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IMPROVING ATTENDANCE TO CERVICAL CANCER SCREENING

EFFECTS OF HPV-TESTING ON SELF-TAKEN SAMPLES IN THE FINNISH CERVICAL CANCER SCREENING PROGRAMME

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ACADEMIC DISSERTATION

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1 ABSTRACT

High coverage amongst those at risk and a high attendance rate are essential in achieving a good impact in a cervical cancer screening programme. In Finland, a substantial proportion of cancer incidence and especially mortality amongst women aged 30–60 years is seen among non-attendees to organized screening. Attendance in the programme is approximately 70% with a slight decreasing trend. The introduction of human papillomavirus (HPV) testing in cervical cancer screening has brought about a new possible means of improving attendance rates, as HPV-testing can be performed on self-collected samples. This offers the opportunity to supply sampling devices directly to the homes of the women (self-sampling).

The aim of this study was to investigate the effects and feasibility of using self-taken samples for HPV-testing to conduct cervical cancer screening of non-attendees to the Finnish cervical screening programme. The effect on attendance to the screening programme, on overall screening test coverage (including also testing outside the screening programme), on the yield of precancerous lesions detected by screening and on the costs of a screening programme were assessed, as were women's views on this new screening modality. The effects of self-sampling were first studied as a first reminder (i.e. among non-attendees after the primary invitation) in a randomized setting in comparison to a reminder letter, and then in a non-randomized setting as a second reminder after two invitation letters.

As a first reminder to non-attendees after the primary invitation, a self-sampling test resulted in somewhat higher attendance than a reminder letter. The difference was small, and in terms of resulting costs, a reminder letter with a pre-assigned appointment time is a more feasible choice than a self-sampling test. However, self-sampling can be used to increase screening attendance as a second reminder after two invitation letters. Overall attendance rates increased by 4-8%, and the combined effect of reminder letters and self-sampling showed a 12-23% increase. As opportunistic screening is very common in Finland, the increase in overall test coverage remained smaller. Based on a questionnaire study conducted alongside self-sampling, home-based self-sampling helps to overcome both practical and emotional barriers to traditional screening, and the participating women reported mainly good experiences.

The invitation protocol preceding the self-sampling option must be carefully arranged to achieve optimal attendance. A total attendance of well over 80% is achievable in the national programme if personal invitations and reminder letters to non-attendees are sent, scheduled appointments are used in both letters and self-sampling tests are sent to those women who still do not attend.

2 FINNISH SUMMARY

Seulontaohjelman tehokkuuteen vaikuttaa ohjelman peittävyyden sekä diagnostiikan ja hoidon laadun lisäksi ennen kaikkea osallistumisaktiivisuus. Kohdunkaulan syövän joukkotarkastuksiin osallistuu nykyisin alle 70 % kutsutuista. Merkittävä osa seulontaikäisistä kohdunkaulan syöpään sairastuneista tai siihen kuolleista naisista onkin jättänyt osallistumatta järjestettyihin joukkotarkastuksiin. Uusi mahdollisuus parantaa seulonnan osallistuvuutta ovat naisten itse kotona ottamat näytteet, joista laboratoriossa tehdään papilloomavirus (HPV) -testi.

Tässä väitöskirjatutkimuksessa selvitettiin mahdollisuutta käyttää kotona tapahtuvaa näytteenottoa ensimmäistä kertaa Suomen seulontaohjelmassa. Seulontaan osallistumattomille naisille lähetettiin näytteenottoväline, ja seurattiin menetelmän vaikutuksia seulontaohjelman osallistuvuuteen, seulontatestien kokonaispeittävyyteen (sisältäen myös ohjelman ulkopuoliset näytteet) ja seulontaohjelmassa todettujen syövän esiasteiden määrään. Lisäksi selvitettiin naisten kokemuksia tästä uudesta seulontatavasta, ja vaikutuksia seulonnan kustannuksiin.

Tutkimuksen ensimmäisessä osassa näytteenottoväline lähetettiin ensimmäisen kutsun jälkeen osallistumattomille naisille ja menetelmää verrattiin satunnaistetussa asetelmassa kirjalliseen uusintakutsuun. Kotinäytteenotolla saavutettiin hieman korkeampi osallistuvuus kuin uusintakutsulla. Ero osallistuvuudessa jäi kuitenkin niin pieneksi, että kotinäytteenoton korkeammat kustannukset eivät tasoittuneet.

Kotinäytteenottoa voidaan kuitenkin suositella käytettäväksi kolmantena kutsuna kahden kirjallisen kutsun jälkeen. Näin käytettynä osallistuvuus nousi kotitestillä 4-8 %, ja uusintakutsulla ja kotitestillä yhteensä 12–23 %. Valtaosa kotinäytteellä seulontaan osallistuneista oli kuitenkin käynyt lähiaikoina seulontaohjelman ulkopuolella Papa-kokeessa ja vaikutukset testien kokonaispeittävyyteen jäivät pieniksi. Osallistuneet naiset raportoivat pääasiassa hyviä kokemuksia kotinäytteenotosta. Kyselytutkimuksen avulla voitiin myös päätellä, että kotinäytteenotolla voidaan ratkaista paitsi joukkotarkastuksiin osallistumiseen liittyviä käytännön ongelmia, myös tunneperäisiä esteitä tavanomaiseen seulontaan.

Jotta joukkotarkastuksissa saavutetaan optimaalinen osallistuvuusaktiivisuus, myös kotinäytteenottoa edeltävän kutsukäytännön on oltava suositusten mukainen. Tutkimus osoittaa, että tavoiteltu yli 80 % kokonaisosallistuvuus on mahdollista saavuttaa, kun käytetään kutsuissa ennalta annettua näytteenottoaikaa, suositusten mukaista uusintakutsua ja tarvittaessa tarjotaan vielä mahdollisuutta ottaa seulontanäyte itse.

3 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals (I-V)

I Virtanen A, Anttila A, Luostarinen T, Nieminen P. Self-sampling versus reminder letter: effects on cervical cancer screening attendance and coverage in Finland. Int J Cancer 2011: 128, 2681–7.

II Virtanen A, Nieminen P, Luostarinen T, Anttila A. Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. Cancer Epidemiol Biomarkers Prev 2011: 20, 1960–9.

III Virtanen A, Anttila A, Luostarinen T, Malila N, Nieminen P. Improving cervical cancer screening attendance in Finland. Int J Cancer 2015: 136, E677–84.

IV Virtanen A, Nieminen P, Niironen M, Luostarinen T, Anttila A. Self-sampling experiences among non-attendees to cervical screening. Gynecol Oncol 2014: 135, 487–94.

V Virtanen A, Anttila A, Nieminen P. The costs of offering HPV-testing on self-taken samples to non-attendees of cervical screening in Finland (submitted)

4 ABBREVIATIONS

AIS	Adenocarcinoma in situ
APTIMA®	HPV detection assay targeting E6/E7 messenger ribonucleic acids (mRNA)
ASC-US	Atypical squamous cells of undetermined significance
CI	(95%) Confidence interval
CIN	Cervical intraepithelial neoplasia
CIN 1-3	Cervical intraepithelial neoplasia, grade 1-3
CIN 2+	Cervical intraepithelial neoplasia, grade 2 or more severe
CIN 3+	Cervical intraepithelial neoplasia, grade 2 or more severe
GP5+/6+	Consensus primers used in PCR amplification
DNA	Deoxyribonucleic acid
E4	Human papillomavirus early gene 4
EDTA	Ethylenediaminetetraacetic acid
FTA	Flinders Technology Associates
GP	General practitioner
HC2	Hybrid Capture® 2 high-risk HPV DNA test
HPV	Human papillomavirus
HPV16/18	Human papillomavirus types 16/18
HSIL	High-grade squamous intraepithelial lesion
hrHPV	High-risk human papillomavirus
IARC	International Agency for Research on Cancer
ICER	Incremental cost-effectiveness ratio
INNO-LiPA	Line probe assay, based on the reverse hybridization principle
L1	Human papillomavirus late gene 1
LA	Linear Array® HPV genotyping test
lrHPV	Low-risk human papillomavirus
LSIL	Low-grade squamous intraepithelial lesion
MAL	T-lymphocyte maturation associated protein
MALDI-TOF	Matrix-assisted laser desorption/ionization (-time of light)
miR-124-2	A type of tumour suppressor microRNA
MY09/11	Primers used in PCR amplification
NA	not applicable/available
NORDCAN	Cancer statistics by the Association of the Nordic Cancer Registries
NPV	Negative predictive value
OR	Odds ratio
p16-INK4a	Cyclin-dependent kinase inhibitor (regulatory protein)
PCR	Polymerase chain reaction
PPV	Positive predictive value
RLU	Relative luciferase unit
RNA	Ribonucleic acid

RR	Relative risk
SES	Socio-economic status
SPF	Short polymerase chain reaction fragments
STM	Specimen transport media/medium
THL	National Institute of Health and Welfare
Tris–HCl	tris(hydroxymethyl)aminomethane-hydrochloric acid
UCM	Universal collection media/medium
UK	The United Kingdom
USA	The United States
VIA	Visual inspection with acetic acid
WHO	World Health Organization

5 INTRODUCTION

Cervical screening at the population level every 3–5 years can reduce cervical cancer incidence by up to 80%, but only in organized screening programmes with optimal quality at every loop and link in the so-called screening chain (IARC 2005). The target population must include those who are truly at the highest risk to ensure cost-effectiveness and minimize potential harms. Of course the screening test used must effectively identify those with disease, guidance for further examinations must be continuous, and the quality of diagnostics and possible treatment for the diseases identified must be high. However, of primary importance is high coverage of screening tests in the target population, obtained as a result of a high participation rate within and throughout the programme. If test coverage and attendance rate are low, the performance and cost-effectiveness of the programme are limited even if all the other loops in the chain function optimally (Koopmanschap et al 1990a).

Factors affecting screening participation originate from various steps of the screening process and are sometimes complex. Barriers to screening might be personal; emotional, attitudinal or stem from practical hindrances among women (Kallio et al 1994, Larsen & Olesen 1998, Knops-Dullens et al 2007). They might also be organizational ones, arising from gaps in the screening chain such as an invitational system that is inadequate in coverage or content, poor organization of the practicalities of screening visits or insufficient informing and education of the population (Arbyn et al 2008, Anttila et al 2010).

When organized and opportunistic screening are not linked, as in the case of Finland, low participation to organized screening may be partly due to the greater use of private opportunistic screening and overall test coverage may actually be much higher than that recorded in the organized programme (Salo et al 2014). Still, as opportunistic screening is often characterized by over-screening among some women and a high coverage among women who are too young to benefit from screening (IARC 2005, Lönnberg et al 2012, Salo et al 2014), this situation produces negative effects in terms of more potential psychosocial harms of screening, reduced efficiency and higher overall costs with unevenly distributed health benefits. Thus, organized screening should be preferred over opportunistic screening (IARC 2005, National Institute for Health and Welfare 2011).

Achieving adequate levels of uptake in cancer screening requires a variety of approaches that need to be shaped by the characteristics of both the screening programme and the target population. Screening guidelines recommend actively inviting the target population, primarily by means of a personal letter (Arbyn et al 2008). Further, using pre-assigned appointment times and locations in invitations (Wilson & Leeming 1987, Segnan et al 1998), postal or telephone reminders to non-attendees (Eaker et al 2004),

and a doctors signature in the invitation letter might increase screening attendance (Bowman et al 1995, Segnan et al 1998).

The introduction of human papillomavirus (HPV) -testing in cervical cancer screening has brought about a possible new means of improving attendance rates. HPV-testing can be performed on self-collected samples, which offers the opportunity to supply sampling devices directly to the homes of the women (self-sampling) (Snijders et al 2012). High risk HPV (hrHPV) -testing on self-taken samples can detect precancerous lesions with a similar sensitivity to that of the routinely used screening test, a Pap smear (Arbyn et al 2014b).

The aim of this study was to investigate effects and feasibility of using home-based HPV self-sampling for the detection of pre-cancerous lesions amongst the non-attendees of the Finnish cervical screening programme. The effects of self-sampling on screening participation were first studied as a first reminder (i.e. among non-attendees after the primary invitation) in a randomized setting in comparison to a reminder letter, and then in a non-randomized setting as a second reminder after two invitation letters. HrHPV-test positivity rates, yield of detected precancerous lesions and women's views and perceptions on this new screening modality were also studied. Reasons for non-attendance were clarified in the process to gain deeper knowledge on the barriers to attendance in Finland.

The study was conducted as a part of the organized screening programme and the results are thus applicable for routine use in Finnish areas or municipalities with suboptimal attendance rates in organized screening. On the other hand, the results are also relevant for other countries where screening programmes have failed to achieve adequate compliance.

6 REVIEW OF THE LITERATURE

6.1 Screening for cervical cancer

Screening is the use of methods for detecting unrecognized health risks or diseases in order to permit timely intervention. Cervical cancer is an ideal disease for screening because it has a precancerous stage with slow disease progression from mild cell abnormalities to pre-cancer, and finally to invasive cancer. This provides the opportunity to detect and treat pre-cancerous disease and thus prevent cancer from developing. The primary aim of cervical screening is to reduce incidence and mortality of the cancer (IARC 2005).

Cervical screening has been shown to be effective in several countries, although not by means of randomized controlled trials. In the Nordic countries, nearly complete coverage of the target population by organized cervical screening programmes in Iceland, Finland, Sweden, and parts of Denmark were soon followed by sharp falls in both incidence and mortality (Läärä et al 1987, Hakama & Louhivuori 1988, Engholm et al 2014; Figure 1).

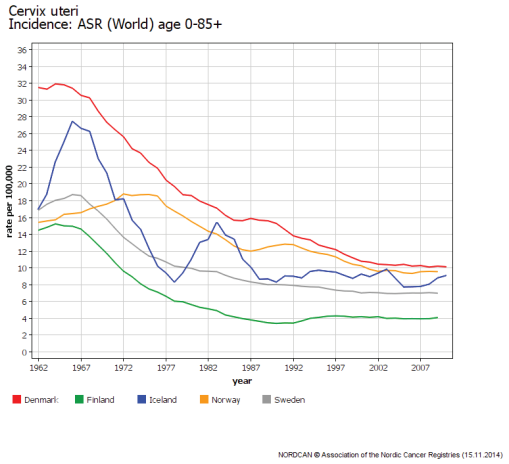

Figure 1 Age standardized incidence of cervical cancer in the Nordic countries. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 6.1 (25.04.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 15/11/2014.

In cancer screening, the achieved benefits should always be accompanied with minimal harm. Possible negative side effects include higher morbidity, unnecessary follow-up due to false-positive results and consequent raised anxiety, unnecessary treatment with possible longer term consequences, and

the false reassurance of false-negative results (Wardle & Pope 1992, IARC 2005, Jakobsson et al 2009, Castanon et al 2014). The optimal balance between benefits and harms can be tried to achieve by minimizing overuse of screening services and defining the right target population, restricted to only those age-groups that are immediately in an increased risk of cancer without screening. This is more easily achieved in an organized screening programme, than in opportunistic screening (Koopmanschap et al 1990a, IARC 2005, Arbyn et al 2008).

6.1.1 Pathogenesis of cervical cancer

The uterine cervix is the lower third of the uterus that extends into the vagina. The cervix is covered by two types of epithelia that can both develop their own type of cervical cancer. The part of the cervix projecting into the vagina, called the ectocervix or portio, is covered by stratified squamous epithelium, and the endocervical canal which communicates with the uterine cavity is covered by columnar epithelial cells. The interphase between these two epithelia is called the squamocolumnar junction. The location of the squamocolumnar junction changes depending upon age and hormonal factors as columnar epithelium is replaced by squamous epithelium by active metaplasia. This area between the original and new junction, called the transformation zone, is the area most susceptible to neoplastic transformation. This is where most squamous-cell carcinomas develop through precursor lesions, histologically recognizable as cervical intraepithelial neoplasia (CIN).

CIN lesions are classified into three groups: CIN1 (mild dysplasia) with morphological changes up to one third of the squamous epithelium, CIN2 (moderate dysplasia) with morphological changes until two thirds, CIN3 (severe dysplasia and carcinoma in situ) with morphological changes in more than two thirds of the epithelium. Only when the epithelial lesion invades through the basal membrane into the stromal tissue to form an invasive cancer is the process irreversible; precancers, i.e. CIN lesions, can progress or regress from one stage to another or persist as they are. The tendency of CIN lesions to regress spontaneously decreases with increasing age and CIN grade (van Oortmarssen & Habbema 1991, Syrjänen et al 1992). Out of all CIN lesions up to 90% will regress spontaneously in women aged 13 to 22, but among women 34 years and older the estimated regression rate is only 40% (van Oortmarssen & Habbema 1991, Moscicki et al 2004). Among women aged 30-60, 38-60% of CIN3 lesions have been estimated to progress into invasive cancer (Hakama & Räsänen-Virtanen 1976, Boyes et al 1982, van Oortmarssen & Habbema 1991).

Columnar cells in the endocervical canal give rise to adenocarcinomas of the cervix. The precursor lesion of the adenocarcinoma is adenocarcinoma in situ (AIS), but the natural history of these lesions is not as well-known as the natural history of squamous lesions.

HPV can be detected in virtually all cervical cancers (Walboomers et al 1999). Of the more than 150 HPV types identified, approximately 40 can infect the cervix and 13 of these are associated with cervical cancer; 12 HPV types are classified as oncogenic or high risk (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and one as probably carcinogenic (type 68) (Schiffman et al 2011, IARC 2012). HPV is a highly infectious sexual transmitted virus; the life-time risk to acquire a genital HPV infection has been estimated to be up to 80% (Syrjänen et al 1990, Koutsky 1997). However, most infections are cleared by the immune system within 2 years and only around 10-20% persist and progress to CIN (Moscicki et al 2004, Stanley 2010).

Although a hrHPV-infection is viewed as a necessary cause for cervical cancer, it is not a sufficient cause on its own. Other factors that play a role in the development of cervical cancer include tobacco smoking, alterations of the immune system, Chlamydia trachomatis infections, early age of sexual debut, use of oral contraceptives, high number of sexual partners, multiparity and a low socio-economic status (IARC 2005).

6.1.2 Screening methods

Cervical cancer screening can be performed by three major screening modalities; the Pap smear, hrHPV-testing and VIA, visual inspection of the cervix aided with acetic-acid treatment, which is used primarily in low-resource settings.

The traditional and predominant cervical screening modality is cytological screening based on the microscopy of cells that have exfoliated from the cervix, the Papanicolau (Pap) smear (Papanicolaou & Traut 1941). This method of identifying abnormal cells as an indication of dysplasia in the squamous epithelium has been used since the 1940's. Modifications of the Pap smear include automation-assisted analysis, and liquid-based cytology (Nieminen et al 2005, Arbyn et al 2008).

Well organized cytological screening, every 3 to 5 years in the age range of 35–64 years reduces the incidence of cervical cancer by 80% or more among screened women (IARC 2005). However, as the evaluation of the smear is always subjective, the quality of testing is highly dependent on the expertise of the laboratory staff and reproducibility of results may be low (Stoler & Schiffman 2001). Thus the sensitivity of a single smear to identify a moderate or severe intraepithelial lesion can vary from 30 to 87%, and specificity from 62 to 100% (Nanda et al 2000). Cytological screening needs strict quality control in order to maintain high programme sensitivity (Arbyn et al 2008, Lönnberg et al 2010). In the future, the proportion of abnormal cell samples in routine screening will decrease as the HPV-vaccinated women enter screening age, and this might lower the applicability of cytology screening.

The viral aetiology of cervical cancer enables the use of hrHPV as a biomarker for cervical cancer. The sensitivity and specificity of different assays to detect the presence of hrHPV varies (Snijders et al 2010, Rebolj et

al 2014), but in general hrHPV-testing is a very sensitive screening method that can detect precancerous lesions earlier than traditional cytology (Leinonen et al 2012, Ronco et al 2014). It has a higher negative predictive value which allows for longer screening intervals after a negative result than cytological screening (Leinonen et al 2012). With high sensitivity however, negative outcomes can arise; hrHPV-testing can detect non-progressive cervical lesions and may thus lead to over-diagnosis and over-treatment (Malila et al 2013). Further, the proportion of women in need of repeated testing might be higher with primary hrHPV screening than with cytology (Leinonen et al 2009). These effects might increase the psychological burden for participating women.

To retain the number of colposcopies and unnecessary distress for women within acceptable limits triage testing, a method to separate women who are at higher risk of CIN or cancer from the group of all hrHPV-positive women, is necessary. Various methods are currently suggested. The most prevalently used one is cytology (Kotaniemi-Talonen et al 2005), but deeper insight into the pathogenesis of cervical cancer has led to the discovery of various biomarkers that could be useful from screening to diagnostic workup. Molecular biomarkers that are currently under study include hrHPV genotyping, methylation of tumour suppressor genes, immunohistochemical staining of proliferation markers, viral markers E4 and L1 and transformation marker p16-INK4a (Cuzick et al 2012). All in all, continuous evaluation of the screening programme is the key to managing the adverse effects of hrHPV-screening (Leinonen 2013).

6.2 Attendance in and coverage of screening

'Participation/attendance rate' applies to organized screening, and is defined as the proportion of eligible women in the target population who participate in screening based on an invitation (IARC 2005). The term 'coverage' is also used, and may be calculated whether opportunistic screening is performed exclusively or in combination with organized screening. Coverage usually takes the whole female population in the target group as the denominator, and may refer to the coverage of any screening test (organized or opportunistic) within the screening interval specified by local guidelines. However, 'invitational coverage' refers to the percentage of target population who had actually been invited within the specified schedule.

A high coverage of screening tests obtained as a high attendance rate is a major determinant of the beneficial health effects and cost-effectiveness of a screening programme, and is thus of primary importance to the success of the programme (Koopmanschap et al 1990a, 1990b, IARC 2005, Arbyn et al 2008). Attendance rate is therefore one of the key performance indicators of a screening programme (Hakama et al 1985).

The coverage of screening tests in any European cervical screening programmes is below 80%, ranging from 10% to 79%. In only five regions – Alsace/France, England, Finland, the Netherlands and Sweden – the coverage is 70% or more, although estimates are not entirely comparable due to variations in screening intervals and integrations of opportunistic testing (Anttila et al 2009). Coverage of any test (including those taken within the programme or opportunistically) of all European countries is the highest in Finland, approaching 90% (Salo et al 2014).

An increase in the attendance rate of organized screening is not only more effective (assessed by the reduction in mortality due to cancer of the cervix) than shortening the screening interval and thus increasing the number of lifetime smears; it is also estimated to be more cost-effective (assessed by how much health improvement can be gained per unit expenditure) (Koopmanschap et al 1990b). For example, the authors of a modelling study comparing the impact and characteristics of screening policies in several European countries estimated that in a screening programme that contains seven Pap smears per lifetime, if screening coverage increases from 50 to 75%, the reduction of life-years lost to cancer obtained by screening increases 48% (van Ballegooijen et al. 2000). However, if screening interval if intensified to 14 Pap smears per lifetime, the reduction of life-years lost to cancer increases only 10%. The authors further estimated that in a screening policy such as the Finnish one with invitations for women aged 30-60 years old in 5-year intervals, by increasing the coverage (participation) from 70 to 80, 85, 90 or 100% would the reduction of life-years-lost to cancer rise from 59 to 67, 71, 76 or 84%, respectively. Indeed, a good example of the importance of high screening coverage comes from England where 4.5 million Pap smears were taken annually in the 1980's, but test coverage among the target group was low. Following the implementation of a call-recall system test coverage rose from 42% in 1988 to 85% in 1994, resulting in dramatic falls in the incidence of invasive disease (Quinn et al 1999).

However, low participation in organized screening does not necessarily result in low overall Pap-test coverage if it is due to or otherwise compensated by the greater use of private opportunistic screening. This is the case in Finland (Salo et al 2014) and Italy (Segnan et al 2000). Still, low participation in public, quality-assured screening programmes produces negative effects in terms of reduced cost-efficacy and even quality of the programme (Arbyn et al 2008, National Institute for Health and Welfare 2011). Because the use of opportunistic testing seems to be concentrated on certain groups of women rather than among all non-attendees to organized screening (Koponen & Luoto 2000, Salo et al 2014), unintegrated opportunistic testing does not entirely level-out the negative effects of lower participation rates in organized screening. For example, despite the high level usage of opportunistic screening in Finland, non-attendees to the organized programme seem to be at a higher risk of cervical cancer. When incidence rates increased in the 1990's, cervical cancer incidence was 1.54-

fold higher in those municipalities where the participation rate in organized screening was poor (<66%), in comparison with those with a very good participation (≥80%) (Anttila et al 1999). Further, a follow-up of 503,000 women invited to screening during 1999-2003 revealed that the age-adjusted relative risk (RR) of cervical cancer was 0.52 among women who attended compared to non-attendees (Anttila et al 2011). The corresponding RR of cervical cancer mortality among attendees was 0.31.

It seems that organized screening programmes with personal invitations are able to reach those women who are less likely to be screened opportunistically and could thus reduce the selection in access to screening (Ronco et al 1994, IARC 2005, Palència et al 2010). It also seems that increasing attendance, for example with reminders, preferentially attracts the least-screened women, and therefore may contribute to a reduction in health inequalities (Koopmanschap et al 1990b). For example, women with low socio-economic status (SES) have a higher-than-average risk for cervical cancer (Pukkala et al 2010) and often below-average attendance at screening (Kallio et al 1994, Segnan 1997). Thus, increasing attendance to organized screening could help to reduce health inequalities resulting from socio-economic differences also in countries with unintegrated organized and opportunistic screening such as Finland.

6.2.1 Socio-demographic predictors of screening participation

Pap smear uptake and coverage not only varies between countries, but differences also exist within countries between different socio-demographic groups; e.g. ethnic origin, age, marital status, education level and socio-economic status.

The effect of age on willingness to take part in screening has varied between studies, perhaps indicating effects of different screening programmes (mainly, organized versus opportunistic). Young women have been more likely to attend screening than older women in studies based on self-reported screening from the USA (Pérez-Stable et al 1995, Mandelblatt et al 1999, Coughlin et al 2002), Canada (Maxwell et al 2001), Germany (Seidel et al 2009) and Spain (Borràs et al 1999). With the exception of Spain, screening in these countries relies mainly on opportunistic tests. Similarly in Finland, opportunistic screening is more common among younger and middle aged women, than older women (Salo et al 2014).

In contrast, studies on organized screening programmes have reported higher attendance rates among older women. This was the case in a pilot-project in Italy (Ronco et al 1994), and in studies on registry-based data in the UK (Lancuck et al 2008, Lancucki et al 2010, Bang et al 2012), and Norway (Hansen et al 2011). Another reported pattern is the attendance rate peaking among women aged 40-50, as was observed in the Netherlands (Tacken et al 2007) and Sweden (Rodvall et al 2005). In the organized

programme of Denmark, however, attendance rate showed a linear decreasing trend from youngest to oldest age groups (Kristensson et al 2014).

In the opportunistic screening systems of USA and Canada, survey studies show associations with higher education and higher income level and the likelihood of having been screened at least once (Calle et al 1993, Katz & Hofer 1994, Pérez-Stable et al 1995, Hsia et al 2000, Maxwell et al 2001, Coughlin et al 2002, Hewitt et al 2002, Selvin & Brett 2003). Associations were also found with ethnic background and being married or having been married (Hsia et al 2000, Maxwell et al 2001, Coughlin et al 2002, Hewitt et al 2002). Similar results of higher participation rates in opportunistic screening among women with higher education and married women were seen in a survey studies from Germany and Belgium (Arbyn et al 1997, Seidel et al 2009). In Belgium income level and employment status also influenced screening participation (Arbyn et al 1997).

In countries with organized population-based screening programmes the effect of socio-economic status or other socio-demographic factors is not as clear. In the organized programme of the Netherlands, education level is not a significant determinant of participation (Tacken et al 2007), but immigrant women have lower attendance rates to screening (Gök et al 2012a). In the UK, studies have found connections between non-attendance to screening and low education level (Sutton & Rutherford 2005, Moser et al 2009), other than white/Caucasian ethnicity (Sabates & Feinstein 2006, Moser et al 2009, Bang et al 2012), not being married (Orbell et al 1995, Sutton & Rutherford 2005) and socio-economic deprivation (Orbell et al 1995, Bang et al 2012).

Studies from Sweden have not found an effect of socio-economic status on attendance to screening (Eaker et al 2001, Rodvall et al 2005). Marital status had an effect in one study (Rodvall et al 2005), but not another (Eaker et al 2001). Participation rate was not lower for immigrant women from developing countries than for those born in Sweden, but was lower for women born in North America and Oceania (Rodvall et al 2005). In Norway, attendance was positively associated with being married/cohabiting, but educational level did not affect women's attendance status (Hansen et al 2011). In Denmark, non-participation was associated with lower education level, not being married and foreign nationality (Kristensson et al 2014).

