Home-based HPV self-sampling improves participation by never- and under-screened women: results from a large randomised trial (iPap) in Australia

Short title: Home-based HPV self-sampling in never- and under-screened women

Authors:

Farhana Sultana

Dallas R English

Julie A Simpson

Kelly T Drennan

Robyn Mullins

Julia ML Brotherton

C David Wrede

Stella Heley

Marion Saville

Dorota M Gertig

Correspondence:

Address: Victorian Cervical Cytology Registry, PO Box 161, Carlton South, Vic. 3053, Australia

Fax: +61 (03) 84176835

Email: dgertig@vcs.org.au

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Novelty and impact

For women who have not had a recent Pap test, HPV self-sampling improves their participation in cervical cancer screening. We conducted the first randomised trial of HPV self-sampling as a strategy for women who have never had a Pap test and showed that for these women it is substantially superior to reminding them to have a Pap test. HPV self-sampling is a useful strategy to recruit never-screened women to cervical screening programs.

Abstract:

We conducted a randomised controlled trial to determine whether HPV self-sampling increases participation in cervical screening by never- and under-screened (not screened in past five years) women when compared with a reminder letter for a Pap test. Never- or under-screened Victorian women aged 30-69 years, not pregnant and with no prior hysterectomy were eligible. Within each stratum (never-screened and under-screened), we randomly allocated 7,140 women to self-sampling and 1,020 to Pap test reminders. The self-sampling kit comprised a nylon tipped flocked swab enclosed in a dry plastic tube. The primary outcome was participation, as indicated by returning a swab or undergoing a Pap test; the secondary outcome, for women in the self-sampling arm with a positive HPV test, was undergoing appropriate clinical investigation. The Roche Cobas® 4800 test was used to measure presence of HPV DNA. Participation was higher for the self-sampling arm: 20.3% versus 6.0% for never-screened women (absolute difference 14.4%, 95% CI: 12.6%-16.1%, $p<0.001$) and 11.5% versus 6.4% for under-screened women (difference 5.1%, 95% CI: 3.4%-6.8%, $p<0.001$). Of the 1,649 women who returned a swab, 45 (2.7%) were positive for HPV16/18 and 95 (5.8%) were positive for other high-risk HPV types. Within six months, 28 (62.2%) women positive for HPV16/18 had colposcopy as recommended and nine (20%) had cytology only. Of women positive for other high-risk HPV types, 78 (82.1%) had a Pap test as recommended. HPV self-sampling improves participation in cervical screening for never- and under-screened women and most women with HPV detected have appropriate clinical investigation.

Introduction

The effectiveness of organized screening for cervical cancer is compromised by nonparticipation as the majority of cervical cancers arise in women who are either never- or under-screened,[1] including in Victoria, Australia.[2] Barriers to women's participation are well documented and commonly relate to fear of the speculum examination, lack of time or access, not finding the right doctor, or a previous negative experience.[3, 4] Strategies that overcome such barriers and improve participation, particularly by engaging hard to reach groups, are imperative to improve coverage of cervical screening programs.

HPV testing is likely to replace Pap testing in many high-income countries, including Australia, in the near future.[5] One advantage of HPV testing is that it can be done on self-collected samples.[6] Although HPV testing of self-collected samples is slightly less sensitive and less specific than HPV testing of practitioner-collected samples unless a validated Polymerase Chain Reaction (PCR) test is used, it has the potential to overcome some of the barriers to conventional screening and facilitate participation by women who would not otherwise participate.[7, 8]

A recent systematic review and meta-analysis of sixteen randomised trials conducted in various countries showed that self-sampling increased participation in cervical cancer screening by non-attendees compared with a reminder to have a Pap/HPV test at a clinic when the kits were directly mailed to women. However, there was substantial heterogeneity between studies.[16] The participation proportions varied widely in the self-sampling arms (range 10% to 39%) and Pap test arms (range 2% to 26%), suggesting that country-specific issues are important.[17-23] Few trials included women who were truly under-screened (i.e. not screened in the past 5 years) and no trials included many never-screened women.[17, 21, 23-25] Compliance with follow-up clinical investigation by HPV positive women also varied widely (range 41% to 100%).[17, 20-23] Given the wide variation in participation and follow-up, trials specific to each program are necessary to determine the likely impact, including costs, of introducing self-sampling.

We conducted a randomised controlled trial to determine whether HPV self-sampling could increase participation in the Australian cervical screening program. For never- and under-screened women separately, we compared participation for HPV self-sampling versus a reminder letter for a Pap test. We also determined the proportion of women with a positive HPV test undergoing appropriate follow-up clinical investigation.

