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EFFECTIVENESS AND EQUITY OF CERVICAL CANCER PREVENTION: REAL-LIFE EVIDENCE FROM ORGANISED PROGRAMMES IN SWEDEN

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The colours on the cover, teal & white, are the colours of the ribbon for cervical cancer awareness.

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To my beloved family

致我亲爱的家人

ABSTRACT

Cervical cancer incidence has substantially declined since cervical screening was implemented five decades ago. The long-term hope of eliminating cervical cancer is promising with the development of effective Human papillomavirus (HPV) vaccines. Optimising effectiveness and promoting high and equal uptake of preventive approaches are essential for achieving this goal. This thesis aimed to use register data in Sweden to perform in-depth evaluation of the effectiveness of cervical screening and investigate the factors associated with HPV vaccine uptake. The work focused in detail upon the uncertain preventive effect against cervical adenocarcinoma in relation to the finding of glandular abnormalities in screening, the effectiveness of screening for the conspicuous incidence of cervical cancer at older ages, as well as social disparity of HPV vaccine uptake in different modes of vaccination delivery.

Effectiveness of cervical screening in preventing invasive cervical cancer has been reported under a case-control audit framework in Sweden, based on cervical cancer cases diagnosed in 1999-2001. Yet, assessing long-term screening history and controlling for confounding factors were hampered by unavailable data, and statistical power was limited to stratify the evaluation by histopathological type. We therefore performed an updated case-control audit based on cervical cancer cases diagnosed in 2002-2011 (Study III), to examine the risk of invasive cervical cancer in relation to screening history in the past two screening rounds, adjusted for education and stratified by the two main histopathological types. We found that non-routine participation to cervical screening was associated with increased risk of invasive cervical cancer. Having an abnormality in previous two screening rounds was associated with elevated risk, particularly if not being screened in the subsequent screening round after an abnormality. The lower effectiveness of cervical screening in preventing adenocarcinoma compared to squamous cell carcinoma resulted from both lower assurance from normal screening results, and higher risk following abnormalities. These findings reinforce the evidence of the cancer-preventive effect of cervical screening and emphasise the importance of routine participation in screening. We also identify relative weaknesses of the screening programme that would guide future research to address improvement.

Atypical glandular cells (AGC) found in cervical screening is a cytological abnormality of the same type of cells giving rise to cervical adenocarcinoma. However, the long-term risk of cervical cancer following AGC has not been comprehensively investigated due to its rarity. We used the Swedish National Cervical Screening Registry (NKCx) to identify all AGC diagnosed in cervical screening from 1980-2011, examined the risk of cervical cancer by histopathological type for up to 15 years, and compared the subsequent histological assessment and risk of cancer to that after high-grade squamous intraepithelial neoplasia (HSIL) (Study I). We found that AGC was associated with a moderate-high proportion of prevalent cancer, and a high long-term risk of incident cervical cancer, especially adenocarcinoma. Only 54% of AGC were followed by histology within six months, and among those being followed with histology, the cancer incidence after AGC was still statistically significantly higher than that after HSIL. Our findings confirm the considerable risk associated with AGC and revealed

suboptimal management following this specific abnormality. We highlight one of the deeper causes of unsatisfactory preventive effects of screening against cervical adenocarcinoma, and the necessity of improving management practice for AGC.

Cervical cancer is generally associated with middle-aged women, but the first Swedish case-control audit revealed that cervical cancer in women over 60 years of age accounted for more than one-third of annual cervical cancer cases. Data from other Nordic countries have also exhibited similar to higher incidence of cervical cancer among older-aged women compared to middle-aged women, leading to uncertainty on the underlying reason of biological or screening effect and the effectiveness of cervical screening after age 60. Therefore, we used NKCx and the Swedish Cancer Registry to investigate the risk of cervical cancer from age 61-80 years by screening history at ages 51-60 years, and evaluated the effectiveness of cervical screening at ages 61-65 stratified by screening history (Study II). We found that screening at ages 61-65 was associated with substantial risk reduction up to age 80 in women unscreened or having abnormalities in their 50s. Yet in women screened with normal results in their 50s, the subsequent risk of cervical cancer was remarkably lower than that in women unscreened or having abnormalities in the past, and in these women screening after age 60 was not associated with any statistically significant risk reduction. Our results should inform the current debate regarding when and how to discontinue cervical screening in older-aged women.

HPV vaccines have been available worldwide since 2006-2007. Their efficacy and effectiveness in preventing cervical precursor lesions have been shown repeatedly. Pursuing high and equal coverage of HPV vaccination is the common goal to reduce inequality of cervical cancer development in the future. Various modes of delivery of HPV vaccination were implemented worldwide and in Sweden. We used Swedish vaccination registers and social-demographic registers to examine girls' HPV vaccine uptake in relation to parental country of birth, education and family income, by three delivery modes of HPV vaccination (Study IV). We found that free-of-charge school-based delivery achieved the highest uptake of HPV vaccination with the lowest social disparity, suggesting the importance of reducing individual payment and providing easy access to promote equality of cervical cancer prevention.

In conclusion, this thesis confirms the overall effectiveness of cervical screening in preventing invasive cervical cancer, addresses specific questions regarding unsatisfactory prevention for cervical adenocarcinoma and cervical cancer in older women, as well as identifies suboptimal aspects in screening for further investigation. It optimises the audit framework as an evaluation tool for screening programme quality assurance, and provides a benchmark for future comparisons with new screening practices. The thesis also verifies the role of delivery mode of HPV vaccination on reaching high and equal uptake of the vaccine, bolstering the hope of ultimate elimination of cervical cancer.

LIST OF SCIENTIFIC PAPERS

I. Wang J, Andrae B, Sundström K, Ström P, Ploner A, Elfström KM, Arnheim-Dahlström L, Dillner J, Sparén P. **Risk of invasive cervical cancer after atypical glandular cells in cervical screening: nationwide cohort study.** *BMJ 2016;352:i276*

II. Wang J, Andrae B, Sundström K, Ploner A, Ström P, Elfström KM, Dillner J, Sparén P. **Effectiveness of cervical screening after age 60 years according to screening history: Nationwide cohort study in Sweden.** *PLoS Med 14(10):e1002414 (2017)*

III. Wang J, Elfström KM, Andrae B, Nordqvist Kleppe S, Ploner A, Lei J, Dillner J, Sundström K, Sparén P**. Cervical cancer case-control audit: results from a routine evaluation of a nationwide cervical screening programme.** *Manuscript*

IV. Wang J, Ploner A, Sparén P, Lepp T, Arnheim-Dahlström L, Sundström K. **Mode of delivery of human papillomavirus vaccination and associated disparities in uptake: nationwide cohort study.** *Manuscript*

RELATED PAPERS

- Sundström K, Lu D, Elfström KM, Wang J, Andrae B, Dillner J, Sparén P. **Follow-up of women with cervical cytological abnormalities showing atypical squamous cells of undertermined significance or low-grade squamous intraepithelial lesion: a nationwide cohort study.** *Am J Obstet Gynecol 2017*.

- Broberg G, Wang J, Östberg AL, Adolfsson A, Nemes S, Sparén P, Strander B. **Socio-economic and demographic determinants affecting participation in the Swedish cervical screening program: A population-based case-control study**. *Submitted*.

CONTENTS

LIST OF ABBREVIATIONS

ACCES	Advancing Cervical Cancer Eradication Strategies
AGC	Atypical glandular cell
AIS	Adenocarcinoma *in situ*
ASCUS	Atypical squamous cells of undetermined significance
ASR	Age-standardised rate
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence interval
CIN	Cervical Intraepithelial Neoplasia
COB	Country of birth
EMA	European Medical Agency
FIGO	International Federation of Gynaecology and Obstetrics staging system
FoHM	The Public Health Agency of Sweden (Folkhälsomyndigheten)
HPV	Human papillomavirus
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesion
ICD	International Statistical Classification of Diseases and Related Health Problems
LISA	Longitudinal integration database for health insurance and labour market studies
LSIL	Low-grade squamous intraepithelial lesion
NKCx	Swedish National Cervical Screening Registry
NVR	National Vaccination Register
OR	Odds ratio
PDR	Prescribed Drug Register
Pap smear (test)	Papanicolaou smear test
PIN	Personal identification number
SCB	Statistics Sweden (Statistiska centralbyrån)
SCC	Squamous cell carcinoma
SNOMED	Systematised Nomenclature of Medicine

SVEVAC	Swedish Vaccination Register
TBS	the Bethesda System
TPR	Total Population Register

1 INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide (1), and is acknowledged as the first cancer able to be effectively prevented. The Papanicolaou (Pap) smear test, being invented in the first half of 20th century, detects not only the malignancy but also pre-malignancies of the cervix by reading morphology of exfoliated cells under the microscope. The detection and treatment of pre-malignancies prevent them from progressing to invasive cervical cancer. Cervical screening using Pap test, therefore, becomes the secondary prevention approach. In recent decades, through the discovery of human papillomavirus (HPV) in carcinogenesis, aetiology of cervical cancer became better understood, and the prophylactic vaccine against the two main oncogenic types of HPV was consequently developed as the primary prevention approach. More recently, screening through detecting high-risk HPV, which has better sensitivity, was widely implemented, and the vaccine protecting against nine types of HPV, which causes 90% of cervical cancer, emerges.

There have been great achievements in cervical screening over five decades of implementation. The age-standardised incidence rate of cervical cancer decreased substantially in countries performing high-quality cervical screening programme (2). In Nordic countries, nearly half of cervical cancer cases were believed to have been prevented (3). Evidence from individual-level data also supported the existence of the cancer-preventive effect of cervical screening (4–6). Nevertheless, the effectiveness of cervical screening remains uncertain in some specific aspects, with the second common histopathological type of cervical cancer, adenocarcinoma, not experiencing evident incidence decline over past decades (7). The cytological abnormality "atypical glandular cells" found in screening, which denotes cellular changes of the same type of cells giving rise to adenocarcinoma, has not been comprehensively investigated regarding the long-term risk for cervical cancer and the status of following management. The conspicuous incidence in women above age 60 years (3) led to debates about the effectiveness of cervical screening at older ages, and the appropriate age and criteria to discontinue cervical screening.

High efficacy and effectiveness of HPV vaccines in preventing precursor lesions of the cervix have been repeatedly reported (8–11). It is anticipated that the inadequate coverage of the vaccination could lead to inequality in cervical cancer development between the vaccinated and unvaccinated individuals. Approaches to promote HPV vaccine uptake and reduce disparities, therefore, need to be investigated.

Entering the next 50 years for cervical cancer prevention, having the ambition to eliminate the disease is no longer impossible. To achieve the goal, improving effectiveness and pursuing high and equal uptake of preventive approaches are essential. Sweden is one of the countries with unique opportunities to facilitate the desired improvements with evidence not only due to the long history of screening practice and the pioneering introduction of the vaccine, but also the abundant resources of individual-linkable registers covering the entire population. This thesis, therefore, aimed to perform an in-depth evaluation of the effectiveness of cervical screening, and investigate the social disparity of HPV vaccine uptake, utilising population register data in Sweden.

2 BACKGROUND

2.1 CERVICAL CANCER

Cervical cancer is the carcinoma developed on the epithelium of the cervix. There are two types of epithelium on the cervix, squamous epithelium formed by multi-layer squamous cells on the ectocervix, and glandular epithelium formed by single-layer columnar cells on the endocervix. The area that the columnar cells transform to squamous cells (so-called squamous metaplasia) is called transformation zone, at where cervical cancer usually arises. The most common histopathological type of cervical cancer is squamous cell carcinoma originating from squamous epithelium. The second common one is adenocarcinoma originating from glandular epithelium.

Human papillomavirus (HPV) is believed to be the necessary but not sufficient cause of cervical cancer (12). So far, the HPV family has more than 170 known types, and more types are continuously found (13). More than 40 types of HPV can cause infection in the genital tract, and 15 types were recognised as high-risk types associated with cervical cancer carcinogenesis (14), of which HPV 16 and 18 causes around 70% of cervical cancers. HPV is ubiquitous, and the infection is not uncommon in population since its global prevalence found in cytologically normal samples are around 12% (15). However, 90% of HPV infections are transient and can be cleared spontaneously by the immune system in one to two years (16). Very few infections with high-risk HPV persist and lead to progression to cervical cancer. Carcinogenesis is caused by gene E6 and E7 of the virus which express oncoproteins that inhibiting tumour suppression proteins p53 and pRB, respectively (17).

Cervical cancer development can take fifteen to twenty years from HPV infection (16). The persistent infection causes cellular change and abnormal proliferation of epithelial cells which poses lesions. Typical progression to squamous cell carcinoma starts with the virus accessing the basal cells of the cervical epithelium and promote transformation and abnormal growth of squamous cells, known as cervical dysplasia. The severity of the dysplasia increases as the transformed and abnormally growing cells forms lesions involving from partial to all layers of epithelium, and the virus DNA from presenting and replicating by episomal state to integrating to host chromosomes. Once the dysplasia breaks the basement membrane, the invasive cervical cancer is developed (18). The severity of dysplasia is indicated by a well-defined spectrum, named cervical intraepithelial neoplasia grade 1 to grade 3 (CIN1, CIN2, CIN3) (Figure 1). Although dysplasia can progress from CIN1 to CIN3 and to invasive cancer, many of the CIN regress to normal. It is reported that the regression rates of CIN1, CIN2, CIN3 are around 60%, 40% and 33%, and the progression rates are around 10%, 20% and 12%, respectively (19). However, the progression pathway of cervical adenocarcinoma and the natural history of glandular dysplasia remains unclear.

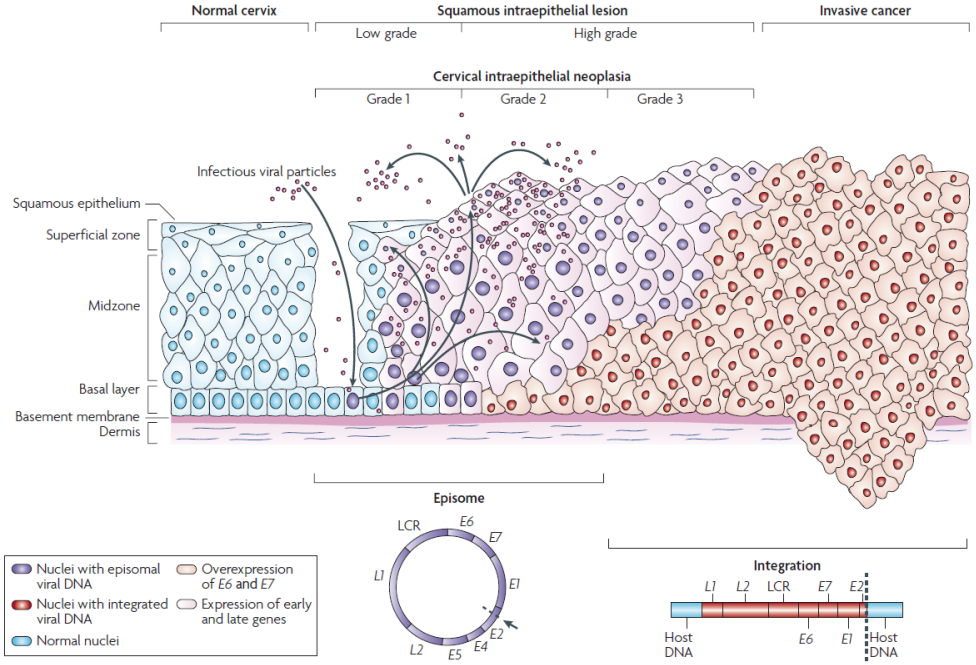


Figure 1: HPV-mediated progression to cervical cancer (From: The natural history of cervical HPV infection: unresolved issues, Woodman et al. 2007)

Besides HPV infection, other external risk factors were found to be associated with cervical cancer development, including early sexual debut (20), high lifetime number of sexual partners (21), smoking (22), multiparity (23) and long-term use of oral contraceptives (24). These factors are believed to be associated with either the susceptibility to HPV infection or the capacity of the immune response to combat the infection (25).