In Finland, the effect of socio-economic characteristics on screening participation was explored in the context of a survey study in 1991 in one neighbourhood of Helsinki with particularly poor attendance rate at the time, 50% (Kallio et al 1994). Younger age (<35 years old), mother tongue other than Finnish or Swedish, and of socio-economic classes of being a student, retiree or unemployed were associated with lower attendance rates, as was lower income level. Religion and education level had no impact in this population.

A study using data from Eurobarometer 66.2 "Health in the European Union" 2006 on self-reported cervical cancer screening participation in 15 European countries was published in 2011 (Walsh et al 2011). In countries

with opportunistic programmes in place (Austria, Belgium, France, Germany, Greece, Ireland, Luxemburg, Portugal and Spain) those within the two lowest socio-economic groups and with lower education levels were less likely to report a screen within 12 months. Such differences were nor seen in countries with population-based screening programmes (Denmark, Finland, Italy, Netherlands, Sweden and the UK). Marital status was significant across both programme types.

Another study using data from the World Health Survey of 2002/2003 in 22 European countries supported these results. Individual-level data for women aged 25–69 years (n=11,770) of self-reported screening participation within the last three years and socio-economic position (assessed as education level) were combined with information on the type of screening programme (organized national/pilot/regional versus opportunistic) in the country (Palència et al 2010). Inequalities with regard to socio-economic position in screening were found in countries with opportunistic screening, but not in countries with nationwide population-based programmes. However, in these results Finland made an exception to other countries with organized programmes. The authors speculated this to be due to the longer five year screening interval, and considerable opportunistic screening activity, which might be taken up primarily by the higher socio-economic groups.

6.2.2 Self-reported barriers to screening

In survey studies, the following barriers to cervical cancer screening have been reported; difficulties in making a suitable appointment (Glasgow et al 2000, Waller et al 2009, 2012, Broberg et al 2013), lack of time due to other commitments (Oscarsson et al 2008a), not getting round to going (Waller et al 2009), not being sexually active (Waller et al 2009, 2012), feeling healthy or otherwise low perception of risk (Glasgow et al 2000, Oscarsson et al 2008a, Waller et al 2012) embarrassment (Glasgow et al 2000, Waller et al 2012), concern about pain or discomfort (Larsen & Olesen 1998, Glasgow et al 2000, Oscarsson et al 2008a, Waller et al 2012) and not trusting the test (Waller et al 2009). Studies from the UK found that practical barriers were more predictive than emotional factors (Waller et al 2009), and adjusting service-related factors such as appointment systems and clinic times may have a positive impact on attendance especially among young women (Waller et al 2012).

Barriers to screening have also been explored separately for some ethnic minority groups in the UK. Hindu women reported fear of pain and the test result, embarrassment, screener's attitude or sex, inconvenient appointment times and difficulty with child care to be barriers to attendance in screening (Cadman et al 2014). Embarrassment was a dominant theme in discussing barriers to attendance at screening among Muslim women; fear that the doctor carrying out the test might be male and fear of pain and discomfort,

and not wanting implicate sexual activity were reported (Szarewski et al 2009). As practical issues, time pressures, not prioritizing one's own health and the language used in screening materials and letters were described.

Blomberg et al. (2011) took an inverse approach and asked non-participants of the screening programme in Sweden what would encourage them to participate. Personal invitation letters were raised as an important factor; with attractive layout, information that's easy to understand and a reference link to a website with further information. The possibility to choose a test venue, drop-in Pap smear clinics, and appointment times outside office hours and possibilities to have a Pap smear taken in conjunction with other examinations were suggested. More information in mass media was regarded important (Blomberg et al 2011).

Reasons for non-participation in traditional screening have also been studied among originally non-attending women who were offered a self-sampling option. In the Netherlands a survey study was conducted among 35,477 non-attendees who were offered a self-sampling device (Bosgraaf et al 2014). Response rate was 95% among those who returned a self-taken sample and 3% among those that did not. Main reasons for non-attendance among women who chose to take part by self-sampling were forgetting to make the appointment for screening, feeling too embarrassed to have a smear taken, not being able to make a suitable appointment, and pregnancy related reasons. Among women who did not take part by self-sampling, the most common reasons were forgetting to make the appointment and being afraid of having a smear taken. The authors concluded that organizational barriers are the main reasons for non-attendance in the cervical screening programme in the Netherlands. In Italy, 40% of originally non-attending women who participated when self-sampling was offered reported that they had not complied with the previous screening invitation because of a recent opportunistic Pap smear, 23% reported they had not had time, and 15% had not received the invitation letter (Giorgi Rossi et al 2011). In a similar setting in the UK, 65% of self-sampling participants reported emotional/attitudinal reasons for non-attendance in traditional screening (uncomfortable, painful, unpleasant, sexual abuse, dislike to doctors or nurses, embarrassment) and 35% practical reasons (lack of time, too busy, no child care, access to clinic, appointment time, transport, disabled) (Szarewski et al 2011). In Sweden, women with no registered smear for >9 years were invited either by self-sampling or a reminder letter with several possible appointment times including on weekends and evenings (Darlin et al 2013b). In both groups, the most common reasons for previous non-attendance was being uncomfortable with vaginal examinations, feeling healthy, lack of time, experience of unfriendly health workers, inflexible appointment times and fear. In the self-sampling group, forgetting to make the appointment was common.

In Finland, self-reported reasons for non-attendance in screening have been studied in the 1960's, 1970's and 1990's. In 1972, all women who were invited to screening in Vaasa County but did not attend (17 % of invitees)

were included in an interview survey (Fortelius et al 1974). The authors classified the reported reasons for non-attendance into "good" reasons (a Pap smear elsewhere, temporary hindrance such as scheduling difficulties or pregnancy, and permanent hindrance such as hysterectomy, illness or disability), and "bad" reasons (negative or indifferent attitude, embarrassment/fear, not knowing the purpose of mass screening, religious reasons and social reasons). Of the non-attendees, 32% were not reached, 40% reported "good" reasons (70% of them a recent Pap smear) and 28% reported "bad" reasons (most commonly negative or indifferent attitude). "Good" reasons, in particularly recent opportunistic screening, were more common among married women, and "bad" reasons, especially embarrassment/fear, were more common among "lonely" women.

In 1991, a survey study was conducted among all invitees to screening in 1991 in the Punavuori neighbourhood of Helsinki which had a poor attendance rate at the time, 50% (Kallio et al 1994). Most commonly reported reasons for non-attendance in organized screening were a recent Pap smear elsewhere (opportunistic screening) or a recent gynaecologic examination, reported by 30% and 37% of non-attending responders, respectively. Difficulties in finding a suitable time were reported by 10%. Among non-attendees who reported no opportunistic testing within one year of the invitation, most common reasons were difficulties in finding a suitable time (21%), forgetting (15%), recent gynaecologic examination (15%) and good perceived health/condition (12%). In an older survey in Helsinki among women aged 50-60 invited to screening in 1966, the most commonly reported reasons for non-attendance were similar: seeing a gynaecologist for an examination in the course of the past year (35%), not having the opportunity to arrange for a suitable time to have a smear taken (14%) and feeling well (10%) (Kauppinen et al 1970).

6.3 Strategies to increase participation in screening programmes

6.3.1 Invitations

A call/recall system based on personal invitations is considered to be a key element of an organized programme in Europe (IARC 2005, Arbyn et al 2008). The nature of the invitations varies from a suggestion or request to contact the smear-taker and make an appointment (open invitations), to letters with pre-assigned date and place for the appointment that can be modified by contacting the organizing quarter.

Several studies from the USA, the UK, Canada and Australia show that coverage of screening increases with personal invitations, usually in comparison to no systematic contact of the target population (i.e. only opportunistic screening at the woman's own or her doctor's initiative). Data

from twelve such studies (Somkin et al, McDowell et al 1989, Pierce et al 1989, Mitchell et al 1991, Lancaster & Elton 1992, Bowman et al 1995, Pritchard et al 1995, Binstock et al 1997, Buehler & Parsons 1997, Burack et al 1998, Vogt et al 2003, Stein et al 2005) were combined in a systematic review from 2012 which concluded that all studies but one showed a positive effect of the invitation letter with a combined relative risk for participation of 1.52 (95% confidence interval (CI) 1.28–1.82) (Ferroni et al 2012). Another meta-analysis of slightly differing twelve trials (Pierce et al 1989, McDowell et al 1989, Lancaster & Elton 1992, Bowman et al 1995, Binstock et al 1997, Buehler & Parsons 1997, Burack et al 1998, 2003, Del Mar et al 1998, Hunt et al 1998, Stein et al 2005, Morrell et al 2005) assessing 99,651 participants, calculated a RR of 1.44 (CI 1.24-1.52) for participation among women who received an invitation in comparison to women who received usual care or no invitation (Everett et al 2011).

Evidence is available also from Nordic countries. In a Danish county where personal invitations were sent for 15 years in the 1970's and 80's, participation rate was at 90% among women aged 30-50 (at the same level with other counties that used invitations), and when the invitations stopped, participation rate dropped to 66%, to the same level with other counties where invitations were not used (Lynge et al 1992). In Norway, opportunistic screening only resulted in a coverage rate of 65% among women aged 25-69. When an invitational system of sending reminders (open invitations) to those women who had not had a smear in three years was set up in 1995, coverage increased to 71% (Nygard et al 2002).

However, invitational systems are not always successful in increasing screening coverage. A recent evaluation from Belgium, where screening remains essentially opportunistic with overall coverage around 60%, used records from reimbursement claims for Pap smears to calculate a three-year screening coverage. Comparison of two areas revealed that a regional invitational system did not result in any obvious impact on screening coverage - in fact coverage was higher in the area that did not have an invitational system (Arbyn et al 2014a).

In randomized trials from the UK, Australia and Italy, compliance rates were significantly higher with letters offering pre-assigned appointment times than with open-ended invitations (Wilson & Leeming 1987, Ronco et al 1994, Pritchard et al 1995, Segnan et al 1998). Pritchard and colleagues randomized 757 clients of a university general practice in Australia to either a) tagging the medical record to remind the doctor to offer a Pap smear, b) sending an open invitation, c) sending an invitation with an appointment or d) control group with no systematic contact. Significantly more Pap smears were taken in the appointment-letter and open invitation -groups than in the control group (odds ratio (OR) 2.13, CI 1.34-3.57, and OR 1.67, CI 1.01-2.77, respectively), and a letter with an appointment reached significantly more women than open invitation (30% versus 26%) (Pritchard et al 1995). In a pilot phase of population-based screening in Italy, a clinic allocated to pre-

fixed appointments had significantly higher compliance rates than a clinic with appointments to be arranged (OR 2.36, CI 1.66-3.36) (Ronco et al 1994). Camilloni et al. calculated a pooled estimate from the results of studies by Wilson&Leeming and Pritchard and colleagues and arrived at a relative risk of 1.56 (CI 1.43-1.69) in favour of a fixed appointment versus an open invitation (Camilloni et al 2013). Survey studies confirm that the fact that women are invited to make an appointment themselves creates a barrier for the current non-attendees of programmes (Knops-Dullens et al 2007, Bosgraaf et al 2014).

Invitations by telephone have also been studied in comparison to no systematic contact. In the previously mentioned systematic reviews and meta-analyses, Ferroni and colleagues (2012) calculated a combined "RR for participation" of 2.16 (CI 1.92–2.42) among women who received a telephone invitation for three such studies (McDowell et al 1989, Binstock et al 1997, Vogt et al 2003) and Everett and colleagues (2011) a relative risk of 2.16 (CI 1.70-2.74) for four trials (McDowell et al 1989, Binstock et al 1997, Vogt et al 2003, Stein et al 2005) .

Further, although not relevant to all screening programmes, attendance following an invitation seems to be higher if the invitation is signed by a general practitioner, rather than by programme staff or a nurse practitioner (Bowman et al 1995, Segnan et al 1998). In Italy, a comparison of a) a letter with a prefixed appointment and a general practitioner's (GP) signature to b) an open invitation with a GP's signature, to c) a letter with a prefixed appointment and a programme coordinators signature, to d) a letter with a prefixed appointment and a GP's signature and extended text was made among women aged 25-64. A letter with a prefixed appointment and a GP's signature (a) resulted in a significant increase in compliance (36.1% participation rate versus 22.7% with open invitation, and 30.9% with programme coordinators signature). The extended text version (d) did not result in further increase to compliance (36.1% versus 36.7%), but it did increase the difference in response rate between women with low educational level and high educational level, in favour of the latter (Segnan et al 1998).

6.3.2 Practicalities of the visit

Screening guidelines recommend that the practicalities of the screening visit should be easy to ensure optimal attendance (Arbyn et al 2008). However, research on the effect of removing these barriers in clinic-based screening is scarce.

In Sweden, 1,500 women who had not had any cervical smears taken for >9 years despite normal reminders were randomized to either to receive a self-sampling kit by mail, or an invitation to a free of charge sampling by a gynaecologist at an outpatient clinic with several alternative appointments in the daytime, evenings or on Saturdays (Darlin et al 2013b). If the women did not turn up, another invitation with five different options for appointments

was sent. Although the flexible appointment approach did reach some of these persistent non-responders, the response rate to hrHPV self-sampling was three times higher; 14.7% compared to 4.2%.

In another study in Sweden, women with no registered cervical smear during the last 5 years attended cervical screening to a greater extent when their individual requirements were met (118/400) than women in a control group with only routine invitations (74/400) (Oscarsson et al 2008b). The required interventions were individually arranged and included sending out invitation letters, making phone calls and helping to make arrangements with ordinary healthcare or taking the cervical smears on holidays and evenings, opening up premises and/or helping the women with transport. However, this type of intensive recruitment was not considered cost-effective by the authors.

6.3.3 Reminders for non-attendees after primary invitation

In the literature, reminder or recall letters sometimes refer to letters sent in systems that integrate opportunistic and organized screening to women who have not participated in opportunistic screening within the local screening interval. Here, only reminders in the context they are used in Finland, i.e. letters sent or other types of contacts to non-attendees after at least one previous invitation, are included.

Eaker and colleagues (2004) conducted a large randomized trial among 12,240 women in Sweden who were due an invitation letter for screening because they had no record of a smear taken in three previous years. All women were first randomized to receive a modified invitation versus the standard invitation letter. Non-attendees after the primary invitation were randomized to receive or not to receive a reminder (2nd reminder), and a certain subgroup of persistent non-attendees after the reminder letter were further randomized to a phone reminder (3rd reminder) or no further reminder. The authors assumed similar attendance between those allocated and not allocated to the study arms of the third intervention. Cumulative attendance rate by primary invitation only after 12 months was 33% (CI 33–34%) for a standard invitation letter and 36% (CI 35–38%) for a modified invitation. The combination of a modified invitation and a reminder letter gave a cumulative attendance of 44% (CI 42–45%), and the combination of a standard invitation with a reminder letter of 41% (CI not reported). Combining a standard/modified invitation, reminder letter, and telephone reminder reached a cumulative attendance of 63/64% showing a marked increase in total achieved attendance with phone reminders, but no evidence of a significant difference caused by the modified invitation (Eaker et al 2004).

Another Swedish study randomized 8,000 women with no record of participation in screening in 6-8 years to a telephone reminder arm or a control group. Participation during the following 12 months was significantly

higher with a telephone reminder than in the control group, 718 (18.0%) versus 422 (10.6%; RR 1.70, CI 1.52–1.90) (Broberg et al 2013).

In the UK, women aged 45-65 with no previous smears were randomized either to receive an open invitation with two similar reminders (n=125), or a letter with a pre-assigned appointment with two similar reminders (n=125). Participation rate in the group with pre-assigned appointments in letters increased from 36% after primary invitation to 44% after second invitation and 47% with third letter. In the group with open invitations, participation increased from 21% to 28% to 32%, respectively (Wilson & Leeming 1987). In another randomized study from the UK among women who had not been screened in the previous 15 years despite the automated call-recall system, a letter from the public health doctor (13/285 attended) was more influential in persuading them to have a cervical smear than either a telephone call (4/285), a letter from a celebrity (5/285) or taking no additional action (4/285) – although this difference was not statistically significant (Stein et al 2005).

In two Italian studies, a postal reminder to non-attendees after the primary invitation increased total attendance from 25 to 32% (Segnan et al 1998) and from 31 to 42% (Ronco et al 1994). In France, 10,662 non-attendees after a primary invitation were randomized to receive either a reminder letter or a telephone call. Uptake at 8 months was 6.3% (CI 5.6-7.0%) for telephone calls, and 5.8% (CI 5.2-6.4%) for letters (Heranney et al 2011). However, another study from France observed no difference in uptake after 9 months among non-attendees who were randomized to receive a reminder letter (11.7%) and a control group with no intervention (9.9%; OR 1.20, CI 0.98-1.47) (Haguenoer et al 2014).

In a study from the USA by Vogt and colleagues (2003), women who were members of a specific managed care organization in Oregon and had no record of a Pap smear in three previous years, were randomized to a) an open invitation with a screening brochure, and a reminder letter or b) similar invitation followed by a telephone call, or c) two phone calls, or d) no systematic contact (control). After 12 weeks, the participation rate among women in the control group was 16%. Among all women allocated for the interventions, total participation rose from 12% to 16% with the letter-letter approach, from 23% to 32% with the letter-phone call approach and from 25% to 27% with the phone call-phone call approach (Vogt et al 2003).

In Australia, 90,000 women with no record of a smear in four years despite automatic reminders from their GP and the screening register were randomized to receive or not to receive another reminder letter. Within a three month follow-up, a smear was recorded from 4% of those women who received a reminder letter and from 2% of those that did not. The difference was small but significant (RR 1.53, CI 1.42-1.65) (Morrell et al 2005).

In Helsinki, Finland the attendance rate was 60-63% in 1990-1995 but increased to 71% when a reminder letter to non-attendees was introduced in 1996 (Tarkkanen et al 2000).

6.3.4 Educational interventions

Personal educational interventions on the essence and benefits of screening might consist of educational printed or video materials and discussions face-to-face or over the telephone. Interventions targeting a larger population include different types of media campaigns and community teaching, for example.

Screening guidelines recommend the use of a leaflet with additional information to accompany the invitation letter (Arbyn et al 2008). However, published evidence on the consequences of such a leaflet is scarce and the effect seems to be limited. In a Swedish randomized study with large sample sizes (>6,000 per arm) among women with no smear in the last three years, an additional information brochure with the standard invitation did not increase attendance compared with the standard invitation letter only (difference 1.3%; CI -0.3-2.9%) (Eaker et al 2004).

The use of large mass media (television) campaigns has been evaluated in a cluster trial in Australia by Byles and colleagues (1994). The use of a) television media only, b) television media combined with personal letter based recruitment, and c) television media combined with education for GPs were compared in a rural locality, a country town and a major rural centre. All three interventions were associated with significant increases in the number of women attending for screening when compared to those observed in the control regions, also among under-screened women. The increase in attendance within a specific area was further compared to the expected increase (based on previous increase within the area); television media alone was associated with a significant increase in attendance only in the rural centre, and the media/letter based campaign in both rural areas. A media/GP education based campaign was associated with significant increases in attendances in all three regions (Byles et al 1994).

Several studies have been conducted specifically among minority groups or in the context of service providers serving mainly minority groups. However, all of the studies within minority groups to be described below were conducted in settings without a systematic invitation (call-recall) system and the results might thus not be generalizable to such settings. The following methods have shown some effect in increasing attendance: face-to-face counselling at home visits in addition to written and audio-visual culturally sensitive education material (McAvoy & Raza 1991, Taylor et al 2002), culturally sensitive educational videos on breast and cervical cancer screening played in the waiting rooms of medical clinics (Yancey et al 1995), and the combination of tailored print materials and telephone counselling (Rimer et al 1999). Solely mailing education material was not effective (McAvoy & Raza 1991, Rimer et al 1999), nor was a media-led community education campaign even though it succeeded in increasing recognition of and intention to undertake screening tests (Jenkins et al 1999).

All in all, the effects of educational interventions seems limited, and indeed, the most recent Cochrane review on interventions to increase

attendance to cervical screening only found evidence to support the use of an invitation letter, and limited evidence to support the effectiveness of the use of educational materials (Everett et al 2011).

6.3.5 Interventions aimed at health care workers

In the UK, where the screening system is organized around general practices, Pierce et al. (1989) conducted a randomized study comparing a written invitation to screening to a notification attached to the patient record of women who are overdue for their screening, so that the GP would remember to encourage the women to make an appointment for screening. A third group acted as a control group. Both of the interventions increased screening attendance in one year, but differences between interventions were non-significant (32% attendance rate with a letter, 27% with physician reminder) (Pierce et al 1989). Similar results of no difference between an invitation letter and a reminder for the GP were also seen in other studies (Pritchard et al 1995, Binstock et al 1997, Burack et al 1998).

In the previously mentioned study on the effects of a mass media campaign (page 27), one of the intervention arms included predisposing GP's to work-shops that aimed at enabling the general practitioners to develop acceptable strategies for use in their community, and to support the implementation of adopted strategies through, for example patient education materials, feedback, and peer support. This GP based campaign in combination with the mass media campaign was the most effective approach in increasing attendance, but it was not examined as a sole intervention (Byles et al 1994).

6.4 Self-sampling for HPV-testing

As hrHPV tests are sensitive in detecting pre-malignant alterations in the cervix with higher negative predictive values than cytology, this method is now considered as an adjunct or an alternative to cytology as a screening method (Leinonen 2013, Ronco et al 2014). HPV-testing further has the advantage of allowing analysis on self-sampled exfoliated cells. Offering self-collection of cervicovaginal material for hrHPV-testing in a laboratory (hereafter referred to as self-sampling) has been suggested to be a new screening alternative for women who are reluctant or unable to attend a health-care facility for routine cervical cancer screening.

Cytologic analysis on self-taken samples has shown inconsistent results. Compared to provider-collected samples, the reported sensitivities for cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) in self-collection techniques range from 42% to 75% and specificities from 81% to 93% (Nobbenhuis et al 2002, Garcia et al 2003, Brink et al 2006, da Silva Rocha et al 2012, Jones et al 2013). One study found that only 1% of self-

lavage specimens were unsatisfactory for cytology reading; however, transformation zone cells were present on only 18% of self-lavage specimens compared to 93% of clinician-collected specimens from the same patients (Jones et al 2013).

6.4.1 Sampling devices

The devices used for self-taking a sample for HPV-testing that have been described to date include brushes, lavage devices (include a liquid for rinsing the sample from vaginal walls), swabs, tampons and urine samples. A recent meta-analysis found no obvious collection device effects in the relative clinical sensitivity of hrHPV-testing on self-samples versus clinician-taken samples (Arbyn et al 2014b).

Self-sampling devices found most commonly in the current literature are listed in Table 1. Most of the studies chosen as reference were selected because they have also evaluated the sensitivity and specificity of the used combination of a sampling device and HPV-assay (discussed in a later section on page 36), or otherwise describe the sampling method in more detail.

Some of the devices used for self-sampling are originally developed for sampling by clinicians, but the following ones are especially developed for self-sampling purposes:

The Evalyn® Brush (Rovers medical devices B.V., Oss, Netherlands) was developed as a self-sampling device on the basis of the VibaBrush® (Rovers medical devices B.V., Oss, Netherlands) used for clinician-sampling. The device has the same brush, but the core has wings indicating a standard depth of insertion and clicking sounds announce the number of rotations to facilitate sampling. Following collection, the brush retracts inside the core of the device, a cap is snapped back onto the applicator and the specimen can be transported dry to the laboratory (van Baars et al 2012a).

The Qvintip® self-sampling device (Aprovix AB, Uppsala, Sweden) is a plastic wand with a similar shape to that of a cotton/dacron swab. The head of the device is broken into a dry tube for transportation (Wikström et al 2011).

The POI/NIH self-sampler with a flocked nylon head and a cardboard tampon like introducer was designed to obtain a larger specimen more selectively from the upper vagina, as the cardboard protects the tip during insertion and removal. However, no evidence was found that the POI/NIH sampler would increase the sensitivity of a self-collected specimen in comparison to a standard conical shaped brush by QIAGEN (Gaithersburg, MD, USA) (Belinson et al 2012). Also the Fournier® self-sampling device (by Arthur M. Fournier) consists of a cardboard tube that houses an ejectable Dacron-tip (Castle et al 2006).

Table 1. Sampling devices used for self-sampling purposes.

Device	Transport media	Analysis method	Reference
Brush devices			
QIAGEN/Digene Cervical Sampler™	STM	HC2	Belinson et al. 2003, Bhatla et al. 2009
	STM	LA	Belinson et al. 2010
	not specified	HC2	Lazcano-Ponce et al. 2011
	careHPV medium	careHPV	Qiao et al. 2008
VibaBrush®	PrecervCyt®	GP5+/6+ PCR	Dijkstra et al. 2012
	FTA elute cartridge	SPF-10 and GP5+/6+ PCR	Geraets et al. 2013
	FTA elute cartridge	PCR	Gustavsson et al. 2011
Evalyn® Brush	dry sample	SPF-10 and GP5+/6+ PCR	van Baars et al. 2012b
	FTA elute cartridge	SPF-10 and GP5+/6+ PCR	Geraets et al. 2013
	FTA elute cartridge	LA	Guan et al. 2013
	PrecervCyt®	HPV-Risk PCR	Hesselink et al. 2014
Cytobrush[1]	saline	PCR	Daponte et al. 2006
APTIMA® cytobrush	APTIMA® specimen transport medium	APTIMA®	Ting et al. 2013
Other unspecified brushes	UCM	HC2	Holanda et al. 2006
	DNA res. sol.	EasyChip®	Twu et al. 2011
Swab devices			
POI/NIH self-sampler	PrecervCyt®	Cervista® and MALDI-TOF	Belinson et al. 2012
	PrecervCyt®	HC2 and APTIMA	Nieves et al. 2013
Dacron (polyester) swab	STM	HC2	Balasubramarian et al. 2010, Belinson et al. 2001, Sellors et al. 2000, Taylor et al. 2011, Wright et
ESwab® (dacron swab)	dry sample	CRT PCR	Eperon et al. 2013
	not specified	HPVDNAChip™	Seo et al. 2006
Cotton swab	saline	MY09/11 PCR	Lorenzato et al. 2002
	STM	HC2	Salmerón et al. 2003
	dry sample	GP5+/6+ PCR	Darlin et al. 2013a
Fournier® device	SurePath™	HC2	Castle et al. 2006
	mouthwash	HC2	Castle et al. 2011
Qvintip®	dry sample	HC2	Stenvall et al. 2007
Lavage devices			
Delphi/Pantarhei Screener®, prev. "Mermaid"	(saline)	GP5+/6+ PCR	Brink et al. 2006
		HC2	Jentschke et al. 2013a
		HC2 and ART PCR	Jentschke et al. 2013b
		HPV-Risk PCR	Hesselink et al. 2014
Tampons			
Unspecified tampons	dry sample	PCR	Khan et al. 2014
	STM	HC2	Longatto-Filho et al. 2012
	PrecervCyt®	MY09/11 PCR	Harper et al. 2002b

[1]Cytobrush by Hospital and Home Care Medical Devices LPD, China
APTIMA= APTIMA® mRNA HPV Assay (Gen-Probe Inc., San Diego, CA, USA)
ART PCR=Abbott RealTime High Risk HPV test (Abbott GmbH & Co. KG, Wiesbaden, Germany)
careHPV=careHPV Test (Qiagen (prev. Digene) Corporation, Gaithersburg, MD, USA)
Cervista® assay by Hologic (Bedford, MA, USA)
CRT PCR=Cobas® 4800 HPV Test, PCR (Roche Diagnostics International Ltd, Rotkreuz, Switzerland)
Delphi Screener® by Delphi Bioscence (prev. Pantarhei)(Scherpenzeel, The Netherlands)
DNA res. sol=DNA reserved solution (10mM Tris–HCl, 1mM EDTA)
EasyChip® HPV Blot by King Car (YiLan, Taiwan)
ESwab® by Copan (Brescia, Italy)
FTA elute cartridge= Indicating FTA elute cartridge (GE Healthcare, Buckinghamshire, UK)
HC2=Hybrid Capture® 2 high-risk HPV DNA test (Qiagen (prev. Digene) Corporation, Gaithersburg, MD, USA)
HPVDNAChip™ by GSI Lumonicsi (Scanarray lite, Ottawa, Canada).
HPV-Risk PCR=HPV-Risk assay (Self-Screen BV, Amsterdam, The Netherlands)

LA=Linear Array® HPV genotyping test (Roche, Pleasanton, CA, USA)
MALDI-TOF=PCR-based mass spectrometry system (BGI-Shenzhen, Shenzhen, China)
PrecervCyt® medium by Hololgic (Bedford, MA, USA)
Qvintip® by Aprovix AB (Uppsala, Sweden)
SPF-10=HPV SPF_{10} PCR-DEIA-$LiPA_{25}$ (Labo Bio-medical Products BV, Rijswijk, The Netherlands)
STM=Specimen Transport Medium™ (Qiagen (prev. Digene) Corporation, Gaithersburg, MD, USA)
SurePath™ by TriPath (Burlington, NC, USA)
UCM=Universal Transport Media™ (Qiagen (prev. Digene) Corporation, Gaithersburg, MD, USA)
Viba-Brush® and Evalyn® Brush by Rovers Medical Devices B.V. (Oss, The Netherlands)

Nobbenhuis et al. first described a lavage-device consisting of an irrigation syringe, a disposable female urine catheter, and a container with 15 ml sterile saline for irrigation (Nobbenhuis et al 2002). The lavage device currently called Delphi Screener® (Delphi Bioscience, Scherpenzeel, The Netherlands; previously Pantarhei Screener®) was first introduced as the 'Mermaid' device (Brink et al 2006). The instrument comes ready-filled with saline. After the insertion of the nozzle into the vagina, the plunger is pushed in order to release the saline via small holes in the nozzle and rinse the upper vagina and the cervix. Then by releasing the plunger, the saline is aspirated back into the instrument with a cell sample. In home-based settings, the sample is then transferred to a plastic container for transportation by pushing the plunger again. The current second generation device has experienced some alteration in shape and lavage volume in comparison to its first generation model, but resulted in equal deoxyribonucleic acid (DNA) yields and comparable hrHPV positivity rates (Verhoef et al 2013).

