Preventive Medicine 173 (2023) 107571

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

HPV self-sampling among cervical cancer screening users in Spain: A randomized clinical trial of on-site training to increase the acceptability

Raquel Ibáñez [a,b,*], Esther Roura [a,b], Amèlia Acera [c], Miguel Andújar [d], Miquel Àngel Pavón [a,b], Laia Bruni [a,b], Silvia de Sanjosé [b,e,f]

[a] Cancer Epidemiology Research Programme, Catalan Institute of Oncology - Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain
[b] Centro de Investigación Biomédica en Red de Epidemiologia y Salud Pública (CIBERESP), Spain
[c] Atenció a la Salut Sexual i Reproductiva (ASSIR), SAP Cerdanyola-Ripollet, Institut Català de la Salut, Ripollet, Barcelona, Spain
[d] Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain
[e] NCI Consultant, 9609 Medical Center, Maryland, MD, United States
[f] ISGlobal, Barcelona, Spain

ARTICLE INFO

Keywords:
HPV
Self-sampling
Acceptability
Randomized clinical trial
On-site
Training
Spain
Cervical cancer
Screening
Regular attenders

ABSTRACT

A randomized clinical trial was conducted to compare the impact of two different instructions on vaginal self-sampling in its acceptability and willingness for future screening rounds among women attending cervical cancer screening (CCS).

From November 2018 to May 2021, women aged 30–65 living in Spain attending CCS were randomized 1:1 in two arms. In the "On-site training arm (TRA)", women took a self-sample at the primary health care centre following provider's instructions. In the "No on-site training arm (NO-TRA)" women only received instructions to take self-sample at home. All women had to return a new sample collected at home one month after the baseline visit and an acceptability questionnaire. The proportion of self-samples returned, and acceptability was computed by the study arm.

A total of 1158 women underwent randomization, 579 women per arm. At follow-up, women in TRA were more likely to return the home sample than women in the NO-TRA (82.4% and 75.5% respectively; $p = 0.005$). Over 87% of all participants favoured home-based self-sampling approach for future CCS, similar by arm. Over 80% of women in both arms chose to collect and return the self-sample at a health centre or pharmacy.

Home-based self-sampling was a highly accepted strategy for CCS in Spain. Trying it first with prior on-site training at the health centre significantly increased the sample's return suggesting that a provider's supervision raised confidence and adherence. It is an option to consider when moving to self-sampling in established CCS. Preferred delivery sites most likely contextual.

Registration on ClinicalTrials.gov: NCT05314907.

1. Introduction

Strong evidence supports that clinically validated for oncogenic types of Human Papillomavirus (HPV) test is more accurate and cost-effective as a primary cervical cancer screening (CCS) test than cytology (Ronco et al., 2014; von Karsa et al., 2015; Torné et al., 2014; Torné et al., 2022; Arbyn et al., 2015; Meijer et al., 2009). The evidence is supported by World Health Organization (WHO), and its updated guidelines recommend using HPV detection as the primary screening test rather than cytology or visual inspection with acetic acid (VIA) in CCS starting at the age of 30 years with regular screening tests every 5 to 10 years (World Health Organisation, 2021). The possibility of detecting viral copies of the HPV with high accuracy instead of cellular changes as a primary screening approach (Arbyn et al., 2018) has led to new strategies in sample collection. The most relevant one is the possibility to use self-sampling, an approach that allows obtaining samples of cervical-

Abbreviations: TRA, On-site training arm; NO-TRA, No on-site training arm; CCS, Cervical cancer screening.

* Corresponding author at: Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Granvia de l'Hospitalet 199-203, 08908 l'Hospitalet de Llobregat, Barcelona, Spain.
E-mail address: raquelip@iconcologia.net (R. Ibáñez).

https://doi.org/10.1016/j.ypmed.2023.107571
Received 28 December 2022; Received in revised form 1 May 2023; Accepted 5 June 2023
Available online 10 June 2023

vaginal secretions through brushing of the vagina by the woman herself without the need for a speculum exam. If self-sampling is acceptable by women, it greatly improves screening coverage impacting cervical cancer incidence and mortality (Castillo et al., 2016; Ibáñez et al., 2015). A strong emphasis is now focusing on self-sampling as a key tool for accelerating the global fight against cervical cancer (World Health Organization, 2021a).Self-sampling is an accurate approach in CCS and comparable to samples collected by the health professional, provided the polymerase chain reaction (PCR) -based HPV test is used (Arbyn et al., 2018; Arbyn et al., 2014; Nishimura et al., 2021; Poljak et al., 2018). Before large launching of self-sampling, local trials are recommended to assess the acceptability, effectiveness, and cost-effectiveness of the approach in a given community (von Karsa et al., 2015; Torné et al., 2022). The range of acceptability is very diverse according to the country and strategy (Verdoodt et al., 2015; Holme et al., 2020).

A systematic review revealed that women who preferred physician sampling to self-sampling expressed concerns about the reliability of self-sampled specimens and not having a face-to-face time with a physician. Counseling before self-sampling invitation, as well as clear instructions and the availability of reliable clinical staff to assist with self-sampling, could solve some of these concerns (Nishimura et al., 2021). The involvement of health professionals in the training of how to use self-sampling could be advisable before a routine program delivers the self-collection kit at home.

In Spain, self-sampling was considered as a population strategy for cervical cancer screening in parallel with the transition from a cytology-based screening to HPV screening. Self-sampling approach was considered to allow for maintaining high levels of quality in CCS while reducing costs. Furthermore, the pandemic situation with COVID-19 demonstrated that using self-sampling in screening could have avoided the need to stop screening programs in lockdowns or to reduce the number of visits to avoid the influence of people in health centers (Lozar et al., 2021).

In Spain, the acceptability of self-sampling has been evaluated based on telephone interviews but the responses were not validated by the return of a self-sample (Besó Delgado et al., 2021; Maldonado-Cárceles et al., 2022). A comprehensive evaluation of acceptability of self-collection should include the participation in the process of self-sampling by the women (Hood et al., 2020).

We present the first study on women's experience and acceptability of self-sampling in Spain. We aimed to evaluate the impact on self-sampling return, as a stronger measure of acceptability, of two different approaches: a try-first on-site self-sampling approach and a verbal information approach. A randomized clinical trial (RCT) was conducted among women attending CCS to compare both approaches.

