Cervical and vaginal cancer
– aspects on risk factors, prevention and treatment

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Illness is the night side of life, a more onerous citizenship. Everyone who is born holds dual citizenship, in the kingdom of the well and in the kingdom of the sick. Although we all prefer to use the good passport, sooner or later each of us is obliged, at least for a spell, to identify ourselves as citizens of that other place.

Susan Sontag, Illness as Metaphor (1)

Abstract

Background: Participation in screening is associated with a major risk reduction in cervical cancer, but there is a lack of knowledge on whether the cost to the individual has an effect on the participation rate. Women with abnormal findings at screenings are referred for colposcopy. The use of the Swedescore scoring system is recommended by the Swedish national guidelines for cervical cancer prevention. There is, however, a lack of effectiveness studies evaluating this assessment. Previous studies have shown that women with cervical high-grade lesions have an increased risk for vaginal cancer, but there is a knowledge gap regarding the risk for hysterectomised women with and without risk factors. Women with early-stage cervical cancer are treated with radical hysterectomy, which can be performed via open or minimally invasive surgery (MIS). Inferior oncologic results of MIS have been reported in international studies, which emphasises the need for further assessment of the technique's oncological safety.

Aims: To study factors influencing the prevention of cervical and vaginal cancer by means of the screening programme for cervical cancer and to evaluate surgical treatment modalities for early-stage cervical cancer.

Material and methods: *Paper I* was a randomised controlled trial (RCT) performed on female (n = 3124) residents of low-resource areas of Gothenburg in 2013. The intervention group did not have a fee, and the control group had the standard fee. Attendance was defined as registered cytological smear within three months of invitation. In *paper II*, population-based register data from the National Patient Register and the Swedish Cancer Register were used in a cohort study design 1987–2011. The cohort was divided into four groups: hysterectomised with benign cervical history, hysterectomised with a history of cervical intraepithelial lesion grade 3 (CIN3), hysterectomised with prevalent CIN at surgery and non-hysterectomised. The main outcome was vaginal cancer. *Paper III* was a cross-sectional study linking data from the Swedish National Cervical Screening Registry (NKCx) with histological samples and a Swedescore assessment and/or colposcopic assessment by identifiable colposcopists. In *Paper IV*, five-year overall survival (OS) and disease-free survival (DFS) were assessed in a population-based cohort study that included

all Swedish women with IA1-IB1 cervical cancer treated with radical hysterectomy from 2011 to 2017. The Swedish Quality Register for Gynecological Cancer (SQRGC) was used for identification.

Results: *Paper I*: No difference in attendance was noted between the intervention and control groups (RR=0.93 95% CI 0.83-1.02). Nor were there any differences according to previous participation or non-participation or between the districts. *Paper II*: 898 vaginal cancers were included. Women with prevalent CIN at hysterectomy had a high incidence rate (IR 51.3/100 000 95% CI 34.4-76.5), followed by women with CIN3 history (IR 17.1/100 000 95% CI 12.5-23.4). *Paper III*: 11 317 colposcopic assessments by Swedescore were included. Sensitivity at Swedescore ≥2 was 97.5%, and the negative predictive value (NPV) was 90.2%. Specificity at ≥8 was 93.3%, and the positive predictive value (PPV) was 60.1%. Area under the ROC curve (AUC) = 0.71. In total, 24 362 colposcopies with identifiable colposcopists were analysed for accuracy. The variability in accuracy differed significantly (p-value <0.001), no effect of experience was noted (k= 0.0024). *Paper IV*: In total, 864 women, 236 open and 628 robotic radical hysterectomies were identified and included. There was no difference in five-year OS between groups (Hazard Ratio (HR) 1.00; 95% CI 0.50-2.01) or DFS (HR 1.08 95% CI 0.66-1.78).

Conclusions: Abolishment of a fee in low-resource settings did not increase attendance. Surveillance should be offered to hysterectomised women with prevalent CIN since their risk of vaginal cancer is elevated. Abstaining from biopsy is not recommended at any Swedescore step; a referral smear should be taken into consideration before 'see and treat' method to lower the risk for overtreatment. The experience of colposcopists did not affect accuracy. Long-term oncological outcomes did not differ between open and robotic radical hysterectomies.

Keywords: cervical cancer, uterine cervical neoplasms, cervical screening, medical fee, vaginal cancer, hysterectomy, Swedescore, effectiveness screening, robotic radical hysterectomy, oncological outcomes.

Sammanfattning på svenska

Icke-deltagande i livmoderhalsscreeningen är förenat med ökad risk för insjuknande i livmoderhalscancer. Screeningen har varit avgiftsbelagd i stora delar av landet men det saknas studier kring om avgiften har betydelse för deltagande. Kvinnor med onormala fynd på cellprov eller HPV-test vid screeningen remitteras till undersökning av livmoderhalsen med hjälp av specialmikroskop (kolposkopi). Nationella riktlinjer rekommenderar Swedescore, ett sätt att systematisera och standardisera undersökningen. Det saknas dock utvärderingar kring hur det fungerar i screeningprogrammet och även om kolposkopistens erfarenhet påverkar precisionen. En del kvinnor med cellförändringar behandlas genom att operera bort livmodern (hysterektomi) eller genomgår det senare i livet av andra orsaker. Tidigare studier har visat att kvinnor som tidigare haft cellförändringar har en ökad risk för vaginal cancer. De överlägset flesta har då genomgått behandling där bara förändringarna tagits bort från livmoderhalsen. Det är dock oklart hur risken ser ut för de som blivit hysterektomerade. En ökad andel kvinnor i Sverige och i världen behandlas för tidig livmoderhalscancer med robotassisterad kirurgi, dock har nationella svenska data för långtidsöverlevnad och recidivfrihet saknats. Syftet med avhandlingen var att studera faktorer som förebygger cervix- och vaginalcancer genom användandet av det befintliga livmoderhalsscreeningprogrammet och utvärdera olika kirurgiska behandlingsmetoder för tidig livmoderhalscancer.

I *delarbete I* erbjöds hälften deltagande i screeningprogrammet utan avgift och hälften med oförändrad avgift, 100kr i en randomiserad kontrollerad studie. Den utfördes i låginkomstområden i Göteborg. Ingen skillnad i deltagande sågs mellan grupperna. Vi såg heller ingen påverkan av patientens tidigare deltagande eller icke-deltagande i screeningen**.**
Delarbete II, analyserade risken för vaginal cancer bland hysterektomerade med eller utan riskfaktorer i form av cellförändringar i livmoderhalsscreeningprogrammet samt för kvinnor som hade kvar sin livmoder. Vi fann att kvinnor som hade cellförändringar vid operationen hade en hög risk att senare utveckla vaginalcancer varför de rekommenderas uppföljning efter operation.
Delarbete III, alla kvinnor i det svenska screeningprogrammet som hade genomgått en kolposkopi där ett vävnadsprov hade tagits inkluderades. Vi fann att vid användande av Swedescore fanns ingen säker tröskelnivå för att avstå

från vävnadsprov och vid direktbehandling av cellförändringar bör man ta hänsyn till föreliggande cytologprov för att undvika överbehandling. Kolposkopisternas erfarenhet påverkade inte deras prestation men precisionen varierade stort mellan olika kolposkopister.

Delarbete IV studerade alla kvinnor med tidig livmoderhalscancer som genomgick radikal hysterektomi i Sverige 2011–2017 med öppen eller robotassisterad teknik. Vi fann ingen skillnad i femårsöverlevnad eller återfall mellan de kirurgiska metoderna.

List of papers

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

I. Alfonzo E, Andersson Ellström A, Nemes S, Strander B. Effect of Fee on Cervical Cancer Screening Attendance-ScreenFee, a Swedish Population-Based Randomised Trial, PLoSOne 2016 Mar 17;11(3): e0150888

II. Alfonzo E, Holmberg E, Sparén P, Milsom I, Strander B. Risk of vaginal cancer among hysterectomised women with cervical intraepithelial neoplasia: a population-based national cohort study, BJOG 2020 Mar;127(4):448-454

III. Alfonzo E, Holmberg E, Daneshpip F, Milsom I, Strander B. Swedescore and the effectiveness of colposcopy in the Swedish screening program, Manuscript

IV. Alfonzo E, Wallin E, Ekdahl L, Staf C, Flöter Rådestad A, Reynisson P, Stålberg K, Falconer H, Persson J, Dahm-Kähler P. No survival difference between robotic and open radical hysterectomy for women with early stage cervical cancer: results from a nationwide population-based cohort study Eur J Cancer 2019 Jul;116:169-177

Content

Abbreviations

AIS	Adenocarcinoma in situ
AUC	Area under the ROC curve
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
DFS	Disease-free survival
FIGO	International Federation of Gynaecology and Obstetrics
HPV	Human papillomavirus
HR	Hazard ratio
HSIL	High-grade squamous intra epithelial lesion
ICD	International Classification of Disease
IR	Incidence rate
IRR	Incidence rate ratio
LVSI	Lymph vascular space invasion
MIS	Minimally invasive surgery
NKCx	Swedish National Cervical Screening Registry
NPV	Negative predictive value
OR	Odds ratio
OS	Overall survival
PPV	Positive predictive value
RCT	Randomised controlled trial
RFS	Relapse-free survival
RH	Radical hysterectomy
RR	Relative risk
SLN	Sentinel lymph node
SQRGC	Swedish Quality Register for Gynecologic Cancer
TZ	Transformation zone
VaIN	Vaginal intraepithelial neoplasia
WHO	The World Health Organization

Introduction

Cervical cancer epidemiology

Every year, approximately 300 000 women die due to cervical cancer. It accounts for the fourth most common cancer globally among women after breast cancer, colorectal cancer and lung cancer (2). Since the mean age of cervical cancer diagnosis is lower than many other types of cancer, it creates more loss of life years and occurs in ages where women often are both economically responsible and caregiving (2, 3). On a global level, the highest rates of incidence and mortality are seen in low-resource countries, and the cumulative rates of incidence and mortality are two to four times lower in the highest resource countries compared with the lowest resource income countries (Figure 1) (2). In total, 84% of the cases are found in low-resource countries (2). This reflects the lack of screening, shortage of effective treatment of precancerous stages and cancer, as well as a geographical difference in exposure due to risk factors such as the human immunodeficiency virus (HIV), human papillomavirus (HPV), chlamydia, smoking and oral contraceptives (2). HPV prevalence among women with normal cytological findings shows a geographical variance ranging from 1.6% to 41.9% (4). When the socioeconomic terms improve, the incidence of cervical cancer decreases, as in the case of India, where incidence has fallen in urban areas but not in rural areas (5, 6).

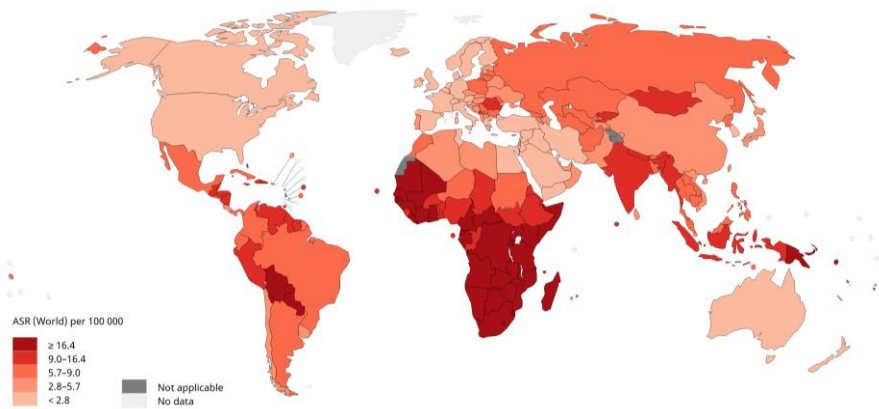


Figure 1. Estimated age standardized (W) mortality rates of cervical cancer all stages 2020. Data source: GLOBOCAN 2020. Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.

Importantly, the fact that cervical cancer is preventable makes it even more prioritised from an ethical and resource point of view to decrease incidence and mortality (3).

Cervical cancer pathogenesis

The development of cervical cancer is in the absolute majority of cases caused by a persistent infection with HPV. HPV infection is considered the most common sexually transmitted disease, and 79% of sexually active women will encounter the infection at least once; however, the majority (90%) clear the infection (7, 8). Ninety-one percent of cervical cancers are positive for high-risk HPV (hrHPV), with a higher degree of HPV positivity for squamous cell carcinoma compared with certain adenocarcinomas (9). HrHPV infects basal epithelial cells, and through the viral proteins E6 and E7, it inactivates the retinoblastoma protein (pRB) and p53 tumour suppressor pathways, causing uncontrolled cell proliferation and inhibiting cellular death (10, 11). Persistent infection may cause precancerous lesions and progress to cancer (12-14). The progression rates for cervical intraepithelial neoplasia grade 2 (CIN2) and grade 3 (CIN3) to invasive cervical cancer are 5% and 12-30%, respectively (12, 13). Known risk factors are smoking, young age at first intercourse, sexually transmitted diseases, multiple sexual partners, an impaired immunological status or oral contraceptives (15-18). HPV vaccination through bivalent (HPV 16,18), quadrivalent (HPV 6,11,16,18,) and nonavalent (HPV 6,11,16,18,31,33,45,52,58) effectively reduces the risk of precancerous lesions and cervical cancer (19, 20).

Cervical screening

Screening a population is indicated when a disease has a prodromal phase that can be diagnosed and accepted by the patients and can be treated (21, 22). Cervical cancer suits these demands perfectly since the natural course of the disease is well mapped, has a long prodromal phase and can be treated. Successful cytological sampling (Figure 2) and treatment of precancerous lesions or cancer have reduced the incidence in Western Europe, Oceania and North America, and has simultaneously compensated for the increase in risk factors such as rising HPV prevalence women have encountered since 1945 (2, 23, 24). This is not the case in countries lacking an efficient screening, such as in eastern Europe, Portugal or Ireland (2).

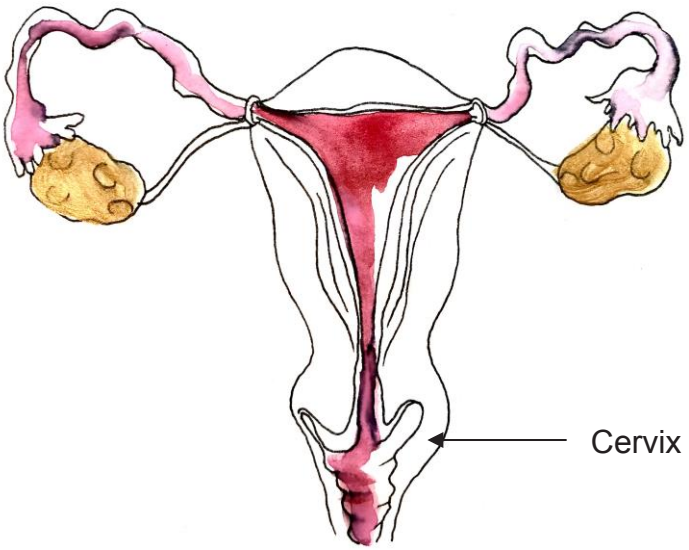


Figure 2. Cervix from where the cytological smear is taken.
Illustration © Lina Lindbergh

Cervical screening in Sweden

Screening with cervical cytology started in Sweden in 1966, and in 1977, all counties had an organised screening organisation (7). Cervical screening in Sweden constitutes a success story since it has reduced the incidence by more than 50% since the start of the 1970s (24), with an incidence at 24/100 000 women years in 1965 to 8/100 000 in 2011, and simultaneously mortality has dropped (Figure 3) (25).

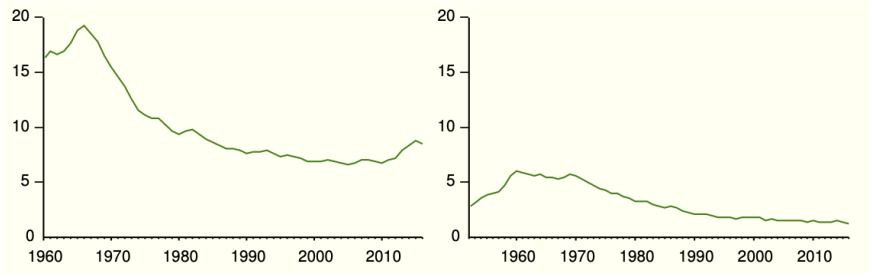


Figure 3. Incidence (World age-standardised rate (ASR W)) of cervical cancer/ 100 000 persons (left) and mortality / 100 000 persons (right) 1960-2016. Data source: NORDCAN (26).