2.2 CERVICAL SCREENING

2.2.1 Screening method

2.2.1.1 Papanicolaou test

The years of progression from pre-malignant dysplasia to invasive cervical cancer provides plentiful opportunities for screening. Papanicolaou smear test, which was invented in early half of 20th century by Greek doctor Georgios Papanikolaou before the aetiology of cervical cancer was known, detects the pre-malignancies as well as micro-invasive disease by sampling the exfoliated cells at and around transformation zone, and examining the morphology of cells under the microscope, thus it is also referred as cytological test. Women who are found cytological abnormalities from Pap smear test are referred to colposcopy, under which the cervical dysplasia are visible. Colposcopy-directed biopsy of the dysplasia can be taken for histological assessment to diagnose precursor lesions or invasive cancer. If precursor lesions are diagnosed, treatments to remove the lesions, including conisation, loop electrosurgical excision procedure, laser excision or ablation and cryotherapy, block the progression, and invasive cancer is therefore prevented.

In the conventional Pap smear test process, a sample of exfoliated cervical cells is smeared on the microscope slide directly by hand, which can cause cells clumping thus makes the single

cells difficult to read. Cells can also distort if being exposed to air for too long. More recently, liquid-based Pap test was invented to solve the problems. It preserves the sampled cells in preservation solution so that the cells are immediately fixed. It also removes other contents of the specimen such as mucus, blood and microorganisms which may disturb the cell reading. Moreover, the samples slides are smeared under laboratory control, to make sure that cells are in monolayer which makes the cell reading much easier. Sample quality is therefore largely improved, and the accuracy of cytological diagnosis is increased (12,26).

A screening test detects the status of cervical epithelial cells at a time point, but dysplasia can initiate afterward. In order to gain optimal "protection" from screening, regular tests with certain time interval are required. The interval is defined by the evidence of duration of the "protective" effect against invasive cancer from a negative screening test, which is acknowledged as three to five years for Pap test (4).

2.2.1.2 HPV testing

After the establishment of the aetiological link between HPV infection and cervical cancer, testing HPV as a screening method is rapidly developed. Since HPV infection initiates years before the onset of precursor lesions, use of this method allows the pre-clinical phase of cervical cancer to be prolonged, thus potentially increases the opportunity to detect pre-malignancies. Furthermore, cytological screening requires manual labour to read the sample, hence the sensitivity is unsatisfactory, and can vary largely between 30%-90% (27), whereas HPV testing provides relatively equal sensitivity which is shown to reach above 90% in detecting CIN2+ (28–30). Evidence also demonstrates that HPV testing does not lead to over-diagnosis but early diagnosis of high-grade precursor lesions, and a negative test result can provide longer "protection" than normal test result from the cytological test (31–33), which implies potential of prolonged screening interval.

Given the advantages, HPV DNA testing is gradually implemented as the primary screening technique replacing cytology in some countries, usually with cytology as a triage method for HPV positivity. Discussions and research are ongoing regarding the optimal ages of implementation and triage strategy.

2.2.2 Opportunistic and organised cervical screening

Cervical screening can be performed opportunistically or through organisation. Opportunistic screening requires women's own initiative to seek the screening service, whereas in organised screening women are invited by the organiser to take a planned test. Organised screening is more effective than opportunistic screening in several aspects: the organisation with invitation manner achieves higher coverage and more equal participation (34); since the interval of screening is regulated by the organiser based on evidence, the optimal protection is assured and over-screening is avoided, thus gains greater cost-effectiveness; quality assurance examined by the organiser further ascertains the high-quality practice over time.

2.2.3 Cervical cancer incidence worldwide in relation to screening implementation

Cervical cancer used to be the second most common cancer among women worldwide (35), while has now been down to the fourth one (1). Strong success of cervical screening was reflected by the changes in cervical cancer incidence worldwide in the past fifty years. A remarkable downward trend of cervical cancer age-standardised incidence rates (ASRs) is observed in countries performing cervical screening (2). However, the ASRs kept stable or even increased in countries where screening was absent (2). A substantial decrease of cervical cancer incidence was observed in Nordic countries including Sweden, where national organised cervical screening programmes are well implemented (2,3). It was estimated that 41-49% of cervical cancer cases had been prevented by the screening since the 1960s (3). Nowadays, the disease burden varied largely between low- and high-income countries, with an estimation of 85% cervical cancer cases occurring in less developed regions, where in some areas it remained the most common cancer among women (36).

2.2.4 Cervical screening programme in Sweden

Screening using Pap smear test was initiated in Sweden in 1964, and organised cervical screening programme was successively implemented in counties during 1967-1977 (37). Each county, as the autonomic screening organiser, invites women regularly to take screening test in nearby maternity care centres. The Swedish National Board of Health and Welfare issues the national recommendations for cervical screening. The recommendation established in 1985 proposed cervical screening being performed in women aged 20-59 every three years, and the recommendation in 1998 revised the starting age to 23, proposed a three-year interval for women aged 23-50, and five-year interval for women aged 50-60. As counties/regions have autonomy in screening organisation, variations in actual performance exist in terms of age-ranges and invitation procedures (38). Nevertheless, the coverage of cervical screening increased gradually all over the country during the past 50 years. By 2016, 82% of women in Sweden have participated in screening in the recent screening round, and around 70% of the screening tests were organised tests (39).

Up to the end of 2016, cytology was used as the primary test, with liquid-based cytology being gradually introduced since the early 2000s. In mid-2015, the recommendation for switching to HPV-primary screening was issued. Women aged 23-29 were recommended to keep cytology-primary screening to avoid over-diagnosis, and women aged 30-64 were recommended to have HPV-primary screening with cytology triage, under 3-year (age 30-49) or 7-year (age 50-64) interval. The implementation started in two counties at the beginning of this year, 2017.

Clinical management of abnormal screening results for a long time followed guidelines issued by each county/region, which are similar to or different from the national recommendations established by Swedish Society of Obstetrics and Gynaecology in 1983, 1997 and 2010. In order to promote equal prevention of cervical cancer over the entire country, Regional Cancer Centres jointly established a national guideline in 2015, and agreed to follow this guideline in their own counties/regions.

2.2.5 Issues to be addressed

2.2.5.1 Weaker prevention for cervical adenocarcinoma by screening

Cervical adenocarcinoma is the second most common histological type of cervical cancer. During the past decades, as opposed to the dramatic decrease of the dominant type squamous cell carcinoma (SCC) (40,41), the incidence of adenocarcinoma experienced a different trend worldwide. Countries including US, Canada, UK, and almost all Nordic countries observed a constant increase in incidence of cervical adenocarcinoma mainly up to 1995 (42–45). Thereafter, several of these countries reported a plateau or slight decline (41,44,46–48) in incidence rates. Consequently, adenocarcinoma has accounted for close to or more than 20% of cervical cancer cases in countries with declined SCC (5,49,50).

Adenocarcinoma and SCC share most of the risk factors with a few discrepancies. A collaborative study showed that a positive test for cervical high-risk HPV-DNA was a strong risk factor for both histological types (51). HPV types 16 and 18 are found to be strongly associated with adenocarcinoma (52), where HPV 18 are more commonly found in adenocarcinoma than in SCC (53–55). However, it is also reported that in samples of cervical cancer cases, adenocarcinoma has lower positivity of HPV DNA (62%) than SCC (87%) (54). Other risk factors for adenocarcinoma are similar to those for SCC: increasing number of sexual partners, younger age at first intercourse, increasing parity, younger age at first full-term pregnancy and increasing duration of oral contraceptive use, with the only exception of smoking (51).

Given the similar risk factors to SCC, the opposite trend of incidence of adenocarcinoma raised the question about the effectiveness of screening on preventing this histological type of cervical cancer. An Australian case-control study published in 1995 initially found there was no significant difference between adenocarcinoma cases and controls in the number of negative cytology reports, or in history of cervical abnormality (56). But others argued that there must be ample time for screening for pre-invasive lesions, as they found a 13-year difference between the mean age of adenocarcinoma in situ (AIS) and invasive adenocarcinoma (50). Larger studies in the recent decade did find a tendency of preventing effect of screening against adenocarcinoma (49,57–59). Liquid-based cytology using ThinPrep Pap test may have contributed to it since it provided better detection of glandular lesions (60). This may have led to the non-increasing incidence of adenocarcinoma since 1995. Moreover, screening was shown to prevent advanced invasive adenocarcinoma (49) thus reduced mortality (61). Nevertheless, the magnitude and duration of the effectiveness are agreed to be far less than that for SCC (49,57,59). Uncertainty remains about whether the inferior effectiveness resulted from the low accuracy of Pap test, insufficient management of detected abnormalities, or both.

2.2.5.2 Uncertain risk of cervical cancer following atypical glandular cells found in Pap test

"Atypical glandular cells" (AGC) is a type of cytological abnormality found in Pap test, denoting the morphological changes of glandular cells, but lacking the features of

adenocarcinoma *in situ* or invasive adenocarcinoma in the cervix uteri. AGC is an uncommon finding that generally comprises less than 1% of the population (39,62). The terminology is defined and modified by the Bethesda System (TBS), a guideline for reporting cervical/vaginal diagnosis. The TBS issued in 1988 recommended "atypical glandular cell of undetermined significance" (63). In 1991, it recommended that a further qualification whether a reactive or a premalignant/malignant process is favoured (64). In order to avoid confusion with atypical squamous cells of undetermined significance (ASCUS), it was changed to "atypical glandular cells" in the 2011 revision. The category "favour reactive" was simultaneously removed (65). Sweden has only used "atypical glandular cells" without subcategories.

AGC can signify a group of conditions, from benign findings such as reactive changes or polyps, to severe dysplasia or even cancer (66). The former term "atypical glandular cell of undetermined significance" made it appear to be the counterpart of ASCUS, thus was considered as a finding meaning low risk for malignancy. However, studies on the clinical significance of AGC found a high proportion of existing premalignant or malignant lesions. Schnatz et al (62) reviewed 24 studies and found that approximately 1.5% of AGC were confirmed to have underlying cervical malignancy at or shortly after diagnosis, 2.9% were adenocarcinoma *in situ*, 8.5% were low-grade squamous intraepithelial lesions, and 11.1% were high-grade squamous intraepithelial lesions. Besides cervical lesions, they also found 4.1% other malignancy including endometrial adenocarcinoma, ovarian and fallopian tube carcinoma and others. This indicates that more than 20% of AGC require further attention and more than 15% of them are severe. The majority of studies included in this review contained small number of AGC smears restricted to one clinic or region, and had only short term follow-up. A population-based study including more than 8000 women with AGC found an 18-fold higher risk of incident cervical cancer in an average follow-up of 6 years after AGC, compared to the general population (67). But the risk profile compared to HSIL or LSIL was not investigated.

Specifically, for the histological type of cancer associated with AGC, studies found 0.6%-3% of invasive adenocarcinoma of the cervix at or shortly after AGC (68–75), but are limited with only 1 to 7 cases of cervical adenocarcinoma and could thus not analytically confirm the association between AGC and adenocarcinoma. Some studies have investigated the age pattern of malignancies related to AGC. Results were partially conflicting about whether neoplasia is more common in young women than older, or vice versa (70,71,76–79).

The clinical management for AGC has been a dilemma as the research of the risk profile are limited due to the rarity of AGC (78). Based on the collective evidence on clinical significance, the American guidelines recommend initial workup for all AGCs using colposcopy with endocervical sampling, and endometrial sampling for women aged above 35 years, and follow-up at 6 months or 12 months depending on HPV status (80). One study has investigated the effectiveness of management arms after cytological finding of AGC and did not reach any conclusive result due to low statistical power (81).

2.2.5.3 Relatively high incidence of cervical cancer among older aged women

Cervical cancer is acknowledged to develop mainly in midlife. In 1960s-1970s, incidence of cervical cancer peaked at ages before 50 years in majority of European countries, and declined rapidly or gradually afterwards (82,83). However, in recent one to three decades, many countries observed a second peak of cervical cancer incidence after age 60 (2,84), and more than one third of annual cases came from women aged 60 or 65 above, which were also detected at more advanced stages (5,6).

The reason behind this age feature was discussed from aspects of biological and screening effect. Early study reported a decline prevalence of HPV over age (85), while recent investigations from some other settings found a bipolar shape of HPV prevalence where the prevalence in postmenopausal ages was higher than in reproductive ages (86,87). The high prevalence was recognised to be a result of longer persistency or re-emergence of latent infection (17), since the new infection was found decreased at older ages (86,88,89). The latency or re-emergence were believed to be due to the degenerated immune system at older ages (17,90), and possibly the use of hormone replacement therapy (91). The effect of cervical screening for older aged women was long been questioned. The initial arguments against screening in this age group were based on the natural history studies, that the incidence and prevalence of abnormality or precursor lesion was found remarkably lower among women aged 50 and above (92–95), which was believed to be due to the unreliability (higher false-negative) of the Pap smear test, namely that the adequate sampling of representative cellular material at the transformation zone is more difficult to obtain for postmenopausal women since the zone tends to migrate inward to the endocervix as women aged (96,97). Yet there was also opposite finding that the prevalence of CIN3 was comparable with younger women (98). In recent decades, population-based evidence demonstrated significant cancer-preventive effect of cervical screening at older ages. A Swedish study found an odds ratio of 0.36 for the protective effect from the past screening for women aged 66 and above (5). A Finnish study found a 51% risk reduction from the screening invitation between ages of 65 and 69, and a 34% risk reduction of the invitation at the age of 65 for a follow-up up to 19 years afterwards, although not statistically significant (6). A UK study found that women with adequate negative screening at age 50–64 had 86% reduced risk of cervical cancer at age 65–83 compared with women who were not screened (99).