Methods

The trial protocol has been published.[26] Here, we present a brief overview of the methods as per the CONSORT Statement.[27] The Human Research Ethics Committee of the Victorian Department of Health approved the study and waived the requirement for informed consent. The trial was registered (ACTRN12613001104741; UTN: U1111-1148-3885).

Study setting

Australia's current screening policy recommends women have Pap tests every two years from 18 years (or two years after onset of sexual activity, whichever is later) until 69 years. From 2017, the program will change to primary HPV testing.[5] Eight jurisdictional Pap test registers, including the Victorian Cervical Cytology Register ("the Registry") support the program. Among its functions, the Registry records all cervical cytology and associated histology reports for Victorian women and sends reminders to women when their Pap test is overdue. Although it is a voluntary (opt-off) database, it has > 99% coverage of Pap tests.

There is no formal system of inviting women to start cervical screening. Women either initiate screening themselves or their doctor recommends they be tested. Once women have had a Pap test in Victoria, the Registry sends them reminder letters 27 months after their last negative test and a second reminder nine months later. Women whose Pap tests were performed outside Victoria do not receive reminders.

The trial was conducted at the Registry, which is part of Victorian Cytology Services Inc (VCS). VCS also has a laboratory that performs about half of all Victorian Pap and HPV tests.

Study sample

Women were eligible if they were Victorian residents, 30-69 years, never-screened or under-screened (not screened in past 5 years), were not pregnant, and had not had a hysterectomy. Apparently never-screened women were women on the Victorian Electoral Roll (citizens must register to vote) for whom no match was found on the Registry (matched on name, address and date of birth), indicating that no cervical screening episode had been recorded. No information on eligibility (other than age) was available for apparently never-screened women before randomisation. Eligible under-screened women were identified from the Registry, which records dates and results of screening episodes and details of hysterectomy.

Randomisation

Randomisation was stratified by prior screening status (apparently never- or under-screened). For each stratum, we randomly selected 8,160 women and randomly allocated them in a 7:1 ratio to the HPV self-sampling arm or to the Pap test arm. For the apparently under-screened stratum, there was additional stratification by time since last Pap test (5, 6, 7, 8, 9, and 10-14 years). Women were randomised in 34 equal-size blocks. The randomisation schedule was computer generated and implemented by a programmer who had no other involvement with the trial. Blinding was not feasible. Figure 1 shows the study design and flow diagram.

Interventions

Women allocated to the self-sampling arm were first sent a pre-invitation letter informing them that they would be sent a self-sampling kit. The letter also invited the women to contact the Registry to update contact details or inform us they did not wish to receive a kit, either because they did not want to participate, or were ineligible because they had had a hysterectomy, a recent Pap test or were

pregnant. After three weeks, if they had not withdrawn and if their pre-invitation letter was not returned unopened (return-to-sender), they were sent the kit. The package included an information brochure on HPV and cervical cancer, a nylon-tipped flocked swab enclosed in a dry plastic tube (Copan Italia, Brescia, Italy) within a resealable plastic bag, an instruction sheet for sample collection, an information form and a postage paid envelope for returning the swab and the form. Women allocated to the Pap test arm received a single invitation letter (never-screened) or a standard reminder letter (under-screened) to have a Pap test; included with the letter was a Pap test brochure, a similar information form and a postage paid envelope to return the form. The initial letters were mailed in 34 batches (i.e. the 34 blocks) between March and July 2014.

The information form asked women for contact details, country of birth, language spoken at home, Aboriginal and Torres Strait Islander status, details of any prior Pap test, time and place of the last Pap test, hysterectomy and pregnancy status. For the self-sampling arm, it also asked for the date of self-sample collection and details of their usual medical practitioner (general practitioner).

Laboratory testing

Returned swabs were tested at VCS Pathology using the Roche Cobas® 4800 HPV test (Roche Diagnostics GmBH) according to the manufacturer's instruction. The test is clinically validated and FDA approved and specifically identifies types HPV16 and HPV18 while concurrently detecting 12 other high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in a single pool. Hereafter, high-risk HPV is referred to as HPV. We previously validated using the dry swab for the Roche Cobas® 4800 HPV test .[28]

Clinical management

The clinical management of HPV positive women was as per the published protocol with the exception that women who were positive for HPV types other than 16/18 and whose subsequent cytology showed low grade squamous-intraepithelial lesions (LSIL) or less were recommended to have a repeat HPV self-sample test at 12 months, with referral to colposcopy if the repeat test was positive for HPV. Originally, we had specified immediate colposcopy for these women, but changed in response to new Australian proposals (Web Appendix figure 1).[5] Results were mailed to women and their general practitioners, who also received letters explaining the study, HPV results and recommendations for follow-up clinical investigation. Study liaison physicians called general practitioners and women who had not had the follow-up recommended in the study protocol.