The cervical screening programme consists of the following: a screening test, i.e. cervical cytology or an HPV test, follow-up of abnormal results with colposcopy, biopsies or intensified HPV testing, postcolposcopic management with treatment of precancerous lesions or cancer and follow-up after treatment (27).
The Swedish health care system is, in comparison with other Western countries, highly decentralised. General recommendations are issued by the Swedish National Board of Health and Welfare. More specific national guidelines based on these recommendations are made by the Confederation of Regional Cancer Centres in Sweden. However, the regional cancer centre in association with the primary care organisation monitors and coordinates the regional cervical screening programme autonomously. Resident women are invited for screenings with a scheduled appointment at their closest maternity clinic. Women who are invited for the first time are identified via the population register, and the following screening invitations are determined since the time of the last cytological smear or HPV test. Women who do not attend are reinvited yearly. The current national guidelines in Sweden recommend screening every third year for women ages 23-29 with cytology and from 30-49 with primary HPV-test (Figure 4) (7). At age 41, women are screened for both HPV and cytology to discover the relatively few cases of HPV-negative cell abnormalities in this group. Primary HPV testing is also used for the age group of 50-64 years who are screened every seventh year.

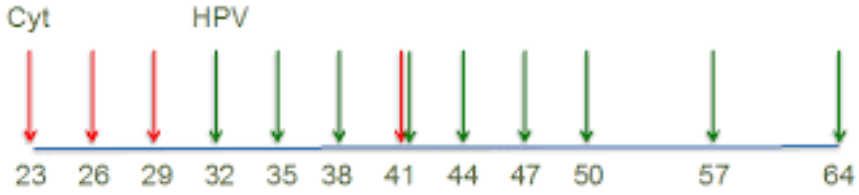


Figure 4. Recommended sampling according to the Swedish screening programme according to age group. Red arrow: primary cytological analysis Green arrow: primary HPV-test. Adapted from (28, 29).

A positive HPV test is triaged with cytology. If cytology is normal, a new HPV test is taken after 18–36 months, and if the test indicates HPV persistence, the woman is followed up with colposcopy. In cases of abnormal cytology, the woman is followed up with colposcopy. However, despite the historical decrease of cervical cancer in Sweden mentioned above, an increase in cervical cancer incidence has been noted since 2014 and in 2017 it reached 11/100 000 (Figure 5). The increase of cervical cancer was noted among women screened with previous normal cytological smears, a possible explanation of the increase was insufficient detection of precursor lesions in the screening (25).

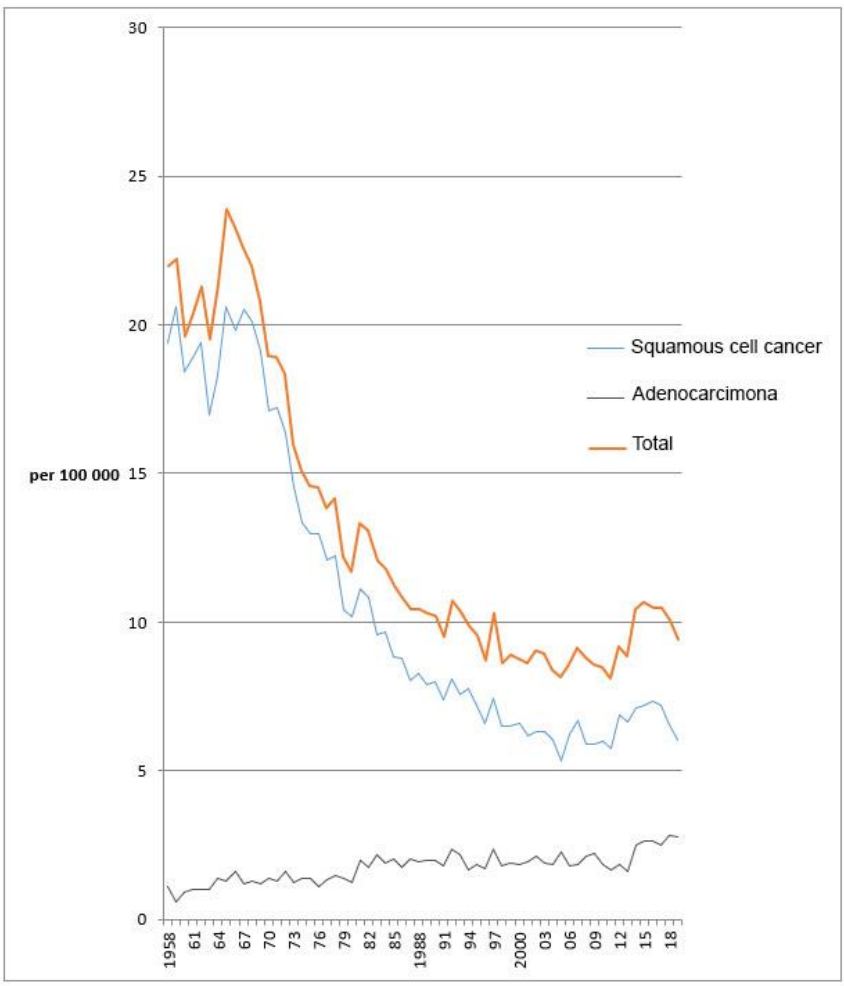


Figure 5. Incidence (ASR Folk och Bostadsräkning 1970) of cervical cancer in Sweden 1958-2018, total incidence and divided into histology type. Data source: Socialstyrelsens statistikdatabas.

Coverage and attendance in the screening programme

The goal of cervical screening in Sweden is primarily to prevent cervical cancer and secondarily to detect early stages of invasive cancer by offering equal opportunities for women to get screened. The National Board of Health and Welfare has identified 12 quality indicators for follow-up of the screening programme, such as attendance rates, coverage and proportion of positive cytological smears. In addition, the Swedish National Cervical Screening Registry (NKCx) has outlined the process, measured the outcomes, added some complimentary quality indicators, and defined benchmarks such as screening coverage in the source population, defined as 85% (30). Not attending is considered the most important factor for cervical cancer associated with the screening programme (31). Irregular screening also elevates the risk. If a woman attended in the recent round but previously had not, her risk was still elevated, odds ratio (OR) 1.6% (95% CI: 1.5–1.8) (32). However, if the woman had not participated at all, her risk was four times higher compared with adequately screened women. Participating in the screening with normal results resulted in a risk reduction of 89% for squamous cell carcinoma compared with unscreened women.

Coverage is crucial for a screening programme, but it is complex and consists of several components. Coverage implies the proportion of women who are included in the screening programme and who take a cytological smear or HPV test during a screening cycle or otherwise defined time span, irrespective of invitation. Internationally, spans of 3.5, 5.5 or 7.5 years are most often used. The longer the time of follow-up, the higher coverage is gained. By using the 7.5-year definition, Sweden achieves 90% coverage for the ages 23–70 in 2019 (33). In Sweden, the coverage of 23–70 aged women was 82% (mean coverage of 3.5 and 7.5 years of follow-up time) in 2019. A regional variation exists, with the highest coverage (89%) seen in Halland and Värmland and the lowest in Kronoberg, Gotland and Uppsala (74–75%) (33). Coverage has increased over time; in 2018, women aged 23–50 years had an 86% coverage counted with 3.5 years of follow-up time, compared with 79% in 2010 (34). Attendance is the proportion of invitations resulting in testing (31). Yearly re-invitations to non-attendees are sometimes included in attendance rate; thus, in areas with lower participation, reminders take a bigger part of the total sum of invitations, which affects attendance rate negatively. In Sweden, both participation within 90 days after sent invitations and after one year, are used (30). Attendance in Sweden, not including yearly reminders, after three months was 58% in 2019 and 71% within one year (33).

Coverage and attendance in the screening programme in West Sweden

Screening coverage in Gothenburg 2018 was 82.2% adjusted for screening intervals of 3.5–5.5 years (30). This is a slight increase from previous years. The coverage varies according to city districts, with the highest rates in Western Gothenburg at 89.5%. The lowest coverage is seen in North-eastern parts of Gothenburg, where the districts Bergsjön had a coverage of 66.5% and Angered 72%. However, the coverage has increased since previous years (35). The attendance rate is lower than the coverage, and in 2018, Gothenburg had a 49.3% attendance rate, including yearly reminders (35).

Gothenburg is considered a socially highly segregated city (36). In fact, life expectancy differs 7.5 years for women between different areas, North-eastern Gothenburg exhibiting the lowest (37). Moreover, a high variation is seen in available income, with the lowest in areas of the north-east and the highest in Western Gothenburg. The districts in North-eastern Gothenburg have a higher unemployment rate and a greater number of foreign-born inhabitants compared with the city in general (38).

Common aspects among non-attendees

Non-attendees in the cervical screening programme in Western countries share many aspects: visiting different gynaecologists, frequency of doctor visits (both visiting physicians very often, <five times/year, or not at all), no use of oral contraceptive methods, no future intention to participate in breast cancer screening and low awareness of the screening interval (39). Many of the non-attendees thought screening aimed at detecting cancer and not precancerous lesions, which is why fear of the result may be an obstacle to participation (39, 40). Underestimation of time since last pap-smear was also a common factor (41). Other studies have shown that mainly practical barriers hindered women from participating, such as lack of time and difficulties making an appointment (42) (43).

There are diverting results regarding the impact of socio-economic status. One Swedish study based on questionnaires with non-attendees and attendees showed no effect (39). This was also confirmed in an analysis of attendance rates in Europe when socio-economic variables such as employment type/unemployment, income and education, were analysed (44). In a study from the USA among immigrants, higher attendance was noted among young women with poorer health, possibly indicating that a more frequent encounter with health care led to higher attendance

(45). Other studies indicated a negative effect on attendance for women with low socio-economic status (46-48). A Swedish population-based registry study from 2018 showed that socio-economic factors such as low income, not being part of the labour force, lower education, receiving welfare benefits and living alone were associated with non-attendance (49). However, these differences between studies should be taken with caution since the studies refer to different health care systems, populations and socio-economic conditions consisting of several components.

A lower participation is noted in immigrant populations in studies from different countries (50-55). Some studies point out that non-attendees are more likely not to know the purpose of screening (39, 56). In addition, other studies show that attendees did not know what cancer they were screened for (57).

Interventions influencing attendance

In Sweden, women are invited to participate in the screening programme in a letter with a fixed time, most often at their closest maternity clinic. Data from a randomised controlled trial (RCT) showed that scheduled appointments were associated with higher attendance (58). The type of invitation also affected attendance positively in two reviews: standardised invitation for women aware of the screening programme and more individualised information for less motivated women (59, 60). HPV self-tests to non-attendant women have improved participation in several RCTs (61-64). Telephone reminders turned out to be an effective method for reaching non-attendees more effectively than mail in two RCTs (65, 66). In a Cochrane review regarding interventions encouraging uptake of cervical screening, it was concluded that invitations and educational interventions were most effective (67). Later, a systematic review concluded that theory-based educational interventions were effective in communities with low literacy rates (68). In a meta-analysis of strategies to increase attendance in different screening programmes, economic incentives such as reducing or removing co-payment were found to be the second most effective intervention after organisational changes (69). Up to 2018, almost all counties had a fee for participating in the screening programme, ranging from 80–200 SEK.

Cervical cytology and HPV test

Implementation of cervical cytology in population-based screening for cervical cancer has had a key role in decreasing the incidence of cervical cancer (70). The precision of cervical cytology has been widely researched, and a great variation is seen in sensitivity and specificity (71, 72). Cervical cytology has low sensitivity; thus, testing has to be repeated at three-or five-year intervals in order not to miss high-grade lesions or cancer (73). Liquid base cytology has advantages compared with conventional cytology, as it has an increased sensitivity for Cervical Intraepithelial Neoplasia grade 2 and worse (CIN2+), a decreased number of inadequate test results, and a reflex test (i.e. tests for HPV) can be performed on the same sample (74).

The accuracy of the HPV test has also been widely studied. In a meta-analysis from 2016, HPV tests had a pooled sensitivity for CIN2+ of 95% and corresponding specificity of 84% (71). A Cochrane review comparing HPV tests, conventional cytology and liquid base cytology had similar results (75).

The National Board of Health and Welfare recommends a combination of primary HPV testing and liquid-based cervical cytology in the Swedish cervical screening programme (7, 29).

Colposcopy

The colposcopic examination determines if and where biopsies are taken in order to detect precancerous or cancerous lesions. With a binocular microscope and a light source, a stereoscopic view of the cervix is provided, magnifying the view 6–40 times. The technique was developed in Germany in the 1920s (76).

Concurrently, the use of cervical cytology evolved, shifting from first identifying cervical carcinoma to precancerous lesions. Countries adopting cytological examinations tended not to use colposcopy as a screening tool, as in the US, whereas countries using colposcopy tended not to use cytological examinations (77). Since the 1970s, colposcopy has become a diagnostic step after cytology, even in countries not using it earlier. However, it is still used as a screening tool in some countries since it offers a quicker diagnosis than cytology, which requires a laboratory.

Colposcopy has, at its best, the ability to predict high-grade squamous lesions, while glandular lesions seldom have any specific colposcopic features (78). It is

not considered a stand-alone diagnostic tool, and the examinations are usually influenced by a result from a referral test (79). It is difficult with a normal colposcopic impression, without biopsies taken, to rule out disease (27). Sensitivity and specificity vary greatly in different studies. In a meta-analysis over the years 1960-1996, sensitivity in distinguishing high-grade squamous intraepithelial lesion (HSIL)/cancer was 64-99%, whereas specificity was 30-93% (80), and an American RCT yielded a sensitivity 54% in detecting CIN3 (81). Criticism against the colposcopic method has been raised, and taking multiple (79, 82-85) or random biopsies (86-88) is advised to lower the risk of missing high-grade lesions and increase sensitivity.

Histopathology is regarded as the gold standard when evaluating colposcopic assessment. Many of the studies evaluating colposcopy with histopathology from punch biopsies suffer from verification bias since the representability of the samples depends upon the colposcopic assessment (89). Furthermore, this also affects the quality and conclusions in the studies. When punch biopsies were compared with excision biopsy performed the same day, sensitivity was 81.4% and specificity 63.3% (83). In another study, the overall agreement was 56% between punch biopsy and excision biopsy taken the same day (85). Interobserver agreement can also affect the result, and analysis shows that the agreement between pathologists was moderate but raised with increasing lesion severity (90).

Colposcopy and the effect of experience

There are divergent results in different studies regarding the influence of the colposcopist experience or medical training on precision. Colposcopic sensitivity in order to detect CIN2+ was similar when nurse practitioners, general gynaecologists, gynaecologic oncology fellows and gynaecologic oncologists were compared (79). Nurses suspected abnormal colposcopy to a higher degree, took a significantly higher amount of punch biopsies, and had a higher sensitivity of detecting high-grade lesions. For all groups, sensitivity increased significantly when ≥ two biopsies were taken. Nor was there any overall difference noted in a large Australian study comparing experienced colposcopists with junior colleagues and their ability to detect HSIL (91). In a study, the juniors had a significantly higher sensitivity compared with the senior group in detecting HSIL (66.7% and 57.5%, respectively), whereas the seniors had a significantly higher positive predictive value (PPV) (56% and 64%, respectively). No learning curve was noted when each group's performance in the first year was compared with the fifth year. In contrast, a small Italian study where only two biopsies were taken per colposcopy showed

a higher sensitivity among senior colposcopists compared with junior colleagues (92). The divergent results in the Italian study may to a certain degree be attributed to the number of biopsies taken, since inexperienced colposcopists tend to compensate by increasing the number, thus giving a raised sensitivity.

Scoring systems

In the beginning of the 1980s, the first scoring system, Reid's colposcopic index (RCI), for colposcopy was developed in order to simplify the learning of colposcopy (93). The system was the most widely used scoring system and included grading of thickness, contour, colour, vascular atypia and iodine staining. In the original article, the agreement with the corresponding histopathological diagnosis was 96%. Since the authors concluded that colour and thickness were less predictive than the other signs, they were replaced by margins in a revised scoring system with as good results: 97% agreement (94). The system has performed better in terms of predictive accuracy than the general colposcopic method (i.e. colposcopic impression) (95, 96).

In 2005, Strander et al. published a new scoring system, Swedescore, which in contrast to RCI also included lesion size and had a scale with somewhat lower requirement for a high score, thereby increasing the actual range of classifications (Table 1) (97). The system was specifically designed to predict high-grade lesions, CIN2+, which normally is the level for treatment. At score ≥8 specificity for HSIL was 90%. In an evaluating British study, at score ≥8, the specificity was 95% (98). The scoring system has performed well in several subsequent studies from different countries (99-103). The high specificity and PPV at the upper scale of Swedescore has led to the possibility of the 'see and treat method' at high Swedescores, i.e. excision biopsy at colposcopy, without prior punch biopsy. This method also has advantages in low-income countries (102, 103).