Given the evidence of effectiveness, countries started to elevate the upper aged limit of cervical screening to cope with the substantial cervical cancer cases in older aged women (99–101). However, age and criteria to discontinue cervical screening remains unclear. A recent study investigating the incidence of cervical cancer in elderly by birth cohort showed that, the high incidence was only observed in older birth cohorts which had poor life-time screening history (102). It implied the necessity of considering screening history when designing and evaluating the screening in older aged women. This issue was addressed by one modelling study, which demonstrated that continued screening after age 65 provides little additional benefit on incidence and mortality among women screened with cytology every 3 years before age 65 (103). One exemplary empirical data reported risk for dysplasia after age 50 in relation to the

screening history before age 50 years (104). More empirical data for even older ages is in demand.

2.3 HPV VACCINATION

Development of HPV vaccine emerged since the recognition of HPV causing cervical cancer. The current commercial prophylactic vaccines contain virus-like particles (VLPs) which are assembled from recombinant HPV capsid protein L1. Once injected, immune response is triggered by the VLPs and enhanced by an adjuvant. Since no HPV DNA is included, the vaccines have no risk for virus infection (105). Two vaccines were approved internationally including European Medical Agency (EMA) in 2006-2007, which are the bivalent vaccine Cervarix™ developed by GlaxoSmithKline protecting against HPV 16 and 18, and quadrivalent vaccine Gardasil™ developed by Merck protecting against HPV 6, 11, 16, and 18. HPV 16 and 18 are the high-risk types causing 70% of cervical cancer, whereas HPV 6 and 11 are low-risk types causing genital condyloma. In 2015, Gardasil9™ which protects against five more high-risk HPV types was authorised by EMA. The five types are HPV 31, 33, 45, 52 and 58 which cause around 20% of cervical cancer. Therefore, in total, 90% of cervical cancer are expected to be prevented by the nine-valent HPV vaccine.

Given the strong efficacy of the vaccine before exposure to HPV, the vaccines are recommended to be given to people from 9 years of age, as early as possible. The vaccines were initially licensed with a 3-dose-schedule, at the months 0, 1, 6 for the bivalent vaccine, and at the months 0, 2, 6 for the quadrivalent vaccine. Since studies found non-inferior effect from two doses in immune response and HPV 16/18 infection among the lowest eligible ages, in 2014, World Health Organisation recommended a two-dose-schedule for people aged 9-14, at the 0 and 6th month (106).

2.3.1 Efficacy, effectiveness and safety

Robust efficacy and effectiveness of the vaccines, from clinical trials and real-population data, have been accumulatively reported. Clinical trials showed a higher immune response after the vaccination compared to nature HPV infection in terms of serum antibody concentration (107–109), and an 90%-100% efficacy for the short-term endpoints such as genital condyloma and HPV 16 and 18 related CIN1 (110), as well as longer-term endpoints of CIN2+ (111). Several years since the introduction of quadrivalent vaccine in some countries, the incidence of genital condyloma in the population declined dramatically (112,113). In recent years, evidence from population data demonstrate an effectiveness of 75% against CIN2+ in those vaccinated before age 17 years (11). Meanwhile, evident herd immunity was also shown, that the HPV 16 and 18 infection, incidence of condyloma exhibited decline trend in the unvaccinated population (114–116).

Although intense attention was paid on various adverse events happening after the vaccination, clinical trials and postlicensure monitoring found that apart from injection-site symptoms, headache and fatigue which were transient, no difference of severe adverse was observed between vaccinated (intervention) and unvaccinated (control) group (117–120). Rigorously

designed population-based studies demonstrated that no severe adverse events, such as autoimmune and neurological diseases (121,122), adverse pregnancy outcomes (123) can be attributed to the vaccination, since the incidence of those events in vaccinated population was not different from the unvaccinated population. Even no evidence of increased new-onset autoimmune diseases observed when the vaccine was given to girls having pre-existing autoimmune disease (124).

2.3.2 Socioeconomic factors associated with HPV vaccine uptake

Socioeconomic factors has been approved to be associated with health care utilisation including the participation in disease preventive programmes, as it affects both access and adherence to the interventions (125–128). It is agreed that generally people of lower socioeconomic status use fewer health services. The explanation of this phenomenon may fall into three categories: financial access or affordability differences; knowledge and attitudinal differences regarding care-seeking; and health care system factors in terms of the organisation or response (129).

Before the introduction of HPV vaccine, studies about people's attitude towards the vaccination had revealed disparities on certain socioeconomic factors. Parents' ethnicity, education, employment status, and disposable family income were found to be associated with their willing to vaccinate their adolescent children (130,131). Similar factors were also reported to be associated with HPV vaccine acceptance in young adults (132–134). A highlighted finding was that higher education was usually associated with lower willingness to vaccinate (131–134). After initiation of the vaccination, disparities in HPV vaccine uptake was investigated in various settings. It was generally reported that girls/adolescences born outside the resident country or with foreign-born parents had lower vaccination uptake (135–137). Level of income was positively associated with vaccine uptake (137–141). The role of education was in discrepancy, with some studies reported positive association between parental education and girls' uptake (137,140), and some studies revealed similar scenario as the attitude studies that higher educated parents vaccinated their daughters less (141–143).

The impact of delivery strategy of HPV vaccination was investigated by a literature review comparing the coverage of HPV vaccination across settings with different delivery strategies. It found that school-based delivery usually presented higher coverage (144). The socioeconomic differences of HPV vaccine uptake in relation to delivery strategy was examined in Canada and Belgium, which reported decreased association between vaccine uptake and socioeconomic status/family income in the school-based delivery (145,146). In these studies, socioeconomic factors were assessed in group level or with single indicator. More comprehensive evidence is needed.

2.3.3 HPV vaccination in Sweden

HPV vaccine was introduced in Sweden in 2006. In May 2007, the cost of vaccination became subsidised by government for girls aged 13-17 years. The subsidy was included in the national healthcare system, meaning that the cost of HPV vaccination, together with other costs of prescriptive medications of each person, was subsidised by the government when exceed the

limit for personal payment (1800SEK by December 2011, approx. 180 euro) in 12 months, which was for up to 50% of the price of HPV vaccine. Quadrivalent vaccine was accounted for 99% of all HPV vaccination. Girls/parents requested the vaccination opportunistically from primary healthcare givers or vaccination centres.

HPV vaccination was introduced to the National Immunisation Programme in 2010 for girls at primary target ages, i.e. 10-12 years. It requires the vaccination to be fully financed by the government and be given in schools. Therefore, in January 2012, a free-of-charge school-based vaccination was initiated for girls born in 1999-2001, together with a free-of-charge catch-up vaccination delivery targeting girls born in 1993-1998 (147). Since 2013, the successive birth cohorts reaching primary target ages were targeted in school-based vaccination, and the catch-up vaccination was offered to girls up to age 18 years in typical implementation. Unlike the school-based vaccination for primary target ages, the catch-up vaccination was administrated in various settings in different counties. Among the 21 counties in the nation, 9 administrate in primary healthcare centres or vaccination centres, 4 in schools, and 7 in both, according to an investigation (147). Between 2014 and 2016, two counties implemented the catch-up vaccination up to age 26 years. Quadrivalent vaccine was offered in the school-based and catch-up vaccination.

The three-dose-schedule was initially administrated. In 2015, the two-dose-schedule was implemented for the primary target group in school-based vaccination.

By the end of 2016, the coverage of HPV vaccination in Sweden exhibited evident diversity across birth cohorts eligible for different vaccination delivery modes (Figure X).

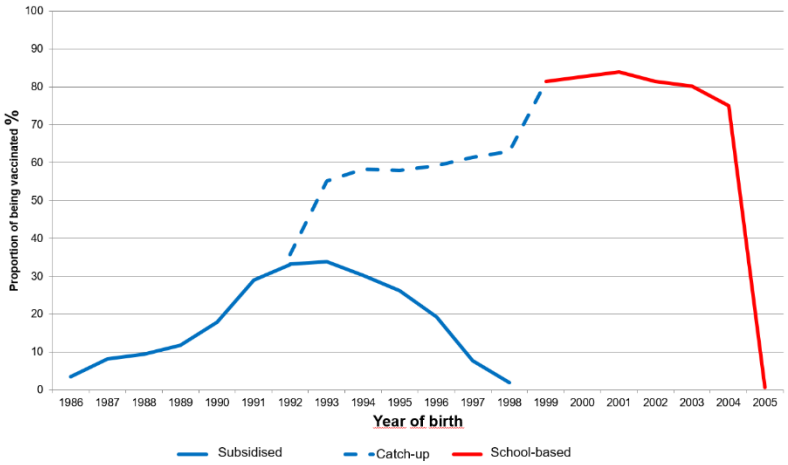


Figure 2: coverage of HPV vaccination in girls or young women by birth cohort, by 31 December 2016 (From Sparén, 2017)

3 AIMS

The overarching aim of the thesis was to use epidemiological approaches to evaluate the effectiveness and weaknesses of cervical screening program from panorama to focal points, and investigate the role of delivery design on pursuing equality of HPV vaccination.

The specific aims of studies were:

- To examine the overall effectiveness and imperfection of cervical screening program with stratification of histopathological type in a case-control audit frameword (Study III)
- To investigate the long-term risk of cervical cancer, especially adenocarinoma, following atypical glandulcar cells found in cervical screening, and compare the risk and following assessment to squamous intraepithelial neoplasia (Study I).
- To examine the effectiveness of cervical screening after age 60, stratefied by screening history at ages 51-60 (Study II)
- To assess the social disparity of HPV vaccine uptake by delivery mode of the vaccination (Study IV)

4 RESEARCH APPROACHES

4.1 DATA SOURCE

4.1.1 ACCES database

Advancing Cervical Cancer Eradication Strategies (ACCES) database was established in 2006 for research of cervical cancer prevention. It was built based on the Swedish National Cervical Screening Registry (NKCx). To obtain related information about all women targeted for screening, NKCx was linked with the Swedish population and healthcare registers, retrieving information regarding demography, cervical cancer, cause of death, hospital care (including surgeries), childbirth, socioeconomic circumstance, etc. These data were held by two government agencies, Statistics Sweden (Statistiska centralbyrån, SCB) for population registers, and the National Board of Health and Welfare (Socialstyrelsen) for healthcare registers. Information on HPV vaccination since 2006, which were held by Public Health Agency of Sweden (Folkhälsomyndigheten, FoHM) and its predecessor, was also added to the database.

All of the studies in this thesis used information in the ACCES database. Information involved was listed in Table 1 and described below.

Table 1: overview of registers used in this thesis

Content	Register	Source	Study
Cervical screening	The Swedish National Cervical Screening Registry	NKCx	I, II, III
Cervical cancer	The Swedish Cancer Registry	Socialstyrelsen	I, II, III
	The National Cervical Cancer Audit Database	Cancer Registry, medical chart, histology review	III
HPV vaccination	Prescribed Drug Register (PDR)	Socialstyrelsen	IV
	Swedish Vaccination Register (SVEVAC)	FoHM	IV
	National Vaccination Register (NVR)	FoHM	IV
Population	Total Population Register	SCB	I-IV
Migration			I-IV
Multi-generation			IV (II, III)
Hysterectomy	The Swedish Patient Register	Socialstyrelsen	I, II, III
Death	The Swedish Cause of Death Register	Socialstyrelsen	I-IV
Education	Longitudinal integration database for health insurance and labour market studies	SCB	II, III, IV
Income			IV

4.1.2 Description of registers

The Swedish National Cervical Screening Registry (NKCx in Swedish acronym)

Since the introduction of cervical screening in late 1960s, the individual counties in Sweden have organised and implemented cervical screening autonomously (38), and started digital

records of screening test successively. In 2002, NKCx was built with aims of nationwide documentary, evaluation and surveillance of cervical screening program. It collects the digital records of screening related information over Swedish counties, including all organised and opportunistic screening tests, histological tests, and invitations to screening. The coverage of cytology tests increased gradually since 1970s, and reached closed to 100% in 1995 (Figure 3). Histology test records reach the full coverage in 1993. The invitation records started in 1990s and completely nationally since 2006.

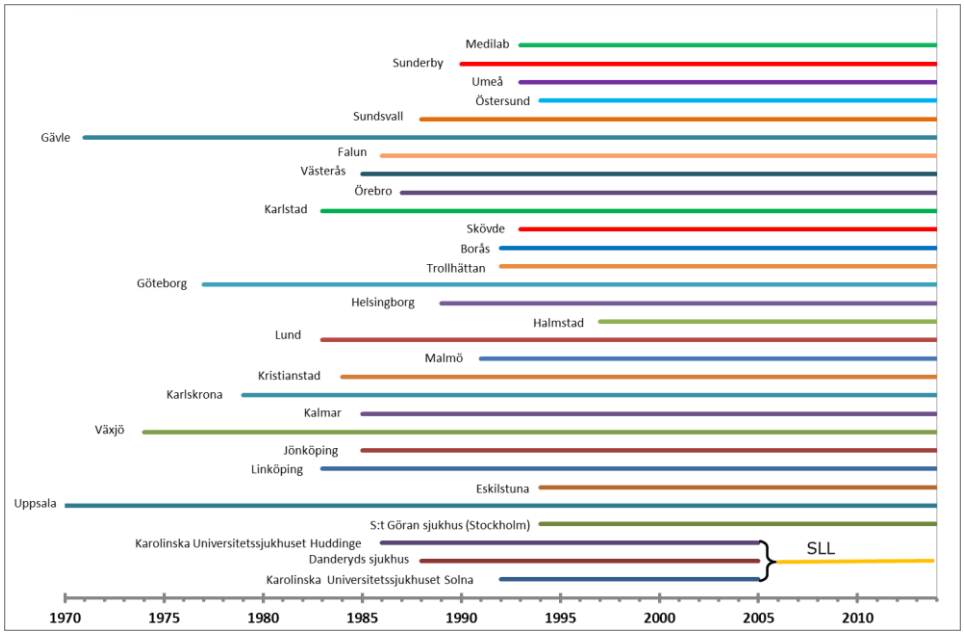


Figure 3: Time of initiating cervical screening records by counties/hospitals

Swedish Cancer Registry

The Swedish Cancer Registry was founded in 1958. The recording is based on compulsory reporting of newly detected cancer by health care providers over the entire country, and subsequently verified and corrected by six regional cancer registers. Information of tumour sites, histological type, date, place of diagnosis, etc. are recorded (148). It has been verified that the completeness of the register is high enough to leave out major impact for most uses of epidemiological studies (149).