Outcomes

The primary outcome was participation in screening at 3 and 6 months after the initial letters were mailed, as indicated by returning a self-sampling swab or having a Pap test. Women in the self-sampling arm who had a Pap test were counted as having participated. We identified women who had Pap tests after randomisation by performing a semi-automated match of the trial database with Registry records of Pap tests conducted in 2014 using a more sensitive algorithm than we used for the original match to the Electoral Roll.

The secondary outcome, which was applicable only to women in the self-sampling arm with a positive HPV test, was compliance with the follow-up clinical investigation. For women positive for HPV16/18 this was colposcopy and for women positive for other HPV types, a Pap test.

Sample size

The sample size was based on estimating the proportion of HPV positive women complying with the follow-up clinical investigation with a 95% confidence interval of +/- 5% points. This required a substantially larger sample than to compare even small differences in participation for the two arms.[26] The 7:1 allocation ratio was employed because of the need to identify sufficient HPV positive women.

Statistical methods

Unless specified otherwise, all confidence intervals (CI) and p-values are exact values based on the binomial distribution. Statistical analyses were performed using Stata 11.1 (StataCorp, College Station, TX).

For the primary analysis of participation, women who reported after randomisation that they were not eligible and women whose letters were returned to sender were analysed as randomised. For each stratum separately, we calculated participation proportions for the self-sampling and the Pap test arms and their absolute difference (95% CI and p-value).

We conducted pre-specified subgroup analyses by age, socioeconomic status (SES) and time since last Pap test. Age was categorised into ten-year groups. SES was estimated from the postcode of residence using an area-based measure derived from census data and categorised into quintiles.[29] Time since last Pap test was categorised as 5, 6, 7, 8, 9 and 10-14 years for the under-screened stratum. To assess effect modification on an absolute scale, we used binomial regression with an identity link with participation as the outcome and fitted interactions between trial arm and each of these variables separately. P-values were derived from the Wald test. We did not report participation by cultural background or Indigenous status as specified in the protocol, as this information was not available for all women.

For the secondary outcome, we estimated the proportions (and 95% CI) of women whose samples tested positive for HPV who completed follow-up clinical investigation as per the protocol. We also calculated the rate of HPV positivity and detection of histologically confirmed cervical intra-epithelial lesion grade 2 or more (CIN2+).

Sensitivity analysis of prior Pap tests and hysterectomy in the never-screened stratum

If an apparently never-screened woman reported a prior Pap test, the Registry was manually searched for her record. This search was more sensitive than the original matching with the Electoral Roll, partly because women amended their details (e.g. change in name, correct date of birth) or gave a specific date and practice of the last Pap test. The same procedure was used to determine that 2% of the apparently under-screened woman had a Pap test within 5 years in Victoria. Further, because the semi-automated search of the Registry for post randomisation Pap tests was also more sensitive than the original match, it also identified some apparently never-screened women who had had a prior Pap

test. Some apparently never-screened women also informed us that they had had a hysterectomy. Therefore, for this stratum, we performed sensitivity analyses to assess the impact of prior Pap tests and hysterectomy on the difference in participation between the two arms.

For the sensitivity analyses, we calculated estimated participation proportions and their differences after excluding from the denominator the number: (1) expected to have had a hysterectomy based on age-specific hysterectomy prevalence from the National Hospital Morbidity Database [30]; (2) found to have had a prior Pap test (either by self-report or from the semi-automated linkage with the Registry) and (3) the number of non-respondents estimated to have had a prior Pap test. To estimate (3), we randomly selected 100 non-respondents and manually searched for them in the Registry. For the numerators, we excluded women who participated but had had a prior Pap test or a hysterectomy.

Results

Participant characteristics

Within each stratum, baseline demographic characteristics were similar for the two arms (table 1). Many initial letters and kits were returned unopened (returned-to-sender), especially for the under-screened stratum (figure 1). Analysis of return-to-sender correspondence was restricted to the initial letters only (pre-invitation letters for the HPV self-sampling arm). For the under-screened stratum, a higher proportion of initial letters sent to women in the Pap test arm than in the self-sampling arm were returned (17.8% versus 12.7%; $p<0.001$), whereas for the never-screened stratum, the proportions returned-to-sender were similar (1.5% versus 1%; $p=0.18$) (table 2 and figure 1). For the under-screened stratum, the proportion of initial letters returned-to-sender decreased with increasing age and increased with increasing time since last Pap test. No trend with age was observed for the never-screened women (table 2). For some women in the self-sampling arm whose initial letters were not returned-to-sender, the kits were returned-to-sender (never screened 135 (1.9%); under-screened 946 (13.3%)) (figure 1).