2. Methods

A RCT was conducted in women aged 30–65 years, attending CCS from November 2018 to May 2021. Women were recruited in two Spanish areas: Catalonia with participant primary care centres of Cerdanyola del Vallès, Barberà del Vallès, Ripollet, Badia del Vallès and Sabadell, and the Canary Islands including primary care centres of Arucas, Gáldar, Prudencio Guzmán, Telde, Vecindario and Maspalomas.

In both settings, CCS is free of charge, opportunistic, performed in primary care centres and with cytology as primary screening test. Self-sampling has not been introduced in the study areas prior to this work. Exclusion criteria included having a hysterectomy, being pregnant, or being under surveillance for an ongoing cervical pathology.

All women who came consecutively for a screening, had a regular screening visit that included a clinician-collected liquid-based cervical sample to be used to perform the screening test. Then, they were invited to participate in the study after brief introduction of the aims of the trial. Women who accepted to participate, signed informed consent, and were provided with a short self-completion sociodemographic questionnaire. Requested information included date of birth, nationality, country of birth, educational level, marital status, occupation, family responsibilities and some questions about CCS history.

2.1. Randomization

At the primary care center, women received a sequential number by the administrator of the center as a regular practice. The number establishes the order of the screening visit by the provider. This order was used to assign women (1:1) into one of two arms. The provider was blinded to the assignment of the sequential number.

2.2. Study arms

1. The "on-site training arm (TRA)" consisted of primary healthcare provider instructing on how to use the self-sampling kit and then prompting the woman to collect a self-sample at the same time (i.e., try-it first). Woman received a leaflet with written and picture-based instructions. If the woman had any questions, they could be solved during that process. Finally, the woman was provided with a new self-sampling kit to take home and instructed to return to the health centre one month later.
2. In the "no one-site training arm (NO-TRA)", the primary healthcare provider only instructed the woman on how to use the self-sampling kit, gave her the same leaflet with pictorial instructions and provided her a self-sampling kit to take home with instructions to return to the health centre one month later. In this arm the women did not collect a self-sampling as training in the health centre.

When returning the self-sampling one month after the screening visit, women were asked to fill a self-collected self-sampling acceptability questionnaire (supplementary material) about their experience, including whether they thought the sample was collected correctly, if they felt pain, how long it took to collect the sample, if they required assistance, their confidence in the test result, if they would recommend it to other women, preference of self-sampling over clinician-collection, recommendation to have self-sampling used in the regular screening, and where they would like to collect and return the self-sampling kit. The questionnaire was based on a thorough review of other questionnaires and tested locally for clarity and cultural fit prior to the implementation in the study.

Women who did not return their self-sample after one month received up to three phone calls as a reminder and to describe reasons for no return.

2.3. Self-sampling kit

The self-sample was collected using Evalyn Brush (Rovers Medical Devices B·V, Oss, Netherlands), validated for HPV detection on multiple PCR-based HPV assays (Hawkes et al., 2020).

2.4. Outcomes

Here we present as the primary outcomes a) the proportion of women that returned the self-sample after one month of the screening visit by trial arm and b) among women returning the self-sample, their proportion of women with preference for home-based self-sampling as part of a future CCS strategy. Both indicators are referred here as a measure of acceptability.

As secondary outcome we measure several aspects of the self-sampling experience, and we report them as percentage of the different gradients (i.e.; from satisfactory to unsatisfactory).

2.5. Sample size and data analyses

To estimate a participation rate of 70%, with a 95% confidence interval and a precision of +/− 5% points, a sample size of 1614 women

was requested. A total of 1158 women were finally recruited, 302 in the Canary Islands and 856 in Catalonia. This sample size was sufficient to detect differences between the two training arms with a statistical power of at least 80%, because participation and acceptability were higher than initially expected.

Information on sociodemographic characteristics and self-sampling acceptability were collected. Data were encrypted anonymously using Research Electronic Data Capture (REDCap) and hosted at Catalan Institute of Oncology (Harris et al., 2009; Harris et al., 2019).

Continuous variables were shown as mean values and categorical variables as percentages. We used Chi-Square test for categorical data and Mann–Whitney *U* test for ordinal data to compare proportions between study arms.

The study was interrupted by the COVID-19 pandemic between mid-March and mid-May 2020. Given the collapse and restructuring of the health system, the study stopped until October 2020. In the study analysis, all women were included, also those affected by the return of the self-sample performed at home once the pandemic was declared and during the time the study was stopped. However, to explore the impact of COVID-19 in the study, a sensitivity analysis of the changes in percent return of the self-sample was done excluding women recruited from February to mid-May 2020.

All statistical tests were two-tailed, and *p*-values below 0.05 were considered statistically significant. Data analyses were carried out using R software version 4.1.0 (R Core Team, 2015).