To avoid the use of a liquid-based medium for transportation of samples, brush samples obtained with the QIAGEN Cervical Sampler™ or the VibaBrush® have been evaluated in combinations with an Indicating FTA Elute cartridge (GE Healthcare, Buckinghamshire, UK) (Gustavsson et al 2011, Geraets et al 2013, Guan et al 2013). The FTA cartridge uses a paper matrix chemically treated to denature and stabilize the DNA in and is infused with an indicator dye that changes colour when the specimen is applied.

6.4.2 HPV-detection on self- versus physician-collected samples

The agreement of HPV-test results on self-collected specimens with clinician-collected specimens has been demonstrated to generally be fairly strong; a summary of some relevant studies can be found in Table 2. If the same HPV-analysis assay has been used for both self- and clinician-obtained samples, agreement rates are often over 80%. Two self-taken samples stored in different transport mediums (dry, in liquid medium, FTA cartridge) have also show good agreement rates (Table 2).

Two meta-analyses have been published on the subject. In 2005, Ogilvie and colleagues conducted a meta-analysis in which they considered results obtained with physician-collected specimens as the gold standard. They made no distinction between hrHPV and low risk HPV (lrHPV). Six studies

Table 2. Studies reporting agreement between self- and clinician obtained samples, or between self-taken samples.

		Self-taken sample			Clinician sample			Agreement		Sensitivity for CIN2+	
Reference	Setting	Device	Assay	Positivity rate	Sampler	Assay	Positivity rate	Agreement rate	kappa	Self	Clinician
Brink et al. 2006	outpatient clinic, n=96	Delphi Screener® (lavage)	PCR GP5+/6+ cytology	61 %	brush	PCR GP5+/6+ cytology	63 %	87 % 60 %	0.71 0.27	92 % 65 %	95 % 84 %
Deleré et al. 2011	follow-up, n=55	Delphi Screener® (lavage)	PCR GP5+/6+ and genotyping	67% (any HPV) 62% (hrHPV) 36% (HPV16)	brush	PCR GP5+/6+	69% (any HPV) 64% (hrHPV) 36% (HPV16)	84 % 84 % 93 %	0.62 0.65 0.84		
	screening, n=101			36% (any HPV) 28% (hrHPV) 17% (HPV16)			31% (any HPV) 27% (hrHPV) 15% (HPV16)	87 % 91 % 94 %	0.71 0.78 0.78		
Jentschke et al. 2013b	colposcopy clinic, n=100	Delphi Screener® (lavage)	ART PCR HC2	37 % 30 %	brush	ART PCR HC2	36 % 31 %	93 % 89 % self vs. self 85% clin vs. clin 83%	0.85 0.74 0.67 0.62	81 % 67 %	54 % 57 %
Sellors et al. 2000	colposcopy clinic, n=200	1. swab (vulva) 2. swab (vagina) 3. urine	HC2	45 % 58 % 35 %	brush	HC2	63 %		0.55 0.76 0.41	62 % 86 % 45 %	98 %
Wright et al. 2000	screening, n=1,415	swab	HC2	21 %	brush	HC2	21 %	82 %	0.45	78 %	89 %
Haguenoer et al. 2014b	screening participants, n=722	swab (dry) swab (in liquid medium)	INNO-LiPA	25 % 26 %	brush	INNO-LiPA	21 %	92 % 90 % self vs. self 93%	0.76 0.71 0.81	89 % 87 %	
Eperon et al. 2013	referral population, n=120	1. swab (dry) 2. swab (in liquid medium)	CRT PCR	54 % 69 %	brush	HC2	54 %	self vs. self: 86% (any HPV) 81% (HPV16/18) 88% (other hrHPV)	0.70	74 % 91 %	70 %

If not otherwise specified, the brush, tampon and swab samples were placed in a liquid medium (STM, UCM) after sampling.

self vs. self = agreement rate between the two self-taken samples; clin vs. clin = agreement rate between the two clinician-obtained samples

ART PCR=Abbott RealTime High Risk HPV test; HC2=Hybrid Capture 2; INNO-LiPA= INNO-LiPA HPV Genotyping Extra (Innogenetics, Ghent, Belgium); CRT PCR=Cobas ® HPV Test

Table 2. Continued

		Self-taken sample			Clinician sample			Agreement		Sensitivity for CIN2+	
Reference	Setting	Device	Assay	Positivity rate	Sampler	Assay	Positivity rate	Agreement rate	kappa	Self	Clinician
Harper et al. 2002	colposcopy clinic, n=103	1. Dacron swab 2. 2 Dacron swabs 3. tampon	GPMY09/11 PCR	31% (hrHPV) 35% (hrHPV) 25% (hrHPV)	1. swab (endoc.) 2. swab (ectoc.)	GPMY09/11 PCR	28% (hrHPV) 31% (hrHPV)	clin vs. clin 88% clin vs. self (sw) 83% clin vs. self (ta) 89% self vs. self: 1 swab vs. 2 swabs 96% all swabs 89% 2 swabs vs. tampon 90% all samples 72%	0.74 0.74 0.63 0.91 0.77	83 % 83 % 83 %	83 %
Stenvall et al. 2007b	referral population, n=43	Qvintip® (dry)	HC2	37 %	brush	PCR (L1 primer)	40 %	70 %	0.36	75 %	100 %
Castle et al. 2006	outpatient clinic, n=135	Fournier®-device	HC2	43 %	brush	HC2	45 %	83 %	0.66		
Castle et al. 2013	screening, n=252 outpatient clinic, n=191	Fournier®-device	LA	55% (any HPV) 27% (hrHPV) 45% (lrHPV)	Dacron swab	LA	42% (any HPV) 18% (hrHPV) 32% (lrHPV)	73% (any HPV) 84% (hrHPV) 75% (lrHPV)	0.48 0.54 0.49		
Gage et al. 2011	screening, n=252 outpatient clinic, n=191	Fournier®-device	HC2 LA Amplicor	18 % 29% (hrHPV+66) 28 %	1. Fournier-device 2. Dacron swab 	HC2 LA Amplicor HC2 LA Amplicor HC2 LA Amplicor	20 % 29% (hrHPV+66) 28 % 20 % 21% (hrHPV+66) 20 %	88 % 84 % 85 % 89 % 82 % 83 % clin vs. clin 90% clin vs. clin 89% clin vs. clin 89%	0.61 0.60 0.61 0.69 0.52 0.52 0.69 0.70 0.69		
Lorenzato et al. 2002	screening, n=253	cotton swab (in saline)	GPMY09/11 PCR	23% (any HPV) 17% (hrHPV)	Ayers spatula and	GPMY09/11 PCR	29% (any HPV) 26% (hrHPV)	80% (any HPV)	0.62 0.60	47 %	74 %

If not otherwise specified, the brush and swab samples were placed in a liquid medium (STM, UCM) after sampling.

self vs. self = agreement rate between the two self-taken samples; clin vs. clin = agreement rate between the two clinician-obtained samples

GPMY09/11 PCR=PCR with MY09/MY11 primers; LA=Linear Array (PGMY09/11 L1 primer PCR assay); Amplicor=AMPLICOR® HPV Test (PCR based)(Roche Diagnostics)

Table 2. Continued

		Self-taken sample			Clinician sample			Agreement		Sensitivity for CIN2+	
Reference	Setting	Device	Assay	Positivity rate	Sampler	Assay	Positivity rate	Agreement rate	kappa	Self	Clinician
Hesselink et al. 2014	refer. population, n=62 refer. population, n=112	Delphi Screener® Viba-Brush®	HPV-risk PCR HPV-risk PCR	61 % 62 %	brush brush	HPV-risk PCR HPV-risk PCR	68 % 65 %	96 % 92 %	0.90 0.82	96 % 96 %	96 % 94 %
van Baars et al. 2012	outpatient clinic, n=134	Evalyn®Brush (dry)	SPF-10 PCR GP5+/6+		brush	SPF-10 PCR GP5+/6+		86 % 87 %	0.72 0.72	82 % 74 %	89 % 82 %
Dijkstra et al. 2012	outpatient clinic, n=135	VibaBrush®	PCR GP5+/6+	63% (hrHPV) 39% (lrHPV)	1. Cervex-brush®	PCR GP5+/6+	62% (hrHPV) 37% (lrHPV)	86% (hrHPV)	0.70 (hrHPV) 0.81 (HPV16) 0.92 (HPV18)	93 %	91 %
					2. Viba Brush®	PCR GP5+/6+	49% (hrHPV) 40% (lrHPV)		0.79 (HPV16) 0.85 (HPV18)		
Lenselink et al. 2009	1. referral population, n=45	VibaBrush® & FTA cartridge	SPF-10	62% (any HPV) 44% (hrHPV) 29% (lrHPV)	brush	SPF-10	60% (any HPV) 38% (hrHPV) 22% (lrHPV)	93 % 93 % 93 %	0.86 0.86 0.83		
	2. self-sampling at home, n=51	1. VibaBrush® & FTA cartridge	SPF-10	26% (any HPV) 18% (hrHPV) 14% (lrHPV)				self vs. self: 100% (any HPV) 100% (hrHPV)	 1.00 1.00		
		2. VibaBrush®	SPF-10	26% (any HPV) 18% (hrHPV) 14% (lrHPV)				96% (lrHPV)	0.83		
Geraets et al. 2013	referral population, n=182	VibaBrush® & FTA cartridge	SPF-10 PCR GP5+/6+	68% (hrHPV) 63% (hrHPV)	brush	SPF-10 GP5+/6+ PCR	75% (hrHPV) 63% (hrHPV)	89 % 82 %	0.73 0.64	96 % 88 %	100 % 98 %
Guan et al. 2013	63 VIA+ women and 111 VIA- women	Qiagen brush & FTA cartridge	LA	30% (any HPV) 24% (hrHPV)	Qiagen brush & FTA	LA	32% (any HPV) 25% (hrHPV)	91 % 91 %	0.80 0.75	 78 %	 100 %
Ting et al. 2013	all cytology ≥HSIL cytology <HSIL	APTIMA® brush	APTIMA®	29 % 79 %	brush	APTIMA®	30 % 86 %		0.59 0.76 0.55		

If not otherwise specified, the brush and swab samples were placed in a liquid medium (STM, UCM) after sampling.

self vs. self=agreement rate between the two self-taken samples; clin vs. clin=agreement rate between the two clinician-obtained samples

HPV-Risk=HPV-Risk assay (PCR based, targets E7-region); SPF-10=HPV SPF10 PCR-DEIA-LiPA25; APTIMA= APTIMA® mRNA HPV Assay

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using swabs or brushes in self-sampling were pooled and had an overall sensitivity of 0.74 (CI 0.61-0.84) and specificity of 0.88 (CI 0.83-0.92) to detect HPV DNA (Hillemanns et al 1999, Sellors et al 2000, Wright Jr et al 2000, Rompalo et al 2001, Harper et al 2002a, Lorenzato et al 2002). Sensitivity and specificity were somewhat higher in the pooled analysis of studies conducted in referral clinics (0.81, CI 0.65-0.91 and 0.90, CI 0.80-0.95, respectively). Sensitivity for PCR ranged from 0.63 to 1.00 and specificity from 0.80 to 1.00. Sensitivity for Hybrid Capture 2 (HC2, QIAGEN) ranged from 0.56 to 0.93 and specificity from 0.79 to 1.00 (Ogilvie et al 2005).

In 2007, Petignant and colleagues conducted a meta-analysis of 18 studies (5441 participants) published in 1966-2005. In all included studies, the participants served as their own controls and any positive test was considered as reference standard. The referred studies used a tampon (Fairley et al 1992, Harper et al 2002a, 2002b), dacron swab (Sellors et al 2000, Wright Jr et al 2000, Gravitt et al 2001, Rompalo et al 2001, Kahn et al 2004, Petignat et al 2005), cotton swab (Chang et al 2002, Lorenzato et al 2002), cytobrush (Hillemanns et al 1999, Dannecker et al 2004, Agorastos et al 2005, Baldwin et al 2005), or a cervicovaginal lavage (Morrison et al 1992, Nobbenhuis et al 2002) as sampling devices, and HPV DNA was detected with HC2 or a variety of polymerase chain reaction (PCR) protocols. The level of concordance between self- and physician-sampling for detection of HPV DNA was 0.87 (CI 0.82-0.91; kappa 0.66, CI 0.56-0.76). When analysis was restricted to hrHPV detection, the average detection rate was 30.5% – the gain in detection yield from physician sampling was 6.4% compared with self-sampling alone, and the gain of self-sampling was 5.7% compared with physician-sampling alone. Three studies (n=530) evaluated lrHPV detection and all reported an increased detection rate of lrHPV in self-obtained samples (Kahn et al 2004, Baldwin et al 2005, Petignat et al 2005).

6.4.3 Clinical sensitivity and specificity

In a recent meta-analysis from 2014, Arbyn and colleagues evaluated the accuracy of hrHPV-testing with self- versus clinician-collected samples to detect underlying CIN2+ lesions. They included 36 studies from years 1990-2013 (154,556 tested women) in a variety of clinical settings (Arbyn et al 2014b). In the included studies histological confirmation on the presence or absence of CIN lesions was confirmed by colposcopy among all enrolled women or among women with at least one positive screening test. Of the 36 studies, 16 were conducted in a primary screening setting in the countries of South Africa (Wright et al 2000), China (Belinson et al 2001, 2012, Qiao et al 2008, Zhao et al 2012, Guan et al 2013), Mexico (Salmerón et al 2003, Lazcano-Ponce et al 2011, Nieves et al 2013), Brazil (Girianelli et al 2006, Holanda et al 2006, Longatto-Filho et al 2012), Argentina (Longatto-Filho et al 2012), UK (Szarewski et al 2007) and Sweden (Wikström et al 2011). Three

studies were conducted among high-risk populations in Brazil (Lorenzato et al 2002), India (Bhatla et al 2009) and the USA (Balasubramanian et al 2010), and 17 among women referred for colposcopy due to previous abnormal test results in USA (Morrison et al 1992, Garcia et al 2003), Mexico and Peru (Garcia et al 2003), Germany (Hillemanns et al 1999, Jentschke et al 2013a, 2013b), Canada (Sellors et al 2000), Netherlands (Nobbenhuis et al 2002, Brink et al 2006, Dijkstra et al 2012, van Baars et al 2012b), Greece (Daponte et al 2006), Korea (Seo et al 2006), Sweden (Gustavsson et al 2011, Darlin et al 2013a), Taiwan (Twu et al 2011), South Africa (Taylor et al 2011) and Spain (Geraets et al 2013).

Overall, when comparing to cytology, hrHPV self-sampling was as sensitive as cytology at cut-off of atypical squamous cells of undetermined significance (ASC-US) in detecting cervical intraepithelial neoplasia grade 3 or more severe (CIN3+) lesions with relative sensitivity of 0.99 (CI 0.94–1.06), but less sensitive in detecting CIN2+ lesions with relative sensitivity of 0.95 (CI 0.91-0.99). When cut-off of low-grade squamous intraepithelial lesion (LSIL) was used for cytology, hrHPV self-sampling was more sensitive in the detection of CIN2+ (relative sensitivity 1.14; CI 1.07-1.21) and CIN3+ (relative sensitivity 1.19; CI 1.09–1.29). Relative specificities for CIN2+ were lower for self-taken samples when compared to cytology at ASC-US cut-off (0.92, CI 0.90-0.94) and at LSIL cut-off (0.88, CI 0.86-0.90).

When comparing to hrHPV-testing on clinician obtained samples, self-sampling was less sensitive and less specific in detecting both CIN2+ and CIN3+ lesions. The pooled estimates showed that the relative sensitivities were 0.89 (CI 0.83–0.96) for CIN3+ and 0.88 (CI 0.85-0.91) for CIN2+. Relative specificity was also lower, 0.96 (CI 0.95-0.97) for CIN2+ and 0.96 (CI 0.93-0.99) for CIN3+. However, the authors stated that the lower pooled sensitivity for CIN2+ was driven by one study with very low sensitivity of 49% by GPMY09/11 PCR amplification in three colposcopy clinics in the USA, Peru, and Mexico (Garcia et al 2003). When this outlying finding was omitted from the analysis, differences in sensitivity were no longer seen (relative sensitivity 0.99, CI 0.96–1.03).

In screening populations, the sensitivity of HPV-testing on self-taken samples ranged between 51% and 93% to detect a CIN2+ lesion and between 63% and 94% to detect a CIN3+ lesion. The absolute pooled sensitivity of a self-taken sample to detect a CIN2+ or CIN3+ lesion was 76% and 84%, respectively, and specificity for excluding a CIN2+ or CIN3+ lesion was 86% and 87%, respectively. The lowest sensitivity (51%) was seen in a study from rural Mexico among 2,049 women using self-taken samples collected with a POI/NIH self-sampler and analysed with HC2 and APTIMA® (Gen-Probe Inc., San Diego, CA, USA) – low sensitivities were observed for both assays (Nieves et al 2013). The authors suspected that the low sensitivity was affected in large part by participants' low understanding of the instructions of how to obtain an adequate sample. The highest sensitivity was seen in a study among 8,556 women from China, comparing two different samplers,

the POI/NIH brush sampler and a brush by QIAGEN, with two different analysis methods, Cervista® (Holologic, Bedford, MA, USA) and PCR-based MALDI-TOF. Both samplers resulted in high sensitivities (91% and 89% for CIN3+) when samples were analysed with MALDI-TOF, whereas analyses with Cervista® resulted in lower sensitivities (72% and 70%) (Belinson et al 2012). Further, the sensitivity for CIN3+ of the self-collected specimens obtained with either sampling device and tested by MALDI-TOF (94.3%) was virtually the same as that of the clinician-collected specimens tested by MALDI-TOF (94.3%) or Cervista® (95.0%). In another comparison of two analysis methods, the Abbott RealTime High-Risk HPV Test (Abbott GmbH & Co. KG, Wiesbaden, Germany) was compared to HC2 on self-collected samples with the Delphi Screener®. The sensitivity and specificity for CIN2+ of RealTime/HC2 were 81%/67% and 54%/57%, respectively (Jentschke et al 2013b).

Indeed, a notable finding in the meta-analysis by Arbyn et al. was the heterogeneity between HPV-testing methods. When PCR-based HPV tests (GP5+/6+ primers or Abbot RealTime) were used on self-taken samples with brushes or lavage devices, the relative sensitivity and specificity were similar to clinician-collected samples. However, when signal-based assays like HC2, or Cervista®, or the mRNA-assay APTIMA® were used, sensitivity of self-sampling was lower, and for HC2 and Cervista® also specificity was lower. For HC2, relative sensitivity of 0.85 (CI 0.81-0.90) and relative specificity of 0.96 (CI 0.93-0.98) was pooled from 18 studies using brushes, lavage devices, swabs or tampons as sampling devices, and the lower sensitivity was seen for all devices.

The lower sensitivity of self-taken samples analysed with HC2 is in concordance with the finding from a study that compared self-taken brush samples and clinician-taken brush samples from four different sites (endocervical, upper vaginal, lower vaginal, perineal) among women with CIN2+ lesions. The sensitivity of the clinician-obtained endocervical specimens for CIN2+ by HC2 (97.9%) exceeded that of the vaginal self-collected specimens by HC2 (80.9%,), but the sensitivity of the self-taken samples increased to 95.7% when analysed by Linear Array® (LA; Roche, Pleasanton, CA, USA) which has a lower cut point, i.e. it can detect lower viral loads in a sample (Belinson et al 2010). The analysis revealed a lower mean HC2 signal strength in the self-collected samples and clinician-collected vaginal samples compared to clinician-collected endocervical samples. The authors speculated that the vaginal self-collected samples either obtain a smaller amount of specimen or the cells in the vagina have a lower viral load per cell, which becomes relevant with the less sensitive analysis methods such as HC2 or Cervista®.

It has also been speculated that the cross-reaction of HC2 with low-risk HPV-types found in excess in the vagina could partially explain the lower specificity of self-taken samples (Castle et al 2002, 2007, 2008b). However, in the previously mentioned study, Belinson and colleagues (2010) found

similar proportions of self-taken and clinician-taken samples that tested positive by HC2, and negative for hrHPV but positive for lrHPV with LA, and thus cross-reactivity attributed only to six of the 41 excess false-positive self-collected hrHPV results. The principal cause of lower specificity might be that there is hrHPV present in the vagina, which is not associated with hrHPV in the endocervix and this hrHPV present solely in the vagina is not associated with CIN2+ lesions (Belinson et al 2010). Indeed, it has been reported that incident vulvovaginal hrHPV infections are more common than incident hrHPV infections in the endocervix (Winer et al 2009).

The authors of the meta-analysis further estimated pooled positive and negative predictive values (PPV and NPV) for CIN3+ on three screening situations with low (0.25%), medium (0.5%), and high (2%) prevalence of CIN3+ lesions. A NPV of 1% after a negative test was regarded as reassuring, whereas a PPV of 10% after a positive test would indicate a referral as being appropriate. A negative screening test yielded a low risk (<1%) of underlying CIN3+ immediately after testing in all cases, but in high-risk populations, the future risk in 5 years exceeded 1% after a negative HC2 test on self-takne sample and after a negative cytology result on a clinician sample. The cross-sectional PPVs on self-taken and clinician-taken samples were usually lower than 10% in low-risk and medium-risk populations, indicating the need for a triage test before referral to colposcopy. In high-risk populations, the PPV for CIN3+ was higher than 10% when using cytology or hrHPV-testing on clinician samples, and also on self-taken samples for MALDI-TOF, but not for HC2 (Arbyn et al 2014b).

Urine samples for hrHPV-detection have been evaluated in smaller clinic-based studies. The sensitivity for CIN2+ has ranged from 45% by HC2 to 81% by PCR and specificity from 53% by PCR to 70% by HC2 (Sellors et al 2000, Sahasrabuddhe et al 2013).

6.4.4 Impact on screening attendance

Table 3 summarizes the characteristics and results of 18 studies using self-sampling in mail-based home sampling settings as an intervention to increase attendance among non-attendees to routine screening programmes.

Eleven studies were conducted in a randomized setting with self-sampling compared to another intervention, usually a reminder letter (Table 3). In general, and across studies, HPV self-sampling results in better participation than a recall for regular cytological testing. Seven studies offered self-sampling to all non-attendees. Self-sampling was offered with one of the three mailing approaches: by mailing it to all women in the study group (direct mailing), or with an opt-out option meaning they received a letter prior to mailing the test and could decline, and self-sampling was sent only to women who did not opt out, or with an opt-in approach, where the sampling device was available upon request.

Self-sampling was used as a first reminder among non-attendees after one invitation to screening in randomized studies conducted in Italy (Giorgi Rossi et al 2011) and France (Piana et al 2011, Sancho-Garnier et al 2013, Haguenoer et al 2014). If the self-sampling device was directly sent to all women in the study cohort, or with an opt-out option, participation rates ranged between 18% and 23%. In the Italian study, some women were randomized to an opt-in arm - in this group the participation rate was only 9%. Participation with the reminder letter ranged from 2% to 18% and was significantly lower than that achieved by self-sampling in all studies, with the exception of the Italian study arm with self-sampling offered on demand (opt in).

Self-sampling was used as a second reminder among non-attendees after two invitation letters in the studies from the Netherlands (Bais et al 2007, Gök et al 2010, 2012b, Verhoef et al 2014a, Bosgraaf et al 2015). In these studies, the participation rate by self-sampling was 28-34%, and participation by a second reminder letter 7-18%.

The Swedish studies are not directly comparable to the studies using self-sampling as first or second reminder after invitation letters, because in the Uppsala and Western Sweden regions women are invited for screening every third/fifth year only if they have no opportunistic smears taken within that time, and non-attendees receive additional annual invitation letters. In these settings, participation rates to self-sampling with an opt-in approach have ranged between 25-39%, and by direct mailing 39-54%. Of note, two of the studies using the opt-in approach also sent reminders to those women who had not ordered the device and/or had not returned a self-taken sample after the order (Sanner et al 2009, Broberg et al 2014), as did one of the studies using a direct mailing approach (Wikström et al 2011). Attendance was significantly higher with self-sampling than with reminder letters (Wikström et al 2011, Broberg et al 2014) or with a telephone reminder (Broberg et al 2013, 2014).

The only study thus far to compare participation rates by two different devices in a randomized setting was conducted in the Netherlands. When non-attendees to routine screening were randomized to receive either the Evalyn®Brush or the Delphi Screener®, the absolute difference in participation rates was 2.7% (CI 1.8–4.2%) in favour of the Evalyn®Brush (Bosgraaf et al 2015).

HrHPV-positivity rates among self-sampling participants varied between 5.2% and 25.6% when samples were analysed with HC2 and between 6.2% and 17.6% when analysed with PCR-based methods. Compliance rates to further examinations by direct colposcopy for all hrHPV-positive women have varied between 85% and 100%. When hrHPV-positive women were invited/referred for a Pap smear, generally 70-98% of women complied. Two studies in France had lower compliance rates to Pap smears, 41% (Sancho-Garnier et al 2013) and 62% (Piana et al 2011).

Table 3. Studies on offering mailed hrHPV self-sampling to non-attendees of cervical screening programs

			Self-sampling								Control intervention			
Reference (country)	Inclusion criteria	Age group, years	n	Direct mailing/ opt-in/ opt-out	**Response rate**	Sampling device	HPV-assay	HrHPV-positivity rate	Follow-up for hrHPV+ women (compliance)	CIN2+ rate[1]	Control intervention	N of invitees	**Response rate**	CIN2+ rate[1]
RANDOMISED STUDIES														
Giorgi Rossi et al. 2011 (IT)	No smear in ≥3 y, 1 invitation	35-65	622	A) direct mailing	**20 %**	Delphi Screener® (lavage)	HC2	20.1 %	direct colposcopy (91%)	0.0 %	C) reminder letter (cytol.)	619	**14 %**	0.0 %
			622	B) opt-in	**9 %**						D) reminder letter (HPV)	617	**15 %**	
Piana et al. 2011 (FR)	No smear in ≥2 years, 1 invitation	35-69	4,400	opt-out	**21 %**	swab	PCR-based	6.2 %	Pap-smear (62%)	0.5 %	reminder letter	4,934	**6 %**	1.0 %
Sancho-Garnier et al. 2011 (FR)	No smear in ≥2 y, 1 invitation	35-69	8,829	direct mailing	**18 %**	Darcon swab (+UTM)	Abbot Real Time	17.6 %	Pap-smear by GP (41%)	0.7 %	reminder letter	9,901	**2 %**	1.0 %
Haguenoer et al. 2014 (FR)	No smear in >3 y, 1 invitation	30-65	1,999	direct mailing	**23 %**	nylon swab (dry)	PCR-based	13.8 %	Pap-smear (91%)	1.1 %	A) no intervention	1,999	**10%**	0.5 %
											B) reminder letter	2,000	**12%**	0.4 %
Bais et al. 2007 (NL)	No smear in ≥5 y, 2 invitations	30-50	2,546	direct mailing	**34%[2]**	Viba Brush® (+UCM)	PCR (GP5+/6+)	8.0 %	direct colpocopy (86%)	1.7 %	reminder letter	284	**18%***	ns
Gök et al. 2010 (NL)	No smear in ≥5 y, 2 invitations	30-60	27,792	direct mailing	**28%[2]**	Delphi Screener® (lavage)	HC2	10.3 %	Pap-smear and HPV-testing by GP (89%)	1.3 %	reminder letter	281	**17%***	ns

[1] among participants

Table 3. Continued

			Self-sampling								Control intervention			
Reference (country)	Inclusion criteria	Age group, years	n	Direct mailing/ opt-in/ opt-out	**Response rate**	Sampling device	HPV-assay	HrHPV-positivity rate	Follow-up for hrHPV+ women (compliance)	CIN2+ rate[1]	Control intervention	N of invitees	**Response rate**	CIN2+ rate[1]
RANDOMISED STUDIES														
Gök et al. 2012 (NL)	No smear in ≥5 y, 2	30-60	26,145	direct mailing	**31%[2]**	Viba Brush®	HC2	8.3 %	Pap-smear and HPV-testing by	1.3 %	reminder letter	264	**7%***	ns
Szarewski et al. 2011 (GB)	No smear after ≥2 invitations	25-64	1,500	direct mailing	**10 %**	cotton swab (Qiagen)	HC2	8.3 %	Pap-smear and direct colposcopy (88%)	2.0 %	reminder letter	1,500	**5 %**	1.5 %
Wikström et al. 2011 (SW)	No smear in ≥6 y[3]	39-60	2,000	direct mailing	**39 %**	Qvintip® (dry swab)	HC2	6.0 %	Pap-smear (98%)	1.2 %	reminder letter	2,060	**9 %**	1.0 %
Darlin et al. 2013 (SW)	No smear in >9 y, >5 invitations	32-65	1,000	direct mailing	**15 %**	cotton swab (dry)	Luminex and PCR-based	6.9 %	Pap-smear (70%)	ns	letter with flexible appointments	500	**4 %**	ns
Broberg et al. 2014 (SW)	No smear in >6-8 y, ≥4 invitations[2,4]	30-62	800	opt-in (+reminder)	**25 %**	Qvintip® (dry swab)	HC2	7.0 %	direct colposcopy (100%)	3.1 %	A) reminder letter	4,000	**11 %**	1.7 %
											B) letter and telephone	4,000	**18 %**	1.9 %
NO CONTROL INTERVENTION														
Sanner et al. 2009 (SW)	No smear in ≥6 y[2,3]	30-58	2,829	opt-in (+reminder)	**39 %**	Qvintip® (dry swab)	HC2	6.7 %	Pap-smear, HPV-testing, colposcopy (85%)	2.0 %				
Wikström et al. 2007 (SW)	No smear in ≥6 y[3]	35-55	198	direct mailing	**54 %**	Qvintip® (dry swab)	HC2 or PCR (GP5+/6+)	6.6 %	Pap-smear (71%)	0.9 %				

[1] among participants

[2] adjusted for hysterectomy

[3] Organised screening in Uppsala region: women aged 25–60 years are invited for screening every third year. Non-attendees receive additional invitation letters once a year.

