

# **Non-attendees need attention**

**Determinants and interventions affecting  
participation in cervical cancer screening**

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Carpe diem

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## Determinants and interventions affecting participation in cervical cancer screening

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### ABSTRACT

**Aim:** Non-attendance is the foremost screening-related risk factor for cervical cancer. The overall aim of this thesis is to contribute to preventing cervical cancer by focusing attention on non-attendees, assessing interventions to increase participation in screening and identifying determinants for non-attendance.

**Methods:** The effectiveness and cost-effectiveness of two interventions to increase participation were studied in a population-based, randomised trial in the context of a well-run screening program in western Sweden. Non-attendees were telephoned and offered an appointment to take a Pap smear or mailed an offer to take a high-risk human papillomavirus (HPV) self-test, and the results were compared with a control group. Midwives' experiences of contacting non-attendees were discussed in focus groups, and analysed by qualitative content analysis. A cross-sectional study with data from population-based registers was carried out to study socioeconomic and demographic factors' affect on screening participation. The results were analysed using univariate and multivariate logistic regression models.

**Results:** Participation during the follow-up period after the interventions was significantly higher in both the telephone arm (18.0%) and the HPV self-test arm (24.5%) than in the control group (10.6%). There were significantly more detected abnormal smears and followed up abnormalities in the telephone arm (39 and 34, respectively) than in the control group (19 and 18, respectively). The midwives realised that there were a number of reasons for non-attendance that could be addressed by improving the screening program. These reasons were often related to logistics, such as scheduling flexibility and appointment booking. Women with high household income or high education or who were living with a partner, born in Sweden, working or not receiving welfare benefits were found to be more likely to attend cervical

screening. The relative risk for attendance related to county of residence varied more than twofold.

**Conclusions:** Long-term non-attendees had a fourfold increase in high-grade cytological atypia, compared with regularly screened women. Both telephone contact and offering a HPV self-test, increased participation among women who had abstained from cervical cancer screening for a long time. The telephone intervention yielded a significant increase in detected and followed up atypical smears. These interventions are also practically feasible and do not seem to increase costs. Offering various screening options can be successful in increasing overall participation rates. Midwives' awareness of women's varying requirements for attending screening provides possibilities to improve access and prevent non-attendance in cervical cancer screening. Low socio-economic status, being born abroad and residing in some Swedish counties are independent factors associated with lower attendance in cervical cancer screening. This indicates there is major potential for improvement of cervical cancer screening routines in Sweden in order to increase participation.

**Keywords:** Cervical cancer, cervical intraepithelial neoplasia, demography, HPV, mass screening, non-attendance, Papanicolaou smear, telephone call and socioeconomic factors

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# SAMMANFATTNING PÅ SVENSKA

**Bakgrund:** Livmoderhalscancer är idag den tredje vanligaste cancerformen bland kvinnor i världen trots att den anses vara möjlig att förebygga. I Sverige har sjukdomen blivit relativt ovanlig sedan organiserad screening med gynekologiskt cellprov infördes i slutet på 1960-talet. Årligen drabbas cirka 450 kvinnor av livmoderhalscancer och cirka 140 dör av sjukdomen. Förutsättning för att screeningprogrammet ska vara framgångsrikt är ett högt deltagande. Kvinnor som inte deltar i gynekologisk cellprovskontroll är en minoritet men utgör störst andel av dem som får livmoderhalscancer, framförallt i avancerad form. Det nyligen införda vaccinationsprogrammet mot humana papillomvirus (HPV) utesluter inte cellprovtagning då tillgängliga vacciner inte skyddar mot alla onkogen HPV. Det kommer också alltid att finnas ovaccinerade kvinnor. Screeningprogram kommer således, även inom överskådlig framtid, vara nödvändiga för att skydda kvinnor mot livmoderhalscancer.

**Syfte:** Det övergripande syftet med avhandlingen är att förebygga livmoderhalscancer genom att fokusera på de kvinnor som inte har deltagit under lång tid, pröva metoder för att öka deltagandet i screening och identifiera faktorer som påverkar deltagandet.

**Metoder:** I en populationsbaserad randomiserad studie studerades effektiviteten och kostnadseffektiviteten av två interventioner för att öka deltagandet i ett välfungerande screeningprogram. Kvinnor som inte deltagit i screening ringdes antingen upp av en barnmorska som erbjöd tid för cellprovtagning eller fick erbjudande per post att göra ett hemtest för högrisk-HPV. Screeningdeltagandet i dessa två grupper jämfördes med en kontrollgrupp. Barnmorskornas erfarenheter av att kontakta kvinnorna diskuterades i fokusgrupper och analyserades med kvalitativ innehållsanalys. En tvärsnittsstudie med data från populationsbaserade register genomfördes för att studera om socioekonomiska och demografiska faktorer påverkar deltagande i screening. Resultaten analyserades med univariat och multivariat logistisk regressionsmodell.

**Resultat:** Deltagandet ökade signifikant i båda interventionsgrupperna, jämfört med kontrollgruppen. I telefongruppen deltog 18,0% och i HPV hemtestgruppen tog 24,5% prov (16,9% HPV hemtest; 8,5% cellprov), jämfört med 10,6% i kontrollgruppen. Antalet avvikande cellprov och antalet utredningar var signifikant högre i telefongruppen (39 respektive 34) än kontrollgruppen (19 respektive 18). Kvinnorna uppgav många olika anledningar till varför de inte deltagit i screeningen. Det vanligaste var praktiska svårigheter som barnmorskorna insåg skulle kunna undanröjas med

ökad tillgänglighet och genom att erbjuda provtagning vid besök av annan anledning.

I Studie IV fann vi att kvinnor med en hög inkomst i familjen eller hög utbildning och de som var sammanboende deltog i högre utsträckning i screeningen. Andra viktiga faktorer förknippande med högt deltagande var att vara född i Sverige, vara yrkesverksam och att inte ha social- eller bostadsbidrag. Kvinnorna i de högre åldersgrupperna var något mer benägna att delta än i de lägre. Deltagandet varierade stort mellan de olika landstingen i Sverige. Dessa skillnader kvarstod även efter att effekten av alla andra variabler hade vägts in.

**Slutsats:** Kvinnor som inte har deltagit i screening under en längre tid hade en fyrfaldig ökad risk att ha höggradiga cellförändringar jämfört med hela screeningpopulationen. Både telefonkontakt och erbjudande om ett HPV hemtest till kvinnor som har avstått från att delta i gynekologisk cellprovskontroll ökade deltagandet, visade sig praktiskt genomförbart och gav inga ökade kostnader. Telefonkontakt ökade även antalet upptäckta och utredda cellförändringar. Erbjudande om alternativa provtagningsmetoder kan främja deltagandet i screeningen. Barnmorskornas förståelse för kvinnors varierande behov kan bidra till att tillgängligheten ökar så att fler ges möjlighet att delta i screeningen. Låg socioekonomisk status, att vara född utanför Sverige eller bosatt i vissa län var oberoende faktorer förknippade med lägre deltagande i gynekologisk cellprovskontroll. Sammantaget indikerar detta att det finns en stor potential att genom förbättringar av screeningen i Sverige öka deltagandet.

**Implikationer:** För att skapa förutsättningar för en mer jämlik vård och ge så många kvinnor som möjligt ett bra skydd mot livmoderhalscancer bör:

- screeningprogram utformas i alla landsting så att möjlighet skapas för alla kvinnor att delta. Viktigt är god tillgänglighet, möjlighet till enkel ombokning av tid och plats via internet samt opportunistisk screening,
- särskilda åtgärder vidtas för kvinnor som inte deltagit under lång tid, som telefonkontakt och/eller erbjudande om alternativ provtagning,
- uppmärksamhet och särskilda insatser riktas mot grupper med lågt deltagande.

Mer framtida forskning behövs för att hinder ska kunna undanröjas för grupper med lågt deltagande.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals:

- I. Broberg G, Miao Jonasson J, Ellis J, Gyrd-Hansen D, Anjemark B, Glantz A, Söderberg L, Ryd M-L, Holtenman M, Milsom I and Strander B. Increasing participation in cervical cancer screening: Telephone contact with long-term non-attendees in Sweden. Results from RACOMIP, a randomized controlled trial.  
*International Journal of Cancer* 2013;133:164-71
- II. Broberg G, Gyrd-Hansen D, Miao Jonasson J, Ryd M-L, Holtenman M, Milsom I and Strander B. Increasing participation in cervical cancer screening: Offering a HPV self-test to long-term non-attendees as part of RACOMIP, a Swedish randomized controlled trial.  
*International Journal of Cancer* 2014; 134: 2223-30
- III. Broberg G, Strander B, Ellis J and Adolfsson A. Attending cervical cancer screening, opportunities and obstacles: A qualitative study on midwives' experiences telephoning non-attendees in Sweden.  
*Scandinavian Journal of Public Health* Published online July 10 2014 DOI: 10.1177/1403494814541594
- IV. Broberg G, Wang J, Östberg A-L, Adolfsson A, Nemes S, Sparén P and Strander B. Socio-economic and demographic determinants affecting participation in the Swedish cervical cancer screening: population based cross sectional study.  
*In manuscript*

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# ABBREVIATIONS

ASCUS	Atypical squamous cells of undetermined significance
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
FIGO	International Federation of Gynaecology and Obstetrics
HPV	Human Papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LEEP	Loop electrosurgical excision procedure
LISA	Longitudinal Database on Health Insurance and Labour Market Studies
OR	Odds ratio
Pap	Papanicolaou
PIN	Personal identity number
RCT	Randomised controlled trial
RR	Relative risk
WHO	World Health Organization

# 1 INTRODUCTION

Cervical cancer has become relatively rare in Sweden since the screening program was introduced in the 1960s. This success is due to a high attendance rate among women eligible for screening. Research in the field has been extensive since screening with the Papanicolau (Pap) smear was introduced. The knowledge that cervical cancer is caused by Human Papillomavirus (HPV), development of HPV tests and vaccine against some HPV types have introduced a new era in cervical cancer prevention. However, the recently initiated vaccination program in Sweden will not have an impact on the incidence of cervical cancer until 2040. The current vaccines also provide limited protection; furthermore, generations of sexually active women are unvaccinated. This means that parallel preventive strategies will be required in future. This thesis aims at contributing to cervical cancer prevention by focusing attention on non-attending women, assessing interventions to increase participation in screening and identifying determinants for non-attendance.

