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**CERVICAL CANCER:**

**INCIDENCE, SCREENING AND  
PROGNOSIS AMONG IMMIGRANT  
WOMEN IN SWEDEN**

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## **ABSTRACT**

Immigrant studies may help further our understanding of the aetiology of cervical cancer and improve its prevention. The overall aim of this thesis is to study the risk of cervical cancer among immigrant women in Sweden, their cervical screening attendance and their prognosis after cervical cancer diagnosis. Quantitative cohort study designs using data from population-based registers were carried out and analysed using Poisson regression and Cox proportional hazard models. A quantitative explorative design was used to analyse the results of focus group discussions (FGDs) according to the principles of content analysis.

Compared to Swedish-born women, immigrant women in Sweden had a higher relative risk of invasive cervical cancer, particularly women from Denmark, Norway and Central America; the opposite was true for immigrant women from Eastern Africa and South Central Asia. Moreover, age at immigration and follow-up time were important effect modifiers for the risk of cervical cancer among immigrant women (Study I). Average cervical screening attendance was 62% and 49% among Swedish-born and immigrant women, respectively, and was lowest among women who immigrated at older ages. Adherence to recommended screening intervals is very effective in preventing cervical cancer (Study II). The qualitative study using FGDs revealed a complex rationale for postponing cervical screening that included aspects related to immigration itself, including competing needs, organisational and structural factors, and differences in mentality (Study III). Non-Nordic immigrant women had a slightly lower risk of dying from cervical cancer than Swedish-born women. Both Swedish-born and immigrant women with symptomatic cervical cancer showed a 3 to 4-fold excess mortality compared to screening-detected cases. Both immigrant and Swedish-born women with low socioeconomic status had an excess risk of dying from cervical cancer (Study IV).

In conclusion, these results suggest a need for targeted prevention both among Swedish-born and immigrant women with low socioeconomic status and immigrant women at high-risk for cervical cancer, particularly those from Denmark, Norway and Central America, and specifically women who immigrate at older ages, during the first 10 years after their arrival. The results on cervical cancer prognosis indicate that there is equal access to health care in Sweden, irrespective of country of birth. The rationale of immigrant women in FGDs to postpone cervical screening reveals an opportunity to motivate these women to attend.

## LIST OF PUBLICATIONS

- I. Fatima Azerkan, Kazem Zendehdel, Per Tillgren, Elisabeth Faxelid and Pär Sparén.  
Risk of cervical cancer among immigrants by age at immigration and follow-up time in Sweden, from 1968 to 2004.  
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- II. Fatima Azerkan, Pär Sparén, Sven Sandin, Per Tillgren, Elisabeth Faxelid and Kazem Zendehdel.  
Cervical screening participation and risk among Swedish-born and immigrant women in Sweden.  
*International Journal of Cancer* 2012; 130: 937-947
- III. Fatima Azerkan, Catarina Widmark, Pär Sparén, Elisabete Weiderpass, Per Tillgren and Elisabeth Faxelid  
When life got in the way: How Danish and Norwegian immigrant women in Sweden reason about cervical screening and why they postpone attendance.  
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- IV. Fatima Azerkan, Jonas Hällgren, Kazem Zendehdel, Sven Sandin, Sanna Tiikkaja, Ruslan Fomkin, Elisabete Weiderpass and Pär Sparén.  
Cervical cancer prognosis by immigration status, cervical screening attendance and socioeconomic status in Sweden  
*European Journal of Epidemiology Submitted*

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## LIST OF ABBREVIATIONS

ASR	age-standardised incidence rate
CI	confidence interval
CIN	cervical intraepithelial neoplasia
FGD	focus group discussion
FIGO	International Federation of Gynaecology and Obstetrics
HPV	human papillomavirus
HR	hazard ratio
ICD	International Classification of Diseases
ICD-7	International Classification of Diseases, 7th Revision
IR	incidence rate
IRR	incidence rate ratio
NCSR	National Cervical Screening Register
Pap smear	Papanicolaou smear
PIN	Personal Identity Number
RR	relative risk
SIR	standardised incidence rate
TPR	Total Population Register

## Foreword

Something I cherish is the belief that knowledge and education comprise some of the best tools possible to help us manage our lives. My father, Abdellah Azerkan, always talked about the importance of studying and acquiring new knowledge during my childhood. He used to say, “Strive for knowledge, not for money”. Both of my parents immigrated to Sweden from Morocco for work reasons, my father in the 1960s and my mother in the 1970s.

My interest in research began when I was in high school, where I studied in the science programme for 3 years. After finalising my nursing and midwifery studies, I worked in various maternity wards, but it was during my years at Danderyd Hospital that I became very interested in how women give birth in low-income countries. So I approached a midwife colleague of mine that was also a PhD student, Marianne Velandia, with my questions about how to further my research ideas. Marianne recommended a researcher named Elisabeth Faxelid, who later became my co-supervisor. I contacted Elisabeth concerning my interest in the home-based delivery care system in a rural province called Chefchaouen in the Northern part of Morocco. Elisabeth accepted to be my formal supervisor and I applied for and was awarded funding from the Swedish International Development Cooperation Agency. I decided that this would be my pilot study, and that its outcome would determine whether or not I would pursue a PhD. It was a fantastic and very interesting time and a great learning experience. Unfortunately, my father, who accompanied me to the study site, had a stroke after 2 months of data collection. We were in the mountains very far from a hospital, and when we finally reached adequate health care facilities, it was too late; the damage caused by the stroke was permanent and his personality was never the same. This experience was so bittersweet that I decided not to continue with research. After some time, Elisabeth approached me asking if I would be interested in working in the epidemiology unit of the Swedish Institute for Communicable Disease Control (in Swedish: Smittskyddsinstitutet) on a project concerning the evaluation of Swedish patients who contracted gonorrhoea and/or chlamydia in Thailand, and later had been tested for HIV in Sweden. This was the first time that I worked in the field of epidemiology, and I found it very interesting. I met Dr Johan Giesecke, the chief of the epidemiology unit, who inspired me to continue in the field of research. I decided that my father’s fate should not be in vain and that I would strive for a PhD, the highest degree in academia. My parents, who were illiterate when they came to Sweden as immigrants, were given great opportunities to learn both Swedish and Arabic, which says something about what a great country Sweden is. The combination of subjects: immigrant status, cervical cancer and research,



was very interesting to me, and it was with gratitude that I learned of my acceptance to the PhD programme, with financial support from the Health Care Sciences Postgraduate School at Karolinska Institutet and the Swedish Research Council...and I never looked back.

This thesis is dedicated to my father Abdellah and my mother Aicha.

# 1 INTRODUCTION

Studies of disease in immigrant populations offer insights into the relative importance of environmental factors versus inherited predispositions in cancer aetiology by comparing disease risk in immigrant populations living in different physical and social environments (1). Cervical cancer is highly associated with persistent infection with sexually transmitted human papillomavirus (HPV), which is a necessary cause of invasive cervical cancer (2-4). Due to the great variation in the proportion of women infected with HPV, and the distribution of HPV types across populations (5), studies on immigrant populations may help identify risk factors, and identify which groups of immigrants constitute high-risk groups in different societies. This knowledge is essential for any cervical cancer prevention programme (6). About 530 000 new cases of cervical cancer are estimated to occur annually worldwide, making it the third most common cancer among women. Cervical cancer is also the fourth most common cause of cancer death among women worldwide, responsible for 275 000 deaths in 2008, of which about 88% occurred in middle-to-low-income countries.

On a global scale, cervical cancer is still considered a serious public health burden. Global cancer statistics show a clear and striking variation in the incidence of cervical cancer by geographical region. High-risk regions include Eastern and Western Africa, Southern Africa, Middle Africa, South Central Asia, and South America. Middle- and low-income countries carry more than 85% of the global burden of cervical cancer (7). The differences in the incidence of cervical cancer by geographical region are mainly due to the establishment of screening programmes in high-income countries. Some differences reflect changing data sources and improved quality of cancer registers (8). The main determinants of the risk of cervical cancer are HPV infection and lack of effective cervical screening. Apart from cervical screening, the effect of external factors are minor compared with the extremely high primary risk conferred by infection with the most carcinogenic HPV types (9).

Most immigrants have a lower risk of cervical cancer and of mortality from cervical cancer in their host country than in their countries of birth (10). Factors associated with persistent HPV infection are HPV type, sexual behaviour, age, HIV infection and history of *Chlamydia trachomatis* infection. Furthermore, several studies have found that smoking, multiparity, use of oral contraceptives and genetic susceptibility increase the risk of dysplasia and cervical

cancer. As for prognosis, immigrant status has been shown as a risk factor for cervical cancer diagnosis at a more advanced stage (11-17).

In 2006, it was estimated that around 95 million women, 1.5% of the world's population, lived outside their country of birth. The magnitude and complexity of this international phenomenon make immigration an important force in a country's development and a high-priority issue for high-, middle-, and low-income countries. Most immigrant women are of reproductive age, which adds to the importance of the role of immigrants in a society (18).

At present, Sweden has a total population of about 4.8 million women, 15% of whom are immigrants (19). Immigrants are a heterogeneous group of people, with different cancer risks (20). Research on immigrant women diagnosed with cervical cancer in countries with high-quality universal health care is scarce. Theoretically, in these countries a standardised quality of care is offered to all legal residents. This thesis consists both of register-based cohort studies and a study based on focus group discussions (FGDs), and explores the risk of cervical cancer among immigrant women in Sweden, their cervical screening attendance and their prognosis after being diagnosed with cervical cancer. Additionally, the effect of follow-up time and age at immigration on cervical cancer has been assessed.

## **2 BACKGROUND**

### **2.1 CERVICAL CANCER**

Invasive cervical cancer is a malignancy that occurs in the epithelium of the cervix. There are three recognised general histological categories of cervical cancer: squamous, glandular, and other (21). Squamous cell carcinomas account for about 80% of cervical cancers followed by adenocarcinomas. Infection with high-risk HPV types is the necessary cause of both squamous and glandular cervical cancer (2-4). It has been estimated that HPV is also associated with 90% of anal cancers, and a little less than 50% of other cancers, such as oropharyngeal, penile, vaginal and vulvar cancers (22).

Cervical cancer usually arises from the cervical transformation zone. Persistent HPV infection can cause changes in cervical cells; these changes are also known as the precancerous lesion cervical intraepithelial neoplasia (CIN) (9). The transformation zone is an area of the cervix that is uniquely susceptible to HPV-induced neoplastic transformation (21). Both squamous cell carcinoma and adenocarcinoma are preceded by distinctive precursor lesions (23). The dynamic character of the transformation zone is an important feature in its susceptibility to cancer. Indeed, although infection with carcinogenic HPV types is equally common in cervical and vaginal specimens (24), cervical cancer is the third most common cancer in women worldwide, whereas vaginal cancer is exceedingly rare (25).

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

##### *Human papillomavirus types*

Over 100 HPV types have been identified, about 40 of which are known to infect the genital tract (26). Genital HPV types have been categorised into low-risk and high-risk types. The low-risk types confer only a negligible risk of cancer, two of which are mainly found in genital warts (HPV6 and 11 responsible for 90% of genital warts) (27). High-risk HPV types, on the other hand, are frequently associated with invasive cervical cancer. The two most carcinogenic HPV types are HPV16 and 18, which are responsible for 70% of cervical cancer and about 50% of CIN3 (28). As such they are primary targets for HPV vaccines (29).

##### *Human papillomavirus infection*

HPV is the world's most common sexually transmitted infection (STI). Genital HPV types are transmitted through skin-to-skin contact during sexual activity and can apparently ascend to

the cervix following infection at the introitus (30). Other HPV transmission routes include vertical transmission from mother to infant, the risk of which is greater after vaginal than caesarean birth (31). Cervical carcinogenesis is a multistep process that begins with HPV infection, and then moves to viral persistence, progression of a clone of persistently infected cells to a precancerous lesion, and finally invasion, which can be reproducibly distinguished. The spontaneous clearance of HPV infection is common. Regression of precancerous lesions to normality does also occur, though it is less frequent (9).

It is likely that most women worldwide have been infected with at least one, if not several HPV types during their sexual life (32). Consistent condom use among partners of newly sexually active women, suggest that condoms do not eliminate the risk of male-to-female genital HPV transmission, though they may reduce it (33). A preliminary association between condom use and decreased persistence or progression of HPV infection has been observed in a few studies (34;35).

Age at first sexual intercourse can be viewed as a proxy for age at first HPV infection, and therefore as a very important variable in cervical cancer development. There is a large peak of cervical HPV infections immediately following first sexual intercourse. As the average age at first sexual intercourse varies by culture, this also affects the average age at which women reach subsequent stages in the carcinogenic process (9). Most HPV infections clear spontaneously within 2 years without ever causing precancerous lesions, whereas the 10% of infections that persist for 2 years or more are highly linked to the development of precancerous lesions. Precancerous lesions are usually detected around 25-30 years of age in regions with cervical screening, or about 10 years after first sexual intercourse (9).

#### *From precancerous lesions to cervical cancer*

There are different grades of severity of precancerous lesions, which are often asymptomatic and discovered only by cytological examination of a Papanicolaou smear (Pap smear) (36). CIN2 is a moderate form of precancerous lesion; CIN3 includes both severe dysplasia and carcinoma *in situ* (meaning that upon histological examination the cancer has not broken through the basal epithelium) prior to invasive cervical cancer. CIN2 can be caused by non-carcinogenic HPV types rarely found in cancer and has substantial regression potential, but it is treated in most regions to provide a safety margin against cancer risk (37).

The majority of women infected with HPV will clear the infection spontaneously, in the same fashion that most precancerous lesions will regress. If effective treatment is not available or administered, precancerous lesions that are not detected by screening or do not regress on their own will not only progress to invasive cancer, but can expand to blood and lymphatic vessels and become metastatic (38). Crude estimates from early studies have suggested a 20-30% risk of progression from precancerous lesions to cervical cancer over a 5-10-year time frame (39). Apart from age and HPV type, the risk factors for invasion are unknown, but HPV16, 18, and 45 are found in a higher fraction of cancers than precancerous lesions compared to other HPV types (28).

### 2.1.2 **Worldwide distribution of human papillomavirus types**

Globally, cervical cancer accounted for 9% of new cancer cases and 8% of cancer deaths among women in 2008. The prevalence of cervical HPV infection is closely related to the corresponding risk of cervical cancer in a given country (40-52), and HPV prevalence varies greatly across populations (5). Globally, it has been estimated that around 10% of women with normal cytology are infected with HPV. However, a broad range of estimates (6.1-35.5%) have been documented, depending on the HPV testing method, study size, age groups, and geographical regions studied (53). One meta-analysis comprising data from more than 1 million women in 59 countries showed that the prevalence of genital HPV infection among women with normal cytology ranges from 1.6% to 41.9% (54). The estimate varies by geographical region and age. African and Latin American regions showed higher average HPV prevalence than European, Northern American, and Asian regions.

A pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys reported regional variation in HPV type distribution among women without cytological abnormalities, and showed a nearly 20-fold variation in overall HPV prevalence across different geographical regions. The highest overall HPV prevalence was observed in sub-Saharan Africa, and the lowest was in Europe, but the variation in HPV prevalence across geographical regions was smaller for HPV16 than for other high-risk and low-risk HPV types. HPV prevalence was approximately five times higher in sub-Saharan Africa than in Europe, with intermediate prevalence in South America and Asia. In all regions HPV16 was twice as frequent as any other high-risk type, except in sub-Saharan Africa, where HPV35 was equally common. HPV-positive women from Europe and South America were significantly more likely to be infected with HPV16 than were women in sub-Saharan Africa, although overall HPV

prevalence in sub-Saharan Africa was higher. The proportion of HPV-positive women infected with HPV18 was similar across regions, with some heterogeneity in South America and Europe. HPV35, 45, 52, 56 and 58 were all more common in HPV-positive women in sub-Saharan Africa than those in Europe (5).

The complex geographical and biological interplay between different HPV types and host immunogenetic factors (e.g., human leukocyte antigen polymorphisms) could be related to differences in type-specific HPV prevalence (55). For example, HPV16, which is considered to be the most carcinogenic HPV type, seems to be less influenced by immune status than other HPV types (56). This finding, coupled with impairment of cellular immunity (e.g., due to chronic cervical inflammation, parasitic infection, malnutrition, and, more recently, HIV), may contribute to a higher penetrance of HPV types other than HPV16 (5).

### 2.1.3 Cervical cancer: aetiology and risk factors

HPV infection and lack of effective screening are major components in the risk of cervical cancer. With the exception of cervical screening, external factors have a small impact on the risk of cervical cancer compared to the extremely high primary risks conferred by infection with the most carcinogenic HPV types (9). Most HPV infections are transient, and the proportion of women with persistent HPV infection that eventually develop cervical cancer is rather small. Therefore there may be other factors that increase the risk of developing cervical cancer. HPV infection is associated with sexual behaviour. Although cervical cancer affects many women later in life, sexual behaviour early in life is thought to play a significant role in cervical cancer development (57).

Early age at first sexual intercourse (21,58) and a high lifetime number of sexual partners for a woman or her partners are considered risk factors for cervical cancer (21). First infection with HPV often occurs soon after first sexual intercourse (59), making early age at first intercourse a reasonable proxy for early age at first exposure to HPV (60).