A common feature of the scoring systems is that the assessment of colposcopy most often corresponds to the terminology of the International Federation for Cervical Pathology and Colposcopy (104).

Table 1. Swedescore. Adapted from © International Agency for Research on Cancer, Atlas of Colposcopy: Principles and Practice https://screening.iarc.fr/atlascolpodetail.php?Index=28&e=,0,1,2,3,8,10,15,19,30,31,43,46,47,60,61,68,73,83,88,89,93,96,102,105,111 (December 2020)] (105).

Swede score	0	1	2
Aceto uptake	Zero or transparent	Shady, milky (not transparent not opaque)	Distinct, opaque white
Margins/surface	Diffuse	Sharp but irregular, jagged, 'geographical' Satellites	Sharp and even, difference in surface level incl. 'cuffing'
Vessels	Fine, regular	Absent	Coarse or atypical
Lesion size	<5mm	5-15mm or 2 quadrants	>15mm or 3-4 quadrants or endocervically undefined
Iodine staining	Brown	Faintly or patchy yellow	Distinct yellow

Recurrent CIN and risk of vaginal cancer

Women with recurrent CIN constitute a clinical challenge. They have often been treated with one or several conisations, limiting further conservative treatment, and they are sometimes treated with hysterectomy, which is considered a final management. Two large Swedish cohort studies have shown that women treated for CIN3 have an increased risk of acquiring cervical or vaginal cancer compared with the general population (106, 107). The standardised incidence ratio for vaginal cancer among these women previously treated for CIN3 ranges from 7–18 according to different studies (106, 108, 109). Further, Strander et al. found that the risk was accentuated at advanced ages and remained even 25 years after treatment (106).

Hysterectomised women with CIN and risk of vaginal cancer

The risk of cancer in the vagina after hysterectomy for CIN3 has been described in a few studies, but they show contradictory results. In a systematic review, no increased risk of vaginal cancer was found among hysterectomised patients with

CIN. However, the authors concluded that the included studies had important methodological or reporting shortcomings that did not allow for a meta-analysis (110). In contrast, other researchers found that women hysterectomised with CIN had a relatively high prevalence of vaginal cancer (111).

Only a few studies have described for how long time the increased risk of vaginal cancer persists after a hysterectomy. In a retrospective study of 341 vaginal cancer cases 1956–1996, hysterectomised women with CIN developed vaginal cancer within an average of five years after surgery (112). Women with a benign condition or endometrial carcinoma as an indication for hysterectomy developed vaginal cancer after an average of 17 and 19 years, respectively. In a systematic review of vaginal vault smears after hysterectomy, no effect of time was seen. However, only one case of vaginal cancer after hysterectomy was described, which limited the conclusions (110). The current Swedish national guidelines for cervical cancer prevention recommend follow-up with cytology and HPV tests six months and five years after surgery for women hysterectomised due to high grade lesions or with a history of high grade lesions (30).

Cervical cancer

In screened populations, squamous cell carcinoma accounts for approximately 70% of cervical cancer cases, whereas adenocarcinoma and adenosquamous cell carcinoma constitute about 25% (113). In addition, there exist other rare histopathological subtypes, such as neuroendocrine carcinomas, clear cell cancer and melanomas, accounting for approximately 5%.

FIGO stage

The staging of cancer is a dynamic process closely linked to scientific developments. According to the International Federation of Gynecology and Obstetrics (FIGO) 2009, the stage is based on clinical examinations with eventual addition of information from simple examinations, such as cystoscopy and rectoscopy, which facilitate uniform staging in low-resource settings (Table 2) (114). The staging in paper IV is according to FIGO 2009. The staging was revised in FIGO 2018 and takes into account imaging modalities if these are available (Table 2) (115).

Table 2. FIGO staging of cervical carcinoma 2009 and 2018. Adapted from (114, 115).

FIGO 2009		FIGO 2018	
IA	IA1 Invasion ≤3 mm and extension ≤7 mm IA2 Invasion >3 mm to ≤5 mm and extension ≤7 mm	IA	IA1 Invasion <3 mm IA2 Invasion ≥3 mm to <5 mm
IB	IB1 Lesion ≤4 cm IB2 Lesion >4 cm	IB	IB1 Invasion ≥5 mm and lesion <2cm IB2 Lesion ≥2 cm and <4 cm IB3 Lesion ≥4 cm
II	IIA1 Lesion ≤4 cm, involvement of upper 2/3 of vagina IIA2 Lesion >4 cm, involvement of upper 2/3 of vagina IIB Parametrial involvement	II	IIA1 Lesion <4 cm involvement of upper 2/3 of vagina IIA2 Lesion ≥4 cm, involvement of upper 2/3 of vagina IIB Parametrial involvement
III	IIIA Involvement of lower 1/3 of vagina IIIB Extension to the pelvic wall/hydronephrosis	III	IIIA Involvement of lower 1/3 of vagina IIIB Extension to the pelvic wall/hydronephrosis IIIC1 Pelvic lymph nodes metastasis IIIC2 Paraaortic lymph nodes metastasis
IV	IVA Spread to adjacent organs IVB Metastasis to distant organs	IV	IVA Spread to adjacent organs IVB Metastasis to distant organs

Prognostic factors

FIGO stage and lymph node status are independent prognostic factors for survival in cervical cancer (19). The presence of lymph node metastases affects survival, and the five-year overall survival (OS) for stage IB1 decreases from 95% to approximately 76% in case of positive lymph nodes (116). Furthermore, the presence of lymph node metastases increases with increasing tumour size and with advanced FIGO stage (117, 118). Tumour size is also an important prognostic factor, which, with increasing size, decreases the five-year OS from 94% for tumours ≤2

cm to 85.1% for tumours 2.1-4 cm and 69.9% for tumours >4 cm (118). Other predictive factors for survival are parametrial involvement, depth of invasion and lymph vascular space invasion (LVSI) (119-122).

Certain histological subtypes, such as small cell neuroendocrine cervical cancers, are associated with a worse prognosis. However, for the most common cervical cancer types, squamous cell cancer and adenocarcinoma, there is no difference in survival or recurrences for early stages if other prognostic factors are adequately adjusted for (123-125). This is further supported by data from the Swedish Quality Register of Gynecological Cancer (SQRGC) showing no relative survival difference between adenocarcinomas, adenosquamous cancer and squamous cell cancer (126).

Surgical treatment

Cervical cancer spreads per continuitatem, and in order to gain tumour-free margins, a simple hysterectomy is in many cases not sufficient treatment for clinically visible stages. Already at the end of the 19th century the first radical hysterectomy was performed (127). It was further evolved by Professor Wertheim. No systemic pelvic lymphadenectomy was performed, and only bulky nodes were removed; however, the procedure had a 19% perioperative mortality (128). The surgical procedure was further developed, a more radical dissection of the parametrium was demonstrated in Japan and in the USA an additional systemic pelvic lymphadenectomy was described (128, 129). The addition of lymphadenectomy is diagnostic rather than therapeutic. Along with improved survival rates, the nerve sparing technique evolved to decrease and minimise morbidity (130).

Further surgical modifications were made, resulting in five classes of extended hysterectomies according to Piver-Ruthledge (131). One of the few RCTs regarding cervical cancer surgery concluded that a less radical surgery, Piver class II, had similar oncologic outcomes and lower morbidity compared with Piver class III (132). In an attempt to simplify and harmonise the different radical hysterectomies, Querleu and Morrow proposed a new classification in 2008 with type of surgery A-D with subtypes (Table 2) (133, 134). Another approach with total mesometrical resection (TMMR) and therapeutic lymphadenectomy was presented by Hoeckel and coworkers in a prospective study from 2009 with impressive five-year OS results of 96% and a DFS of 94%, but these findings are still awaiting to be reproduced (135, 136).

Early-stage tumours, according to FIGO 2018, ≤ IB2 + IIA1, are generally recommended primary surgery. For the IA1-IA2 stages, a conisation or simple hysterectomy is recommended, and in the presence of LVSI, a pelvic lymphadenectomy or sentinel lymph node dissection (SLN) is performed. For stage IB1-2+ IIA1, a radical hysterectomy with systemic pelvic lymphadenectomy is the treatment of choice. Fertility-sparing surgery, or trachelectomy, may be recommended and performed for tumours ≤ 2cm except if high-risk histology is present. More advanced stages, IB3, IIA2-IVB, are treated with definitive chemoradiotherapy.
Radical hysterectomy can be performed by different surgical techniques, such as laparotomy, vaginally or by minimally invasive surgery (MIS), including conventional laparoscopy or robot-assisted laparoscopic technique. In Sweden, radical hysterectomy according to Querleu and Morrow type B-C is the most common procedure performed (Table 3).

Table 3. Radical hysterectomy according to Querleu and Morrow. Adapted from (19, 133, 134).

	Type of hysterectomy	Mobilisation of the ureter	Lateral dissection	Vagina	Sacrouterin-ligament	Vesicouterine ligament
A	Extrafascial	None	Close to cervix	Minimal resection	Dissection close to cervix	Dissection close to cervix
B	Modified radical	Partial	Medial to the ureter	10 mm	Partial resection	Partial resection
C	Classical radical	Complete	Lateral to the ureter. C1: caudal part preserved C2: including the caudal part.	15–20 mm	Dissection close to rectum. C1: Nervesparing. C2: Hypogastric nerve is sacrified	Transection at the bladder. C1: Nervesparing. C2: Bladder nerves are sacrified
D	Laterally extended	Complete	At the pelvic wall, at the exit of a. Iliaca interna. Exposing the root of n. Ischiadicus. ischiadicus	15-20 mm	Dissection close to rectum.	Transection at the bladder.

The surgery is, to a certain degree, associated with complications such as injuries of vessels, ureters and nerves as well as lymphedema, the latter linked to pelvic lymphadenectomy (137). According to the Swedish national guidelines for cervical cancer, SLN dissection may only be recommended for stage IA tumours to ensure oncological safety (19). An ongoing RCT will hopefully answer whether it can be safely recommended for the other surgically treated stages (138).

For tumours ≤ 2cm, the risk of parametrial involvement is very low. The ongoing SHAPE trial evaluates whether a simple hysterectomy instead of a radical hysterectomy may be feasible and oncologically safe for these small tumours (139). The updated Swedish national guidelines for cervical cancer state that simple hysterectomy can be performed for stage IA2 (FIGO 2018), which is in line with recent published data from the USA showing no difference in survival for this stage when a simple hysterectomy was performed instead of a radical hysterectomy (140). Along with improved imaging modalities leading to adequate and uniform staging, a potentially decreasing number of patients will undergo multiple treatment modalities due to peri- or postoperative findings of tumour spread and lymph node metastases. Studies suggest no difference in survival, although a higher morbidity caused by the multiple modality increases the risk for adverse side effects (141, 142); however, new data is expected (143).

Minimally invasive surgery

The first laparoscopic radical hysterectomy was performed in the early 1990s (144). Subsequent studies with mainly morbidity outcomes were promising compared with the open surgical approach (145-148). In the USA, the Food and Drug Administration (FDA) approved robot-assisted laparoscopy for gynaecological surgical treatments in 2005, and the year after the first case report of a robot-assisted laparoscopic radical hysterectomy was published (149). Compared with the laparoscopic technique, which is considered highly challenging, the robotic surgery provided improved surgical conditions, especially in the deep and narrow pelvic cavity, with improved precision by robotics (150). Moreover, in comparison with laparotomy, the robotic technique offers several advantages, which have been presented in numerous publications, such as decreased blood loss, relatively acceptable operation time and shorter length of stay (151-157). The robotic approach has spread throughout the world, including Sweden, where it has almost replaced the open approach at many centres during the last decade (Figure 6).

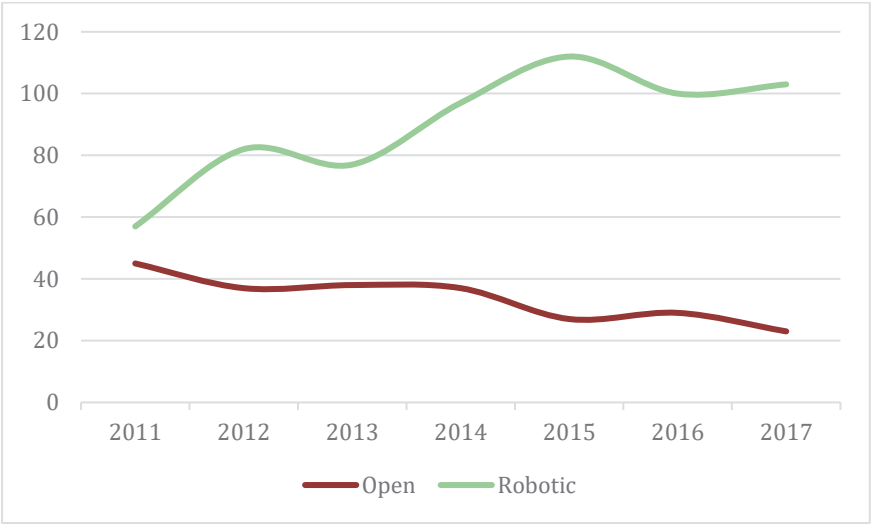


Figure 6. Number of open and radical hysterectomies performed 2011–2017 in Sweden included in paper IV.

Interestingly, there has been a lack of studies reporting oncological outcomes after radical hysterectomy comparing different surgical approaches. The few existing studies reported oncological survival outcomes comparable to laparotomy (Table 8) (156, 158-161). Nevertheless, none of these studies were RCTs. International guidelines, including the previous Swedish national guidelines for cervical cancer, considered MIS safe for early-stage cervical cancer (162-164). In 2018, the first large multicentre RCT comparing MIS (laparoscopic or robotic) and open surgery was published, the Laparoscopic Approach to Cervical Cancer study (LACC) (165). In contrast to the previous studies, inferior survival results for MIS compared to open surgery were presented. The DFS at 4.5 years for MIS and open was 86.0% vs. 96.5%, respectively. The hazard ratio (HR) was 3.74 (95% CI 1.63-8.58) and the three-year OS was 93.8% vs 99.0% for the MIS and open cohort, respectively (HR: 6.00 95% CI 1.77-20.30). The LACC trial started in 2008 and was stopped prematurely by the data and safety monitoring committee in 2017 due to the alarming results with the inferior result for MIS. At study closure 631, out of the planned 740, women with stage IA1+LVSI, IA2 and IB1 were included from 33 centres worldwide. Additionally, a population-based study was published, with data from the United States National Cancer Database, showing similar results (166). In this study, a total of 2 203 women diagnosed in 2010–2013 with stage IA2-IB1 were included. Mortality in the MIS group vs. open was 9.1% and 5.3%, respectively (HR 1.62 95% CI 1.20–2.19). The reasons for the difference in oncological outcomes between the surgical methods have since been intensively debated

and not fully understood. Nevertheless, the LACC trial dramatically changed the previously considered knowledge that MIS is as safe as open surgery for early-stage cervical cancer. The LACC study is still under debate within the gynaecological oncology society, and new studies evaluating surgical methods in cervical cancer are ongoing, including an RCT comparing robotic and open surgery (167).

Vaginal cancer

Vaginal cancer has a low incidence in Sweden < 1/100 000 (168) and similar incidence is found worldwide (169). Over time, the incidence in Sweden has only undergone minor changes (Figure 7). This is in contrast to cervical cancer, of which the incidence has decreased as a result of the launched population-based screening (168).

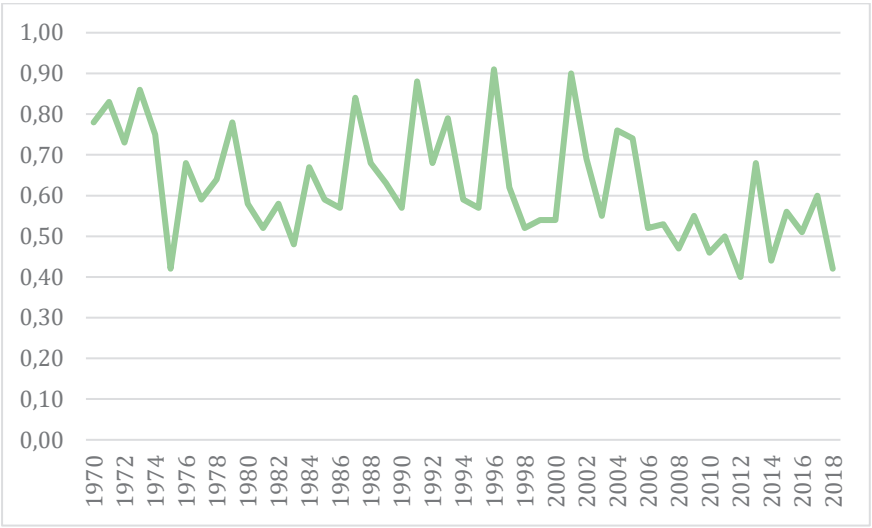


Figure 7. Incidence of vaginal cancer (ASR) per 100 000 persons 1970–2018. Data source: Socialstyrelsens statistikdatabas.