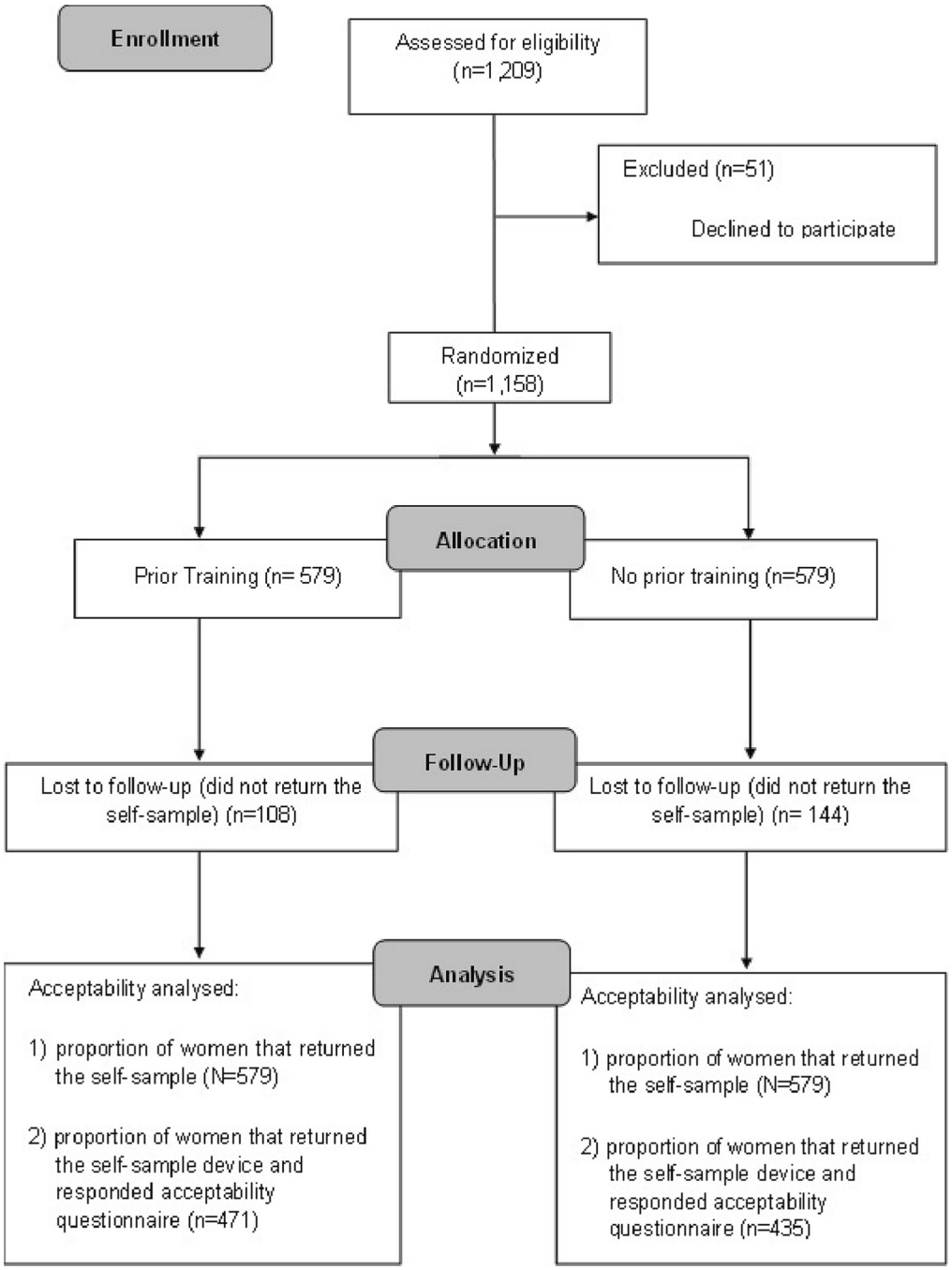

Fig. 1. CONSORT 2010 Flow Diagram.

2.6. Ethical aspects and trial registration

The project was approved by the ethical committees of Bellvitge University Hospital (PR223/17), University Institute for Primary Health Care Research (IDIAP) Jordi Gol i Gurina (P18/099), and Maternal and Child Insular University Hospital Complex of Gran Canaria (2018–178-1). All the women who accepted to participate in the study signed informed consent. The trial was registered on ClinicalTrials.gov with the ID NCT05314907.

3. Results

A total of 1209 women were invited to participate in the trial, of whom 1158 (95.8%) accepted, 302 (26.1%) from the Canary Islands and 856 (73.9%) from Catalonia. There were 579 women randomized in each arm (Fig. 1). The mean age of participants was 44 years.

Table 1 shows the sociodemographic characteristics and previous CCS history by study arm. There were no statistically significant differences. Most (84.8%) women were Spanish nationals, 30.5% had university-level education and 69.2% were married or living with a partner. More than half of women (55.7%) had family responsibilities in caring children or elderly, and 70.1% had had CCS in the last 3–4 years.

Table 2 summarises self-sample return and preferential use as primary sample collection method in future CCS. A high self-sample return was observed in both arms, but the return in the TRA arm was higher than in NO-TRA group (82.4% vs. 75.5%; $p = 0.005$). Women aged <50 years of age were also more likely to return the self-sample in the TRA arm as compared to the non-TRA arm.

There were 244 women who did not return the self-sampling (102 in TRA arm and 142 in NO-TRA arm). Among them, 80 (32.8%) women did not have a reminder call recorded (36 women were in TRA group and 44 in the NO-TRA group), and 164 (67.2%) were called as a reminder (66 in TRA arm and 98 in NO-TRA arm). Among these, the main reasons for not returning the kit included, in 22.6% of cases, not having enough time to take a sample, 1.2% reported they were not interested in the study, 6.7% said they had forgotten to take the self-sample, 1.8% reported having pain in the cervix/vaginal area, 28% for reasons related to the covid-19 pandemic, 12.8% did not want to give any reason and finally, 26.8% of the women could not be locate (supplementary material). The differences between the TRA and NO-TRA arms in terms of receiving or not a reminder call for not returning the self-sampling on time were not statistically significant ($p = 0.57$).

Among women who returned the self-sample performed at home, there was no difference in expressing a preference for using self-sampling in future screening (88.1% in the TRA arm and 87.4% in the NO-TRA arm p = 0.57).

In the sensitivity analysis, excluding women recruited from February to mid-May 2020 to whom the return of the home self-sampling coincided with the COVID-19 lockdown, the proportion of women who returned the self-sampling rose to 86.4% for the TRA and 81.2% for the NO-TRA arm, maintaining significant differences between both arms ($p = 0.03$) (data not shown). Preference for self-sampling in future CCS was no different to the overall study group (88.4% in TRA and 87.8% in NO-TRA; $p = 0.73$).

Experience and satisfaction with self-sampling were largely very good or good in both arms (89.4% in the TRA vs 88% in the NO-TRA, $p = 0.53$) (Table 3). >92% of the women in both arms found the instructions given by the manufacturer to be very or quite clear and easy to understand ($p = 0.12$). About 70% of women were confident that they collected the sample properly, while 23–25% had doubts ($p = 0.48$). Requiring help to understand the instruction was significantly higher in the TRA compared to the NO-TRA arm (16.4% versus 10.9%, $p = 0.001$), although >79% of the women in both arms did not require help to collect the sample. >98% of women in both arms believed that the test was safe and provides health benefits, trusted the result, and would recommend it.

Table 1
Sociodemographic characteristics and previous screening history of participants by study arm.