Participation (as randomised)

Apparently never-screened: Within six months of the initial letter, 1452 (20.3%) of the 7140 women in the self-sampling arm had participated, either by returning a swab (n=1,131) or by having a Pap test (n=321), while 61 (6%) of 1,020 women in the Pap test arm had had a Pap test (table 3). The absolute difference between the arms was 14.4% (95% CI: 12.6%-16.1%, $p <0.001$) (figure 2).

Apparently under-screened: Within six months, 818 (11.5%) of the women in the self-sampling arm had participated, either by returning a swab (n=518) or having a Pap test (n=300), while 65 (6.4%) of the 1,020 women in the Pap test arm had had a Pap test (table 3). The absolute difference between the two arms was 5.1% (95% CI: 3.4%-6.8%, $p<0.001$) (figure 2)

Participation by different sub groups

For all age categories, participation was higher for never-screened women than for under-screened women and higher in the self-sampling arm than the Pap test arm in both strata (figure 2). In the never-screened stratum, participation decreased with increasing age in both arms. In contrast, participation in the under-screened stratum increased with increasing age in both arms (Web Appendix figure 2). The absolute difference in participation also varied with age in both strata (p-values for interaction $p<0.001$ for never-screened and $p=0.03$ for under-screened) (figure 2).

Within each SES category, participation was higher in the never-screened stratum than the under-screened stratum as was the difference in participation for the two arms (figure 2). However, within each stratum, the difference in participation between trial arms was similar across the different SES categories (p-value for interaction for never-screened=0.87 and for under-screened, p=0.40) (figure 2; Web Appendix figure 2).

For under-screened women, participation was higher in the self-sampling arm than the Pap test arm in all categories of time since last Pap test (figure 2). However, the participation decreased with increasing time since last Pap test in both arms of the trial and the difference in participation between the trial arms was greatest for women with the most recent previous Pap test (p-value for interaction= 0.04) (figure 2; Web Appendix figure 2).

Post randomisation ineligibility: prior hysterectomy

After receiving their initial letters, 887 women (809 in the HPV self-sampling arm and 78 in the Pap test arm) informed us that they had had a hysterectomy (figure 1). The proportion of women in the never-screened stratum who reported a hysterectomy was higher for the self-sampling arm than for the Pap test arm (10.1% versus 6.4%; $p<0.001$), but for under-screened women, the proportions were low and similar for both groups (1.2% versus 1.3%; $p=0.87$). Of the 1,452 apparently never-screened women in the self-sampling arm who participated, 85 (5.9%) reported a hysterectomy. Of the 61 participants in the Pap test arm of the apparently never-screened stratum, 3 (4.9%) reported a hysterectomy. For the under-screened stratum, of those who participated, 8 (1%) women in the self-sampling arm and 1 (1.5%) in the Pap test arm reported a hysterectomy (figure 1).

Misclassification of prior screening status of apparently never-screened women

Details of self-reported prior Pap tests and those identified in the Registry are shown in Web Appendix table 1. A substantial proportion of women in this stratum either reported or were found after randomisation to have had a prior Pap test: 1134 (15.9%) of women allocated to HPV self-sampling and 143 (14%) of women in the control arm, including 745 in the self-sampling arm and 31 in the Pap test arm who participated. In addition, 12 of the random sample of 100 non-respondents were found to have had a record giving an estimate of 12% (95% CI: 6.3 – 20%).

Sensitivity analysis of participation by apparently never-screened women

The estimated participation proportions and their differences are presented for the different scenarios in Web Appendix table 2. After accounting for hysterectomy and the estimated number of women

with prior Pap tests the estimated participation proportions were 14.2% for the self-sampling arm and 4.2% for the Pap test arm, with an absolute difference of 10%.

HPV testing of self-sampled material

All 1,649 returned swabs were tested for HPV; 1500 (91%) tested negative, 45 (2.7%, 95% CI 2.0-3.6%) were positive for HPV16/18, 95 (5.8%, 95% CI 4.7-7.0%) were positive for other HPV types and 9 (0.6%) were unsatisfactory. The proportions that were HPV positive were similar in the two strata (data not shown).