## 1.1 Cervical cancer

### 1.1.1 Epidemiology

Cervical cancer is one of few malignancies that can be considered to be mainly preventable in the twenty-first century, through vaccination and/or adequate screening. However, cervical cancer is still considered to be a public health burden in the global perspective [1]. It is the third most common cancer in women, with 529,000 new cases in 2008, and is the cause of 275,000 deaths [2]. The incidence varies widely among geographic areas due to HPV prevalence and effective screening. More than 80% of the global burden occurs in developing countries, in which cervical cancer is the leading female malignancy and a common cause of death among middle-aged women who are still raising families [3]. In developed populations with good screening options, invasive cervical cancer is a relatively rare condition, whereas its precursors and equivocal cytology represent a major health burden [4, 5]. High-risk regions include Eastern and Western Africa, Southern Africa, South-Central Asia, Middle Africa and South America, while the risks are lowest in Western Asia, North America and Australia/New Zealand [1].

## **1.1.1 From HPV transmission to invasive cervical cancer**

### **Types of HPV**

About 40 of the more than 100 identified types of HPV are known to infect the anogenital tract [6]. The HPV types are categorised as low-risk or high-risk, of which about 15 are recognised as high-risk and associated with invasive cervical cancer [7, 8]. The causal role of HPV in almost all cancers of the cervix has been firmly established [9, 10]. The two most carcinogenic HPV types are HPV16 and HPV18, which cause 70% of cervical cancer and about 50% of cervical intraepithelial neoplasia (CIN) 3, while other HPV types account for the remaining 30% of cervical cancer cases [11]. HPV16 and HPV18 also account for about 70% of cancers of the vagina and anus and about 30–40% of cancers of the vulva, penis and oropharynx. Other cancers causally linked to HPV are non-melanoma skin cancer and cancer of the conjunctiva [8]. Low-risk HPV type 6 and 11 account for 90% of genital warts [12].

### **HPV infection**

HPV infection is the world's most common sexually transmitted infection (STI) [13]. Transmission occurs by skin-to-skin or mucosa-to-mucosa contact [14] and HPV can be transferred to the cervix from an original infection at the introitus [15]. Most women in the world probably become infected with at least one, if not several, HPV types during their sexual life [16]. The majority of women infected with HPV will clear the infection spontaneously, and most precancerous lesions will regress [2, 17, 18] (Figure 1). Cervical cancer arises from the cervical transformation zone, the area where transformation from columnar epithelium to stratified squamous epithelium occurs. Persistent HPV infection at the transformation zone targets the cervical epithelium. Infection with carcinogenic HPV types is equally common in cervical and vaginal specimens [19]. However, while cervical cancer is the third most common cancer in women worldwide, as mentioned above, vaginal cancer is exceedingly rare [20].

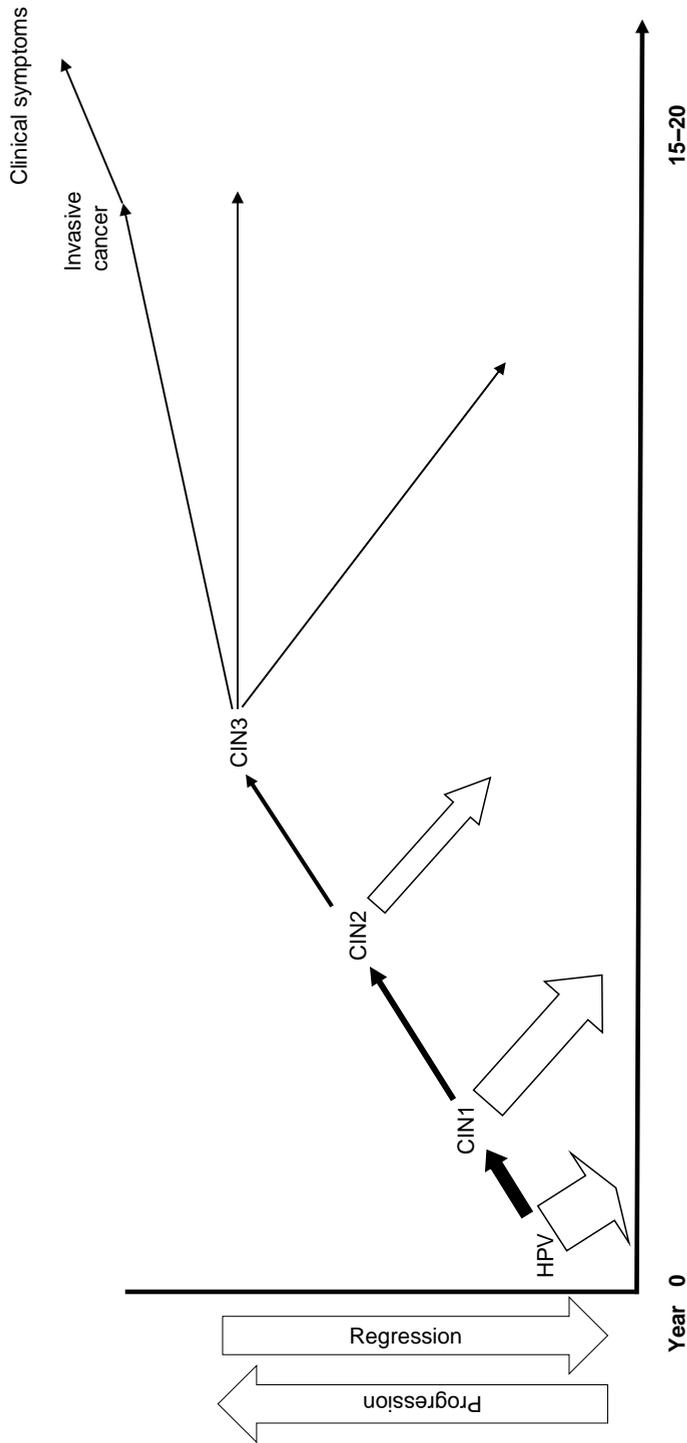


Figure 1. Clearance, persistence and progression of carcinogenic HPV infections (based on original by B Strander).

## **Cofactors in the aetiology of cervical cancer**

Although many women contract cervical HPV infections, most do not progress to cervical cancer, as mentioned above. The precise risk magnitude and timing concerning invasion, if precancerous lesions were left untreated, will remain unknown because contemporary cohort studies, in which treatment of precancerous lesions is mandated, cannot study invasion ethically [21]. Crude estimates from early studies of large precancerous lesions suggested a 20–30% risk of invasion over a 5–10-year time frame [22–24]. The average time between HPV infection and establishment of a precancerous lesion seems to be much shorter than the average duration of precancerous lesions growth leading to invasion. There are many more precancerous lesions than cancers, suggesting that only a minority invade. In addition to HPV infection, a number of other cofactors are likely to be involved in the disease process. Age at first sexual intercourse is a very important variable in cervical cancer development, although it is often equal to age at first infection. There is a large peak of cervical HPV infections rapidly following the initiation of sexual activity [17]. Other potential cofactors are multiparity [25], smoking [26], long-term use of hormonal contraceptives [27] and co-infections with other sexually transmitted agents [28]. The woman's immunological status is of major importance. Individuals given immunosuppressive therapy in connection with organ transplants [29] and those infected with human immunodeficiency virus (HIV) [30, 31] are therefore particularly at risk of developing pre-invasive disease.

## **Precancerous lesions**

The natural history of cervical carcinoma is a slowly progressing process, starting with HPV transmission, followed by progression of persistently infected cells, preclinical dysplasia, carcinoma in situ (CIS), asymptomatic invasive cancer and, finally, symptomatic cancer [17] (Figure 1). CIN is classified from CIN1 to CIN3. The carcinogenic process is reversible until invasion occurs. While most precancerous lesions will regress, as mentioned above, CIN2 is treated in most regions in order to provide a safety margin against cancer risk [32]. The primary treatment option for CIN is the loop electrosurgical excision procedure (LEEP) [33, 34].

Precancerous lesions are usually detected around age 25–30 in regions with cytological screening, or about 10 years after the initiation of sexual activity [17]. In unscreened populations, the risk of invasive cervical cancer peaks or reaches a plateau earlier than that of most adult cancers, i.e. at age 35–55 [35]. This is due to the fact that cervical cancer originates mainly from HPV infections transmitted sexually in late adolescence and early adulthood.

## **Invasive cancer**

Three histological categories of cervical cancer are recognised: squamous, glandular and other [36]. Squamous cell carcinomas account for about 80% of cases, followed by adenocarcinomas. Invasive cervical cancer is subdivided into stages, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, in order to determine treatment and prognosis. Radical hysterectomy has been the preferred treatment for stage I cases, but minimally invasive surgery has become an option, especially for young women who wish to preserve their fertility [37]. Advanced-stage cervical cancer (stages II–IV) requires radiotherapy treatment [36], sometimes combined with chemotherapy [38].

## **1.2 Prevention of cervical cancer**

Today, both primary and secondary prevention for cervical cancer are available. Primary prevention aims at avoiding the disease altogether, and is applicable to cervical cancer, the cause of which is known. A consistent use of condoms among partners of sexually active women may reduce, but not eliminate, the risk of male-to-female genital HPV transmission [39]. An association between condom use and decreased persistence or progression of HPV infection has been seen in a few studies [40, 41]. However, a new era in primary prevention of cervical cancer started with the development of HPV vaccines. The ethos of secondary prevention lies in screening for cervical cancer precursors and early disease [42].

### **1.2.1 HPV vaccination**

The first HPV vaccine was approved for use in Europe in 2006. The two HPV vaccines currently available are a quadrivalent vaccine that protects against HPV16 and HPV18 and two non-oncogenic types (6 and 11), claimed to account for 90% of genital warts, as well as a bivalent vaccine that protects against HPV16 and HPV18. Vaccination against HPV infection has been introduced in western countries as primary prevention [43]. In Sweden, girls aged 11 and 12 have been offered HPV vaccination as part of the general national vaccination programme since 2012. Both vaccines have a good safety profile. Local reactions are fairly common but no serious side effects have been reported [44]. Since 30% of cervical cancer cases are caused by other HPV types, for which there is no vaccine at present, and since the vaccinations' protective effect duration is uncertain, cervical screening is as essential in vaccinated as in non-vaccinated women [9, 45, 46].