	On-site training arm, N (%)		No on-site training arm, N (%)		p-value*
	n = 579		n = 579		
Age (in years)					
<30	15	(2.6)	13	(2.2)	
30–39	201	(34.7)	199	(34.4)	
40–49	198	(34.2)	196	(33.9)	0.94
50–59	132	(22.8)	142	(24.5)	
≥60	33	(5.7)	29	(5)	
Trial-site					
The Canary Islands	154	(26.6)	148	(25.6)	0.74
Catalonia	425	(73.4)	431	(74.4)	
Country of birth					
Spain	492	(85)	490	(84.6)	0.93
Outside Spain	87	(15)	89	(15.4)	
Education level					
Less than elementary school	19	(3.3)	24	(4.2)	
Elementary school	109	(18.9)	115	(20)	
Secondary school	51	(8.8)	37	(6.4)	0.34
Vocational training	137	(23.7)	156	(27.1)	
High school	75	(13)	79	(13.7)	
University	187	(32.4)	165	(28.6)	
Missing	1	–	3	–	
Marital status					
Single	110	(19)	110	(19.1)	
Divorced / separated	55	(9.5)	59	(10.2)	
Married / living with a partner	403	(69.7)	396	(68.8)	0.97
Widowed	10	(1.7)	11	(1.9)	
Missing	1	–	3	–	
Current occupation					
Yes, with paid salary	455	(79)	444	(77.6)	
Housewife, without paid salary	29	(5)	39	(6.8)	
Unemployed / not working	71	(12.3)	70	(12.2)	0.64
Retired	21	(3.6)	19	(3.3)	
Missing	3	–	7	–	
Family responsibilities					
No	257	(44.5)	255	(44.1)	0.95
Yes**:	321	(55.5)	323	(55.9)	
Children under 18 years old or with any dependency	281	(87.5)	283	(87.6)	
Older relatives (father, mother, in-laws, …)	31	(9.7)	21	(6.5)	
Husband	20	(6.2)	19	(5.9)	
Children over 18 years old	13	(4)	19	(5.9)	
Missing	0	–	3	–	
Missing	1	–	1	–	
Any previous screening test					
No	3	(0.5)	9	(1.6)	0.14
Yes	576	(99.5)	567	(98.4)	
Missing	0	–	3	–	
Last self-reported screening test among ever tested					
< 3 years	156	(27.7)	166	(29.7)	
3–4 years	402	(71.3)	384	(68.8)	0.61
≥ 5 years	6	(1.1)	8	(1.4)	
Missing	12	–	9	–	
Number of self-reported screening tests in lifetime among ever tested					
1	41	(7.4)	25	(4.6)	
2 to 4	188	(33.8)	185	(34)	
5 to 7	142	(25.5)	139	(25.6)	0.09
8 to 10	79	(14.2)	103	(18.9)	
> 10	107	(19.2)	92	(16.9)	
Missing	19	–	23	–	

*Chi-Square test. The missing category was excluded from the statistical analysis. ** Within the family responsibilities options, the N and the % add up to more than the global N and 100% since the same person could choose more than one option.

On-site training arm: Clinician-led explanation on how to proceed with self-sampling prior to collect a self-sample at the primary health care centre. No **on-site training arm:** Same training as the On-site training arm but without practicing self-sampling collection.

Table 2
Acceptability of self-sampling by study arm.

	Women who returned the sample collected at home					Women who returned the self-sample who express preference for self-sampling in future screening				
	On-site training arm, N (%)		No on-site training arm, N (%)			On-site training arm, N (%)		No on-site training arm, N (%)		
	n = 579		n = 579		*p* value*	*n* = 471[c]		*n* = 435[c]		p value*
Global	477	(82.4)	437	(75.5)	**0.005**	415	(88.1)	380	(87.4)	0.57
By trial-site										
The Canary Islands	119	(77.3)	104	(70.2)	0.21	102	(89.5)	88	(85.4)	0.30
Catalonia	358	(84.2)	333	(77.3)	**0.01**	313	(87.7)	292	(88.0)	0.97
By age (years)										
<50	325	(78.5)	286	(70.1)	**0.007**	290	(90.3)	250	(88.0)	0.87
≥ 50	152	(92.1)	151	(88.3)	0.32	125	(83.3)	130	(86.1)	0.71

*Chi-Square test. The missing category was excluded from the statistical analysis. cIncludes women who answered "I don't know / I prefer not to answer". CI: Confidence Interval.
On-site training arm: Clinician-led explanation on how to proceed with self-sampling prior to collect a self-sample at the primary health care centre. **No on-site training arm:** Same training as the On-site training arm but without practicing self-sampling collection.

Only 13% of women in both arms expressed preference for a healthcare professional to collect the sample. Women in the TRA arm favoured significantly the collection and the return of the kit at the health centre (58.5% and 71%) as compared to women in the NO-TRA arm (41.4% and 56.9%, $p < 0.001$); 15% of women preferred the sampling kit to be sent to their home, similar by study arm.

Fig. 2 shows women's experiences of self-sampling by study arm. Women in both study arms reported being more comfortable, calm, safe, having greater privacy and felt no fear or anxiety after using the self-sampling kit. However, even though >80% of women in both arms did not feel shame or frustration, differences between arms were statistically significant ($p = 0.004$ and $p = 0.003$ respectively). Further, only 1.1% of women in the TRA and 0.7% of the NO-TRA arm felt nervous, but differences were significant ($p = 0.035$).

4. Discussion

Our results show that home-based self-sampling is feasible and highly accepted by participants. About eight out of ten women returned the self-sampling kit in the TRA arm and seven out of ten in the NO-TRA arm one month after the screening visit. The addition of on-site training was efficacious in the return of the self-sampling kit, although with little impact. We observed a slightly higher effect of the onsite instruction in the Catalonia site compared to the Canary Islands, which may indicate regional differences in perception of self-sampling compared to traditional screening approaches. Interestingly, over 80% of women in both arms preferred to collect and return the self-sample at a health center or pharmacy, and only 15% chose a mailing approach. Preference for a future screening using self-sampling was very positive and similar in both arms among those women that had returned the self-sample.

Indeed, the fact that a professional explains the use of a self-sampling kit to women may increases confidence in the procedure. Other studies identified the importance of a trusted healthcare provider in answering questions and providing reassurance that cervical self-sampling was conducted correctly (Nishimura et al., 2021; McLachlan et al., 2018). Interestingly, our reported that the preferable option for the collection and return of self-samples were places where a professional can attend to the woman (health centres, pharmacies) and not home delivery and courier delivery as it is being used in other settings (Pedersen et al., 2018). However, the differences observed by trial site suggest the need to adapt kit delivery to local preferences.