Most cases of vaginal cancer are diagnosed among postmenopausal women (112). Vaginal cancer shares many risk factors with cervical cancer, such as smoking, multiple sex partners and young age at first intercourse (170). Other known risk factors for vaginal cancer are a history of CIN, vaginal intraepithelial neoplasia (VaIN) and cervical cancer (106, 108, 109, 112, 171-174) as well as prior pelvic radiation (175) and exposure to diethylestradiol (176). Studies have shown that approximately 30% of cases were preceded by treatment of an anogenital cancer,

most often cervical cancer (170, 175). The progression rate of VaIN to vaginal cancer is 3–15%, with VaIN3 exhibiting the highest progression grade (177-179). This is far less than the progression rate for CIN3 to cervical cancer, which in some materials is >12% to 31% (12, 13).

Vaginal cancer is to 90% histologically squamous cell carcinoma (176). Infection with HPV plays an important part in the development of vaginal cancer; however, the association is lower than for cervical cancer (170). HPV positivity is seen in 60–74% of the cancers, whereas VaIN2/3 are HPV positive in approximately 90% of cases and (170, 180, 181) corresponding overall HPV-positivity for cervical cancer is at least 95% (182). The link to HPV seems to be higher among younger women than the elderly, where hormonal factors and trauma might be more associated with the aetiology (112).

Aims

The overall aims of this thesis were: (i) to study aspects of the screening programme influencing the prevention of cervical and vaginal cancer and (ii) to evaluate surgical treatment modalities for early-stage cervical cancer.

The specific aims were:

Paper I

- To investigate whether abolishment of a fee influences attendance in the cervical screening programme.

Paper II

- To study hysterectomised women with and without cervical intraepithelial neoplasia (CIN) and their risk of vaginal cancer.

Paper III

- To study the effectiveness of colposcopic assessment by Swedescore in the cervical screening programme and to investigate the scope and variation of colposcopic accuracy among colposcopists and how it is related to experience.

Paper IV

- To compare oncological outcomes after open and robotic radical hysterectomy for early-stage cervical cancer in a nationwide population-based cohort.

Study groups and methods

Three different methodological research types are used in this thesis. The first study is an RCT, the second and fourth are population-based cohort studies and the third is a cross-sectional study. Papers II–IV are registry-based studies using the National Patient Register (Paper II), the Swedish Cancer Register (Paper II), the process register at the Swedish National Cervical Screening Registry (NKCx) (Paper III) and the Swedish Quality Register of Gynecological Cancer (SQRGC) (Paper IV). Paper I was performed within the cervical screening programme, and outcome data was retrieved from the process register at the NKCx.

Registers

The Swedish National Cervical Screening Registry (NKCx)

Since the start of 2012, the NKCx (Nationellt Kvalitetsregister för Cervixcancer prevention) contains national data regarding invitations to the screening programme, cervical cytology, HPV tests and histopathology (34). The register contains data from 1969 and has been considered complete nationwide since 1995. Women are informed in the invitation letter to screening about the quality register, coherent record keeping and saved samples in a bio bank, and they can negate this. The register is divided into the analysis register and the process register. The analysis register is considered to have 100% coverage for all invitations, cytological smears, HPV tests and histological samples (33), and is updated yearly with data from laboratories. The process register started in 2002 in Western Sweden, now has 85% coverage, and 19 of 21 counties are included (28). Weekly, the register is updated with new data from cytology/virology and pathology laboratories and offers clinicians a real-time view of the patient's attendance, screening results and reminders if a new cervical cytology/HPV test is indicated. The register also contains information regarding colposcopies and treatment of dysplasia. Data from the NKCx were used in papers I and III.

The National Patient Register

The National Patient Register at the National Board of Health and Welfare started in 1964 and has been considered complete nationwide since 1987. It is compulsory for physicians working in public health care and in the private sector to report to the register and thus contain information regarding inpatient care and, since 2001, specialised outpatient care. Registered data are: (i) patient related such as personal number, age and county, (ii) caregiver data, i.e. hospital, (iii) administrative data such as duration of stay, (iv) medical data such as main and secondary diagnosis according to the ICD system (International Classification of Diseases) at discharge and surgical interventions. Missing data for the most frequent variables, such as main diagnosis, is approximately 1% (183). In a review and validation study of the register, the coverage of somatic discharges was 99%, and the correctness of the diagnosis in the register compared with medical charts was 85–95% (184). Further, sensitivity on surgical interventions compared with national quality registers was high, and the main diagnosis was missing in only 0.5% of general surgery cases. The authors concluded that a more severe diagnosis was probably more valid in the register than a mild diagnosis. Data from the National Patient Register was used in Paper II.

The Swedish Cancer Register

Data on cancer incidence and survival are registered in the Swedish Cancer Register at the National Board of Health and Welfare, containing data from 1958 (113). It is mandatory for both pathologists and clinicians to report precancerous conditions, cancer cases and some benign conditions to the registry. The report is sent to the regional cancer registry at the Regional Cancer Centre, which annually reports to the Swedish Cancer Register.

Through each patient's unique personal identification number, the register contains data on residence, gender, reporting hospital, date of diagnosis, histological type, and site of tumour. Diagnosis based on autopsy is included. The register also contains information about date and cause of death provided from the Swedish Cause of Death Register and data on migration provided by the Statistics Sweden Population Register (113). In a survey regarding the completeness of the register towards the Swedish Cause of Death Register (185) and the National Patient Register (186), malignant tumours had 97–98% coverage in the register, and 99% were morphologically verified (186). However, underreporting exists. In 1998, 3.7% of diagnoses were underreported towards the National Patient Register. For gynaecological cancers, it was lower (3.4%) compared with other cancer forms such

leukaemia (16.9%) or nervous system (13.9%). Furthermore, advanced age and lack of pathological or cytological diagnosis were connected to underreporting (186). Data from the Swedish Cancer Register were used in Paper II.

The Swedish Quality Register of Gynecological Cancer (SQRGC)

To provide quality assurance and improvement of Swedish gynaecological cancer care, the SQRGC was implemented in 2008 and consists of four sub registers for each gynaecological cancer diagnosis: ovarian cancer started in 2008, uterine cancer in 2010, cervical and vaginal cancer in 2011 and vulvar cancer in 2012 (187). Patients who are 18 and above are included, and diagnosis must be based on histopathology or cytology. Cases from autopsy are not registered. In the case of synchronic tumours, each tumour is registered separately.

The registered data consists of five different forms: (i) diagnosis including, among other variables, date of diagnosis and FIGO stage, (ii) details concerning surgery, (iii) received primary treatment and (iv) follow-up with recurrences. It is prospectively and consequently registered in a web-based system by clinicians in all Swedish regions, and follow-up data covers five years. The data is monitored regularly by the regional cancer centres. On a daily basis, the register is updated with survival data from the Swedish population register. Data from SQRGC is also the foundation for enrolment in the Swedish Cancer register. Patients are informed upon admission at hospital that they are registered in a quality register and can opt out from registration.

In a national validation study regarding the completeness of the register of ovarian and endometrial cancer, medical records and selected core outcomes were compared with the SQRGC, and the coverage was measured relative to the Swedish Cancer Register (188). The coverage was 94–96% for diagnosis and stage, surgical data (68-78%), recurrences (74-80%), and follow-up data (71-72%). Data from the SQRGC were used in Paper IV.

Methods, outcomes and statistical analysis

Paper I

The patients enrolled in Paper I were all part of the regular screening programme in the districts Angered, Bergsjön and Biskopsgården in Gothenburg (Figure 8). The study location was chosen based on the fact that coverage in these areas is lower than in wealthier parts of town. These areas have a high degree of immigrants who in general have a lower participation in the screening programme (189). In addition, a Swedish cohort study has shown that immigrants from certain high-risk areas have a higher incidence of cervical cancer (190). The hypothesis was that an abolished fee had the most effect there. The study participants were routinely invited by the Invitation Office at the Primary Care Centre. Women were randomised 1:1 using a random allocation generator by the company Insieme, managing the screening invitations at the primary care office. The regular invitation was used, with a change in two words in the invitation letter. To the intervention group: 'The visit is free'; and to the control group: 'The visits cost 100kr. An invoice will be sent' (Figure 9). To detect a relative change in attendance of 20%, which was considered a clinically relevant change after an abolished fee, the power analysis revealed that 2502 women had to be invited to reach 80% power with a significance level of 0.05% with a two-sided test. At study closure, 3 124 women had been included, thus reaching 88% power.

The study was single blinded, the midwives performing the tests were unaware of the type of invitation the participant had received. Since it was the women's behaviour after invitation that we wanted to study, the RCT could not per definition be double blinded. The participants in the control group were billed by mail after participation, which was according to the regular routine. Aggregated data regarding study arm, district, age, previous pap-smear history and attendance were retrieved from the NKCx. The results were calculated as relative risks, confidence intervals calculated with the Wilson method and statistical analyses were performed in R 3.0.2.

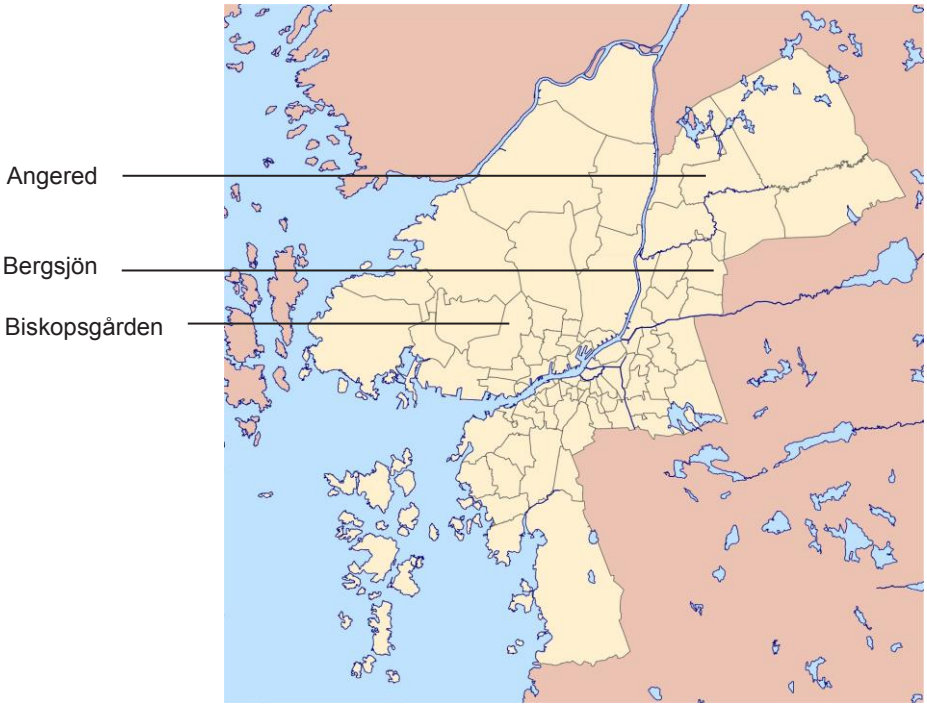
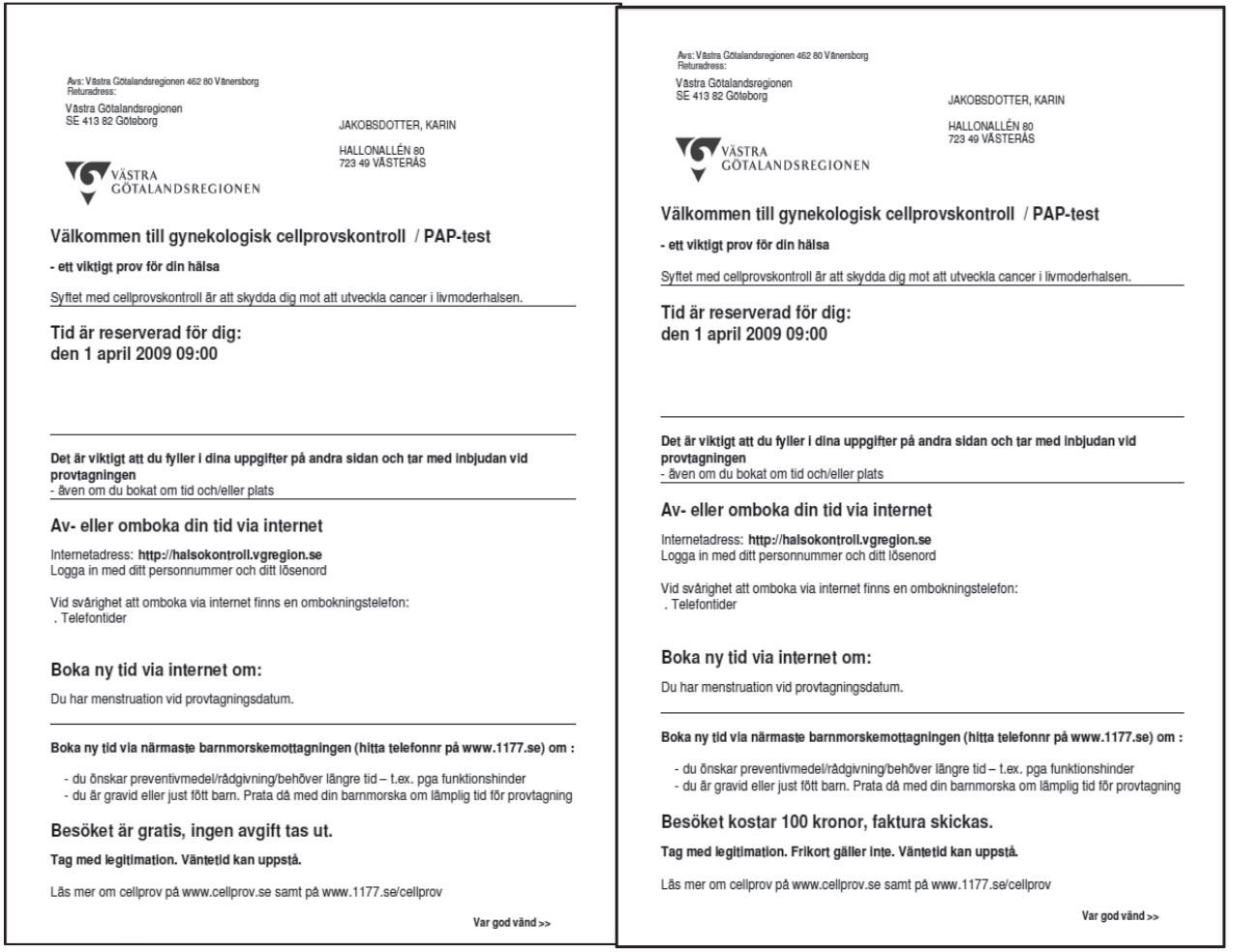


Figure 8. Districts included in the study, Angered, Bergsjön and Biskopsgården Adapted from https://sv.wikipedia.org/wiki/Stadsplanering_i_Göteborg#/media/Fil:Göteborgs_stadsdelar_170511.svg (December 2020).



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VÄSTRA GÖTALANDSREGIONEN

Välkommen till gynekologisk cellprovskontroll / PAP-test

- ett viktigt prov för din hälsa

Syftet med cellprovskontroll är att skydda dig mot att utveckla cancer i livmoderhalsen.

Tid är reserverad för dig:
den 1 april 2009 09:00

Det är viktigt att du fyller i dina uppgifter på andra sidan och tar med inbjudan vid provtagningen
- även om du bokat om tid och/eller plats

Av- eller omboka din tid via internet

Internetadress: **http://halsokontroll.vgregion.se**
Logga in med ditt personnummer och ditt lösenord

Vid svårighet att omboka via internet finns en ombokningstelefon:
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Du har menstruation vid provtagningsdatum.