Compliance with follow-up clinical investigation by women with HPV positive results

Overall, 106 (75.7%) of 140 women whose samples tested positive for HPV had the appropriate clinical follow-up within six months of receiving their HPV test results (table 4). Of the 45 women with HPV16/18 positive results, 28 (62.2%) complied by having colposcopy. All except two of these 28 women also had a Pap test. Nine (20%) women had a Pap test only. The Pap test results appeared to influence the decision for referral to colposcopy: all eight women who had high grade squamous intraepithelial lesions (HSIL) or possible HSIL had colposcopy compared with 18 of 27 whose Pap tests were negative or showed LSIL only. Two women refused any clinical investigation. The remaining six women were sent reminder letters at 3 and 6 months but had no known investigations. Of the 95 women positive for other HPV types, 78 (82.1%) had a Pap test within six months of receiving their HPV test result.

Biopsy-confirmed cervical intraepithelial neoplasia

Ten women (six with HPV16/18) had CIN3 and one (with HPV16/18) had CIN2. Assuming that none of the women who had no clinical follow-up had CIN2+, the estimated prevalence of CIN2+ was 6.7 (95% CI: 3.3 – 11.9) per 1,000 women screened by HPV self-sampling (i.e., 11/1649).

Discussion

Overall findings: Inviting women to self-sample for HPV testing resulted in a substantially greater participation in screening than an invitation or reminder letter for a Pap test, in both strata of never and under-screened women (20.3% versus 6% and 11.5% versus 6.4%, respectively). For the never-screened stratum, after accounting for the number expected to have had a hysterectomy and the number estimated to have had prior Pap tests, the difference was smaller (10%), but still larger than for the under-screened stratum. For never-screened women, the increase in participation was greater for young women whereas for under-screened women the increase in participation was greater for older women. For under-screened women, the difference in participation reduced with increasing time since their last Pap test. The effect of self-sampling did not vary by SES. Of the women positive for HPV16/18, about 60% had a colposcopy as recommended within six months, while 82% of women positive for other HPV types had the recommended Pap test.

Strengths: Our study has several strengths. It is the first trial that included many never-screened women. Second, the sample size was large with sufficient power to assess participation by different

subgroups. Third, the trial was conducted within an organised screening program in a situation similar to routine practice. Fourth, we used a dry flocked swab that is acceptable, cheap, easy to use and safe in the home environment. Only 0.6% of the dry samples returned were unsatisfactory for evaluation, which was similar to that found in a trial in Italy (0.7%) [31] and The Netherlands (0.5%) [32]; both these trials used a lavage like device (wet sample). Finally, we used a PCR based test that identified HPV16/18 separate to other high-risk types.

Limitations: Our initial matching of the Victorian Electoral Roll with the Registry misclassified some women with a prior Pap test in Victoria as never screened. Subsequent reviews showed this problem was greatest when the most recent Pap test was many years ago, as the probability of a change to name and/or address increases over time (e.g. after marriage). Further, some apparently never-screened women reported Pap tests that had been performed outside Victoria. For the never-screened group, we were also unable to exclude women who had had a hysterectomy before randomisation, and it is likely that for under-screened women, their hysterectomy status was incompletely recorded by the Registry, particularly if it was in the distant past. For under-screened women, the positive associations between age and participation and the inverse associations with time since last Pap test could be an artefact due to a greater proportion of incorrect addresses for younger women and women screened in the distant past.

Comparison with other studies: Our findings are broadly consistent with other trials of HPV self-sampling in high-income countries with organised screening programs. [10-15, 23, 26, 27] Recently, Verdoodt et al reported a systematic review and meta-analysis of existing trials.[16] Almost all trials in which kits were directly mailed to women showed increased participation in the self-sampling arm compared with reminder/invitation to have a Pap/HPV test at a clinic. However, there was substantial heterogeneity in the effects (I^2=97.4%; p<0.001) that was not explained by age or type of non-attendees targeted. For three trials in which women had to opt-in to receive the self-sampling kit, the pooled estimate of overall participation was similar for the two arms. These trials also showed substantial heterogeneity (I^2 = 94.9%; p<0.001), and in such circumstances, pooled estimates are difficult to interpret. Several self-sampling devices were also used and it is unclear from the Verdoodt et al review if the device or the type of intervention (kit only, initial letter+kit or kit+reminder) influenced participation. There could also be other factors that might affect participation and which were not widely reported or measured in the various trials (e.g. SES, urbanisation, screening history). Thus, while there is substantial heterogeneity in the effects, reasons for the heterogeneity are unclear.