The National Cervical Cancer Audit Database

The national cervical cancer audit aims to provide quality control indicators for an optimal cervical screening program, by performing standard analyses of the association between cervical screening and cervical cancer development in a case-control framework. The present audit database comprises cervical cancer cases diagnosed in Sweden during 2002-2011. The cancer cases were originally identified from Swedish Cancer Registry, and subsequently underwent thorough clinical and histological review. The clinical review went through each cancer case's original medical charts stored in regional hospitals, verified and complemented crucial information of the cancer diagnosis. The histological review re-evaluated the histopathology of 91% of cancer cases by reading the sample slides collected from pathological

laboratories all over the country. After the review, those who were not cancer of cervical origin, not epithelial, not primary cancer, and recurrent cancer were excluded.

Registers for HPV vaccination

Since HPV vaccine was on market in Sweden in 2006, three registers have been involved in recording the vaccination. From 2006-2012, it was recorded primarily in Swedish Vaccination Register (SVEVAC) (150). At the same time, the vaccinations were also recorded in Prescribed Drug Register (PDR), since the vaccine needs to be prescribed by clinicians in order to receive reimbursement. PDR records drug prescriptions for outpatient care in the entire country. Since the start of school-based vaccination in January 2012, the PDR does not record the school-based and catch-up HPV vaccination, as girls received the vaccine directly at school or vaccination centre without prescription. However, as SVEVAC is a voluntary reporting register around 25% of the vaccinations were without the identity of girls, i.e. being anonymous vaccinations that unable to link with other registers. In 2013, a compulsory reporting register for childhood vaccinations, National Vaccination Register (NVR), was initiated. Since then, all school-based HPV vaccination was registered with identity.

Total population register

The church of Sweden has kept a register of the population of Sweden since the 17th century. In 1968, after a large proportion of data were computerised, the Total Population Register (TPR) started. It records a large scope of individual information of all Swedish residents, from date and country of birth, place of residence, marital status, to migration record (both immigration and emigration), and multi-generation relationships (151).

Cause of Death Register

The Swedish Cause of Death Register records all deaths of people registered in Sweden. The computerised annual-updated registration started in 1961, yet the records from 1952 to 1960 were compiled retrospectively. The register contains information of death date, place, the underlying and contributing reasons of death denoted with International Statistical Classification of Diseases and Related Health Problems (ICD) codes, etc. Validation study shows a high completion and quality of the register (152).

Patient Register

The Swedish Patient Register was established in 1964. It started by recording information of patients discharging from inpatient care, including personal related information, date of admission and discharge, primary and additional diagnoses, surgery procedure, etc. It did not reach nationwide completion until 1987. In 2001, it began to include records of hospital-based outpatient care (153). In this thesis work, the surgery of total hysterectomy was obtained from the Patient Register. As total hysterectomy was performed in inpatient care, the information was available since 1964 and complete since 1987.

LISA database

Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym) contains a great amount of information of individual from the labour market, educational and social sectors, as well as the relative relations with their families and employers. The database holds annual registers since 1990, covering all Swedish residents aged 16 and above (154). Education and family disposable income was used in this thesis work.

4.2 ETHICAL CONSIDERATION AND DATA LINKAGE

Swedish law regulates the use of individual-based register data for research. According to its provisions, informed consent from individuals in the registers is not required, yet the ethical approval of the research aim and protocol granted by an ethical review board is prerequisite (155). The ACCES database received ethical approvals from the regional ethics committee in Stockholm, Sweden. The studies in this thesis involved approvals of Dnr 02-556, Dnr 2011/921-32, Dnr 2012/216-32, Dnr 2011/1026-31/4.

Once ethical approval was granted, the requested data were extracted from registers held by each agency. SCB gathered all data and conducted the data linkage on the individual basis via personal identification number (PIN). PIN is assigned by the Tax Agency in Sweden for all citizens and inhabitants who intend to live in Sweden for at least one year, and is used as identity indicator in numerous aspects of personal and social. Therefore, to protect integrity of registered individuals, SCB replaced PIN with randomly generated sequence number when sending the linked data to researchers. Even though, the linked data remains under secrecy, because theoretically individuals are still identifiable backward by combining information in the data. The use of the individual-level research data is therefore under strict management to avoid any leakage or illegal dissemination.

4.3 MAIN MEASUREMENTS

4.3.1 Cervical screening status and cytological classification of the result

Any Pap test record in NKCx in certain study period can be considered as being screened, which means organised and opportunistic screening tests are both included when defining screening status. However, since the register of screening did not complete nationwide before 1995, no screening record in the register did not necessarily indicate that no screening was performed before the initiation of screening register in certain county. This issue particularly affects study III where the study population was the older birth cohorts, and their screening history since age 51 was prerequisite. To avoid misclassification of screening status, we excluded women living in the counties where cervical screening records were not initiated before they turned 51 years of age. For the remaining women being included in the study population, no record in the register during the defined study period was considered unscreened.

Result of Pap test is the key information in study I, II, and III. It was originally recorded by regional laboratories, which analysed the smears, in varied coding systems. After collecting data, NKCx translated the codes into the uniform SNOMED (Systematised Nomenclature of Medicine) coding system defined by Swedish Association for Clinical Cytology.

The result of Pap test was classified into: low-grade abnormality, if women had ASCUS (atypical squamous cells of undetermined significance) or mild squamous dysplasia; and high-grade abnormality, if women had moderate or severe squamous dysplasia, atypical cells of uncertain origin, adenocarcinoma in situ, cytological implication of squamous cell carcinoma, adenocarcinoma, or malignancy of uncertain origin. According to the finding of study I, atypical glandular cells were classified as high-grade abnormality in study II and III.

Table 2. SNOMED codes for cytological diagnoses in the study, defined by the Swedish Association for Clinical Cytology

Cytological diagnosis	SNOMED code
Normal cytology	M00110
Low-grade abnormalities	
Atypical squamous cells of undetermined significance	M69710
Mild squamous dysplasia	M74006
High-grade abnormalities	
Suspected high-grade squamous dysplasia	M69719
Moderate squamous dysplasia	M74007
Severe squamous dysplasia	M80702
Atypical glandular cells	M69720
Atypical cells of uncertain origin	M69700
Squamous cell carcinoma	M80703
Adenocarcinoma/Adenocarcinoma in situ	M81403

Pap tests recorded in NKCx can be either screening tests that were performed in asymptomatic women, or diagnostic tests when women having symptoms suspicious for cervical cancer. The indication of the test is not recorded in the register, but can be speculated by time of the cancer diagnosis following the Pap test. Presence of suspicious symptoms leads to prioritised analysis of the Pap test thus accelerating the whole diagnostic process to usually within around one month. The analysis of asymptomatic Pap test usually takes three months, and the following diagnostic workup triggered by that abnormal test usually takes one to three months. This time-frame was verified in the National Cervical Cancer Audit Database including cancer cases in 2002-2011, in which the mode of detection (i.e. screen-detected or symptomatic cancer) were collected from the medical chart (Figure 3). If the Pap test was performed due to symptoms but no cervical cancer was diagnosed after that, the Pap test would serve similarly as a screening test, i.e. confirm normal cervical tissue or detecting precursor lesions, thus can be considered as a screening test. We therefore believe that using a time frame of around one month between the Pap test and cervical cancer diagnosis can distinguish diagnostic tests from screening tests. In study II when specifically assessing the impact of screening at ages 61-65, we verified the time frame between cancer diagnostic date and the first abnormal Pap test results within one year prior to cancer diagnosis, among cancer cases diagnosed at ages 61-65 during 2002-2011. The mode of detection of cases in 2002-2011 was derived from medical charts. We found that 50-day was a reasonable time frame to differentiate symptomatic cancer from screen-detected cancer.

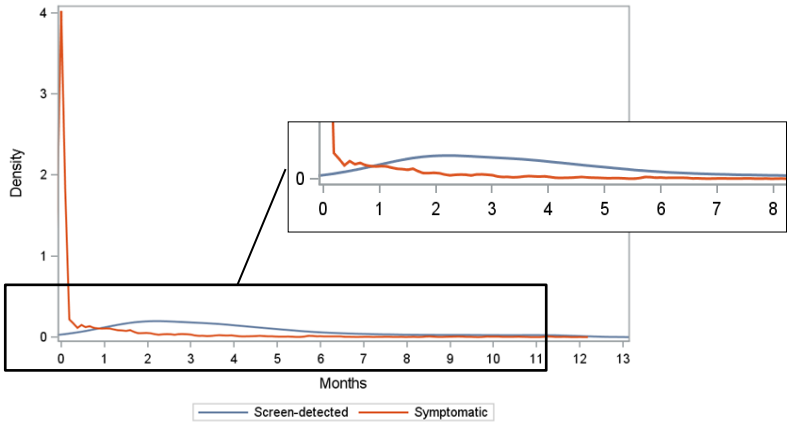


Figure 4: distribution of months between the first abnormality in the past year and cervical cancer diagnosis

4.3.2 Biopsy and histological assessment of cervix tissue

Taking biopsy under the colposcopy for histological diagnosis of cervical disease is one of the standard procedures following certain abnormal findings in Pap test. Determining whether one should take the biopsy and the method by which depends on the clinical guideline as well as colposcopists' assessment regarding the type of cytological abnormality, the visual lesion under colposcopy, characteristics of women, etc. The histological diagnosis of the disease determines further management and treatment. Thus taking a biopsy is key in the process of cervical cancer prevention. In study I, we identified women who had histological tests of cervical samples performed within six months following the initial abnormality as being biopsied. In study III, being biopsied was defined as having histological tests within one year following the initial abnormality. The different design in time span was due to study purpose.

4.3.3 Invasive cervical cancer

Diagnosis of invasive cervical cancer in study I and II was retrieved from National Cancer Registry, with ICD-7 (international statistical classification of diseases, seventh revision) code "171". The histological type of cervical cancer was classified in to squamous cell carcinoma and adenocarcinoma by the WHO/HS/Canc/24.1 histology code for anatomical location (156). Study III utilised the National Cervical Cancer Audit Database which included verified invasive cervical cancer cases in 2002-2011. Date and place of diagnosis, FIGO stage (International Federation of Gynaecology and Obstetrics staging system), and mode of detection (i.e. screen-detected or symptomatic cancer) were verified through clinical review, and histopathology of the cancer cases were determined by a comprehensive evaluation of the sources from histological review, medical chart and record in cancer registry.

4.3.4 Total hysterectomy

Hysterectomy, a surgical procedure to remove the uterus, is the treatment of many gynaecological diseases, mostly for benign conditions. It is not an uncommon surgery as estimations showed that one in three US women, and one in five British women will receive it during lifetime (157–159). In Sweden, the average age at hysterectomy was around 47-52 years (159). Unlike the subtotal hysterectomy that only removes the body of uterus, total

hysterectomy accounted for around 60% of hysterectomy surgeries for benign indications and involves removing the entire uterus including the cervix. Our research group found that 6.5% of women at age 60 years in 1983-2011 had been totally hysterectomised. Women who undergo a total hysterectomy will not develop cervical cancer and thus normally do not go to cervical screening anymore, especially if the indication of the total hysterectomy was benign. Including this sizable amount of women when evaluating cervical screening may introduce non-negligible bias. Therefore, for study I, II, and III, we excluded women who had undergone a total hysterectomy from the study population, or we censored them during follow-up, depending on the research purposes. Date of hysterectomy was derived from the Swedish Patient Register.

4.3.5 HPV vaccine uptake

HPV vaccine uptake is the outcome in study IV. Girls were defined as being HPV vaccinated at the first dose, which was identified from the PDR, SVEVAC or NVR. In PDR, using Anatomical Therapeutic Chemical (ATC) Classification System codes J07BBM01 and J07BBM02 for the quadrivalent and bivalent vaccine, respectively. We used the date of the first dose of the vaccine as it indicates under which vaccination delivery mode a girl was vaccinated with regard to her birth year. Type of the vaccine was ignored in the study, as 99% of the vaccine taken before 2012 was quadrivalent, and only the quadrivalent vaccine was eligible for school-based and catch-up vaccination since 2012. Although SVEVAC had issue of anonymous vaccination, before 2012 the problem was compensated by PDR, and since 2013 NVR offered records of school-based vaccination with identities of the girls. The anonymous vaccinations in SVEVAC mainly affect the school-based vaccination in 2012, and the catch-up vaccination from 2012 to the end of follow-up which was December 2014.

Dose completion was defined as number of time of receiving the vaccine. Each girl's multiple records of vaccination in one or more registers within 14 days apart were considered as the same dose.

4.4 STUDY POPULATION, DESIGN AND STATISTICAL ANALYSES

4.4.1 Study I

This population-based cohort study included women who lived in Sweden and had any record of cervical cytological test at ages 23-59 at any time from 1 January 1980 to 1 July 2011. Women who had a diagnosis of invasive cervical cancer or a total hysterectomy before their first cytology record were excluded. In total, 3,054,328 women were included in the study cohort.

We extracted women's first abnormal smear in the screening record, and classified them into AGC (14,625 women), LSIL (244,168 women) and HSIL (65,633 women). Women having been screened with normal results were defined as reference group for five years following each normal test. We assessed the proportion of prevalent cervical cancers which were diagnosed within six months following AGC and the incidence rate of cervical cancer from the

seventh month to 15.5 years after AGC. Using Poisson regression models, we further estimated the incidence rate ratio in relation to the same aged women who were screened with only normal results. The assessments were stratified by age at AGC, and histological type of cervical cancer. They were compared with the corresponding estimations following LSIL and HSIL. We also assessed the proportion of being followed with histology assessment from biopsy within six months after AGC, and the subsequent cancer incidence among the biopsied subgroup, comparing to the corresponding findings for LSIL and HSIL.

4.4.2 Study II

This population-based cohort study included 569,132 women born between 1 January 1919 and 31 December 1945, resident in Sweden since age 51, and at age 51 or younger when their county of residence started to record cervical screening. Women entered the cohort when turned age 61. They contributed to the unscreened group before the first Pap test at age 61-65 years, and contributed to the screened group since the first Pap test. They were followed until diagnosis of cervical cancer, receiving total hysterectomy, emigration, death, or the end of age 80 years.

We assessed the cumulative incidence of cervical cancer from age 61-80 years by screening status at age 61-65 years, stratified by five screening history groups at age 51-60 years, which were 1) adequately screened (at least two separate Pap tests) with normal results only; 2) inadequately screened (only one Pap test) with normal result; 3) unscreened; 4) having low-grade abnormality; 5) having high-grade abnormality. It was estimated by cumulative incidence function considering competing events of death and total hysterectomy. We also estimated the hazard ratios of cervical cancer in relation to screening status at age 61-65 years across the five screening history groups using Cox regression models, adjusted for education and birth cohort. We further examined the difference in FIGO stage distribution of cervical cancer found at age 61-65 years by screening status at this age span.