[4] Organised screening in Western Sweden: women aged 23-50/51-60 years are invited for screening every third/fifth year with annual reminders for non-attendees.

Table 3. Continued

			Self-sampling								Control intervention			
Reference (country)	Inclusion criteria	Age group, years	n	Direct mailing/ opt-in/ opt-out	**Response rate**	Sampling device	HPV-assay	HrHPV-positivity rate	Primary follow-up for HrHPV+ women (compliance)	CIN2+ rate[1]	Control intervention	N of invitees	**Response rate**	CIN2+ rate[1]
NO CONTROL INTERVENTION														
Wikström et al. 2007 (SW)	No smear in ≥4 y, 1 invitation	55-60	301	direct mailing	**39 %**	Qvintip® (dry swab)	HC2	5.2 %	Pap-smear (83%)	0.9 %				
Stenvall et al. 2007 (SW)	No smear in ≥6 y[3]	35-50	369	opt-in	**32 %**	Qvintip® (dry swab)	HC2	25.6 %	contact gynecologist (70%)	0.9 %				
Lindell et al. 2012 (SW)	No smear in >6 y[2]	50-65	3,618	opt-in	**39 %**	Qvintip® (dry swab)	HC2	4.6 %	direct colposcopy (85%)	0.7 %				
Verhoef et al. 2014 (NL)	No smear in ≥5 y, 2 invitations[5]	33-63	46,001	opt-out	**28 %**	Delphi Screener® (lavage)	PCR (GP5+/6+)	8.1 %	A) Pap-smear (98%) B) methylation analysis (100%)	1.3% A:75/518 B:90/520				
Bosgraaf et al. 2014 (NL)	No smear in ≥5 y, 2 invitations	33-63	A) 15,077	opt-out	**35%[6]**	Evalyn® brush (dry)	PCR (GP5+/6+)	8.3 %	Pap-smear (96%)	2.0 %				
			B) 15,053	opt-out	**32%[6]**	Delphi Screener® (lavage)	PCR (GP5+/6+)	8.3 %	Pap-smear (97%)	1.9 %				

[1] among participants

[2] adjusted for hysterectomy

[3] Organised screening in Uppsala region: women aged 25–60 are invited for screening every third year. Non-attendees receive additional annual invitation letters.

[5] women with previous hysterectomy and a history of CIN2 or worse, or abnormal cytology in the preceding 2 years excluded

[6] Participation rates and numbers of invitees after opt-out. Total participation among all women included in the study was 10,027/35,477=28%

6.4.5 Costs of offering self-sampling to non-attendees of screening

Three studies have made cost estimates for offering self-sampling to the non-attendees of the screening programme.

Haguenoer and colleagues (2014) calculated incremental cost-effectiveness ratios (ICERs) per extra screened woman by self-sampling, by a reminder letter, or without any extra intervention by dividing the between-strategy cost difference by the between-strategy number of screened women. The ICER per extra screened woman by self-sampling was estimated at 63.2 euros and 77.8 euros by reminder letter. The authors concluded that the self-sampling strategy could be cost-effective as compared with a reminder letter if using an inexpensive self-sampling device (2.3 euros in the estimate), as additional costs of the self-sampling strategy were offset by the substantial difference in participation (23 versus 10%) (Haguenoer et al 2014).

In the Netherlands the total costs per CIN2+ lesion detected by self-sampling were estimated to be in the same range as those calculated for conventional cytological screening (8,836 euros vs. 7,599 euros) (Bais et al 2007). This included organizational cost, costs involved with testing (with a price of 2 euros for the self-sampling device) and costs for diagnosis and treatment.

In Sweden total costs per additional detected and eradicated case of CIN2+ was calculated to be 2,670 euros for reminder letter, and 3,003–4,660 euros for self-sampling with an opt-in approach (including treatment and follow-up) (Broberg et al 2014). By applying a ratio of six treated CIN2+ lesions to avert one cancer, the authors concluded this intervention would likely be cost-saving and at least cost neutral.

6.4.6 Self-sampling in low-resource settings

In developing countries, cervical cancer is one of the leading causes of female cancer death, but basic health care services are often lacking or inaccessible resulting thus in significant barriers for preventive care implementation (IARC 2005). Self-sampling has been studied as a screening alternative in low- and middle-income countries that have failed to successfully introduce cytological testing. A key feature of the self-sampling strategy with HPV-testing is the move of the primary screening activities from the clinic to the community (Gravitt et al 2011). As these settings differ markedly from the current study, studies in low-resource settings are not discussed in detail. However, self-sampling has been used as a screening tool for example as a part of mother-child prevention study in Peru (Levinson et al 2013), in a community-based setting in India (Sowjanya et al 2009), in a home-based setting in rural Mexico (Lazcano-Ponce et al 2011), and combined with home visits by community health workers in Argentina (Arrossi et al 2015). In rural China self-sampling was more sensitive and less

specific than VIA and liquid based cytology but less sensitive and similarly specific compared with physician HPV-testing (Belinson et al 2001, 2003, 2010, Zhao et al 2012). It was concluded that hrHPV-testing by self-sampling is significantly more effective than the World Health Organization (WHO) recommended VIA at detecting CIN2+ and CIN3+ lesions, as unlike VIA, it provides age-, practitioner- and training independent sensitivity (Zhao et al 2012).

6.4.7 Acceptability among women

Acceptability of self-sampling, in the meaning of women's experience of the procedure, not solely response rate, has been previously studied by focus group discussions and surveys with self-sampling being introduced but not necessarily used by the participants (Forrest et al 2004, Sanchaisuriya et al 2004, Barata et al 2008, Howard et al 2009, Szarewski et al 2009, Mitchell et al 2011, Berner et al 2013, Cadman et al 2014, Mullins et al 2014), and in comparison to a Pap smear among screening participants or patients at a clinic (Dzuba et al 2002, Nobbenhuis et al 2002, Anhang et al 2005, Waller et al 2006). Some studies among non-attendees to screening who have been offered the self-sampling option have gathered information on the women's preferences for self-collection or clinician-collection and the reasons for their preference (Wikström et al 2007a, Giorgi Rossi et al 2011, Bosgraaf et al 2014). Only one previous study thus far has explored more specific aspects of user-friendliness of a home-based self-sampling procedure in a population-based setting among non-attendees (Bosgraaf et al 2015). Pain, discomfort, degree of embarrassment, level of privacy and ease of use and trust or confidence in the results are commonly measured as parameters for acceptability.

In the studies that described women's preferences after the women experienced both self- and clinician sampling, a commonly reported concern was that women were unsure if they had taken the sample properly and the women had greater confidence in the accuracy of the clinician sampling (Anhang et al 2005, Dzuba et al 2002, Waller et al 2006). For example in the UK, when women rated aspects of acceptability, clinician-testing resulted in higher mean scores on embarrassment, anxiety, discomfort and unpleasantness than self-testing, but clinician-testing scored higher on confidence that the test was done properly (Waller et al 2006). Similarly in Mexico, the Pap test consistently provoked more discomfort, pain, and embarrassment than self-sampling (Dzuba et al 2002). These studies also found differences in attitudes to self-sampling between different socio-economic groups. In the USA, preference for self-sampling was more common among women with higher levels of income and education (Anhang et al 2005), and in the UK single and separated women had more negative attitudes towards self-sampling than married women (Waller et al 2006). In

Mexico, preference for self-sampling over clinician-sampling was positively associated with monthly household income (Dzuba et al 2002).

Ethnicity seems to be a factor in participation to routine screening (Hsia et al 2000, Maxwell et al 2001, Coughlin et al 2002, Hewitt et al 2002, Sabates & Feinstein 2006, Moser et al 2009, Bang et al 2012, Kristensson et al 2014), but knowledge on how ethnicity affects self-sampling acceptability is quite scarce and inconclusive, and none of the previously published studies addressing this matter are conducted specifically among non-attendees to routine screening. Among non-attendees to routine screening in the Netherlands it was noticed that uptake of self-sampling was lower among immigrants than among native-born Dutch women. Reasons for this were not explored (Gök et al 2012a). Focus-groups discussions have been conducted among ethnic minority groups in the UK and Canada – again, concerned about not doing the test correctly was the main concern in self-sampling and the majority preferred clinician-sampling (Forrest et al 2004, Szarewski et al 2009, Cadman et al 2014). Very few (2%) women of Indian, Pakistani, African-Caribbean and white British origin reported that using the self-test would go against their cultural or religious beliefs, and there were no differences between ethnic groups on this item (Forrest et al 2004). In a Canadian focus-group study among Canadian-born, Arabic, Chinese, Somali, Afghani and Hispanic women, perceptions of self-sampling were similar across cultures and pertained to two significant barriers to self-collection: the women's concerns that they would not take the sample properly, and their fear of experiencing pain. Only Chinese women linked the lack of acceptance to a cultural issue, mainly in relation to their lack of tampon use (Howard et al 2009). In the UK, Asian women had more negative attitudes than women in other ethnic groups (Waller et al 2006).

Ease of use, convenience (faster, could be done at home on one's own time), comfort or the procedure being less painful, "could do it myself", privacy and less embarrassment have been described as desirable characteristics of the self-sampling procedure (Anhang et al 2005, Jones et al 2012, Mullins et al 2014). A Canadian focus group study using a health behavioural model found that uncertainty over doing the test properly and worries on test accuracy were the main reason for the preference for physician sampling, but reduced discomfort and embarrassment by avoiding the gynaecological exam were seen as potential benefits of self-sampling (Barata et al 2008). The authors concluded that self-sampling provides a different benefits-minus-barriers equation to that of Pap-testing, which might make it a preferred screening option for some, but not all, women, and if self-sampling were to be implemented, it should be optional, not a replacement for clinician-testing.

Studies on offering self-sampling to the non-attendees to routine screening have also explored the perceived benefits of self-sampling as reported by participants. In Sweden, the most often mentioned benefits of the home sample among self-sampling participants were that it was easy for

practical reasons (no time limits, that they did not have to book time or travel; 93% of participants), time saving (29%), and emotionally easier as they did not have to undergo a gynaecological examination (22%). Both self-sampling participants and non-participants felt uncertain if they had taken, or could take, the sample appropriately (22% and 38%, respectively) (Wikström et al 2007a). In Italy, 88% of self-sampling participants viewed it as easy, and 12% were unsure whether the sample taking was successful (Giorgi Rossi et al 2011). Appreciated features of self-sampling included the do-it-yourself opportunity, privacy, absence of speculum and no need to be undressed in front of doctor. Of self-sampling participants, 78% preferred self-sampling to clinician-testing. Among non-attendees to routine screening in the Netherlands, the most common reasons for accepting the self-sampling offer were being able to do it in their own time setting at home, taking less effort than having a cervical smear, and being able to do it themselves (self-control) (Bosgraaf et al 2014). Reduction of embarrassment was a more significant reason among younger than older women.

Does the acceptability of self-sampling differ between different types of sampling devices? In focus group discussions in North Carolina, the majority of the participants preferred the idea of a cervical brush by QIAGEN (70%), followed by the Fournier® device (67%) and the Delphi Screener® (43%) (Richman et al 2011). Women reported liking the lavage because it seemed easy to use; they liked the Fournier device because of its inviting green colour, and liked the brush because of its small size and familiarity. Women reported disliking the lavage because the liquid seemed messy and unsanitary, disliked the Fournier® device due to the 15–20 recommended turns, and disliked the brush because it was short, and the tip seemed abrasive. Muslim women in the UK reported an overwhelming preference for the QIAGEN swab over the Delphi lavage kit (Szarewski et al 2009), and Hindu women preferred the Dacron swab to the Evalyn®Brush (Cadman et al 2014). However, when out-clinic patients in Italy were randomized to self-sampling either by the QIAGEN Cervical Sampler or by the Delphi Screener®, a higher percentage gave the maximum general acceptability score and a low embarrassment score to the Delphi Screener®. Both self-sampling methods were physically well accepted, not painful, and easy to perform (Igidbashian et al 2011). A comparison of a polyester swab transported dry to a flocked swab transported in liquid medium in Switzerland found no difference between the two in overall acceptability. No differences were reported in ease of use and the testing methods were viewed as equally reliable (Eperon et al 2013). No differences were seen in the acceptability rates between tampons and swabs either (Harper et al 2002a).

The only study thus far comparing acceptance rates and women's views on two different tests in a mail-based setting among non-attendees to the current screening programme was conducted in the Netherlands. Women were randomized to receive either the Evalyn®Brush or Delphi Screener® lavage kit. The Evalyn®Brush resulted in a slightly, but significantly higher

attendance (Bosgraaf et al 2015). The overall rating of the device was good to very good in 97% and 98% of cases in the brush and lavage groups, respectively. However, in each group, 20% of the women were concerned about doing the self- sampling properly. Reports on user comfort, shame, feeling at ease, usability, stress, discomfort and pain did not differ between tests. Overall, most women (80.5%) preferred the self-sampling over a physician-taken smear for a next screening round, while 13% had no preference.

6.5 Screening in Finland: effect and current challenges

In Finland, an organized screening programme based on cytological screening was launched in 1963 and became nationwide in the early 1970's. Since the introduction of the programme, age-adjusted cervical cancer incidence and mortality rates in Finland have been reduced by up to 80% (Hakama & Räsänen-Virtanen 1976, Hristova & Hakama 1997, Anttila et al 1999). In the 1950's and early 1960's before the organized screening programme was launched, the incidence of cervical cancer in Finland was 13-15 cases per 100,000 woman-years (age-adjusted to the world standard population), and mortality 7-9 cases per 100,000 woman-years (Engholm et al 2014). A rapid decrease in both incidence and mortality followed after the implementation of the programme. In 1991, the incidence or invasive cancer was at its lowest, 2.8 per 100,000 woman-years, and mortality 1.7 (Engholm et al 2014). This indicates an overall decrease of 70-80% in the age-adjusted incidence rate, but almost exclusively in squamous cell carcinomas (Nieminen et al 1995).

After 1991, the overall age-adjusted incidence started to rise, and in 1995 it was 61% higher than in 1991, at 4.5 per 100,000 woman-years (Anttila et al 1999). Since then the incidence has remained higher, varying between 3.4 and 4.7 per 100,000 woman-years (Engholm et al 2014). No similar rise has been seen in mortality rates, which have been around 1 per 100 000 woman-years in the last decade.

6.5.1 Coverage of screening in Finland

The coverage of screening invitations among those in the national target group in Finland (women aged 30-60) is excellent, 99%. Participation rate in the organized screening programme has been at approximately 70% in the last decades, but lately with a decreasing trend. Participation is highly age dependent (Finnish Cancer Registry Statistics). In 2011, the total participation rate was 68%, but among women aged 25-30 only 55%. Compliance rose linearly with age, and was 77% among women aged 60-65 (Finnish Cancer Registry Statistics). Participation rate also varies in different

Hospital Districts, between 60% in Åland and almost 80% in Southern Ostrobothnia (Anttila et al 2014).

As the opportunistic smears are not recorded in a common database, exact annual coverage of all smears (organized and opportunistic) among women targeted in screening in that particular year is hard to collect. Overall coverages of Pap smears have been studied in national surveys in the 1990's and in one registry-based study from Helsinki metropolitan area.

In a national health survey in 1997 among 2,500 women aged 15-64 (mean response rate 76%), 52% of women aged 15-24 years, 5% of women aged 25-34 years and only 1% of women aged 35-64 years responded that they had never given a Pap smear (organized or opportunistic) (Helakorpi et al 1997). Of the responders aged 25-64 years 19% reported that they had a Pap smear every year, 53% every 2 to 4 years, 16% about every 5 years and 9% more seldom than that.

Another survey study with systematic sampling of 5,304 women aged 18 years or older from all five hospital districts was conducted in 2000-2001. It reached a good response rate, 87% (Koponen & Luoto 2000). Out of all responders, 74% and out of responders in screening ages (aged 30-64 years) 87% had had a Pap smear within the last 5-years; 83% of women aged 18-29 years, 92% of women aged 30-44 years and with a decreasing proportion as age increased, to 38% among women aged 65-74 years, 19% of women aged 75-84 years and only 7% of women older than that. Age-adjusted 5-year coverage of all Pap smears was highest in the Hospital district of Helsinki and Uusimaa, and among women with higher education level (OR 5.91, CI 4.76–7.33 with lowest education level as reference).

A study combining registry data of opportunistic and organized screening in the Helsinki metropolitan region from 2004-2008 used data from Hospital Discharge Register (public secondary health care), Social Insurance Institution Register of special reimbursements (private health care services), Student Health Service Register (health care services for undergraduate university students), and HUSLAB Pathology Laboratory Register (public primary health care and secondary health care tests) and the Mass Screening Registry (Salo et al 2014). In this study, the overall 5-year coverage of any Pap smears among women aged 25-69 was 87%. Of the Pap smears taken for screening purposes, 40% were taken within the organized program and 60% opportunistically; 5% in secondary health care and 55% opportunistically; 30% in private health care, 22% in public primary health care, and 2% in student health care. (Salo et al 2014).

6.5.2 Current challenges

The rise in cervical cancer incidence observed in the early 1990's occurred mainly among women aged 25-54 (Figure 2), and in most parts of the country (Anttila et al 1999). When the increase was observed, the coverage of invitations and participation rate in screening did not decrease, and neither

did the detection rates of CIN lesions; in fact, the detection rates of CIN2/3 lesions even slightly increased. This suggests for the rise in incidence of invasive cancer to be due to a rise in the biological background risk of developing cervical cancer in the Finnish population. Mainly, HPV-infections and tobacco smoking among women became more prevalent (Laukkanen 2003, Lehtinen et al 2006, Varis & Virtanen 2013). As the sensitivity of the Pap smear in detecting precursor lesions is limited (Nanda et al 2000), this rise in background risk has reflected in higher cancer incidence.

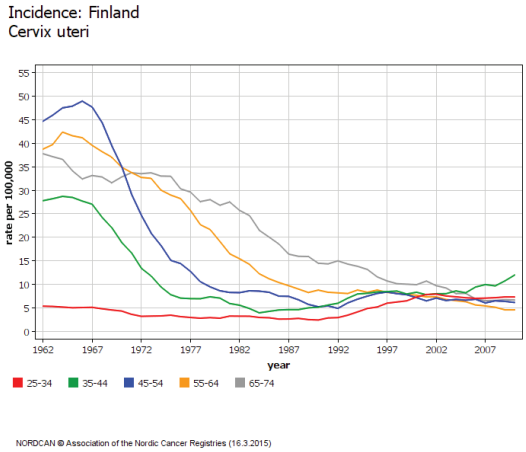

Figure 2 Time trends in cervical cancer incidence in Finland in different age groups. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.0 (17.12.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 16/03/2015

However, as the change in incidence was relatively abrupt to be solely due to biological changes, inadequacies in the effectiveness in the screening programme may have contributed. These inadequacies may include complications in the quality of testing (Nieminen 2002), but also suboptimal attendance to the programme (Finnish Cancer Registry Statistics). This is supported by a finding of a low participation in organized screening within a municipality correlating strongly with a high or increased incidence of cervical cancer (Anttila et al 1999), and further by recent case-control studies that show that invited non-attendees to organized screening contribute to between a quarter to one third of all cervical cancer cases and deaths (Lönnberg et al 2012, 2013).

When the screening programme was launched, opportunistic screening alongside the organized programme started spreading as well. The previously mentioned study by Salo et al. estimated that currently 60% of smears taken in screening purposes and over 70% of screening costs arise from opportunistic screening. Opportunistic screening is especially extensive among young women, and despite the fact that young women targeted by

organized screening have lowest participation rates in the programme, in the Helsinki metropolitan region coverage of any smear was actually highest among women aged 30-35 (Salo et al 2014). Further, 65% of women aged 20–24 had had an opportunistic Pap test taken at least once over the 5-year period – even though national guidelines do not recommend cancer screening below the age of 25 (Current Care Guidelines 2010). Screening at ages 25-30 is associated with a clearly smaller reduction in cancer risk than screening at older ages (Lönnberg et al 2012), but there is currently significant CIN burden among young women (Salo et al 2013), and the first peak in cancer incidence is seen at the age of 30-40 (Figure 3).

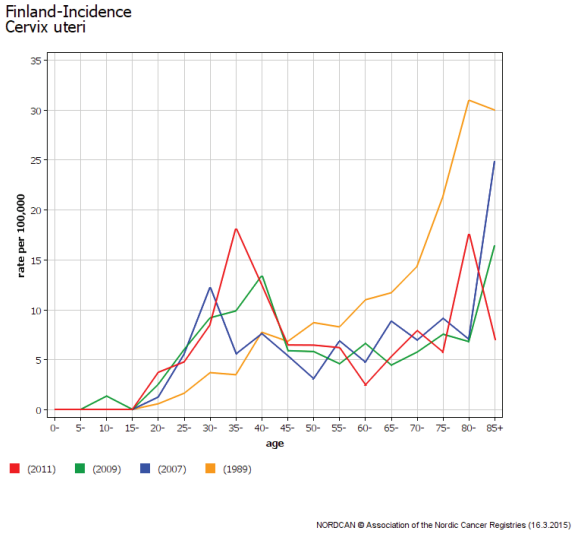

Figure 3 Cervical cancer incidence in Finland by age in 1989, 2007, 2009 and 2011. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.0 (17.12.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 16/03/2014.

As opportunistic smears are not included or taken into account in the organized programme or recorded in common databases, their effects on cancer incidence and mortality are hard to evaluate. A Finnish case-control study did nonetheless indicate that the preventive effect of participating in organized screening was about two-fold higher than the effect of opportunistic screening, 75 vs. 43% (Nieminen et al 1999). Further, opportunistic screening results in significantly higher costs with less benefit that is unequally distributed (Koopmanschap et al 1990a, Salo et al 2013, 2014). With testing done too frequently and from women that are too young to benefit from it (Sasieni et al 2009, Arbyn et al 2010), it can also result in unnecessary harms to psychosocial and reproductive health (Wardle & Pope 1992, Jakobsson et al 2009, Current Care Guidelines 2010, Castanon et al 2014). In order to optimize the cost-efficacy and impact of cervical cancer

screening in Finland and minimize potential harms, a shift from the currently extensive opportunistic screening to organized screening, i.e. a drastic decrease in the number of opportunistic samples and an increase in the attendance to organized screening, is imperative (National Institute for Health and Welfare 2011).

Thus, when tackling the elevated incidence rates, one must optimize cancer prevention from both biological and organizational points of view and aim at a good preventive effect and appropriate balance between harm and benefit. HPV-vaccinations and tobacco education could decrease the background risk, also in young ages where conventional cytological screening has not been shown effective (Sasieni et al 2009). More efficient secondary prevention could be achieved by optimization of the screening programme by introducing more sensitive HPV-testing (National Institute for Health and Welfare 2011, Leinonen et al 2012, Ronco et al 2014) and improving screening attendance in age groups where screening is expected to be effective (National Institute for Health and Welfare 2011, Lönnberg et al 2012).

7 AIMS OF THE STUDY

The aim of this study was to investigate the feasibility and effects of using home-based self-sampling for HPV-testing among the non-attendees of the Finnish cervical screening programme.

The more specific aims were to study:

- The effects of a hrHPV self-sampling test on screening participation, as a first reminder to the non-attendees after the primary invitation, in comparison to a reminder letter

- The effects of a hrHPV self-sampling test on screening participation, as a second reminder to the non-attendees after the two written invitations

- The effects of reminder letters and self-sampling tests on the overall 5-year coverage of screening test (including also opportunistic tests)

- The effect of reminder letters and self-sampling as a first or second reminder on the CIN2+ lesion yield detected by screening

- Women's experience and perceptions on self-sampling (acceptability of the method)

- The costs of adding reminder letters and/or self-sampling to the invitational protocol of screening

- Reason's for non-attendance in traditional screening, as reported by the non-attending women

- Socio-demographic factors related to screening attendance

The results from these evaluations will help to set guidelines on the correct invitational process in cervical cancer screening.

8 MATERIALS AND METHODS

8.1 Cervical screening in Finland

The Government Decree on Screenings (339/2011) states that Finnish municipalities shall organize cervical cancer screening every five years for women aged between 30 and 60 years. This includes the definition of the target group, individual advice and guidance, performing and analysing the screening tests, delivery of feedback information, referral to further examinations and organization of the necessary health services. In addition to the obligatory age groups, some municipalities start inviting women at the age of 25 and/or continue the invitations to the age of 65.

Screening is free of charge to the participants and all women in the defined target group are equally entitled to participate. Previous opportunistic screening does not exclude women from organized screening invitations.

The responsibility to organize screening lies within individual municipalities. Nowadays the municipalities often buy some or all of the components of the screening service from private screening laboratories or other health care providers. Women eligible for screening, in the usual case women of 30, 35, 40, 45, 50, 55 and 60 years of age, are identified from the central population register annually on the basis of the birth-year and home municipality. In addition, those women belonging to a risk group based on the previous abnormal screening results or anamnestic data are invited within one to two years after the previous screening round. Personal invitation letters are usually sent by screening laboratories or local sample takers in the municipalities. The smears are taken in public health centres or maternity/family planning clinics by nurses or midwives, or the municipalities may buy the service from a private service provider. The smears are then analysed in defined laboratories under quality control that are further responsible for feedback information and referring women with abnormal results to local hospitals for further investigations. Diagnostic confirmations, treatments and follow-up are conducted according to national Current Care Guidelines (Current Care Guidelines 2010). Information on screening invitations, performed test, referrals and further investigations are centrally collected and registered in the Mass Screening Registry at the Finnish Cancer Registry. The Mass Screening Registry maintains national databases for all cancer screening programmes, provides annual statistics and evaluates the impact of screening and quality of the programmes.

Every year approximately 270,000 women are invited to cervical screening. Participation rate has been at approximately 70% in the last decades, but lately with a decreasing trend (Finnish Cancer Registry Statistics). As invitations are sent annually to a specific group of women and

are usually valid for that year, the reported participation/compliance rates are proportions of women who were invited that particular year, and participated. As women in Finland are not excluded from screening invitations or services after hysterectomy, and they may choose to participate, this adjustment for participation rates is not used in the Finnish statistics.

Extensive opportunistic screening occurs alongside the organized programme in Finland (Koponen & Luoto 2000, Salo et al 2014).

8.2 Study populations and data sources

This study is based on two separate evaluations on the use of self-sampling among non-attendees of routine cervical screening. Both evaluations were conducted as parts of the routine screening programmes of the partaking municipalities. Data was collected from the database of the Mass Screening Registry of the Finnish Cancer Registry, from Statistics Finland and by surveys among women invited to screening in the partaking municipalities in study years.

The Mass Screening Register receives and records individual level data on all screening invitations (year, municipality, reason for invitation, sometimes invitation date, and time of the given appointment), screening visits (screening laboratory, time of the visit, result of the screening test and possible referral for further investigations), and results of further investigations when appropriate (date of the investigation, histologic diagnoses, treatment). Gynaecologic anamnestic data collected at the screening visits (abnormal bleeding symptoms, year of hysterectomy, Pap smear history, possible previous cytologic/histologic abnormalities of the cervix and possible treatments) is also recorded. The data is recorded using unique personal identifiers.