One of the explanations for the association between early age at first sexual intercourse and risk of cervical cancer is that it may affect the cervix at a time when it is still developing. Exposure to carcinogens such as HPV shortly after menarche has been reported to be a likely factor in the development of invasive cervical cancer later in life (61). Another explanation for this association may be that it is correlated with other high-risk behaviour later in life, for

example a lower tendency to practice safe sex (62). The International Collaboration of Epidemiological Studies of Cervical Cancer collected data on sexual behaviour from 21 national or international epidemiological studies and found a gradually increasing risk with earlier age at first sexual intercourse ( $\leq 14$  years of age versus  $\geq 25$  years of age), controlling for lifetime number of sexual partners, parity and age at first full-term pregnancy (63).

Male circumcision has been shown to decrease the risk of HPV infection and cervical cancer in the female partner. This effect was strongest in women whose male partners engaged in sexual practices known to increase the risk of exposure to HPV, for example having sexual intercourse before 17 years of age, having had six or more sexual partners in one's lifetime, and having a history of contact with sex workers (64).

Other risk factors for cervical cancer have also been considered, such as smoking (65), having more than five full-term pregnancies, and use of oral contraceptives for 5 years or more (66). The reported 2.5 to 4-fold increase in risk for these co-factors are in general highly consistent. The presence of antibodies against *Chlamydia trachomatis* or herpes simplex virus type 2 also modifies the risk of progression to cervical cancer (21,21). HPV-positive women with low socioeconomic status might be at higher risk for precancerous lesions (67). With regard to nutritional co-factors, there are some indications of a possible protective association between higher folate and the risk of precancerous lesions (68). Furthermore, vitamin A deficiency is known to be associated with carcinogenesis in humans (69). Findings from a meta-analysis indicated that vitamin A intake and blood vitamin A levels can decrease the risk of cervical cancer. However, these findings need to be confirmed in large randomised clinical trials of vitamin A supplementation (70).

#### **2.1.4 Immigrant registration in Sweden**

Immigration is a major component of population change in Sweden (71). To be registered as an immigrant, the person immigrating must intend to stay in Sweden for at least 1 year. Likewise, to register as an emigrant the person emigrating must intend to reside abroad for at least 1 year. Immigrants from outside the Nordic countries must obtain a residence permit to be registered as immigrants. The time of immigration is defined as the actual day of immigration if it is reported to the Population Register within 1 week of immigration. However, if the immigration is reported after 1 week, it is registered to have taken place the day it is reported.



In the Population Register each immigrant is assigned a Personal Identity Number (PIN) by which they can be identified. Information from the Swedish Migration Board on people who have been granted residence permits in Sweden is shared annually with Statistics Sweden. The information includes the reason for immigration and the date of immigration (72).

A residence permit is generally given if asylum is granted. A residence permit gives the right to live and work in Sweden. Anyone with a permanent residence permit can also be entered in the Population Register, which is managed by the Tax Agency. Those included in this register are then included in the Swedish Total Population Register (TPR), managed by Statistics Sweden. It is not until the person is registered in the TPR that they are considered “immigrated” in national statistics. Some of the most used register variables for immigrants are PIN, place of residence, sex, age, citizenship, country of birth, and year of immigration (72).

#### **2.1.5 Human genetic variation, race and ethnicity**

The patterns of human genetic variation show that 5-15% of genetic variation occurs between large groups living on different continents, with the remaining majority of the variation occurring within these groups (73,74). Therefore, the rationale of using race to distinguish these genetically different population groups has been widely questioned (75-78). Moreover, a person’s self-ascribed race can differ from assigned race (79). The problems surrounding the word “race” became increasingly apparent during the 20th century, so researchers began to employ the term “ethnicity” (80).

Ethnicity typically emphasises the cultural, socioeconomic, religious, and political qualities of a population rather than their genetic ancestry. It can comprise language, diet, religion, dress, customs, kinship systems, or historical or territorial identity (81). Ethnic groups can share a belief in a common ancestral origin (81), which also can be a characteristic of a racial group. Furthermore, ethnic groups tend to promote marriage within the group, which creates an expectation of biological cohesion regardless of whether that cohesion existed in the past (82). Ethnic groups may come into existence and then dissolve as a result of broad historical or social trends. Individuals might change ethnic groups over the course of their life, or identify with more than one group. A researcher, clinician, or government official might assign a certain ethnicity to an individual that is quite different from the one that person would acknowledge (79). Also, ascribing an ethnic identity to a group can imply a much greater degree of uniformity than actually exists (83).

Despite attempts to distinguish “ethnicity” from “race,” the two terms are often used interchangeably (84). Individuals can be assigned to population categories in many different ways, and which way is the most appropriate is a question that is still being investigated (85,86). In public health, race and/or ethnicity or other equivalent terminology has been traditionally used for several different purposes, such as to describe vital and health statistics, as a risk indicator for health outcomes, to improve the delivery of health services, as a marker of unmeasured biological differences, and as a proxy for unmeasured social indicators (87). In scientific studies the applied proxy for ethnicity is highly dependent on the availability and completeness of information. However, despite its validity limitations with regard to cultural and ethnic identity, country of birth is the most commonly used and accepted proxy, and is therefore used in this thesis (88). Country of birth is as relevant an indicator for exposure to risk factors as ethnicity, but the advantage with country of birth is that it doesn’t change over time and can usually be determined with good precision (unlike ethnicity). Except for genetic characteristics, factors related to culture can be accessed by ethnicity and country of birth (1).

#### **2.1.6 Cultural factors in the epidemiology of disease**

Cultural factors such as specific beliefs and behaviours, can cause, contribute to, or protect from disease. Cultural factors are not independent or isolated factors, and should be placed in their specific contexts, which may include poverty, social inequality and gender relations. Economic situation, marriage patterns, sexual behaviour, contraceptive patterns, pregnancy, and childbirth practices are all cultural factors that may be of relevance in epidemiological studies. Cervical cancer is a well-documented example of the role of these factors, first and foremost the role of sexual norms and behaviour in the distribution of a disease (89).

Various studies have shown that cervical cancer is extremely uncommon among nuns and common among sex workers. It was originally thought that a woman’s sexual behaviour alone could determine her risk of cervical cancer. However, in the 1980s Skegg et al (90) showed that in some communities, such as Latin America, a woman’s risk of getting the disease depends less on her sexual behaviour than on that of her husband or partner. Therefore sexual behaviour in the whole society is of interest, including that of men (90). Sexual behaviour includes age at first sexual intercourse, whether premarital or extramarital sexual relations are encouraged or forbidden, whether these sexual norms apply to men, to women or both, whether contact with sex workers is socially acceptable, which sexual

practices are regarded as acceptable, and whether there are taboos on sexual intercourse during pregnancy, menstruation, lactation, or puerperium. Although, cultural beliefs and practices play a role in a woman's risk of cervical cancer, it is important not to overemphasise their importance (89).

### **2.1.7 The global movement of people: the immigrants**

There is an on-going global movement of people, ideas, services and ideologies in the world (89), and this thesis focuses on immigration and immigrants' countries of birth. Large numbers of people are moving across the globe in search of work, refuge, pleasure, or a new life. According to the International Migration Report, more people live outside their country of birth today than ever before in history, and these numbers are expected to continue to rise. The number of immigrants worldwide reached almost 191 million in 2005, which was 3% of the world population. There is an increasing concentration of international migrants in high-income countries; in 2005 60% of the world's immigrants were in high-income countries. Globally, almost half of all immigrants are women. Immigrants are increasingly concentrated in certain regions, specifically North America, Asia and Europe (91). Large population flows between neighbouring countries is also common. For example, between Mexico and the United States, between countries in North Africa and Spain, and between countries in Eastern and Western Europe (92). This is also the case between Sweden and Finland, Denmark, and Norway (93).

Many immigrants leave their countries of birth voluntarily in pursuit of better economic prospects, higher standards of living, improved access to education and health care, and a better future. Others are forced to flee due to war, oppression or natural disasters (89). By 2005, the total number of refugees was approximately 9.2 million (91). The 1951 Geneva Convention defines a refugee as a person who is at risk for oppression because of race, religion, nationality, or political views, and states that being a refugee is grounds for granting asylum. Moreover, many countries acknowledge "alternative protection" on humanitarian grounds, which offers protection to people who are not refugees (89).

Most host countries allow family reunification for immigrants under certain conditions. Internationally, the legal basis for family reunification is an individual's right to family life. However, what constitutes family reunification and the conditions under which it is permissible vary across countries. Generally, a fundamental distinction is made between

temporary migrants and those with long-term residence. Aside from highly skilled workers, foreigners granted temporary permission to stay, work, or study are usually not allowed to bring in their families (94). While most women immigrate as a part of family units, there are increasing numbers of women immigrating independently (89).

### **2.1.8 Influence of immigration on HPV infection**

Immigrants comprise a highly mobile labour force, and widening income differences between nationals and immigrants leads to increasing disparities in health and living conditions. Employment-related immigration has been characterised as a major contributor to the transmission of STIs (95). The vulnerability of immigrant populations to STIs can be explained by factors such as immigrant demographics, lack of skills, knowledge and training, restrictive policies on acquiring legal residence status and access to health care services, and high levels of perceived stigma of STIs and at-risk groups (sex workers). Reduced pressure to conform to the social and sexual norms of the country of birth is a consequence of immigration, and may further erode traditional prohibitions against non-marital sex, potentially predisposing immigrants to exposure to STIs, including HPV. Immigrant men and women may be more likely to engage in high-risk sexual behaviour, such as contact with sex workers (95,96).

Separation from family and partners, isolation and loneliness, can encourage people to engage in high-risk sexual behaviour. The mobility of immigrants itself makes it harder to reach them with prevention information, condoms, counselling and testing services or care. Immigrants are often socially, culturally, economically and linguistically marginalised, which also increases the barriers to health care access (97).

Immigration therefore offers an opportunity for sexual “bridging”, i.e., sexual connections that are formed between members of high and low prevalence sub-populations, and provides a channel for infection between them. The impact of immigration on sexual behaviour and STIs has been documented (98-104). A study in Spain showed that HPV was detected three times more frequently among immigrant women compared to non-immigrant women in the host country, leading the authors to conclude that an immigrant women’s risk of HPV infection corresponds to the risk in their countries of birth (98). Furthermore, immigration has been shown to increase the practice of extramarital sex (102). Immigrants more likely to contract a STI than non-immigrants (104), are more likely to have three or more casual sexual

partners and unprotected sex (103). However, it is neither immigrants nor immigration *per se* that increases immigrants' risk of contracting STIs, but the trying conditions and hardships that many face after emigrating from their country of birth (105-107).

### 2.1.9 Sexual behaviour

Sexual behaviour is an important determinant of STI transmission, and contributes substantially to the burden of STI-related disease (108-110). Despite the generalisations and trends that can be observed across countries, one of the most striking elements of sexual behaviour is its substantial heterogeneity both between and within countries, and even within local populations. These regional variations in sexual behaviour emphasise the powerful role of environmental factors such as poverty, education, and employment in shaping sexual behaviour, and their consequences in regard to sexual health (96).

### 2.1.10 The immigrant population in Sweden

In 2011, 15% of the population of Sweden was born abroad (93) compared to 4% in 1960 (71). Sweden opened its borders to immigrants in 1930. Immigration to Sweden can be divided into three phases, the first of which occurred at the end of Second World War (1945-1960). The immigrant flow consisted mainly of refugees from the Baltic States and Eastern European countries. The second phase occurred in the 1950s and 1960s, when Swedish industries and the public sector were in need of labour. During this period immigrants came predominately from Sweden's Nordic neighbours, Finland, Denmark and Norway, though there were also some from other parts of Europe. When labour force immigration peaked in 1969-1970, the trade unions demanded more restrictive immigration laws. Thereafter, immigrants needed residence, a work permit and a place to live before they immigrated to Sweden. The third phase occurred in 1970-1985, and can be seen as a transitional phase from labour immigration to refugee immigration and family reunification. Since the 1980s immigration to Sweden has been dominated by this third phase. Sweden has accepted large groups of refugees from a number of countries, such as Chile, Iran, Lebanon, Poland and Turkey. Since the beginning of the 1990s large numbers of people have immigrated to Sweden from the former Yugoslavia due to conflicts. The largest groups that immigrate for family reunification are from Somalia and Thailand (93).

It is estimated that one-third of Sweden's immigrants are from Nordic countries, one-third from the rest of Europe, and the last third from non-European countries. The majority of Sweden's

immigrants have lived there for more than 10 years, and around 40% have lived there for more than 20 years (93). Immigration between the Nordic countries is dependent on the economic situation. (72)

#### 2.1.11 **Socioeconomic status**

Socioeconomic status is linked to an extensive range of health problems, including cancer (111). Traditionally, socioeconomic status has been determined using education level, income, and occupation, all of which have different relationships with various health outcomes (112). Education level is one of the most basic components of socioeconomic status, since it shapes future occupational opportunities and creates earning possibilities. It also provides knowledge and life skills that allow better-educated people to increase their access to information and resources, and thereby promote their own health (113). Higher income provides means for purchasing health care, better nutrition, housing, schooling, and recreation. Independent of actual income levels, the distribution of income within countries has been linked to mortality rates (114). Although the association between income and health is stronger at lower income levels, the effect of income persists above the poverty level (115).

Occupational class is a more multifaceted variable. One aspect is whether or not one is employed, since individuals who are employed tend to be healthier than those who are unemployed (116,117). However, it must be kept in mind that some of this association is a function of the “healthy worker” effect (112). Among the employed, occupations differ in their prestige, qualifications, rewards, and job characteristics, and each of these indicators of occupational class is linked to risk of mortality (118).

It has been estimated that socioeconomic status underlies 80% of premature mortality, and that health behaviour and lifestyle accounts for about 50% of this (112). Regarding cervical cancer, it has been indicated that differences in socioeconomic status can partly explain differences in HPV prevalence, and that men's sexual behaviour, particularly contact with sex workers, might be a major contributor to the higher HPV prevalence among the poor (119). Differences in screening practices by socioeconomic status tend to decrease when participation is encouraged, cultural and economic barriers are removed, and social support is offered. In high-income, and middle-to-low-income countries alike, women with low socioeconomic status have a higher than average risk of cervical cancer, and a lower than average participation in cervical

screening (120). In Sweden, the income discrepancies are relatively small and the country has a high GDP (121).

#### **2.1.12 The health care system in Sweden**

The health care system in Sweden is highly decentralised and the major funding sources are local and national taxes. Privately-financed health care also exists, but remains marginal. Sweden is a country with high-quality universal health care and as such it theoretically offers a standardised quality of care to all legal residents (122). Health care delivery is dominated by hospitals and primary care is given in health centres. In addition to county hospitals, there are tertiary university hospitals in each of the six health care regions of Sweden that provide highly specialised services and are also teaching hospitals. Within each of the health care regions, an oncological centre coordinates cancer care resources, establishes regional cancer registers and promotes a series of cancer care and prevention initiatives. There is a strong commitment to equal access to care in Sweden, based on the 1982 Health Care Act. To assure all cancer patients equal care, ‘cancer care programmes’ for almost all of the different types of cancer have been developed, based on standardised management protocols. Nationwide cervical screening is available in Sweden (123). According to the recommendations of the Swedish National Board of Health and Welfare, women in Sweden are advised to undergo cervical screening by Pap smear test conducted by the counties (124).

A report from the Social and Cultural Planning Office of the Netherlands compared health care in Australia, Canada, New Zealand, the United States, and 25 European Union Member States. Many different indicators were used: waiting time for non-acute care, public confidence in health services, and health status (a combination of life expectancy, quality-adjusted life years as a percentage of life expectancy, infant mortality, and subjectively assessed health). The health care systems in France, Sweden, and Austria ranked highest (125). However, with regard to public confidence in health care services, Sweden was middle-ranking in comparison with other European Union Member States. There have been indications that reliable information on public and patient perception of quality of care, and on the ability to receive individualised care, is lacking. Inadequate continuity and fragmentary care with long waiting lists, resulting in anxiety and uncertainty have been reported (126).

### 2.1.13 Cervical cancer among immigrants

#### *Immigrants from Nordic and other European countries*

Immigrants from Nordic countries in Sweden (127) have differing risks of cervical cancer, with Danish and Norwegian women having an increased risk (standardised incidence rate (SIR) 1.64 and 1.33, respectively) and Finnish women having a decreased risk (SIR 0.88) compared to Swedish-born women(128). One possible explanation is the difference in HPV prevalence between the country of birth and the host country (129). For example, there have been indications that HPV prevalence in Danish-born women with normal cervical cytology is three times higher than that in Swedish-born women (130), and the risk of cervical cancer has been shown to be higher in Denmark (ASR=10.1) than in Sweden (ASR=7.0) and other Nordic countries (Finland=3.9, Norway=9.6, Iceland=7.9) (131). Immigrants from former Yugoslavia and Eastern Europe residing in Sweden have shown an increased risk of cervical cancer (SIR 1.21 and SIR 1.35, respectively). A high proportion of Eastern European immigrants with normal cervical cytology and HPV infection (56.1%) was observed in Italy (132).

#### *Immigrants from Africa*

In Africa, about 25% of women in the general population are estimated to be infected with HPV (130). Higher rates of cervical cancer were found among Jewish women of North African origin in Israel compared with all other ethnic groups in the country, and the study also indicated that this observation is valid for the second generation of North African women. The authors suggested that the similar incidence rates (IRs) seen in both generations may be attributed to genetic factors that do not change within one generation (133), therefore it has been suggested that genetic factors may modify the risk of cervical cancer development after exposure to a carcinogenic agent. However, a meta-analysis on the association between the polymorphism and cervical cancer in different populations showed inconsistent results (134).