"Try it first" option could be especially beneficial for women who are hesitant to use self-sampling. A systematic review and meta-analysis in underscreened women, comparing a mailed self-sampling kit at home with an on-site sampling by the professional, identified an increased participation of 9.9% (95% CI = 5.8–13.9%) among those in the self-sampling arm (Verdoodt et al., 2015). It may suggest that trying it first might further improve its usability taking advantage of the screening visit with the professional. Contrary to other studies, women younger than 50 years were more likely to return the self-sample if they were in the on-site training arm (Nishimura et al., 2021; Polman et al., 2019; Hermansson et al., 2020). There were no age differences between both arms between Catalonia and the Canary Islands. In the TRA arm, the mean age among women from Catalonia and the Canary Islands was 43.6 and 44.4 years, respectively ($p = 0.32$). While in the NO-TRA group, the mean age was 44.0 in both sites ($p = 0.99$). Therefore, the reason why younger women return more samples does not appear to be a geographic cause. It would be interesting to further explore age differences in future studies.

Today, many countries are transitioning from cytology-based screening to HPV test-based screening (Serrano et al., 2022). Added to that, after the COVID-19 pandemic, self-collection has taken on a relevant role as a sample collection method. Switching from clinician-collected to self-collected HPV testing in cervical screening is cost-effective and makes it easier for women to continue be screened (World Health Organization, 2021b; Pedersen et al., 2022). The involvement of the professional in explaining the self-sampling use and that women could be offered the possibility to try it first, could increase the use of self-sampling in screening and retain women for continued being screened.

In line with our results, several negative aspects of self-sampling are detected occasionally. A prior metanalysis of 37 studies included 18,516 women from 24 countries across five continents, the most frequently cited reasons by women for disliking self-sampling were uncertainty about taking the sample correctly (21%), experience of pain or physical discomfort (10%), anxiety (15%) and not wanting to touch themselves (6%) (Nelson et al., 2017). In another large study conducted among 1878 women in The Netherlands and in good agreement with our data, participants cited pain (19.2%), nervousness (38%), and doubts on obtaining the self-sample correctly (46.3%) (Polman et al., 2019). To improve acceptability, these aspects should be considered in future campaigns to improve the self-sampling experience.

Most studies of self-sampling acceptability generally asked women about preference for future CCS. We observed that >87% of women of both arms preferred a self-sampling approach, a finding consistent with previous studies, the majority of which were conducted among underscreened women (Polman et al., 2019; Hermansson et al., 2020; Sultana et al., 2015). In a meta-analysis including over 10,000 women, 59% (95%CI: 48–69%) reported preference for self-sampling over clinician-based sampling, (Nelson et al., 2017). Another recent systematic review reported a range between 65% and 93% and found a high self-sampling acceptability regardless of study location and sampling method, device, setting or participant demographics (Nishimura et al., 2021). Polman and colleagues found similar results to ours, in a study

Table 3
Self-sampling experience between study arms.

Self-sampling experience	On-site training arm, N (%)		No on-site training arm N (%)		p-value*
	n = 471		n = 435		
Global experience					
Very good or good	421	(89.4)	382	(88.0)	0.53
Neither good nor bad	48	(10.2)	52	(12.0)	
Bad / very bad	2	(0.4)	0	(0.0)	
I don't know / I prefer not to answer	0	–	1	–	
User instructions					
Very or quite clear and easy to understand	446	(94.1)	400	(92.1)	0.12
Normal, not so simple or so complicated	23	(4.9)	30	(6.9)	
Bit difficult or very difficult to understand	2	(0.4)	4	(0.9)	
I don't know / I prefer not to answer	0	–	1	–	
Accurate of self-collection					
I'm sure I collected it properly	337	(71.9)	300	(69.4)	0.48
I have some doubts I collected it properly	108	(23.0)	112	(25.9)	
I'm not sure I collected it properly/ I'm sure I didn't collected it properly	24	(5.1)	20	(4.6)	
I don't know / I prefer not to answer	2	–	3	–	
Help collecting the sample					
Yes, but only to understand the instructions	77	(16.4)	47	(10.9)	**0.001**
Yes, to understand the instructions and to collect the sample	20	(4.3)	6	(1.4)	
No, I did it myself	372	(79.3)	379	(87.7)	
I don't know / I prefer not to answer	2	–	3	–	
Pain					
I did not feel any pain	388	(82.9)	343	(80.0)	0.28
I felt some discomfort	70	(15.0)	79	(18.4)	
A little intensive or an intensive pain	10	(2.1)	7	(1.6)	
I don't know / I prefer not to answer	3	–	6	–	
Safety of the test					
Yes	441	(98.0)	407	(98.5)	0.72
No	9	(2.0)	6	(1.5)	
I don't know / I prefer not to answer	21	–	22	–	
Trust the test result					
Yes	424	(97.2)	387	(97.7)	0.83
No	12	(2.8)	9	(2.3)	
I don't know / I prefer not to answer	35	–	39	–	
Benefits of your health					
Yes	448	(98.5)	412	(98.3)	1
No	7	(1.5)	7	(1.7)	
I don't know / I prefer not to answer	16	–	16	–	
Recommendation of the test					
Yes	447	(98.7)	409	(99.8)	0.13
No	6	(1.3)	1	(0.2)	
I don't know / I prefer not to answer	18	–	25	–	
Preference of screening test					
Myself	217	(46.3)	227	(52.4)	0.16
Healthcare professional	62	(13.2)	54	(12.5)	
I'm OK with both options	190	(40.5)	151	(34.9)	
None of the options	0	(0.0)	1	(0.2)	
I don't know / I prefer not to answer	2	–	2	–	
Where to pick-up the self-sampling kit in the future					
At the primary health service Centre	276	(58.8)	179	(41.4)	< **0.001**
At a pharmacy	121	(25.7)	186	(43.1)	
At a post office or mailbox	2	(0.4)	1	(0.2)	
To be shipped to my house	71	(15.1)	66	(15.3)	
I don't know / I prefer not to answer	1	–	3	–	
Where to return the self-sampling kit in the future					
At the primary health service Centre	333	(71.0)	246	(56.9)	< **0.001**
At a pharmacy	130	(27.7)	185	(42.7)	
At a post office or mailbox	6	(1.3)	2	(0.5)	
I don't know / I prefer not to answer	2	–	2	–	

*Mann-Whitney U test for ordinal data and Chi-Square test for nominal data. The missing category and the "I don't know / I prefer not to answer" category were excluded from the statistical analysis.
On-site training arm: Clinician-led explanation on how to proceed with self-sampling prior to collect a self-sample at the primary health care centre. **No on-site training arm:** Same training as the On-site training arm but without practicing self-sampling collection. The missing category was excluded from the statistical analysis.

including regular users of screening: 80% of women reported preference of self-sampling over clinician-based sampling for future CCS (Polman et al., 2019).