Statistics Finland collects individual level data and datasets describing various aspects of the society. It develops the national statistical service in co-operation with other Government officials. This data is available for research purposes with separate permissions.

8.2.1 Study 1 (Papers I-II)

The first study was conducted as a part of the routine cervical screening programme of the city of Espoo in 2008-2009 (referred from here on as 'Study 1'). The study population consisted of all 25,597 women (12,839 in 2008 and 12,758 in 2009) identified for screening in 2008 and 2009 from the Population Register Centre.

The women were individually randomized at the Finnish Cancer Registry to self-sampling arm or to reminder letter arm with a randomization ratio of

1:2.7. The invitees did not know their randomization status at the time of primary invitation.

The screening data from Mass Screening Registry formed the basis of the study register. Self-reported information on previous Pap smears (including opportunistic ones) was collected with a separate questionnaire, completed with information from the mass screening register when appropriate, and combined to the screening data. Also reasons for previous non-attendance were enquired from both arms and combined to the study register with written consent from the partaking women.

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

8.2.2 Study 2 (Papers III-IV)

The second study assessed the effect of using self-sampling as a second reminder (i.e. among non-attendees after a primary invitation and a reminder letter) in a non-randomized setting in 31 Finnish municipalities in 2011-2012 (referred from here on as 'Study 2'; Table 4). Overall the cohort consisted of 31,053 women identified for screening from the Population Register Centre in the partaking municipalities in study years. Screening visits were arranged locally, but all participating municipalities used the same screening laboratory of the Cancer Society of Finland for the analysis of the samples.

The screening data from the Mass Screening Registry formed the basis of the study register. This data was further combined with that from Statistics Finland containing individual level information on education level, type of home municipality and marital status. The linkage was made by personal identification numbers. Self-reported information on previous Pap smears (including opportunistic ones) was collected with a separate questionnaire, completed with information from the mass screening register when appropriate.

An additional aim of Study 2 was to assess women's perceptions (acceptability) on self-sampling as a screening option, their reasons for previous non-attendance in traditional screening, and reasons to decline the self-sampling option. The data for this purpose was collected with a questionnaire form sent with self-sampling kits, and separately for those non-attendees who did not receive the self-sampling kit. The data was combined to the study register with written consent from the partaking women.

The study was approved by the Ethical committee of the Hospital District of Helsinki and Uusimaa (79/13/03/03/2011) and National Institute for Health and Welfare (THL/1465/6.02.00/2013).

Table 4. Municipalities in Study 2 grouped by invitational protocol (use of pre-assigned appointment times in invitation letters).

			Municipality type		Hospital	N identified for screening		Follow-up protocol/ HPV+
Municipality	2011	2012	2011	2012	district	2,011	2,012	women
Primary invitations and reminder letters with pre-assigned appointments								
Turku	X	X	1	1	03	8,398	8,498	PAP+DC
Hamina	X	X	1	1	08	1,114	1,039	PAP+DC
Kuusamo	X	X	2	2	18	742	725	PAP+DC
Haapavesi	X	X	2	3	18	327	379	PAP+DC
Siikalatva	X	X	3	3	18	287	266	PAP+DC
Pyhäntä	X	X	3	3	18	76	70	PAP+DC
Tornio	X	X	1	1	20	1,071	1,007	PAP
Sodankylä	X	X	2	3	21	389	380	PAP+DC
Muonio	X	X	3	3	21	144	121	PAP+DC
Enontekiö	X	X	3	3	21	90	123	PAP+DC
Pelkosenniemi	X	X	3	3	21	43	38	PAP+DC
Savukoski	X		3		21	51		PAP+DC
Haapajärvi	X		2		18	336		PAP+DC
Kärsämäki	X		3		18	135		PAP+DC
Reisjärvi	X		3		18	124		PAP+DC
Pyhäjärvi	X		3		18	232		PAP+DC
Keminmaa		X		2	20		382	PAP+DC
Tervola		X		3	20		130	PAP+DC
Kempele		X		1	18		786	PAP+DC
Liminka		X		3	18		454	PAP+DC
Kalajoki		X		2	18		607	PAP+DC
Merijärvi		X		3	18		53	PAP+DC
Kolari		X		3	21		189	PAP+DC
Inari		X		3	21		367	PAP
Salla		X		3	21		149	PAP
Total						13,559	15,763	
Primary invitations with pre-assigned appointments, reminder letters as open invitations								
Forssa	X		1		05	869		PAP+DC
Tammela	X		3		05	311		PAP+DC
Jokioinen	X		3		05	273		PAP+DC
Humppila	X		3		05	126		PAP+DC
Ypäjä	X		3		05	113		PAP+DC
Total						1,692		
Primary invitation and reminder letter as an open invitations								
Hailuoto	X		3		18	39	51	PAP+DC
Total	22	20				15,290	15,763	

Municipality type: 1=urban, 2=semi urban, 3=rural

Hospital district: 03=Southwest Finland, 05=Kanta-Häme, 08=Kymenlaakso, 18=North Ostrobothnia , 20=Länsi-Pohja, 21=Lapland

Follow-up protocol: PAP+DC=women aged <40 years invited for a Pap-smear, women aged ≥40 years referred for direct colposcopy; PAP=all women invited for a Pap-smear

8.3 The process of reminders and self-sampling

In both studies the used self-sampling device was Delphi Screener® (previously Pantarhei Screener®), which is a syringe-like lavage device prefilled with saline (Delphi Bioscience BV, The Netherlands). The woman to be screened inserts the nozzle of the instrument into her vagina and pushes the slide in to release the saline that then rinses the upper vagina and the cervix. Releasing the plunger aspirates the saline with the sample cells back into the syringe. The sample was then moved to a smaller container and mailed to the screening laboratory in a pre-paid envelope using regular mail. Between the two studies, the appearance of the device underwent some changes (Figures 4 and 5), but the principles of sample taking remained very similar with similar clinical performance (Verhoef et al 2013).

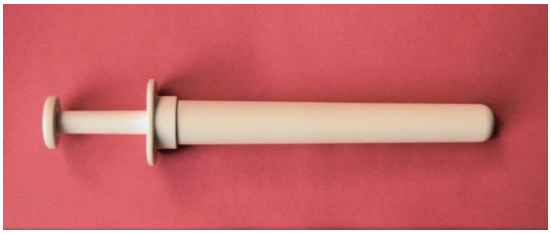

Figure 4 1st generation Delphi Screener (Previous Pantarhei Screener, previous Mermaid).

Figure 5 2nd generation Delphi Screener

8.3.1 Study 1 (Papers I-II)

Two to six months after the primary screening invitation, invited women without a sampling date or a valid appointment for screening were identified from the screening database, and their address information was updated from the Population Register Centre. Only women still living in Espoo for whom a valid address was available were included in following interventions because of the municipally controlled nature of screening in Finland.

The self-sampling kit mailed to non-attendees in the self-sampling arm included: the self-sampling device with user instructions and return envelope for the sample, an information letter on the study, an informed consent

document, an educational leaflet on HPV infections and cervical cancer screening and a questionnaire that included the standard anamnestic data for screening (recent gynaecological health history and previous Pap smears) and some additional questions. A few weeks prior to the self-sampling kit, the women received a letter informing them of the upcoming self-sampling kit, and in 2009, this letter included an option for the cancellation of the kit (opt out option). All material in self-sampling group was sent as bilingual (Finnish and Swedish), or in Finnish or Swedish according to the mother tongue of the woman in question, with the exception that those women that had a mother tongue other than Finnish or Swedish received the Finnish material. In 2009, study material was available also in English by order.

The control arm received a new invitation letter with a new pre-assigned appointment for screening and the same questionnaire as the self-sampling arm (questions on self-sampling excluded) with an information letter about the study.

In 2009, those women who received a reminder letter in the first two mailing batches of 2009 but did not participate were identified to receive a self-sampling kit as a third intervention (1,315 women; 54% of all non-attendees in reminder letter arm in 2009). This intervention had no additional control group.

The self-taken samples were analysed in the Laboratory of the Finnish Cancer Organizations in Helsinki.

8.3.2 Study 2 (Papers III-IV)

Non-attendees after the primary invitation received a second invitation (1st reminder) within the same year. However, in 2012 women were not sent a reminder letter if they declined from screening altogether when cancelling the given appointment (a feature added in 2012 to the programme used for sending out the invitations).

Two to six months after the reminder letters, invited women without a sampling date or a valid appointment for screening were identified from the screening database for self-sampling, and their address information was updated from the Population Register Centre. Only women still living in the original inviting municipality for whom a valid address was available were included in the self-sampling group. Again, women who had declined from screening altogether when cancelling the given appointment/s were excluded.

Reminder letters were sent with the same standard template in all partaking municipalities. In 2011, six municipalities sent reminder letters without a pre-booked appointment, and 16 with a pre-booked appointment. In 2012, all reminder letters were sent with a pre-booked appointment (Table 3, page 39-41).

The self-sampling kit was very similar to the one used in Study 1, with the exception of a more extensive questionnaire form. The self-sampling

possibility was introduced in an invitation letter with an opt-out option. The invitation letter was in three languages, Finnish, Swedish and English, and the self-sampling kits in Finnish or Swedish but available upon request in English. The mailings of the self-sampling procedure were sent out centrally from the Mass Screening Registry. The self-taken samples were analysed in the laboratory of the Cancer Society of Finland in Oulu.

The questionnaire used in Study 2 included again standard anamnestic data for screening and additional questions relating to test acceptability, reasons on previous non-attendance, use of other gynaecological health services and socio-demographic background information. Women's experience of self-sampling was measured using a 16 item Likert-type scale from "totally agree" to "totally disagree" and a "cannot say" option; 13 on test acceptability and sampling experiences and three on the clarity of the user instruction.

8.4 HPV-analysis

Laboratory personnel at the screening laboratories received training for the use of the HC2 assay by the manufacturer's representatives.

As the sample arrived to the laboratory, it was centrifuged at 1,500 rounds per minute in the test tube it arrived in. The resulting supernatant was discarded and the cell pellet was suspended in one millilitre of STM. A part of the sample was transported into a screen plate for HC2 analysis and the rest was frozen in a QIAGEN HC2 tube. Further HC2 analysis was conducted with positive and negative controls according to the manufacturer's guidelines similarly and simultaneously with HPV-samples from routine screening obtained by QIAGEN/Digene Cytobrushes (22, 27). HC2 analysis is a qualitative test that targets 13 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The HC2-technique can detect HPV DNA concentrations over 1 pg/ml, which is proportional to the light emission of the positive control and corresponds to 5,000 HPV genomes per specimen in the well. A sample containing hrHPV DNA equivalent to concentration of 1 pg/ml or above was considered to indicate a hrHPV infection (i.e., cut-off value = 1 relative luciferase units, RLU).

If the sample contained a visible cell pellet after centrifugation, it was considered adequate and the result of the hrHPV analysis reliable. Women who returned samples that did not meet this criterion, were offered the chance to re-try sample-taking. Only women who returned an adequate sample are considered as participants in the analysis.

8.5 Follow-up for women with a hrHPV-positive self-taken sample

Follow-up after a hrHPV-positive (RLU>1) self-taken sample was arranged according to the age of the screened woman in Study 1 and in 28 out of 31 municipalities in Study 2 (Table 4, page 55).

Women younger than 40 with a positive hrHPV-result were invited for a Pap smear and in the case of positive cytology (≥LSIL) or repeated HPV positivity, referred for a colposcopy in local hospitals by the screening laboratories. HrHPV-positive women with normal or borderline (ASC-US) cytologic findings in the Pap smear were considered to have reason for intensified screening and were called to a new screening test in one to two years (risk group screening invitation). If the repeated screening test did not give reason (persistent HPV infection and/or cytologic abnormalities) to further examinations by colposcopy, they returned to the normal 5-year screening interval. The Pap smears were taken at the same local screening clinics or public health centres where routine screening samples were taken. In Study 1, the invitations for a Pap smear were sent with pre-assigned appointments that could be changed, and in Study 2, the invitations were open ones, asking the women contact the local units to make an appointment.

HrHPV-positive women aged 40 or above were referred for a colposcopy at local hospitals. Colposcopy directed biopsies were taken for histological examination from suspected areas on the cervix according to standard procedures in Finland (Current Care Guidelines 2010). Histological examinations were done in local pathology (hospital) laboratories. Further examinations and treatments after colposcopy were conducted according to current Finnish guidelines (Current Care Guidelines 2010). Of the histologic samples obtained within a year of participation date in screening, the more severe one was taken into consideration in the analysis, providing that the samples were taken within three months of each other (i.e., most likely, a diagnostic biopsy and treatment).

Three of the 31 municipalities in Study 2 invited all self-sampling HPV-positive women for a Pap smear irrespective of age. The protocol then followed as described for women aged less than 40 years above.

8.6 Statistical analysis

In all of the studies, participation by primary invitation was defined as a screening visit with successful sample taking irrespective of whether the primary invitation was sent or not (some women made appointments by phone before their invitation was mailed). Participation by reminder letter was defined as a screening visit that occurred at the earliest two days after a reminder letter was sent. In the analysis of self-sampling as a second

reminder, only women who received a reminder letter prior to the self-sampling kit were included in the analysis. Women identified for screening that had no screening appointment during the invitation year or the first two months of the following year were regarded as non-attendees after primary invitation and/or reminder letter.

Self-sampling kits were mailed at the end of the original invitation year and in the beginning of the following year. Participation by self-sampling was defined as mailing a successful self-taken sample (sufficient material for HC2 analysis) to the screening laboratory by a pre-announced dead-line date, or, by intention-to-treat principle, a screening visit that occurred at the earliest two days after a self-sampling kit or information letter was sent.

The coverage of screening was defined by the coverage of any screening test in or outside the programme within the 5-year screening interval (i.e. during the past 4 years) and was assessed by self-reported information on previous Pap smears.

In all of the analyses, the population was divided to seven 5-year age groups from 30 to 60, and women aged <29 (from municipalities inviting women aged 25) and women aged >65 (from municipalities inviting women aged 65) were combined to the youngest and oldest age groups, respectively. Mother tongues were grouped into Finnish, Swedish or other.

8.6.1 Study 1 (Papers I-II)

In the interim analysis of Study 1 including the 2008 study population the primary outcomes were increases in the effects of self-sampling versus a reminder letter were increase in total participation rate and increase in screening coverage achieved by self-sampling or reminder letters. The RRs and 95% CIs for participation in screening (after primary invitation, by self-sampling and by reminder letter) were estimated by log-binomial regression, using SAS Relrisk8 macro with SAS 9.1 software (SAS Institute, Cary, NC). The calculations were adjusted for invitational mode (5-year interval or intensified screening), age and mother tongue. Similar RRs were calculated for coverage of screening, i.e. the relative risk for self-sampling or reminder letter to cover women not screened in or outside the screening programme during the past 4 years; with adjustment for mother tongue and age. In this analysis all women with intensified screening as invitational mode and those with missing information were excluded. CIs for the total participation rates (after primary invitation and after interventions) were estimated with the Clopper–Pearson method.

In the analysis of the entire study population of 2008-2009, primary outcomes were increases in total participation rate and in screening coverage achieved by three types of interventions: 1) a self-sampling kit, 2) a reminder letter, or 3) a reminder letter and then self-sampling kit. Secondary outcomes were the prevalence of hrHPV test positivity and yield of CINs among first invitation and second/third intervention attendees. Age-, mother tongue-,

and invitational mode–adjusted RRs and 95% CIs for participation in the self-sampling arm were estimated by log-binomial regression, using SAS GENMOD procedure with SAS 9.1 software, with reminder letter arm participants as reference. STATA 10.0 software (StataCorp LP, College Station, Texas) was used to estimate 95% Wald confidence limits for participation rates, proportions of previous Pap smears among screening participants, and hrHPV-positivity rates, as well as exact confidence limits for the yields of CIN findings and PPV of colposcopy referrals after each invitation.

As the addition of a self-sampling kit sent as a second reminder to a part of the reminder letter attendees in 2009 was an 'ad-hoc' addition to the study protocol, there was no allocation to the third intervention before sending the screening invitations. The effects of this invitational protocol in overall attendance were thus estimated assuming similar attendance to third intervention among those identified and not identified for the third intervention in reminder letter arm in 2009. The effects were only assessed as raw (estimated) participation rates by primary invitation, reminder letter and self-sampling in total and by invitational mode, age- and mother tongue groups.

8.6.2 Study 2 (Paper III)

The primary outcome of Study 2 was to assess the increase in screening attendance by reminder letters (first reminder) and self-sampling tests (second reminder). Secondary outcome was to study how socio-economic characteristics affect screening participation.

Results were first analysed by age, mother tongue, marital status, education level, municipality type and geographic location. Additional post hoc analysis was conducted by socio-economic status, adjusted for those factors that had an effect in the previous model; age, mother tongue, marital status, education level and municipality type. Data from Statistics Finland was grouped as follows: The division of municipalities was used as defined by Statistics Finland, urban, semi-rural and rural, according to the proportion of people living in urban settlements and the population of the largest urban settlement. Education level is recorded in Statistics Finland for those who have completed lower secondary education or higher. For the purposes of this study, we divided the education level into three categories; primary (including only primary education and including also those with information missing as to the registration protocol in Statistics Finland), secondary (upper and lower secondary education) and tertiary (upper and lower tertiary education and doctoral degree or equivalent). Socio-economic status groups were self-employed, upper-level employees, lower-level employees, manual workers, retirees, students, long-time unemployed and those with missing information. Municipalities were divided to two geographical locations, north and south, using University Hospital areas as guidelines; the University

Hospital area of Oulu representing the Northern part and all other areas the Southern part.

The results were analysed using Stata 12.0. Age-, mother tongue-, municipality type-, marital status-, education level- and geographic location or socio-economic status adjusted RRs with 95% CIs for participation in screening by primary invitation and reminder letter (combined) and by self-sampling were calculated with using Poisson's regression. CIs for the increase in total participation after reminder letters and self-sampling were calculated with Student's paired t-test. This calculation was done in the entire study population, as well as for groups of municipalities in 2009 with two different types of reminder letters (invitations with pre-booked appointments versus open invitations), and for groups of municipalities with varying participation rates by primary invitation (<70%, 70-74.9%, 75-79.9%, >80%).

Pearson's chi-squared was applied to test the independence of socio-demographic variables and screening status regarding also opportunistic smears (grouped by time since previous Pap smear<4 years, or ≥5 years/never).

8.6.3 Study 2 (Paper IV)

The primary aim was to study women's experiences and perceptions on self-sampling based screening among non-attendees to traditional cervical screening and how demographic factors (age, mother tongue, education level, marital status and home municipality type) affect the self-sampling experience. Secondary outcomes were to study women's reasons for non-attendance to routine screening and women's reasons for declining the self-sampling option.

Responses to the Likert-type questions on test acceptability were examined by socio-demographic characteristics; age, mother tongue, municipality type, education level and marital status. The responses were grouped into three categories, "agree" (totally and somewhat agree), "neither agree nor disagree" and "disagree" (totally and somewhat disagree). Women who answered "cannot say" or did not answer at all were excluded from the tabulations. Fisher's exact test was applied to test the independence of socio-demographic and response variables. The problem of multiple comparisons was approached by Holm-Bonferroni method (Holm 1979) The table cell/cells contributing most to the observed interactions were detected with Pearson residuals and their squares. The statistical analyses were conducted using Stata 12.0.

Women's reasons for previous non-attendance in traditional screening were examined as raw frequencies among all non-attendees after reminder letters and in three subgroups: among participants and non-participants by self-sampling and among those women, who stated that their previous Pap smear was ≥5 years ago or never (under-screened). Women's reasons

declining the self-sampling option were examined as raw frequencies among non-attendees after the reminder letters who were offered the self-sampling option, but did not participate.

8.7 Cost analysis

In the cost analysis, the average participation rates, referral rates and precursor lesion yields after each intervention observed in the two studies were used to estimate screening costs in a hypothetical population of 100,000 women invited to screening.

We calculated a cost per screened woman by including only costs of the invitational system, primary screening test and in the case of self-sampling possible triage testing. The cost per one treated CIN2+ case included all costs from invitational system and primary testing to colposcopic investigations, treatment and subsequent follow-up testing and was calculated for the entire population to be screened and divided with the number of CIN2+ cases detected by screening.

First, the differences in costs of using self-sampling or reminder letter as first intervention to non-attendees was estimated by calculating the cost per extra screened woman and the cost per one detected and treated CIN2+ case for both intervention types. The aim was to compare which reminder might be more effective in terms of value for money spent. In the original study the CIN yields after respective interventions differed somewhat between arms, but the numbers were too small for reliable comparisons in the background cancer risks of the participants by respective interventions. Thus, in the cost analysis the CIN detection rate is assumed to be similar in both interventions and was calculated as the combined rate of both interventions in the original study. Additional analysis was made assuming 20% higher detection rate by self-sampling.

Second, the increase in screening costs brought on by self-sampling as a second intervention after two letters, as well as the cost per one extra treated CIN2+ case by self-sampling was estimated. CIN2+ was used as a proxy for the potential of increasing the impact of the programme, because no outcome information was available after the original studies on increasing attendance. The cost per one extra eradicated CIN2+ case by the reminders was compared to the cost of eradicating a CIN2+ case in routine screening under the speculation that if the price of an eradicated CIN2+ lesion in routine screening is regarded acceptable and the price per lesion does not increase after adding one to two reminders to the protocol, the cost increase might be acceptable.

The estimate was calculated assuming 70% attendance rate, use of Pap smear as a screening test and current national rates of CIN lesions among participants after primary invitation as baselines. Participation rate with self-sampling as second reminder was set at 32% and as second reminder at 21%.

Participation with reminder letter was estimated at 27% as observed for reminder letters sent with pre-assigned appointments, but additional analysis was performed to estimate the effect of open invitations with lower participation rate of 14% as was observed for invitations without a pre-assigned appointment time. HPV-positivity rate was set at 12% as observed for HC2 in the studies. The main analysis was calculated for a setting that mails self-sampling tests to all non-attendees, but calculations with an opt-out option in which women could refuse from self-sampling before the samplers were mailed were made as an additional analysis with 15% opt-out rate.

The cost estimates for Pap smears, diagnostic colposcopies and management of CIN2+ diseases were derived from a previous evaluation on the costs of prevention and management of HPV-related diseases in Finland that used mean national prices (Salo et al 2013). The costs were evaluated from the health care provider perspective and were here presented in 2012 prices. Cost estimates for self-sampling were obtained using the actual mean costs in the study of 2011-2012. However, as prices of self-sampling devices have substantially decreased internationally, we made calculations based on a lower price for the device (2 euros), but used a higher price of 6.5 euros in additional analysis. The cost of HPV-analysis was estimated at 20 euros, and additional analysis was conducted with cost estimate of 30 euros.

The follow-up strategy used in the comparison of self-sampling and reminder letter as a first reminder was a Pap smear triage follow-up with 82% compliance rate as observed in Study 1. In the estimates of using self-sampling as a second reminder, estimates were calculated for two different follow-up strategies for women with a hrHPV-positive result in a self-taken sample; for the strategy of inviting all hrHPV-positive women for a triage Pap smear, and for the strategy of referring all of them directly for colposcopy and biopsies. For Pap smear triage, the compliance rate was set at 79% as seen in Study 1 (when invitations to follow-up testing were sent with pre-assigned appointment times), but a lower rate of 70% (as seen in Study 2 with open invitations to follow-up testing) was used in additional analysis. Compliance to direct colposcopy was set at 90% as observed in the studies.

9 RESULTS

9.1 Effects on screening attendance

9.1.1 Effect of one reminder

Participation rates by reminders and the effect of using one (self-sampling or reminder letter) or two reminders (reminder letter, then self-sampling) on total screening attendance in the two studies is shown in Table 5.

As a first reminder, self-sampling resulted in a higher increase in attendance than a reminder letter. The age, mother tongue, and invitational mode adjusted RR for participation by self-sampling as a first reminder in comparison to a reminder letter was 1.21 (CI 1.13–1.30). Participation by self-sampling was higher than by reminder letter among women aged 30-34 (RR for participation 1.23), 45-49 (RR 1.35), 55-59 (RR 1.47) and 60-64 (RR 1.40). Among women with a mother tongue other than Finnish or Swedish, self-sampling reached a higher crude participation rate than a reminder letter, 27% versus 20%, but in the adjusted model the difference was not significant (RR 1.27, CI 0.96-1.67).

The achieved increase in total attendance by self-sampling was 11 percentage points (17% increase). Reminder letters with pre-assigned appointments increased attendance by 9 percentage points in Study 1 (14%), and by 7 percentage points in Study 2 (9%). Open reminder letters increased attendance by 5 percentage points (6%, Study 2).

In different age groups, the increase in participation was highest among women aged 35 to 39 years (+22% and +20% by self- sampling and reminder letter, respectively). Increase was lowest among women aged 60-64 years in self-sampling arm (+13%), and among women aged 55-59 years in reminder letter arm (+10%).

9.1.2 Effect of two reminders

Participation rates among women invited to screening by self-sampling as a second reminder were 19.9% (CI 17.8-22.2%) in Study 1 and 20.7% (CI 19.5-21.9%) in Study 2 (Table 5).

The achieved increase in attendance by two reminders when using reminder letters with pre-assigned appointments among all women identified for screening was 15 percentage points (23%) in Study 1 and 10 percentage points (13%) in Study 2. When reminder letters were open ones in Study 2, the total increase was 8 percentage points (12%).

Participation rate by two reminders according to original attendance rate in Study 2 is shown in Table 6. In those municipalities that had an annual

Table 5. Effect of self-sampling and reminder letters on screening participation. Observed participation rates in the studies and additive (+add) and relative (+%rel) increase in total participation rate.

	Study 1						Study 2			
	Primary invitation + one reminder				Primary invitation + two reminders		Primary invitation + two reminders			
1st reminder	**self-sampling**		**reminder letter** (with appointment)		**reminder letter** (with appointment)		**reminder letter** (with appointment)		**reminder letter** (open invitation)	
2nd reminder					**self-sampling**		**self-sampling**		**self-sampling**	
Study population[1]	7,027		18,377		8,922		29,098		1,690	
Attendance rate: 1st reminder	31.5% (756/2,397)		25.9% (1,631/6,302)		25.6% (836/3,272)		28.8 % (1,985/6,888)		14.0 % (68/487)	
Attendance rate: 2nd reminder					19.9% (262/1,315)		20.8% (859/4,130)		19.0 % (74/389)	
Total participation rate (%) and increase (+%)	% (+add)	+%rel	% (+add)	+%rel	% (+add)[2]	+%rel	% (+add)	+%rel	% (+add)	+%rel
After primary invitation	63.1		62.6		63.3		73.3		71.2	
After 1st reminder	73.9 (+10.8)	17.1	71.5 (+8.9)	14.2	72.7 (+9.4)	14.8	80.1 (+6.8)	9.3	75.2 (+4.0)	5.7
After 2nd reminder					78.1 (+5.4)	7.5	83.1 (+3.0)	3.7	79.6 (+4.4)	5.8
Total	**73.9**	17.1	**71.5**	14.2	**78.1**	23.4	**83.1**	13.3	**79.6**	11.8

[1] including only women who received the primary invitation

[2] assuming similar attendance among those identified and not identified for the second reminder

participation rate of below the national average of 70% (range 52.9-69.9%), attendance rate increased 12% by reminder letters and further 6% by self-sampling tests, to total participation rate of 78%. Also in municipalities with original attendance rate over 75% or 80% (range 80.2-83.7% in the latter group), attendance increased by 9% and 7% with reminder letters and further by 3% and 4% with self-sampling tests. Besides the 3% increase by self-sampling in the group of municipalities with original attendance rate of 75-79.9%, all increases with reminder letters and self-sampling were significant irrespective of original attendance level.

Table 6. Increase in attendace by original attendance rate. Including only municipalities with pre-assigned appointments in both invitation letters.