## 1.2.2 Cervical cancer screening

The World Health Organization (WHO) states that prevention programs are aimed at identifying individuals at risk of developing disease in a population of healthy people with some form of medical technology [47]. Cervical cancer is an important health problem and has a long preclinical progress stage, thus meeting the WHO condition for a suitable disease for secondary prevention in the form of screening [47]. The aims of population-based cervical cancer screening programs are to identify women at risk of developing cervical cancer, to detect invasive cancer at lower stages (“down-staging”), to improve the chances of successful treatment and to reduce incidence and mortality [48, 49]. Broad coverage and full follow-up of abnormalities are the key requirements for reducing the incidence of cervical cancer by screening [17]. While HPV vaccination will probably play a major role in the primary prevention of cervical cancer for birth cohorts in the future, cervical screening will remain the principal strategy to prevent cervical cancer for many decades [45].

### Cervical cancer screening in Sweden

Population-based cervical cancer screening was introduced in Sweden during the 1960s and was fully implemented in the 1970s [50]. The organised cervical cancer screening programme is one of the best examples of successful preventive cancer care, with a 67% decrease in the overall incidence of cervical cancer over a 40-year period [51], concomitant with the introduction of the screening program [52]. Cytological screening (i.e. Pap smear) for cervical cancer is highly effective in reducing the incidence of squamous cell cancer, although the adenocarcinoma incidence has not been reduced [49, 53]. Almost 700,000 Pap smears are taken in Sweden annually and approximately 25,000 atypical Pap smears requiring follow-up are diagnosed [54].

Cervical cancer screening includes Pap smear screening; triage of equivocal cytology; colposcopically guided biopsy of abnormal screening results; decision to treat; treatment; and post-treatment follow-up, including eventual return to routine screening intervals if appropriate [17]. Every link in this chain has its strengths and weaknesses, contributing to success or failure. In Sweden, the different components of prevention are administered by different organisations [55], which increases the risk of losing information. Coordination and surveillance are thus crucial.

Primary screening was originally offered every four years to women aged 30–49 years [56]. The guidelines have gradually been altered with respect to target groups and screening intervals. The most recent guidelines from the Swedish National Board of Health and Welfare recommend Pap smears at three-year screening intervals for women aged 23–50 and at five-year intervals for women aged 51–60 [55]. Women older than 60 years are not offered screening, because adequate screening attendance up to age 60, with no abnormal smears, is considered to entail low risk of cervical cancer [55]. There are very few cases of invasive cervical cancer in women younger than 23 years and screening is thus considered unnecessary before that age [57].

Health care in Sweden is organised at the county level, and there are differences in how the national recommendations are implemented in the 21 counties [55]. The basic guidelines concerning age limits and screening intervals are generally adhered to, but practical routines vary. There are differences in whether reminders are sent out when a woman fails to attend after invitation, as well as in accessibility and opening hours, invitation wording, whether scheduled appointments are offered, the possibility to reschedule an appointment over the Internet and cost.

Women who are eligible for invitation to the screening program are identified according to interval since their last Pap smear, regardless of whether it was taken as part of the screening program or elsewhere. Information on all Pap smears taken within or outside the organised screening program is stored in a database.

## **Coverage**

One prerequisite for a successful screening program is that women participate. Non-attendance has been shown to be the foremost risk factor for cervical cancer related to the screening program [57-62]. Other risk factors in screened women, such as an atypical smear or previous treatment for CIN, have not been reported to constitute the same amount of risk as abstaining from screening [57, 60-62].

Coverage is the most relevant measure of the protection provided by screening to the women in a catchment area [63]. The overall coverage recommended in the EU is 85% [64], which also has been set as the target in Sweden [65]. In 2012, 80% of women in Sweden attended cervical screening within the recommended screening intervals [54]. However, there is no universally accepted definition of coverage, which makes comparison between areas difficult or impossible. Coverage figures reported in the international literature can be derived from surveys and interviews [17] and

only a few countries can report national figures [63]. In Sweden, coverage is either calculated at the individual level or at the population level. In the former case, the number of unique individuals of screening age who have taken a Pap smear within a stipulated period is divided by the number of women of the same age in the area. Population-based calculation consists of dividing the Pap tests taken in the area by the number of women in the area. Coverage includes all Pap smears, regardless of whether they were taken as part of organised screening or during another consultation with a gynaecologist or a midwife, for instance in connection with pregnancy or family planning (opportunistic screening). Smears taken on medical indication or related to follow-up are also included in coverage figures [50]. Attendance after invitation in cervical cancer screening should not be confused with coverage. This is considered as a measure of availability rather than of how well-protected the population is against the disease.

### **Preventing negative side effects of screening**

The main focus of cervical screening programs is to increase participation. However, this must be effected in the context of informed consent and understanding of what screening entails [66]. It is recognised that informed consent is important since screening can cause harm, with inevitable false negatives leading to women being wrongly reassured and false positives resulting in unnecessary anxiety, further investigations and even treatment. One prerequisite for informed consent is that professionals provide relevant information about risks and benefits and focus on women's individual questions. The International Code of Ethics for Midwives [67] states that midwives should respect women's informed right to choice and promote their acceptance of responsibility for the outcomes of their choices.

### **Non-attendance**

The major obstacle to the success of cervical cancer screening is thus non-attendance [57-60]. The various reasons for women never taking a smear or failing to continue attending are difficult to assess. Contributing factors such as anxiety, feeling healthy, embarrassment and fear of cancer have been identified [68, 69]. Practical barriers have been found to be predictive for non-attendance in cervical cancer screening [69]. There are differences in Pap smear uptake and coverage between different socio-demographic groups, based on factors including immigration status, socio-economic status and age. Lower uptake rates have been found in women who are older [70], single [70-72], less educated [71, 73-78] and from lower socio-economic groups [73, 74]. Immigrants generally have lower attendance rates in cervical cancer screening [71, 79-89]. There are conflicting results concerning age and urban/rural residence, most probably due to heterogeneity among the

populations studied [73, 77, 90-92]. There are also major differences both between and within countries in how the screening programs are designed, concerning factors such as screening intervals, target ages and health care provider.

### **Encouraging attendance**

Identifying ways to facilitate attendance in the program is crucial for coverage. Sending an invitation letter to eligible women increases uptake, compared to no invitation [93-96] [36, 97]; the same applies to a scheduled appointment [92, 94, 98, 99]. A reminder letter has been shown, in several studies, to increase participation [96, 100, 101] and a telephone reminder was found to generate a significantly higher uptake [93, 96, 101, 102]. Opportunistic screening [90, 103-106] or offering a HPV self-test are suggested ways to increase screening attendance [107-113].

## 2 AIMS OF THE THESIS

The overall aim of this thesis is to contribute to cervical cancer prevention by focusing attention on non-attendees, assessing interventions to increase participation in screening and identifying determinants for non-attendance.

### **Specific aims**

#### Paper I

To assess the effectiveness and cost-effectiveness of a telephone call, offering non-attending women an appointment for a Pap smear, in the context of a well-run screening program.

#### Paper II

To assess the effectiveness and cost-effectiveness of offering non-attending women a HPV self-test by mail, in the context of a well-run screening program.

#### Paper III

To explore midwives' experiences of telephoning non-attendees and offering Pap smear appointments.

#### Paper IV

To identify socio-economic and demographic determinants for attendance in cervical cancer screening in Sweden.

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## 3 MATERIAL AND METHODS

### 3.1 Study design

In the research underlying this thesis, both quantitative (Studies I, II and IV) and qualitative (Study III) approaches were applied, resulting in a complementary and enriched understanding of the subject and providing different perspectives [114]. An overview of methods and analyses is summarised in Table 1.

### 3.2 Studies I and II

In these studies, we compared the effect of two methods to increase participation in cervical cancer screening with a control group.

#### 3.2.1 Participants

The source population consisted of the female residents aged 30–62 years in the Western Region of Sweden. When the trial was initiated in August 2009, we included women with no registered Pap smear in the Register for Prevention of Cervical Cancer in Western Sweden for more than six years if aged 30–53, more than seven years if aged 54 and more than eight years if aged 55–62. These women were defined as “non-attendees”. According to regional guidelines, women are not invited for screening after total hysterectomy if they have had no high-grade dysplasia for at least 10 years. The women who had not been invited for screening due to hysterectomy and those not confirmed to be residents of the region during the whole period were excluded from the study. Our final study sample comprised 24,755 non-attendees, of whom 8,800 were selected and randomised, in parallel groups with a 5:1:5 ratio, into two intervention arms (telephone contact and self-test for HPV) and a control group.

#### 3.2.2 Interventions

In the telephone arm, a letter was sent to 4,000 women informing them of the aim and procedure of the study and that a midwife would telephone them in 14 days to offer an appointment to take a Pap smear. A response form and a stamped addressed envelope were enclosed, to be returned within seven days if the woman declined to be telephoned. Alternatively, the women could use the form to provide contact information.

Table 1. Overview of the studies.

Study	Aim	Design	N	Data collection and period	Outcome measures	Analyses
I	To assess the effectiveness of a telephone call offering an appointment for a Pap smear	RCT	8,800 women	Extraction from NQCx/Process register. September 2009–September 2010	Frequency of testing, abnormal smears and of further assessment of abnormal smears and cost-effectiveness of intervention	Relative risk and cost-effectiveness analysis
II	To assess the effectiveness of by mail offering a HPV self-test	RCT	8,800 wocostemen	Extraction from NQCx/Process register. September 2009–September 2010	Frequency of testing and cost-effectiveness of intervention	Relative risk and cost-effectiveness analysis
III	To explore the midwives' experience of calling non-attendees and offering Pap smear appointments	Qualitative explorative	20 midwives	Focus group discussion. January 2010–February 2010	The content of midwives experiences	Manifest and latent content analysis
IV	To identify socio-economic and demographic determinants for attendance in cervical screening in Sweden	Cross-sectional cohort/ Register study	314,302 non-attending women/ 266,706 attending women age 30–60	Extraction from NQCx/Analysis register and the Total Population Register and LISA Register. January 2005–December 2012	Determinants for attendance	Risk ratios and odds ratios, univariate and multivariate logistic regression

Telephone numbers were retrieved from a database by a commercial directory service and manually retrieved from Internet telephone directories. Midwives representing all 71 Antenatal Health Clinics in western Sweden received lists of names and telephone numbers. They sorted out those who had declined and tried to contact the others, to help and encourage them to book a Pap smear appointment. If there were missing or erroneous telephone numbers, the midwives were instructed to search maternity records if available. A maximum of 10 attempts to make contact was set and a maximum total of 20 minutes was to be spent on each woman, including searching for telephone numbers and the actual time spent on the call. Whether and at what time contact was made, the number of attempts and the total time spent on each woman were all noted in the study protocol. Although regular screening appointments were generally offered, women sometimes made special requests for booking an appointment; the midwives noted the requests and whether they could be met in the protocol. Whether or not an appointment was booked and any spontaneously expressed reasons for not booking were also noted in the protocol. Abnormal smears were followed up by referral to a gynaecologist, according to the normal screening routine.