Although cervical cancer is proportionately the most common cancer among women in sub-Saharan Africa and other high-risk geographical regions (135), a significantly decreased risk has been observed among African immigrants in Sweden (standardised incidence rate, SIR 0.32, 95% confidence interval, CI 0.10-0.74). The authors suggested that this was most likely due to the fact that many African women who immigrated were married, and married women have a decreased risk of cervical cancer (136-138).



One study found no significant difference among African immigrants in France compared to French-born women (139). In another study, cervical cancer mortality was observed to be significantly lower among Eastern African immigrants in England and Wales compared to that in the English- and Wales-born population (relative risk, RR 0.4, 95% CI 0.2-0.7) (140). In both these studies (139,140) it was suggested that the results may have been due to the relatively higher socioeconomic status of these African immigrants. In Italy, a high burden of HPV infection has been reported among immigrants from Western Africa, 55.5% compared to 19.4% among Italian women with normal cytology. It was suggested that the higher prevalence may reflect either a high viral prevalence in their country of birth or the fact that migrant women attending gynaecological clinics are strongly selected to be at high-risk for STIs (132).

#### *Immigrants from Asia*

A study of cancer registry data in the United States, a nearly five-fold increased risk of cervical cancer has been observed among immigrants from Southeast Asia compared to non-Hispanic white women. The study also showed that the excess invasive cervical cancer burden appears to be concentrated among women 40 years of age and older (141). Furthermore, a report from the state of California showed an incidence of cervical cancer among Filipino women (age-standardised incidence rate, ASR=8.5/100 000) that was higher than that in whites (ASR=7.3/100 000), although not as high as that among Korean (ASR 11.4/100.000) and Vietnamese women in California (ASR= 14/100.000) (142).

#### *Immigrants from South and Central America*

Higher age-adjusted IRs and mortality rates for cervical cancer have been reported in the Hispanic population in the United States compared with white women (143). However, in a more recent population-based study, Hispanic patients had a 26% decreased risk of cervical cancer mortality compared to white women (after adjustment for age at diagnosis, histology, stage and treatment). This significant increase in survival is thought to reflect the young age at diagnosis of Hispanic women, which appears to confer a significant prognostic advantage. The equally high rates of cervical screening reported among Hispanics and non-Hispanics may also reflect better health care access (144). Because younger women are less likely to have comorbid conditions than older women, curative treatment is more often recommended for younger women (145).

Immigrants from South and Central America residing in Italy have shown an HPV prevalence of 62.5% compared to 19.4% among Italian-born women with normal cytology. High-risk HPV types accounted for 80% of HPV infections among women from South and Central America. This prevalence correlates very well with the high incidence of cervical cancer among women born in South and Central America and the Caribbean (60.5 per 100 000) (146). A similar increased prevalence of high-risk HPV types was observed in Latin American women in Spain compared to Spanish-born women, and resembled more the prevalence of their countries of birth (98).

Incidence of cervical cancer was significantly higher among Caribbean immigrants in England compared to English- and Wales-born women (RR 1.3, 95% CI: 1.1-1.5) (140). In 2007-2009 Haitian immigrant women residing in Miami-Dade County had the highest IRs of cervical cancer in South Florida (34 per 100 000 women), nearly four times higher than the incidence reported for the Miami metropolitan area overall (9 per 100 000 women). The prevalence of HPV and high-risk HPV infection was not elevated among women in Little Haiti relative to the general population of the United States. However, differences in study populations, statistical uncertainty, and HPV sampling and detection methods likely account for some of the differences (147).

#### **2.1.14 Treatment of precancerous lesions and cervical cancer**

Once a diagnosis of invasive cancer is set, a stage must be assigned according to the International Federation of Gynaecology and Obstetrics (FIGO) classification to indicate the clinical extent of disease. The stage of cervical cancer helps determine treatment and prognosis (148). Most of these abnormalities clear without treatment, making aggressive treatment unwarranted (149). Nevertheless, these abnormalities cannot be overlooked, as most precancerous lesions and cancers are diagnosed in women with equivocal or mildly abnormal cytology (150). In many countries fertility-sparing treatments for CIN are preferred, such as limited excision of the transformational zone and cryotherapy (151). The dominant method of treatment in Sweden and globally is loop electrosurgical excision procedure, or large loop excision of the transformation zone (152).

Previously the preferred treatment for early-stage invasive cervical cancer was radical hysterectomy (removal of the uterus, cervix, parametria, cuff of vagina and utero-sacral ligaments). However, recently minimally invasive surgery has become an option for younger

women with early-stage cervical cancer who are considering future pregnancy. These fertility-preserving procedures consist of either radical conisation, or removal the cervix, while leaving the uterus intact (153). The current recommendation for the treatment of microinvasive adenocarcinoma is the same as for squamous cell carcinoma.

Radiotherapy is still the primary choice for women with advanced-stage cervical cancer (stage II-IV). Standard radiotherapy consists of radical external beam radiation and brachytherapy (21). Several randomised studies have shown improvement in survival when radiotherapy is combined with chemotherapy, usually cisplatin chemotherapy (21,154). The single most important prognostic factor for long-term survival is the clinical stage of disease at presentation. Advancing age also impacts survival rates. Stage IA disease presents a range of 5-year survival rates from 90-95%, whereas the rates are 80-85% for stage IB, 50-65% for stage IIA, 25-35% for stage III and <5% for stage IV disease (148). Most deaths due to cervical cancer worldwide occur in middle-to-low-income countries which is mainly due to poor access to, and poor quality of cervical cancer prevention and control programmes (155). Most women in low-income countries present with advanced-stage disease, which is often either untreatable, or suitable only for palliation (156).

#### **2.1.15 Prognosis of cervical cancer among immigrant women**

Immigrant status has been shown to be a risk factor for advanced-stage cervical cancer (11-17). However, improved prognosis among Korean, Vietnamese and Filipino women compared to non-Hispanic white women in the United States has recently been shown (157), which could not be explained despite adjustment for well-established factors that influence prognosis, such as age, stage, socioeconomic status and treatment. Another study from the United States showed no association between race and medical funding on cervical screening attendance, stage at diagnosis, or survival (158).

#### **2.1.16 Prevention of cervical cancer**

##### *Prevention strategies*

There is no universal solution regarding the best sexual health intervention. Most health education programmes generally lead to a change in knowledge and attitudes, but have less effect on sexual and contraceptive behaviour (159). Hence, the development of HPV vaccines may be a major stride in cervical cancer prevention. Two HPV vaccines are currently available: a bivalent vaccine that protects against HPV16 and 18, and a quadrivalent vaccine that

protects against HPV16 and 18, as well as two non-carcinogenic types that cause genital warts (HPV6 and 11). HPV vaccination has been introduced in Sweden and other Western countries as primary cervical cancer prevention (160). However, the vaccines do not eliminate the need for cervical screening later in life, as 30% of all cervical cancer cases are due to HPV types other than 16 and 18. Furthermore, the public health benefits of HPV vaccines offer an opportunity to address disparities in cervical cancer incidence, though a substantial decrease in the burden of cervical cancer will only be attained if HPV vaccines are accepted and used by at-risk populations (161).

### *Screening*

Secondary prevention of cervical cancer involves cervical screening, the goal of which is to detect and treat abnormal or precancerous cervical lesions before they progress to invasive cervical cancer. Indeed, early detection of precancerous lesions improves the chances of successful treatment, and is important if cervical cancer mortality is to be reduced (162,163). The “cervical screening programme” will be referred in this thesis rather than “cervical cancer screening programme”. The incidence of squamous cell carcinoma has been effectively reduced since the introduction of cytology-based cervical screening, although there has been no reduction in the incidence of adenocarcinoma (162,163). Organised cervical screening also led to a significant decrease in cervical cancer mortality (21), including adenocarcinomas.

Cervical screening programmes have been established in most high-income countries. Cervical screening is not only about having a Pap smear (164), but also includes triage of equivocal results, colposcopically-guided biopsies of abnormal screening results, decisions on whether or not to treat, which treatment to apply, and post-treatment follow-up (including eventual return to routine screening intervals when appropriate). Cervical cancer prevention programmes vary widely by country (9). Cervical screening was introduced without formal evidence of efficacy from randomised trials, but thanks to observational studies that, over time, have provided convincing evidence that a large proportion of cervical cancer can be prevented (6,21,163,165).

In Sweden, population-based cervical screening was introduced during the 1960s and was implemented on a national level in the 1970s (166). The 50-85% reduction in the IRs of cervical cancer in the Nordic countries over the last 50 years is mainly a consequence of

high-quality organised cervical screening programmes (167). The organised cervical screening programme in Sweden is one of the best examples of successful preventive cancer care, with a 67% decrease in the overall incidence of cancer over a 40-year period. In 1965 the overall incidence of cervical cancer declined from 20 cases per 100 000 women (world standard rate) in 1965, to 6.6 cases per 100 000 women in 2005 (168).

In the beginning, all women 30-49 years of age (and later those 25-49 years of age) were invited to attend every 3-4 years. According to the recommendations of the Swedish National Board of Health and Welfare, women 23-50 years of age are advised to undergo cervical screening by Pap smear test every 3 years and women 51-60 years of age are advised to go every 5 years (124). The overall coverage according to European Union recommendations is 85% (169), which is the ultimate goal in Sweden (126). In 2007, it was estimated that 79% of Swedish women adhered to recommended screening intervals (170), although this proportion was slightly lower in women 23-25 (65-70%) and 26-30 years of age (~75%) (171). While HPV vaccination will probably play a major role in the primary prevention of cervical cancer for young birth cohorts in the future, cervical screening will remain the principal strategy to prevent cervical cancer for many decades (172).

#### *Invitation, attendance and coverage*

Invitation letters are used by organised cervical screening programmes in many high-income countries to encourage participation among under-screened and unscreened women (21,173-175). Coverage is defined as the proportion of women within a catchment area who have at least one Pap smear within a pre-set time with or without invitation (176). Cervical screening attendance is the proportion of women who actually respond to an invitation and have a Pap smear taken. Although there are a number of definitions of cervical screening attendance, no reference to any national or international standard unanimously defines it (177). According to a national report, attendance is defined as any Pap smear taken within 1 year of receiving an invitation (176). In this thesis cervical screening attendance corresponds to attendance according to the current recommendation for organised cervical cancer screening in Sweden (124).

#### *Cervical screening among immigrant women*

While cervical cancer is easily prevented in most cases through regular screening, screening is less common among immigrant populations than among women in the host countries. A

growing body of evidence indicates that immigrants generally have lower rates of cervical screening attendance (178-187), especially immigrant women 50-69 years of age (188). In the United States, it was estimated that at least 50% of women diagnosed with cervical cancer never attended cervical screening (161,189). A recent audit of the Swedish cervical screening programme revealed that women who had not adhered to the recommended screening intervals had a more than a two-fold excess risk of developing cervical cancer (190).

Considerable differences in risk of cervical cancer may reflect inequities in cervical screening attendance among immigrant women. However, most studies conducted so far have data from organised cervical screening programmes alone (178), or opportunistic screening alone (191), or questionnaires/in-depth interviews/chart reviews alone (179-187). The main reasons for differences in the incidence of cervical cancer among women are disparities in the utilisation of cervical screening and/or follow-up services following abnormal results (6,21,163,165), which has been specifically shown among immigrant women and women in the host country (178-180,192).

Despite numerous studies on sexual health interventions, there is limited research regarding immigrant women. A systematic review of studies published in 1990-2006 revealed that multicomponent interventions involving the patient and the provider offer the greatest potential to increase cervical screening and treatment in immigrant populations (193). Prominent interventions include: telephone reminders for screening intervals in the woman's native language coupled with educational messages about cervical cancer, providing transportation, using female physicians and interpreters, and establishing coalitions between trusted community organisations and screening providers. In order to increase cervical screening and education for a particular immigrant population, programme managers and clinicians must understand the population's unique belief system, and modify interventions to diminish any underlying factors that may negatively influence cervical screening attendance, such as modesty or embarrassment, improper hygiene beliefs, and karma/fate (193). Knowledge of cervical screening guidelines is one of the strongest motivators for having a Pap smear among all immigrant groups (193,194). Last but not the least, understanding differences in cervical screening attendance in high-risk populations with the intention to reduce disparities over time is important when evaluating preventive cancer strategies (6).

### 3 AIMS

The overall aim of this thesis is to study the risk of cervical cancer among immigrant women in Sweden, their cervical screening attendance and their prognosis after cervical cancer diagnosis. To address this overall aim, the four studies included in the thesis had the following specific aims:

- I. To estimate the risk of invasive cervical cancer among immigrant women in Sweden. The aim was also to evaluate whether the risk of invasive cervical cancer was modified by follow-up time and age at immigration.
- II. To estimate cervical screening attendance among immigrant and Swedish-born women and their subsequent risk of developing cervical cancer.
- III. To explore how Danish and Norwegian immigrant women in Sweden reason about attending cervical screening, focusing on women's perceptions as to why they and their compatriots do not attend.
- IV. To examine the prognosis of cervical cancer among women in Sweden with regard to immigrant status, cervical screening attendance and socioeconomic status, as measured by occupational class and education level.

## **4 MATERIALS AND METHODS**

### **4.1 QUANTITATIVE AND QUALITATIVE APPROACHES**

In this thesis both quantitative (Studies I, II and IV) and qualitative approaches (Study III) were used. These approaches were chosen as they suited the research aims by providing different perspectives, and complemented each other. A range of methods is needed in order to understand the complexities of modern health (195-197). The main features of qualitative and quantitative approaches are described briefly here.

The quantitative approach involves the analysis of numerical data, with the goal of classifying and counting features, and constructing statistical models to analyse the data collected to reveal eventual associations in an attempt to explain observations. The goal is to measure and determine the relationships among variables. All aspects of the study are carefully designed before data is collected. Researchers use tools such as questionnaires or equipment to collect numerical data. Data is in the form of numbers and statistics. The purpose is generalisability, prediction and causal explanations, and the goal is to measure and determine the relationships between variables. The quantitative approach aims to be objective and to render precise measurement and analysis of target concepts, e.g., uses surveys, questionnaires etc. Quantitative data is more efficient and can be used to test hypotheses, but may miss contextual detail. Researchers tend to remain objectively separated from the subject matter (197).

The goal of the qualitative approach is to present a complete, detailed description, and involves analysis of data such as words (e.g., from interviews) and pictures (e.g., video). The design emerges as the study unfolds. The purpose is contextualisation, interpretation and understanding participants' perspectives. The researcher is the data gathering instrument. The research method, for example in-depth interviews, is subjective, as importance is placed on the individual's interpretation of events. Qualitative data is rich, complex and time-consuming to collect. One of the most common misconceptions about qualitative research is that the sample size is too small to allow generalisation of findings. Although it is true that qualitative findings cannot be generalised in the same way quantitative findings can be, i.e., through statistical inference, qualitative findings are generalisable to settings that are similar to those under investigation. The degree to which a given study setting is similar to a setting outside a study depends on how many of their key factors are similar. Depending of the level of similarity, the findings can be viewed either as lessons that can be applied to other settings, or



simply as working hypotheses (198). The researcher is intensely engaged in the process before, during, and after data collection (197).

The quantitative approach was employed in Studies I, II and IV, using a cohort study design due to the nature of the research aims. The respective goals were to estimate the risk of invasive cervical cancer among immigrant women (Study I), to estimate cervical screening attendance among immigrant and Swedish-born women in Sweden (Study II), and to examine the prognosis of cervical cancer among immigrant women (Study IV). The research aim of Study III was to understand women's reasoning regarding cervical screening attendance. Thus the explorative character of the study required a qualitative approach with FGDs. The quantitative studies allowed us to examine the relationships among variables. As the quantitative approach is not effective when it comes to exploring these relationships, the qualitative approach was used in an attempt to explain the factors underlying the broad relationships between variables.

## **4.2 REGISTER-BASED STUDIES AND THE PERSONAL IDENTITY NUMBER**

Sweden is a country that provides unique, exceptional opportunities in the way of register-based studies, which is mostly due to the systematic use of the PIN, which is assigned to all Swedish citizens at birth, and to legal residents (199). The 10-digit PIN is maintained by the Tax Agency for all individuals who have lived in Sweden since 1947. A unique PIN is created for each person, consisting of six digits for birth year, month and day, combined with four more digits. The PIN remains the same throughout a person's lifetime, and does not change if you move from or to Sweden (200). The Swedish health care system and national health registers are dependent on the PIN (199).

The quality of Swedish registers is very high, due to both the long history of collecting population-based data, which provides an excellent base for monitoring disease, and to the ability to link individual information from different population-based registers through the PIN. A register is a complete list of people in a certain population. Information about the identity of these individuals has to be available so that the register can be updated, and new variables added if applicable. These registers are stored in databases. Registers either consist of data collected from national surveys, or are administrative registers compiled by different national authorities and organisations. Longitudinal studies are studies where a group of individuals are followed during a set period of time. All registered individuals in Sweden can be followed via their PIN, which can be used to link information on different variables from different registers.

When performing linkages, the number of individuals changes over time as people are born, move or die. The theoretical concepts in the research aim have to be operational, which means they can be translated into conceptualised measures. In the TPR a variable has been created to determine whether individuals are foreign-born or native-born, using four other variables, including the person's country of birth, duration of residence in Sweden, and father's and the mother's country of birth.

When death and emigration is not reported, it results in over-coverage, while unreported births and immigration result in under-coverage in the register. In addition to these issues of coverage, there may also be issues with irrelevance. One important aspect of irrelevance is the difference between the population of interest and the target population. There are probably about 25 000-50 000 legal Swedish residents who do not live permanently in Sweden. Estimates show that 4-8% of non-Nordic immigrants have left Sweden without reporting it (201).