In the studies reviewed, and, in general, line with our results, the most commonly cited reasons for preferring self-sampling were ease of use (91%), less embarrassing (91%), increased privacy (88%), more comfortable (88%), ability to sample on their own (69%) and convenience (65%) (Nelson et al., 2017). Besides, factors such as scheduling appointments at the gynecology centre, location of the centre, and childcare considerations may be other reasons for challenges accessing clinician-based CCS. Thus, the ability to self-sample at home and at a time convenient to each woman may facilitate increased screening uptake (Nelson et al., 2017).

4.1. Strengths and limitations

The main strength is that this is the first randomized controlled trial to assess feasibility and acceptability of self-sampling in regular attenders from public CCS in Spain, and where self-sampling acceptability was evaluated based on the training given by the professional. There was no concern on the quality of self-samples and professional samples as only one sample in each group was informed as inadequate. Our study population was comparable in terms of educational level to the general population of Spain (Instituto Nacional de Estadística, 2022).

As limitations, in this study, the learning materials and instructions on how to perform self-sampling have not been evaluated. Those provided by the manufacturer were used. We did not evaluate the training and opinion of the health professionals involved in the study with respect to self-sampling. However, the high acceptability obtained in both arms suggests that the material and training was adequate. The study requested to the return of the self-sampling kit in a short period after the contact with the women. We cannot ensure that the return would be as high as it is in the study in a longer interval between contact with the services. Given the disruption and restructuring of the health system after lockdown due to COVID-19 pandemic in Spain, the study had to accommodate changes in the flow of patients in both trial sites. When we tried to evaluate the impact of them, no differences were however observed in acceptability.

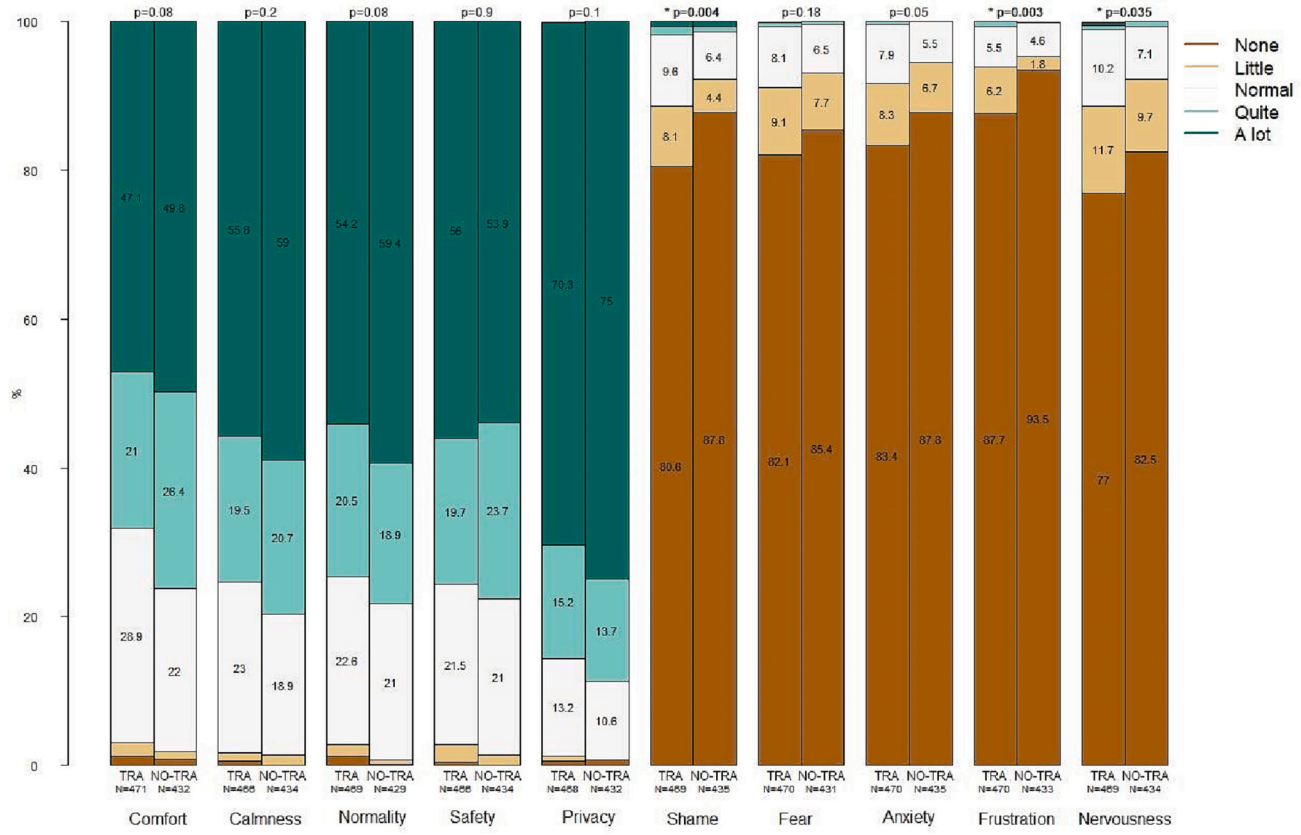

Fig. 2. Perceptions of self-sampling use between study arms.

5. Conclusions

Home-based self-sampling was a highly accepted strategy for CCS in Spain. 7 out of 10 women attending public CCS services returned the self-sample kit when offered by the healthcare provider. Trying first with on-site training on self-sampling at the health centre was efficacious in increasing the return of the self-sample.

There was high acceptability of self-sampling device for future CCS in all women irrespective of study arm, and most women would prefer to take the sample herself. The most suitable places for delivery and return self-samples must be evaluated according to the place where they are implemented. A "Try it first" option could be beneficial for women who are hesitant to use self-sampling. These data can be used for improved coverage of population-based screening programs.