In the HPV self-test arm, a letter was sent to the 800 women, with an offer to order a commercially available dry self-test. The price (€ 111) of the available self-test was so high at the time that it limited the size of this intervention arm. The recipients were informed that the self-tests were to be returned to the laboratory for analysis after sampling. We used the same information, albeit slightly adjusted for the study, as in Uppsala County, where cervical screening non-attendees were routinely offered this self-test. The information described HPV infections and stated that the test is an alternative to the Pap smear and that ordering it is an alternative way of participating in the screening program. The recipients were furthermore informed that they were required to pay the equivalent of the regular Pap smear screening fee for the test (€ 11) and recommended to participate in regular screening if they declined this offer. The women who accepted returned a coupon in a postage-free envelope and received a self-test kit within a few days. After sampling, the kits were returned in another postage-free envelope to the laboratory where the HPV test was performed. A reminder was sent if a kit was ordered but not returned. All participants with negative tests were informed of the results by mail. Women with positive tests were referred to a gynaecologist for colposcopy, according to normal routine for abnormal cytology within the screening program. A designated colposcopy clinic was responsible for follow-up of women with abnormal smears in the particular screening area.

Eight weeks after the invitation only a few self-tests had been ordered and no more orders arrived, so we decided to extend the study protocol with an ad hoc intervention. The women (n=571) who had not responded to the first offer were sent a second invitation ten weeks after the initial invitation. As in the first stage, yet another reminder was sent to the women who had ordered a test but not returned it. The last woman was included three months after the ad hoc reminder was sent out.

The control group consisted of 4,000 women who were not subject to any particular intervention. According to ordinary screening program routines, these women received annual invitations until a smear was registered. In order to elucidate the effect of the described interventions, in addition to the regular screening routine, this procedure was also followed in the two intervention arms. A reference group was established for comparison of atypical smears. This group consisted of all women participating in the regular screening program, aged 30–62, with smears taken during the same period, September 9 2009–September 8 2010. The control group was included but the intervention groups were excluded from this reference group. Moderate and severe squamous atypia (HSIL) and high-grade glandular atypia were defined as high-grade atypical smears. Hence, any resource use associated with these regular invitations was excluded from the analysis, as it was assumed to be constant across all study arms.

### **3.2.3 Cost-effectiveness analysis**

Resource use was registered for both the control and intervention arms in order to ascertain costs. In Study I, the cost of the intervention was calculated as the cost of sending out information letters, finding telephone numbers and making calls, including time spent by midwives (based on hourly wage). In Study II, the cost of the intervention was calculated as the cost of invitation letters, reminders, logistic costs, HPV self-test kit and HPV analysis. We applied the same baseline unit cost for the HPV self-test kit (€ 24) as in the Uppsala studies [110, 113] in order to facilitate comparison with those studies. However, as prices have declined internationally, we also made calculations based on a substantially lower cost (€ 2).

The cost of the Pap smear in the ordinary screening program (identical in all arms) was calculated on the basis of the time spent per smear (15 minutes) multiplied by the midwives' hourly wage (€ 29/h) plus laboratory analysis costs (€ 23). In Study I, the costs of further diagnostic assessment were estimated on the basis of current clinical guidelines [115]. The cost of the triage HPV test for atypical squamous cells of unknown significance

(ASCUS) or CIN1 was € 44 and a colposcopy cost € 167. The cost of CIN2+ was assumed to be € 400 per treatment, according to current prices in the region. We report our results as cost per case of CIN2+ detected and eradicated. Estimated baseline costs (controls) and costs of the interventions are restricted to the first year; we did not attempt to calculate the costs of possible follow-up over a longer time period.

Extrapolation of data from the telephone arm was used to estimate the number of expected participants and prevented cervical cancers in western Sweden, as well as in all of Sweden, by the respective intervention as a one-time effort. One cervical cancer was estimated to be prevented per six CIN2+ eradications [116]. Health care costs incurred by the programs did not include the co-payment of € 11, thus rendering the cost-effectiveness estimates conservative. This decision was made in order to make results independent of future co-payment policies. Costs were calculated in both SEK and euro. We used the exchange rate of € 1 = 9 SEK.

### 3.2.4 Statistical analysis

The primary analysed outcomes were in the telephone arm and control group: the difference in frequency of testing, i.e. Pap smears (followed up after 12 months) and in the HPV self-test arm: HPV self-tests (followed up after 3 months) and Pap smears (followed up after 12 months). The frequency of abnormal smears, frequency of further assessment of abnormal smears, frequency of treated CIN2+ and number of invasive cancers detected (classified by FIGO stage) and treated were the secondary outcomes, followed up after 15 months in the telephone arm and control group. The HPV self-test arm was not designed to identify differences in abnormal smears. The results of the follow-up of all abnormal smears in the telephone arm, as well as the frequency of high-grade abnormalities, were considered to be representative for the HPV self-test arm as well.

The study was dimensioned so that a 30% difference in frequency of testing in Study II, based on an expected 20% participation in the control group, could be detected with 80% statistical power at a 5% level of significance. In Study I we had the frequency of abnormal smears as a secondary outcome. Here the study size gave an 80% power to detect a relative difference, calculated as relative risk, of 1.6 in the frequency of abnormal smears, based on an expected proportion of 7% abnormal Pap smears in the control group. The results are presented as intention to treat unless otherwise stated. The RRs and 95% confidence intervals (CI) were calculated. In Study I, differences in frequencies of abnormal smears were calculated with the

screening population as the reference in a logistic regression model adjusted for age. In Study II, trends in participation rate were tested with the  $\chi^2$  test for Trend in Proportions. Homogeneity of the effect measures between strata were tested with the Woolf Test of Homogeneity of Odds Ratios.

## **3.3 Study III**

### **3.3.1 Participants**

All 56 midwives, representing all 71 Antenatal Health Clinics in western Sweden, who participated in Study I received a questionnaire and were asked to participate in a focus group discussion, to share their experiences of the study. Eighteen expressed interest and could participate; they received e-mail invitations to one of three focus group discussions. Two midwives who had worked in areas with large immigrant populations were invited to an additional focus group discussion, created to investigate experiences of contacting immigrants. The focus group discussion participants had made a total of 1,088 telephone contacts with the 2,110 women who were reached.

### **3.3.2 Data collection**

A qualitative approach with focus group discussion was used to obtain a better understanding of the midwives' experience of telephoning non-attendees [117]. This method is suitable for collecting data concerning experiences and perceptions. The focus group discussions took place in January and February of 2010. The first author moderated the focus group discussion and another midwife served as a facilitator; both were present during all discussions. The discussion was initiated with an open question: "What are your experiences of calling non-attendees?". The participants were encouraged to speak spontaneously and openly and the conversation flowed freely in a comfortable, productive atmosphere. The tape-recorded focus group discussions lasted 50–80 minutes and were transcribed verbatim [117].

### **3.3.3 Data analysis**

Qualitative content analysis was used to elicit the meaning of the text and categorise the midwives' statements and conclusions. The basis of content analysis are meaning units, i.e. words, sentences or paragraphs containing aspects that are related to each other through their content and context [118]. Sentences or paragraphs were used in Study III. In the next step, the meaning units were condensed, which entails reducing the text while retaining the core. The condensed text was abstracted, i.e. interpreted on a higher logical level. This phase includes the formations of codes, categories and themes.

The creation of codes is the process of labelling the condensed meaning unit with a code that represents a descriptive level of content and can be seen as an expression of the manifest content of the text. The condensed meaning units were coded and merged into sub-categories, categories and finally, into a theme including latent content [119]. Manifest content analysis focuses on what the text really says, whereas latent content analysis tries to capture the underlying meaning within the text.

## **3.4 Study IV**

### **3.4.1 Participants**

The source population consisted of the entire Swedish female population between 30–60 years of age, a total of 1,931,894 women on December 31 2012. In the study group, we included women without a registered Pap smear during the last six years if aged 30–53, the last seven years if aged 54 and the last eight years if aged 55–60, up until December 31, 2012. We defined these women as “non-attendees”. 104,613 women who had immigrated to Sweden during the study period and 58,612 women who had undergone hysterectomy were excluded. In the control group, we included all women who had received an original invitation (i.e. not a reminder) between January 1 and December 31 2012 and had attended screening within 90 days after being invited. These women were defined as “attendees”. Our final study sample comprised 314,302 non-attendees and 206,306 attendees.

### **3.4.2 Data sources**

The population was identified through the Total Population Register, which also contains information on place of residence, country of birth and date of immigration. Information on cervical screening attendance and invitations was retrieved from the National Quality Register for Cervical Cancer Prevention. The register has complete coverage since 1993 and contains data about all Pap smears taken in Sweden, both inside and outside the organised screening programs. The register also includes data on all screening invitations issued by the Swedish counties to their residents. The unique personal identity number (PIN) assigned to every legal resident in Sweden was used for record linkage between the Total Population Register and the National Quality Register for Cervical Cancer Prevention [120]. Information on total hysterectomy was retrieved from the National Patient Register. Information on cohabitation status, family’s disposable income, employment status, unemployment benefits, social benefits and education level were retrieved from the Longitudinal Database on Health Insurance and Labour Market Studies (LISA), managed by Statistics Sweden. All Swedish residents

aged 16 and above, who were alive and residing in Sweden in 1991, are included in the LISA database. For confidentiality purposes, the PIN was replaced by a unique sequence number assigned to each woman by Statistics Sweden.

### 3.4.3 Determinants

Attendees and non-attendees were compared concerning six categorical variables used as socio-economic indicators: “family’s disposable income” was stratified into quartile groups (in euro); “in the labor force”, defined as women who had income information provided to the tax authorities, was classified as yes or no; “unemployment benefits” was defined as full-time or part-time unemployment compensation and classified in this study as yes or no; “welfare benefits” was defined as social welfare and housing benefits and classified as yes or no; “education level” (the highest formal education attained) was classified into three categories according to the Swedish educational system: primary school ( $\leq 9$  years), secondary school (10–12 years) and higher education ( $>12$  years); and “cohabitation” was categorised as yes or no. Additional factors considered in the analysis were age, stratified into six categories (30–34, 35–39, 40–44, 45–49, 50–54 and 55–60); country of birth, stratified into regions based on the United Nations Population Division; and the county of residence in Sweden.