### **4.3 INTERNATIONAL CLASSIFICATION OF DISEASES**

Cervical cancer diagnoses are coded according to the International Classification of Diseases (ICD), a statistical classification system used to group diseases and causes of death. The ICD is a standard diagnostic tool for epidemiological, health management and clinical purposes, including the analysis of the general health of population groups. It is used to oversee the incidence and prevalence of diseases and other health problems, and also provides the basis for national mortality statistics in the Member States of the World Health Organisation (202). In Studies I, II and IV, the 7th revision of the ICD (ICD-7) was used.

### **4.4 STUDY DESIGNS IN THE THESIS**

A cohort study is an epidemiological study design (quantitative), which was used in Studies I, II and IV (Table 1). All cohort studies used longitudinal, based on national Swedish data that comprised immigrant women (defined as women with different countries of birth) or Swedish-born women.

**Table 1. Summary of the materials and methods used in Studies I, II and IV**

	<b>Study I</b>	<b>Study II</b>	<b>Study IV</b>
<b>Design</b>	Cohort study	Cohort study	Cohort study
<b>Subjects</b>	Women: Immigrant/Swedish-born	Women: Immigrant/Swedish-born	Women: Immigrant/Swedish-born with a diagnosis of invasive cervical cancer
<b>Number of women Immigrant/Swedish-born</b>	758 002/4 737 549	445 547/2 176 255	2535/23 681
<b>Inclusion criteria for age (years)</b>	13-100	23-70	15-99
<b>Time period (years)</b>	1968-2004	1993-2005	1960-2005 1993-2005
<b>Data sources</b>	TPR The Migration Register The National Swedish Cause of Death Register NCSR	NCSR‡ TPR The Migration Register The National Swedish Cause of Death Register The Swedish Cancer Register	TPR The Swedish Cancer Register The National Swedish Cause of Death Register 1960, 1970, 1980 and 1990 Swedish Censuses The National Swedish Education Register NCSR
<b>Exposure</b>	Immigrant status Country of birth	Immigrant status Country of birth Age at immigration Participation in cervical screening	Immigrant status Country of birth Cervical screening Household occupational class Education level
<b>Outcomes</b>	Invasive cervical cancer	Degree of cervical screening participation  IRR <sub>s</sub> †	Death due to cervical cancer
<b>Analysis</b>	Poisson regression model stratified by follow-up time, age at immigration, country of birth	Poisson regression model stratified by adherence to cervical screening, age at immigration, country of birth	Cox proportional hazard model

‡NCSR: National Cervical Screening Register

† IRR: incidence rate ratio

In Study III, a qualitative study design with FGDs was used to collect data (Table 2).

**Table 2. A summary of the materials and methods used for Study III**

<b>Design and method</b>	Qualitative explorative design with FGDs
<b>Subjects and number of individuals</b>	Immigrant women: 27 Danish/13 Norwegian
<b>Inclusion criteria for age (years)</b>	23-70
<b>Time period (year)</b>	2010
<b>Data sources</b>	Stockholm: Data collected via FGDs of recruited participants of immigrant women living in the Stockholm area
<b>Aim</b>	To explore how Danish and Norwegian immigrant women in Sweden reason about attending cervical screening, focusing on women's perceptions as to why they and their compatriots do not attend.
<b>Analysis</b>	Latent content analysis

#### 4.4.1 Cohort study design (Studies I, II, IV)

A cohort study is an observational study that follows all individuals in a source population over time. The subjects are classified according to their exposure status (exposed and non-exposed) to investigate a given outcome (203). Cohort studies can either be prospective or retrospective. In a retrospective cohort study, data is gathered for a cohort that was formed sometime in the past; records have been kept, and all exposures and outcomes have already occurred. The incidence of disease can thereby be studied over time by the IR. Cohort studies provide information about the cause of disease and the most direct measure of the risk of developing disease. Cohort studies are major undertakings and may require long periods of follow-up, as disease may occur long after exposure (204).

The cohort study design was a good fit for Studies I, II and IV because of the uniqueness of the register data available in Sweden. Studies I, II and IV were all retrospective cohort studies with prospective follow-up of individuals. The PIN easily enabled linkages of the registers used, and records of country of birth and date of immigration were almost complete. Swedish registers provided an essentially complete follow-up and enabled identification of almost all incident cervical cancer cases that occurred during the study periods.

#### 4.4.2 Focus group discussions (Study III)

For Study III FGDs were conducted to collect data about attitudes, experiences, and conceptions (205). FGDs can also be used for sensitive questions if certain criteria are met (206). In this study the FGD participants were offered the possibility to ask questions after the FGD, and if they were interested, they were provided with information on cervical cancer and cervical screening, and told where to go if they had additional questions or needed to discuss any issues more in-depth. The use of FGDs gave a more profound understanding, as it allowed us to explore how Danish and Norwegian immigrant women in Sweden reason about attending cervical screening, focusing on their perceptions as to why they and their compatriots do not attend. We also chose immigrant women from Central America and Middle Africa, who had the highest risk of cervical cancer among all immigrants in Sweden, and low cervical screening attendance compared to Swedish-born women (Table 3). However, results from these groups are not included in this thesis, as the recruitment process was challenging in different ways. Therefore analyses in Study III were based only on FGDs among Danish and Norwegian immigrant women (Table 3).

**Table 3. Overview of data collection in FGDs of immigrant women**

Country/region of birth	Method			Total number of participants
	FGD (Number of participants)	Personal interview	Telephone interview	
Denmark	5 (27)	1	2	30
Norway	3 (13)	3	10	26
Middle Africa	5 (21)	4	2	27
Central America	5 (23)	3	2	29
Total	18 (84)	11	15	112

## 4.5 STUDY SETTING

### 4.5.1 Swedish population (Studies I, II, IV)

Studies I, II and IV comprised national Swedish data. Sweden is a long, narrow country that comprises 21 counties and is sparsely populated. The population is unevenly distributed across the country, with the largest proportion of people living in the southern parts. (72). At present, Sweden has a total population of about 4.8 million women, 15% of whom were born

outside Sweden and have immigrated to the country (19). In 1960, only 4% of the population was born outside Sweden.

#### **4.5.2 Stockholm population (Study III)**

The participants in Study III were Danish and Norwegian women living in the Stockholm area. Stockholm is the capital of Sweden, the Stockholm area hosts a population of 1 055 390 Swedish-born women and 233 489 (22%) immigrant women. The proportion of immigrants in Stockholm is higher than in the rest of the country (207).

### **4.6 DATA SOURCES (STUDIES I, II, IV)**

Studies I, II and IV all involved data from a linkage of seven Swedish nationwide registers, namely the TPR, the Swedish Cancer Register, the Swedish Cause of Death Register, the Migration Register, the National Cervical Screening Register (NCSR), the Swedish Education Register and the Swedish Censuses (1960, 1970, 1980 and 1990). Information on follow-up time and age at immigration offered the possibility to evaluate the effect of time spent in Sweden.

#### **4.6.1 Swedish Total Population Register and Migration Register**

The TPR is the basic register of the population of Sweden. Population registration in Sweden has a long history and was originally administered by the church; the oldest preserved church registers are from the early 17th century. Nowadays, the TPR is administered by the Tax Agency in Sweden, which receives most of the information from other public agencies. Data from this register contains, among others, PIN, place of birth, citizenship status, marital status, name of spouse, name of children, name of parents, address, municipality in which you are registered, immigration to and emigration from Sweden, address abroad and vital status (200). In 1968, when population statistics in Sweden were computerised, the Migration Register was created by Statistics Sweden based on information in the TPR, comprising information on immigration and emigration (72).

#### **4.6.2 Swedish Cancer Register**

The Swedish Cancer Register was established in 1958 and covers the entire Swedish population. It is mandatory for every health care provider (physicians as well as pathologists/cytologists) to report newly detected cancer cases to the register. There are six regional registers associated with the oncological centres in each medical region of Sweden,

where registration, coding and major checking of the information is performed. This regional process allows for the maintenance of close contact between the register and the reporting physician, which in turn simplifies the checking correcting of information. There are three different types of information in the Swedish Cancer Register: data on the patient (e.g., PIN, sex and place of residence), medical data (e.g., tumour site, histological type and date of diagnosis) and follow-up data (e.g., date of death and cause of death) (208).

#### **4.6.3 Swedish Cause of Death Register**

The Swedish Cause of Death Register was established 1749 when a nationwide report system for deaths was initiated. Today, The National Board of Health and Welfare is responsible for Swedish mortality statistics. Cause of death is classified according to the ICD (209). The register covers all deaths since 1997. However, in 0.5% of all deaths the Board of Health and Welfare was not able to obtain a death certificate. Information on these deaths is still included in the Cause of Death Register, but without any medical information. Whenever possible, the cause of death is registered for Swedish residents, whether the deceased was a Swedish citizen or not, and whether the death occurred in Sweden or abroad. Non-residents who died in Sweden, and Swedish residents who emigrated and are not registered as living in Sweden, are not included in the statistics (209). The main variables included in the register are PIN, sex, date of birth, date of death, place of residence, cause of death and whether death occurred abroad (210).

#### **4.6.4 National Cervical Screening Register**

In Sweden the initiation of an organised cervical screening programme started between the late 1960s and the end of 1970s (165,166). In the beginning all women 30-49 years of age were invited to attend every 3-4 years. Since the end of 1990s, women have been invited every third year from 23-50 years of age and every fifth year thereafter until 60 years of age. The NCSR includes information on cytological and histological diagnoses, and the laboratory where the samples were analysed. Longitudinal information on cervical screening in Sweden, starting from 1970 and encompassing the entire country as from 1995, are included in the NCSR. Information on cervical screening attendance, and date of Pap smear comprises information on Pap smears taken both within and outside the organised cervical screening programme (170). Recently, the NCSR was renamed the National Quality Register for Cervical Cancer Prevention (211).

#### 4.6.5 Swedish Censuses

The Swedish population and housing censuses are a count of the population taken by the government primarily for demographic, or taxation purposes. The censuses include enumeration of the population, apartments and households, families and cohabitation, occupational information, employment, income, and socioeconomic status. The type of data requested in the censuses is based on a questionnaire to the public, and available registers, and varies between the censuses (207). The data are collected by Statistics Sweden in cooperation with the Tax Agency, municipalities and church offices. Though it is required by law to provide census information, the completeness was 97.5% in the 1990 Swedish Census. One of the main reasons given for not providing complete information was invasion of privacy (207).

Information on occupations are coded and verified with the Occupational Register (212). Information on occupation is also compared with information from the employer. The completeness in both the 1960 and 1980 Census was 99%, whereas in the 1990 Census it was 98% (213-215).

#### 4.6.6 Swedish Education Register

The Swedish Education Register was initiated in 1985. The register consists of graduation and educational background data from the censuses and is updated each year with graduation/examination data from educational institutions in Sweden. The register contains demographic information from the TPR and educational data in addition to the PIN (216). The register comprises the population 16-74 years of age registered as residents in Sweden as of 1 January of each year. The register contains data on demographics and education, in addition to the PIN, which is necessary to link to other registers for updating purposes. The main variables are age, sex, municipality of residence, country of birth, highest attained education level and completion year (217). The data on highest attained education level is matched with the TPR for the actual population 16-74 years of age living in Sweden on 1 January. The register carried out special surveys called “education completed abroad” in 1995 and 1999, including people 20-59 years of age born in countries other than Sweden, where data on attained education level was missing. The purpose of the study was to improve the statistics on education completed abroad. Since 2000, an annual questionnaire is administered to newly-immigrated individuals who were born outside Sweden, who have missing information on education level (217).



## **4.7 DATA COLLECTION (STUDY III)**

### **4.7.1 Focus group discussion guide**

The research team, which consisted of midwives, public health experts, epidemiologists and a medical doctor, developed the FGD guide. It was used in FGDs of immigrant women from different countries of birth, with different socioeconomic status and who lived in different parts of Stockholm. The final version was pilot tested on another group of immigrant women who were students at Karolinska Institutet.

The FGD guide included mainly open-ended questions related women's perception of health, disease and prevention, cervical cancer, cervical screening and obstacles and motivators to attend cervical screening. Questions included, for instance, "How did you experience receiving the invitation letter?", "How important is having a Pap smear to you?" and "Why do you think some women do not have a Pap smear?".

### **4.7.2 Moderators**

Two moderators, who were native speakers of Danish and Norwegian, respectively, were enrolled to lead the discussions. The purpose of this was to encourage the participation of women who were hesitant to participate due to language problems, and also to facilitate discussion by offering the opportunity for the participants to discuss in their own language if they so wished for clarity of thought. The Danish moderator worked as a research assistant and the Norwegian moderator was a midwife who worked in a clinical setting. The moderators were trained for 8 hours on two different occasions in subjects related to cervical cancer and cervical screening attendance among immigrant women in Sweden, and how to handle different situations that could arise during FGDs. The FGD guide was also discussed with the moderators during their training. Data was collected between April and May 2010 at Karolinska Institutet.

All participants completed a questionnaire that collected their background data before the FGDs started. The participants were also offered light refreshment prior to the FGD. They all understood Swedish, and were encouraged to speak Swedish during the discussion, although they were aware of the possibility to speak their native language if the need presented itself. When necessary, due to the more or less developed Swedish linguistic refractive of the immigrant women, clarification was requested by either the moderator or the assistant, either

in Swedish, or in the native language. While it rarely occurred, if participants gave a response to a clarifying question in their native language, the moderator translated the response into Swedish and confirmed the translation with the participant. This was possible given the linguistic similarity between Nordic countries. Therefore, the transcripts used for this analysis contained Swedish-language responses only.

The FGDs began with a short presentation by the moderator, followed by a brief presentation of the study and the guiding principles of the discussion. The moderator led the discussion and made sure that all participants had a chance to voice their thoughts. The discussions were tape recorded but an assistant also took notes, which included a description of the discussion environment, keywords of what the participants said, and anything of value regarding the quality of the FGD with special attention paid to the interaction between participants. It was also the role of the assistant to ask follow-up questions on issues that needed clarification at any time during the FGD.

A summary based on the notes and a debriefing session between the moderator and the assistant were also tape recorded immediately after each FGD. The FGDs lasted 1 to 1½ hours, during which time the women talked openly and freely. The moderator balanced the discussion so that all topics in the FGD guide were evoked. The FGD participants were offered the possibility to ask questions after the FGD, and if they were interested, they were provided with information on cervical cancer and screening, and told where to go if they had additional questions or needed to discuss any issues more in-depth. All participants were offered a gift as a token of appreciation: they could choose between two movie tickets or a gift certificate to a flower shop worth 150 Swedish Kronor.

#### **4.8 STUDY PARTICIPANTS AND SAMPLING (STUDIES I, II AND IV)**

Studies of immigrant groups represent individuals or families that move or are forced to move from one environment to another. This thesis comprises a study population of immigrant women from 168 different countries.

##### **4.8.1 Study I**

There were 6 713 558 women registered in the TPR during the period 1968-2004. We used the PIN to follow the cohort members through linkages to the Swedish Cancer Register, the Cause of Death Register and the Migration Register. To analyse the at-risk population, we

excluded girls who were younger than 13 years of age at the end of the study period (8%) and women who were 80 years of age or older at cohort entry (1.5%). In addition, we excluded women who died (3.9%), emigrated (3.6%) or had a history of cervical cancer (0.1%) before cohort entry, and immigrants for whom information on country of birth or date of immigration were missing (0.7%). Because PINs of women who die are occasionally reused for newborn children or immigrants, we further excluded cohort members who were older than 100 years of age during follow-up (0.3%). Our final study sample comprised 4 737 549 Swedish-born and 758 002 immigrant women who were followed until a diagnosis of cervical cancer, death, emigration from Sweden, or December 31, 2004, whichever came first.

#### 4.8.2 Study II

The TPR was used to establish a cohort of women who were alive and residing in Sweden at some point during the period 1993-2005. Immigrant status (whether women were born outside Sweden and had immigrated, or were Swedish-born) was obtained from the TPR. The PIN was used to link the cohort to the Swedish Migration Register, Cause of Death Register and the Swedish Cancer Register.

Follow-up commenced at 23 years of age, date of immigration to Sweden or 1 January 1993, whichever came last. Women with a date of emigration from Sweden, women who died, and those with cervical carcinoma *in situ* or invasive cervical cancer before cohort entry were excluded (1.0%). Immigrant women with no information on country of birth or date of immigration were also excluded (0.04%). Women 23-60 years of age were eligible to enter the study, and were followed until 70 years of age, a diagnosis of invasive cervical cancer, cervical carcinoma *in situ*, date of emigration from Sweden, death, or December 31, 2005, whichever came first. The study cohort was matched to the NCSR, and longitudinal records of cervical screening attendance were obtained. Pap smears taken beyond the screening ages of the organised screening programme (23-60 years of age) or beyond the study period (1993-2005) were not counted in this study. In addition, Pap smears taken within 6 months of diagnosis were not counted in a woman's screening history, as it would not have been possible to prevent the existing invasive cancer. For this reason, we excluded 9530 Pap smears from a total of 10 948 015 (0.09%). The ICD-7 code 171 was used to identify invasive cervical cancer cases.