Funding

This study was supported by grants from the Instituto de Salud Carlos III (Spanish Government) through the projects PI17/01179, PI17/01456, and PI20/00485, AEPCC investiga 2019 – Xavier Castellsagué Grant, CIBERESP CB06/02/0073 (Co-funded by European Regional Development Fund, ERDF, a way to build Europe), and the Secretariat for Universities and Research of the Department of Business and Knowledge of the Government of Catalonia grants to support the activities of research groups (SGR 2017–2021) (Grant number 2021SGR1029 and 2021SGR1354). We thank the CERCA Program / Generalitat de Catalunya for institutional support. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

Raquel Ibáñez: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Methodology, Resources, Software, Supervision, Visualization, Validation, Writing – original draft, Writing – review & editing. **Esther Roura:** Data curation, Formal analysis, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Amèlia Acera:** Investigation, Resources, Writing – review & editing. **Miguel Andújar:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Visualization, Writing – review & editing. **Miquel Àngel Pavón:** Data curation, Investigation, Validation, Writing – review & editing. **Laia Bruni:** Formal analysis, Writing – review & editing. **Silvia de Sanjosé:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The Cancer Epidemiology Research Program (with which Raquel Ibáñez, Esther Roura, Laia Bruni and Miquel Àngel Pavón are affiliated) has received HPV test kits at no cost from Roche for research purposes. All other authors report no potential conflicts.

Data availability

Data will be made available on request.

Acknowledgments

We would like thanks to Juan Antonio Alvarez Molina for his administrative support in the study; Ana M. Hervas, Carme Basset,

Inmaculada Rodríguez, Marga Robert, Montserrat Martínez and Noelia Valiente from Catalan specialized care centers in sexual and reproductive health and Amina Lubrano, M Angeles Naya, Pilar Cruz, Manuel Sosa, Luisa Gutierrez, M. Elena Pérez, Patricia Escamilla, J Miguel Flacón, Carmen Molo, Yaiza Schamann, Yaiza Machado, Mariazell García and Elena Cortés from Canary specialized care centers belonging to the Obstetrics and Gynecology service of the Complejo Hospitalario Universitario Insular-Materno Infantil, for their support in recruiting women and collecting samples. Also, Vanesa Camon and Yolanda Florencia for their work in the management of self-samples in the laboratory. And finally, we thank Hellen Kelly for careful editing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2023.107571.

References

Arbyn, M., Verdoodt, F., Snijders, P.J.F., Verhoef, V.M.J., Suonio, E., Dillner, L., et al., 2014. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol. [Internet] 15 (2), 172–183. Available from: https://doi.org/10.1016/S1470-2045(13)70570-9. Available from:

Arbyn, M., Depuydt, C., Benoy, I., Bogers, J., Cuschieri, K., Schmitt, M., et al., 2015. VALGENT: a protocol for clinical validation of human papillomavirus assays. J. Clin. Virol. [Internet] 76, S14–S21. Available from: https://doi.org/10.1016/j.jcv.2015.09.014. Available from:

Arbyn, M., Smith, S., Temin, S., Sultana, F., Castle, P., Testing on behalf of the C on S-S and H, 2018. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ [Internet] 363, k4823. Available from. https://doi.org/10.1136/bmj.k4823. Available from.

Besó Delgado, M., Ibáñez Cabanell, J., Molina-Barceló, A., Zurriaga Llorens, O., Salas, Trejo D., 2021. ¿Aceptan las mujeres de la Comunidad Valenciana la autotoma como forma de cribado de cáncer de cérvix? Rev Esp Salud Publica 95, 1–18.

Castillo, M., Astudillo, A., Clavero, O., Velasco, J., Ibáñez, R., Desanjosé, S., et al., 2016. Poor cervical cancer screening attendance and false negatives. A call for organized screening. PLoS One [Internet] 11 (8), 1–9. Available from: https://doi.org/10.1371/journal.pone.0161403. Available from:

Harris, P., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. [Internet] 42 (2), 377–381. Available from: https://doi.org/10.1016/j.jbi.2008.08.010. Available from:

Harris, P., Taylor, R., Minor, B., Elliott, V., Fernandez, M., O'Neal, L., et al., 2019. The REDCap consortium: building an international community of software platform partners. J. Biomed. Inform. [Internet] 95, 103208. Available from: https://doi.org/10.1016/j.jbi.2019.103208. Available from:

Hawkes, D., Keung, M.H.T., Huang, Y., McDermott, T.L., Romano, J., Saville, M., et al., 2020. Self-collection for cervical screening programs: from research to reality. Cancers (Basel) [Internet] 12 (4), 1–14. Available from: https://doi.org/10.3390/cancers12041053. Available from:

Hermansson, R.S., Olovsson, M., Gustavsson, C., Lindström, A.K., 2020. Elderly women's experiences of self-sampling for HPV testing. BMC Cancer [Internet] 20 (1), 1–8. Available from: https://doi.org/10.1186/s12885-020-06977-0. Available from:

Holme, F., Jeronimo, J., Maldonado, F., Camel, C., Sandoval, M., Martinez-Granera, B., et al., 2020. Introduction of HPV testing for cervical cancer screening in Central America: the scale-up project. Prev. Med. (Baltim.) [Internet] 135. https://doi.org/10.1016/j.ypmed.2020.106076 (July 2019):106076. Available from.

Hood, R.B., Turner, A.N., Huber-Krum, S., Lancaster, K.E., Mwapasa, V., Poindexter, T., et al., 2020. For human papillomavirus self-sampling, stated willingness does not correspond with subsequent uptake by rural Malawian women. Sex Transm Dis. [Internet] 47 (4), 275–279. Available from: https://doi.org/10.1097/OLQ.0000000000001119. Available from:

Ibáñez, R., Alejo, M., Combalia, N., Tarroch, X., Autonell, J., Codina, L., et al., 2015. Underscreened women remain overrepresented in the pool of cervical cancer cases in Spain : a need to rethink the screening interventions. Biomed. Res. Int. [Internet]. https://doi.org/10.1155/2015/605375, 2015(ID 605375):9 pages. Available from.

Instituto Nacional de Estadística, 2022. Explotación de las variables educativas de la Encuesta de Población Activa (INE). [Internet] [cited 2022 Jun 9]. Available from. https://www.ine.es/index.htm.

Lozar, T., Nagvekar, R., Racheal, C.R., Mandishora, S.D., Megan, U.I., Fitzpatrick, B., 2021. Cervical cancer screening postpandemic: self-sampling opportunities to accelerate the elimination of cervical cancer. Int. J. Women's Health 13 (August), 841–859.