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Figure 9. Invitation letter to the intervention and control group

Paper II

The study cohort was identified via the National Patient Register and the Swedish Cancer Register. A virtual linkage at Karolinska Institutet enabled the connection. Since data from the National Patient Register has been considered complete since 1987, this was chosen as the study start. The database contains data up to and including 2011, which defined our study end. Information regarding vaginal cancer, cervical cancer, CIN3 and AIS was available from 1958. Appropriate codes in ICD-7 and WHO C24 pathological anatomical diagnosis in the Swedish Cancer Register were used. Later ICD systems such as ICD-8, 9, 10, ICD-0-2 and ICD-0-3 are encoded according to ICD-7 in this register. The National Patient Register provided data on hysterectomies and subtotal hysterectomies performed from 1968 and CIN1-CIN3 coded with ICD-9 and 10. Calculations for time at risk started from the date of hysterectomy, which was treated as a time-dependent exposure. This was done in order to use the women's risk time as non-hysterectomised. For women who had not turned 20 before study start, we calculated time at risk from the date they turned 20. We chose this age threshold because we believed hysterectomies performed at earlier ages were unlikely. Women who emigrated were excluded from that date. Since the Swedish Cancer Register does not include diagnosis of relapses and women with a recurrence of cervical cancer could be misclassified as vaginal cancer, these women were excluded. The cohort was grouped into four categories: hysterectomised with benign cervical history (i.e. no history of CIN3 nor prevalence of any CIN at hysterectomy), hysterectomised + CIN3 or AIS history, hysterectomised + prevalent CIN (any degree of CIN at the time of hysterectomy) and non-hysterectomised (no total hysterectomy and no cervical cancer recorded up to end of study). The results were presented as incidence rate (IR), incidence rate ratio (IRR) and cumulative incidence using Kaplan-Meier failure function. An interaction analysis was performed for exposure group and attained age and for follow-up time and exposure group. IRR by exposure group was calculated in a Poisson regression model with hysterectomised women with benign cervical history as reference group. The model controlled for attained age since age increases with rising follow-up time.

Cumulative incidence of vaginal cancer among the hysterectomised groups was compared with the combined outcome of cervix and vaginal cancer among the non-hysterectomised general population in order to assess differences in lifetime risk with a screened population. Statistical analysis was performed in STATA 15.1.

Paper III

In the cross-sectional study, all women with a colposcopy linked to a histology sample in the process register of the Swedish National Screening Registry aged 18 and above were included. Exclusions were made for women younger than 18, unclassifiable histology samples, transformation zone (TZ) type 3 (Figure 10) and when data of TZ were missing and thus colposcopic impression could not be assessed.

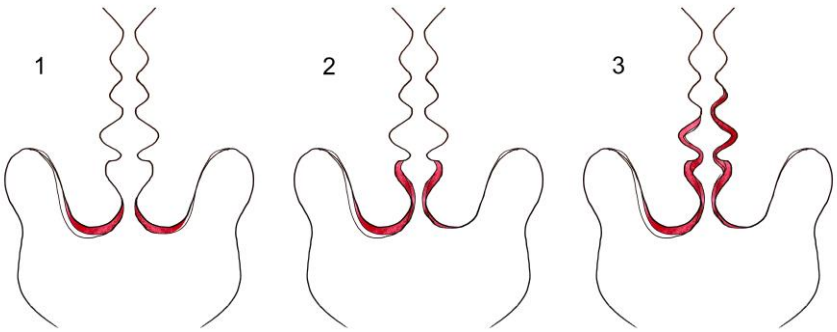

Figure 10. Transformation zone 1-3.1: TZ is completely visible and ectocervical. 2: TZ is completely visible but has an endocervical component 3: TZ is not completely visible and has an endocervical component. Illustration © Freija Frändberg Adapted from (191).

The study participants were identified via the process register at the NKCx. Since national data at NKCx has been considered complete for cytological samples since 1999, this was chosen as the study start. However, the process register within NKCx was launched in 2002 in Western Sweden and has gradually gained more coverage nationwide over the years. In the process, register histopathology SNOMED based diagnosis are classified into four classes: 0 = diagnosis not relevant to cervix uteri 1 = benign 2 = cervical dysplasia/premalignant 3 = malignant. Included patients were allocated an anonymised ID originating from the personal ID number, which enabled linkage between cytology, histopathologic and HPV samples as well as colposcopic assessments. Registrations of the colposcopist, either via examiner ID used primarily before 2012 or HSA-ID (Register of addresses at the health care, providing a unique ID per examiner) from 2012 and onwards, with colposcopic-outcome enabled analysis of the examiner's experience. Colposcopic assessment by Swedescore was analysed in a univariable regression model. Sensitivity, specificity, PPV and negative predictive value (NPV) were calculated. Multivariable logistic regression analysis was performed, including cytology (+/-21 days from colposcopy date), HPV (+/-21 days), former cytology (-22 to -180

days from colposcopy) and former HPV (-22 to -180 days), age and TZ. A regression model for Swedescore mimicking the clinical situation, including cytology and HPV at colposcopy, was created and analysed. The area under the ROC curve (AUC) was calculated for all regression models. The following analyses were performed for the analysis of accuracy and experience of the colposcopist: (i) Chi-squared test for accuracy per colposcopist; (ii) Pearson's correlation coefficient for the total number of colposcopies per examiner and accuracy; and (iii) linear regression coefficient for gained experience at every colposcopy and accuracy.

Paper IV

The study cohort was identified through the SQRGC. Cervical cancer was included in the quality register from 2011, and therefore identified as the starting point of the study. All women with a registered radical hysterectomy and cervical cancer stage IA1-IB1 from January 1st 2011 until December 31st 2017 were included and followed up with until October 24th 2018 or to death if this occurred earlier. In addition, hospital records and local registries were used to identify eligible women not yet registered in the SQRGC. All relevant clinical data of the included women were thoroughly reviewed through the hospital records. The reviewed predefined clinical parameters were: patient data (age, body mass index, smoking), tumour characteristics (tumour size, histology, LVSI, margins), number of extracted lymph nodes and status, FIGO stage edition 2009, perioperative and postoperative complications, sites of recurrence, death and cause of death, if expert pathology review had been performed, location of surgery, divided in tertiary centre (Umeå, Uppsala, Stockholm, Linköping, Örebro, Gothenburg, Lund) or regional hospital and if adjuvant treatment was received.

Exclusion criteria were defined as: other histologies than squamous, adenosquamous and adenocarcinoma, an aborted radical hysterectomy due to intraoperative finding or surgery in conjunction with caesarean section. Continuous variables were compared with Student's t-test and categorical variables with Fisher's exact test or Chi-squared test. Five years of follow-up was used, counted from the date of diagnosis. Univariable and multivariable regression models with OS and DFS as endpoints were calculated. Propensity score by nearest neighbour matching was used (192). Pairs were created with similar propensity score based on defined covariates; age, year of diagnosis, grade, LVSI, tumour size, lymph node status and primary treatment. Hereby, bias was reduced and the method mimics randomisation. For survival calculations, the Kaplan-Meier estimator was used. The difference in survival was measured with hazard ratio (HR), and p-values < 0.05 were considered significant. Statistical analysis was performed using R statistical software version 3.5.1.

Ethical considerations

Ethical approval was obtained from the regional ethical board at Gothenburg University for Paper I (Dnr 742-12). Patients participating in the screening programme are informed in the invitation for testing that data is registered in a database for quality assurance and if not consenting, the data would be deleted. No one chose this option. The regional ethical board at Gothenburg University also approved Paper II (Dnr 1035-16) and Paper IV (Dnr 397-18). For Paper III, ethical approval was obtained from the newly established Swedish Ethical Review Authority (Dnr 2020-02271).

Results

Paper I

The aim of this trial was to study whether attendance to cervical screening increases if an existing fee is eliminated in low-resource areas where different interventions stimulating attendance have already been applied.

In total, 3 124 women were included in the study, 1 562 in the intervention group without fee and 1 562 in the control group with a remaining fee (Figure 11). No protocol deviations were made.

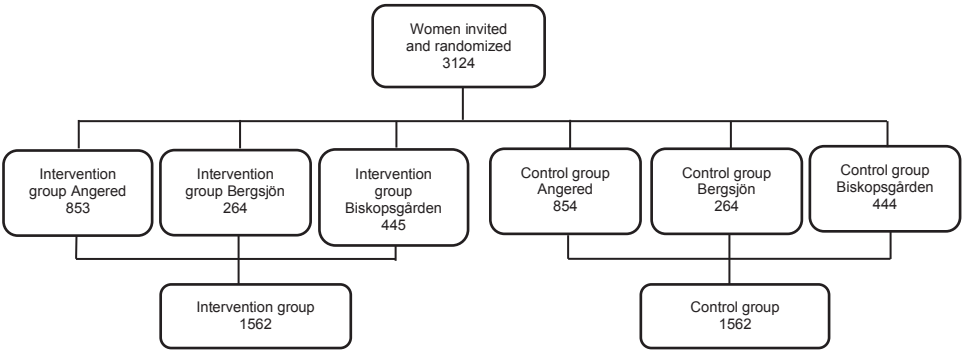

Figure 11. Flow chart of women in paper I. Adapted from (193).

There was a minor and non-significant difference in mean age between the groups (35 vs. 37 years); however, median age was similar. There were minor differences in mean age when comparing the districts (Figure 12).

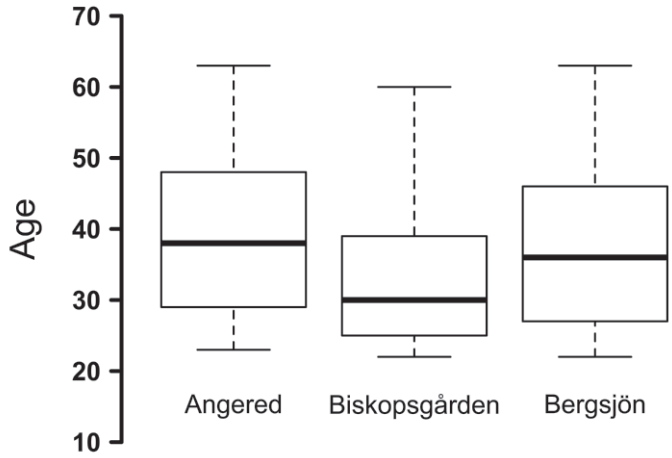

Figure 12. Mean age within the districts.

No significant difference in attendance was noted between the groups, intervention 36.7% and control 39.2% (relative risk (RR) 0.94, 95% CI 0.86-1.03) (Table 4).

Table 4. Attendance in the intervention and control group.

	Intervention group No fee	Control group Fee	RR (95 % CI)
Invited	1 562	1 562	
Attended	572	612	
	36,7%	39,2%	0,94 (0,86-1,03)

Subgroup analysis yielded a significant difference in lower attendance for 41–50 years old in the intervention group (RR 0.72, 95% CI 0.61-0.86). Previous pap-smear history or participation per district did not show any significant differences in attendance. Nor did previous non-attendance have an impact on attendance after the intervention (RR 0.89 95% CI 0.69–1.14).

Paper II

The aim of this study was to investigate the risk of vaginal cancer among hysterectomised women with and without cervical intraepithelial neoplasia (CIN).

In total 4 991 127 women were included in the study. Division per group is seen in Figure 13.

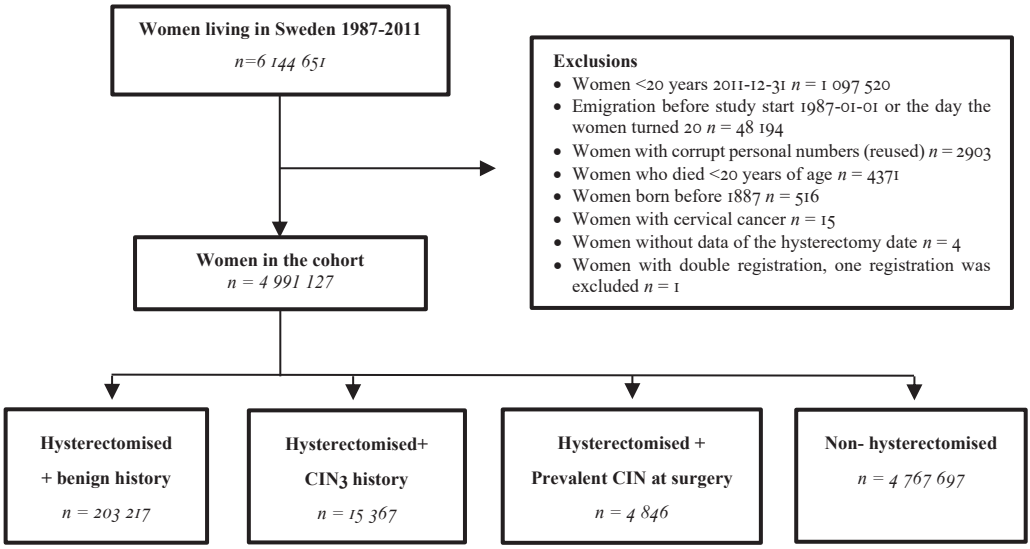

Figure 13. Flow chart of study population. Adapted from (194). Grant of licence 4933611018460.

Among the hysterectomised groups, the majority had benign cervical history, followed by women with CIN3 history. Characteristics of the study population with age and person-years are shown in Table 5.

Table 5. Patient characteristics within the subgroups presented with total number, median age and person-years Data source: Adapted from (194). Grant of licence 4933611018460.

	Total	Hysterec-omised+ be-nign	Hysterecto-mised + CIN3 history	Hysterecto-mised + preva-lent CIN	Non-hys-terecto-mised
Total n	4 991 1 27	203 217	15 367	4 846	4 767 697
Median age*	35.2	53.5	49.2	47.9	33.5
Person-years**	88 148 579	2 630 749	227 633	46 815	85 243 382
The same woman can be included and contribute with person-years in different groups. *Median age at hysterectomy and for non-hysterectomised median age at start of follow-up. **Number of person-years. Women with cervical cancer were excluded from all groups.					

In the cohort, 898 vaginal cancer cases were found, the majority (n = 739) among the non-hysterectomised. IR were highest for women with CIN at the time of hysterectomy (prevalent CIN) (51.3 (95% CI 34.4–76.5)) and CIN3 history (17.1 (95% CI 12.5–23.4)) (Table 6). An interaction test was performed to detect differences between exposure groups and measure the difference. For attained age and exposure group the interaction test had a significant result *($p < 0.001$)*. Thus, depending on which attained age group the individual belonged to, the risk of vaginal cancer was different in different exposure groups. However, the tendency of increased risk of vaginal cancer with attained age did not differ between the exposure groups.

Table 6. IR for vaginal cancer according to subgroup.

	Hysterecto-mised+ benign	Hysterecto-mised+ CIN3 history	Hysterecto-mised+ prevalent CIN	Non-hysterecto-mised
Vaginal cancer n	96	39	24	739
IR*	3.65(2.99-4.46)	17.1 (12.5-23.4)	51.3 (34.3-76.5)	0.87 (0.81-0.93)
*IR per 100 000 person-years				

Analysis of vaginal cancer cases by follow-up time with hysterectomised with benign cervical history as the reference group, showed the highest IRR for the women with prevalent CIN (IRR=21.0 (95% CI 13.4–32.9)). The corresponding result for women with a history of CIN 3 was 5.81 (95% CI 4.00–8.43%). Hysterectomised women with benign cervical history had a more than doubled risk compared with non-hysterectomised women (IRR 0.37; 95% CI 0.30–0.46). The interaction test between follow-up time and exposure group showed a significant result (*$p=0.023$)*. Thus, dependent on follow-up time the relative risk of vaginal cancer varied between exposure groups when compared with the reference group:

hysterectomised benign cervical history. In other words, dependent on exposure group, the relative risk was different over the follow-up time. However, with a large study population, even minor variations between attained age groups or follow-up time and exposure group, will result in a significant interaction test.

The cumulative incidence of vaginal cancer among the hysterectomised groups was highest in the group with prevalent CIN. At 85 years, these women had an incidence above 2.5%. The difference increased with age but was apparent from 45 years. As a reference, the cumulative incidence of the combined outcome cervix and vaginal cancer in the general screened non-hysterectomised is 1% at age 85 (Figure 14). The cumulative incidence of hysterectomised women with benign cervical history is 0.02% at age 85, for hysterectomised women with CIN3 history approximately 1% and for hysterectomised women with prevalent CIN almost 3%.