4.4.3 Study III

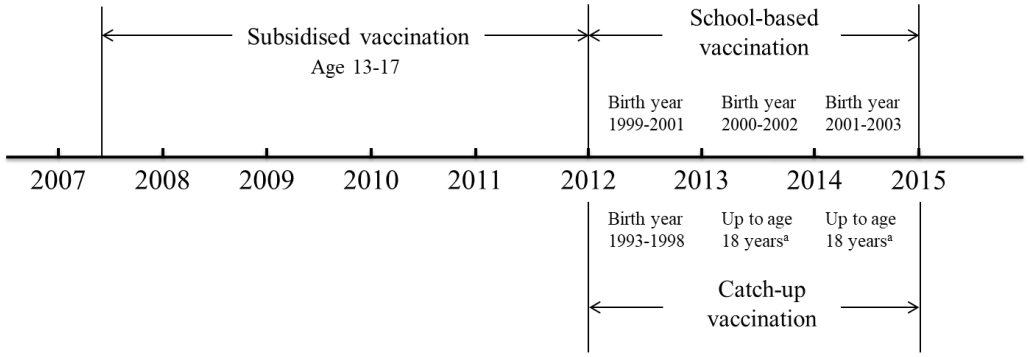
This population-based case-control study included 4254 women diagnosed with primary invasive cervical cancer during 2002-2011. For each cancer case, 30 controls were randomly selected from the population who were free of cervical cancer up to the cancer diagnostic date of the corresponding cancer case, matched on birth cohort. Control subjects who had received total hysterectomy at the cancer diagnostic date of the corresponding cancer cases were further excluded.

We assessed the cervical screening in two screening rounds prior to cancer diagnosis. The Pap test within six months prior to cancer diagnosis was disregarded, as cancer already existed when the test was performed. The length of previous two screening rounds varied by age at cancer diagnosis, which was six years for age 29-53, eight years for age 54-58, ten years for age 59-65, and screening at age 56-65 for those with cancer diagnosis above age 65.

We mainly used conditional logistic regression models to estimate: 1) relative risk of cervical cancer in women unscreened or inadequately screened compared to women screened in time in the past two screening rounds; 2) relative risk in women having abnormality in different patterns with biopsy status, compared to women screened in time with normal results only; 3) relative risk in women screened in time with normal results only, compared to women unscreened.

4.4.4 Study IV

This population-based cohort study included girls born between 1990 and 2003, and resident in Sweden between May 2007 and December 2014. Girls dead or emigrated before being eligible for the vaccination delivery, or immigrated after becoming eligible for the delivery, or vaccinated before being eligible were excluded. The cohort finally comprised 689,676 girls. They entered the cohort since being eligible for one delivery, and were followed until being vaccinated, emigration, death, or end of 2014. One can contribute to multiple delivery modes if eligible, before being HPV vaccinated. The eligibility for delivery modes by birth cohort or age was illustrated in Figure 5. Girls' biological or foster parents were linked, and the parental country of birth (COB), level of education and disposable income in the year before the girl was eligible, was categorised.



a. According to typical implementation

Figure 5: eligibility of girls for different vaccination delivery by calendar year, based on birth cohort

We plotted cumulative incidence curves of being vaccinated with the first dose (i.e. cumulative uptake) by parental COB, education and family income, as well as vaccination delivery mode. We then performed Cox regression models for each delivery mode to estimate hazard ratios of being vaccinated in relation to the three parental characteristics.

5 MAIN FINDINGS AND DISCUSSION

5.1 SUCCESS AND WEAKNESSES OF CERVICAL SCREENING PROGRAMME

5.1.1 Routine participation associated with significantly reduced risk

In the previous case-control audit based on cervical cancer cases in 1999-2001, it was found that non-participation to cervical screening in the most recent screening round was associated with a higher incidence of cervical cancer (5). It was direct empirical evidence demonstrating a strong cervical cancer-preventive effect from screening. In the present case-control audit based on cervical cancer cases in 2002-2011, we examined the impact of previous two screening rounds, and found that being unscreened in the previous two screening rounds was associated with higher risk of cervical cancer (OR=4.1, 95%CI=3.8-4.5) than the risk associated with being unscreened for only the most recent round (OR=2.4, 95%CI=2.2-2.7). Moreover, we found that being unscreened in the previous screening round and screened in the most recent round was still associated with a statistically significant elevated risk compared to women screened in both of the screening rounds (OR=1.6, 95%CI=1.5-1.8) (Figure 6).

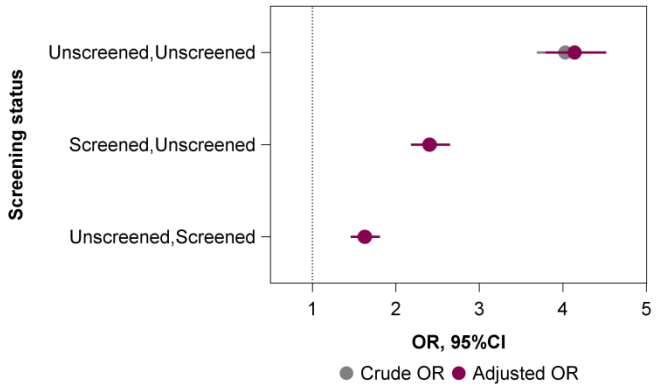


Figure 6: odds ratios of cervical cancer of women with different screening status in the past two screening rounds, compared to women screened in both rounds (crude odds ratio in grey, adjusted odds ratio in purple)

It suggests that a screening test may have a longer-term benefit, and the loss from missing one scheduled screening may not be completely compensated by the screening test in the next round. It may be due to the imperfect sensitivity of cytological test, thus repeat tests provide higher accuracy for disease-free status, and increase the chance to detect abnormalities. This emphasises the importance of routine participation to the screening.

5.1.2 Being screened after abnormality associated with reduced risk

The previous audit reported the benefit of taking biopsy shortly after an abnormality. In the present audit, we further evaluated the role of subsequent screening, and found that being screened in the most recent round in women having abnormality in the previous round was associated with statistically significantly reduced risk, no matter the initial abnormality was low-grade or high-grade, any biopsy was followed or not (Table 3). This finding confirmed the importance of keeping screening following an abnormality.

Table 3: odds ratios of cervical cancer (all types and stages) in women screened and unscreened in the recent screening round following abnormal result in the previous round, by type of abnormality and biopsy status

Screening and biopsy history[a]	No. of case sub.	No. of control sub.	Adjusted OR[b] with same reference group	Adjusted OR[b] with different reference groups
Low-grade, biopsied - screened	23	649	Ref.	Ref.
Low-grade, biopsied - unscreened	14	70	5.7 (2.8-11.6)	5.9 (2.8-12.4)
Low-grade, unbiopsied - screened	39	465	2.3 (1.4-3.9)	Ref.
Low-grade, unbiopsied - unscreened	27	105	7.5 (4.1-13.7)	3.3 (1.9-5.7)
High-grade, biopsied - screened	77	649	3.4 (2.1-5.4)	Ref.
High-grade, biopsied - unscreened	21	76	7.7 (4.0-14.6)	2.1 (1.2-3.8)
High-grade, unbiopsied - screened	18	158	3.1 (1.6-5.9)	Ref.
High-grade, unbiopsied - unscreened	22	32	19.3 (9.5-39.3)	7.1 (3.1-16.3)

a. Left hand side of hyphen represents the previous screening round, and right hand side represents the most recent screening round

b. Unconditional logistic regression, adjusted for age group and education

5.1.3 Having abnormality associated with universally increased risk

Nevertheless, we found that having an abnormality in any of the two previous screening rounds was always associated with an increased risk of cervical cancer. Even if the abnormality was found in the previous screening round and the screening in the most recent round showed normal, the risk was four times higher than women screened in time with normal results only (OR=4.0, 95%CI=3.2-5.1). It is understandable that having abnormality naturally yields increased risk, and the risk may not be completely eliminated by clinical management and treatment presumably due to potential immune susceptibility for recurrent disease. But since the primary aim of cervical screening is to prevent cancer by treating abnormalities, one need to consider to what extent the risk increase following abnormalities is acceptable, and whether the excess risk can be minimised by improving the management. At least the results highlighted that the close surveillance following an abnormality may warrant continuation for a certain period of time even if a normal result has been found.

5.1.4 Lower effectiveness for preventing adenocarcinoma due to lower "protection" from normal test results and higher risk following abnormalities

Studies constantly found that cervical screening using cytology was less beneficial in preventing adenocarcinoma of the cervix (56,59,61), which was also seen in our present audit. We found that 74% of cervical adenocarcinoma cases had participated in screening in the past two screening rounds, which was much higher than squamous cell carcinoma cases (53%). Furthermore, we found that, being screened with normal results in the past two screening rounds was associated with 89% risk reduction for squamous cell carcinoma (OR=0.11, 95%CI=0.10-0.13) but only 60% for adenocarcinoma (OR=0.40, 95%CI=0.32-0.52) compared to women unscreened. The odds ratios in relation to having abnormalities in the past two screening rounds compared to women unscreened was much higher for adenocarcinoma than for squamous cell carcinoma (Table 4).

Table 4: odds ratios of cervical cancer among women having abnormalities compared to women unscreened in the past two screening rounds, by stage and histological type

Screening history[a]	Squamous cell carcinoma			Adenocarcinoma		
	No. of case	No. of control	OR adjusted[b]	No. of case	No. of control	OR adjusted[b]
All stages (age 29+)						
Unscreened – Unscreened	1368	22099	Ref.	207	5103	Ref.
Abnormal – Normal	52	1139	0.5 (0.4- 0.7)	27	354	1.6 (1.1- 2.5)
Abnormal – Unscreened	62	206	3.5 (2.6- 4.7)	17	57	6.2 (3.5-11.1)
Nornal/Unscreened – Abnormal	272	1199	2.5 (2.1- 2.9)	74	317	4.9 (3.6- 6.7)
Abnormal – Abnormal	45	226	2.2 (1.6- 3.1)	23	68	7.2 (4.4-12.0)

a. Left hand side of hyphen represents the previous screening round, and right hand side represents the most recent screening round

b. adjusted for education and age group

Besides confirming the inferior preventive effect of screening for adenocarcinoma, our study further explained the cause of the inferior preventive effect, which were both lower "protection" from normal results and suboptimal effectiveness of managing abnormalities. The former was speculated to be associated with insufficient sampling of endocervical cells in Pap test. But the likelihood might not be high, because our previous analysis found that under the circumstance of 90% presence of endocervical cells over all Pap tests in Sweden (160), absence of endocervical cell in screening was not associated with increased risk of cervical cancer in the subsequent screening interval (OR=1.03, 95%CI=0.84-1.26). Therefore, it might be more likely to be due to the difficulty in sampling lesions locating up into deep cervical canal (161), or the lesion occur beneath the transformation zone and may thus be covered by normal or metaplasitic epithelium (162). It might also be likely that the pre-invasive lesions for adenocarcinoma progress rapidly so that the regular three-year interval is too long to detect it. The suboptimal effectiveness of managing abnormalities may arise from insufficient understanding of the risk following certain abnormalities, so that the following management is not optimally addressed.

5.2 ATYPICAL GLANDULAR CELLS IN SCREENING ASSOCIATED HIGH RISK OF CERVICAL CANCER, ESPECIALLY ADENOCARCINOMA

One of the suboptimal management following abnormality mentioned above may manifest in an uncommon cytological finding "atypical glandular cells" (AGC).

In study I, we found that women having AGC in cervical screening were associated with a remarkably increased risk of invasive cervical cancer in the subsequent six years, and the increased risk lasted for 15 years compared to women with normal screening results (Table 3 in paper I). The incidence from 0.5 to 6.5 years was higher than HSIL. Adenocarcinoma was the dominant histological type of cervical cancer following AGC (Figure 7).

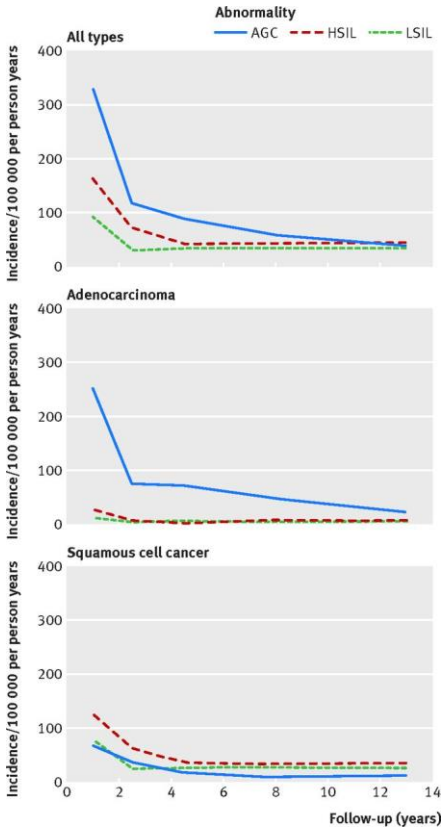


Figure 7: Crude incidence rates of incident cervical cancers at follow-up of AGC, HSIL, and LSIL, by histopathology of cancer. To avoid sparse and fluctuating data, right end point of follow-up time, denotes incidence at 10.5-15.5 years (Fig 3 in paper I)

We considered that although cancer cases found in the first six months following AGC were presented separately as prevalent cancer, there might still be residual prevalent cancer being detected later due to no immediate histology assessment, potentially resulting in a higher incidence than HSIL. We therefore did further analyses taking histology assessment in to consideration, and found that only 54% of women having AGC were followed by histology within six months, which was much lower than the 86% following HSIL. Within women being assessed with histology, 2.8% of women with AGC were found to have prevalent cancer, which was close to 3.2% for HSIL, and the cancer incidence in the subsequent six years following AGC was still significantly higher than that following HSIL (Table 5).

Table 5: Prevalent and incident cervical cancer (all histopathologies) associated with AGC, HSIL, and LSIL among women with histology assessment within six months, by follow-up time (Table 6 in paper I)

	Prevalent cancer			0.5-3.5 years			3.5-6.5 years			6.5-15.5 years		
	No of cases*	Prevalence %†	P value	No of cases*	IR‡	IRR (95% CI)§	No of cases*	IR‡	IRR (95% CI)§	No of cases*	IR‡	IRR (95% CI)§
AGC	162	2.8	Reference	19	136.1	Reference	12	109.9	Reference	6	35.1	Reference
HSIL	1288	3.2	0.10	68	68.6	0.6 (0.3 to 1.0¶)	28	36.6	0.4 (0.2 to 0.8)	36	29.7	1.0 (0.4 to 2.3)
LSIL	311	0.4	<0.001	64	31.1	0.3 (0.2 to 0.5)	25	16.1	0.2 (0.1 to 0.3)	53	22.4	0.7 (0.3 to 1.7)

*No of cases of cervical cancer.
†Percentage of having prevalent cancer among women with abnormality.
‡Observed incidence rate, per 100 000 person years.
§Incidence rate ratio and 95% confidence interval, relative to women with AGC, adjusted for age at abnormality.
¶0.9764, significant.

