at 36–40 weeks or 40–44 weeks after the original invitation were associated with a significantly lower participation at 43% (8382 / 19,433) and 45% (12,889 / 28,603) respectively, with aORs 0.86 (0.82–0.91)

Table 1. The study population and the single repeat / comparison cohort letter chains.

	Study population	Single repeat	Comparison
Invitation letters	3,352,211	428,673	450,708
Age (mean (SD))	38.76 (12.47)	36.16 (11.41)	35.07 (12.16)
Test type (%)			
Cytology	1,394,293 (41.6)	191,160 (44.6)	102,203 (22.7)
HPV	1,589,402 (47.4)	237,513 (55.4)	138,363 (30.7)
None	368,516 (11.0)	0 (0.0)	210,142 (46.6)
Repeat invitation letters (%)			
0	2,472,830 (73.8)	0 (0.0)	0 (0.0)
1	512,690 (15.3)	428,673 (100.0)	84,017 (18.6)
2	183,539 (5.5)	0 (0.0)	183,539 (40.7)
3	86,956 (2.6)	0 (0.0)	86,956 (19.3)
4	44,557 (1.3)	0 (0.0)	44,557 (9.9)
5	25,011 (0.7)	0 (0.0)	25,011 (5.5)
6+	26,628 (0.8)	0 (0.0)	26,628 (5.9)

Each invitation letter represents a letter chain containing zero or more repeat invitations (RIs). Age represents the age at the time the invitation letter was sent. Test type shows what kind of screening test was effected by the letter chain, if any. While 18.6% of comparison letter chains have only a single RI, none of these led to a screening test.

and 0.87 (0.83–0.9) (Figure 1A). Numeric and binary coefficients can be seen in the online supplementary material, with and without adjustment for region (Supplementary Table 1 and Supplementary Table 2). The sensitivity analysis showed a significant difference for weeks 32–36 only, with no impact on the findings (Supplementary Figure 1). For comparison, the results are also shown with 8–12 weeks as baseline (Supplementary Figure 2). The number of weeks between invitation and RI showed a significant interaction with calendar month ($p < 0.0001$), and all ORs were calculated as subsets with the related week interval and the reference group. Age showed an interactive effect with week interval at $p < 0.05$.

Calendar month of RI was also associated with a statistically significantly higher participation, regardless of within which timeframe after the initial invitation the RI was sent. November and December were consistently associated with around 50% higher participation subsequently, compared to the reference month of January (Supplementary Table 3).

The SRs and comparisons were more even in age distribution (36.16 vs 35.07, Table 1) than when comparing by test type for the letter chain (34.00 vs 42.79 for cytology and HPV respectively, Table 2). The distribution of letters over the calendar months did not show significant differences either (Figure 2).

Effect of repeat invitations

The entire study population consisted of 3,352,211 letter chains, of which 879,381 (26%) had at least one RI. Participation rates based on RI decreased with each additional letter sent, with the first RI resulting in 49% (428,673 / 879,381) participation, the second RI resulting in 37% (136,607 / 366,691) participation, and the seventh resulting in 21% (2732 / 13,006) participation (Figure 3A). The number of recipients also decreased with number of letters sent, from 879,381 receiving a first RI letter down to 13,006 receiving a seventh RI letter (Figure 3B). Only 11,312 letter chains contained more than seven RI letters.

Individuals 50 or above

The cohort aged 50 or above contained 130,385 invitation letters, of which 62,718 were SRs and 67,667 were comparisons. The strongest interval, 8–12 weeks, had an aOR of 1.95 (1.63–2.32) with 72% (1401 / 1938) participation rate, and the second, 4–8 weeks, an aOR of 1.37 (1.18–1.59) with 68% (1530 / 2248) participation rate. The lowest, 16–20 weeks after the original invitation, had an aOR of 0.69 (0.6–0.8) with 53% (2184 / 4093) participation rate, followed by weeks 36–40 at 0.74 (0.63–0.86) with 50% (1030 / 2068) participation rate (Figure 1C). Effect of calendar month differed the most for weeks 16–20 (Supplementary Table 3) compared to the average values of the full cohort.