### 3.4.4 Statistical analysis

The associations between non-participation and socio-economic factors were estimated using RRs and odds ratios (OR) with corresponding 95% CIs, using a binomial generalised linear regression with log- and logit-link functions. Due to the high number of strata, multivariate RR could not be estimated; multivariate regressions were thus only run with logit-link. CIs not including 1.0 or a  $p < 0.05$  were considered to be statistically significant.

Statistical analyses were run on complete samples; observations with one or more missing values were removed. Due to the large sample size, no imputations were performed.

## 3.5 Ethical considerations

Studies I and II were granted ethical approval by the Regional Ethical Review Board at the University of Gothenburg (Dnr 128/09). In designing the study, necessary steps were taken in order to respect the women’s autonomy. Since the intention in Study I was to establish telephone contact, an information letter was sent out, stating the aim and procedure of the study and that participation was voluntary, but also providing an opportunity to

decline participation. For the last study (Paper IV), ethical approval was granted by the Regional Ethics Committee in Stockholm (Dnr 98-002, 02-556 and 2011/921-32). The database information in the register-based study was anonymised after the necessary linkages were concluded, thereby ensuring that the women included could not be identified. The PIN was used to follow participants through linkages to the registers used in Study IV. For confidentiality purposes, instead of PINs, a unique identification number was used and assigned to each woman by Statistics Sweden. No names or PINs were provided to the researchers by Statistics Sweden. Ethical approval was not mandatory according to Swedish law for Study III, but the Helsinki Declaration rules were followed and the participants gave informed consent before the interview. Permission to undertake Studies I–III was granted by the head of each Antenatal Health Clinics in the county.

## 4 RESULTS

### Studies I and II

An overview of Studies I and II is shown as a flow chart (Figure 2). From the 24,755 women who fulfilled the inclusion criteria, 8,800 women were randomly selected. The distributions of age and Pap smear history in the telephone intervention arm and control group were similar.

In Study I, the midwives tried to contact 4,000 women. They called 2,586 (65%) women, contact was made with 2,110 (53%) women and 1,176 (29%) appointments were booked (Figure 2). Spontaneously expressed requests were related to appointments, mostly related to practical problems, and most of these were met. The women sometimes also expressed their reasons for declining to book an appointment. Hysterectomy was reported in 265 cases and 669 had other various reasons.

The interventions yielded significantly increased participation within twelve months of follow-up, compared to the control arm (Table 2), 718 (18.0%) and 422 (10.6%) respectively (RR 1.70, 95% CI 1.52–1.90). After the ad hoc intervention and two reminders, 128 (16.0%) submitted HPV self-tests and an additional 68 women (8.5%) attended for a Pap smear out of the 800 women who were offered a self-test kit. This yielded a total response in the HPV self-test arm of 196 (24.5%), a significantly higher rate than in the control arm (RR 2.32, 95% CI 2.00–2.70) or the telephone arm (RR 1.36, 95% CI 1.19–1.57). Women aged 30–40 responded to the telephone intervention to a higher extent than women aged 41–62. In the HPV self-test arm, the proportion of self-tests, compared to cytology, increased with age (Table 3). Among the youngest women (aged 30–40) in the HPV self-test arm, 16.9% took a self-test and 14.0% had a Pap smear (RR 1.21, 95% CI 0.79–1.83). When it came to women aged 52–62, 13.5% took a self-test and 4.4% had a Pap smear (RR 2.75, 95% CI 1.45–5.21). We also found that women who had a Pap smear registered during the last ten years participated to a greater extent in both intervention arms than those who had not.

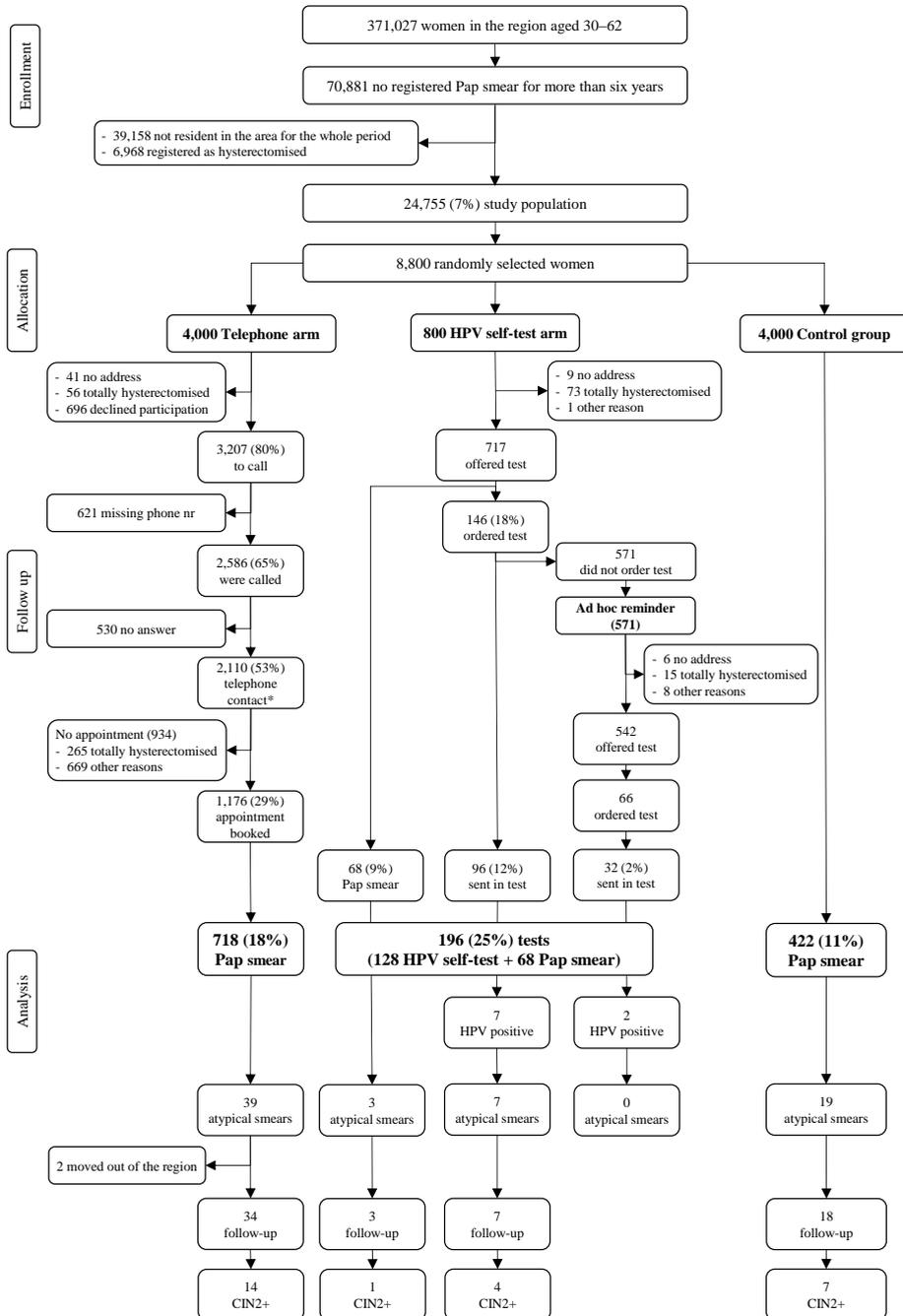


Figure 2. Flow-chart of Studies I and II.

\*Some of the women who had declined participation were nonetheless called as the midwife had received the response note too late.

Table 2. Primary outcome. Comparison between telephone arm and control group and total participation in HPV self-test arm and control group. Secondary outcomes and CIN detected and treated. Comparison between telephone arm and control group. Relative difference in participation rate.

	Control arm		Telephone arm		Telephone arm/ Control arm		HPV self-test arm <sup>a</sup>		Total participation HPV self-test arm/ Control arm	
	n (%)	n (%)	n (%)	n (%)	RR	95% CI	Total n (%)	RR	95% CI	
Participation in screening	422/4,000 (10.6)	718/4,000 (18.0)			1.70	1.52–1.90	196/800 (24.5)	2.32	2.00–2.70	
<b>Secondary outcomes:</b>										
Abnormal cytology	19 (0.5)	39 (1.0)			2.05	1.19–3.55				
Further assessment	18 (0.5)	33 (0.8)			1.83	1.03–3.25				
<b>Off the protocol:</b>										
CIN1+ lesions detected and treated	11 (0.3)	16 (0.4)			1.45	0.68–3.13				
CIN2+ lesions detected and treated	7 (0.2)	14 (0.4)			2	0.81–4.95				

<sup>a</sup>Study not powered to detect difference in secondary outcome between groups.

Table 3. Participation in telephone arm, HPV self-test arm (HPV self-test and Pap smear, including reminders) and control group. Comparison between telephone arm and control group, and between total participation in HPV self-test arm and control group. Relative difference in participation rate according to age and Pap smear history.

	Control arm			Telephone arm			HPV self-test arm						
	n (%)	RR (95% CI)	n (%)	RR (95% CI)	Total n (%)	HPV self-test			Pap smear				
						n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	95% CI	
Participation in screening	422/4,000 (10.6)		718/4,000 (18.0)		196/800 (24.5)	128/800 (16.9)		68/800 (8.5)					
Age distribution <sup>a</sup>													
30–40	198/1,210 (16.4)	reference	294/1,170 (25.1)	reference	75/243 (30.9)	41/243 (16.9)	reference	34/243 (14.0)	reference				reference
41–51	143/1,343 (10.6)	0.65 (0.53–0.80)	273/1,418 (19.3)	0.77 (0.66–0.89)	72/283 (25.4)	50/283 (17.7)	1.05 (0.2–1.52)	22/283 (7.8)	0.56 (0.33–0.92)				
52–62	81/1,447 (5.6)	0.32 (0.27–0.44)	151/1,412 (10.7)	0.38 (0.32–0.46)	49/274 (17.9)	37/274 (13.5)	0.80 (0.53–1.21)	12/274 (4.4)	0.31 (0.17–0.59)				
Pap smear history <sup>b</sup>													
A Pap smear last ten years	168/993 (16.9)	reference	275/974 (28.2)	reference	77/194 (39.7)	43/194 (22.2)	reference	34/194 (17.5)	reference				reference
A Pap smear > ten years ago	100/1,423 (7.0)	0.42 (0.33–0.52)	192/1,414 (13.6)	0.48 (0.41–0.57)	57/281 (20.3)	45/281 (16.0)	0.72 (0.50–1.05)	12/281 (4.3)	0.24 (0.13–0.46)				
No registered Pap smear	154/1,584 (9.7)	0.57 (0.47–0.70)	251/1,612 (15.6)	0.55 (0.47–0.64)	62/325 (19.1)	40/325 (12.3)	0.56 (0.38–0.82)	22/325 (6.8)	0.39 (0.23–0.64)				

<sup>a</sup>Participation in age groups are compared within respective group. Reference youngest age group.