The results suggest that, AGC may be associated with the development of cervical adenocarcinoma, hence it spontaneously possesses a considerable risk of developing cervical adenocarcinoma, and the risk was not suppressed by following management to the similar to

that as for HSIL for squamous cell carcinoma. The lower proportion of follow-up with histology indicated that the potential high risk may not have been well recognised, and the higher risk than HSIL after being followed with histology implied that the current management approaches, established mainly from empirical evidence for addressing squamous cell abnormalities, may not be similarly effective for addressing glandular ones. The glandular lesions may hide up in the cervical canal and are therefore not visible under colposcopy, and the blind biopsy, if performed, may barely access the lesion. Moreover, the precursor lesion, adenocarcinoma *in situ* (AIS), may progression to invasive adenocarcinoma in shorter time, and thus the regular follow-up interval may not be short enough to catch AIS. Furthermore, even if AIS was found, the treatment for AIS does not appear as effective as the treatment for CIN3 in terms of reducing subsequent invasive cancer (163–165). That may be partially manifested by our finding that the cancer risk was higher among younger ages when AGC was found, since the treatment may be less aggressive considering patients' demand of childbearing.

Although our findings were based on cytological screening, it could be of great significance in upcoming HPV primary screening, as cytology will be performed as one of the reliable triages, and others have found that HPV-positive AGC had much higher risk of cervical cancer than HPV-negative ones in the subsequent five years (166). Therefore, AGC found in cytology triage under HPV primary screening warrants particular attention. Clinicians should be made aware of these patients, and more aggressive management strategy may be considered, such as biopsy into upper endocervix, and closer surveillance afterwards.

Although this study showed a clear association between AGC and cervical adenocarcinoma, anticipating a great improvement of prevention against adenocarcinoma by optimising management of AGC may not be practical, as we found in the above audit data that only around 10% of cervical adenocarcinoma cases had history of AGC in the past two screening rounds (Table 6). Other efforts still need to be made.

Table 6: Proportion of abnormalities among adenocarcinoma and squamous cell carcinoma in cancer cases during 2002-2011

Abnormality	% among adenocarcinoma	% among squamous cell carcinoma
LSIL	7.2	13.3
HSIL	4.1	9.5
AGC	4.4	1.1
AGC&LSIL	3.4	0.7
AGC&HSIL	1.8	0.7

5.3 CERVICAL CANCER RISK AND THE EFFECTIVENESS OF SCREENING AFTER AGE 60 VARIED LARGELY BY SCREENING HISTORY AT AGE 51-60 YEARS

Giving the unexpected high incidence of cervical cancer among women aged 60 and above, we tried to investigate the underlying reasons, and explore whether performing additional screening after age 60 would ease the problem.

In study II, we first assessed the distribution of screening history among women aged 51-60 over decades, and plotted the cervical cancer incidence rates at age 60-79 years. We found that along with the increase in proportion of women being adequately screened at age 51-60 years, there was a decrease of cervical cancer incidence rates after age 60 years (Figure 8). This finding supported the explanation given by an recent ecological study, which suggested that the observed high incidence of cervical cancer in older-aged women in Nordic countries may due to insufficient earlier-life screening background of the older birth cohorts, although that study was only able to assess age-specific cervical cancer incidence by birth cohorts (102).

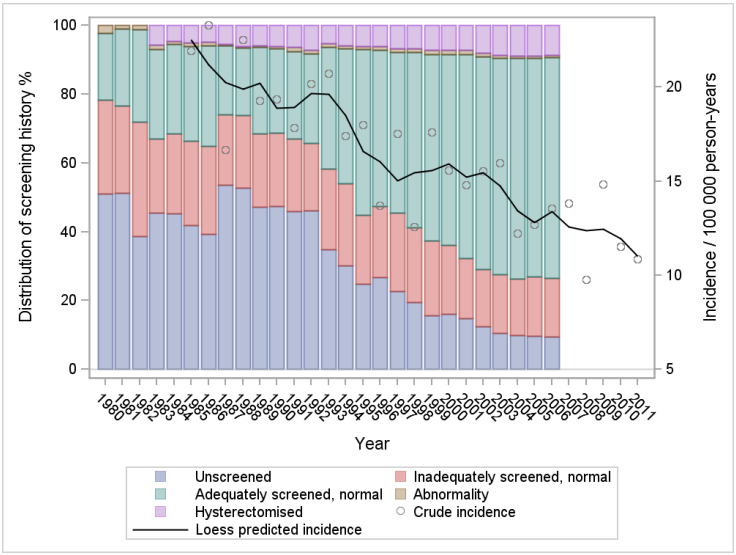


Figure 8: Distribution of screening status among women aged 51-60 years and incidence of invasive cervical cancer in women aged 60-79 years by calendar year

To further justify this argument, we performed the individual-level cohort study, and found that women who were adequately screened with normal results at age 51-60 presented a relatively low cumulative incidence of cervical cancer, which was 1.6 per 1000 women, from age 61 to 80 years. The cumulative incidence was much lower than among women unscreened, having low-grade or high-grade abnormalities in their 50s, which were 5.0, 9.7 and 15.3 per 1000 women, respectively (Table 2 in paper II). This evidence further confirmed that cervical cancer incidence at older ages depended largely on screening history.

In addition, we found that the impact of cervical screening after age 60 also varied by screening history (Figure 9). In women unscreened or having abnormalities in their 50s, being screened at age 61-65 years was associated with close to or more than 50% risk reduction up to age 80 years (HR=0.42, 0.53 and 0.59 in women unscreened, having low-grade or high-grade abnormality in their 50s, respectively). However, in women screened with normal results in their 50s, no statistically significant risk reduction was found to be associated with further screening (HR=0.90, 95%CI=0.69-1.17), but only a down-staging effect. This finding suggested a potential wane of cancer preventive effect from cervical screening with age, and it was preliminarily supported by our supplementary finding that the screening at ages 56-60 was associated with statistically significant risk reduction up to age 80 in women previously screened with normal results (HR=0.69, 95%CI=0.55-0.86). The potential wane of effect was

expected by previous findings that the detection rate of cervical precursor lesions decreased over age (92), especially among women being screened in the past (167,168). The low detection rate may be caused by both rare development of the diseases due to less HPV exposure after reproductive ages, and low sensitivity of cytological test at older ages when the transformation zone moves up into cervical cannel following hormone changes.

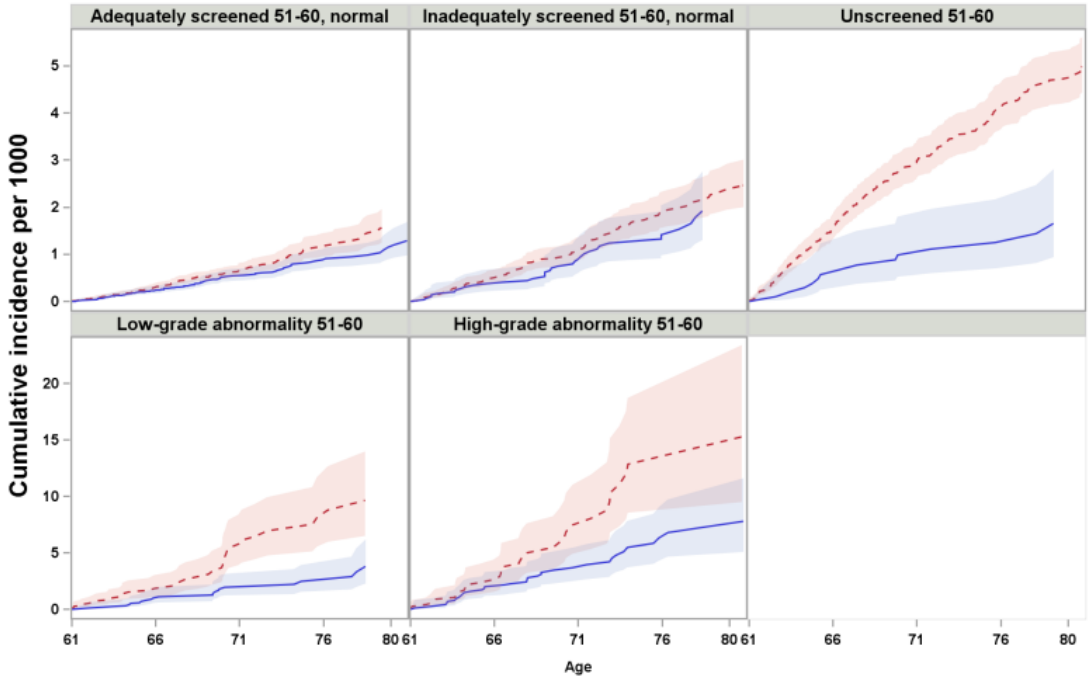


Figure 9: Cumulative incidence and 95% confidence intervals of cervical cancer among women screened and unscreened at age 61-65, by screening history at age 51-60, considering death and total hysterectomy as competing events. Red dotted line: unscreened at age 61-65; blue solid line: screened at age 61-65. Note that the scales of y-axis are different between the first and second row (Fig 3 in paper 2).

The above two causes for low detection rate of precursor lesions hint that HPV primary screening may have better performance at older ages, since HPV negative testing results may mean longer "protection" given the lower probability of acquiring new infection than younger ages (88,89), and HPV-primary screening may detect more precursor lesions by closer follow-up of HPV-positive cytology-negative women. We could speculate that performing HPV testing after age 60 in women screened with cytological normal results in their 50s may yield a further reduction of the residual subsequent risk. While it would also be of great interest to investigate whether the HPV test after age 60 is beneficial for those having been tested with repeat HPV-negative results in their 50s.

Previous studies reported significant effect of cervical screening after age 60 years in preventing cervical cancer regardless of screening history (4,6,169). This justifies performing the screening in this age group when a large proportion of women turning 60 years of age were not adequately screened in their 50s. As time goes on, increasing number of women will be adequately screened, thus a cost-efficient screening program for older aged women may have to be based on an individualised strategy.

Mortality is usually examined when evaluating effectiveness of screening. It was not included in this study because 1) cervical cancer-specific mortality was very rare at the studied age group as death from other reasons, which was not uncommon, was a strong competing event for cervical cancer death; 2) difference in overall mortality between screened and unscreened women may largely reflect the influence of life-style factors associated with screening attendance, thus was hardly attributed to screening alone.

5.4 DELIVERY MODE OF HPV VACCINATION ASSOCIATED WITH DISPARITIES OF VACCINE UPTAKE

In study IV, we found that the free-of-charge school-based vaccination yielded the highest overall uptake and lowest disparities in parental country of birth, education and family income, followed by the free-of-charge catch-up vaccination administrating outside of schools. The subsidised opportunistic vaccination showed the lowest uptake and strongest socioeconomic disparities (Figure 10).

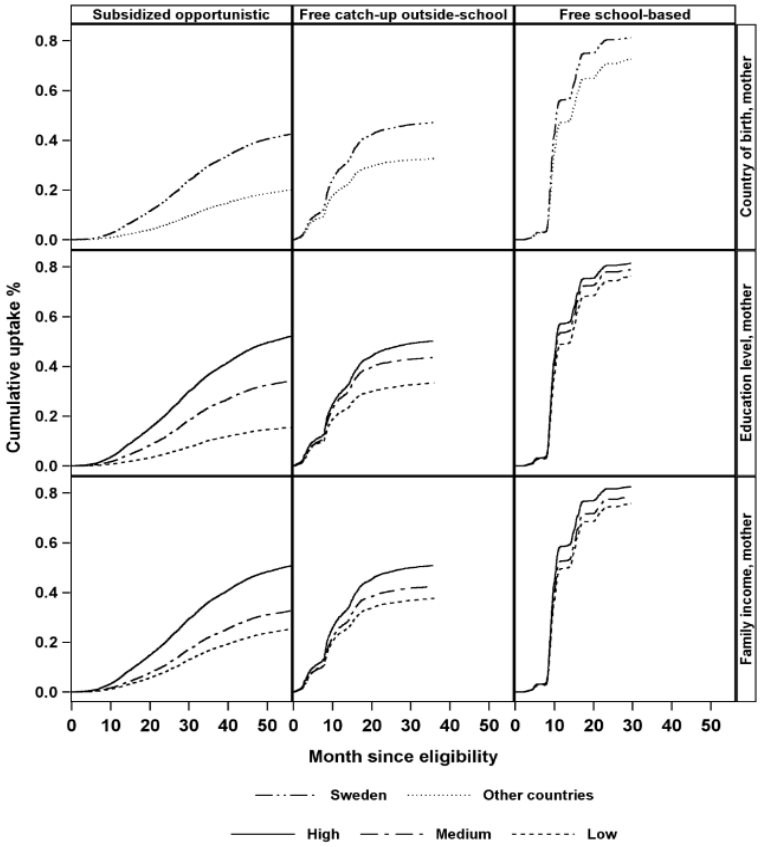


Figure 10: Cumulative uptake of HPV vaccine by maternal characteristics and vaccination policy (Figure 4 in paper IV)

The experience from healthcare services shows that individuals with migration or lower socioeconomic background are usually hard to reach (125,127,128,170,171). This is particularly seen in the subsidised opportunistic HPV vaccination in this study, where girls with foreign-born, lower educated, or lower income parents were vaccinated to the lowest level. In catch-up vaccination, the co-payment for individuals was rescinded. Although many information channels, e.g. school or media commercial, invitation letter, etc., were organised

by each county (147), in counties administrating the vaccination outside of schools, the uptake was suboptimal and disparities were still pronounced despite an improvement from the subsidised vaccination. The achievement of school-based vaccination, however, suggests that school organisation, which offers convenient access, may play important role on improving uptake in all socioeconomic groups. One important limitation of this study was that assessment of the uptake in counties administrating catch-up vaccination in schools was hampered, because the two counties fulfilling the criteria were small in population and co-located, thus the scenario may be different from other counties. Even though, in our supplementary analysis, the two counties exhibited similar overall uptake of the vaccine as school-based vaccination, and the socioeconomic disparities were mostly close to the school-based vaccination (Table 7). On the basis of previous findings that school organisation achieved higher vaccination coverage in adolescence, our study further demonstrated that it could also assisted on attaining social equality in vaccine uptake.

Table 7: adjusted hazard ratio of HPV vaccine associated with maternal characteristics, including catch-up vaccination administrated in schools

	Free catch-up outside-school	**Free catch-up in-school**	**Free school-based**
Country of birth			
Sweden	Ref.	Ref.	Ref.
Other countries	0.68 (0.65-0.71)	0.91 (0.84-0.99)	0.82 (0.81-0.83)
Education level			
High	Ref.	Ref.	Ref.
Medium	0.87 (0.85-0.90)	0.92 (0.88-0.97)	0.95 (0.94-0.96)
Low	0.73 (0.69-0.77)	0.90 (0.83-0.98)	0.92 (0.91-0.94)
Family income			
High	Ref.	Ref.	Ref.
Medium	0.87 (0.84-0.90)	0.91 (0.86-0.96)	0.92 (0.91-0.94)
Low	0.79 (0.76-0.82)	0.79 (0.74-0.84)	0.87 (0.85-0.88)

Having migration or lower socioeconomic background was also found to be associated with lower participation to cervical screening (172,173). Although school administration was not applicable for the delivery of cervical screening, the essence of providing convenient access of the service may be referred for diminishing socioeconomic inequality of screening participation, for instance offering self-sampling screening test for non-attendants.