In our study, participation in the under-screened stratum for the self-sampling arm (11.5%) was similar to that reported in a UK trial (10.2%)[17] but lower than in three Swedish trials (14.7%, 24.5% and 39%) [21, 24, 25] and three trials in The Netherlands (34.2%, 26.6% and 30.8%).[23, 33, 35] In both Sweden and The Netherlands, researchers had more up-to-date information on women (e.g. current address, hysterectomy status) and fewer ineligible women received the kit. In contrast, in the UK, the high level of population mobility (and the lack of a central monitoring system) made it almost

impossible for the researchers to be certain that the invitations reached the women.[17] This was also evident in the under-screened stratum of our study, where participation was lower by younger women and those whose last Pap tests were longer ago; in both groups the proportion of letters returned-to-sender was high.

In our study, self-sampling appeared to be more effective for never-screened women, although in the sensitivity analysis, the difference between the trial arms for the never-screened women was not as large as in the intention-to-treat analysis. Nevertheless, it could be that screening barriers for never-screened women are different from those of under-screened women and self-sampling might overcome these barriers and increase participation. Never-screened women were also more likely to respond than under-screened women (25% versus 23%; $p<0.001$) in a study in The Netherlands.[32]

Participation in the Australian program is lower in women who reside in areas of lower SES. In our trial, SES was not a determinant of participation nor of the difference, making this method successful independent of SES. However, higher participation in the self-sampling arm compared with the reminder letter arm in the lowest SES category is an indication that interventions targeting women in low SES areas could improve participation in screening.

In our study a small proportion of never-screened women who participated had had a previous hysterectomy and almost a third had had a Pap test within 5 years. Therefore, it is important to develop strategies to make self-sampling available to women who are truly never- and under-screened but which avoid encouraging women already undergoing usual screening to switch to self-sampling. This is also essential to make self-sampling cost-effective.

For self-sampling to be successful as a strategy, high compliance with follow-up is essential. Only about 60% of the women positive for HPV16/18 had a colposcopy as recommended; a further 20% had a Pap test only. All HPV16/18 positive women whose subsequent Pap tests had HSIL had colposcopy whereas not all women who had negative Pap tests had colposcopy, suggesting that medical practitioners did not refer women for colposcopy when subsequent cytology was negative. A higher proportion (80%) of women positive for other high-risk types had follow-up cytology as recommended. In a recent study in Sweden, 100% follow-up was achieved where non-compliant women were repeatedly contacted by telephone.[24] In another study in The Netherlands that recorded a follow-up of 97% at 15 months, 3 month reminder letters were sent to women and their doctors.[32] In an Italian study, follow-up was 91% where women were contacted by phone and letter and offered counselling prior to follow-up.[20] In contrast, in a French trial conducted in a low SES area, despite multiple contacts with women and their doctors, the follow-up was only 41%.[22] We also used an intensive follow-up schedule that included reminders to women. Liaison physicians at VCS also made contact at 6 weeks with women and their doctors, where appropriate, to discuss results and facilitate follow-up arrangements if necessary. The relatively short cut-off time for follow-up (i.e. 6 months) might explain the low colposcopy rates in our study. Educating general practitioners about

the need for colposcopy if a woman is 16/18 positive, regardless of accompanying cytology, is important.

HPV positivity rates and detection of CIN2+ : The proportion of women positive for HPV in our study (8.5%) was similar to that found in the UK (8.3%) [17] and Dutch studies (10.3%) [23] but slightly higher than that found in the Swedish trial (6%).[21] Most of these studies used hybrid capture 2 and type-specific results were not available. The positivity rates in our study (HPV16/18: 2.7%, other HPV types: 5.8%) were several times higher than those in a primary HPV screening trial in Australia [0.5% (95% CI: 0.3-0.9%) for HPV 16/18 and 3% (95% CI: 2.4-3.7%) for other HPV types], using the same HPV test, in unvaccinated women aged 33+ years, suggesting that as expected never- and under-screened women are at higher risk of HPV infection.[37] The overall detection of CIN2+ in our study was 6.7 per 1000 women screened (95% CI: 3.3-11.9), which is similar to the figure of 5.3 per 1000 women screened (95% CI: 4.9-5.4) for all Victorian women aged 30-69 years (estimated from unpublished data from VCCR). However, the confidence interval for our estimated prevalence of CIN2+ was wide, and any similarity with general population data may simply be due to chance rather than to poor specificity of the HPV test on self-collected samples.