### 4.8.3 Study IV

Women with a diagnosis of cervical cancer recorded in the Swedish Cancer Register during the period 1960-2005 were included. Immigrant status was identified through the TPR. Linkages between the Swedish Cancer Register and the TPR, as well as other data sources, were carried out. Information on occupational class for the study women and the members of their household was retrieved from the 1960, 1970, 1980 and 1990 Swedish Censuses. Information on education level was also retrieved from these censuses and from the 1985 Swedish Education Register. Date and cause of death were retrieved from the Swedish Cause of Death Register and information on cervical screening attendance and dates of Pap smear were retrieved from the NCSR. ICD-7 code 171 was used to identify cases of invasive cervical cancer. Death from cervical cancer was identified based on the ICD-7 code 171 in 1960-1968, ICD-8 code 180 in 1969-1986, ICD-9 code 180 in 1987-1996, and ICD-10 code C53 in 1997-2005. Deaths among women with unspecified uterine cancers and a previous diagnosis of cervical cancer were included as deaths from cervical cancer.

We identified 26 237 women diagnosed with cervical cancer in Sweden between 1 January 1960 and 31 December 2005. We excluded cases with unknown country of birth (n=20) and implausible ages (n=1). The final study sample comprised 23 681 Swedish-born (90%) and 2535 immigrant (10%) women, who were followed up until date of death, date of first emigration from Sweden, or end of follow-up (31 December 2005), whichever came first.

### 4.9 STUDY PARTICIPANTS AND SAMPLING (STUDY III)

The target population for Study III was immigrant women 23-70 years of age from Denmark and Norway living in the Stockholm area. Since the goal was to get a deeper understanding of women's reasoning regarding cervical screening in general, there was no special effort made to recruit only non-attenders. Previous studies showed us that less than 50% of immigrant women adhere to the screening intervals recommended by the Swedish National Board of Health and Welfare for cervical screening.

A list of women 23-70 years of age residing in Stockholm County was obtained from the Swedish Tax Agency. Sampling was then done in two steps. First, we randomly selected 440 Danish (of 1258 eligible) and 400 (of 2612 eligible) Norwegian immigrant women from the list using a computer sampling programme. These numbers were chosen based on previous

experiences of low response rates when recruiting FGD participants. The selected women were contacted by mail and asked to participate in the study; they could respond by email or phone. As expected, very few women responded (<5). Therefore in a second step all randomly-selected women who had not responded were contacted by phone and asked if they were interested in participating in the study. However, phone numbers for 72 Danish and 98 Norwegian immigrant women could not be retrieved, so these women were sent a second letter reminding them of the study and asking them to send their contact information. None of these women responded. Fifty-three Danish women and 28 Norwegian women accepted to participate in the FGDs. However, at the last minute 26 and 15 women, respectively, were not able to attend due to illness, work or other social priorities.

Most women who were contacted by phone either did not respond, despite repeated calls, were not interested in participating in the study, expressed interest but were hindered by a variety of practical and logistical obstacles, or declined to participate in the FGDs but agreed to be interviewed individually. These women were interviewed individually, but data from these interviews are not included in this thesis. In total, five FGDs with 27 Danish participants, and three FGDs with 13 Norwegian participants, were conducted (Table 4). Each focus group consisted of three to seven participants, who were assigned to an FGD by country of birth and age group (23-40 years and 41-70 years). The intention was to attain homogeneity in the group in order to facilitate an open atmosphere. Preliminary analysis was done continuously, in parallel with data collection. A minor change to the FGD guide was made in the initial phase of data collection.

#### **4.10 DATA ANALYSIS FOR STUDIES I, II AND IV**

SAS statistical software was used in all data analyses in Studies I (version 9.1), II (version 9.2) and IV (version 9.3). In Studies I and II, Poisson regression models were used, while in Study IV Cox's proportional hazards models were used.

##### **4.10.1 Regression modelling**

Regression models and stratification are the two main statistical procedures that are used in data analysis to deal with confounding. In order to adjust simultaneously for several confounders, regression modelling methods may be necessary. Regression models summarise the relationship between an outcome (dependent) variable and one or several explanatory (independent) variable(s) as a mathematical equation. There are different types of regression

models, which are commonly used in epidemiological studies. One of the most important advantages of regression models is that all explanatory variables are treated in the same way, and it does not require one to define which explanatory variable is the exposure and which are the potential confounders. While Poisson regression models are used to estimate rate ratios using person-time data (Studies I and II), the Cox proportional hazards model is used when the time to an event is the main interest, such as in survival analyses (Study IV) (218).

*Poisson regression model (Studies I and II)*

The Poisson regression model is used to describe the probability of occurrence of count data during a set period of observation. The RR is the probability that a member of an exposed group will develop a disease relative to the probability that a member of an unexposed group will develop the same disease. In cancer research, RR is used in prospective (forward looking) studies, such as cohort studies. A RR of one means there is no difference between two groups in terms of their risk of cancer, based on whether or not they were exposed to a certain factor. A RR greater than one means that being exposed to a certain factor increases the risk, whereas a RR less than one shows a decreased risk.

*Poisson regression model (Study I)*

Exposure information:

The main variable was being an immigrant or Swedish-born woman living in Sweden, as per data obtained from the TPR. Immigrant women from 168 different countries were categorised into 19 birth regions based on the United Nations Population Division, a classification previously used by the International Agency for Research on Cancer to provide global cancer statistics (Globocan 2002) (219).



**Figure 1 Map Showing the World Areas Studied in Globocan 2002.**  
**From Parkin et al (8)**

Because of intercountry variations within these regions, the countries were further categorised into low-, medium- and high-risk regions for cervical cancer according to the ASRs (less than 10, 10-20 and >20 per 100 000 women, respectively). If there were more than 10 000 immigrants from a particular country, or if there were fewer but from a country with an ASR different than those of the other countries in their region, they were studied separately. For all categories of risk regions average ASRs were calculated from the country-specific ASRs provided by Globocan 2002.

In Study I Poisson regression models were used to estimate RRs and corresponding 95% CIs among immigrant women compared to Swedish-born women, adjusted for attained age and calendar period in 5-year categories. Immigrant women may have prevalent cancers at the time they arrive in the host country, which could lead to biased estimates. Therefore the analyses were repeated after excluding the first 2 years of follow-up. Because this restriction did not change the results notably, all the available data were used in the analyses.

### *Poisson regression model (Study II)*

#### Exposure information:

The main exposures were cervical screening attendance and country of birth. Women were classified as being an immigrant or Swedish-born as previously described in Study I. In Study II the RR, IR and incidence rate ratio (IRR) of cervical cancer for women who did and did not get screened according to the recommendations of organised cervical screening programme in Sweden were reported.

### *Cervical screening (Study II)*

Women were assumed to be non-attenders at cohort entry unless they had record of screening within the 6 years before cohort entry. Women 23-50 years of age were considered to be attenders for 3 years from the date of their last Pap smear, while women 51-60 years of age were considered to be attenders for 5 years after their last Pap smear. These time intervals correspond to the screening schedule of the organised cervical screened programme in Sweden (124,170). Three or 5 years after a Pap smear test, women were considered non-attenders unless they had another registered Pap smear. Non-attenders with a Pap smear would shift to the group of participants, and vice versa. Women who attended cervical screening at the last invitation after 55 years of age were assumed to be attenders until the end of follow-up. Women who attended screening regularly were assumed to be participants throughout follow-up, while other women provided risk time for both the attendance and non-attendance groups based on their screening history. Women who had no record of screening (neither organised nor opportunistic screening) during follow-up were assumed to be non-attenders throughout the follow-up period. To estimate the risk of cervical cancer for attending and non-attending women, cervical cancer cases and person-time of adherence and non-adherence to the cervical screening programme was summed for immigrant women, and for Swedish-born women.

### *Relative risk of cervical cancer (Study II)*

R Rs of cervical cancer and corresponding two-sided 95% CIs among immigrant women compared to Swedish-born women, stratified by adherence to the cervical screening programme, and adjusted for attained age (in 5-year categories), were also estimated. Finally, to evaluate whether differences in the RR of cervical cancer between immigrant women and Swedish-born women were due to adherence to cervical screening, Poisson regression models were fitted. The RR of cervical cancer was assessed among all immigrant women compared to Swedish-born women, as well as among selected groups of immigrant women where the power



was considered sufficient (at least 5 cancer cases during follow-up). The models were adjusted for attained age (in 5-year categories), calendar period (in 5-year categories) and county (all 21 counties in Sweden), and then further adjusted for screening adherence as a time-dependant covariate. The same type of models were also fitted among immigrant women only, to evaluate whether any differences in the risk of cervical cancer, depending on age at immigration, were due to adherence to cervical screening.

*The incidence of cervical cancer (Study II)*

Incidence refers to the number of new cancer cases that occur in a defined population of disease-free individuals. To calculate the IR, the varying lengths of follow-up time need to be taken into account. The follow-up time is the sum of time each individual remained under observation for developing the disease, and ends early when and if they become a cancer case. This time is viewed as the person-time at risk and is expressed as person-years. The sum of all individuals' time at risk equals the total person-years at risk (218).

$$IR = \frac{\text{number of new cases of disease arising in a defined population over a given period of time}}{\text{total person-time at risk during that period}}$$

Crude IRs may be calculated for the whole population, or IRs can be calculated separately for specific sub-groups (strata) of the population, referred to as stratum-specific measures. Age-specific IRs are an example of a stratum-specific measure, and can be used to gain greater epidemiological understanding of the disease under study. Age-specific IRs can be calculated as follows (218):

$$\text{Age-specific IR per 100 000 person-years} = \frac{\text{number of new cases in an age group of a defined population over a specific period of time}}{\text{person-years at risk in that age group in the same population and during the same period of time}}$$

In Study II the impact of adherence to cervical screening on the incidence of cervical cancer were assessed by calculation of age-specific IRs of cervical cancer for immigrant and Swedish-born women, stratified by adherence to screening (Figure 2).

*Age-adjusted incidence of cervical cancer (Study II)*

Crude IRs are influenced by the underlying age distribution of a country's population. Even if two countries have identical AIRs, the country with the relatively older population will

generally have higher crude IRs, as IRs for most cancers increase with age. The age distribution of a population (i.e., the proportion of people in particular age categories) can change over time and can be different in different geographical regions. The use of AIRs ensures that differences in incidence over time, or between geographical regions, are not due to differences in the age distribution of the populations being compared. AIRs of cervical cancer stratified by adherence to the cervical screening programme, were calculated for the immigrant group and for Swedish-born women using Poisson regression models in Study II.

#### *Incidence rate ratios of cervical cancer (Study II)*

IRRs, adjusted for attained age, where the absolute risk of cervical cancer for non-adherent women was compared to that of adherent women, were estimated for each immigrant group and Swedish-born women in Poisson regression models in Study II. IRRs use the difference in IR rates to provide a better estimate of the effects of intervention (or treatment) in groups under study that have different lengths of follow up. Thereby, the IRR provides a relative measure of the effect of a given intervention and is derived as the IR of the intervention group divided by the IR of the non-intervention group.

#### *Cox proportional hazards model (Study IV)*

In Study IV the data were analysed using Cox proportional hazard models using calendar time (days) since diagnosis as the time scale to calculate differences in risk of mortality adjusted for known confounders. The Cox proportional hazards model is one of the most commonly used statistical methods in medical time-to-event studies (220) and is one form of survival analysis. The hazards function is another name for IR and is based on time to event. Survival analysis focuses on the distribution of survival times and examines the relationship between survival and one or more predictors, usually termed covariates. Survival analysis is suitable for data from a cohort study design. The main effect measure is the hazard ratio (HR) and is defined as the hazard in the exposed group divided by that in the unexposed group.

The Cox proportional hazards model assumes that the hazards for patient subgroups are proportional throughout follow-up. Since this is a strong assumption, its applicability should always be evaluated. There are different methods to evaluate the proportionality assumption, such as plotting the log cumulative hazards function over time and checking for parallelism. In Study IV the Kaplan-Meier estimate was used, one of the best options to measure the fraction of women living up to 10 years after cervical cancer diagnosis, and the survival curve was

calculated. The time starting from a defined point to the occurrence of a given event, which was death in Study IV, is called survival time. Survival time can be affected when some of the subjects experience neither the event nor death before the end of the study, though they would have if observation continued, or if they could not be followed up and were lost midway in the study. We label these situations as censored observations. The Kaplan-Meier estimate computes survival over time in spite of the difficulties associated with subjects and situations.

The immigrant women included in Study IV were from 76 countries, which were classified into 12 regions/countries of birth. For the purposes of this analysis, immigrant women were considered together (all immigrants), separated into Nordic- and non-Nordic categories, or separated into regions/countries of birth as detailed in Table 4.

**Table 4 Definition of regions/countries of birth used in Study IV**

<b>Region/country of birth</b>	<b>Countries included in the regions/countries of birth</b>
<b>Africa</b>	Ethiopia, Angola, Morocco, Algeria, South African Republic, Egypt, Botswana, Somalia, Republic of Mauritius, Republic of Madagascar.
<b>America</b>	Uruguay, Brazil, Ecuador, Bolivia, Argentina, Peru, Chile, Colombia, Costa Rica, El Salvador, Honduras, Barbados, USA, Canada.
<b>Asia and Australia</b>	Turkey, Vietnam, Indonesia, Lebanon, Iraq, Jordan, Syria, Palestine, Taiwan, Iran, India, Thailand, China, Republic of Korea, Philippines, Afghanistan, Israel, Singapore, Sri Lanka, Japan, Australia.
<b>Denmark</b>	Denmark
<b>Norway</b>	Norway
<b>Finland</b>	Finland
<b>Baltic states</b>	Latvia, Lithuania, Estonia.
<b>Germany</b>	Germany
<b>Former Yugoslavia</b>	Bosnia Herzegovina, Croatia, Macedonia, Slovenia, Yugoslavia.
<b>Other Europe</b>	Iceland, Ukraine, Poland, Spain, Hungary, Austria, Czech republic, Romania, United Kingdom and North-Ireland, Portugal, Greece, Russian Federation, Soviet Union, Italy, Belgium, France, The Netherlands, Bulgaria, Switzerland.

In Study IV analyses were first run un-adjusted and then adjusted for age at diagnosis in 5-year categories, calendar time at diagnosis in 10-year categories (1960-1969, 1970-1979, 1980-1989, 1990-1999 and 2000-2005) and county of residence at diagnosis. The HRs of 10-year mortality risk due to cervical cancer were estimated for the time period 1960-2005, with corresponding 95% CIs, by country/region of birth.

The national coverage of register data for cervical screening was almost complete for the period 1993-2005 and therefore we performed analysis of cervical screening on a subset of the data restricted to this period. Furthermore, HRs and corresponding 95% CIs were estimated among

Swedish-born and immigrant women separately, by household occupational class and education level; in separate models cervical screening attendance was also added. Separate analyses were also used to test if age at immigration modified the effect of education level on mortality risks. All tests of statistical hypothesis were considered significant on the two-sided 5% level of significance.

#### *Prognosis and history of cervical screening*

We assessed the history of cervical screening attendance prior to cervical cancer diagnosis as a proxy for clinical stage at diagnosis (221). Women were considered screening-detected cases if they had a Pap smear 1-6 months prior to diagnosis. All other women were considered symptomatic cases. Women with Pap smears taken within 1 month of diagnosis were also considered symptomatic cases. Symptomatic cases were divided into three groups: those with a Pap smear within the recommended screening interval, those with Pap smears beyond the screening interval, and those with no registered Pap smears.

#### *Prognosis and occupational class and education level*

Household occupational class and women's education level were utilised as indicators of socioeconomic status. Household occupational class was determined using the "dominance order" (222) to retrieve information about the highest occupational class in the household prior to cervical cancer diagnosis, and was mainly based on information regarding the index woman and her cohabitants (husband, companion or other adult). The housing identification number from the censuses was used to find women's cohabitants. Household occupational class was classified into eight categories: high non-manual, low non-manual, high manual, low manual, self-employed, farmer, unclassifiable, and not in the labour force. Missing occupational information was included as a separate category. Women's highest education level prior to cervical cancer diagnosis was used and classified into three categories: high (13 years or more of schooling), medium (10-12 years of schooling) and low (9 years of schooling or less). Missing education level was included as a separate category.

#### **4.10.2 Stratification**

Stratification is another way of dealing with confounding in data analysis. Stratification divides data as strata based on a potential confounding variable. More specifically, confounding is controlled when the association of interest is evaluated within distinct, relatively homogeneous subgroups (strata) constituted by individuals with respect to the

confounding variable (223). Stratification was used in Studies I and II, and will be described in detail for each study.

#### *Follow-up time and age at immigration*

To evaluate the change in risk of cervical cancer in the host country in Study I, the effect of living less or more than 10 years in Sweden was analysed, assuming that 10 years in the host country would be sufficient to affect the risk of cervical cancer. In these analyses, all the immigrant women contributed person-time from cohort entry until 10 years of follow-up, and were switched to a new cohort if they stayed more than 10 years in Sweden, after which they were followed until the end of the study period. The analyses in Study I were also stratified by age at immigration ( $\leq 30$  or  $> 30$  years of age). The statistical test of homogeneity is a statistical evaluation of the extent to which variation in the estimates of the strata is consistent with random behaviour and represents a decision to simplify analysis and reporting of effect modification. The test of homogeneity examines the hypothesis that the estimate has a constant value across the strata (203). P-values for the interaction between country of birth and follow-up time, and age at immigration, respectively, were calculated in the regression model.

Further stratifications for follow-up time and age at immigration were done for the immigrants from the Nordic countries and the Baltic States, as this data had reasonable power. In these analyses, median values of follow-up time and age at immigration in each stratum was used to test for trends. The test for trend is a statistical test that assesses whether the outcome measure tends to increase or decrease in value as the exposure score increases. The test considers the null hypothesis, which means that the measures are not associated with the exposure score. Therefore, a small p-value means the association was detected by the test (203).