		Original attendace	After reminder letter			After self-sampling			Total	
	n	% (95% CI)	% (95% CI)	+add%	**+rel%**	% (95% CI)	+add%	**+rel%**	+add%	**+rel%**
<70%	3,699	65.7 (64.1-67.2)	73.4 (72.0-74.8)	7.7	**11.7**	77.6 (76.2-78.9)	4.2	**5.7**	11.9	**18.1**
70-74.9%	21,236	72.7 (72.2-73.4)	79.5 (78.9-80.0)	6.8	**9.4**	81.7 (81.7-82.7)	2.3	**2.9**	9.1	**12.3**
75-79.9%	2,703	76.4 (74.8-78.0)	83.1 (81.7-84.5)	6.7	**8.8**	85.8 (84.5-87.1)	2.7	**3.2**	9.4	**12.3**
≥80%	1,684	81.4 (79.5-83.2)	87.3 (85.7-88.9)	5.9	**7.3**	90.4 (89.0-91.8)	3.1	**3.5**	9.0	**11.1**
Total	29,322	72.7 (72.2-73.2)	79.5 (79.0-80.0)	6.8	**9.4**	82.4 (82.0-82.9)	2.9	**3.6**	9.7	**13.3**

95% confidence intervals (CI) from paired t-test
add%= additive increase, rel%=relative increase

9.1.3 Socio-demographic determinants of screening attendance

Socio-demographic factors related to significantly lower participation in routine screening after two invitation letters were: young age (participation increased with increasing age), a mother tongue other than Finnish or Swedish, a lower education level, living in a rural municipality and having never been married. No differences were seen between women living in the northern half of Finland (here municipalities in the University Hospital area of Oulu) and the southern half (municipalities in other hospital districts). In different socio-economic groups, crude participation rates after two invitations was lower among students, long-term unemployed persons, pensioners and those with unknown socio-economic group (Table 7). However, when adjusted for other socio-demographic factors, the only groups with significantly lower attendance were pensioners and women of unknown socio-economic group (self-employed as reference).

When self-sampling was used as a first reminder, no significant differences in participation were seen within the group between different age, mother tongue or invitational mode groups in the adjusted model.

When self-sampling was used as a second reminder, there was slight variation (non-significant in the adjusted model) in the crude participation rates to self-sampling within different age groups (18-23%), but no trend with regard to decreasing or increasing age. Marital status and geographical

location of home municipality (northern or southern half of Finland) did not have an effect on participation in screening by self-sampling. A higher education level resulted in significantly higher participation, the difference being almost twofold between the lowest and higher levels of education (RR 1.85, CI 1.49-1.85). By socio-economic group, students, pensioners, long-term unemployed and women of unknown socio-economic group had again somewhat lower than average crude participation rates, but differing from the participation to traditional screening, so did self-employed persons (Table 7). Of note, differences by educational level were still significant when socio-economic group was entered into the adjusted model both in participation to traditional screening and participation by self-sampling (data not shown).

Table 7. Participation in routine screening after two invitations and participation by self-sampling by socioeconomic group in Study 2: Crude participation rates among invited women and adjusted relative risks (RR) for participation.

	Participation in routine screening after two invitations				Participation by self-sampling			
	Invited	Participated		Adjusted[1] RR for	Invited	Participated		Adjusted[1] RR for participation
Socio-economic group	n	n	%	RR (95% CI)	n	n	%	RR (95% CI)
Self-employed[2]	1,980	1,586	80.1	1	310	53	17.1	1
Upper-level empoyees	4,982	4,076	81.8	1.01 (0.95-1.08)	633	143	22.6	1.28 (0.93-1.78)
Lower-level employees	11,659	9,733	83.5	1.05 (0.99-1.10)	1,398	321	23.0	1.34 (1.00-1.79)
Manual workers	4,557	3,692	81.0	1.05 (0.99-1.11)	659	154	23.4	1.56 (1.14-2.14)
Students	1,034	730	70.6	0.97 (0.89-1.06)	221	38	17.2	1.11 (0.73-1.71)
Pensioners	2,863	2,081	72.7	0.89 (0.83-0.95)	550	97	17.6	1.25 (0.88-1.78)
Long-term unemployed	2,813	2,070	73.6	0.94 (0.88-1.01)	558	100	17.9	1.30 (0.92-1.83)
Unknown	1,165	632	54.2	0.74 (0.67-0.81)	207	33	15.9	1.16 (0.75-1.80)

[1] adjusted for age, mother tongue group, marital status, municipality type and educational level

[2] includes agricultural self-empoyed persons, small employers, self-employed persons (unspecified), own-account workers, self-employed persons in liberal professions

Participation by self-sampling as a second reminder was lower among women with a mother tongue other than Finnish or Swedish; crude attendance rate was 13 versus 21-22% among Finnish and Swedish speaking women and adjusted relative risk for participation was 0.77 (CI 0.57-1.04). Lappish, Russian and Vietnamese speaking women achieved total attendance rates similar to Finnish and Swedish speaking women (Figure 6). Lowest rates, below 60% even after reminders, were seen among Arabic, Chinese, Somali, English and German speaking women. Among Arabic, Somali and English speaking women participation rate by self-sampling was 0%. In study 1, participation rates by self-sampling in these three groups were 29% (2/7), 12% (2/17) and 0% (0/13), respectively and 5% (1/19), 5% (2/44) and 20 % (8/40) by reminder letter, respectively.

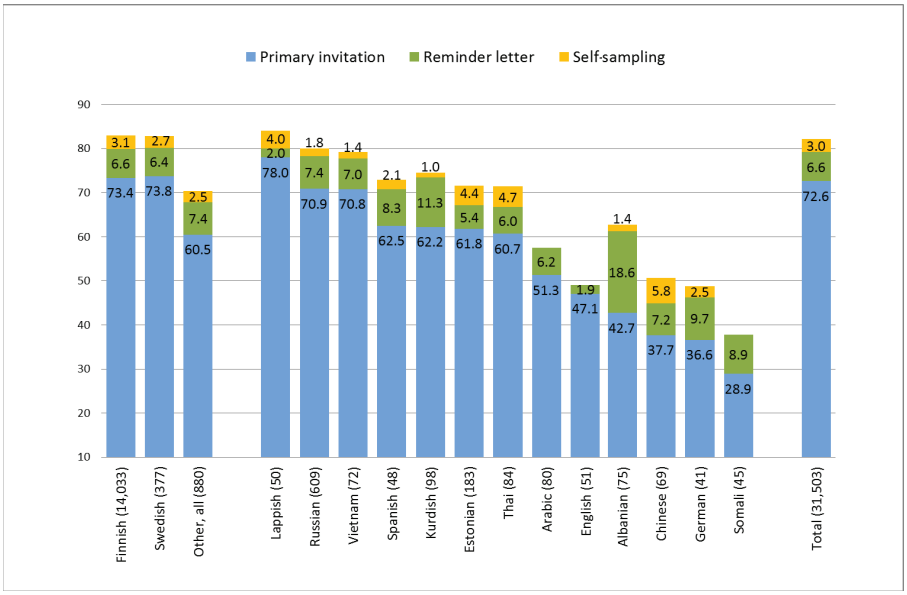

Figure 6 Participation in screening in Study 2 by mother tongue, including 13 most common mother tongues other than Finnish or Swedish.

9.2 Effects on screening coverage

Women with no Pap smear within the 5-year screening interval were regarded under-screened and their participation with interventions could thus be regarded as an increase to overall screening coverage (including opportunistic testing).

With regard to the effect of first reminders, self-sampling seemed to be more attractive than a reminder letter among women who had never had a Pap smear: in Study 1 3.5% (CI 2.1–4.8%) versus 0.8 % (CI 0.3–1.2%) of participants with the respective interventions reported no previous Pap smears. However, there was no difference in the proportion of all under-screened participants by the two interventions (20.5% and 21.5% of participants by self-sampling and reminder letter, respectively).

In Study 1, older women were more likely under screened then younger women in both arms (adjusted RR for self-sampling or reminder letter to cover an under-screened woman aged 30-39 years 0.46 (CI 0.23-0.92) and 0.39 (CI 0.25-0.60), respectively; with women aged 60-64 as reference). Women with a mother tongue other than Finnish or Swedish taking part with the interventions were more likely under-screened than Finnish or Swedish speaking participants (adjusted RR in self-sampling arm 2.31 (CI 1.26-4.23) and RR in reminder arm letter 1.52 (CI 0.98-2.37); with Finnish speaking women as reference).

In combined data from the two studies participants among after the first reminders, 71.0% (self-sampling) and 71.2% (reminder letter) had been screened 0-4 years ago (Table 8).

Table 8. Effect of self-sampling on screening coverage: Time from previous Pap-smear (organized or opportunistic) among screening participants in Studies 1 and 2.

	Participants after primary invitation		Participants after 1st reminder				Participants after 2nd reminder	
			Reminder letter		Self-sampling		Self-sampling	
Time from previous smear	**n**	**%[1]**	**n**	**%[1]**	**n**	**%[1]**	**n**	**%[1]**
< 5 years	24,204	62.9 %	2,627	71.2 %	537	71.0 %	704	58.7 %
>5 years or never	12,687	33.0 %	896	24.3 %	147	19.4 %	323	26.9 %
No information	1,589	4.1 %	165	4.5 %	72	9.5 %	172	14.3 %
Total	38,480		3,688		756		1,199	

[1] of participants

Among women who received the self-sampling kit as a second reminder, 6.5% of participants in Study 1 and 4.3% in Study 2 had never been screened before. Altogether 58.7% of participants with a second reminder reported that a Pap smear had been taken 0-4 years ago and 26.9% (31% if cases with missing information are excluded) of the participants could be regarded under-screened prior to the participation with self-sampling (Table 8).

The participants after primary invitation showed a very similar profile to the ones seen among participants to reminders; proportion of women who, prior to their participation in screening, had been screened within the screening interval was 63%, and 33% had not been screened (Table 8). When women aged 30, who most likely received their first invitation to screening, are excluded, the percentage of under-screened women increased only slightly and was 36%. Of note, among women in Study 1 (papers I-II) conducted in the Helsinki metropolitan area, 70% of participants with the primary invitation were screened within 0-4 years, whereas the same percentage in Study 2 that was conducted within municipalities from four other hospital districts was 58%.

With regard to socio-demographic characteristic of the participants after the second reminder, differences in the proportion of under-screened participants and those up to date with screening were seen by age and educational level, but not with regard to marital status or mother tongue (Table 9). Especially self-sampling participants with low educational level were more often under-screened (52%) than up to date with screening (48%). Further, almost half (46%) of self-sampling participants aged 50-64 were under-screened. Those participants with a mother tongue other than Finnish or Swedish who were under-screened (38%), often had actually never been screened (22.5%).

Table 9. Proportion of under-screened women (previous Pap-smear >5 years ago or never) and women up to date with screening (previous Pap-smear 0-4 years ago) among participants to self-sampling as a second reminder (women with missing information excluded). Propotion of women who had never been screened prior to their participation with self-sampling as additional column.

		Previous Pap-smear			
		< 5 years ago	≥5 years ago or never		Never screened
		n (%[1])	n (%[1])		n (%[1])
Age					
30-39		240 (76.4)	74 (23.6)		25 (8.0)
40-49		140 (67.0)	69 (33.0)		12 (5.7)
50-64		150 (54.4)	126 (45.7)		3 (1.1)
	p-value			*0.000*	
Mother tongue					
Finnish		494 (66.5)	249 (33.5)		28 (3.8)
Swedish		11 (68.8)	5 (31.3)		3 (18.8)
Other		25 (62.5)	15 (37.5)		9 (22.5)
	p-value			*0.855*	
Educational level					
Primary		38 (48.1)	41 (51.9)		6 (7.6)
Secondary		236 (62.3)	143 (37.7)		18 (4.7)
Tertiary		256 (75.1)	85 (24.9)		16 (5.0)
	p-value			*0.000*	
Marital status					
Never married		180 (60.2)	119 (39.8)		27 (9.0)
Married		276 (71.1)	112 (28.9)		12 (3.1)
Divorced		70 (66.7)	35 (33.3)		0 (0.0)
Widowed		4 (57.1)	3 (42.9)		1 (14.3)
	p-value			*0.025*	

p-values from Pearson's Chi[2]

[1] Percentages based on the number of completed responses (women with missing information excluded)

9.3 Effects on CIN yield detected by screening

Compliance to follow-up among HPV-positive women invited for a Pap smear was 82/79% in Study 1 (self-sampling as a first/second reminder, respectively), and 70% in Study 2. Compliance to follow-up among women referred to a colposcopy was 90/94% in Study 1 (self-sampling as a first/second reminder, respectively) and 89% in Study 2.

The observed test-positivity rate in the self-taken samples was 12% (12.3% in Study 1 and 11.8% in Study 2).

Table 10. Yield of moderate or more severe (CIN2+) and severe (CIN3+) cervical lesions with CIs in studies conducted in Studies 1 and 2, and increase in total CIN yields of screening within study years.

	Partic.	**CIN1**			**≥CIN2**			**≥CIN3**		
	n	n	% (95% CI)	+%	n	% (95% CI)	+%	n	% (95% CI)	+%
Study 1										
Self-sampling arm										
1^{ary} invitation	4,434	9	0.2 (0.1-0.4)		23	0.5 (0.3-0.8)		15	0.3 (0.2-0.6)	
1st reminder: self-sampling	756	2	0.3 (0.0-1.0)	22.2 %	3	0.4 (0.1-1.2)	13.0 %	2	0.3 (0.0-1.0)	13.3 %
Reminder letter arm										
1^{ary} invitation	11,503	18	0.2 (0.1-0.2)		47	0.4 (0.3-0.5)		26	0.2 (0.1-0.3)	
1st reminder: remider letter	1,631	3	0.2 (0.0-0.5)	16.7 %	10	0.6 (0.3-1.1)	21.3 %	5	0.3 (0.1-0.7)	19.2 %
Total increase by one reminder	2,387	5	0.2 (0.1-0.5)	18.5 %	13	0.5 (0.3-0.9)	18.6 %	7	0.3 (0.1-0.6)	17.1 %
Subpopulation of reminder letter arm invitees in 2009 with self-sampling as 2nd reminder										
1^{ary} invitation	5,650	9	0.2 (0.1-0.3)		21	0.4 (0.2-0.6)		12	0.2 (0.1-0.4)	
1st reminder (letter)	836	2	0.2 (0.0-0.9)	22.2 %	3	0.4 (0.1-1.0)	14.3 %	1	0.1 (0.0-0.7)	8.3 %
2nd reminder: self-sampling[1]	443	2	0.5 (0.1-1.6)	18.2 %	4	0.9 (0.1-3.0)	16.7 %	2	0.5 (0.0-2.3)	15.4 %
Total increase by two reminders	1,279	4	0.3	44.4 %	7	0.5	33.3 %	3	0.2	25.0 %
Study 2										
1^{ary} invitation	22,543	20	0.1 (0.1-0.1)		67	0.3 (0.2-0.4)		38	0.2 (0.1-0.2)	
1st reminder (letter)	2,057	1	0.0 (0.0-0.3)	5.0 %	11	0.5 (0.3-1.0)	16.4 %	5	0.2 (0.0-0.6)	13.2 %
2nd reminder: self-sampling	939	5	0.5 (0.2-1.2)	23.8 %	6	0.6 (0.2-1.4)	7.7 %	4	0.4 (0.1-1.1)	9.3 %
Total increase by two reminders	2,996	6	0.2	30.0 %	17	0.6	25.4 %	9	0.6	23.7 %

[1] Assuming similar attendance and CIN yield among those identified (1,315 of 2,436 non-attendees after reminder letter) and not identified for the third intervention in reminder letter arm in 2009. Observed yield of CIN2+ lesions was 2/239 participants and yield of CIN3+ lesions 1/239 participants. CIs of the true observed rates.

The effect of reminders on the yield of detected CIN lesions in the studies is shown in Table 10. In Study 1, despite the randomized setting, rate of detected CIN2+/3+ lesions by primary invitation was slightly higher in self-sampling arm. In study populations that used two reminders (Study 2 and a subpopulation of reminder letter arm attendees in Study 1), there seemed to be a tendency of attendees after the first reminder having higher detection rates of CIN2+/3+ lesions than primary invitation attendees, and attendees after the second reminder yet a higher detection rate than attendees after first reminder.

Of those eight women who were diagnosed with a CIN2+ lesion after they attended with self-sampling as a second reminder, five had had a Pap smear within one year and one within two years of their participation with self-sampling (together 75% of cases) and five with reportedly normal results. One had been screened four years ago (normal results) and one had been screened previously, but could not remember when.

Test-positive self-sampling attendees were included in risk-group screening invitations approximately one year after their participation by self-sampling. Among attendees to self-sampling as a first reminder, 86% (65/76) of test-positive women with no CIN diagnosis were invited, and participation rate was 49% (including also women who were non-compliant to original follow-up). Among test-positive attendees to self-sampling as a second reminder with no CIN diagnosis, 95% (74/78) were invited, and participation rate was 47%. No new CIN cases were detected among participants to risk-group screening.

9.4 Women's perceptions on self-sampling

Women's perceptions on self-sampling were enquired in Study 2 with a questionnaire with 13 questions on sample taking experiences and three on the user instruction. Response rate among self-sampling participants (n=920) was very good as 909 (98.8%) women returned the questionnaire and 883 (96.0%) gave an answer to at least one of the statements regarding acceptability.

Figure 7 shows women's responses to these statements.

In the open answers, the most commonly reported concerns were related to the plunger of the device not releasing properly, fluid leaking out during sample taking and the volume of the collected sample seeming small.

With regard to age, education level, municipality type or marital status, no significant differences in experiences were found. Experiences of insecurity during sample taking were significantly more common among women with a mother tongue other than Finnish or Swedish (51% versus 21% and 12%, respectively, p=0.001), as were feelings of fear/anxiety (18% versus 3% and 6%, respectively, p=0.004). Feelings of discomfort or unpleasantness were also reported more often in this group, but this difference did not reach

statistical significance (25% versus 7% and 12%, respectively, p=0.010). Numbers were too small for comparisons between different mother tongues in the group of women with a mother tongue other than Finnish or Swedish.

When women were asked which screening method they would choose in the future, 66% of responders chose self-sampling and 10% traditional screening. Most common reasons for choosing self-sampling were convenience and it being more private. Women who chose traditional screening felt that this way they can trust that the sample is taken correctly and gives the right result.

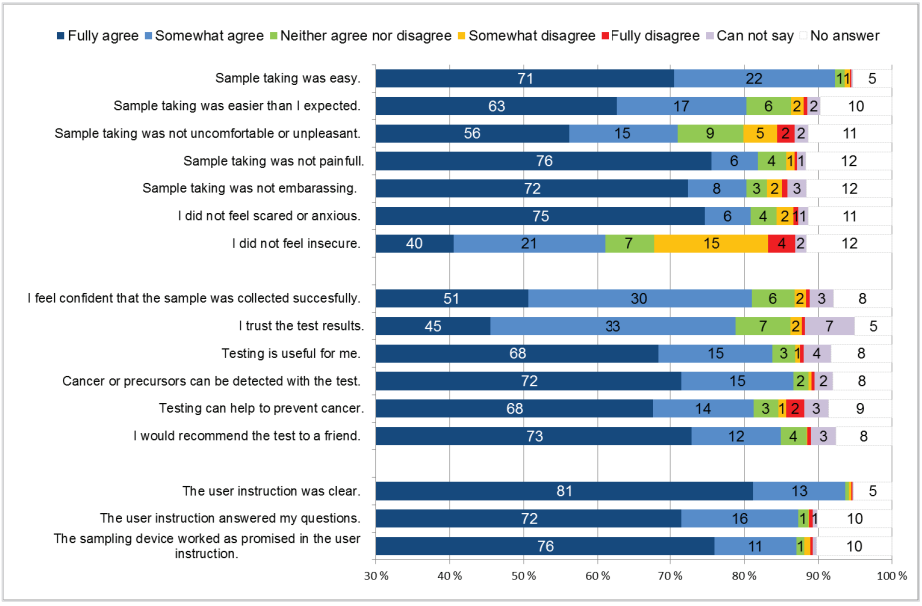

Figure 7 Women's experience of self-sampling. Response frequencies among all women who took part in screening with a self-taken sample and returned the questionnaire (n= 909). Adapted from Virtanen A, Nieminen P, Niironen M, Luostarinen T, Anttila A. Self-sampling experiences among non-attendees to cervical screening. Gynecol Oncol 2014; 135: 487–94.

Of the 3,589 women who received the self-sampling offer but did not return a self-taken sample, 356 women (10%) returned the questionnaire and gave a reason for turning down the self-sampling option. 67% (237/356) reported they had had a Pap smear taken elsewhere, 10% (37/356) declined due to pregnancy or recent labour, 9% (33/356) would rather go to a Pap smear than preform self-sampling, 7% (23/356) found screening unnecessary and 6% (21/356) did not believe in their ability to take the sample herself. Only 4 responders (1%) declined because they thought the result would not be reliable and equally many did not know why they should take part in screening.

Also in Study 1 self-sampling participants were asked to fill out a short questionnaire. 86% and 92% of participants with self-sampling as first or second reminder (respectively) responded. Sample-taking with the earlier version of Delphi Screener® was regarded as easy by somewhat lower percentage of participants, by 88% and 86 % of responders, than what was observed in Study 2 (97% of responders). When asked which screening method they would choose in the future, self-sampling or traditional clinic based screening, 65% and 67% (self-sampling as first or second reminder) chose self-sampling, 23% and 16% chose traditional screening and 12% and 16% had no preference.

9.5 Reasons for non-attendance

Reasons for non-attendance were studied by questionnaires in both studies.

In Study 1, 86% (623/756) of self-sampling participants and 58% (833/1631) of reminder letter arm participants returned the questionnaire and gave a reason for previous non-attendance. No obvious differences were seen among responders and non-responders to the questionnaire in either arm with regard to age, but among self-sampling participants, the response rate was slightly lower among Swedish speaking women (76% versus 81%/Finnish and 81%/other) and among reminder letter arm participants women with a mother tongue other than Finnish or Swedish responded less often (48% versus 59%/Finnish and 64%/Swedish).

In Study 2, 96.1% (887/920) of participants to self-sampling as second reminder gave a reason for previous non-attendance. However, response rate was only 10.8% (408/3,768) among those women that did not take part in screening by self-sampling, and thus total response rate among all non-attendees after two invitations remained at 28%. Responses of non-attending women with lower education level and a mother tongue other than Finnish or Swedish (immigrants) were under-represented in the results. Further, questionnaire responses among those who did not take part with self-sampling seem to have been obtained from a lower risk population; only 13% of the responders were under-screened regarding also opportunistic activities, and only 8% reported being regular smokers, which is fewer than the average in Finnish female population aged 25-64 (Varis & Virtanen 2013). Most likely, response bias plays thus a role in these results.

Reported reasons for non-attendance are shown in Table 11. For Study 2, responses are further shown separately for those women who according to their self-reported information on previous Pap smears were under-screened (previous Pap smear ≥5 years ago or never).

In study 1, no marked differences were seen between participants by self-sampling or by reminder letter. Practical reasons were most commonly reported as reasons for non-attendance with the primary invitation. They were reported by half of the responders in both arms, and were most

commonly not receiving the sent invitation, or pregnancy related reasons. Approximately one third of participants in both arms had attended screening elsewhere. Emotional barriers were reported by 7% in self-sampling arm (most commonly reluctance to undergo a gynaecological examination), and by 9% in the reminder letter arm (most commonly finding screening unnecessary due to previous hysterectomy).

Table 11. Reasons for non-attendance in routine screening. Self-reported reasons for previous non-attendance among non-attendees after primary invitation (Study 1) or primary invitation and reminder letter (Study 2).

	Non-attendees after primary invitation (Study 1)		Non-attendees after two invitations (Study 2)				
					All responders		
	Self-sampling attendees	Reminder letter attendees	Self-sampling attendees	Non-attendees	All	No smear within 5 years[1]	Mother tongue other than Fin/Swe
	n (%)	n (%)	n (%)				
Total number of women in group	756		920	3768	4688	na	378
Question answered by	623 (82.4)	833 (51.1)	884 (96.1)	408 (10.8)	1292 (27.6)	352 (na)	46 (12.2)
Attend elsewhere	*248 (39.8)*	*292 (35.1)*	*312 (35.3)*	*286 (70.1)*	*598 (46.3)*	*23 (6.5)*	*19 (41.3)*
Recent Pap-smear elsewhere	241 (38.7)	282 (33.9)	234 (26.5)	234 (57.4)	468 (36.2)	10 (2.8)	11 (23.9)
Regular check-ups with own gynaecologist							
Follow-ups due to previous lesions/disease	7 (1.1)	10 (1.2)	9 (1.0)	22 (5.4)	31 (2.4)	0 (0)	1 (2.2)
Practical reasons	*331 (53.1)*	*422 (50.7)*	*424 (48)*	*119 (29.2)*	*543 (42.0)*	*169 (48)*	*21 (45.7)*
No suitable time available at the clinic	9 (1.4)	9 (1.1)	70 (7.9)	10 (2.5)	80 (6.2)	24 (6.8)	5 (10.9)
Pregnancy or recent labour	32 (5.1)	72 (8.6)	67 (7.6)	60 (14.7)	127 (9.8)	16 (4.5)	1 (2.2)
Scheduling difficulties, work, no child care	23 (3.7)	23 (2.8)	64 (7.2)	10 (2.5)	74 (5.7)	30 (8.5)	1 (2.2)
Did not receive an invitation	47 (7.5)	87 (10.4)	37 (4.2)	4 (1.0)	41 (3.2)	14 (4.0)	2 (4.3)
Travelling	24 (3.9)	20 (2.4)	31 (3.5)	9 (2.2)	40 (3.1)	14 (4.0)	0 (0)
Health related (disability, chronic illness)	18 (2.9)	37 (4.4)	27 (3.1)	10 (2.5)	37 (2.9)	13 (3.7)	2 (4.3)
Other or unspecified practical reason[2]	178 (28.6)	174 (20.9)	158 (17.9)	27 (6.6)	37 (2.9)	70 (19.9)	11 (23.9)
Emotional or attitudinal reasons	*47 (7.5)*	*34 (4.1)*	*165 (18.7)*	*49 (12)*	*214 (16.6)*	*126 (35.8)*	*9 (19.6)*
Reluctance to gyneacological examination	19 (3.0)	6 (0.7)	81 (9.2)	14 (3.4)	95 (7.4)	61 (17.3)	5 (10.9)
Does not find screening necessary	15 (2.4)	21 (2.5)	34 (3.8)	26 (6.4)	60 (4.6)	34 (9.7)	2 (4.3)
Bad experiences of mass screening	5 (0.8)	3 (0.4)	27 (3.1)	5 (1.2)	32 (2.5)	16 (4.5)	0 (0)
Other emotional/attitudinal reason[2]	8 (1.3)	4 (0.5)	44 (5.0)	11 (2.7)	55 (4.3)	34 (9.7)	2 (4.3)
Forgot	*85 (13.6)*	*166 (19.9)*	*184 (20.8)*	*21 (5.1)*	*205 (15.9)*	*73 (20.7)*	*7 (15.2)*
Other reason[2]	*11 (1.8)*	*16 (1.9)*	*11 (1.2)*	*3 (0.7)*	*14 (1.1)*	*5 (1.4)*	*0 (0)*

Multiple answers allowed; additive percetage >100.

[1] Non-attending women who in the questionnaire did not report a Pap-smear in or outside the screening programme wihtin five years of study year

[2] Includes answers that did not form groups constituting over two percent.

Partially adapted from Virtanen A, Nieminen P, Niironen M, Luostarinen T, Anttila A. Self-sampling experiences among non-attendees to cervical screening. Gynecol Oncol 2014: 135, 487-94.

Among participants to self-sampling as a second reminder (Study 2), again one third (35%) answered that they attended elsewhere and almost half (48%) of the participants had practical barriers to previous attendance. In this study the most common practical barrier was a difficulty in finding a suitable free appointment time at the screening clinic, which was reported notably more often than in Study 1. Pregnancy or recent labour, and other scheduling difficulties due to family or work commitments were also common. Emotional or attitudinal reasons accounted for 19% of the answers in this group, and especially reluctance to gynaecological examinations was more commonly reported than among participants after the first reminder.

Women who are also non-attendees to opportunistic activities are especially important to engage in screening activities. Compared to all

responders, emotional barriers were more common among under-screened women; 36% reported emotional or attitudinal reasons for their non-attendance, most commonly reluctance to undergo a gynaecological examination. 48% did not take part due to practical difficulties. 79% (100/126) of under-screened women reporting emotional reasons and 86% (146/169) of those reporting practical reasons took part in screening by self-sampling. This indicates that self-sampling helps to remove both emotional and practical barriers to traditional screening among the truly under-screened women.

Among non-attendees after two invitations who remained non-attendees even after the self-sampling offer, 70% stated that they attended elsewhere and thus did not take part in mass screening. As stated, response bias probably plays a role in the received responses.

The profile of reported reasons among responders with a mother tongue other than Finnish or Swedish (Study 2) did not differ from the entire study population. Again, however, response bias may play a role.

9.6 Costs of screening

The resource required for screening a population of 100,000 women in different invitation strategies is shown in Table 12.

As a first reminder, self-sampling was more expensive than a reminder letter. The cost per extra participating woman (including only invitational costs and primary testing, and triage testing for self-sampling) was 43 euros by self-sampling, and 33 euros by reminder letter. Further, assuming similar CIN detection rates per screened woman by both interventions, the cost per detected and eradicated CIN2+ lesion remained over 50% higher by self-sampling, even with the low sampler price of 2 euros and an opt-out option. Assuming a 20% or 50% higher detection rate by self-sampling the cost per lesion was still higher than with a reminder letter (14,100/11,700 euros versus 10,300 euros per lesion).

The cost per eradicated CIN2+ after a reminder letter was not higher than that after a primary invitation; the use of reminder letters actually lowered the cost in the estimate due to a higher number of detected lesions per woman screened.