Individuals below 50

The cohort below age 50 consisted of 724,959 invitation letters, of which 355,953 were SRs and 369,006 were comparisons. The interval 8–12 weeks after the initial invitation letter was the most distinct at aOR 1.35 (1.28–1.44) with 64% (6809 / 10,559) participation rate. After that came 4–8 weeks at 1.25 (1.19–1.32) with 62% (7494/12,185) participation rate. The lowest interval aORs were 40–44 weeks at 0.88 (0.84–0.92) with 45% (10,719 / 23,637) participation rate, followed by weeks 36–40 at 0.89 (0.85–0.94) and 43% (6993 / 16,439) participation rate (Figure 1B).

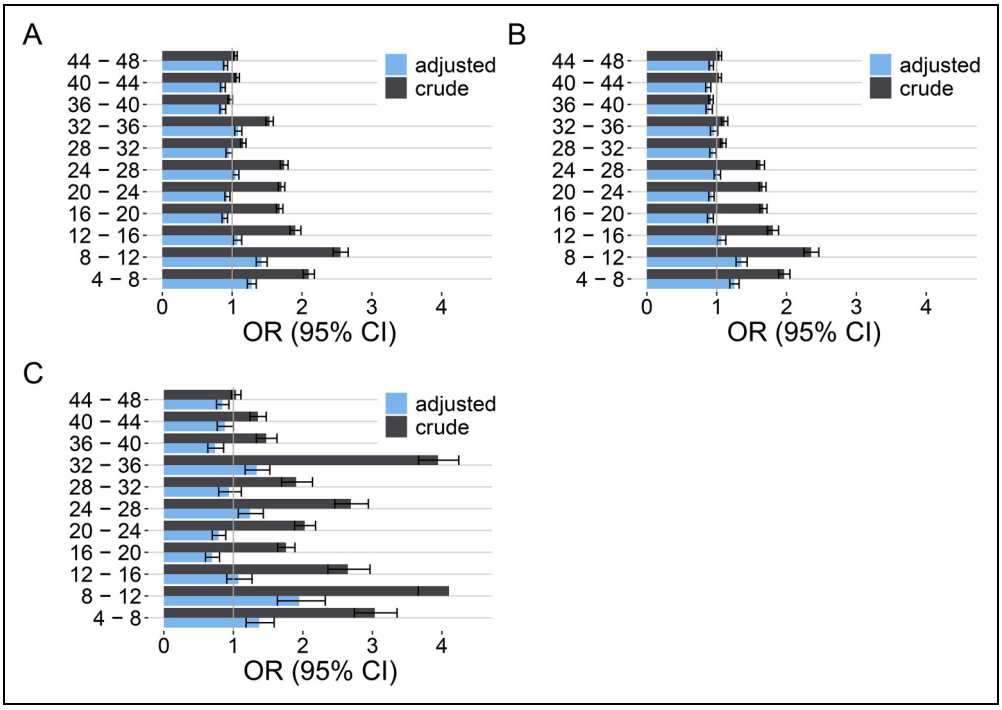


Figure 1. Odds ratios (OR) and confidence intervals (CI) for cervical screening program participation after one repeat invitation (RI). ORs are presented as either crude values or with adjustments for age, calendar time, year, healthcare region, and test type (HPV or cytology). The reference is the interval week 48 to week 56; the same as the Swedish guidelines. A) Odds ratios of screening participation based on the week the RI was sent after the initial invitation for the entire cohort of women. B) Odds ratios of screening participation based on the week the RI was sent after the initial invitation for women under the age of 50 at the time of the letter. C) Odds ratios of participation based on the week the RI was sent after the initial invitation for women of age 50 or above at the time of the letter.