#### **4.10.3 The age-standardised incidence rates (Study I)**

When comparing cancer IRs between two areas with two different populations, it is important to take into consideration differences in the age structure of the populations. Age-standardisation is a method that uses a hypothetical population, referred to as the standard population, the age-structure of which is known. In the standardisation process the populations in each age group of the standard population are known as the weights. The standard population enables comparisons of disease incidence that are controlled for differences in the age structure of the study populations (218). In Study I, we estimated the ASRs for different groups of immigrants in Sweden using the age distribution of the world

standard population, and compared these rates with the ASRs provided by the Globocan 2002 database (224).

## **4.11 DATA ANALYSIS FOR STUDY III**

### **4.11.1 Content analysis**

Manifest content analysis focuses on what the text really says, whereas latent content analysis tries to catch the underlying meaning (225,226). However, Graneheim et al also stated that both manifest and latent analyses are interpretations with variations in depth and level of abstraction (225). In Study III, manifest content analysis was used when analysing the data. Latent content analysis was used to build the theme based on the categories derived in the manifest content analysis. The aim of the theme was to communicate the underlying meaning of the text (225).

The basis of content analysis are meaning units, i.e., words, sentences or paragraphs containing aspects that are related to each other through their content and context. In Study III paragraphs were used. This was followed by the analysis phase, which includes the process of condensation, i.e., the process of shortening the text while still preserving the core (225,227). The process whereby the condensed text is abstracted has been called abstraction, because it entails descriptions and interpretations on a higher logical level. This phase includes the formations of codes, categories and themes. The creation of codes is the process of labelling the condensed meaning unit with a code that represents a descriptive level of content and can be seen as an expression of the manifest content of the text. The theme is referred to as the interpretative level of the underlying meaning, through condensed meaning units, codes or categories (225). A description of the analytic process is displayed in Table 4.

**Table 4 Examples of the analytical process**

Meaning unit (participants quotes)	Condensed meaning unit	Code	Sub-Category	Category	Theme
[D] "P2: I mean this is the way I think, I have so little...I should have done it [had the Pap smear] when I should have, and if I had been in Denmark then I would have had seven [Pap smears], I would have been there seven times. Now I attended once in seven years, sort of. So that...yes, I wasn't proud of myself, no I am not.	In Denmark had a pap smear once per year but after the move to Sweden had once in seven years.	Postponing cervical screening attendance-changed behaviour related to immigration.	Postponing cervical screening attendance	Postponing cervical screening attendance	Women have a comprehensive rationale for postponing cervical screening, yet do not view themselves as non-attenders
	Doesn't feel proud not having had a Pap smear	Negative feelings not having had the Pap smear	Psychological factor	Previous experiences, psychological and individual factors	
P2: All the people were new and so was everything, for me it was like...went from being single to being married. Went from not having any children to taking care of three children. Went from studying to having a job. So everything was new all at once. So I was so completely exhausted when I went to bed and I didn't dream for two years. And then you receive all this information in the letterbox, "welcome to this thing" and "welcome to that" and now you can become Swedish and everything in through the door. (...) Well it was a bit like that, that's to say all this stuff that comes in through the door is impossible to relate to. There were so many other things you should...."	Feeling there were so many changes in life when moving to Sweden that you get a sense of exhaustion	Competing needs related to the move to Sweden	Competing needs related to immigration	Competing needs related to immigration	
	Hard to relate to all information that comes in through the door in the letterbox. There were so many other things you should...	Prioritisation of needs	Competing needs related to immigration	Competing needs related to immigration	
[F] "P:5: I will not do it [have a Pap smear] -so I waited for the next invitation as I said and there was someone who said of course you should do it! I think it was my Mum who said it, you must go and do it, it is very important. Oh, it is? But does it hurt? (...)"	Thought that no I will not do it [have a Pap smear] -so waited for the next invitation The Mum said you must go and do it [have a Pap smear], it is very important.	Waited for the next invitation Reminded by a relative	Postponing cervical screening attendance Social support-motivation	Postponing cervical screening attendance Social support-motivation	Women have a comprehensive rationale for postponing cervical screening, yet do not view themselves as non-attenders
"P:4. I thought they explained very well why you should have a pap smear, so I went at once."	Good explanation in the letter [why have a Pap smear]-went at once.	Good information in the invitation -motivates having a Pap smear.	Organisational and structural factors-Motivation	Organisational and structural factors-motivation	
K: What was it that made you think no? "P5: So the pain, does it hurt? I was worried about that. And I don't know if there was anything in the letter to explain to me why, but anyhow I did not read it because I have a bit of problem reading and taking in information that I am not interested in. I don't read it, it is difficult for me."	Worried to feel pain when having a Pap smear and therefore didn't want to [have a Pap smear]. Didn't know if there was anything in the letter to explain why you should have a Pap smear, but did not read it anyhow. Have problem reading and taking in information that you are not interested in- it is difficult for you.	Afraid that having a Pap smear should hurt. Tiresome read and understand written information.	Psychological factor Individual factor	Previous experiences, psychological and individual factors	
"So no, I was just worried that it would hurt. But it wasn't so bad when I had it done. I felt a little bit on...there were three spatulas they scraped with so now I feel that now yes...now I shall go. "	Worried to feel pain when having a Pap smear It wasn't so bad having a Pap smear. You felt a little bit so now you feel that you will have your Pap smear.	Afraid that having a Pap smear should hurt. Having had pap smear despite fear. Positive experience-motivated having Pap smear	Psychological factor Previous experiences, psychological factor		

## 5 ETHICAL CONSIDERATIONS

All studies included in this thesis received ethical clearance before study commencement. Ethical clearance for Study I was given by the Regional Ethics Committee at Karolinska Institutet, and for Studies II, III and IV by the Regional Ethics Committee in Stockholm.

The database information in the register-based studies was anonymised after the necessary linkages were conducted, thereby ensuring that the women included could not be identified. The analyses in the quantitative studies (Studies I, II and IV) were presented as statistical calculations and as numbers in tables, in which any specific individuals are not identifiable. The PIN was used to follow cohort participants through linkages to the registers used in each study (Studies I, II and IV). For confidentiality purposes, instead of PINs, a unique identification number was used and assigned to each woman by Statistics Sweden. Therefore no names or PINs were provided to the researchers by Statistics Sweden.

In Study III the participants were informed about the aim of the study, and were informed that participation was voluntary. Verbal consent was obtained from all participants, and the FGDs were tape recorded after acceptance by the participants. During the explanation of the guiding principles of the FGDs, the moderators also urged the women to respect the personal nature of the discussion, and to maintain confidentiality by not discussing the information brought up during the FGDs outside the group. The incentives used in this study are considered to be too small to have motivated women to participate (228), and were used more as tokens of appreciation. All summaries and presentations were conducted in such a way that no specific individual can be identified. FGDs can also be used as an appropriate method for posing sensitive questions (206). However, certain requirements in the data collection procedures must be met. The FGD participants were offered the possibility to ask questions after the FGD if they were interested they were provided with information on cervical cancer and cervical screening, and told where to go if they had additional questions or needed to discuss any issues more in-depth.

The law of secrecy applies to all those in the research group. A written agreement for professional secrecy was signed by the moderators, the assistants and the transcriber of



the data. The possible harm caused by violation of privacy of the participants in all studies comprised by this thesis should be considered minimal.

## 6 MAIN FINDINGS

### 6.1 AGE-STANDARDISED RATES OF CERVICAL CANCER

Comparison of the ASRs of cervical cancer between immigrant women in Sweden and women in their countries of birth revealed a mixed pattern. The ASRs for most immigrant women in Sweden were lower than that in their countries of birth. However, the ASR for Central American immigrant women remained as high as in their country of birth (ASR 31.4 per 100 000 women). Immigrant women from medium-risk countries in Northern Europe (ASR 11 per 100 000 women), the low-risk country Turkey (ASR 7 per 100 000 women), and medium-risk countries in Northern Africa (ASR 17.3 per 100 000 women) had higher ASRs in Sweden than the Globocan 2002 estimates. ASRs among immigrant women from Denmark, Norway and Finland were considerably higher than in their countries of birth (Table 5).

**Table 5: ASRs for immigrant women from Denmark, Norway and Finland in Sweden, 1968-2004.**

Birth region/country	ASR	
	Globocan 2002	Sweden
Denmark	12.6	17.2
Finland	4.3	9.1
Norway	10.4	15.8
Sweden	8.2	9.3

### 6.2 RELATIVE RISK OF CERVICAL CANCER (STUDY I)

After adjustment for age and calendar period, we observed increased risks of cervical cancer among immigrant women from European countries compared to Swedish-born women; the highest RRs were found among immigrant women from Denmark (RR 1.8, 95% CI 1.6-2.1) and Norway (RR 1.7, 95% CI 1.5-1.9), followed by women from Romania (RR 1.6, 95% CI 1.0-2.4), the former Yugoslavia (RR 1.4, 95% CI 1.2-1.6) and Poland (RR 1.3, 95% CI 1.1-1.5). Among immigrant women from non-European countries, we observed decreased risks for women from Eastern Africa (RR 0.2, 95% CI 0.1-0.6), South Central Asia (RR 0.4, 95% CI 0.2-0.6) and Western Asia (RR 0.5, 95% CI 0.4-0.7). RRs were significantly higher among women from Middle Africa (RR 3.0, 95% CI 1.0-9.3), Central America (RR 2.5, 95% CI 1.3-4.9), Chile (RR 1.5, 95% CI 1.1-2.0) and high-risk countries of South Eastern Asia (RR 1.8, 95% CI 1.2-2.7), compared to Swedish-born women.

## 6.3 RELATIVE RISKS BY FOLLOW-UP TIME AND AGE AT IMMIGRATION (STUDY I)

### 6.3.1 Follow-up time

Analysis of follow-up time among all immigrant women combined revealed a significantly lower RR after living more than 10 years in Sweden (RR 1.03, 95% CI 0.97-1.10) than during the first 10 years of follow-up (RR 1.25 95% CI 1.17-1.33;  $p < 0.0001$ ). It is noteworthy that excess RRs among immigrant women from most European countries significantly decreased toward the same risk as Swedish-born women after 10 years of follow-up. A significant increasing trend was observed among immigrant women from Western Asia who had lived in Sweden for more than 10 years ( $p = 0.006$ ).

Further stratification of follow-up among immigrant women from Nordic countries revealed that the RRs among these women continued to decrease the longer they lived in Sweden. The RR of 1.1 in the first 10 years among Finnish women dropped to 0.7 after living in Sweden for 30 years ( $p$  for trend = 0.01).

**Table 6. RRs and corresponding 95% CIs of invasive cervical cancer among immigrant women from the Nordic countries in Sweden compared to the Swedish-born women, stratified by follow-up time and age at immigration, 1968-2004**

	Denmark (cases n=193)	Finland (cases n=620)	Norway (cases n=256)	All immigrants (cases n=1991)
<b>Overall</b>	1.8 (1.6-2.1)	1.0 (0.9-1.1)	1.7 (1.5-1.9)	1.13 (1.08-1.18)
<b>Follow-up time (year)</b>				
<10	2.3 (1.9-2.7)	1.1 (1.0-1.2)	1.9 (1.6-2.2)	1.25 (1.17-1.33)
10-19	1.8 (1.3-2.3)	1.0 (0.9-1.1)	1.5 (1.2-1.9)	1.04 (0.96-1.13)
20-29	1.4 (1.0-2.0)	0.9 (0.8-1.1)	1.5 (1.1-2.0)	1.02 (0.92-1.14)
≥30	1.2 (0.7-2.2)	0.7 (0.5-1.0)	1.7 (1.1-2.6)	0.98 (0.82-1.17)
P-value for trend	0.3	0.01	0.4	<0.0001
<b>Age at immigration (year)</b>				
<30	1.4 (1.0-1.9)	0.8 (0.7-0.9)	1.6 (1.2-2.1)	0.90 (0.83-0.97)
30-49	1.7 (1.4-2.1)	0.9 (0.8-1.0)	1.5 (1.3-1.8)	1.07 (1.00-1.14)
≥50	2.9 (2.2-3.8)	1.8 (1.6-2.2)	2.1 (1.7-2.6)	1.75 (1.60-1.91)
P-value for trend	0.01	0.07	0.2	<0.0001

### 6.3.2 Age at immigration

Analyses stratified by age at immigration showed that calendar period and age-adjusted RR of cervical cancer among all immigrant women who came to Sweden when they were over 30 years of age was significantly higher than that among Swedish-born women (RR 1.25, 95% CI 1.17-1.32). We observed striking excess RRs among immigrant women who were older than 50 years of age at immigration from the Nordic

countries and the Baltic States. Furthermore, we observed a significantly increasing trend by age at immigration for Danish women ( $p=0.01$ ). It is worth noting that the RR was significantly higher even among Finnish women who were older than 50 years of age at immigration (RR 1.8, 95% CI 1.6-2.2), who otherwise showed no overall excess risk relative to Swedish-born women.

## **6.4 ASSESSMENT OF CERVICAL SCREENING (STUDIES II AND III)**

### **6.4.1 Cervical screening attendance (Study II)**

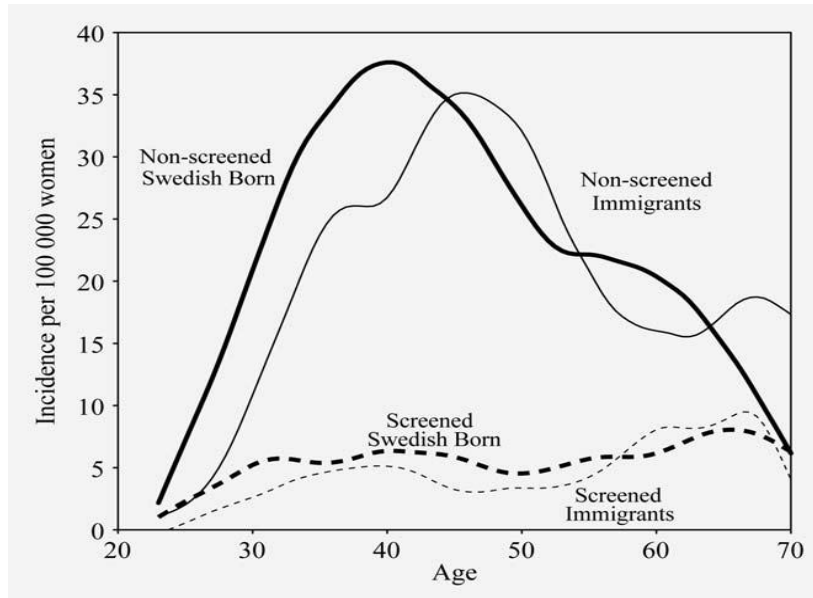
On average, mean adherence to cervical screening at recommended screening intervals was 62% for Swedish-born women, whereas it was 49% for immigrant women, and there was a higher proportion of immigrant women who did not attend screening at all. However, there was a large variation in cervical screening attendance within, and between immigrant groups. Mean cervical screening attendance ranged from about 32% among immigrant women from Australia and New Zealand up to 58% among Finnish immigrant women.

Additional analyses, stratified by age at immigration, revealed that cervical screening attendance was inversely associated with age at immigration, being highest among those who immigrated when they were younger than 30 years of age, and then generally decreasing with increasing age at immigration. However, this pattern varied between immigrant groups. Among women from Chile, the highest attendance was seen among women who immigrated at 20-49 years of age, whereas women from Eastern Africa had a low cervical screening attendance even at a young age at immigration. Immigrant women from the United States, Canada, Australia, and New Zealand who were 20 years of age or older at immigration had a very low cervical screening attendance. Immigrants who moved to Sweden after 50 years of age invariably showed the lowest cervical screening attendance.

### **6.4.2 Cervical screening and the incidence of cervical cancer (Study II)**

To assess the impact of cervical screening attendance on the incidence of cervical cancer, we calculated age-specific IRs of cervical cancer for immigrant and Swedish-born women, stratified by screening attendance (Fig. 1). The age-specific IRs of cervical cancer were similarly low (below 10 per 100 000 women) among immigrant and Swedish-born women who attended cervical screening. For non-attenders, the

incidence of cervical cancer increased rapidly from 25-30 years of age, peaking at 40-50 years of age (around 35 cases per 100 000 women). Incidence increased and peaked at an older age (5-10 years later) among immigrant non-attenders compared to Swedish-born non-attenders.



**Figure 2** Age-specific IRs (cases per 100 000) among Swedish-born (thick lines) and immigrant women (thin lines) who attended screening (dotted lines) and did not attend screening (solid lines) in Sweden, 1993-2005.

### 6.4.3 Cervical screening and age-adjusted incidence rate (Study II)

The AIRs of cervical cancer were extremely low among both immigrant (age-adjusted IR 3.1 per 100 000) and Swedish-born (age-adjusted IR 4.3 per 100 000) women who attended cervical screening, whereas immigrant and Swedish-born non-attenders showed AIRs of 16.9 and 21.7, respectively. Among all immigrant women, the RRs of cervical cancer were significantly lower both among women who did not attend cervical screening (RR 0.8, 95% CI 0.7-0.9) and those who did (RR 0.7, 95% CI 0.6-0.9) compared to Swedish-born women. Among non-attenders from the Baltic States (Estonia, Lithuania and Latvia) and Norway, the RR of cervical cancer was not significantly different from that of Swedish-born women. However, among women from these countries who did attend cervical screening, the RR was significantly higher among women from Norway (RR 2.3, 95% CI 1.2-4.5) and the Baltic States (RR 3.9, 95% CI 1.5-10.4). Women who were non-attenders from Western Asia (RR 0.3, 95% CI 0.2-0.5) and South Central Asia (RR 0.3, 95% CI 0.1-0.6) showed significantly lower RRs whether or not they attended cervical screening in Sweden (attenders

Western Asia: RR 0.3, 95% CI 0.1-0.8; attendees South Central Asia: RR 0.1, 95% CI 0.0-0.8).