<sup>b</sup>Participation in relation to Pap smear history. Reference least time since last Pap smear.

Abnormal cytology was found in 39 cases in the telephone arm, compared to 19 in the control group (RR 2.05, 95% CI 1.19–3.55) (Table 2). Abnormal tests were further assessed to similar extents, i.e. 34 (two of the five who were not followed up had moved out of the region) and 18, respectively. Fourteen and seven cases of CIN2+, respectively, were detected and treated (RR 2.0, 95% CI 0.81–4.95). The frequency of abnormal cytology was 5.4% in the telephone arm, 4.5% in the control arm, and 2.7% among all women aged 30–62 in the regular screening program. A multiple logistic regression model, adjusted for age, showed that there were significantly increased risks of abnormal cytology in both the telephone arm (RR1.97, 95% CI 1.45–2.69) and the control arm (RR 1.59, 95% CI 1.03–2.48), compared with women in the regular screening program (Figure 3). The RR for a woman in the telephone arm to have a high-grade abnormal smear, compared with women in the reference group of regularly screened women, was 3.93 (95% CI 2.39–6.46).

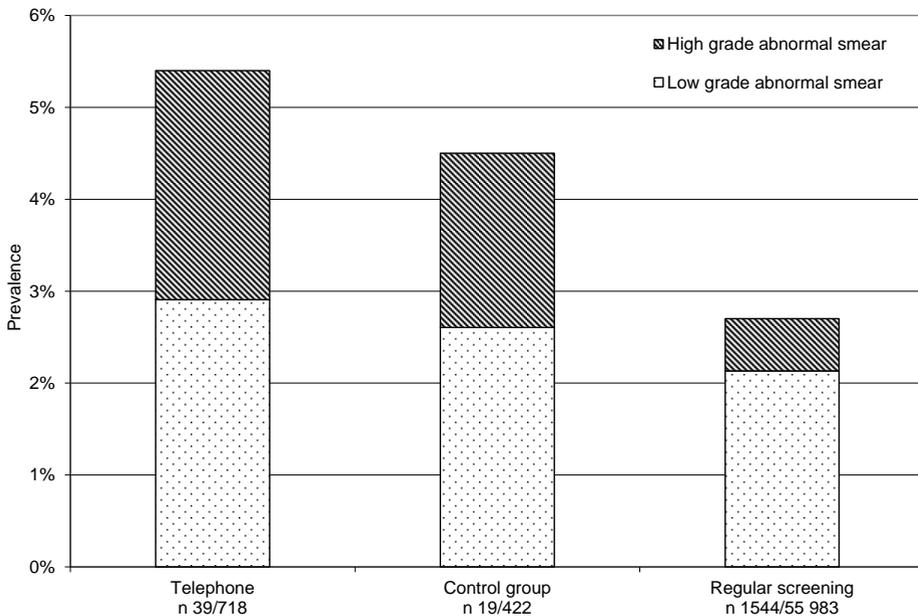


Figure 3. Prevalence of low and high grade abnormal smear in telephone arm, control group and regular screening.

Nine (7%) of 128 women who submitted a self-test were positive for high-risk HPV. All nine responded to the subsequent invitation for colposcopy and Pap smear. Seven had abnormal cytology and four were found to have CIN2+. Three (4.4%) of the 68 women who preferred a Pap smear to a self-test had abnormal cytology and one was found to have CIN2+, yielding a total of five CIN2+ in the HPV self-test arm.

The total cost of the telephone intervention was € 15,843, including costs for information letters (€ 3,806), searching for telephone numbers (€ 724), midwives' salaries (€ 11,036) and telephone calls (€ 278). The intervention resulted in a higher Pap smear rate and a higher detection rate of abnormal cytology and thus additional treatments for CIN2+, which generated additional health care costs: 296 extra smears (unit cost: € 31), 11 extra HPV tests (unit cost: € 44), 11 extra colposcopies (unit cost: € 167) and seven additional treatments of CIN2+ (unit cost: € 400). The total additional costs generated by the intervention amounted to € 30,142, corresponding to € 4,927 per extra detected and eradicated case of CIN2+. Incremental cost ratios are reported with a focus on the cost of additional CIN2+ eradications, as the level of ambition increases from routine invitation, over telephone invitation, to HPV self-test invitation. The marginal cost per CIN2+ eradication in the HPV self-test arm increases from € 2,670 (routine invitation) to between € 3,003 and € 4,660 (HPV self-test invitation), depending on the presumed unit cost of the HPV self-test kit.

### Study III

Exploring midwives' thoughts and feelings about calling non-attendees was another aspect of increasing participation in cervical screening in this thesis. "Become aware of the non-attendees' complex situation and opportunities to improve cervical cancer screening", was the main theme summarising the reflections of the midwives who took part in this qualitative study. This main theme was generated from five categories representing the midwives' experiences of participating in Study I (Figure 4).

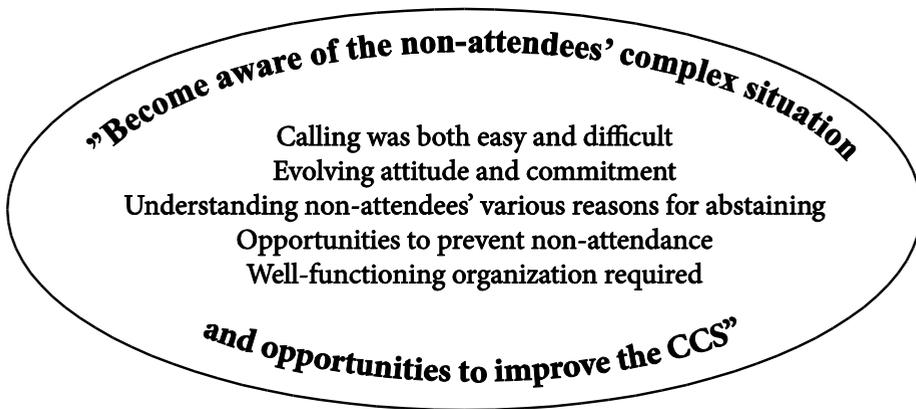


Figure 4. Theme and categories Study III.

We found that the midwives realised that the women's reasons for non-attendance varied, and that many obstacles could be removed by adaptations in the screening program. The midwives categorised non-attending women as those who definitely did not want to be tested, those who were hysterectomised and did not need a test, those who had individual needs or those who just required increased accessibility. It was especially easy to help women with reasons for non-attending of a practical nature, such as being too busy with work or family or requiring a suitable appointment time. The main suggested improvements were increasing flexibility with an online booking system, enabling women to change appointment time and location and expanding the range of bookable appointments. Participation could also be improved if screening were adapted to local conditions. Offering women smears when they visited the clinic for other reasons was also suggested in order to increase participation. The normal screening routines were regarded as inappropriate for women with emotional obstacles to attending. The

telephone contact was described as an opportunity to be informed about and attempt to meet special needs in a more individualised consultation.

Some women simply did not want to attend screening for various reasons. The midwives were hopeful that the telephone contact might encourage some to attend in future but understood that others would never participate. The issue of how intrusive it was to call and where the line should be drawn was discussed. The telephone calls went more smoothly than the midwives had initially expected. The women seemed positive to being called and to the opportunity to talk with a midwife. Actually connecting was the main obstacle. The midwives expressed deeper understanding of non-attendees' varying needs after the calls, stimulating their own interest in cervical cancer screening, of which they were proud to be part, since it was important for preventing disease and premature mortality.

#### **Study IV**

In Study IV, we included 314,302 women who were identified as non-attendees and 266,706 who were identified as attendees. There were large amounts of data missing for some variables, mainly for non-attendees and mostly relating to women born outside Sweden.

In order to assess whether the family's disposable income affected cervical cancer screening attendance, income below the lowest quartile was used as the reference. Participation increased with higher family income, including after adjustment for all other variables. More education also predicted higher attendance, compared with less education. Women not working were less likely to participate in screening than women who were. In the univariate model, women receiving unemployment benefits were less likely to participate than women who did not, but when we adjusted for other covariates this variable predicted higher participation. Women receiving welfare benefits participated to a lower extent than those who did not. Women with medium and higher education participated to a greater extent than women with the lowest education level. These associations also proved significant in the adjusted model. Cohabitation strongly affected attendance in both the univariate and the multivariate model, in which cohabiting women were more likely to attend than single women.

The immigrant women included in the study were from 163 different countries, grouped in 19 of the 21 United Nations' Population Division regions. In the univariate model, being born in another country than Sweden predicted significantly lower participation, except for Melanesia which was based on small numbers. Attendance varied among the other regions, ranging

from the lowest among Eastern African women to the highest among Central American women, who still attended to a lower extent than Swedish-born women. After adjustment for all covariates, being born in Southeast Asia predicted statistically significantly higher attendance than in the Swedish reference population. Attendance among women born in South and Central America, Central and Western Africa and Western Asia was equal to that among Swedish-born women in this analysis.

There were wide variations in attendance, depending on county of residence, compared with the reference county (Västra Götaland in Western Sweden). These differences remained after adjusting for all other variables.

Women in the youngest age group (30–34) were found to be less likely to attend than women in all older age groups in the univariate model. This effect persisted after adjusting for all other covariates in all age groups except age 50–54. Women in this latter age group were predicted to have lower attendance than women in the youngest age group after adjustments.

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## 5 DISCUSSION

### 5.1 Interventions

#### Participation rate

The primary outcome in the three-arm randomised trial (Studies I and II) was the number of women screened. We found that long-term abstainers can be encouraged to attend cervical cancer screening by a telephone call or by an offer of a HPV self-test. Ultimately, the HPV self-test arm was the most successful intervention in the trial. It should be noted that the interventions had qualitative differences, so this should be interpreted with some caution. We decided to extend the HPV self-test arm protocol with an ad hoc reminder when self-test orders stopped coming in and relatively few had been ordered. Women who preferred to attend regular Pap smear screening, although randomised to the HPV self-test arm, were included in the results of the intention to treat analysis of this arm.