The individuals aged under 50 showed a similar relevance by month as the full cohort (Supplementary Table 3).

Discussion

Sending RIs 8–12 weeks after the original invitation letter was associated with the best participation rates while the lowest participation rates were observed 36–40 weeks after the original invitation letter (Figure 1A). As time since invitation was measured without chronological anchoring, and invitation letters were sent at any point in time over the year, we discarded the hypothesis that the low participation rates when sent one year apart were due to recurring individual obligations within that timeframe. The elevated participation rates within the initial three month period could be influenced by an implicit social contract of varying form,[18–20] especially when combined with a preset examination appointment. The decreasing effect of RIs over time from the original invitation timepoint supports this hypothesis. Chronological month also seems to play a role in participation, with October, November and December having the most positive associations with the ORs, while February and June have the most negative associations. This phenomenon is likely based on national school schedules and population level competing interests, with February and June associated with optional holidays requiring childcare. This overlap has previously been found to suppress adherence to healthcare appointments.[21] October through December have no optional holidays during which a screening test can be scheduled, nor many distractions.

Limiting the age range in the analysis showed a divide in ORs between women above and below 50 with those above displaying a higher participation rate to early RI letters. Notably, while the ORs differ, the highest participation intervals remained consistent and, as such, no change in strategy is required to best approach the two age bands with regards to RI timeframes.

Sending RI letters to the screening population increased participation, with each new wave of letters resulting in observing a lower participation rate from a smaller recipient pool (Figure 3). While sending letters has marginal cost, the delay in screening and resources booked for this may lead to negative outcomes for both the screening program and the individuals involved. A prolonged absence of screening is associated with an increased risk of cancer,[1] and as participation rates declined with each new wave of RIs a new participation strategy for this group of non-participants becomes increasingly important. With RIs sent every

Table 2. The study population by test type.

	Study population	Cytology	HPV
Invitation letters	3,352,211	1,394,293	1,589,402
Age (mean (SD))	38.76 (12.47)	34.00 (11.19)	42.79 (11.85)
Reminders (%)			
0	2,472,830 (73.8)	1,100,930 (79.0)	1,213,526 (76.4)
1	512,690 (15.3)	191,160 (13.7)	237,513 (14.9)
2	183,539 (5.5)	60,023 (4.3)	76,584 (4.8)
3	86,956 (2.6)	23,978 (1.7)	32,413 (2.0)
4	44,557 (1.3)	10,469 (0.8)	14,575 (0.9)
5	25,011 (0.7)	4914 (0.4)	7167 (0.5)
6+	26,628 (0.8)	2819 (0.2)	7624 (0.5)
Participation after 1 reminder (%)			
Yes	428,673 (12.8)	191,160 (13.7)	237,513 (14.9)
No	450,708 (13.4)	102,203 (7.3)	138,363 (8.7)
NA	2,472,830 (73.8)	1,100,930 (79.0)	1,213,526 (76.4)

NA = not applicable.