#### **6.4.4 Cervical screening and incidence rate ratio of cervical cancer (Study II)**

Differences in IRRs of cervical cancer for women who did not, compared to women who did, attend cervical screening were more than five-fold, both among immigrant women (IRR 5.4, 95% CI 4.3-6.8) and Swedish-born women (IRR 5.1, 95% CI 4.7-5.5). The point estimates for IRRs were noticeably higher (although they had wide CIs) among immigrant women from Denmark (IRR 10.3, 95% CI 2.4-44.9), Poland (IRR 9.4, 95% CI 3.7-24.3), high-risk areas in South America (IRR 15.8, 95% CI 2.0-123.7), Turkey (IRR 17.1, 95% CI 2.2-132.1), South Central Asia (IRR 12.4, 95% CI 1.6-99.1) and high-risk areas in South Eastern Asia (IRR 15.2, 95% CI 2.0-116.9).

#### **6.4.5 Cervical screening and relative risk of cervical cancer (Study II)**

The RR of cervical cancer among all immigrant women, stratified by age at immigration to Sweden, showed increased risks for those who immigrated between at 40-49 years of age (RR 2.0, 95% CI 1.4-2.8) and at 50 years of age and above (RR 2.2, 95% CI 1.3-3.7), compared to women who immigrated at 20-29 years of age. Adjusting for cervical screening attendance decreased the RR by 20-30% among those 40-49 years of age (RR 1.6, 95% CI 1.2-2.3). However, for women who immigrated before 20 years of age, the risk of cervical cancer increased after adjustment for cervical screening attendance (RR 1.4, 95% CI 1.1-1.7).

Immigrant women from Norway and the Baltic States showed statistically significantly increased risks of cervical cancer, compared to Swedish-born women, in both the group that did not (RR 1.7 and 2.3, respectively) and that did attend cervical screening (RR 1.5 and 2.0, respectively). Immigrant women from the former Yugoslavia also showed a significantly increased risk of cervical cancer (RR 1.4, 95% CI 1.1-1.8), but after adjustment for screening attendance the RR decreased slightly and was no longer statistically significant (RR 1.2, 95% CI 0.9-1.4). We observed strikingly decreased risks of cervical cancer for women from Western Asia and South Central Asia (RR 0.3, 95% CI 0.2-0.5 and 0.1-0.5, respectively) compared to Swedish-born women, both before and after adjustment for screening attendance.

#### 6.4.6 **How immigrant women reason about cervical screening (Study III)**

Another perspective of the assessment of cervical screening in this thesis focused on exploring how women reason about cervical screening and more specifically what reasons they attribute to themselves and to their compatriots for not attending. “Women have a comprehensive rationale for postponing cervical screening, yet do not view themselves as non-attenders”, was the main theme that summarised the views of Danish and Norwegian immigrant women who took part in this qualitative study. This view was apparent even when women had postponed their attendance for several years. The main theme was generated from eight categories that seemed to influence the delay in cervical screening attendance. The key findings showed categories that were viewed by the women to be related to immigration, such as competing needs due to immigration, but also organisational and structural factors, and differences in mentality. Other categories that were discussed by the women were previous experiences, psychological and individual factors, childbearing-related factors, social support and social network, and risk perception. However, for some women these factors were considered to enable cervical screening attendance. The women described these factors as being intertwined when discussing their reasoning for postponing cervical screening attendance, thereby revealing the underlying complexity of this issue.

Postponing cervical screening attendance was the core category that linked all the reasons why women didn't attend cervical screening more promptly after receiving the invitation letter from the organised cervical screening programme. It was discussed in all groups that women who were invited to participate in cervical screening justified postponing it according to their personal rationale. As they described it, cervical screening attendance was given low priority at the time, and they therefore waited to attend, forgot about it, had the intention to attend later on, thought that they would attend after receiving the next invitation, or simply put it aside.

Immigration to Sweden *per se* seemed to influence our participating Danish and Norwegian immigrant women not to adhere to recommended screening intervals. The women discussed specifically how their energy and focus were consumed by the change of environment, attempts to learn how different societal systems worked in the new country, and to their resettlement efforts, all of which are related to competing needs due to immigration.

Women mentioned that organisational and structural factors also negatively influenced cervical screening attendance. The aspects brought up by the women were differences between the health care system in their country of birth and that in Sweden, the perception of the cervical screening invitation system as impersonal, logistical challenges and the importance of having a relationship with their caregivers.

The women also discussed how differences in mentality influenced their cervical screening attendance. In this category, the reasons why women delayed their cervical screening attendance were related to their perception of large differences between their country of birth and Sweden, which led to overwhelming experiences that were energy-consuming. Other reasons discussed were the reluctance of women to accept regular health controls and governmental involvement in private life, and a more anxious approach towards things one should or should not do in Sweden in comparison with a more easy-going approach in their country of birth.

## **6.5 PROGNOSIS OF CERVICAL CANCER (STUDY IV)**

The distribution of different types of cervical cancer among Swedish-born and immigrant women was similar, with squamous cell carcinoma being the predominant histological type (around 80% of all cases). The investigation of how the prognosis of women with cervical cancer was influenced by immigrant status, cervical screening attendance, occupational class, and education level showed that immigrant women had a slightly lower risk of cervical cancer mortality than Swedish-born women (HR 0.9, 95% CI 0.8-0.9). The point estimate remained the same when adjusted for age, calendar period and county of residence at diagnosis. However, when the analysis was stratified by region/country of birth, a 20% lower risk of mortality was observed in the adjusted analysis among non-Nordic immigrants (HR 0.8, 95% CI 0.7-0.9) compared to Swedish-born women, while it did not differ among Nordic immigrant women.

The excess risk of mortality was four-fold (HR 4.1, 95% CI 3.3-5.2) among symptomatic cases with no history of cervical screening attendance, while symptomatic cases diagnosed within or beyond the screening interval showed a three-fold increased risk of mortality (HR 3.0, 95% CI 2.3-3.8 and HR 3.3, 95% CI 2.6-4.3, respectively). The pattern was the same when stratification by immigrant status was performed.



An excess risk of cervical cancer mortality was observed among both Swedish-born and immigrant women with a low education level, independent of history of cervical screening attendance. The effect of education level on prognosis of cervical cancer showed that Swedish-born women with a medium education level had a 30% excess risk of mortality (HR 1.3, 95% CI 1.1-1.6), and those with a low education level had a 60% increased risk of mortality (HR 1.6, 95% CI 1.4-2.0), compared to those with a high education level. Immigrant women with a low education level had a more than two-fold statistically significant excess risk of mortality (HR 2.2, 95% CI 1.2-3.8) compared to those with a high education level. Immigrant women with missing information on education level showed a nearly three-fold excess risk of mortality before adjustment for history of cervical screening attendance (HR 2.7, 95% CI 1.4-5.1), although adjustment for this variable did not change the estimates notably.

This pattern was also seen among Swedish-born women with low manual household occupational class, women from households not in the labour force and women with missing information on occupational class. Swedish-born women from households that were not in the labour force showed an 82% increased risk of mortality (HR 1.82, 95% CI 1.40-2.36) compared to Swedish-born women from high non-manual households. After adjustment for history of cervical screening attendance, this excess risk remained (HR 1.74, 95% CI 1.34-2.25). Swedish-born women with low manual household occupational class had a slightly increased risk of mortality (HR 1.23, 95% CI 1.04-1.47, before and HR 1.20, 95% CI 1.01-1.43 after adjustment for history of screening attendance). Swedish-born women with missing information on occupational class had a 51% increased risk of mortality before adjustment for history of screening attendance (HR 1.51, 95% CI 1.02-2.24), but results were no longer significant after adjustment for this variable (HR 1.37, CI 0.92-2.03).

## **7 DISCUSSION**

### **7.1 SUMMARY**

The overall aim of this thesis was to study the risk of cervical cancer among immigrant women in Sweden, their cervical screening attendance and their prognosis after cervical cancer diagnosis. Study I showed which groups of immigrant women were at high risk for cervical cancer, and demonstrated that both age at immigration and follow-up time modifies the risk of cervical cancer. To further increase the understanding of immigrant women's cervical screening attendance, Study II was carried out, which showed that immigrant women attend cervical screening less than Swedish-born women. Adherence to recommended screening intervals was shown to be strongly associated with cervical cancer prevention. Following the results of Study II, it was decided to qualitatively explore how Danish and Norwegian immigrant women in Sweden reason about attending cervical screening, focusing on women's perceptions as to why they and their compatriots do not attend, which became the object of Study III. Investigation of women's rationale for non-attendance after being invited to cervical screening revealed some complex reasons related to immigration itself, including competing needs, but also organisational and structural factors, and differences in mentality between the country of birth, and Sweden, the host country. Study IV was carried out to examine the prognosis of cervical cancer among women in Sweden with regard to immigrant status, cervical screening attendance and socioeconomic status, as measured by occupational class and education level. The methodological aspects will be discussed separately for the register-based studies (Studies I, II and IV) and the qualitative study (Study III).

### **7.2 METHODOLOGICAL CONSIDERATIONS**

#### **7.2.1 Sources of error in epidemiological studies (Studies I, II and IV)**

Though epidemiological studies aim to provide accurate estimates, different types of errors may occur. Sources of error in epidemiological studies can be either random, or systematic. Random errors are related to problems with precision; systematic errors stem from issues such as selection bias, confounding and misclassification. Internal validity refers to the absence of systematic errors, and is the degree to which the results are correct for the group under study. External validity (generalisability) refers to extent to which the study's results can be applied to people outside the study sample. The reliability of a study

refers to the degree to which the results can be replicated, and depends on both validity and precision.

### 7.2.2 Random error

Random error is when a value of the sample measurement deviates from that of the true population value by chance alone. Random error cannot be completely eliminated in epidemiological studies, as only a sample of the reference population is used. Random error causes inaccurate measures of association. The best way to reduce random error is to increase the size of the study sample. High precision may also eliminate random errors. To assess whether the results of the register-based studies could be due to chance, the likelihood that the observed result was due to sampling variability was determined using statistical tests. In epidemiological research, the use of statistical methods in assessing risk estimates in combination with the calculation of 95% CIs aims to show the degree of precision and the risk of random error. In Studies I, II and IV 95% CIs and p-values were used to show the level of precision of the estimates. Results where the 95% CI included 1, or where p-values were more than 0.05, were considered to have occurred by chance. In other words, there is a 95% probability that the result was due to chance. It should be noted that narrow CIs and very low p-values show higher precision. The register-based studies in this thesis (Studies I, II and IV) were population-based. These registers cover the entire population in Sweden, including the legal immigrant population, which is relatively large. Therefore the sample size could be considered reasonably large, and capable of rendering reliable estimates. However, some of the subgroup analyses within the study samples were based on small numbers, and therefore involved a larger statistical uncertainty.

In Study I the change in the risk of cervical cancer was evaluated by follow-up time in the host country in stratified analyses. Because the 10-year follow-up time in Study I was fairly short, few cancers were detected, making it difficult to interpret the results estimated for this stratum. In addition, power problems were encountered as immigrants from most low- and medium-resource countries were young, and did not reach an age at which cancer usually presents itself. The power problems were especially present when studying the effect of age at immigration and follow-up time.

In Study II there was limited power to study the hypothesis of adherence to recommended screening intervals and risk of cervical cancer for every country of birth considered. Left truncation led to a further loss of study power in the analyses. In Study II, follow-up time was from 1993-2005 because of incomplete data on cervical screening attendance, whereas in Study I it was from 1968-2004. Left truncation occurs when individuals who have already passed the milestone, in this case the diagnosis of cervical cancer, at the time of study recruitment (229) are not included in the study. The RR of cervical cancer was therefore estimated, controlling for screening adherence, both for all immigrants and for selected groups of immigrants in Study II, where the power was reasonable. Moreover, the lower RR of cervical cancer among all immigrants, compared to Swedish-born women contrasted with a previous report (230). This left truncation may therefore have led to over-representation of women with a low risk of cervical cancer.

In Study IV the countries of birth were partially collapsed into larger regions to meet the requirements of statistical power calculations. Using statistical power in STATA, the power calculations showed that it at least 294 women were needed to detect a HR of 0.7 with 80% power. However, even if efforts were made to keep the same categorisation that was used in Studies I and II, some modification was needed in order to create groups that were large enough to allow for meaningful interpretations of any differences (or lack thereof). All groups of immigrant women had at least 110 cervical cancer cases or more, except for immigrant women from Africa, among whom only 15 cases were observed. Therefore, the assessment of 10-year survival and HRs with 95% CIs for cervical cancer among Swedish-born and immigrant women in Sweden in 1960-2005 involved larger statistical uncertainty.

### 7.2.3 Systematic error

Systematic error arises when results differ in a systematic manner from the true values (204). The main possible sources of systematic error are selection bias, information bias and confounding (203).

### *Selection bias*

If there is a systematic difference between the characteristics of individuals in a study sample and those who are not, and if those characteristics are related to either the exposure, or the outcome under study, selection bias has occurred. Selection bias leads to a distortion of the effect as a consequence of the way participants are included in study samples (204).

### *The “healthy migrant effect”*

Because the focus of this thesis was to study immigrant status in relation to cervical cancer, adherence to cervical screening and cervical cancer prognosis (risk of mortality), the women included were selected by their immigrant status and country of birth. Migrant populations are a self-selected sample of the population of their country of birth. Very often they come from quite limited geographical areas. Moreover, those with poor health in the labour immigrant group are commonly underrepresented, introducing an inherent selection bias, a “healthy migrant effect” similar to the “healthy worker effect” (1). For example, immigrants from the former Yugoslavia that moved to Sweden in 1960s and 1970s were often recruited as workers, whereas immigrants from Czechoslovakia and Poland were often highly educated refugees and arrived in Sweden during the 1980s (231). The “healthy migrant effect” may be a result of the fact that seeking a new life overseas infers a population that has resources and is active (1). Nevertheless, there is no evidence for positive selection bias in the studies in this thesis, which would be the case if cancer-prone individuals or cancer patients preferentially immigrated, or were preferentially allowed immigrant status. However, it is plausible that a “healthy migrant effect” has occurred.

### *Information bias*

Measurement errors in one variable, i.e. exposure or disease can cause bias in estimating an effect which is called information bias. Misclassification of an exposure is sometimes non-differential with respect to outcome status, i.e. equally present whether the subject is a case or not. Non-differential misclassification tends to lead to an underestimation of the true strength of the relationship. Differential misclassification occurs when the misclassification is unequally distributed with respect to outcome. This will either exaggerate or underestimate the effect, and the direction may sometimes be difficult to predict. Information on the exposures and outcomes used in Studies I, II and IV

was taken from national registers. A quality assessment of these registers has been presented in this thesis.

The classification of cervical cancer as the outcome in Study I was not a notable concern. The completeness of the Swedish Cancer Register in 1984 showed that reporting of cancer cases was more than 98% complete, which made it possible to identify almost all incident cases of cervical cancer. Cancers recorded in the Swedish Cancer Register are classified by ICD code (232). In 2000, 100% of the registered cervical cancer cases had been verified by either cytology or histology (233).

In Study IV the outcome was death due to cervical cancer. As from 1995, the Cause of Death Register has included a correct underlying cause of death in 77% of all deaths, and in 90% of deaths from malignant tumours (234). However, in Study IV the finding of improved prognosis among non-Nordic women may partly be attributable to an underestimation of deaths in the Cause of Death Register for these women, i.e. a woman may return to her country of birth after cancer diagnosis and in the event of death she will not be registered as a deceased non-Nordic immigrant in the Swedish register, although the Nordic countries have coordinated their population changes since 1969 (201). Women who die outside Sweden and are registered as Swedish residents will have their death recorded in Sweden, though the cause of death will not always be registered. In this thesis, these women were censored because of the possibility that they died of other causes, but in the previous scenario they were assumed to be alive until the end of follow-up. However, the magnitude of this potential problem is expected to be very small. According to the Cause of Death Register, in 2007 0.8% of registered deaths among women who died outside Sweden had an unknown cause of death (235).

When a woman was classified as an immigrant in Studies I, II and IV, the exposure information was based both on country of birth and immigrant status from the TPR and Migration Register, respectively. The TPR only includes immigrants that are legal residents and have a PIN. The fact that immigrant and emigrant registration does not necessarily cover every migrant, such as those who stay less than 1 year (236), refugees who do not yet have their residence permit (72), and immigrants from Nordic countries who do not need work permits or immigration documents (72), inaccuracies in person-year calculations are unavoidable. However, most probably this did not affect the results

significantly, since the desire among immigrants to become registered is strong as it comes with the right to collect benefits (237). Furthermore, even though 65% of all asylum seekers were granted a residence permit in 1996-1997 (because of the war in the Balkans), this number fell to 30% in 2001. It was estimated that 11 235 women sought asylum in 2003 (238). The estimated figure on short-term immigrants was 41 000 individuals (men and women) in 2004, but according to Statistics Sweden this estimation should be taken with caution. The under-coverage should be negligible, and if it affects the estimations in Studies I, II and IV in any direction, it overestimates them.