Policy implications: The Australian screening program will change to five-yearly primary HPV testing in 2017. Medical practitioners who provide mainstream cervical screening will offer self-collection as an option to never- or under-screened women. This approach may overcome a number of issues with self-sampling identified in our study, in particular women's expressed uncertainty about the accuracy of the test[4] and should improve timely follow-up of positive results. However, prior to implementation, education of practitioners regarding appropriate management for women positive for high-risk HPV, especially 16/18 is essential. Nonetheless, mailed kits may have a place in targeted campaigns, particularly for low SES areas. The planned implementation of a national screening register for Australia should overcome some of the problems we identified with the accurate identification of the true screening history and status of individual women.

Conclusion:

In conclusion, home-based self-sampling improved participation in cervical screening compared to a reminder letter to attend for a Pap test in both never- and under-screened women in all categories of age, SES and time since last Pap test. Most of the women who were HPV positive had appropriate clinical investigation, but general practitioners did not always refer women positive for HPV16/18 for colposcopy if subsequent cytology was negative.

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Table 1: Baseline characteristics of women randomised by stratum (never and under-screened) and trial arm: the iPap trial

Characteristics	Apparently never-screened				Apparently under-screened			
	HPV self sampling		Pap test		HPV self sampling		Pap test	
	N	%	N	%	N	%	N	%
Total	7140		1,020		7,140		1,020	
Age (years)								
30-39	1,950	27.3	276	27.1	2,334	32.7	323	31.7
40-49	1,342	18.8	176	17.3	2,351	32.9	358	35.1
50-59	1,453	20.4	198	19.4	1,453	20.4	207	20.3
60-69	2,395	33.5	370	36.3	1,002	14.0	132	12.9
Socio-economic status[‡]								
1 (lowest)	1,506	21.1	229	22.5	1,335	18.7	196	19.2
2	1,507	21.1	202	19.8	1,451	20.3	181	17.8
3	1,452	20.3	213	20.9	1,317	18.5	230	22.6
4	1,382	19.4	186	18.2	1,549	21.7	190	18.6
5 (Highest)	1,292	18.1	190	18.6	1,488	20.8	223	21.9
Area remoteness[†]								
Major cities	5,399	75.6	781	76.6	5,667	79.4	820	80.4
Inner regional	1,407	19.7	197	19.3	1,199	16.8	165	16.2
Outer regional	325	4.5	41	4.0	270	3.8	33	3.2
Remote	9	0.1	1	0.1	5	0.1	2	0.2
Outside Australia	1	0.0	0	0.0	0	0.0	0	0.0

[‡]Calculated using the residential postcodes according to the Socio-Economic Indexes for Areas (SEIFA) Index of relative socio-economic disadvantage for 2011.

[†]Women were allocated to a remoteness area using their residential postcode according to the Australian Statistical Geography Standard (ASGS) for 2011.

[‡†]One woman from Electoral Roll had an overseas address and could not be assigned to any socioeconomic status or area remoteness.

[‡]Seven women provided a PO Box address, which might not represent their location of residence.

Table 2: Initial letters returned to sender by age and time since last Pap test for never- and under-screened women: the iPap trial

	Under-screened				Never-screened			
	HPV self sampling*		Pap test		HPV self sampling*		Pap test	
	N	%	N	%	N=	%	N	%
Total	7,140		1,020		7,140		1,020	
Returned to sender	903	12.7	181	17.8	72	1	15	1.5
Age (years)								
30-39	314	34.8	68	37.6	26	36.1	7	46.7
40-49	312	34.6	72	39.8	15	20.8	1	6.7
50-59	161	17.8	25	13.8	16	22.2	2	13.3
60-69	116	12.9	16	8.8	15	20.8	5	33.3
Years since last Pap test								
5	79	8.8	18	9.9				
6	134	14.8	17	9.4				
7	147	16.3	33	18.2				
8	163	18.1	34	18.8				
9	159	17.6	32	17.7				
10-14	221	24.5	47	25.9				

* **For women in the HPV self-sampling arm, the letters were the pre-invitation letters**

Table 3: Participation at 6 months by stratum (never- and under-screened) and trial arm: the iPap trial

	Apparently never-screened				Apparently underscreened			
	HPV self sampling		Pap test		HPV self sampling		Pap test	
	N	%	N	%	N	%	N	%
Total	7,140		1,020		7,140		1,020	
Returned a swab	1,131	15.8	-	-	518	7.3	-	-
Had a Pap test	321	4.5	61	6.0	300	4.2	65	6.4
Returned swab or had a Pap test	1,452	20.3	61	6.0	818	11.5	65	6.4

Table 4: Compliance with clinical management protocol within six months of receipt of their HPV test results by women positive for HPV