Younger women generally attended to a greater extent than older women in all arms. The fact that 9% of the invited women in both intervention arms were hysterectomised, a condition more common with increasing age, might be one explanation [121]. Negative experiences of and other emotional barriers to gynaecological examinations might be more common among older women. The fact that older women chose the self-test to the same extent as younger women but were significantly less responsive to the regular Pap smear invitation, in both intervention arms as well as among controls, might be an indication of this [68, 69]. In the subgroup of women who had abstained from screening for more than ten years, attendance reached 20%. Among these women who had ignored annual invitations, four out of five ordered and returned a HPV self-test, while the remaining women had a Pap smear.

One third of the women who made an appointment never showed up to take a Pap smear. This is not surprising, since these non-participating women have, as a group, already shown strong reluctance to take a smear. Furthermore, there will always be some women who are unwilling to participate in any screening program [122].

## **Prevalence of atypical smears**

In the telephone arm, there was a twofold increase in the number of atypical smears, compared with the controls, which is a significant finding in evaluating the effectiveness of this intervention. When the entire group of women without a Pap smear for six years or more (telephone arm and control group) was compared with an age-adjusted reference group consisting of all women in the regular screening program, we found a twofold increase in the frequency of atypical smears and an almost fourfold increase in highly abnormal smears. This indicates that women who have abstained from screening have a high incidence of atypical smears, and underlines the importance of facilitating testing in this group. Furthermore, the increase in atypical smears is almost fully attributable to the increase in high-grade lesions. This is consistent with a higher regression rate of low-grade lesions, compared with high-grade lesions [123]. Seven percent of the tests were positive for high-risk HPV, concurring with other studies [109-113, 124]. Nearly all women with atypical smears and all those who were positive for high-risk HPV did attend for follow-up. This was encouraging since we had a hypothesis and a concern that women who had abstained from taking smears despite repeated offers might, to a high extent, refuse follow-up of atypical results.

These findings are important for prevention of cervical cancer, regardless of the screening method. Investments in more sophisticated screening tests, such as liquid-based cytology or HPV testing, will have limited effect unless participation is high. Very few advanced cervical cancers develop among women who participate in screening, even with conventional cytology [57].

## **Cost-effectiveness**

Prevention of cervical cancer and associated treatment leads to significant cost savings [125]. Based on prior treatment cost estimates [126] and stage distributions of symptom-detected cancer [127], the average cost of treating cervical cancer in a unscreened population is € 38,900. The cost per eradicated case of CIN2+ was € 2,670 for routine invitation, € 4,330 for the extra CIN2+ case eradicated in the telephone arm and € 3,003–4,660 for the additional CIN2+ eradications achieved if the self-test invitation replaced the telephone call. One cancer is suggested to be avoided per six CIN2+ eradications [116], implying that the marginal costs per cancer avoided are € 16,000 (routine invitation), € 26,000 (telephone invitation) and € 18,000–28,000 (HPV self-test invitation). The additional cost associated with the HPV self-test arm was found to be dependent on the price of the self-test kit. At present, several new self-test devices are marketed or under development and prices are declining. This suggests that the HPV self-test strategy is more

effective, and possibly also more cost-effective, than a telephone reminder in terms of cost per eradicated CIN2+ case. A full picture of the cost savings involved suggests that introduction of such a strategy would be cost-saving or at least cost-neutral. Furthermore, sending out HPV self-test invitations (rather than following the other schemes) would save a significant number of additional lives, especially if the strategy was introduced at the national level. An extrapolation of our results suggests a reduction in the number of cervical cancers at the national level by 73 cases with an offer of a HPV self-test and by 42 cases with a telephone contact. This extrapolation is not without limitations, since screening programs in different counties differ, as seen in Study IV. However, the overall coverage of screening uptake in the population in western Sweden is at about the national average; this extrapolation thus provides a fair idea of the magnitude of benefit gainable from this limited effort.

## 5.2 Non-attendance

Our and others' research generates an impression of multifactorial reasons for women to abstain from cervical cancer screening [68, 69, 90, 128, 129] and facilitating attendance is a challenge. For instance, a Pap smear entails undergoing what many women feel is an embarrassing examination and it is thus likely to be postponed. Indeed, the women whom the midwives managed to contact did report widely varying reasons for non-attendance. Many of them stated that they did intend to attend but had not gotten around to it. However, the non-attendees, especially young women [129], very often mentioned practical obstacles as reasons for non-attendance [68, 69, 90]. The most common special request was for a convenient appointment and more than half actually booked outside the regular screening schedule. This may be a manifestation of poor accessibility in the regular screening program [130] or a desire to avoid screening under assembly-line conditions.

However, some women simply do not want to participate. While these women's decision not to participate must be respected, it is nonetheless important to provide them with adequate information so that their choice is informed.

In addition to the individual perspective, non-attendance can be regarded on the group level. In Study IV, socio-economic and demographic determinants for attending screening were identified. We chose two groups at each end of the spectrum and compared their respective attendance rates. Those who had not attended for at least six years were compared with women who attended screening within 90 days after being invited. We found that all studied

variables had statistically significant impact on attendance in cervical cancer screening.

High vs. low family income turned out to be the strongest factor determining attendance; this finding was unaltered after adjustment for the other variables. Long vs. short education was related to a 60% difference, and not working, living without a partner, receiving welfare benefits, young age and being born outside Sweden were strongly related to non-attendance. In accordance with other studies, socio-economic status was a strong predictor of non-attendance [131-133].

Being born outside Sweden had a significant impact on the probability of being a non-attendeer [89]. However, the fairly large number of women from South America, Southeast Asia and Western Asia living in Sweden attended to the same or greater extent than Swedish-born women, after adjustment for socio-economic and other demographic factors.

We found that young women had a slightly increased risk of non-attendance, compared to older women. However, quality register data show that attendance rates among the youngest age group of women in Sweden, not included in this study, have increased in recent years. One reason for this might be the media attention devoted to cervical cancer in connection with HPV vaccination. Other studies, however, found the reverse association between age and attendance [131].

Screening programs are administered independently in the Swedish counties. The county in which the studied women were resident was found to significantly affect participation, concurring with the coverage by county reported in by the National Quality Register for Cervical Cancer Prevention [54]. This indicates uneven access to screening; improvements are thus needed to address the issue of equality [65].

Almost 9% of the women included in Studies I and II were found to be hysterectomised; not excluding or reporting hysterectomised women may therefore bias the results of participation studies. The regional invitation systems have procedures for excluding women who have undergone total hysterectomy but they obviously rely on incomplete data, indicating that a substantial number of invitations are unnecessarily distributed annually, generating negative reactions, as well as incurring unnecessary expense [121, 134]. An immediate effect of this study is that routines to exclude totally hysterectomised women from invitation for screening have been improved in western Sweden. Thus, even in a setting in which attempts have been made to

systematically exclude hysterectomised women, this category might constitute a substantial proportion of those assumed to be at risk of cervical cancer.

### 5.3 Facilitating participation

Mortality from cervical cancer is dominated by women who have not participated in screening as recommended. Facilitating attendance is an important equal care provision issue. As mentioned above, a convenient appointment was extensively requested in our study. One way to facilitate this is a flexible cervical cancer screening schedule, offering appointments during extended parts of the day and the week [135]. Simplifying rebooking to a suitable time and location with online re-booking systems would make it easier for women who desire to attend [136]. Indeed, an online re-booking system has been introduced in western Sweden. However, it is important that the opportunity remains to easily re-book appointments by telephone.

The new guidelines for cervical cancer screening in western Sweden recommend opportunistic screening, offered when visiting midwives or physicians for other reasons, in order to facilitate attendance and increase participation [90, 103-106]. However, to avoid over-screening, the date of the last smear must be readily available to the provider, as it cannot be reported reliably by many women [90]. All women benefit from the possibility to have an opportunistic Pap smear taken, and opportunistic screening may determine whether some women participate in screening at all. In addition to being time-saving for busy women, the face-to-face situation might be more encouraging than an invitation letter to women with obstacles of an emotional nature. Offering opportunistic Pap smears to women with language difficulties, through an interpreter who is present anyway for the respective healthcare consultation, may provide them with better information about the screening. The fact that resources can be saved, since no invitation must be sent and no appointment reserved for organised screening, is another advantage to opportunistic screening.

Offering a HPV self-test increases attendance [107-109, 137] and the results of Study II indicate that a HPV self-test might be a particularly attractive screening alternative for women with emotional barriers to attending. This implies that a combination of different screening strategies, targeting non-attendees in different age groups, may be an effective option.

Telephone contact [96] with non-attendees is an opportunity to meet individual needs [138] when routine cervical cancer screening, consisting of

short appointments under assembly-line conditions, is inappropriate. It has also been shown that participation increases when requirements from non-attendees are met [135].

The non-attendees seldom requested information about cervical cancer screening. The knowledge of screening does not differ between attendees and non-attendees [68, 139].

Very few women requested a test free of charge in our study. A screening fee is charged in most counties in Sweden. The fee is quite limited (€ 10–20) and the only Swedish county that does not charge a fee, Stockholm, is among the areas with the lowest attendance. No differences in attendance were found between the women who paid a modest fee and those who were offered a Pap smear free of charge in a randomised study in a socio-economically deprived area [140]. Thus, a fee does not appear to be a major barrier to attending cervical cancer screening but may nonetheless be a significant impediment for some individuals.

## 5.4 Implementation

We have studied the effectiveness of these interventions in the context of a Swedish population-based cervical screening program, finding them to be not only effective and potentially cost-effective, but also feasible in this context. Other studies have shown a higher impact of telephone contact [96] and HPV self-test [107-109, 112, 141] interventions than in this population. However, the interventions were undertaken in the context of a program in which more convenient and cheap measures, such as scheduled appointments, annual reminders and, to a limited extent, re-booking on the Internet, had already been implemented. The telephone calls were made by midwives within the context of the regular program. They were assigned a limited time for making telephone calls, 20 minutes per woman, and actually used an average of only seven minutes per accessible telephone number. Although calls were made during normal working hours, 80% of the women with a known telephone number could be reached. In a smaller Swedish study with different inclusion criteria, no reported time limits and two investigators making all calls, 71% of non-attendees were reached by telephone [96]. If the telephone calls in our study had been made during the evening as well, more might have been reached as many women work daytime and are unable to answer their home telephones [142]. The HPV self-test kit had to be actively ordered by the women in order to minimize the number of unused kits. In other studies with high participation rates [107-109, 112, 141], the kit was sent home with the invitation letter. However, as mentioned above, prices

have declined internationally; a lower price might make it cost-effective to send the HPV self-test kit with the invitation letter.