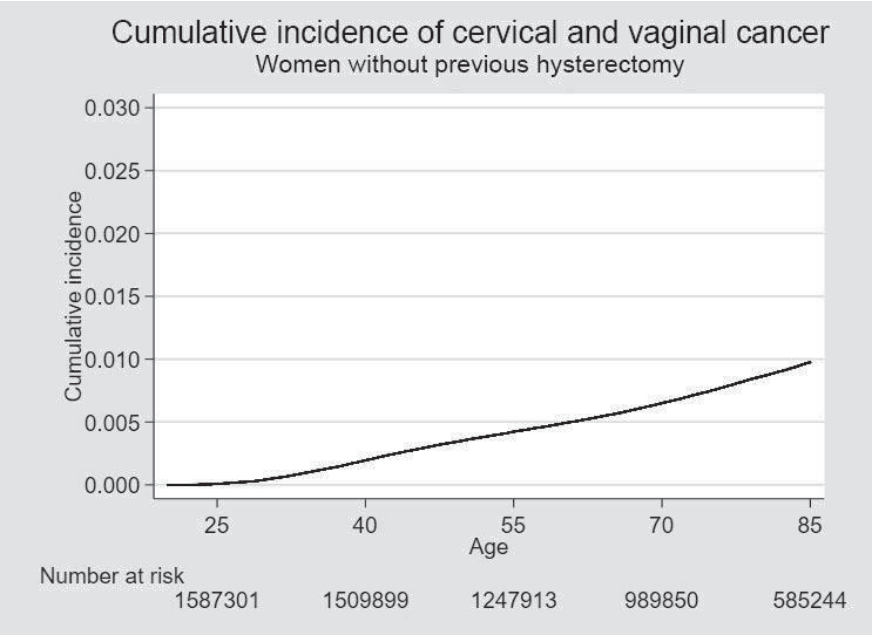

Figure 14. Cumulative incidence of cervical and vaginal cancer among non-hysterectomised women.

Paper III

The aim of this study was to study the effectiveness of colposcopic assessment by Swedescore in the cervical screening programme and investigate if colposcopic accuracy is affected by the experience of the colposcopist.

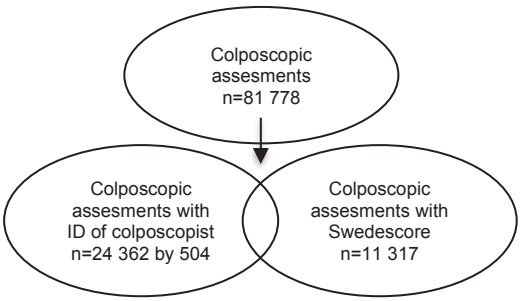

Figure 15. Schematic overview of study population.

In total, 81 778 colposcopies were linked to a histopathology sample (Figure 15). Out of these, 11 317 had a Swedescore assessment with a total of 10 211 women. The age distribution was 18 to 86 years, with the majority aged under 30. Almost 50% of the colposcopies were classified as Swedescore 4 and under, whereas 12% of the colposcopies were classified as Swedescore 8 and above. The majority of former cytology was low grade (67.6%). At colposcopy, CIN2+ constituted 28.8%. Cytology taken at colposcopy had an equal distribution between benign (41.8%) and low grade (42.7%). HPV at colposcopy was 16/18 positive in 41.8% and negative in 39.3% of cases. With a higher Swedescore, an increasing odds' ratio (OR) was seen. Sensitivity for CIN2+ at Swedescore ≥4 was 88.8% and NPV 87.7%. At Swedescore ≥8 specificity was 93.3% and the PPV was 60.1%. The AUC for Swedescore in the univariable analysis was 0.71. Logistic regression models were done for former cytology and HPV, cytology and HPV at colposcopy and age +TZ. AUC was improved in the models with cytology (AUC=0.83) and HPV (AUC=0.81) at colposcopy. Former cytology and HPV did not improve AUC, nor did age and TZ type 1 or 2. To simulate reality, we built a multivariable logistic regression model including cytology and HPV taken at colposcopy, which had an AUC (0.88) compared with only Swedescore.

In total, 504 colposcopists performed 24 362 colposcopies with a linked histopathological sample. Their overall accuracy was 67.3%. For analysis of their experience, colposcopists who performed ≥20 colposcopies were analysed. This resulted in 143 colposcopists with 22 937 colposcopies. No evidence for a correlation between accuracy and total number of colposcopies was noted since the correlation coefficient was close to zero (0.0024). Nor was there any evidence for correlation between accuracy and experience since the regression coefficient was close to zero (-0.00016). However, we observed a significant difference in accuracy between different colposcopists (p <0.0001).

Paper IV

The aim of this study was to compare oncological outcomes after open and robotic radical hysterectomy for early-stage cervical cancer in a nationwide population-based cohort.

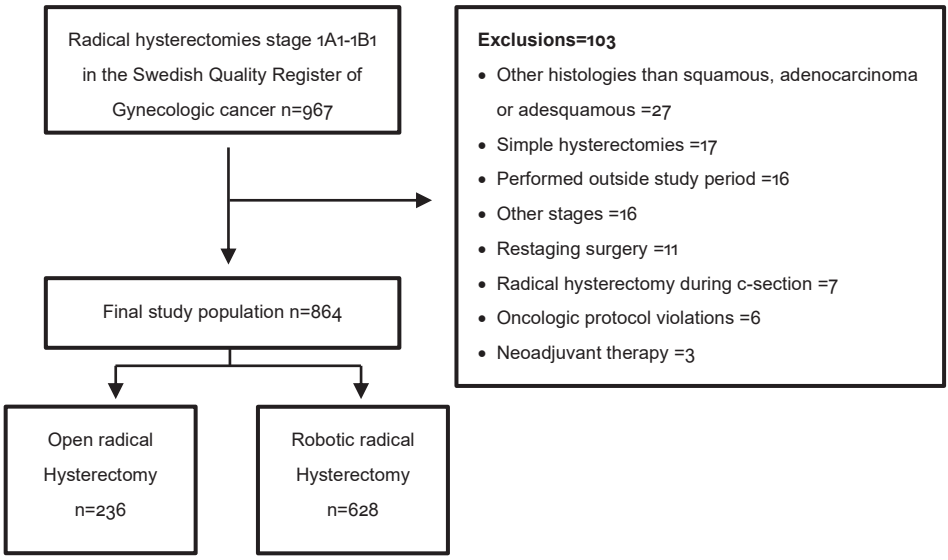

Figure 16. Flow chart of the study. Adapted from (195).

In the study, 864 patients were included, 628 (73%) in the robotic group and 236 (27%) in the open group (Figure 16). FIGO stage, histology type or number of positive lymph nodes did not differ between the groups. There was a difference regarding LVSI ($p < 0.001$) with 39% positive in the open group compared with 26.6% in the robotic group. Tumour size also differed between the groups ($p < 0.020$) with larger tumours in the open group. A significant difference ($p < 0.001$) was further noted regarding adjuvant treatment, the open group received it to a larger extent (32.2%) compared with the robotic group (20.9%).

The robotic group had a shorter follow-up time (p <0.001) than the open group. However, no difference in recurrence rate (p = 0.119) nor site of recurrence was noted (p= 0.269).

Table 7. 5-year OS and 5-year DFS for the complete cohort respectively after propensity score analysis.

Surgical method	5-year overall survival complete cohort	5-year overall propensity score matched cohort	5-year disease-free survival complete cohort	5-year disease-free survival propensity score matched cohort
Open	92% (95% CI 88-96)	92% (95% CI 88-96)	84% (95% CI 79-90)	85% (95% CI 80-90)
Robotic	94% (95% CI 91-96)	92% (95% CI 87-96)	88% (95% CI 85-91)	84% (95% CI 78-90)

The estimated five-year OS did not differ significantly between the groups: open 92% (95% CI 88-96) and robotic 94% (95% CI 91-96) (Table 7). Neither did estimated five-year OS according to tumour size reveal any differences between the two groups (Figure 17).

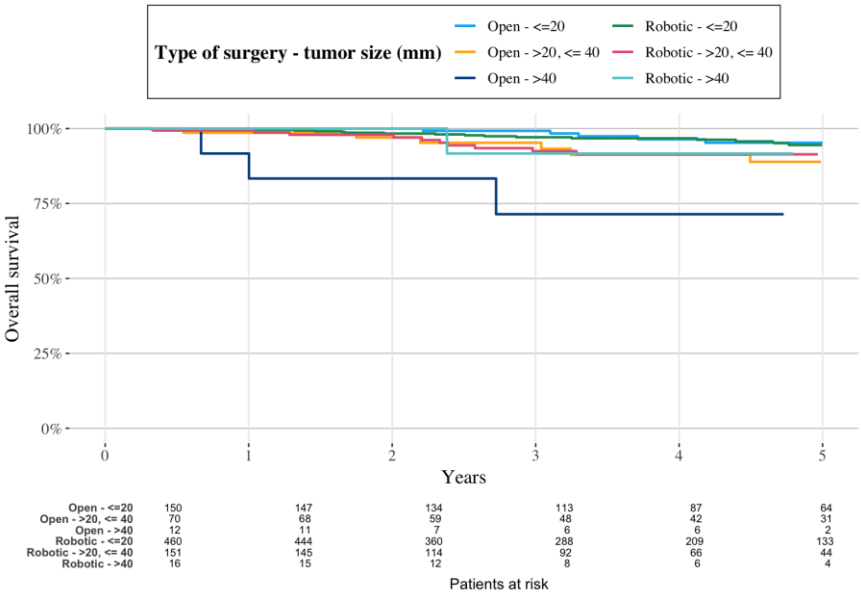

Figure 17. Overall survival according to tumour size and surgery group. Data source: (195).

When OS was stratified for surgery with or without adjuvant treatment, both open and robotic surgery showed a 95% OS. The corresponding results for combination treatment were 86% (95% CI, 78–95) for open and 88% (95% CI, 82–95) for robotic. No differences were consequently seen between the groups. Grade, tumour size, LVSI, lymph node status and adjuvant therapy after surgery were associated with significantly inferior survival in the univariable analysis, with OS as the endpoint. However, no significant prognostic factors were found in the multivariable analysis.

With DFS as an endpoint, the same prognostic factors (grade, tumour size, LVSI, lymph node status and adjuvant therapy) were found to be significantly associated with a higher risk of recurrence. In the multivariable analysis, tumour differentiation grade 3 ($p = 0.02$) and tumour size ($p < 0.001$) remained as significant risk factors. There was no significant difference in five-year DFS between the groups: open 84% (95% CI 79-90) and robotic 88% (95% CI 85-91) (Table 7). DFS stratified for tumour size did not reveal any differences. Nor did DFS stratified into surgery alone or in combination with adjuvant treatment differ between the groups.

Importantly, propensity score matching with 232 patients in each surgical group did not reveal any differences in the characteristics between the groups or any significant differences in OS. Both groups had an estimated five-year OS of 92% (Table 7) (HR = 1.003 (95% CI 0.50–2.01; $p = 0.99$)). No difference was seen in estimated five-year DFS between the groups, with 85% in the open and 84% in the robotic group (Table 7) (HR 1.08 (95% CI, 0.66–1.78; $p = 0.756$)).

Discussion

Methodological considerations

Observational studies as registry-based studies with large study samples increase precision and reduce random errors. Furthermore, a strength of these studies is often the long follow-up time with the possibility of detecting long-term adverse events (196). In addition, registry-based studies and other observational studies are sometimes the only methodological way of investigating certain associations that the investigator cannot control for or for ethical reasons cannot be performed in an RCT. Moreover, data collection is performed independently from a specific study in a register, thus reducing the risk of certain bias, such as recall bias. However, there are drawbacks with registry-based studies, other observational studies and descriptive studies i.e. ecological studies and cross-sectional studies. Assessing if a correlation exists and if it is due to a causal association is often a challenge in these studies due to the susceptibility of systematic errors. Thus, descriptive studies and observational studies, are generally regarded as hypothesis generating rather than hypothesis testing. Data collection in registries is performed by several individuals, sometimes resulting in poor data quality in registry-based studies. Data on confounders may also be missing. These limitations are often a strength of an RCT. The random assignment of study participants increases the internal validity, which reduces the risk of selection bias and confounding, albeit at the expense of impaired generalizability (196).
In Paper I, we used an RCT design. Paper II and IV were population-based studies and Paper III was based on national data from the cervical screening program, which can be seen as reflecting effectiveness, real world data in contrast to an RCT.

Random errors

Random errors are a variability of the data due to chance (197). The precision and reliability of a study increases if random errors can be reduced. CI and p-values estimates random errors. A wide CI indicate lower precision whereas a narrow CI indicate higher precision. With an increased sample size, random errors can be reduced. Sample size calculation was performed in Paper I. In Paper II, III and IV no sample size calculations were performed since we used the available registry

based data which in Paper II and IV were population based. In Paper II, even though the study population was large, the outcome was rare in some subgroups and the CI were wide, indicating lower precision. In papers III and IV, the sample sizes were relatively large which contributed to narrow CI and improved data precision.

Systematic errors

Systematic errors are non-random errors and deviations from the true value due to incorrect selection of study participants, measurements of study variables or a not fully controlled confounding factor (197). Possible systematic errors in the papers included in the thesis are discussed in this chapter.

Selection bias

Selection bias occurs due to an inaccurate selection of the study population (197). The random assignment in Paper I eliminated the risk of selection bias. In Paper II, there is a risk of selection bias due to underestimation of hysterectomies as well as CIN1-3 diagnosis. This could have diluted the exposure, and the true difference between exposure groups could have been higher. In Paper III, as women without histopathology samples taken at colposcopy were not included, this introduces a selection bias. It can be assumed that the majority of these colposcopies were considered normal, making this category underrepresented in the studied population. This would influence the NPV and PPV but not the sensitivity or specificity and the ROC curve deriving from this data. In Paper IV, some centres had limited access to robotic surgery, which may have contributed to a selection bias with a higher degree of unfavourable risk factors in the open group. There was an imbalance between the groups with a higher degree of understaged patients or with positive lymph nodes in the open group. These factors should be taken into consideration when evaluating our results, although the extent of implemented robotic systems was not in a particular order concerning experience or high-volume university hospitals. Over the years, an improvement in diagnostic imaging and a trend of increasing primary radiotherapies has occurred. Simultaneously, the frequency of robotic surgery has increased. Nevertheless, these discrepancies were analysed in the proportional hazard model and minimised in the propensity score matching. Furthermore, interrupted robotic surgery due to metastatic SLN was excluded, possibly introducing a selection bias. In the study, we evaluated the impact of the surgical procedures on why we abstained from performing an intention-to-treat analysis.

Information bias

Information bias is an error in collecting data, leading to misclassification of categories (197). By using register data in papers II–IV, even though the registers are of high quality, there is a risk of misclassification and underreporting.
In Paper III, as mentioned previously, the sample was most often derived from a biopsy and sometimes from an excision biopsy. The representability of the punch biopsy is determined by the colposopic assessment, and even if only excision biopsies were used as the gold standard, interobserver variability also exists among pathologists (90). Studies show that biopsies may underestimate the true existence of CIN2+ compared with an excisional specimen (198). In addition, the fact that the doctor performing the colposcopy was not blinded to the referral cytology could cause information bias. Furthermore, we do not assume all colposcopies performed by the colposcopists are registered. This infers a risk of underestimation of colposcopists' experience, which could influence the analysis of the accuracy. However, we perceive this to have a limited influence on the results and not be a systematic error, as it probably would be evenly distributed across all colposcopists.

Verification bias

Verification bias can occur when testing differs between individuals or groups, leading to different ways of verifying the disease. In Paper III, a verification bias exists since the sample representability towards the true histopathological diagnosis depends upon the assessment of the colposcopist, taking a punch biopsy in the area the examiner considers most abnormal. This bias can lead to an overestimation of the sensitivity of colposcopy. Excision biopsy, where the entire TZ is removed, just about eliminates this bias. Excisional specimens are included among the histopathological samples in this study, but to what extent we have no data, and it is most probably a minority.

Confounding

Confounding factors are associated with both the exposure and the outcome but are not an effect of either of them (197). In Paper I, the RCT design eliminated the risk of confounding factors such as age, city district, previous attendance or no previous smear. We did not investigate confounding factors such as education, ethnicity, religion, income or occupancy level, but the random assignment should probably have minimised these factors. In Paper II, women with CIN in the non-

hysterectomised group can be a confounding factor in why hysterectomised with benign cervical history were chosen as the reference group. We also chose this reference group because we wanted to study whether hysterectomy as such had an effect on the outcome. In the analysis, we assessed if age or follow-up time had an effect, but we did not analyse confounding factors such as HPV status, smoking, screening intensity or socioeconomic status.

In Paper IV, a possible confounding factor is the lack of assessment of the surgeon's experience or frequency of MIS in general per centre or specifically for radical hysterectomy. A further analysis of the data regarding this is recently published (199). Socioeconomic status, smoking and occupancy level were not adjusted for; however, Swedish public health care contributes to more equal access to care, which may reduce the impact of socioeconomic status compared with other countries.

External validity

External validity is the feature to generalise research outside the study context. In Paper I, two of three of the included districts had undergone systematic changes 2011-2012, one year before the study, in order to improve attendance. A rise in attendance in the districts from 2011 until 2013 may have been attributed to this factor (Figure 21). These circumstances may have influenced the external validity. However, attendance also increased in the district that had not undergone systematic changes, and a general increase in coverage is also seen nationally (200). In our study, we did not find any change in attendance after intervention within any of the districts, which reduces the risk of threatened external validity. Selecting low-resource areas for study location and its impact on external validity can be discussed. At first, the study was planned to be a pilot study for a subsequent larger RCT in the region, which did not take place because of the findings in Paper I. We cannot exclude that the result would be different in mixed resource areas since previous findings indicate the highest attendance raise in screening took place in the wealthier districts after an abolished fee in mammography (201). Furthermore, we cannot exclude another result in low-resource areas with lower awareness of the screening programme than in our studied districts.