	N	%	95% CI (%)
HPV – any high risk type			
Total	140		
Complied with protocol	106	75.7	67.8-82.6
Did not comply with protocol	34	24.3	
HPV16/18			
Total	45		
Complied with protocol (colposcopy)	28	62.2	46.5-76.2
Pap test only	9	20.0	9.6-34.6
No investigation	8	17.8	
HPV other high risk types			
Total	95		
Complied with protocol (Pap test)†	78	82.1	72.9-89.2
No Pap test	17	17.9	

† Does not include compliance with recommendation for a repeat HPV test 12 months after a ≤LSIL Pap test

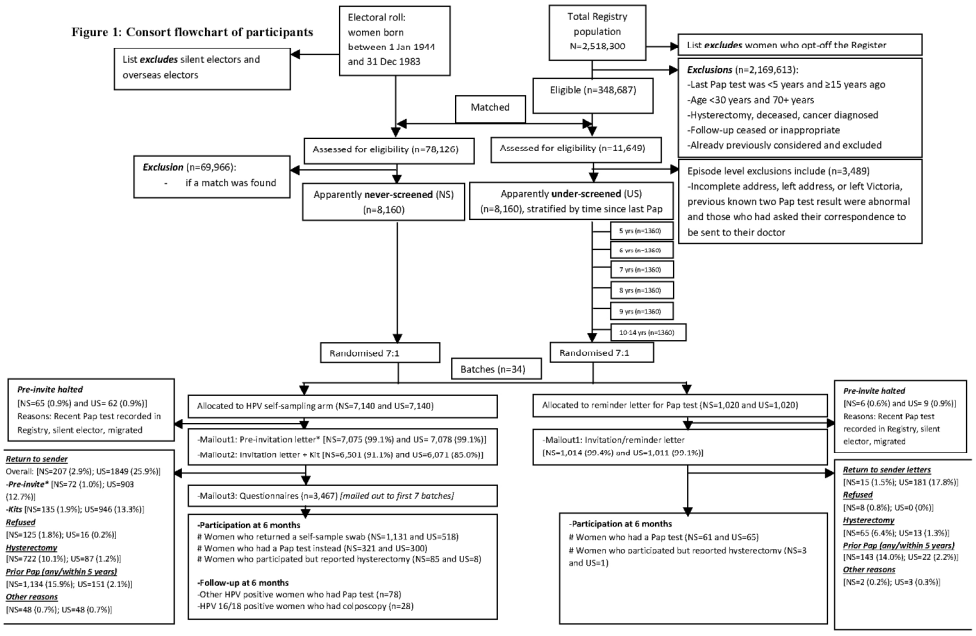

Figure 1: CONSORT flowchart of participants
297x209mm (200 x 200 DPI)

Figure 2: Difference in participation (95% CI) at 6 months by stratum (never- and under-screened) and pre-specified subgroups: the iPap trial

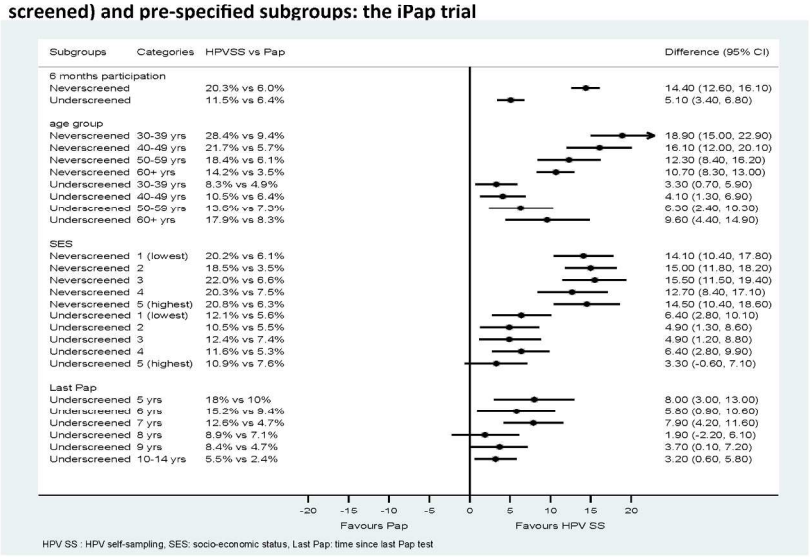

Figure 2: Difference in participation (95% CI) at 6 months by stratum (never- and under- screened) and pre-specified subgroups: the iPap trial
297x209mm (200 x 200 DPI)

Author/s:
Sultana, F;English, DR;Simpson, JA;Drennan, KT;Mullins, R;Brotherton, JML;Wrede, CD;Heley, S;Saville, M;Gertig, DM

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