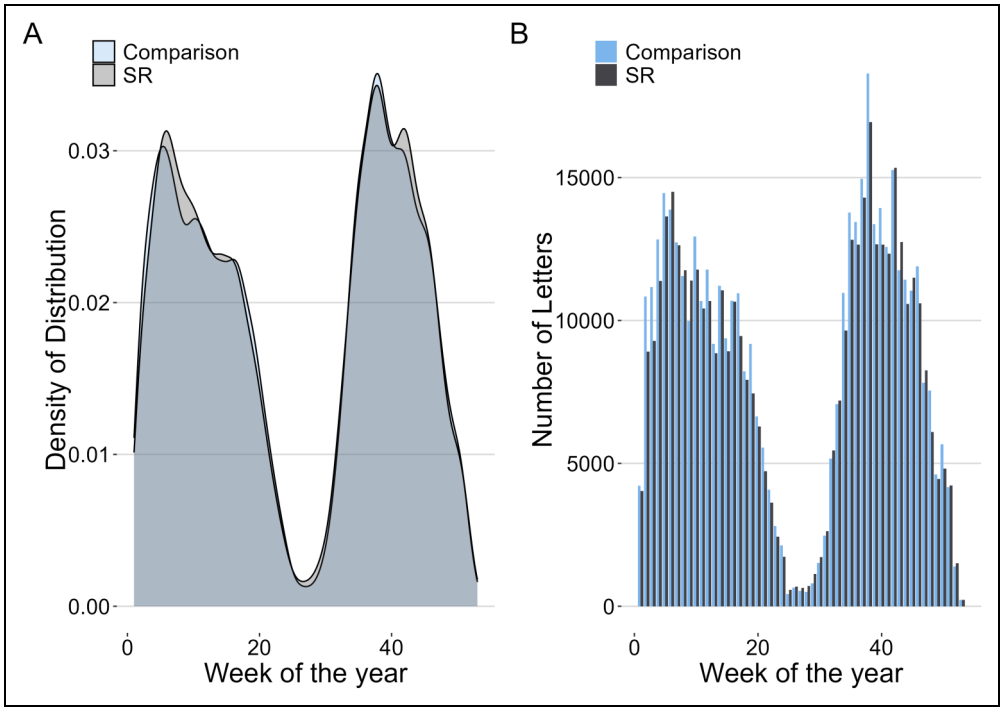


Figure 2. Single repeat invitation to participation (SR) and comparison group characteristics. A) The density of invitation letters sent in the SR and comparison groups over the year. B) The number of invitation letters sent over the year, stratified by calendar week.

year, individuals relying on cytological screening would be considered at high risk after receiving two RI letters, and with HPV screening after four RI letters. Participation rates of 31% and 23% (Figure 3A) are insufficient for handling these at-risk individuals. Only 10.9% (Figure 3B) of the RI letter population require a fourth RI letter, suggesting that enhanced approaches such as phone calls or unsolicited home-testing kits may be cost-effective strategies. As further RI letters are sent to these non-participants, new strategies become increasingly cost-efficient and risk-reducing.

NKCx is a comprehensive registry of all invitations and all tests regarding cervical cancer screening in Sweden as well as all opportunistic events for Swedish citizens and foreigners. The data we have used for this study encompass the entirety of the screening population in Sweden.

The organized cervical screening program in Sweden first introduced self-sampling in 2019, and this option became popular during the Covid-19 pandemic. In 2019 there were 28,416 invitation letters that included self-sampling kits sent, increasing to 792,485 letters in 2023.