Invited women in the screening receive an invitation letter accompanied by a pamphlet describing the goal of the screening programme in a few sentences translated into 11 languages. There was no information in this translated pamphlet about the existing fee of 100 SEK, and the pamphlet was not changed in the study. Some

women might not have understood that the test was free. Likewise, in the control arm, some women might not have understood that they would have to pay a fee. The randomised design evens out the effect of the low exposure of the fee/no fee in the invitation. It is of course possible that there had been an effect if the message 'NOW FREE OF CHARGE' had been more pronounced but giving the same display to the question of fee as in the routine invitation we found most correct.

The registers used in papers II and IV are validated with high quality and coverage (184-186). The results in Paper II also have a validity in other countries with developed organised screening programmes. The SQRGC, used in Paper IV, has not yet been validated for cervical cancer. However, the validity probably does not differ from the already validated ovarian and endometrial cancer diagnosis. The results in Paper IV have validity in other settings with nationally centralised cervical cancer care when surgery is performed only by experienced gyne-oncologist surgeons. The register used in Paper III, NKCx, is not validated but reports 100% coverage for data regarding invitation letters as well as cytological and histological diagnosis (33). A factor influencing the validity of Paper III is the lack of requirements for the colposcopists in Sweden, which is also similar in many other countries. This is not the case in, for example, the United Kingdom, where colposcopists are certified and have continuous re-certifications.

Findings and comments

Elimination of cervical cancer, defined as an incidence below 4/100 000 women, is a stated goal by the World Health Organization (WHO) and is believed to be achieved through a higher coverage of vaccination and screening programmes as well as through greater access to treatment of precancerous and cancerous lesions (202, 203). However, for most countries and also for Sweden, further efforts need to be taken to achieve this goal. In contrast to the WHO aims, Swedish national data disclosed a 2.5% rise of cervical cancer each year in the last decade (30, 204). Altogether to be able to eradicate cervical cancer, there is a need for (i) further improvement of the screening programme by increasing coverage and improving quality assurance and feedback to providers as well as treatment of precancerous lesions, (ii) prevention through vaccination and (iii) in case of cervical cancer, despite preventative measures, a safe and effective treatment without jeopardising oncologic outcomes. The focus of this thesis was the screening programme and surgical treatment of early-stage cervical cancer as well as another HPV-related disease, vaginal cancer. More specifically, on prevention in the screening by attendance (Paper I) and evaluating colposcopic assessment (Paper III), assessing

risk factors for cancer in the remaining target organ (vagina) after hysterectomy (Paper II) as well as by evaluating the oncological outcomes of two surgical methods of cervical cancer (Paper IV).

Paper I

Fees in a health care system aim to steer patients to the right level of care and also to increase the income of the health care (201). Only the latter is applicable for screening programmes. However, the fees are associated with administrative costs, and the net income is low compared with the total costs of the screening programmes. In Sweden, the range of the fee has varied between regions, and in some regions, it has been free. In 2018, the government decided to remove the fee from the cervical screening programme (205). This was followed by a law, decided by parliament, instituting for the first time that cervical screening should be carried out by the Swedish regions, and that it should be free of charge. The decision was based on the conclusions that co-payments have a negative effect on attendance in a meta-analysis from 2002 (69). The Swedish government report concluded that a fee could restrain women from participating, thereby jeopardising the cost effectiveness with a fee. Abolishing the fee could also be justified as an attempt to offer more equal care.

In Paper I, we showed that abolishment of a modest fee in socially disadvantaged areas with low screening coverage does not have an impact on attendance in the cervical screening programme.
Factors influencing participation in cervical screening have been widely studied, but the difference in health infrastructure and screening programmes between countries reduces the direct applicability to the Swedish setting. Many of the recommended organisational interventions, such as invitation letters with a fixed appointment, offering re-bookable appointments via the internet, and reminders to non-attenders, have already been implemented in many regions in Sweden (7, 67, 69).

The coverage of cervical screening in Western Sweden and in Sweden in general has increased over the years nationally, reaching 79% (ranging from 67–86%) for 23–70 years old in 2018 (Figure 18).

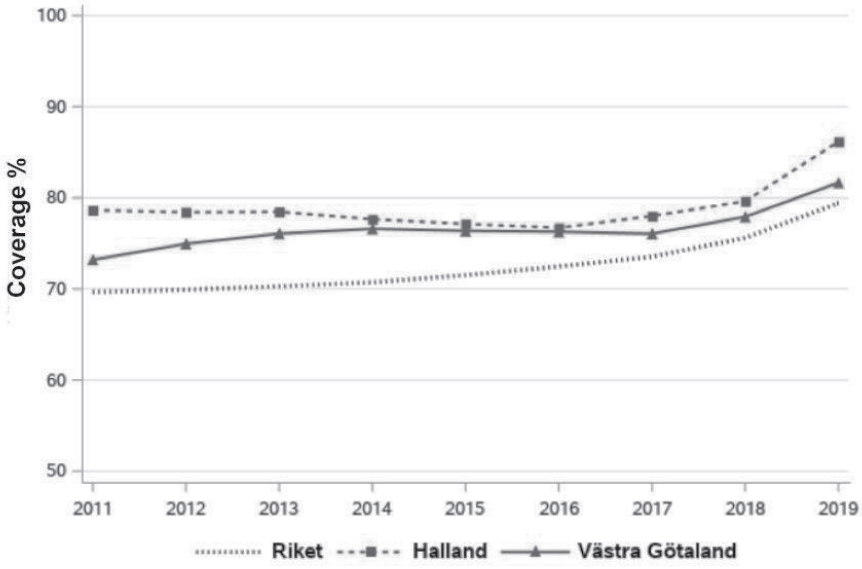

Figure 18. Coverage in Western Sweden (Västra Götaland and Halland) and nationally 2008–2018 for women aged 23–70. Data source: (33).

Interventions in order to increase attendance took place in the study districts: Angered and Bergsjön, before the study started. Focus groups with doulas working within maternity care in these districts were created to identify barriers to taking a pap smear and solutions for increased participation (206, 207). Further, the project 'Bring a friend' was launched, and subsequently an increased coverage was noticed 2011–2013 (206). After finalising Paper I, attendance has only increased in Bergsjön. In the other two districts, the attendance rate is lower compared with 2013. It is unclear why there is an attendance rise in some areas but not in others. However, in Gothenburg in general, the trend of attendance is rising (Figure 19). As attendance rate defined as participation in the screening is counted as a registered cytological smear within three months after sent invitation and includes yearly reminders, the apparently low results in these city districts should not be confused with coverage, which is the proportion of women taking a cytological smear within 3.5 or 5.5 years.

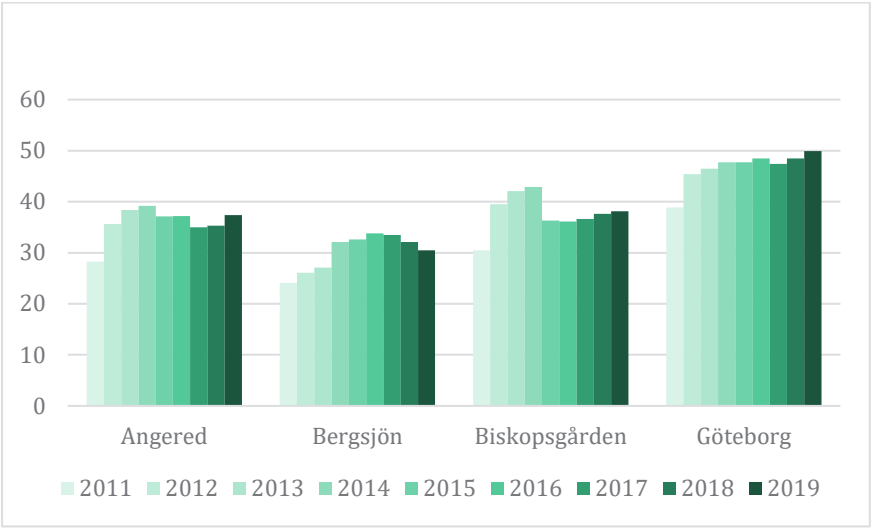

Figure 19. Attendance* (%) in Angered, Bergsjön, Biskopsgården and Gothenburg 2011–2019 Data source: (208). *Attendance: Registered cytological smear within three months from invitation letter.

There are other factors than the fee that we can take into account and improve in the Swedish context in order to increase attendance and reach the goal of 85% coverage (209). Some studies highlight fear of the examination (210) or fear of cancer as an obstacle to attendance (40). Interventions such as offering HPV-self-test to non-attendees is one solution with proven effect (211). Another important aspect is information about the cervical-smear either face-to-face or by printed materials (39, 67). If fear of cancer prevents some women from participating, we could develop the information explaining that the aim of the screening programme is mainly to detect precursor lesions. Educational interventions had an effect in a Cochrane review (67) and a meta-analysis (68), raising awareness about the purpose of the screening programme and thus raises the question of whether this will influence attendance.

In a Swedish study regarding determinants of non-attendance, county of residence had a major effect on attendance (49). The organisation of the screening programme and implementation of new routines differs nationwide. Organisational changes with proven effects, such as telephone reminders in order to reach non-attendees, engage community health workers and doulas and facilitate appointments (60, 66, 67, 206, 207) can be implemented in an attempt to increase attendance in all counties as well as in order to make health care equal nationwide.

Paper II

In Paper II we conclude that hysterectomised women with prevalent CIN or with a history of CIN3 have an increased risk of vaginal cancer compared with hysterectomised women with benign cervical history. These findings are in concordance with the few studies separately reporting data on hysterectomised women (111, 177). Contradictory results are shown in an older systematic review (110). Nevertheless, their selection criterion was hysterectomised women followed up by vault cytology and not vaginal cancer, which is why the true cancer rate may be underestimated.

The cumulative incidence of vaginal cancer for hysterectomised women with benign cervical history was 0.2%, whereas the cumulative incidence of cervical and vaginal cancer among non-hysterectomised women was 1% (Figure 14). Thus, our findings confirm that by removing the cervix, the absolute risk of cancer in the area is severely reduced. This indicates that hysterectomy can be regarded as protective against HPV-induced cancer for women with a benign cervical history. However, our comparison group, non-hysterectomised women, is heterogeneous in the sense that they consist of both women with and without CIN. For hysterectomised women with CIN3 history, the cumulative incidence was approximately 1%, which is similar to the cumulative incidence of cervical and vaginal cancer among non-hysterectomised women. To answer whether hysterectomy can be regarded as protective for these women, we can also compare the IR (IR=17.1) with non-hysterectomised women with a history of CIN3. Strander et al. showed that they had a change of incidence of 21.5 for cervical cancer, which exceeds the IR for hysterectomised women with CIN3 history (106). This indicates that hysterectomy can also be protective for them, even though the risk of vaginal cancer aged > 60 is not negligible. For women with prevalent CIN, the cumulative incidence was noticeably higher (> 2.5%), and hysterectomy cannot be regarded as protective. Nevertheless, when analysing IR for the single outcome vaginal cancer, hysterectomised women, regardless of group, have a higher risk of vaginal cancer than non-hysterectomised women. HPV-induced disease develops as cervical cancer among non-hysterectomised women and vaginal cancer among hysterectomised women. As far as we know, this is a new finding, and the reason for this is unknown. It can be hypothesised that although hysterectomy is protective for HPV-induced cancer, the cancer burden of HPV is partly moved to the remaining susceptible organ, the vagina. It can also be an effect of excluding hysterectomised women from surveillance or screening.

Women with prevalent CIN had a persistent elevated risk of vaginal cancer for at least 15 years after treatment. The increased risk of the groups with prevalent CIN

or CIN3 history can be attributed to a higher inability to clear an HPV infection or due to limited surveillance guidelines and consequently missed detection of precursor lesions (212-214).

Our results should be put in context with the Swedish cervical cancer incidence, which was 10.7/100 000 in 2018 (215). However, the absolute risk of vaginal cancer is low after hysterectomy, even if the relative risk is elevated. The threshold for surveillance of risk groups for vaginal cancer is different from cervical cancer. This is because the natural history of VaIN is less known, the diagnosis is more difficult and invasive, and the treatment is more complicated and accompanied by more complications. In Paper II, we therefore propose that women with prevalent CIN, and possibly also for some women with CIN3 history, need some sort of surveillance, which is also recommended in the Swedish guidelines with cervical cytology and HPV test at six months and five years after hysterectomy. An alternative is using primarily HPV tests and, for positive cases, cytology (216). If VaIN is indicated, referral to a skilled specialist is warranted. In cases of completely excised CIN and negative HPV test six months after hysterectomy, some researchers argue for cessation of surveillance (216).

Paper III

In Paper III, we conclude that Swedescore functioned in the Swedish cervical screening programme since the proportion of CIN2+ increases for every step in the score. However, in comparison with previous studies, sensitivity and specificity were lower in Paper III (97, 98). The colposcopic assessment measured with AUC improved in regression models with cytology or HPV tests taken at colposcopy but not with former cytology or HPV. In the analysis of the colposcopists' performance, the variation was wide, but we did not see any effect of experience.

The safety threshold to abstain from punch biopsies at low Swedescores derived from studies with a limited number of colposcopists and patients (97, 99, 100). In the original study by Strander et al., punch biopsies were recommended if Swedescore was ≥5 with a caution that abstaining from biopsies at a lower score needed quality assurance and feedback that this works in the hand of the individual colposcopist (97). The result in Paper III with a sensitivity of 88.8% at Swedescore ≥4 and a NPV of 87.7% is lower than in the original study (97) and in a British study evaluating Swedescore (98). In Paper III, even at Swedescore 0–1, the proportion of CIN2+ was 10%. In the study, we propose a 5% threshold for CIN2+ as

acceptable within professionals if abstaining from biopsy. This demand was met only if a number of specified conditions were fulfilled.

The original study (97) and subsequent studies (102, 103, 217) have opened up for 'select and treat' or 'see and treat' at high Swedescores, which means the colposcopic assessment gave a high enough probability of CIN2+ making punch biopsy unnecessary before excision biopsy. In the original study, this was at ≥8, since specificity at this score and above was high (90%). In Paper III, we found a similar specificity (93.3%), but the PPV was only 60.1%. In the case of a high-grade referral smear at Swedescore 8, the 'see and treat' method could still be an alternative since the proportion of CIN2+ was 81%. This is also in agreement with the present Swedish national guidelines for cervical cancer prevention (7). However, former HPV along with Swedescore did not give enough support to the clinician whether to perform 'see and treat' or not, since even in the case of HPV 16/18 at Swedescore 8, the proportion of CIN2+ was only 58%. Thus, without information on former cytology, 'see and treat' can lead to overtreatment. Quality measures exist for which level of excision biopsies should contain CIN2+ and a maximum level of benign excisions (7). We have no data on the number of 'see and treat' performed without prior high-grade cytology. Nevertheless, Western Sweden, which is the setting for most of the colposcopies included in the study, accomplishes the quality measurements (35).

In our study, we noted that accuracy was not dependent on the experience of the colposcopist. These findings are in line with other studies (79, 91, 218) even though the contrary is also shown in a small study (92). The performances of the colposcopists differed widely, and some colposcopists performed significantly better than others. Our data did not reveal which colposcopic education any of the colposcopists had nor which colposcopic experience they had at study start or eventually got during the study period. We do not know what distinguishes more skilled colposcopists from less skilled, but differences in experience were not an explanation. Interestingly, there is a lack of prospective studies regarding whether education in colposcopy can improve accuracy. All previous studies are retrospective, describing either professional background or years at service. Future trials are needed to answer the question of whether accuracy can improve by education and if an effect is seen; how should this education be shaped and maintained for professionals? For the time being, our results can support knowledge transfer through courses and colposcopic image discussions and quality assurance, including detection of and support of colposcopists who have poorer performance.