When the participation rate of reminder letters was set at a lower level of 14% (as observed for open invitations), the increase in total costs reduced from 14 to 8%. However, the price per participant was still lower than by self-sampling (35 versus 43 euros, 40 with opt-out strategy).

As a second reminder after two invitation letters, self-sampling increased total costs of screening by 11-14% if self-sampling was followed with Pap smear triage, and by 23-25% with direct referral for colposcopy. The combined increase of two reminders to original costs was 26-43%. An opt-out strategy reduced the costs of self-sampling by 7%.

Table 12. Total resource required for screening a population of 100 000 women in different invitation strategies. Estimates in self-sampling as a 2nd remider for two different follow-up strategies after a hrHPV-positive self-taken sample (sampler price = 2 euros).

		One reminder		Two reminders	
	Primary invitation only	**Reminder by self-sampling**	**Reminder by reminder letter**	**Reminder letter & self-sampling**	**Reminder letter & self-sampling**
		Pap-smear triage[1], compliance 82%		Pap-smear triage[1], compliance 79%	Direct colposcopy[1], compliance 90%
Primary invitation					
Cost per screened woman (prim. testing[2])	31	31	31	31	31
Total costs (incl. treatment and follow-up)	3,210,443	3,210,443	3,210,443	3,210,443	3,210,443
Cost per treated CIN2+	15,288	15,288	15,288	15,288	15,288
1st reminder					
Cost per extra screened woman (prim. testing[2])		43	33	33	33
Total costs (incl. treatment and follow-up)		707,049	452,496	452,496	452,496
Cost per extra treated CIN2+		16,443	10,284	10,284	10,284
2nd reminder					
Cost per extra screened woman (prim. testing[2])				53	50
Total costs (incl. treatment and follow-up)				396,944	826,393
Cost per extra treated CIN2+				12,805	23,611
Total costs of screening					
Cost per screened woman (prim. testing[2])	31	33	31	33	32
Total costs	3,210,443	3,917,492	3,662,939	4,059,883	4,489,332
Increase in costs by reminders	-	22 %	14 %	26 %	40 %
Cost per treated CIN2+	15,288	15,484	14,421	14,245	15,534
Additional analysis:					
Self-sampling opt-out rate 15%					
Cost per detected CIN2+ (by reminder)		15,930		12,285	23,175
Compliance to Pap-smear triage 70%					
Cost per detected CIN2+ (by reminder)		18,553		13,966	
Cost per CIN2+ lesion (total)		15,766		14,377	
Sampler price = 6.5 euros					
Cost per CIN2+ lesion (by reminder)		19,583		15,984	26,427
Cost per CIN2+ lesion (total)		16,018		14,591	15,875
Cost of HPV-analysis = 30 euros					
Cost per CIN2+ lesion (by reminder)		18,676		14,288	24,925
Cost per CIN2+ lesion (total)		15,864		14,407	15,693
Sampler price = 6.5 euros & cost of HPV-analysis = 30 euros					
Cost per CIN2+ lesion (by reminder)		21,815		17,467	27,741
Cost per CIN2+ lesion (total)		16,397		14,752	16,034

Assuming 70% attendance rate with the primary invitation, 27/32% attendance with first reminder (reminder letter/self-sampling, respectively), and 21% attendance rate with self-sampling as second reminder

[1] Follow-up for women with a HPV-positive result from the self-taken sample

[2] Includes costs of invitational system, primary screening test and possible triage testing

Adapted from: Virtanen A, Anttila A, Nieminen P. The costs of offering HPV-testing on self-taken samples to non-attendees of cervical screening in Finland

The cost per extra screened woman by self-sampling as a second reminder was 49-75 euros depending on the price of the sampler (2 or 6.5 euros), and whether an opt-out strategy was used. If the cost per woman screened by self-sampling is calculated only for the under-screened self-sampling participants, it rises up to 170-259 euros. A HPV-analysis assay which would decrease the HPV-positivity to 8% would slightly lower the cost per woman screened by self-sampling from 53 to 52 euros (sampler price 2 euros, no opt-out), but if the price of the analysis simultaneously increased to 30 euros, the cost per woman would be up to 62 euros, 59 with an opt-out strategy.

With the CIN detection rates observed in the studies, with low sampler price and Pap smear triage as follow-up strategy, a CIN2+ lesion detected by self-sampling was not more expensive than one detected in routine screening after primary invitation only (12,800 euros versus 15, 300 euros). A lower follow-up compliance rate of 70% compliance would increase the cost per detected CIN2+ lesion to 14,000 euros, but it would still be lower than the price per lesion with primary invitation only. Further, the addition of two reminders to the invitation protocol did not increase the price of an eradicated CIN2+ lesion in the entire screened population if a Pap smear triage was used for women with a HPV-positive result in the self-taken sample, irrespective of sampler price (2 or 6.5 euros) or the price of the HPV-analysis (20 or 30 euros).

10 DISCUSSION

The Government Degree on Screenings in Finland does not dictate which testing method should be used for cervical cancer screening, or how screening invitations and other practicalities should be organized to ensure optimal uptake. Despite international (Arbyn et al 2008) and national guidelines directed to officials at the municipalities (Voipio-Pulkki et al 2013) and in health care (Current Care Guidelines 2010), the invitational practicalities in individual municipalities are varying. In addition to this, a common practice nowadays is that the screening services are bought from private providers that might change as often as annually. Thus the implementation of actions to improve screening attendance rates is challenging, and in recent decades the trend in national attendance rate has been a decreasing one.

Self-sampling has been an effective approach among non-attendees in other countries in Europe (Table 3, page 39-41). The aim of this study was to assess the effects of reminder letters, and most importantly the effects and feasibility of using home-based self-sampling for hrHPV-testing in the Finnish setting.

10.1 Self-reported reasons for non-attendance

Survey studies have shown that barriers to attend screening can be divided into organizational (clinic-level) barriers such as inconvenient clinic hours, test-level barriers such as discomfort, embarrassment or anticipation of pain or discomfort, and barriers at personal level. Personal barriers further include cognitive barriers (knowledge about screening, understanding the purpose or benefits of the test), emotional barriers (fear, social stigma), economic barriers (taking time off work, insurance coverage, test charge), logistic barriers (childcare, transportation, scheduling difficulties), social barriers (lack of support from family or friends), cultural or language barriers and perhaps a low priority being accorded to cervical screening. In countries with unintegrated organized and opportunistic screening, non-attendance in the programme is often due to recent spontaneous testing.

Barriers to screening seem to vary between populations and are dependent on the used screening setting. Here, the current results are discussed in the context to those previous studies that are most closely associated: previous Finnish studies on reasons for non-attendance, and to previous studies that reported barriers to traditional screening among self-sampling attendees.

In recent Dutch and Italian self-sampling studies among non-attendees, practical issues were the main barriers to previous non-attendance (Giorgi

Rossi et al 2011, Bosgraaf et al 2014). In a self-sampling study from the UK, emotional barriers (uncomfortable, painful) to traditional screening were most commonly reported, and practical issues (lack of time, no child care, access to clinic) came only after this (Szarewski et al 2011).

Similarly to the Dutch and Italian studies, practical barriers to traditional screening were more commonly reported than emotional barriers in our study as well. They were also more often reported than emotional factors when considering only women who were non-attendees to both organized and opportunistic activities within the 5-year screening interval. As for women who reported opportunistic screening as their reason for non-participation in the organized programme, one in five additionally reported practical barriers, and only one in twenty emotional reasons, suggesting that removing practical barriers related to organized screening might have an effect when making it more appealing to the women currently using the opportunistic services. Further, difficulties in finding a suitable free appointment time and other scheduling difficulties were more common among the non-attendees after primary invitation (Study 1, papers I-II) than among non-attendees after two invitations (Study 2, paper III). The observed difference might be due to women with scheduling difficulties having concentrated more to the group of women unable to attend traditional screening even after two invitations. Another possible reason is that the screening clinic involved in Study 1 offered screening appointments in the evenings, whereas half of the study population in Study 2 consisted of municipalities that used health care centres as screening clinics and thus opening hours were restricted to office hours. Based on these results, the most important organizational way to remove practical barriers in traditional screening seems to be offering an adequate amount of free screening appointments, and also outside office hours when work and childcare commitments are easier to overcome.

In our study, emotional barriers to screening (reluctance to undergo a pelvic examination, not finding screening necessary due to previous hysterectomy or low perceived risk of cancer, bad experiences of mass screenings) were more common among women who attended with the first reminder (Study 1) than among women who attended with the second reminder (Study 2), and further, more common among attendees by self-sampling than attendees by reminder letter (Study 1). This indicates that women with emotional barriers to screening might be harder to reach and require several reminders and different approaches such as self-sampling. Emotional barriers were especially relevant among those non-attendees who were under-screened (non-attendees also to opportunistic activities in the last five years) – reported by approximately one third. Taking part with self-sampling was equally common among under-screened women reporting emotional or practical reasons for previous non-attendance, which indicates that self-sampling was able to remove both emotional and practical barriers to traditional screening.

In the study from the Netherlands, the main reason for non-attendance in the routine cervical screening programme was that women forgot to schedule an appointment to have a cervical smear taken (Bosgraaf et al 2014). As invitations were sent with pre-assigned appointment times in our study, this was not an issue. Still, forgetting to attend after primary invitation was reported by 17 % (13% in self-sampling arm and 20% in reminder letter arm) among participants to the second reminder (Study1). Forgetting to attend was almost as common among non-attendees after two invitations, reported by 16% of all responders. Forgetting to take part still being this common among women invited with two invitations was surprising. This can be a reflection of women finding it hard to prioritize cervical screening either due to a busy lifestyle with other demands, or just due to low perceived risk. Further reminders by phone, e-mail or text messages might activate some women, but using self-sampling as a third reminder has clear benefits in comparison to these, because it offers a screening option with no scheduling demands.

In all of the previous Finnish studies from 1960's, 1970's and 1990's, previous opportunistic screening or gynaecologic examination has been the most common reason for non-participation in organized screening. In 1966 in Helsinki, this reason was reported by 35% (Kauppinen et al 1970), in 1972 in Vaasa by 50% of responders (Fortelius et al 1974), in 1991 in Helsinki by 67% of responders (Kallio et al 1994), and in the current study by 46% of all responders (Table 11, page 76). Both studies from Helsinki also reported scheduling difficulties as a fairly common reason, 14% in 1966 and 10% in 1991. This was repeated in the current study by 12% of all responders. If the same is generalizable to all of Finland, resolving scheduling difficulties would increase screening attendance from 70 to 73-74%.

In the most recent study from Helsinki, when regarding only non-attendees who reported no opportunistic testing within one year of the invitation, most common reasons were difficulties in finding a suitable time (21%), forgetting (15%), recent gynaecologic examination (15%) and good perceived health/condition (12%) (Kallio et al 1994). When comparing to the responses received from under-screened women (no smear within 4 years) in the current study, difficulties in making an appointment and forgetting were still often reported reasons, but regular check-ups with own doctor were reported by only 4% and good perceived health was a very rare reason in the current study, reported by less than 1%. Granted, the under-screened responders in the current study were women who for the most part did eventually take part in screening by self-sampling, and thus probably do recognize the importance of screening even without any existing symptoms. Other possible reason for this difference was that this particular reason was not offered as a ready-made choice, perhaps women would have chosen it had it been offered.

10.2 Ways to improve screening attendance

10.2.1 Reminder letters

Among non-attendees to screening after at least one invitation, the effect of a second invitation (reminder letter) has varied between 4 and 12 percentage point increase in total attendance (Wilson & Leeming 1987, Ronco et al 1994, Segnan et al 1998, Tarkkanen et al 2000, Vogt et al 2003, Eaker et al 2004, Heranney et al 2011, Haguenoer et al 2014) and the effect of a telephone reminder between 6 and 9 percentage point increase in previous studies (Vogt et al 2003, Eaker et al 2004, Stein et al 2005, Heranney et al 2011, Broberg et al 2013). The effect of the reminder letter in our study, 7-9 percentage point increase in attendance (Table 5, page 66), was similar to these previous results.

In our study, the increase was smaller, 4 percentage points (6%), with open invitations. Another study comparing open reminders to those with pre-assigned appointments observed an increase of 7 percentage points (21 to 28%) with open invitations and 8 percentage points (36 to 44%) with pre-assigned appointment times (Wilson & Leeming 1987). The difference between open reminders and those with appointment times was smaller than in our study, which might be explained by the lower original attendance rate and the fact that the letter preceding the open reminder was also without an appointment and thus resulted in lower original attendance.

Many self-sampling studies among non-attendees have used a reminder letters as a control for self-sampling (Table 3, page 39-41). They often only report attendance rates among women who were invited with the reminders, not increases in total participation, perhaps due to different types of recording systems for the coverage of smears and attendance by invitation. Participation rates by reminder letters as first reminder have ranged between 2 and 15%, i.e. notably lower than the 26-29% in our study with pre-booked appointments. The studies did not specify whether the invitations included an appointment (most likely not).

The use of reminder letters for non-attendees after primary invitation was a part of international (Arbyn et al 2008) and national recommendations (Current Care Guidelines 2010, Voipio-Pulkki et al 2013) already before this study was launched. Still, they are not used in all Finnish municipalities. In fact, when Study 2 was launched, 13 more municipalities were originally included in the study cohort, but had to withdraw their participation due to a lack of local resources needed for the reminder letters and associated sample taking. These municipalities ended up sending only primary invitations and their average attendance in 2011 remained at 69%, lower than the 73% after primary invitations in the partaking municipalities. Further, although the recommendation in the study protocol was that reminder letters were to be sent with pre-assigned appointments, five municipalities refused to do so and referred to a lack of resources, not wanting to hold appointments for women

of whom a majority would not show up, and partly not wanting to irritate women who already had cancelled one appointment. It is understandable that an "opt in" approach of open invitations might appeal to the organizers of screening, but it introduces problems in possible preferential uptake by low-risk groups, and, as was seen in the results, lower overall attendance rates. When using pre-assigned appointment times, the observed attendance rates by reminder letters can be used to calculate an optimal degree of over-booking to ensure efficient use of time.

10.2.2 Self-sampling as a first reminder

Of the previous studies on self-sampling among non-attendees, randomized studies conducted in Italy (Giorgi Rossi et al 2011) and France (Piana et al 2011, Sancho-Garnier et al 2013, Haguenoer et al 2014) used self-sampling as a first reminder. With direct mailing of the self-sampling devices (or opt-out), participation to screening among women who received the self-sampling test ranged between 18%-23%. In an opt-in approach the participation rate was only 9% (Giorgi Rossi et al 2011). In our study, the participation rate by self-sampling was higher, 32%, most likely reflecting overall large differences in screening systems and populations. For example in France, no national organized programme is at place and screening is largely opportunistic. The studies were conducted within regional screening programmes that are fairly new, started in 2009-2010. Further, in France the most frequent reason for not having a Pap smear is a cultural reluctance to undergo a clinical gynaecological examination (Sancho-Garnier et al 2013), which differs from the self-reported reasons in Finland. As in our study, participation with the reminder letter was significantly lower than what was achieved by self-sampling in all these previous studies, with the exception of the Italian study arm with self-sampling offered with an opt-in approach (9% participation by opt-in self-sampling versus 14-15% by reminder letter) (Giorgi Rossi et al 2011).

10.2.3 Self-sampling as a second reminder

Self-sampling studies in the Netherlands have been conducted among non-attendees after two invitation letters, i.e. as a second reminder. They have used brushes and lavage devices as samplers and reached attendance rates have varied between 28-34% (adjusted for hysterectomy) (Bais et al 2007, Gök et al 2010, 2012b, Verhoef et al 2014a, Bosgraaf et al 2015). The higher attendance rate than that observed in our study for self-sampling as a second reminder (21%) might be due to the difference in study population: in the Netherlands, organized and opportunistic screenings are integrated and invitations are sent only to women with no record of a smear in the 5-year screening interval. Thus the study population in the Netherlands consisted mainly of truly under-screened women, whereas in our study the sampler

was often offered to a woman already screened opportunistically and participation rates were lower.

The same possible reason for higher participation rates applies to the Swedish self-sampling studies that have achieved participation rates of 39-54% in direct mailing settings (Wikström et al 2007a, 2007b, 2011) and 25-39% in opt-in settings (Stenvall et al 2007, Sanner et al 2009, Lindell et al 2012, Broberg et al 2014). Some of the Swedish studies also included reminder letters sent to women who had received the sampler to increase participation (Sanner et al 2009, Wikström et al 2011, Broberg et al 2014). On the other hand, one Swedish study included only participants with over 9 years of not being screened and reached a lower participation rate of 15% (although still higher than with a letter, 4%). In this study being uncomfortable with vaginal examination was the most common reason for previous non-attendance, showing that although attendance among these frequent non-responders was lower than in other studies, a specific subgroup of women might be inclined to take part with self-sampling.

Across all studies that used a second reminder letter as a control, participation rates with the letter were significantly lower, 4-18% (Bais et al 2007, Gök et al 2010, 2012a, Szarewski et al 2011, Wikström et al 2011, Darlin et al 2013b, Broberg et al 2014), and one using a telephone reminder as another control found that the 18% participation with this reminder was higher than with a letter (11%), but lower than by self-sampling (25%) (Broberg et al 2014).

Only study that has reached lower participation rates than the one observed in our study when using self-sampling as a reminder after two invitations was conducted in the UK (Szarewski et al 2011). In this study the response rate to self-sampling was 6.4%, and additionally 3.8% of those sent self-sampling kits attended for cytology screening, resulting in a 10.2% participation rate in total. The authors speculated that some of the invitations/kits did not reach the women due to high mobility in the area and absence of identity numbers.

10.2.4 Socio-demographic determinants of attendance by self-sampling

The self-sampling study from the UK noticed lower participation rates in areas that were most socially deprived (Szarewski et al 2011) - a factor that has not been studied in many of the other self-sampling studies. The two French studies (self-sampling as a second reminder) were conducted among women from low socio-economic group in an area of mainly immigrants living on low incomes (Sancho-Garnier et al 2013), and among women of middle socio-economic status (Piana et al 2011), and reached participation rates of 18 and 26%, respectively. In our study upper and lower level employees and manual workers had higher crude participation rates to screening by self-sampling, and students, pensioners, long-term unemployed

persons and perhaps surprisingly self-employed persons had lower than average participation rates. Incidence of squamous cell cancer is more than two-fold higher in the lowest social class as compared with the highest one (Pukkala et al 2010). High attendance to screening would thus be important in these groups, but a previous Finnish study (Kallio et al 1994) and the current study showed lower attendance rates to traditional screening among students, pensioners and long-term unemployed women. Clearly, self-sampling is not the sole solution to improve the current situation.

Generally, as was seen in our study, participation rates to self-sampling have not varied markedly with regard to different age groups in other self-sampling studies either (Sanner et al 2009, Bosgraaf et al 2015), although some Swedish studies show higher participation rates for younger women (Wikström et al 2007a, 2007b, Broberg et al 2014).

The participation rate to screening by self-sampling was notably lower among immigrants than among Finnish or Swedish speaking women. The same was observed also in the Netherlands (Gök et al 2012a). The five most common mother tongues in the group of self-sampling participants in our study were Russian, Estonian, Thai, Chinese and Japanese, together constituting 63% of the group. In some language groups (for example Arabic, Somali) the participation rate to self-sampling was zero (Figure 6, page 69). Women with immigrant background furthermore reported experiences of insecurity and fear or anxiousness more often than Finnish or Swedish speaking women when collecting their own screening sample. The low participation rate among immigrants can be due to a lack of knowledge on screening in general or to mistrust on self-sampling. Cultural and religious barriers might play a factor as well, although many previous studies on the acceptability of self-sampling conducted for example among Muslim and Hindu women have found no clear indications of this (Anhang et al 2005, Szarewski et al 2009, Jones et al 2012, Cadman et al 2014), with perhaps the exception of Indian and African-Caribbean (Forrest et al 2004), Asian (Waller et al 2006) or Chinese (Howard et al 2009) women.

Language barriers might be a big issue to address among immigrants, both in traditional and self-sampling based screening (Szarewski et al 2009). There were indications of this also in the questionnaires collected with self-sampling devices in our study; women reported they had not understood the invitation letters or the user instruction of the self-sampling device.

Proper education on the benefits of screening is essential, but for the women reluctant to attend traditional screening, a broader familiarity of the self-sampling option might result in higher attendance. There is evidence that peer-support and the example of role models might be important in encouraging participation to screening. A behavioural survey study conducted by telephone interview showed that attendees perceived more positive social influence, had more positive role models, talked more often with others about screening and received significantly more social support from their partner, women next door and children than non-attendees

(Knops-Dullens et al 2007). Thus, raising conversations on cervical cancer screening and screening methods, including self-sampling might increase attendance rates, not only among immigrants but among all women.

As a general remark, questionnaire studies conducted among screening populations have been shown to decrease screening attendance (Helander et al 2014). The extra effort requested from self-sampling participants by sending a questionnaire with the sampling device, as well as the resulting implication that this screening modality is still under research, may have also reduced the attendance rate in our study, and attendance rates may be different in more of a routine setting, especially if the familiarity of self-sampling increases.

10.3 The effects of improved attendance on overall screening coverage

With regard to effects on screening coverage, all of the other studies on the use of self-sampling as a second reminder were conducted in setting, where non-attendance was verified from a common database for organized and opportunistic smears and self-sampling devices were only sent to non-attendees of both modalities. Thus, almost all self-sampling participants in these studies increased screening coverage. Gök et al. (2010) estimated that in the Netherlands where approximately 65% of women attend the screening programme, offering self-sampling to non-attendees, and taking into account the 18% loss of cytology in the follow-up in this group, the effect on attendance would be an extra 5.2%. The total attendance in the screening programme would then increase from 65 to 70.2%.

As we have no exact knowledge on what proportion of those women who were non-attendees to screening prior to the interventions are actually under-screened, we could not make exact calculations on how much the interventions increased overall screening coverage (organized and opportunistic combined). If we assume for the approximately 90% overall 5-year test coverage observed in previous studies (Koponen & Luoto 2000, Salo et al 2014) to be true also in the study populations of 56,650 women, 18% of the approximately 5,700 under-screened women took part by first reminder (1,043/5,665; Table 5 page 66) and further 7% by self-sampling as a second reminder (369/5,665; assuming similar attendance among those identified and not identified for second intervention in Study 1). This would increase overall test coverage from 90% to approximately 92.5%. Or using data from Study 2, 19% of the approximately 3,100 under-screened women took part by first reminder (566/3,105) and a further 9% by self-sampling as a second reminder (269/3,105). This would increase overall test coverage to approximately 92.8%.

In the Italian self-sampling study, the authors used the self-reported information collected among self-sampling participants to calculate the

impact on 3-year population coverage according to the following formula: ((under-covered self-sampling respondents, 34)/(total randomized sample, 438))x(proportion of non-responders at first invitation, 65%) and estimated that the increase in 3-year screening coverage might be 5%, and 2% in 5-year screening coverage (Giorgi Rossi et al., 2011). Using the same formula in the results of our Study 1, self-sampling as a first reminder would have increased overall coverage by 2.1% ((147/2397) x 0.35 = +2.1%) and the reminder letter by 1.8% ((330/6302) x 0.35 = +1.8%). If used in the observations in Study 2, a reminder letter would have increased coverage by 2.1% ((566 under-screened participants/7,397 women invited) x (proportion of non-attendees, 27%) = +2.1%) and self-sampling further by 1.2% ((269/4,536) x 0.21 = +1.2%). This brings us to a similar conclusion as the previous calculations, assuming 90% original coverage an increase to 93%.

From previous studies we know that even though young women (aged 30-35) have low participation rates to organized screening, they frequently attend opportunistic screening and their overall 5-year screening coverage is highest of all age groups, approximately 95% (Salo et al 2014). Self-reported age-adjusted 5-year coverage has also been reported to be highest in the Hospital district of Helsinki and Uusimaa (as was seen in the current results among participants after primary invitation, page 70), and among women with higher education level (Koponen & Luoto 2000). Consistently with these previous results, older self-sampling participants and participants with lower education level were more often under-screened (previous Pap smear ≥5 years ago or never) than younger women and women with higher education level (Table 9, page 71). In fact, self-sampling participants with only primary education were slightly more often under-screened than up to date with screening. This is encouraging as self-sampling thus seems to attract under-screened women of lower educational levels although their overall participation rate remained lower. Further, never married women have lower attendance rates to traditional screening, but their attendance rate by self-sampling was not lower than average, and never married self-sampling participants seemed to be under-screened more often than married or divorced women (Table 9). As never being married is a determinant of higher hrHPV-prevalence (Leinonen et al 2008), these women are important to engage in screening activities.

Perhaps surprisingly, self-sampling participants with a mother tongue other than Finnish or Swedish were not more often under-screened than Finnish or Swedish speaking participants. Overall Pap smear coverage among immigrants versus native Finnish women has not been investigated previously either. Clearly this is a subject that should be studied further, as it is clear that women with a mother tongue other than Finnish and Swedish (immigrants) have low participation rates to traditional screening, but reported reasons obtained in this study did not differ from all responders (Table 11, page 76). Response rate to the questionnaire was low, 12%, and most likely thus affected by response bias. Different research methods,

culturally sensitive questionnaires, face to face interviews or focus group discussions might be more efficient.

10.4 The effects of improved attendance on the yield of CIN lesions detected by screening

The observed test-positivity rate in the self-taken samples, 12%, was higher than that observed among samples from attendees to primary HPV-screening similarly analysed with HC2, 8% (Leinonen et al., 2008, 2012). This may be explained by the cross-reaction of HC2 with low-risk HPV-types found in excess in the vagina, and the fact that there also seems to be high-risk HPV present in the vagina, which is not associated with hrHPV in the endocervix or with CIN2+ lesions (Belinson et al., 2010; Castle et al., 2007, 2002).

However, although CIN yields observed in the studies were small and susceptible to chance, a higher prevalence of also CIN2+ in the originally non-attending population was observed in both studies. Adding two reminders to the invitation protocol increased the yield of CIN2+ lesions by 25-33% (Table 10, page 72). It seems that the second reminder targets women that are at higher risk of CIN2+ than women reached via the first reminder, and that the first reminder targets women with a higher CIN2+ risk than the attendees after the primary invitation. This suggests that the originally non-attending population might be a population of higher risk for cervical cancer in comparison to the population that attends with routine screening invitations. Differences in the sensitivities of the two tests (HPV-testing on self-taken samples and cytological screening) to detect CIN2+ lesions are not a probable reason for the observed difference as the sensitivities have been shown to be similar or for HPV self-sampling even slightly lower (Arbyn et al 2014b).

The same phenomenon was observed in studies from Sweden the Netherlands, CIN2+ detection rates of 2-3.1% among self-sampling attendees (Table 3, pages 39-41), compared to approximately 1% in routine screening in both countries (Sanner et al 2009, Gök et al 2010, 2012b, Broberg et al 2014). In the Netherlands this rate included also lesions detected at follow-up after one year, which accounted for up to 8% of the lesions. In Sweden, the detection rate among self-sampling attendees, 3.1%, was also higher than among reminder letter or telephone reminder participants, 1.7-1.9% (Broberg et al., 2014). The study group in the Netherlands linked this increased risk for CIN2+ among self-sampling attendees especially to women who were frequent non-attendees to the programme or had never been screened (Gök et al 2012a). Likewise in the Swedish studies with high detection rates, all participants had been non-attendees to screening for at least six years (Sanner et al 2009, Broberg et al 2014). In our study, the participants after reminders were not more frequently under-screened than participants after

primary invitation when regarding also opportunistic smears (Table 8, page 70), and 75% of CIN2+ cases detected among participants after the second reminder were detected among women who had been screened within one to two years.

The CIN1 yield increased by 30% with two reminders (Table 10, page 72). The detection rate of CIN1 lesions by reminder letters was similar to that among primary invitation attendees, but higher among attendees after self-sampling (0.5 versus 0.1-0.2%). CIN1 lesions were detected evenly in all age groups. In primary hrHPV-screening as well more CIN1 and CIN2 lesions were detected by primary hrHPV-testing than by primary cytology (Leinonen 2012). As CIN1 lesions have low progression rates to invasive cancer (Syrjänen et al 1992), this too may be a reflection of the lower specificity of HPV-testing, and especially hrHPV-testing with self-taken samples, for more severe CIN lesions. The increase in CIN1 lesions might indicate potential over-screening/diagnosis with consequent over-treatment and psychosocial harms and should thus be followed carefully if self-sampling becomes more common. Although, in contrast to primary hrHPV-screening, self-sampling among non-attendees affects only a minor part of the entire population to be screened and the effects of lower specificity or slight over-screening are not as pronounced.

However, the higher cancer risk of the population not attending organized screening in Finland is further supported by tobacco-related findings from the questionnaires. Both current and former smokers have a significantly increased risk of squamous cell carcinoma of the cervix compared to never smokers (Appleby et al 2006). In 2011-2012, 14-15% of Finnish women aged 25-64 years were daily smokers (Varis & Virtanen 2013). In our study tobacco smoking seemed to become more common among those women who were consistently non-attendees; 17-19% of participants after first reminder reported to be current smokers, but the rate increased to 28-30% among attendees after the second reminder.