6 METHODOLOGICAL CONSIDERTATIONS

6.1 STUDIY DESIGN

In this thesis work, two main observational study designs, cohort and case-control design, were utilised. Cohort study is generally considered to be at high rank of evidence hierarchy among observational study designs (174). However, the case-control design conducted in this thesis should provide similar validity on measuring relative risk, as in this instance if first using register data to collect the exposure avoided the exposure status being influenced by the occurrence of the outcome, from which the conventional retrospective case-control design usually suffers. Second, it was performed as a nested case-control study using density-based sampling for control selection, which meant that the control subjects were randomly selected from the population which had the same key characteristics as the corresponding case, and at risk of cervical cancer at the time of the diagnosis of the case. This was achieved through matching on birth cohort, and allowing a case to also act as the control for other cases before diagnosis. It ensured that the controls were from same the population that gave rise to the cases. Under these conditions, the odds ratios estimated in case-control study can be considered equivalent to the incidence rate ratios estimated in a cohort study.

Theoretically, these four studies could have all been performed with an alternative design. However, there are particular strengths of each design that suitable for specific research questions. The absolute risks are of particular interest in study I, II and IV (absolute risk of cervical cancer after AGC, after age 60, and absolute uptake of HPV vaccine, respectively), whereupon cohort design offering direct and flexible measures of the absolute risk is more appropriate. Particularly in study I, as AGC is a rare exposure, cohort design which makes use of all cytological diagnosis of AGC in the database is more sufficient. Yet in study III, the absolute risk of cervical cancer by screening status is not a primary interest, thus case-control design involving less subjects becomes more efficient in estimating the relative risk. Moreover, by restricting the cancer cases to a defined time period, the collection of information from medical charts and verification of histological type of the cancer cases becomes feasible and convenient.

6.2 REGRESSION MODEL

Within each study design, statistical models were also carefully selected according to specific research questions of the four studies. In cohort design, Poisson and Cox regressions can both estimate the relative risk associated with the exposure. Poisson regression allows flexible estimations of relative risk on the underlying time scale of follow-up, whereas Cox regression assumes a constant effect of the exposure over the entire follow-up, so called proportional hazard assumption. In study I where the long-term risk following AGC was examined, the risk in relation to women with normal screening results were substantially heterogeneous over the 15 years, and the heterogeneity over time was of interest as a research question. Hence it is much easier to model with Poisson regression. On the other hand in study II and IV, the “effect” of screening after age 60 years for cervical cancer development, and socioeconomic status for

HPV vaccine uptake, was quite constant over the follow-up period, which was approved by the tests of proportional hazard assumption, thus Cox regression model provides plain and straightforward measurement of the association.

Logistic regression model is generally used for case-control studies. In study III, as the case and control subjects were matched on birth cohort, using conditional logistic regression which models the probability stratifying by the matching clusters, is crucial as it removes the bias that were potentially introduced by matching if analysed via regular approach. However, in specific sub-analyses when the exposure was extremely rare, for instance when assessing the effect of screening following different grade of abnormalities as well as biopsy status, using conditional logistic regression ended up with poor precision. We therefore used ordinary logistic regression model adjusting for age, which captured the key influence from birth cohort in the only ten-year study period. This model also largely reduced the impact of potential bias introduced by matching.

6.3 CONFOUNDING

Observational studies usually suffer from confounders, which bridge a synthetic association between examined exposure and outcome. Existence of confounding factors distorts the magnitude of the true association between exposure and outcome, and disables the causal interpretation of the association, because it hinders the exchangeability between the exposed and unexposed group hence the two groups are not considered homogenous besides the exposure factor. By adjusting confounding factors in analyses, the association is amended, and the causality is defended as conditional exchangeability is yielded.

In this thesis, examining the effect of cervical screening on cervical cancer risk is prone to suffer from several potential confounding factors: a) Birth cohort. The older birth cohorts generally had poorer screening profile, and may have lower baseline risk of cervical cancer due to different sexual behaviour pattern compared to younger birth cohorts. Therefore, the effect of screening may be diluted if not adjusting for it. b) Age. Women at different ages have different levels of screening participation, and age is an important risk factor for cervical cancer. c) Education. Higher education is generally associated with higher screening participation, and may also directly relate to lower cancer risk due to lifestyle or environmental conditions. Hence the effect of screening may be amplified. d) Behaviour factors, such as age at sexual debut, number of partners, parity and smoking, are well-established risk factors of cervical cancer. They may also be positively or negatively associated with screening participation depending on individuals' perceived risk of developing cervical cancer as well as health consciousness. e) Health consciousness. People who are more health-conscious usually are more likely to adhere to screening, health consciousness may also have influence on cervical cancer development through lifestyle or psychological factors.

6.3.1 Addressing confounding from birth cohort and age

Birth cohort has close relationship with age and calendar period, so controlling for birth cohort may capture confounding effect from different aspects in different studies. In study II where

age at screening was defined, adjusting for birth cohort also controlled for potential confounding from calendar period. The results that the magnitude of hazard ratios was slightly changed after adjusting for birth cohort supported the existence of the confounding effect. In study III, cases and controls were matched by birth cohort, which was an efficient approach to control for confounders in case-control design. Since the time period for cancer cases was defined as only ten years, matching on birth cohort captured more of confounding from age than the calendar period. When matching, the magnitude of confounding effect of the matching factor was not possible to estimate.

Confounding from age was also considered in study I when comparing the risk of cervical cancer following AGC to women screened with normal results, since both the prevalence of AGC and risk of cervical cancer were highly related to age. We adjusted for attained age when assessing the relative risk of cancer following AGC, which makes sure that the risk ratio at each time point during follow-up reflects the comparison with women having normal screening results at the same age.

6.3.2 Addressing and discussing confounding from education, behaviour and health consciousness

Previous studies evaluating effectiveness of cervical screening rarely controlled for social-psychology-behaviour factors, thus were challenged that the association could be confounded by self-selection, that women participating to screening are a selected group of certain characteristics which may have low underlying risk of cervical cancer even without screening. Those characteristics may include education, behaviours, and health consciousness, which are intimately associated with each other.

Education was adjusted in study II and III. We found in study II that the estimates of hazard ratio of developing cervical cancer in relation to screening status at age 61-65 years was barely changed when adjusted for education only. Similarly in study III, adjusting for education did not alter the odds ratio. We therefore speculate that education may be associated with screening participation, but has a weakly direct association with cervical cancer development.

However, great majority of cervical cancer related behaviour factors were impossible to be addressed in this thesis, since they were not recorded in register data. The only factor with relatively complete register data over time was parity, for which the number of children of each woman was recorded in Multi-Generation Register. High parity is usually related to lower screening participation because screening was usually not performed among pregnant women. And parity is an established risk factor for cervical cancer which may be due to hormone related cervical ectopy and cervical trauma during vaginal delivery (175,176). However, we found in study II and III that adjusting for parity did not alter the results. To assess how unmeasured sexual behaviour factors may confound our results, we extracted data from a survey conducted in 2007 in Sweden covering young women under age 30 years (132), and found that in women aged 25-30 years, age at sexual debut and condom use with temporary partners was not associated with screening participation, while women having more than one partners in the past

year participated slightly less to cervical screening compared to women having no or one partner (Table 8). This suggests that, if the association was similar among other ages, the reported association between screening participation and cervical cancer development in study II and III might be slightly overestimated, but the influence was minimal.

Table 8: screening participation by sexual behaviour factors in young women, from survey 2007

		% of screening participation	p-value from chi-sq test
Age at sexual debut	<15 (22%)	89.3	0.13
	>=15 (78%)	91.2	
No. partners past year	>1 (24%)	86.7	<0.01
	0-1 (76%)	91.7	
Condom use with temp. partners	Rarely or never (21%)	89.2	0.13
	Use (79%)	90.9	

Health consciousness was also impossible to measure in our register-based study. However, since it is closely associated with socioeconomic status (177,178), the adjustment for education may have reduced its influence. In addition, we consider that the impact of health consciousness on the association between screening and cervical cancer risk may be related to the coverage of screening, that the confounding effect could be stronger if very few women in the population went to screening. Thus when evaluating the effectiveness of screening after age 60 in study II, since only a part of counties organised or encouraged screening above age 60 years, the coverage of screening varied. We performed sensitivity analysis restricting to counties that had more than 40% women screened at ages 61-65, to ensure that counties that had very few women being screened did not dominated the result that otherwise might be strongly health-conscious. In study III, as the coverage of screening was above 70% in the entire population (160), we consider that the confounding effect from health consciousness may not overwhelm the true effect of screening, especially after adjusting for education.

6.4 BIAS

Generally, bias is a factor that causes distortion of the association between studied exposure and outcome, thus confounding and misclassification can be considered as sources of bias. In conventional understanding, bias usually comes from incorrect selection of study population, i.e. selection bias, and incorrect measurements of exposure and outcome factors, i.e. information bias. The four studies in this thesis generally suffered little from selection and information bias, because the study population were the entire population in Sweden, and the information of exposures and outcomes were derived from registers instead of reported by individuals relying on recall.

One potential selection bias could exist in study II, since only women living in the counties that started cervical screening register before they turned age 51 years were included in the study. It was mainly due to county-based administration. However, there would be bias if the characteristics of population were systematically different between counties that started the record of screening in early and later years. To evaluate the difference between women included and excluded due to availability of screening record, we compared the level of education between the two groups, and found that women included in the study were slightly

higher educated, yet the difference was minimal (Table B in S2 text of study 2). Furthermore, since the inclusion due to screening record availability also results in different proportion of inclusion by birth cohorts, i.e. women born in later years had larger proportion of having screening record available since age 51 years (Figure 11), we performed sensitivity analysis restricting to younger birth cohorts, and found the results almost unaltered (Table E in S2 text of study 2). We thus believe that the selection bias in study II was not a major concern.

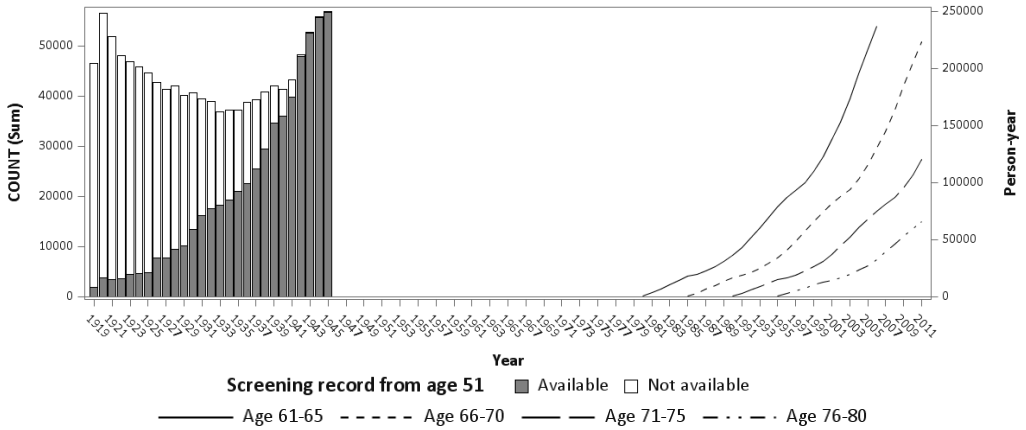


Figure 11: Number of women having (grey bar) or not having (white bar) cervical screening records from age 51 by year of birth, and amount of person-years of follow-up contributed in women having screening records from age 51 by age category and calendar year (lines)

Table 9: Characteristics of population in counties included and excluded in study IV due to anonymous vaccination issue

	16 counties in study	5 counties having 30% anonymous vaccination
Mean age	42.0	42.8
Country of birth		
Sweden	84.0%	86.3%
Other countries	15.9%	13.6%
Missing	0.1%	0.1%
Education in ages 35-65		
low	12.9%	13.4%
Medium	45.1%	47.2%
high	41.1%	38.7%
Missing	0.9%	0.7%
Family income in ages 35-65		
low	33.8%	34.6%
Medium	32.8%	34.4%
high	33.0%	30.7%
Missing	0.4%	0.4

Another potential selection bias could exist in study IV when five out of 21 counties that had more than 30% anonymous vaccination in SVEVAC was excluded from the analysis. Four of the five counties are small to middle size in population, and one county is the second large county in Sweden. We compared the population characteristics of the five counties to the other 16 counties, and found that there were slightly more Swedish-born, and slightly lower education and income in the five counties (Table 9). However, the differences were too small to justify an obvious selection bias.

6.5 MISCLASSIFICATION

The only clear misclassification in this thesis work was the vaccination status in study IV. Due to anonymous vaccination in the register SVEVAC, girls vaccinated without identity were classified as unvaccinated. It was hardly known whether the misclassification was differential or non-differential in relation to the studied social disparity factors, because the characteristics of the girls in terms of socioeconomic status cannot be assessed without identity of the girls. To minimise the influence of misclassification, we excluded the counties that had more than 30% anonymous vaccination, and performed sensitivity analysis restricting to counties having less than 15% anonymous vaccination, in which the results of association between parental socioeconomic factors and girls' HPV vaccine uptake across delivery modes of the vaccination were not changed. This suggested that the misclassification may not have considerable influence on the results.

Unknown misclassification associated with registers may exist, as register data is by no means 100% correct. Yet we believe that the potential unknown misclassifications were most likely non-differential between the examined exposures and outcomes, thus may have little impact on the results other than slightly diluted the examined associations.

6.6 GENERALISABILITY

Whether the results of the four studies can be generalised to other settings deserve a discussion. The effectiveness of screening found in our studies may not directly translate to other countries, because firstly, the sensitivity of cytological test which relies on subjective judgement, is close to 80% in Sweden, yet varied between 30% and 90% across settings (27); and secondly, the management following abnormalities also differs. It may lead to various magnitudes of effectiveness of cervical screening, although the beneficial effect may hardly be overturned. Policy making for screening practice referencing our results should therefore be cautious on potential inaccurate prediction of cost-benefit if the sensitivity of Pap test or management following abnormalities are different from Sweden.