The main results in Studies I and II, focusing on facilitating attendance, have affected the contents of the national action plan and have also been implemented in the new guidelines for cervical cancer screening in Western Sweden (Figure 5) [143]. The allocation of responsibility within the organisation is clearly described in the document. The screening population is defined, as is the group to be excluded as well as routines for excluding, for example, women who have undergone hysterectomy. Invitations offering scheduled appointments are sent out when three and five years, respectively, have elapsed since the last smear was taken. Women are given the option to reschedule appointment time and location, both online and by telephone. The management of specific groups, such as women who are homeless or with a protected identity, has been taken into account. When six years have passed since the last Pap smear was registered, a midwife at the Antenatal Health Clinic will telephone the non-attendeo offering an appointment for a Pap smear, making a maximum of three attempts to call. If there is still no test registered after seven years, a HPV self-test kit will be sent to the woman. As long as the woman fails to attend, she will receive annual reminders until a Pap smear is registered. All pregnant women visiting the Antenatal Health Clinic are offered a smear if less than six months remain until the next Pap smear is due. Quality indicators are also described in the guidelines.

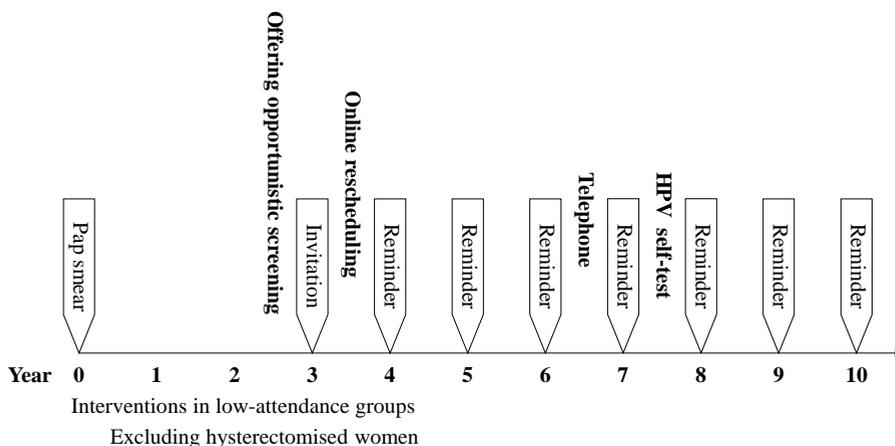


Figure 5. Sequence of offers to non-attendeos in cervical cancer screening guidelines for West Sweden (2014).

## 5.5 Strengths

The purpose of this thesis was to assess interventions to increase participation in screening and identify determinants for non-attendance. In order to obtain different perspectives on the research questions, both qualitative and quantitative methods were used.

One strength of Studies I and II is the population-based, randomised design, with access to a database covering all cytology activities concerning cervical cancer prevention in the region. Data on previous smear-taking is thus reliable and, additionally, includes all tests taken outside the screening program. The studied women can be considered to be real non-attendees, who had resisted multiple previous opportunities to be screened. In contrast to our data, other studies calculate participation based only on reports from organised screening or self-reported interval since the last smear [107, 109], which tend to be underestimated [90, 144]. We also ensured that women had been residents in the area during the entire period in question since we only had access to the regional register. Non-participation was defined as the absence of any Pap smear, within or outside the screening program. Long-term follow-up (one year) and calculations based on the entire target population (intention to treat) in this study yielded more valid results, as we have shown that short follow-up duration yields biased results.

The trial was conducted in an entire large region inhabited by more than 1.5 million residents. As mentioned above, several measures had already been implemented to increase attendance in the area. All Antenatal Health Clinics in the region were involved, which increased the study's possibility to credibly demonstrate the effectiveness of the telephone intervention. We have presented detailed data of importance for implementing the intervention as a clinical routine. The studies conform to the Consort Statement and checklist for randomised studies [145].

The concepts of credibility, dependability and transferability are often used to describe the trustworthiness of qualitative studies [119]. Credibility refers to confidence in how well the data and analysis processes address the research objectives under study. Dependability takes into account the degree to which data change over time and alterations made in the researcher's decisions during the analysis process. Transferability means the extent to which research findings can be transferred to a different context; this is achieved by carefully describing the research process. In Study III, credibility was enhanced by the midwives' range of experience of both cervical cancer screening and telephoning the non-attendees. The midwives and the women

they called represented both urban and rural areas in the region, which also contributed to a richer variation in the data, which we think is unique. The number of narratives can be regarded as an asset of the study, as can the fact that midwives spoke with more than 1,000 non-attendees. The dynamics in the focus group discussions enabled the midwives to reflect on their experiences, which further enabled them to zero in on the most significant topics [117]. Qualitative content analysis was a suitable method to handle the large amount of data generated from the process [119]. A table in Paper III illustrating how meaning units, condensations and abstractions were made facilitates judging the credibility of the findings. The authors worked individually and together during the various steps of the analysis, ensuring that no relevant data were excluded or irrelevant data included [119]. Dependability was achieved by using unstructured interviews, supplemented only by mild guidance to help the informants relate to the same issue. The context, selection and characteristics of participants, data collection, process analysis and quotes were described to enable the reader to determine whether or not the findings are transferable to other contexts.

Study IV is a very large study with two cohorts derived from the entire Swedish female population aged 30–60. We assessed several indicators of socio-economic status to obtain a better estimation of the women's social situation in relation to cervical cancer screening attendance. Our results are based on objective, instead of self-reported, data from high-quality national registers containing reliable individual information on screening attendance, socio-economic status and immigration status.

## 5.6 Limitations

One limitation is the small sample size in Study II, which was due to the cost of the HPV self-test kit. The power calculation demonstrated that the number of women invited was sufficient to show a clinically significant difference in frequency of testing, but not to directly compare the detection and further workup of abnormal smears. However, in accordance with the study protocol, cost calculations for the HPV self-test arm could be extrapolated from the results of the telephone arm, as there is no reason to believe that the rate of abnormal smears or CIN2+ cases per participating woman would differ between the study arms. This assumption is confirmed by the similar rates of abnormal smears in the control arm and the telephone arm. In order to minimise the number of unused self-test kits, the study was designed so that the women had to actively order the kits. We observed that 40% of those who ordered the kit did not return them, resulting in an overall response rate of

16.0%. This can be regarded as a limitation, as Rossi [141] reports a higher response rate when the self-test kit was sent to the woman with the invitation (19.6%), compared to when the test had to be requested at her own initiative by telephone (8.7%). In several other studies with high participation rates [107-109, 112, 141], the self-test kit was also sent home together with the invitation. However, it has been estimated that 13–16.6 kits are sent out for every one returned when kit and invitation are sent out together to under-screened women [107, 111, 141]. Such low response rates will undoubtedly have severe implications for the cost-effectiveness of the program, although declining prices of self-test kits will make sending them with the invitation a more attractive option.

As shown in Study IV, there are large disparities between different counties/regions in Sweden. The fact that Studies I and II were conducted in one region might, as mentioned above, have affected the validity of our extrapolation of the results.

The midwives in Study III did not always enquire about or document special requests or reasons not to book an appointment. These parameters cannot be precisely quantified, but the variety of comments listed indicates a need for multiple interventions to reach this group of non-attendees. The conditions for making calls, e.g. the possibility to schedule specific appointments and the number of women to be called, varied. These are limitations but also a consequence of measuring the effectiveness of the interventions related to an existing screening program rather than experimental efficacy.

Study III coincided with the swine flu vaccination campaign, entailing a high workload at the Antenatal Health Clinics and resulting, together with logistic obstacles, in only 18 midwives participating in the focus group discussions. An additional focus group consisted of only two participants, leading to a smaller range of potential responses than in a larger group [117]. On the other hand, those two midwives had more time to discuss their specific experiences of calling immigrants. Another limitation of the study was that the reported reasons for non-attendance could be interpreted as second-hand information from the midwives.

It is noteworthy that the OR, calculated in Study IV, consistently overestimate associations and must be interpreted with some caution. Data concerning some variables were missing to a large extent. This can lead to biased results and false interpretations of the circumstances. However, the data on socio-economic factors were missing mainly for non-attending immigrant women and we have reasons to believe that this led to an

underestimation of the difference between groups rather than an overestimation of the effect. Information about screening is obviously not offered on equal terms to the population, who also live in counties with differing screening programs and attendance-enhancement measures, and these differences in attendance exist across socio-economic strata.

## 6 CONCLUSIONS

In conclusion, these results suggest there is major potential for improvement of cervical cancer screening routines in Sweden in order to increase participation.

- Women who have not attended screening for six years or more had a fourfold increase in high-grade cytological atypia, compared with a normal screening population.
- Telephone contact with women who had abstained from cervical cancer screening for at least six years:
  - increased participation,
  - yielded a significant increase in detected and followed up atypical smears,
  - was practically feasible in a cervical cancer screening program,
  - did not seem to increase costs.
- Offering a self-test for HPV to long-term non-attendees in a well-run cervical cancer screening program, with reminders to order and return the tests, led to increased participation, most likely at no additional cost to the healthcare sector. With a lower cost for the test kit, this intervention will probably be cost-reducing.
- Offering various screening options can be successful in increasing overall attendance rates.
- There is a potential to reduce non-attendance and improve access in cervical cancer screening when midwives become aware of women's varying requirements for attending screening.
- Low education, not working, low household income, young age, being single and being born abroad are independent factors associated with lower cervical cancer screening attendance.
- Residence in a particular county is a strong independent factor affecting attendance.

## 7 FUTURE PERSPECTIVES

In order to create conditions making it possible for all eligible women who so wish to attend cervical cancer screening and to enhance screening program credibility, we must:

- minimize differences in management in different Swedish counties,
- offer opportunistic screening when suitable,
- offer different screening strategies targeting non-attendees,
- exclude hysterectomised women from screening invitations,
- devote special efforts to subgroups of women with low attendance, such as immigrants.

There is still a great need for more research concerning how low-attendance groups should be targeted.

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