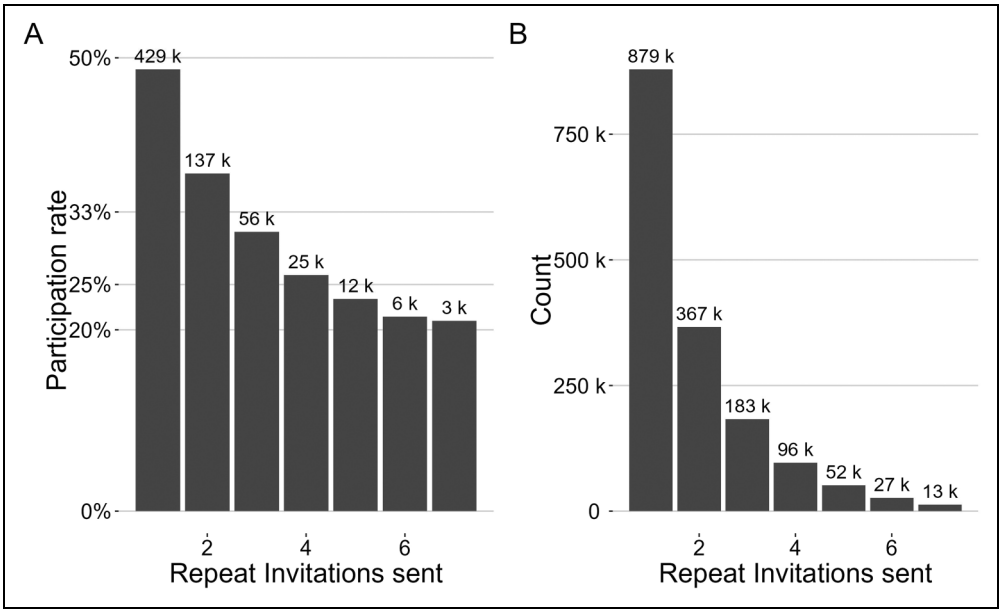


Figure 3. Participation and repeat invitations (RIs) sent. A) Participation in the screening program by number of RI letters sent after the invitation letter. The y axis shows the marks for number of letters sent per successful participation (one in two, one in three, etc), and the number atop each bar represents the absolute number of participations in our study population. After four RI letters, fewer than one in four letters sent lead to participation. B) The number of letters sent for each grouping of RIs. The number atop each bar shows the absolute number of letters sent within each RI grouping. The number of recipients decline rapidly, and out of the original 3,35 m recipients, 96k receive a fourth RI, and of these approximately 25k participate as a result.

The self-sampling initiative has seen the greatest peak of adoption in the age range 30–32 with 218,340 letters over the course of the initiative. Conversely, of those 70 years old, only 17,871 received a self-sampling kit letter. Switching from clinic to self-sampling, which was handled as opt-out, has shown a strong bias towards individuals with a preference for over-screening[11] (33% over-screened participants vs 10% absentees). This phenomenon has likely reduced the number of diligent participants in the current study as use of self-sampling is mutually exclusive with clinic-based testing in the screening program. We have only used clinic-based testing here to ensure similar conditions for every participant across the entire age range. As a result, participation rates, especially in the below 50 cohort, are likely higher than what is reported.

There is a question pertaining to whether the RIs sent shortly after the invitation letters impact participation, or whether these individuals would have attended screening regardless. Camilloni et al. showed in a systematic review that an invitation–RI strategy was better than an invitation-only strategy with a pooled risk ratio of 1.71 (1.60–1.83),[22] and Tavasoli et al. showed that RIs after four weeks resulted in an increased participation during the subsequent timeframe, with total attendance 14.1% vs 8.5% after 36 weeks in a Canadian setting.[5] For comparison, and to ensure that any RI sent was received after the scheduled appointment to not skew the early data, we used four weeks as a starting point for the analysis. We also right-censored invitation letters, but not RI letters, one year before end-of-data to avoid early outcomes bias towards the end of the study period.

Self-sampling was not included in this study as the conditions that may affect screening participation likely differ between appointment-based testing at a clinic and self-sampling at home. As such, evaluating the efficacy of self-sampling RIs is better suited for a separate study.

Conclusion

In this national observational study spanning over a decade, RIs after an initial invitation were beneficially associated with participation in organized cervical screening. This association was greater than previously reported and similar across ages of the women invited as well as whether the screening was HPV- or cytology-based. The most successful interval to issue repeat invitations was 8–12 weeks after the first letter, issued during late fall or winter.

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Ethics approval and consent to participate

Ethical approval was granted by the Regional Ethical Review Board of Stockholm (2011/1026-31/4), which determined that, due to the population-based and pseudonymized nature of the data, informed consent from the study participants was not required.

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Competing interests

The authors declare no competing interests, but an author has received grant money from an organisation with interests in adjacent general areas. In ICMJE format the authors declare: no support from any organisation for the submitted work; Karin Sundström declares having received grant money from Merck, which has no interest in nor benefit from the manuscript, for other work; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

The individual participant data underlying this article were subject to ethical approval and cannot be shared publicly.

Supplemental material

Supplemental material for this article is available online.

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