Studies indicate that multiple biopsies or random biopsies at colposcopy lower the risk of missing CIN2+ (79, 82, 85-87, 219). Also our neighbouring country, Denmark, recommends in their national guideline one punch biopsy per quadrant for every woman undergoing colposcopy (220). Our study has not taken into account the number of biopsies taken, so we conclude that abstaining from biopsy can lead to missed CIN2+ diagnosis. However, our data can to some extent be extrapolated and support these studies' findings by taking biopsies from normal appearing areas to reduce the risk of missing CIN2+. Further, the performance of Swedescore improved in regression models where cytology and HPV at colposcopy were included; thus, colposcopy should not be considered a stand-alone method. Can random biopsies in all quadrants be a solution? Multiple random biopsies on all women referred to colposcopy infer increased laboratory costs, prolonged examination and more discomfort for women. Can colposcopy reach a standard where such a procedure is not necessary? Can education and continuous feedback on performance to individual colposcopists have an effect? Is simultaneously taking HPV and cytology samples sufficient complements to an imperfect colposcopy to act as a safety net?

Paper IV

In Paper IV, we did not observe any difference in oncologic outcome for open compared with robot surgery for early-stage cervical cancer. New surgical methods are not preceded by rigorous safety studies, as in the case of pharmaceutical or vaccine trials and regulatory standards are in many cases less strict compared with new drugs (221, 222). Surgical innovations often develop out of a clinical need and are commonly evaluated by feasibility instead of efficacy (223). In addition, randomised controlled trials may be difficult to perform at an early stage. However, the dilemma is complex since the use of robotic surgery may be perceived as a quality indicator for patients, putting pressure on hospital administrators and doctors to offer new surgical techniques (224). There is to a certain extent also cooperation between the industry and surgeons in order to develop and improve the surgery and new methods according to the requirements of the surgeons. To be fully transparent, in our study two of the co-authors are proctors for the robotic surgical company, even though we believe this fact has not influenced our results. Furthermore, clinical research moves slower than advances in surgical techniques, which challenges study planning.

Interestingly, extrapolated data with non-inferior oncological outcomes in RCTs of laparoscopic surgery for endometrial cancer (225-227) reassured the profession

before the Laparoscopic Approach to Cervical Cancer (LACC) trial (165) as well as observational studies on cervical cancer with similar results (Table 8) (156, 158-161, 228, 229). Also for other cancer diagnoses, few studies have compared long-term OS and DFS of open and MIS including the robotic approach. In urology, no statistical differences were noted between robotic and open radical prostatectomy (230, 231). Regarding rectal cancer, no statistical differences were shown in one RCT comparing robotic and laparoscopy technique (232) and in a meta-analysis of robotic and open surgery (233). Several trials have compared open and laparoscopic surgical treatment of rectal cancer. However, only a few have published long term oncological data, such as the RCT COLOR II with no significant differences between the techniques (234).

Robotic surgery is considered a development of conventional laparoscopy, and results from laparoscopic studies may also be considered applicable for the robotic technique. The results of the LACC trial (165) were unexpected and correspondingly gave interest to investigate the Swedish cervical cancer cohort and initiated our study. The inferior oncologic outcome for MIS in early-stage cervical cancer, seen in the LACC trial as well in a large US cohort study (166), has been followed by several observational studies confirming the result (Table 8) (235-239).

Table 8. Oncologic outcomes of open and MIS for early-stage cervical cancer in different studies. Adapted from (222) and used with the kind permission of Dr.Wallin.

Author Year	Cases ORH/RRH[1]	Study design	Follow-up ORH/RRH (months, median)	OS ORH/RRH HR for MIS with 95%CI	DFS ORH/RRH HR for MIS with 95%CI	Findings
Cantrell(158) (2010)	127 (64/63)	RS	28/12	DSS 93% ORH 94% RRH	89% ORH 94% RRH	No difference between ORH and RRH
Sert(228) (2011)	68 26/42 83% RRH	RS	70/36	1 death RRH	5 recurrences RRH	
Hoo-gendam(229) (2014)	100 RRH	RS	30	88.7% DSS	81.4%	
Mendivil(159) (2016)	146 107/39 54%RRH	RS	39	92.3% ORH 96.6% RRH 95.9% LRH	84.6%ORH 89.7%RRH 89.8% LRH	No difference between ORH and MIS
Sert(156) (2016)	491 232/259	RM	45/35	Mortality 4% ORH 3% RRH	Recurrences 9% both groups	No difference between ORH and RRH
Zanagnolo(160) (2016)	307 (203/107)	RS	50/36	NA	Recurrences 10.6% ORH 8.8% RRH	No difference between ORH and RRH
Shah(161) (2017)	311 202/109	RS	NA	97.2% ORH 95% RRH HR=0.88 (0.23-3.32)	89.1% ORH 89.9% RRH HR=1.6(0.75-3.43)	No difference between ORH and RRH
Wallin(157) (2017)	304 155/149	RS	88/36	Mortality 9.7% ORH 4% RRH	Recurrences 10.3% ORH 13.4% RRH HR=2.13 (1.06-4.26)	Better onco-logic out-come with ORH
Melamed(166) (2018)	2461 1225/1236 79.8% RRH	RM	45[2]	Mortality 5.3% ORH[2] 9.1% RRH[2] HR[2]=1.65 (1.22-2.22)	NA	Better onco-logic out-come with ORH
Ramirez(165) (2018)	631 312/319 15.6% RRH	RCT M	30	99% ORH 93.8% MIS HR=6.0 (1.77-20.30)	97.1% ORH 91.2% MIS HR=3.74 (1.63-8.58)	Better onco-logic out-come with ORH
Alfonzo(195) (2019)	864 236/628	RP	46.5	92% ORH[2] 92% RRH[2] HR[2] =1.0 (0.5-2.01)	85% ORH[2] 84% RRH[2] HR[2]=1.08 (0.66-1.78)	No difference between ORH and RRH

Author Year	Cases ORH/RRH[1]	Study design	Follow-up ORH/RRH (months, median)	OS ORH/RRH HR for MIS with 95%CI	DFS ORH/RRH HR for MIS with 95%CI	Findings
Cusimano(236) (2019)	1096 485/473 10% RRH	RS	72/60	Mortality 9.5 ORH 8.2 MIS Stage IB1 HR= 2.20 (1.15-4.19)	Recurrences 10.9 ORH 12.1 MIS Stage IB1 HR=1.97 (1.10-3.50)	Better oncologic outcome with ORH
Doo(237) (2019)	105 56/49	RS	25	Mortality 5% ORH 14% RRH HR=0.40 (0.12-1.40)	Recurrences 14% ORH 24% RRH HR=0.61 (0.25-1.47)	No difference between ORH and MIS[3]
Gil-Moreno(240) (2019)	188 76/112 20% RRH	RS	112	81.3% ORH 92.8% MIS	Recurrences 14.4% ORH 15.1% MIS	Better oncologic outcome with MIS[4]
Chen(235) (2020)	10 314 9266/1048	RM	48/24	97.8%ORH[2] 94.4% RRH[2] HR[2]=2.86 (1.59-5.16)	95.4% ORH[2] 91.1% RRH[2] HR[2]=2.34 (1.54-3.56)	Better oncologic outcome with ORH
Chiva(238) (2020)	693 402/291 21.5% RRH	RM	60/56	97% ORH 89% MIS HR=2.42 (1.34-4.39)	89% ORH 79% MIS HR=2.07 (1.35-3.15)	Better oncologic outcome with ORH
Jensen(241) (2020)	1125 530/595 94.9% RRH	RM	113/42	92.3% Group 1[5] 94.4% Group 2[5] HR=0.60 (0.32-1.11)	91.8% Group 1[5] 91.0% Group 2[5] HR=1.23 (0.79-1.93)	No difference between ORH and MIS
Wenzel(242) (2020)	1109 740/369 73% RRH	RM	60/46 (OS) 37/29 (DFS)	95.2% ORH[2] 95.5% MIS[2] HR[2]=0.94(0.43-2.04)[4]	89.4% ORH[2] 90. 2%MIS[2] HR[2]=0.92 (0.52-1.60)	No difference between ORH and MIS
Uppal(239) (2020)	815 255/560 89.3% RRH	RM	45/31	Mortality[2] 3.2% ORH[2] 5.1% MIS[2] HR[2]=0.60 (0.19-1.85)	Recurrences[2] 4.4% ORH[2] 11.5% RRH[2] HR[2]=2.83 (1.10-7.18)	Better oncologic outcome with ORH

ORH: Open Radical Hysterectomy RRH: Robotic Radical Hysterectomy LRH: Laparoscopic Radical Hysterectomy NA: Non-available R: Retrospective M: Multicentre S: Single centre P: Population-based DSS: Disease specific survival. [1]In case of MIS: % of RRH in the MIS group. [2]Results from propensity score method. [3]Better oncologic outcome for open with tumours ≥2cm. [4]Better OS for MIS vs open but no difference in OS when 3 groups were compared: RRH, LRH ORH and no difference in cancer-specific survival and DFS of MIS vs ORH. [5]Group1: before MIS introduction Group 2: after MIS introduction.

A recent meta-analysis including 15 studies concluded that MIS compared with open surgery was associated with an increased risk of death and recurrence (243). Nevertheless, a few later published observational studies are in line with our results and show no difference in survival between the two surgical methods (Table 8) (241, 242). Albeit LACC is an RCT, limitations are present. The recurrences were concentrated in a few centres; the majority (84.4%) of the MIS group had undergone laparoscopy and not robotic surgery, and the follow-up data was not complete.

Possible explanations of the results of the LACC trial have been proposed and studied: the use of uterine manipulators, insufflation of CO_2 or as an effect of a learning curve in robotic surgery (238, 244, 245). In addition, Swedish data suggested an impact of a learning curve; in a regional study, the first 50 cases of robotic radical hysterectomies had an inferior DFS compared with the last 50 (157). These results were confirmed in a recent Swedish study with national data where a decreased recurrence rate after robotic surgery was noted with increased surgical experience (199). However, the findings are contradictory to a Canadian study where MIS had inferior oncologic outcomes even after controlling for surgeon's experience, albeit the majority of MIS were laparoscopic (236). Further, a protective effect of early vaginal closure in patients undergoing MIS has been discussed and noted (238). Some suggest that early vaginal closing and/or removal of the cervical tumour by conisation before the radical hysterectomy and opening of the vagina perioperatively may affect survival positively. Taken together, further studies are needed to explore these hypotheses and ensure patient safety.

The limitations of the LACC trial and the heterogeneity of the studies in the meta-analysis by Nitecki et al. (243) preclude direct comparability to the Swedish setting. The results in Paper IV stand out in relation to other studies; however, they are in concordance with a Danish study (241). Possible reasons are the fast adoption of MIS in Sweden and Denmark, centralised care for the majority of gynaecological cancers, including cervical cancer, with treatment guidelines according to national guidelines and without the use of uterine manipulators. The national survival 2011–2019, presented as relative survival, is unchanged (Figure 20).

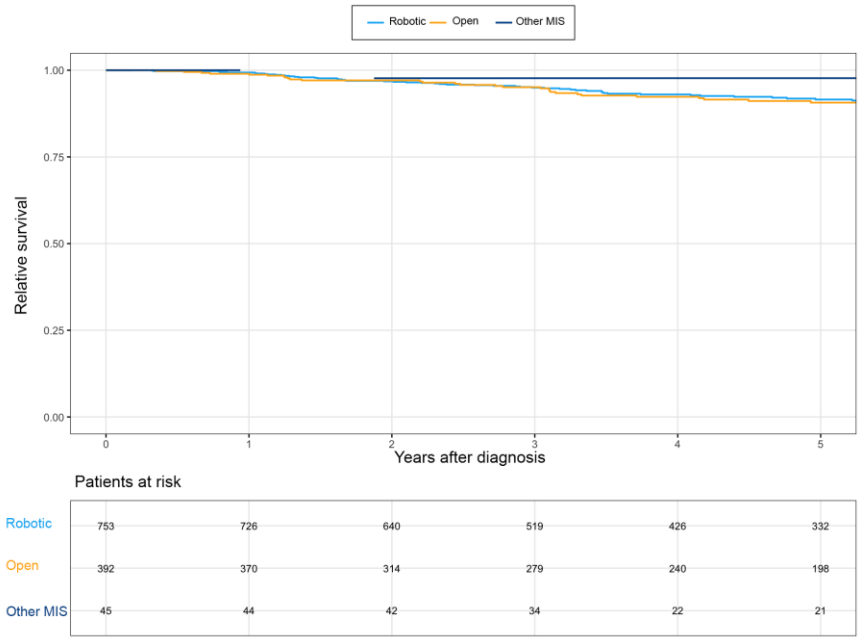

Figure 20. Relative survival of early-stage cervical cancer treated with radical hysterectomy according to stage 2011-2019 after robotic radical hysterectomy (blue line) open radical hysterectomy (yellow line) FIGO stage IA1, IA2, IB1, IB2 Data source: Regional cancer centre west.

Oncologic safety and not offering women an inferior surgical method is crucial despite the advantages of MIS in short-term surgical outcomes. MIS is no longer the gold standard surgical method according to the European Society of Gynaecological Oncology (ESGO) and the National Comprehensive Cancer Network (NCCN) (246, 247). In the Swedish national guidelines for cervical cancer from 2020, open surgery is now recommended as the standard of care (19). Robotic surgery is allowed within trials such as in the Robot-assisted approach to cervical cancer (RACC) trial, which explores whether robotic surgery is as safe as open surgery (167). Furthermore, ongoing studies may guide us as to whether simple hysterectomies are an alternative for tumours ≤ 2cm (139) and if SLNs have similar oncologic results compared with the prevailing treatment (138). Studies regarding whether therapeutic vaccines (248) and immunotherapy have a role in the treatment are also awaiting (249).

Conclusions

- Abolishment of a modest fee in socially disadvantaged areas with low screening coverage did not affect attendance to the cervical screening programme. Other interventions may have a larger impact on attendance in these areas (*Paper I*)

- Hysterectomised women with prevalent cervical intraepithelial neoplasia (CIN) at surgery have an elevated risk of vaginal cancer and should be offered surveillance after surgery. Hysterectomised women with a history of CIN3 have an increased risk among the elderly, which indicates the need for some surveillance. Women with benign cervical history have a low risk of vaginal cancer after hysterectomy, and surveillance is not motivated (*Paper II*).

- The probability of high-grade lesions (CIN2+) increases with a rising Swedescore in routine colposcopic use within a screening programme. Colposcopies, assessed by the scoring system, had an inferior performance compared with previous studies. Judging from these real-life data, abstaining from punch biopsies at low Swedescores results in unacceptable proportions of missed high-grade lesions (CIN2+). Treatment without biopsy confirmation is possible only at high Swedescores in the presence of a high-grade cytology referral sample. The accuracy of routine colposcopy in Sweden was low and not affected by the experience of the colposcopist; however, the performance varied considerably (*Paper III*).

- Open and robotic radical hysterectomy have similar five-year disease-free and overall survival when performed by experienced gyne-oncologist surgeons at tertiary centres in a centralised cervical cancer care system (*Paper IV*).

Future perspectives

As a result of a combination of high coverage of HPV vaccinations and effective screening programmes, we will probably observe a different panorama of precancerous lesions and cervical cancer in the future (203). Due to this shift, the screening programme needs to be under dynamic improvement, and treatment of early stages of cervical cancer needs to be further optimised.

- The interventions with proven effect for attendance stated in the national guidelines are as yet not available in all regions; thus, efforts should be made to increase equality on a national basis.

- Further research, both qualitative and quantitative, is needed to analyse non-attending populations. Areas of research may include determining whether knowledge about cervical screening has an effect on participation. Certain non-attending groups may need a more tailored organisation with easier access for participating in order to increase attendance and coverage, and different approaches can be evaluated in experimental trials.

- With an increasing proportion of women being vaccinated against oncogenic HPV-types, the prevalence of high-grade lesions will be reduced; thus, the positive predictive value of colposcopy in detecting high-grade lesions will be affected negatively. Therefore, new methods to risk stratify women who have an elevated risk for high-grade lesions needing treatment are needed.

- Prospective trials are needed regarding colposcopic education and its effects on accuracy. The development of guidance on where to take punch biopsies is under development with promising results (250). In addition, studies analysing features of the colposcopists with a high accuracy compared with those who had inferior performance are needed. Along with the advocacy for multiple or random biopsies, there is a demand for studies analysing the experience of women in relation to multiple biopsies as well as aspects of the health economy.

- The number of vaginal cancer cases will probably increase globally as the population ages, and it will take time before the impact of HPV vaccinations will compensate for this. Adequate follow-up for risk groups is thus of continuous importance, and hopefully more studies on how to improve surveillance of these women will tailor the follow-up further.

- For the women who develop cervical cancer despite a nationwide screening programme or for those the screening has not reached, future studies will hopefully guide us towards the most optimal management with maintained oncologic safety and minimised morbidity. Some aspects to take into consideration are the learning curve in MIS among surgeons, reducing the risk of tumour spread in MIS, and which surgery to offer for tumours ≤ 2 cm. Hopefully also additive treatment options such as therapeutic vaccines will also further help affected women.

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