The results of socioeconomic disparities in HPV vaccine uptake by delivery mode of the vaccination may to a large extent generalisable to wider settings, as we considered the comparability with other countries or cultures when choosing the indicators for migration and socioeconomic background. However, marginal differences may remain, because there could still be residual discrepancies in sociological significance for the same indicators in other settings. For instance, the foreign-born groups in North America or Asia could have different composition from those in Sweden in terms of cultural background, and the immigrants in different countries may develop different attitudes. Besides, as the overall income in Sweden is relatively high over countries worldwide, the individuals' sensitivity to the price or price change of the HPV vaccine could be different from that in low-income countries, and the social stratification by income may be more likely to imply differences in other socio-psychological aspects than the amount of income itself. Particularly when facing a newly introduced vaccine, the discrepant degrees of trust to authorities as well as impact of anti-vaccine movement may

all affect the attitude and behaviour in different socioeconomic groups across different countries. Hence, similar evaluations from different settings will be of particular value.

6.7 CHALLENGE IN EVALUATING THE EFFECTIVENESS OF CERVICAL SCREENING

Cervical screening test can both detect the existing cervical cancer and prevent cancer that would develop in the future. Therefore, a screening test could lead to an increase of cervical cancer incidence within a short period of time, and a decrease of incidence in the long run. Figure 12 illustrates a likely pattern of the differences in observed cervical cancer incidence between screened and unscreened women at different time period following a screening test (the black dot). During the initial six months, due to the diagnosis of existing cancer (or called prevalent cancer) detected by screening, women being screened were found more cancer cases than those unscreened. Then in the following time period (the blue line), the unscreened group presents with a higher incidence than the screened group, partially because the cancer cases that are diagnosed by the screening test during the initial six months, usually before symptom onset, in the screened group are diagnosed in this period in the unscreened group. Thus it can be considered as a "washout period" for the cancer cases having onset in the initial six months. Thereafter, a lower incidence in the screened group may still be observed during certain time period, which should be due to the preventive effect of the initial screening test. After this period, the effect of this screening test wanes thus the screened and unscreened group will present similar incidence.

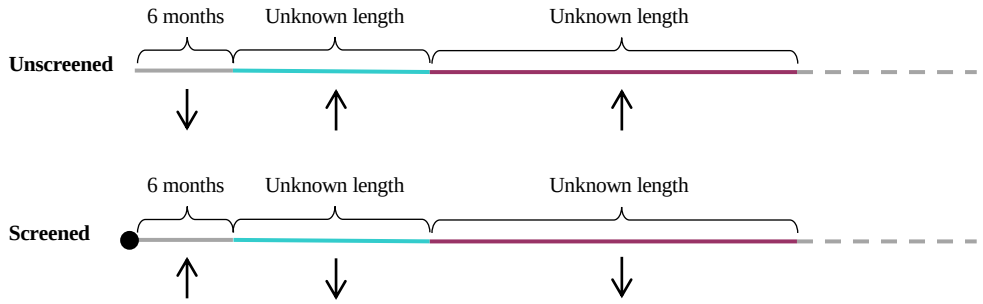


Figure 12: Pattern of cancer detection following a screening test (arrows represent relatively higher or lower detection rate of cervical cancer comparing screened and unscreened group)

The challenging point of evaluating the effectiveness of cervical screening is how to accurately examine the preventive effect, because the effect observed during the blue line involves both the "washout" effect caused by early detection of unpreventable cancer cases, and the true preventive effect by detecting and removing precursor lesions. For instance, stage IA cancer detected by screening within the initial six months may have been diagnosed in one to two years if the screening were not performed, thus the incidence difference observed between screened and unscreened group in the following one to two years is not a preventive effect; Whereas, CIN3 or adenocarcinoma *in situ* detected at the screening would have progressed to invasive cervical cancer in one to two years if the screening were not performed, in this case the incidence difference observed in one to two years represents a true preventive effect.

In study II, since the primary research question was whether the screening test after age 60 can prevent cervical cancer, we performed a cohort analysis evaluating the cumulative incidence of cervical cancer, and allowed the screen-detected prevalent cancer cases to be the outcome of the screened group. The beauty of this approach is that one does not need to for the timeline to distinguish the cancer cases that can and cannot be prevented by the screening test, which is the key challenge described above. As long as there is a difference in cumulative incidence that can be observed by the end of follow-up, there must be preventive effect occurring during follow-up. And it presents an intuitive short-term and long-term impact of one single screening test.

However in study III, where the main aim was to accurately quantify the pure preventive effect of screening, it is important to distinguish which screening tests can serve to prevent a cancer case. Obviously, in the case-control frame, the screening test within six months prior to cancer diagnosis should be disregarded, which was done in the current analysis, as well as the first audit (5) and the audit in UK (4). However, in addition, screening tests during a time period preceding the six months may also need to be disregarded, corresponding to the "washout" period in the above schema with prospective view. Figure 13 is the corresponding schema with retrospective view in case-control design frame. The scenario during the blue line time here is as tricky as above, the difference in odds of having screening test during the blue line between the cases and controls mixed "washout" effect and true preventive effect. The "washout" effect is originated because for the case subjects the cancer may already have developed at time of the blue line, so if a Pap test were performed, the cancer would have been diagnosed at that time point. Hence a cancer case diagnosed at time X may be very unlikely to have a Pap test during the blue line time. And the true preventive effect comes from the likely situation that a CIN3 or adenocarcinoma *in situ* is detected in a control subject during the blue line time - thus the cancer that would have appeared at time X is prevented. The crucial handling to examine the true preventive effect is to find a cut-off time point at the blue line that can maximally distinguish the "washout" and preventive effect. The "washout" period echoes the concept of occult invasive phase of cervical cancer, which is the time between the onset of cancer and the symptom, with the screening for early detection of the cancer usually taking place during this time. However, the length of occult invasive phase of cervical cancer does not directly translate to the length of the washout period in our study, because for a screen-detected cancer the length of the washout period is the length of the true occult invasive phase minus the time that gained by the screening. The length of occult invasive phase of cervical cancer remained unclear. One study reported from modelling that up to two years all cervical cancer cases diagnosed at occult invasive stage progress to clinical stage (179). Consider that 29% of cancer cases were screen-detected in our study then the average length of the washout period might be estimated to approximately one to one and a half year. It is also reported that very few cervical cancer were diagnosed within one to two year after detection of CIN3 (180). Therefore we performed the sensitivity analysis in study III disregarding Pap test within 12 months and 18 months prior to cancer diagnosis, and found that the point estimates of odds ratios were slightly reduced, but the confidence intervals were mostly overlapped with the original analysis, and the significance

compare to women screened in time did not change (Table 10). The conclusions were therefore not violated.

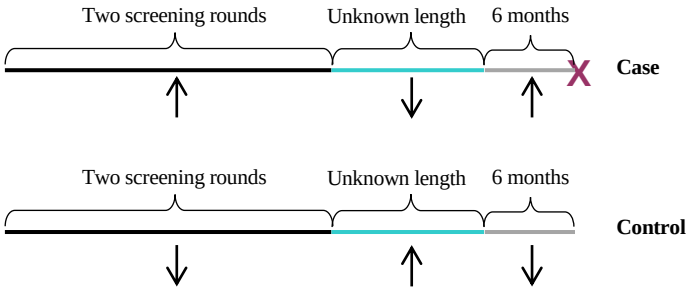


Figure 13: Pattern of screening history prior to cancer diagnosis in case and the corresponding control (arrows represent relatively higher or lower probability of having a screening test comparing case and control)

Table 10: adjusted odds ratios[a] of cervical cancer in relation to screening status in the past two screening rounds, by number of months prior to cancer diagnosis for disregarding non-preventive Pap test

	6 months	12 months	18 months
Unscreened – Unscreened	4.14 (3.79-4.52)	3.91 (3.58-4.27)	3.56 (3.27-3.88)
Screened – Unscreened	2.40 (2.18-2.65)	2.03 (1.84-2.24)	1.63 (1.47-1.81)
Unscreened – Screened	1.63 (1.46-1.81)	1.54 (1.38-1.71)	1.49 (1.34-1.66)
Screened – Screened	Ref.	Ref.	Ref.

a. adjusted for education and age group

More research is needed to find out the optimal cut-off to distinguish the washout and preventive effect, perhaps taking the stage of the cancer cases into consideration.

7 CONCLUSIONS

Participating to cervical screening following a recommended interval was associated with a substantially reduced risk of invasive cervical cancer. Missing scheduled screening yielded an increased risk of cervical cancer in both the short and longer term, and the excess risk was not completely eliminated even if participated in the next round of screening.

Having an abnormality in cervical screening was associated with an increased risk of cervical cancer compared to having normal results only. Being screened in the subsequent round following abnormality yielded a clear reduction of the elevated risk. However, a residual excess risk remained even if the screening in the subsequent round reported normal.

The inferior preventive effect of cervical screening against adenocarcinoma compared to squamous cell carcinoma of the cervix was due to both lower assurance from repeat normal test results, and higher risk following abnormalities.

Atypical glandular cells found in cervical screening implies increased risk of incident cervical cancer in the subsequent 15 years, especially for adenocarcinoma of the cervix. The incidence was higher than following high-grade squamous intraepithelial lesions in the subsequent 6 years, even the initial histology assessment was performed.

Cervical screening at ages 61-65 was associated with substantially reduced risk of cervical cancer up to age 80 in women being unscreened or having abnormalities in their 50s. Yet in women screened with normal result(s) in their 50s, the subsequent risk of invasive cervical cancer was not sizable, and the screening after age 60 was not associated with statistically significant risk reduction.

The free-of-charge school-based delivery of HPV vaccination achieved the highest vaccine uptake with lowest social disparity, compared to the delivery modes requiring co-payment and/or administrating outside of schools.

8 IMPLICATIONS AND FUTURE DIRECTIONS

Through optimised study design, we reinforced the evidence of the effectiveness of cervical screening, and justified the importance of routine participation to screening. We also identified suboptimal aspects in cervical screening programme, which may guide further efforts in research and practice for improvement. As examples of such further research, we utilised the rich register database to address two specific clinical questions of wide concern, regarding risk of glandular abnormalities in relation to unsatisfactory cancer prevention for adenocarcinoma, and effectiveness of screening for older aged women. The findings provided real-life evidence for potential amendments in practice to improve the screening performance. Furthermore, we verified the role of delivery mode in reducing disparities of HPV vaccine uptake, which informed the exertion of promoting equal acquisition of cervical cancer prevention.

Research and practice following present findings may facilitate the elimination of cervical cancer. Despite an up to 70-80% coverage of cervical screening, more than 50% of cervical cancer cases arose from women being not screened or not routinely screened. Reaching the rest 20-30% and encouraging routine participation will be a long-term effort. A randomised trial found that offering reminder, especially phone reminder to the short-term non-attendants can increase attendance (181), and the ongoing trial of offering self-sampling HPV test for the long-term non-attendants appears promising. Self-sampling provides easy access, thus may reduce the socioeconomic disparities of the screening attendance given the experience from vaccine uptake, while lower socioeconomic status was shown to be significantly associated with lower screening participation (173,182–184).

Optimising clinical management for abnormalities found in screening could further enhance the preventive effect of screening. Take the studied AGC as example, since a higher cervical cancer incidence was seen even after histology assessment, the natural history of glandular dysplasia of the cervix need to be comprehensively examined, and if adenocarcinoma *in situ* (AIS) is the downstream lesion on the progression pathway, the optimal follow-up interval after AGC needs to be investigated in order to detect AIS. Furthermore, since the effectiveness of treatment for AIS is less satisfactory compared to the treatment for squamous cell carcinoma *in situ* (163–165), research about improved treatment or follow-up strategy after treatment of AIS is crucial. Similar research would also meet the needs of reducing increased risk following other abnormalities, especially focusing on the management after treatment, and the sufficient number of normal test results after abnormality or treatment to safely return women back to regular screening interval. The optimal management strategy might be different for different abnormalities, which warrants specific research focus, and particular attention in practice.

To improve prevention against adenocarcinoma, optimising management for AGC and AIS is not enough, as more than 30% cervical adenocarcinoma cases had only normal results in the recent screening round. Questions remain about whether the abnormality has been missed; if not, what is the reason for the rapid development, whether there is any indicator for rapid development such as infection of specific type of HPV, or immune characteristics; what is the

rationale of better prevention of HPV primary testing which was found in randomised trial (185), and whether it relies on specific triage technique or interval strategy for women with HPV positive results.

For concrete evidence of discontinuing screening at older ages, future studies can consider addressing a systematic evaluation of effectiveness of cervical screening over ages 45-70 years, including not only quantification of the preventive and down-staging effect against invasive cervical cancer, but also assessment of detection rate of precursor lesions, in relation to previous screening results. Moreover, although the effectiveness of cervical screening after age 60 was not found to be significant in women screened with normal results in their 50s according to our study, factors for residual risk of developing cervical cancer in this group still need to be thoroughly investigated, aiming for a most secure release of women from screening. Previous study found that women who have had carcinoma *in situ* at any point of life exhibited increased risk of cervical cancer especially at older ages (186). Other factors such as immune deficiency and history of HPV infection could also be examined. The collective evidence may clue us in an individualised screening strategy, which would acknowledge both efficiency and cost, and face the potential mode of healthcare in the future when abundant information from individual and environment becomes increasingly available.

Cervical screening programme in Sweden and many countries over the world is switching to HPV primary screening. Our studies presented not only a benchmark of the success and weaknesses from conventional screening, but also an evaluation framework that can be used for repeat performance comparable over time. In the near future, routine case-control audit needs to be carried out in HPV primary screening programme to examine whether implemented improvements work as expected.

After ten years' administration of HPV vaccination, vaccinated cohorts are gradually entering screening ages. Currently the cohorts reaching screening ages have low vaccination coverage, but in the near future for the cohorts who underwent the catch-up or even school-based vaccination, the adapted screening strategy warrants series of research, such as whether HPV primary screening can be performed under age 30 due to potential improved positive predictive value; could the interval be extended, etc. There are also ongoing discussions about population strategy according to coverage of vaccination by cohort versus individualised strategy referring to vaccination history of each woman. In addition, the screening attendance after being vaccinated in population deserves attention. Current evidence shows that the unvaccinated group participated less in screening compared to the vaccinated group, but it was from the cohorts with very low vaccine coverage thus would reflect impact of health consciousness (187). The scenario in birth cohorts undergone catch-up or school-based vaccination is of great interest. If the same pattern is followed, given the lower vaccine uptake in family of foreign-born and lower socioeconomic background, the social disparity in cervical cancer in the future might be enlarged, for which more effective approaches to reach these groups would become critical.

Although observational study is considered inferior to systematic review and randomised control trial in evidence hierarchy under the framework of Evidence Based Medicine, randomised trial is not always feasible in terms of ethics, time consumption and economic cost. Meanwhile, along with the rapid development of information technology, real-life data is becoming increasingly available with strengthened quantity and quality. This thesis work would serve as an attempt of utilising the large-scale observational data. In the future, exploration of sufficient use of real-life data with rigorous study design may efficiently benefit the evidence body for medical and healthcare decision-making.

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