Maldonado-Cárceles, A., Belmonte, M., Cascales, M., Sanchez, M., Granados, J., Huertas, M., et al., 2022. Aceptabilidad de la autotoma como método de cribado de cáncer de cérvix en mujeres de la región de Murcia. Rev Esp Salud Publica 96, 1–15.

McLachlan, E., Anderson, S., Hawkes, D., Saville, M., Arabena, K., 2018. Completing the cervical screening pathway: factors that facilitate the increase of self-collection uptake among under-screened and never-screened women, an Australian pilot study. Curr. Oncol. [Internet] 25 (1), e17–e26. Available from: https://doi.org/10.3747/co.25.3916. Available from:

Meijer, C.J.L.M., Berkhof, J., Castle, P.E., Hesselink, A.T., Franco, E.L., Ronco, G., et al., 2009. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int. J. Cancer [Internet] 124 (3), 516–520. Available from: https://doi.org/10.1002/ijc.24010. Available from:

Nelson, E.J., Maynard, B.R., Loux, T., Fatla, J., Gordon, R., Arnold, L.D., 2017. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. Sex Transm Infect. [Internet] 93 (1), 56–61. Available from: https://doi.org/10.1136/sextrans-2016-052609. Available from:

Nishimura, H., Yeh, P.T., Oguntade, H., Kennedy, C.E., Narasimhan, M., 2021. HPV self-sampling for cervical cancer screening: a systematic review of values and preferences. BMJ Glob. Heal. [Internet] 6 (5), 1–14. Available from: https://doi.org/10.1136/bmjgh-2020-003743. Available from:

Pedersen, H.N., Smith, L.W., Racey, S.S., Cook, D., Krajden, M., van Niekerk, D., et al., 2018. Implementation considerations using HPV self-collection to reach women under-screened for cervical cancer in high-income settings. Curr. Oncol. [Internet] 25 (1), e4–e7. Available from: https://doi.org/10.3747/co.25.3827. Available from:

Pedersen, K., Portnoy, A., Sy, S., Hansen, B.T., Tropé, A., Kim, J.J., et al., 2022. Switching clinic-based cervical cancer screening programs to human papillomavirus self-sampling : a cost-effectiveness analysis of vaccinated and unvaccinated Norwegian women. Int. J. Cancer [Internet] 491–501. Available from: https://doi.org/10.1002/ijc.33850. Available from:

Poljak, M., Bonde, J., Cocuzza, C., Zhao, F.H., Vorsters, A., 2018. VALHUDES: a protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples. J. Clin. Virol. [Internet]. https://doi.org/10.1016/j.jcv.2018.08.006. Available from.

Polman, N.J., de Haan, Y., Veldhuijzen, N.J., Heideman, D.A.M., de Vet, H.C.W., Meijer, C.J.L.M., et al., 2019. Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in the Netherlands. Prev Med (Baltim) [Internet]. 125 (April), 5–11. Available from: https://doi.org/10.1016/j.ypmed.2019.04.025. Available from:

R Core Team, . R: A Language and Environment for Statistical Computing., Vienna, Austria. URL. https://www.R-project.org/. R Foundation for Statistical Computing, Vienna (Austria).

Ronco, G., Dillner, J., Elfström, K.M., Tunesi, S., Snijders, P.J.F., Arbyn, M., et al., 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet [Internet] 383 (13), 524–532. Feb. Available from: https://doi.org/10.1016/S0140-6736(13)62218-7. Feb. Available from:

Serrano, B., Ibáñez, R., Robles, C., Peremiquel-Trillas, P., de Sanjosé, S., Bruni, L., 2022. Worldwide use of HPV self-sampling for cervical cancer screening. Prev Med (Baltim) [Internet]. 154, 199–203. Available from: https://doi.org/10.1016/j.ypmed.2021.106900. Available from:

Sultana, F., Mullins, R., English, D.R., Simpson, J.A., Drennan, K.T., Heley, S., et al., 2015. Women ' s experience with home-based self- sampling for human papillomavirus testing. BMC Cancer [Internet] 1–10. Available from: https://doi.org/10.1186/s12885-015-1804-x. Available from:

Torné, A., del Pino, M., Cusidó, M., Alameda, F., Andia, D., Castellsagué, X., et al., 2014. Guía de cribado del cáncer de cuello de útero en España, 2014. Progresos Obstet y Ginecol. 57 (1), 1–53.

Torné, A., Andía, D., Bruni, L., Centeno, C., Coronado, P., Cruz Quílez, J., de la Fuente, J., de Sanjosé, S., Granados, R., Ibáñez, R., Lloveras, B., Lubrano A Matías Guiu, X., Medina, N., Ordi, J., Ramírez, M., del Pino, M., 2022. AEPCC-Guía: Prevención Secundaria del Cancer de Cuello del Útero, 2022. Conducta Clínica Ante Resultados Anormales de las Pruebas de Cribado, 133 p.

Verdoodt, F., Jentschke, M., Hillemanns, P., Racey, C.S.S., Snijders, P.J.F.J.F., Arbyn, M., 2015. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. Eur. J. Cancer [Internet] 51 (16), 2375–2385. Available from: https://doi.org/10.1016/j.ejca.2015.07.006. Available from:

von Karsa, L., Arbyn, M., De Vuyst, H., Dillner, J., Dillner, L., Franceschi, S., et al., 2015. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Res. [Internet] 1–10. Available from. https://doi.org/10.1016/j.pvr.2015.06.006. Available from.

World Health Organisation, 2021. In: World Health Organization (Ed.), WHO Guideline for Screening and Treatment of Cervical Pre-Cancer Lesions for Cervical Cancer Prevention, Second Edition. [Internet], Second. CC BY-NC-SA 3.0 IGO, Geneva. Available from. https://www.who.int/publications/i/item/9789240030824.

World Health Organization, 2021a. WHO Guideline on Self-Care Interventions for Health and Well-Being [Internet]. Licence: CC BY-NC-SA 3.0 IGO, Geneva, 181 p. Available from. https://www.who.int/publications/i/item/9789240052192.

World Health Organization, 2021b. Web Annex A. Syntheses of evidence. In: WHO Guideline for Screening and Treatment of Cervical Pre-Cancer Lesions for Cervical Cancer Prevention, second edition. Geneva.