10.5 Follow-up after a hrHPV-positive self-taken sample

A way to increase the specificity of hrHPV-testing on self-taken samples is a further triage test that could help to identify hrHPV-positive women with the highest risk for CIN3+ or cancer.

A Pap smear is currently the most obvious choice for triage testing. However, in the group of original non-attendees to traditional screening, the problem of non-compliance to triage testing arises. Compliance to follow-up Pap smears has varied between 41-62% in France to 70-98% in Sweden, Netherlands and UK (Table 3, page 39-41). In our study, compliance to triage Pap smear was 79% in Study 1 (paper II), but in Study 2 (paper III) it was actually as low as 70%. This is most likely due to the fact that in the latter study the letters informing women about the result of the HPV-analysis and

inviting them to a Pap smear did not include pre-assigned appointments for Pap smears as was done in the first study. Other studies have also found ways to increase compliance to follow-up. Haguenoer and colleagues (2014) achieved a compliance rate of 91% by sending the result of the sample both to the patient and the GP responsible for smear taking, and further reminding the non-compliant women with a letter and a phone call. Similarly, in studies from the Netherlands compliance increased from 89-91 to 97-99% by sending test results and, when needed, a reminder letter both to the women and their physicians (Verhoef et al 2014a, Bosgraaf et al 2015). From these experiences it could be speculated that in the Finnish setting using pre-assigned appointments in the letters, and/or a phone call from the local screening personnel could be recommended. As the number of test positives among non-attendees is small, even phone calls would not require unreasonable amounts of resources.

In our study, compliance to risk-group screening among test-positive self-sampling participants with no CIN diagnosis were low, below 50%, compared to the national participation rate in risk-group screening, 71-74% in recent years (Finnish Cancer Registry Statistics). Granted, this low compliance might be partially due to follow-up possibly organized by the hospitals. Similarly, studies from the Netherlands have reported low compliance rates of 57-58% to follow-up after one year among women who were test-positive in the self-taken samples but no CIN was found (Gök et al 2010, 2012b). However, also this compliance increased to 75% when reminders were sent to both the participating women and their physicians, and the follow-up algorithm was reduced to six months instead of one year (Bosgraaf et al 2015). Perhaps the sense of urgency might decrease in longer follow-up intervals. As compliance to risk-group screening seems to be lower among these originally harder to reach women, it would be important to detect as many CIN cases as possible within the primary screening round. This highlights the importance of achieving good compliance rates in initial follow-up of test-positive women.

Triage by cytology requires an extra visit to a clinic. Thus a triage test conducted on the original self-taken sample would most likely decrease loss-to follow-up. Since cytology is not convincingly reliable on self-sampled material (Garcia et al 2003, Brink et al 2006, Jones et al 2013), non-morphology based triage tests that can be directly applied to self-sampled specimens are receiving growing interest. HPV16/18 typing has shown to be a feasible triage test on self-sampled material (Hesselink et al 2014), but does not detect all cervical cancers since only approximately 70% is HPV16/18 positive (Bosch et al 1995). Combined methylation marker analysis of two genes, MAL and miR-124-2, on HPV-positive self-collected cervicovaginal lavage material distinguished CIN2+ with minimum sensitivity of 71.3% and CIN3+ with sensitivity of 77.0%, at specificity of 50% (Hesselink et al 2014). In a large randomized study within an actual home-based screening setting, half of the women who took part in screening by self-taken samples using the

Delphi Screener® were randomized for a Pap smear triage and half to direct methylation marker analysis of MAL and miR-124-2 genes performed on the original self-taken sample (Verhoef et al. 2014). The detection of CIN2+ with methylation triage was non-inferior to that with cytology triage (17% versus 15%; RR 1.19, CI 0.90–1.57). Women who received molecular triage showed a better compliance (100% versus 98%) and shorter diagnostic track to CIN2+ diagnosis (mean 96 versus 158 days), at the cost of 1.9 times higher rate of colposcopy referrals (55% versus 29% of HPV-positive women). A further post hoc analysis revealed that increasing the threshold of MAL/miR-124-2 methylation analysis and combining it to HPV16/18 genotyping gives a lower colposcopy referral rate, while retaining a sufficiently high sensitivity (Verhoef et al 2014b). If methylation markers are to be used in the triage of self-sampling attendees, the choice of sampler device might be important as the amount of cells collected by the brush self-sampler device might be lower than with a lavage device (Gök et al 2012b).

Direct referral to colposcopy is of course an option for follow-up of test-positives in the self-taken sample. It reduces one possible step from the follow-up algorithm and women might feel more obliged to attend after an invitation from the hospital. This has resulted on average in higher compliance rates than follow-up by Pap smear. In our study, follow-up by direct colposcopy resulted in 90% compliance to follow-up, and in previous studies, 85-91% compliances (Table 3, page 39-41). However, this approach requires more resources at hospitals. If all hrHPV-positive women among attendees to self-sampling as a second reminder in the study populations would have been invited for colposcopy, the annual number of referrals for diagnostic confirmation would have increased by 53% in Study 1 and by 47% in Study 2. Nationwide, this would increase the current annual number of 1,600–2,000 referrals from organized screening by 800-1,000 - although the referrals from organized screening are only a small proportion of the total burden of annual colposcopies. Still, the positive predictive value of a referral after a HPV-positive self-taken sample would remain quite low; 6% for CIN2+ and 4% for CIN3+. One guideline previously proposed for the risk threshold in referrals for CIN3+ is PPV≥10% (Castle et al 2008a). This supports the need for triage testing, as was also observed in pooled PPVs of a recent meta-analysis (Arbyn 2014). For Pap smear triage, using the referral rate after a triage Pap smear observed in our studies (among women aged <40), the PPV of a referral for CIN2+ would be 26%, similar to the app. 30% what was observed among attendees after primary invitation screened by cytology.

10.6 Acceptability of screening by self-taken samples

Insecurity and concern over doing the test properly seems to be the most commonly expressed negative experience and barrier to self-sampling across

studies, populations and sampling devices (Forrest et al. 2004, Berner et al. 2013, Mithchell et al 2011, Szarewski et al. 2009, Barata et al. 2008, Cadman et al. 2014, Howard et al. 2009, Anhang et al. 2005, Nobbenhuis et al. 2002, Bosgraaf et al. 2015, Wikström et al 2007, Guan 2012). Our results are well in line with this, as insecurity during sample taking was the most commonly reported negative experience, reported by 19% of all self-sampling participants (Figure 7, page 74). A commonly reported concrete source of insecurity was whether the amount of fluid was sufficient for analysis. Use of collection devices with indicators of proper sample collection that would be visible to the woman, such as the FTA elute cartilages that change colour when sample is applied, could reduce these concerns. However, in our study over 80% of the responders expressed their trust in successful sample collection and the test results. Further, mistrust in test results and/or one's ability to take the sample were rare reasons for declining the self-sampling option among those women who gave a reason for their refusal. In the Netherlands, the most common reason for declining the self-sampling option was preference for a Pap smear, but reasons for this preference were not reported. Mistrust in self-sampling was not specified as a separate reason (Bosgraaf 2014). However, the response rate to the questionnaire among women who declined the self-sampling option was very low in our study (10%) and in the study in Netherlands (4%) and thus might not represent the non-attending women as a whole.

In the literature, features of the self-test that appealed to women included; being able to do the test on their own (Giorgi Rossi et al 2011, Bosgraaf et al 2014), privacy (Anhang et al 2005, Giorgi Rossi et al 2011), not having to travel (Wikström et al 2007a, Howard et al 2009), less time consuming (Forrest et al 2004, Wikström et al 2007a, Jones et al 2012, Bosgraaf et al 2014), overall more convenient (Guan et al 2012, Mullins et al 2014), not being painful (Anhang et al 2005, van Baars et al 2012a, Berner et al 2013) or otherwise more comfortable than clinician sampling (Dzuba et al 2002, Waller et al 2006, Barata et al 2008, Guan 2012, Jones et al 2012, Berner et al 2013) and causes less embarrassment (Dzuba et al 2002, Forrest et al 2004, Waller et al 2006, Barata et al 2008, Howard et al 2009, Szarewski et al 2009, Guan 2012, Jones et al 2012, Berner et al 2013, Bosgraaf et al 2014, Mullins et al 2014). The most common reasons to prefer self-sampling to traditional screening in our study population were convenience and self-sampling being more private.

To my knowledge, only one other study thus far has explored more specific aspects of user-friendliness of a home-based self-sampling in a population-based setting among non-attendees (Bosgraaf et al., 2015) in addition to the current one. Overall, negative experiences seem to be rare among those non-attendees to traditional screening who choose to take up the offer of self-sampling, both in our study and the previous one in the Netherlands. However, more research is needed on whether barriers to self-sampling among those declining both traditional screening and self-sampling

could be overcome. In Finland, especially immigrants are a subgroup of women who should be studied further as they reported feelings of insecurity, fear/anxiety and discomfort more often than Finnish or Swedish speaking women.

10.7 Costs of screening

To my knowledge there are currently three studies that have also evaluated the costs of using self-sampling as a reminder to non-attendees (Bais et al 2007, Broberg et al 2014, Haguenoer et al 2014). As no cancer outcome information is available, these studies have either used a proxy for the potential of increasing the impact of the programme (for example CIN2+ detection/eradication) or simply calculated the relative costs in increasing screening attendance between two interventions. Still, all three previous cost evaluations have arrived at the conclusion that offering self-sampling could be cost-effective or at least cost-neutral. However, as both the effect of reminders on screening attendance and CIN yield are highly dependent on the screening settings (organized and opportunistic) and population (underlying cancer risk) and the local costs (price level), cost evaluations are almost always non-generalizable.

In the Netherlands it was estimated that the total costs per CIN2+ lesion detected by self-sampling were in the same range as those calculated for conventional cytological screening (8,836 euros vs. 7,599 euros) (Bais et al. 2007). This included the costs of organization invitation, costs involved with testing (with a price of two euros for the self-sampling device) and costs for diagnosis and treatment. This study used a significantly lower unit price, perhaps a more realistic one, for diagnostic colposcopy and follow-up of HPV-positive cases with no CIN diagnoses (500 euros), than the one used in our estimate (1,000 euros). The price per detected lesion was also lower than the ones observed in our study (Table 12, page 78) due to a more than threefold higher rate of detected CIN2+ lesions (1.7% versus 0.5% in our study).

A recent Swedish trial reported total costs of self-sampling per additional detected case of CIN2+. By applying a ratio of six treated CIN2+ lesions to avert one cancer, the authors concluded this intervention would likely be cost-saving and at least cost neutral as the marginal cost per avoided cancer by self-sampling was 18,000-28,000 euros depending on sampler price, and the average cost of treating cervical cancer in a unscreened population is 38,900 euros (Broberg et al 2013, 2014). This study estimated significantly lower costs per CIN2+ lesion (3,000-5,000 euros depending on sampler price) than that we estimated for Finland, partly due to higher CIN detection rate among participants (1.4% versus 0.5% of participants), and lower unit costs, but mostly due to an opt-in strategy where samplers were only sent to women by order.

An opt-in strategy would most likely reduce the costs of self-sampling in Finland as well. It does, however require more of an initiative from the women who are already harder to reach, and has generally resulted in lower attendance rates, especially if contact letters offering self-sampling are limited to only one or two (Giorgi Rossi et al 2011, Broberg et al 2014). In the Swedish study women were contacted by as many as four letters when needed (initial invitation and reminders to order and/or return the sampler/sample). In the Finnish setting, after two invitation letters within the same year and opportunistic testing being common among non-attendees, this most likely would not be acceptable to the women.

In France, Haguenoer and colleagues calculated that the incremental cost-effectiveness ratio (ICER) per extra screened woman was 63.2 euros by self-sampling and 77.8 euros by reminder letter in comparison to no intervention, and concluded that the self-sampling strategy (with an inexpensive self-sampling device) could be cost-effective as compared with a reminder letter (Haguenoer et al 2014). Assuming there would have been no screening attendance in the reminded population without the interventions, the costs per extra screened woman calculated in the cost evaluation in our study are actually comparable to the ICERs calculated in the French study. The difference in attendance with the interventions was so noticeable in the French study (23 versus 10%) that it compensated for the additional costs of the self-sampling strategy. Based on our cost evaluation, this was not the case in the Finnish setting as costs per participant were 33 euros for reminder letter and 43 euros for self-sampling. The cost per participant remained lower by reminder letters also when participation rate was set at a lower level of 14% (as observed for open invitations). Further, even with a 20% or 50% higher CIN2+ detection rate by self-sampling the cost per treated lesion was still higher than with a reminder letter.

The implementation of reminder letters and self-sampling into the invitational protocol could increase the amount of detected and treated lesions without increasing the price per lesion. Thus, also from the point of view of resulting costs, the implementation of self-sampling into areas where other actions do not increase screening attendance sufficiently is worth exploring further. However, implementing interventions to increase attendance in screening programmes often face the problem of fixed budgets; even if more lesions could be detected at the same price per lesion as earlier, higher compliance means higher costs. For opportunistic screening, even non-private funding comes from many directions, for example municipal health care budget, Kela (Finnish special reimbursements for medical expenses) and student health care, and is not recorded or evaluated with regularity. Thus restrictions to resources allocated to opportunistic screening are harder to apply than to those allocated to organized screening - although it is acknowledged that opportunistic screening with high coverage among young, perhaps too young, women and significant over-screening among

some women leads to small amounts of health effects and is not efficient (IARC 2005, Lönnberg et al 2012).

Currently, out of all Pap tests obtained for screening purposes, opportunistic screening accounted for 60% of the 446,000 annual tests and 78% of the 22.4 million total costs (Salo 2013). The price of an opportunistic Pap smear is clearly higher than one taken within the organized programme, 54-82 versus 30 euros. The price of an opportunistic screening test is also higher than the combined price of the invitational system and primary testing per participant in the current estimate, even with one or two reminders (31-34 euros; Table 12 page 78). Decreasing the number of unnecessary opportunistic testing and increasing attendance in organized screening will thus most likely decrease overall costs, and importantly, the health benefit will hopefully be more evenly distributed.

However, sending reminders will not entirely fix the problem. Although self-sampling did manage to include some previously under-screened women into the screening programme, the effect on coverage remained small. In Belgium though, over-screening was decreased substantially by restricting reimbursements to only every two years. This reduced the total volume of cervical cytology examinations performed by 40%. In the Finnish setting with a highly effective screening programme in place, perhaps a restriction of imbursements for opportunistic testing, education of health personnel and a reform of the screening programme to make it more appealing and feasible for women could encourage women to shift sides, from opportunistic attendance to compliance with the organized programme. In the end, organized screening is not only a question of saving public resources, most of all it is a question of optimizing the effectiveness and minimizing the adverse effects of screening among women who are in most cases disease free.

10.8 Strengths and limitations

This study was conducted as a part of routine screening programmes in a large variety of Finnish municipalities. The first study was conducted in a setting where original attendance with primary invitation (63%) was lower and the second one in a setting with higher (73%) level of attendance than the national average of 70%. They both achieved similar rates of participation by interventions and these results can thus be regarded reliable and quite generalizable to the Finnish setting. The studies used the infrastructure of the organized programme with the exception that the mailings of the self-sampling tests were organized by the study group. The results are thus easily applicable for routine use.

In the evaluation of self-sampling as a second reminder, many of the factors affecting screening rates, most importantly invitations with pre-assigned appointments and reminder letters, but also a web-based programme for easy scheduling, were used in the screening protocol of the

partaking municipalities before self-sampling was introduced. The municipalities did not, however, offer screening appointments outside office hours which might have increased the effects of regular screening invitations, in which the effect of self-sampling on screening participation might have been smaller.

The use of self-sampling as a first reminder to non-attendees was compared to the current recommendation of a reminder letter in an individually randomized setting when most biases should be avoided. However, the effects of self-sampling as a second reminder were evaluated in a non-randomized setting, i.e. it was not compared to another type of second reminder, for example a second reminder letter as has been done in other countries. Further, the effect of the reminders on screening participation was not tested against a group that didn't receive any additional interventions. Usually the invitation to screening is valid to the end of the year. As especially reminder letters were sent within the one screening year, the participation rate by primary invitation was set to be what it was prior to sending out the reminder letters, even though it still might have increased by the end of the year. This might exaggerate the effects of the reminder letters to some extent. Self-sampling tests were for the most part sent later, when the invitation to screening was no longer valid, and the previously described source of potential exaggeration does not apply. However, when self-sampling tests were sent, more time had elapsed since the original invitation, and women who were not willing to take part earlier due to for example pregnancy or recent opportunistic screening, might have been willing to participate when self-sampling was offered. A case like this might exaggerate the effect of self-sampling because the enticing factor was not necessarily self-sampling as a screening invitation, but the timing of the invitation. A control group of a second reminder letter sent at the same time would have helped to clarify this potential bias.

The response rate to the questionnaire among self-sampling participants was very high and the demographic profile of the responders represents well the group as a whole. However, among those non-attendees that declined the self-sampling option as well, the response rate to the questionnaire was very low (10%), and as a result, the total response rate to the questionnaire among all non-attendees was only 28%. Selective response to questionnaires is an important barrier for studies on determinants of uptake of cervical cancer screening. In the Netherlands, a non-response study was conducted in context of a survey study; non-responders to the questionnaire, including both non-attendees and attendees to screening were interviewed by telephone. The researcher found that women who dropped out of the survey thought they were in less danger or were more convinced that cancer was fatal. (Tacken et al 2007) In our study responses of non-attending women with lower education level and a mother tongue other than Finnish or Swedish, i.e. women who have lower participation rates to both traditional and self-sampling screening, were under-represented. Further, based on

reported smoking habits and attendance to gynaecologic check-ups, the questionnaire responses that were obtained from women who did not take part with self-sampling seem to have been obtained from a lower risk population. Thus, there is a risk of response bias, and the reported reasons for non-attendance and reasons for declining the self-sampling option might not represent the non-attending population as a whole.

The evaluation of costs has several limitations. Firstly, in the absence of information on longer term health benefits achieved by the increase in attendance, such as cancer reduction or life years gained, this evaluation focused on cost per eradicated CIN2+ lesion, which is clearly an incomplete surrogate. Estimates on how many CIN2+ lesions must be treated to prevent one case of invasive cancer vary from four to eight (Raffle et al 2003, National Institute for Health and Welfare 2011, Barken et al 2012), whereas the corresponding estimates for CIN3+ vary from three to six (Hakama & Räsänen-Virtanen 1976, Magnus et al 1987, Forsmo et al 1997, McCredie et al 2008) . Even though CIN3+ is a better surrogate for cancer prevention, CIN2+ was chosen as a proxy for comparability with other studies. Secondly, the studies were powered to observe differences in attendance rates, not in CIN yields. The resulting CIN yields remained small, and are susceptible to chance. Further, referral rates, CIN yields and resulting costs might be dependent on the used HPV-assay decreasing thus the generalizability of the results. Thirdly, in the original studies, the follow-up protocol was to refer women with a hrHPV-positive self-taken sample aged 40 years or older directly to a colposcopy and invite women aged less than 40 years for a triage Pap smear. Thus in the cost evaluation, the number of further referrals for colposcopies from the Pap smear triage was estimated based on the colposcopy rate of women under 40 years in the studies, even though the referral rate might be age dependent in reality (although in this case this is more likely an over- rather than under-estimation of the rate). Lastly, the cost used for colposcopic examinations and follow-up for women with no CIN diagnoses was quite high, 1,047 euros (versus cost of colposcopy and biopsies alone, 300-500 euros). Women referred for colposcopy on the basis on HPV-positivity without cytological changes (direct colposcopy after self-sampling) might need less intensive follow-up than women referred due to cytological abnormalities, and for them the used average cost and thus the cost per CIN2+ case is most likely an over estimation.

However, the cost per extra screened woman is based on participation rates by interventions with rather narrow confidence limits adding reliability to the results. The results and calculations were presented in a manner that allows for recalculations with different unit costs and are thus applicable for different settings, to be used for example by municipalities or screening laboratories.

The lack of comprehensive reliable data on opportunistic smears and thus on overall test coverage within the study population is a clear, and perhaps the biggest, limitation of this entire study. Estimates on the effects on

screening coverage relied on self-reported data, which might be unreliable (Walter et al 1988, Eaker et al 2001), and was here available essentially only for self-sampling participants. Thus, the effects on overall screening coverage in the study population could not be reliably evaluated. Further, although some under-screened women were demonstrably screened by self-sampling these women were a minority among self-sampling participants. As the study was conducted in the Finnish population that is already over-screened (Salo et al 2014), for a large part self-sampling only increased the level of over-screening - with high costs as was seen in the cost evaluation.

10.9 Summary and implications

Achieving adequate levels of uptake in cancer screening may require a variety of approaches that need to be shaped by the characteristics of both the screening programme and the target population. Practical barriers (dependency on clinic hours and scheduling difficulties due to other commitments) were more commonly reported as reasons for non-attendance to traditional clinic based screening, but emotional barriers (discomfort and embarrassment associated with the gynaecological exam) play a significant role as well, especially among those in non-attendees who are non-attendees to opportunistic activities as well. Forgetting to take part was surprisingly common even after two invitation letters.

Self-sampling, being able to collect one's own sample at home, removes both practical and emotional barriers to traditional screening and has thus the potential to improve participation among women who are hard to reach. Trials comparing self-collected hrHPV-test samples to physician-collected samples found that generally both methods provided equally viable samples for detecting hrHPV. In addition, self-sampling for hrHPV-testing is as sensitive as or even more sensitive than the currently predominantly used Pap smear to detect moderate or severe precursor lesions. With PCR-based testing self-sampling is also as sensitive and specific to detect severe precursors as hrHPV-testing by a clinician.

As a first reminder to non-attendees after the primary invitation, a self-sampling test resulted in somewhat higher attendance than a reminder letter; a self-sampling test increased screening attendance by 11 percentage points, a reminder letter with a pre-booked appointment by 7-9 percentage points and a reminder letter with no appointment by 4 percentage points. However, although significant, the difference in participation rates was modest, and the reminder letter with a pre-booked screening appointment is still most likely a better choice in terms of price per extra screened woman, and most likely also price per detected and eradicated CIN2+ lesion. Further, as hrHPV-screening is most likely the future of cervical cancer screening in Finland (National Institute for Health and Welfare 2011, Leinonen 2013), based on the current knowledge, invitations to sampling by a clinician should be the

primary option - especially if a screening programme uses signal-based assays such as HC2 for hrHPV-analysis (Arbyn 2014). Reminder letters increase attendance to this primary screening option almost to the same extent as self-sampling offered as the first reminder, and self-sampling can then be used as an additional strategy to reach women still not participating in the regular screening programme. Based on the literature, also telephone reminders are worth considering as interventions to non-attendees or future research aspects in Finland.

As a second reminder to non-attendees after two reminder letters, a self-sampling test increased attendance to screening by 3-5 percentage points. Using two reminders (reminder letter, then self-sampling), increased the yield of detected CIN2+ and CIN3+ lesions by 25-33 and 24-25%, respectively. In the current screening setting with abundant opportunistic testing, the effect on overall screening coverage most likely remained small, approximately 2-3% increase. Still, although CIN yields observed in the studies were small and susceptible to chance, a higher prevalence of precursors in the originally non-attending population was observed in both studies, which supports previous findings that the non-attending population might be one with a higher risk for cancer. Thus, in the absence of evaluations on cancer outcomes, these surrogate findings support the importance of using reminders for non-attendees after the primary invitation.

Based on the cost analysis, it seems that the higher prevalence of precursors in the non-attending population could even out the higher costs of self-sampling in terms of price per eradicated precursor lesion. A challenge in the future is to evaluate whether it would be wise to direct the interventions among non-attendees only to those women who are truly under-screened, not only non-attendees to the organized programme, because this would offer significant cost savings. And importantly, how this could be achieved without breaking the aim at equality, that all women are entitled to similar preventive actions, which is important in a public health activity such as cancer screening.

With the recent meta-analysis by Arbyn et al. it became clear that an essential aspect of hrHPV-testing on self-taken samples is the heterogeneity between hrHPV-testing methods. For the assay used in these studies, HC2, relative sensitivity of 0.85 (0.81-0.90) and relative specificity of 0.96 (0.93-0.98) was pooled from 18 studies using brushes, lavage devices, swabs or tampons as sampling devices, and the lower sensitivity was seen for all devices. The implications of more sensitive analysis methods on referral rates and CIN yield by self-sampling should be evaluated in the Finnish setting as well. Furthermore, although it seems that different devices don't have diverse implications on disease detection, they might have different effects on attendance and direct comparative studies are important on this aspect. A gradual implementation allows for simultaneous evaluation on what would be the most feasible and cost-effective set of a self-sampling device and

hrHPV-analysis method for the local setting, as well as developing an optimal follow-up protocol for hrHPV-positive women.

With the implementation of the HPV vaccination programme, the screening programme will still be needed for optimal cancer prevention also in the vaccinated population, but the programme most likely will require adaptation (National Institute for Health and Welfare 2011). Self-sampling can help to achieve adequate screening attendance in the future scenarios as well.

Achieving optimal attendance in screening is highly dependent on the invitational protocol. We have shown that a total attendance and coverage of well over 80% is achievable solely within the organized screening programme, if reminder letters are sent to non-attendees after primary invitations, scheduled appointments are used in both letters and self-sampling tests are sent those women who still do not attend. The highest overall attendance rate of 83% was achieved among municipalities following this exact protocol. Thus, a nationwide use of pre-assigned appointment times and reminder letters should finally be established. There are also already screening laboratories which are able to carry out HPV-testing, and it is likely that the numbers and capability will increase in the near future if hrHPV-testing becomes the primary screening modality. As self-sampling seems to be acceptable to non-attenders, it would thus be possible to make it widely available and consider a gradual implementation of self-sampling to areas where the previously mentioned actions don't result in an attendance rate of clearly over 80%.

11 CONCLUSIONS

The following conclusions can be drawn:

- As a first reminder to non-attendees after the primary invitation, a self-sampling test resulted in somewhat higher attendance than a reminder letter; participation rate among non-attending women who were offered self-sampling as a first reminder was 32% and among women invited with a reminder letter 14 to 27% (open invitations and invitations with pre-assigned appointment times, respectively). A self-sampling test increased screening attendance by 11 percentage points (17%), a reminder letter with a pre-booked appointment by 7-9 percentage points (9-14%) and a reminder letter with no appointment (open invitation) by 4 percentage points (6%).

- As a second reminder to non-attendees after two reminder letters, the participation rate among women offered the self-sampling test was 21%, and increase in total attendance was 3-5 percentage points (4-8%). Total increase with two reminders was 8-15 percentage points (12-23%) depending on original attendance rate and whether reminder letters were sent with pre-booked appointments or not.

- As opportunistic screening is very common in Finland, 70% of attendees by reminder letter and 59% of attendees by self-sampling as a second reminder had in fact been screened opportunistically within the five-year screening interval. Thus the increase in overall test coverage remained small, approximately 2-3%.

- When original non-attendees were included in screening, the yield of detected CIN2+ lesions increased by 8-19% with one reminder and 25-33% with two reminders.

- Women who took part in screening by self-sampling reported mainly positive experiences. Negative experiences were more common among women with a mother tongue other than Finnish or Swedish.

- As a first reminder, the price per extra screened woman and price per detected CIN2+ lesion was lower with a reminder letter than by self-sampling. When self-sampling was used as a second reminder with a low sampler price and a triage Pap smear as a follow-up test for hrHPV-positive women instead of direct colposcopy referral, the eradication of a CIN2+ lesion by self-sampling was not more expensive than in routine screening. The combined increase of two

interventions (reminder letter, then self-sampling) to original overall costs was 26-43%.

- Most common self-reported reasons for non-attendance in screening were a recent opportunistic Pap smear and practical reasons, such as scheduling difficulties. Emotional reasons were more common among women who were non-attendees also to opportunistic activities. Home-based self-sampling helps to overcome both practical and emotional barriers to traditional screening.

- Socio-demographic factors related to significantly lower participation in routine screening are young age, a mother tongue other than Finnish or Swedish, a lower education level, living in a rural municipality, having never been married and being retired. A mother tongue other than Finnish or Swedish and a lower education level affected also attendance rates to self-sampling.

All in all, as a first reminder to non-attendees after the primary invitation, a self-sampling test resulted in somewhat higher attendance than a reminder letter. However, in terms of resulting costs, a reminder letter with a pre-assigned appointment time is a more feasible choice than a self-sampling test.

Self-sampling for hrHPV-testing can be used to increase screening attendance as a second reminder after two invitation letters. The invitation protocol preceding the self-sampling option must be carefully arranged to achieve optimal attendance. A total attendance of well over 80% is achievable if personal invitations and reminder letters to non-attendees are sent, scheduled appointments are used in both letters, and self-sampling tests are sent to those women who still do not attend.

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