Register-based follow-up of immigrants may be a concern if they emigrate without reporting this to the authorities, leading to over-coverage in the population statistics. The continuous follow-up of individuals who emigrate without any censor events, i.e., cancer (Studies I and II) or death (Study IV), accrues person-time to the cohort, and thus underestimates the incidence of cancer or prognosis. A report from Statistics Sweden in 1999 estimated a 4-8% over-coverage of non-Nordic immigrants in the TPR, although, as previously mentioned, the Nordic countries have coordinated their population changes since 1969 (201). Moreover, because of the high-quality health care system (123) and health insurance in Sweden, a woman with cancer might prefer to return to Sweden if she is still a registered legal immigrant in Sweden. Therefore, the over-coverage is an unlikely explanation for the findings in Studies I and II.

In Studies II and IV, data on screening attendance in 1993-2005 was used, but during this period screening registration was not entirely complete: screening information was lacking from two out of 30 pathological laboratories in Sweden. All women were assumed to be non-attenders at cohort entry. However, if they had any record of cervical screening at cohort entry, or up to 6 years before that, they were assumed to be attenders at cohort entry. Non-differential misclassification may have occurred if we assumed women were non-attenders due to the lack of information from these two pathological laboratories, when they were in fact attenders. From 1995 onwards, the NCSR covered all of Sweden. Thus, the inclusion of data from 1993 and 1994 may underestimate the results in Study II, where the main exposure was cervical screening attendance, but it probably did not affect our results to any great extent.

Household occupational class and women's education level were utilised as indicators of socioeconomic status in Study IV. The information on household occupational class was retrieved from the Swedish Censuses. The response rate in both the 1960 and 1980 Censuses was 99%, whereas in the 1990 Census it was 98%, which makes the data reliable. The information on education level was based on information from the National Swedish Education Register, and it is estimated that the proportion of Swedish-born individuals with an unknown education level is less than 1%, while among immigrants it is 7%.

Individuals who have never attended school are included in the group with unknown education level (missing information) both among Swedish-born individuals and immigrants in the National Swedish Education Register. Investigation of the individuals with missing information shows that if they had been accurately classified they would most likely have been assigned a low education level (9 years of schooling or less). Furthermore, 87% of Swedish-born women and 70% of immigrant women have an education level that is correctly classified. According to the population and welfare statistics in Sweden there is an overestimation of individuals with a low education level and underestimation of those with a high education level among both Swedish-born and immigrant women (217).

An aspect specific to cervical cancer epidemiology is that incidence and mortality rates are calculated using the entire female population as the 'population at risk'. However, women who have had a total hysterectomy for reasons other than cervical cancer are not at risk for the disease (21). Hysterectomy is estimated at 2.1 per 1000 female residents in Sweden (239). A slight underestimation of the IRs might therefore have taken place.

### *Confounding*

Confounding occurs when another exposure (or risk factor) exists in the study population and is associated with both the disease and the exposure being studied, but is not part of the causal pathway between the exposure and the outcome. Therefore, when the effects of two exposures (risk factors) have not been separated, it can lead to the incorrect conclusion that the effect is due to one rather than the other variable.



Confounding can be neutralised at the design phase of a research project (for example, by restriction) and/or at the analysis phase (for example through stratification and multivariate statistical modelling), as long as all the confounders have been measured properly. Stratification includes the measurement of the strength of associations in well-defined and homogeneous categories (strata) of the confounding variable (for example, age groups). However, a large study sample is needed to perform stratification, and stratification does not allow to control for many factors simultaneously. Multivariate statistical modelling is required to estimate the strength of associations while controlling for several confounding variables simultaneously. In the analysis phase of Studies I, II and IV confounding was dealt with by adjustment for known variables in regression models. We adjusted for attained age, calendar time and county of residence at diagnosis (Studies I, II and IV).

One of the limitations of the register-based data used in Studies I, II and IV is the lack of information on possible confounders, which may have introduced residual confounding in our studies. The potential impact of confounding factors depends on their occurrence in the study population, and the strength of their association with the outcome. The potential confounders smoking, early age at first sexual intercourse, high lifetime number of sexual partners, use of oral contraceptives, high parity, other STIs (240,241), and marital status (136-138) may affect the association between immigrant status and risk of cervical cancer or immigrant status and cervical screening attendance.

Clinical stage at presentation may act as a confounder in cases of differences in prognosis between the immigrant and Swedish-born women. Unfortunately, in Study IV information on clinical stage at diagnosis or treatment was not available, which may have affected the relationship between invasive cervical cancer diagnosis and prognosis. As only small differences were found in the risk of cervical cancer mortality between Swedish-born and immigrant women (with an advantage for the latter group), access to this information would most likely not have changed the study results to a large extent. Based on information from previous studies, it is known that history of cervical screening attendance is a good proxy for clinical stage at diagnosis (190,221), and adjusting for screening history in the present study did not change the main result. Adjustment for calendar time helped account for gross changes in cancer treatment over time, but it did not provide insight into the equality or inequality of treatment according to education

level. However, adjustment for calendar time in the analyses from 1993-2005 did not change the results substantially, indicating that no major changes occurred in cancer treatment during this time period. Furthermore, since it was postulated that follow-up after cervical cancer diagnosis could vary by county, we tested for interaction between history of cervical screening attendance and county of residence at diagnosis; the result showed no significant difference. Moreover, the prevalence of co-morbidities was not investigated in Study IV. Although nutrition and psychosocial supports are known to vary across socioeconomic groups, there is less evidence to determine the extent to which these variables account for differences in cervical cancer prognosis (242).

#### *Effect modification and interaction*

Effect modification refers to the effect of a certain exposure on an outcome which is not the same depending on the value of a third variable. Therefore, the measure of effect changes over the value of this third variable. When effect modification is detected, it needs to be managed, either by stratifying the analyses by this third variable, or by conducting an interaction analysis where the variation introduced by this third variable is considered. In Study I p-values were calculated for the interaction between country of birth, follow-up time and age at immigration, respectively, in the regression model. Further stratifications for follow-up time and age at immigration were done for the immigrants from Nordic countries and the Baltic States, where there was reasonable power in the data. In Study II, stratification by age at immigration was done to assess immigrant women's cervical screening attendance. In Study IV, the effect of education level on the prognosis of immigrant women by age at immigration was assessed, but the affect was not altered.

#### **7.2.4 Other methodological considerations**

Reverse causality was tested by excluding cervical cancer cases from the study sample in Studies I and II to address the concern of prevalent cancer among immigrant women arriving in the host country, which would lead to biased estimates of cervical cancer incidence. To allay this concern the analyses were repeated after excluding the first 2 years of follow-up. Since this did not notably change the results, all the available data were used in the analyses.

In Study II, all Pap smears taken within 6 months of a cervical cancer diagnosis were excluded, since screening attendance was different from diagnostic screening. Neither were these Pap smears counted as screening history, as they would not have prevented invasive cancer through detection and removal of a pre-invasive lesion, as the invasive cancer was already present. Out of a total of 10 948 015 Pap smears, 9530 were excluded (0.09%).

#### **7.2.5 External validity**

External validity or generalisability refers to how relevant the results for a given study sample are to the general population. If the results are not trustworthy within a study, i.e., if the internal validity is not good, it is worthless to consider whether they can be applied to the general population. In addition, in order to create a fair sample of the source population, researchers must select a representative sample of that population.

The possibility of constructing a sample of immigrant women that are representative of the population of their country of birth is debateable. Although the “healthy migrant effect” may partially explain differences in the incidence of cervical cancer among our immigrant women compared to that among women in their countries of birth, it is likely that less selection occurs among immigrants from countries that are geographically close to the host country, and more selection occurs among immigrant from countries that are farther away. The register-based studies in this thesis are population-based cohort studies based on Swedish registers. Therefore the results should be generalisable to the legal resident immigrant women in Sweden. In Study II the study sample was taken from women attending cervical screening, both opportunistic and organised, in Sweden, and therefore the results should be generalisable to a large part of the female population in Sweden.

#### **7.2.6 Rigor and trustworthiness (Study III)**

Concepts used in qualitative research to describe trustworthiness of the research are credibility, dependability and transferability as opposed to concepts mostly used in quantitative research such as validity, reliability and generalisability (225). In Study III credibility was increased through triangulation, reflexivity and peer debriefing. Common standard practice was also used for qualitative studies, such as supervision, training, tape recording and transcription. Credibility refers to confidence in how well the data and the processes of analysis address the research objectives under study.

Credibility concerns issues such as context, participants, and different approaches to data collection. Furthermore, variance of interviewees and observers' perspectives of the phenomenon under study contributes to richer data (225).

Another important aspect of trustworthiness is dependability, which refers to an assessment of the quality of the processes of data collection, data analysis, and theory generation (243). Graneheim et al argues that it is possible within a research team to address dependability by having an open dialogue about "the degree to which data change over time and alterations made in the researcher's decisions during the analysis process" (225).

### *Study design*

FGD is a data collection technique that relies on the dynamic of group interactions to stimulate the discussion. Through these interactions the health-related beliefs and behaviours of the women under study contribute to produce rich and detailed data from individual perspectives that could not have been obtained using other methodological strategies (228,244).

### *FGD participants and sampling*

FGDs may consist of 4-12 participants. With fewer participants a research topic may be discussed more in depth, and with more participants it may bring a greater variety of views (228). In Study III each focus group consisted of three to seven participants. We experienced sampling difficulties, especially among Norwegian women, and some women who expressed interest in participating were hindered by a variety of practical and logistical obstacles inherent to their life situations, which has also been reported in previous research (245). Therefore we cannot be certain that saturation was reached (i.e., that no more new information was surfacing during the FGDs) for Norwegian women. Difficulties in recruiting hard-to-reach populations, such as minorities, pose challenges in accessing and gaining the trust of potential participants (246). The FGDs in Study III were held at Karolinska Institutet, which was comfortable and accessible to the participants (247). Furthermore, participating women expressed that they saw the invitation to participate in the FGD at Karolinska Institutet to be of significant value.

### *Reflexivity*

As reflexivity, i.e., the influence of the researcher on the setting or individuals studied, can threaten credibility, the goal in a qualitative study is not to eliminate this influence, but rather to understand it and use it productively (248). The moderators were trained in subjects related to cervical cancer and cervical screening attendance among immigrant women in Sweden, and in how to handle different situations that could arise during FGDs. Furthermore, the actions taken by the assistant who attended the FGDs (previously described in detail in Material and Methods) were meant to enhance the study's credibility and trustworthiness.

The FGDs began with a 10-20-minute presentation by the moderator of the study and the guiding principles of the discussion. Participants were also asked to introduce themselves. The duration of discussion preceding the FGD was chosen as participants' awareness of the situation was likely reduced after this period of time.

Another way the undesirable consequences of reflexivity were minimised was to avoid leading questions by discussing the FGD guide with different researchers outside the research team and the moderators. Furthermore, the multidisciplinary nature of the research team brought varied and practical expertise, as is recommended in studies among immigrants (249). The research team that participated in the design, data collection and analysis were well versed in conducting qualitative studies. The team approach was also used for data analysis in order to strengthen the trustworthiness of the categorisation and interpretations of the findings. According to Krueger (228), analysis benefits from multiple insights and perspectives, such as those from co-researchers. In Study III, three of the six research team members had direct experience in the area of investigation, took an active part in data collection, and were also helpful in the interpreting of findings. Therefore I believe that this approach strengthened the trustworthiness of the categorisation and interpretations.

### *Triangulation and peer debriefing*

Triangulation and peer debriefing were also used. Triangulation is a technique in which the researcher uses several methods and perspectives of different people or groups to produce comprehensive findings (250). Triangulation is based on the idea that no single method can adequately answer the research problem and that by using various methods

of data collection and analysis, different aspects of empirical reality are revealed (251). Method triangulation, investigator triangulation and triangulation of data sources are common triangulation methods (252,253).

In Study III, data was collected from multiple sources using immigrant groups from two countries, with two age groups defined within each immigrant group, thus achieving triangulation of data sources. Investigator triangulation was also used by using two native speakers, one Danish speaker and one Norwegian speaker, as moderators, with a two-fold purpose. One purpose was to reach a varied sample by encouraging women who were hesitant to participate due to language problems to participate. The other reason was to encourage richer exchanges by facilitating discussion through the opportunity for the participants to discuss in their own language if they so wished for clarity of thought. I believe the triangulation methods have strengthened the credibility of the study. Peer debriefing of both researchers and professional colleagues was carried out, during which information on what was emerging from the study was shared, and feedback and valuable comments were received (250,254).

### *Transferability*

Transferability is also an important aspect regarding trustworthiness; it refers to how applicable the results may be to other contexts. Graneheim et al argued that the researcher can facilitate and suggest transferability, but that it is for the reader to judge whether it is transferable or not (225). It is important to give as thorough a description of the context of the study as possible. The description of how participants were selected, their characteristics, and how data was collected and analysed must be clear to facilitate the transferability of research findings to other contexts. However, the purpose of this study was not to collect data that can be used to make general statements, but to explore different aspects of the research topic. Although the credibility of generalisations from a qualitative study is not as good as that from a quantitative study, this does not mean that no generalisation can be made beyond the setting or informants in qualitative studies. It is important to be aware that qualitative studies often have what is called face generalisability: “there is no obvious reason not to believe that the results apply more generally” (255). The FGDs were held with a limited number of women in one urban area. The results can thus not be generalised to the larger Danish and Norwegian immigrant population in Sweden in our view. However, obtaining a more profound

understanding of how immigrant women reason about their cervical screening attendance requires a qualitative approach.

### **7.3 DISCUSSION OF MAIN FINDINGS**

Populations of immigrant women comprise a substantial number of individuals who have undergone a change in their environment, both socio-culturally and physically. Because of great variation in the prevalence of HPV infection and other risk factors for cervical cancer worldwide, immigrant studies may help further the understanding of the aetiology, and improve the prevention of cervical cancer. One of the main intentions of this thesis was to infer changes in the risk of cervical cancer among immigrant women given the relative aetiological importance of environmental factors versus inherited predisposition.

The degree of convergence between immigrant women and the population ASRs of Swedish-born women, and divergence between the rates in immigrant women and those in the country of birth, were investigated in this thesis. This may indicate that the ASRs for most low- and medium-resource countries are underestimated. Additionally, results are presented in this thesis for immigrant groups that originated from countries with no cancer registration, such as Turkey, Iraq, Iran, Lebanon, Chile, Greece, Romania and Hungary (8). These results may serve as estimates of the cancer rates in their countries of birth, but with debatable accuracy, since this assumes that no large selection has taken place. Furthermore, it must be remembered that figures presented by Globocan 2002 measure incidence long after the implementation of cervical screening in many European countries, while data in this thesis is based on a long follow-up time. The time period covered in this thesis comprises both ends of the spectrum in Sweden: the initial phase, where the incidence of cervical cancer was still high and cervical screening had just been introduced, and the long phase of low cancer incidence after the introduction of cervical screening. This may partially explain the higher ASR estimates presented in this thesis.

The variable immigrant status, although highly reproducible and subject to little misclassification, is a proxy for a host of unmeasured exposures and genetic predispositions. An association was shown between immigrant status and the risk of cervical cancer, and the association was significantly modified by follow-up time and age at immigration. The risk of cervical cancer decreased by follow-up time for most

immigrant groups, and the older women were when they immigrated to Sweden, the higher their risk of cervical cancer. In order to evaluate the change in the risk of cervical cancer among immigrant groups in the host country, 10 years was assumed to be sufficient to affect the risk of cervical cancer. The pattern of changes in risk of cervical cancer experienced by immigrants may suggest that sustained exposure is needed before the risk of cervical cancer is altered, or that the agent is only important with respect to exposures early in life. It has been postulated that the first 2 decades of life are what establish the risk of cancer development later in life. Therefore, if an immigrant woman enters Sweden in her 20s it may already be too late to influence her environmentally imprinted cancer development programme (129).

The estimation of risk of cervical cancer by follow-up time in the new host country and age at immigration used in this thesis is one of two possible approaches to investigate the rate of change of risk in immigrants, namely the study of risk in relation to age at immigration/duration of residence and the comparison of risk in immigrants and their offspring. However, as age itself is such a strong determinant of the risk of cervical cancer, and is an essential factor in any analysis, there is no variability left in follow-up time after controlling for age at immigration, or vice versa. Thus, these two variables are closely inter-related, which implies difficulties in distinguishing the effects of one variable from that of the other. A pragmatic solution was adopted in this thesis: to examine each variable in turn (age/follow-up time or age/age at immigration) to see which provided the most plausible pattern of change in risk, bearing in mind that follow-up time and age at immigration are inevitably mutually confounded (1).

The risk of cervical cancer was heavily reduced among immigrant women who adhered to the recommended screening intervals. However, adherent Norwegian and Baltic immigrant women showed IRs as high as 10 and 17 per 100 000. This may indicate a high prevalence of risk factors that are not fully addressed by cervical screening, such as changes in lifestyle factors and/or the detection of prevalent cancers through the screening programme. The influence of environmental factors on cancer risk and immigration embraces not only the abrupt change in physical surroundings, but also comprises elements of lifestyle. Examples of lifestyle factors are childbearing patterns, alcohol and tobacco consumption, and sexual behaviour (1).



The sexual behaviour of immigrant women and their partners in the host country is one of the lifestyle factors that needs to be considered in this thesis. The public health interest in sexual behaviour is due to the association between reproductive health and STIs such as HPV, which is a causal factor in cervical cancer development. Although immigrants to countries with a liberal sexual attitudes such as Sweden clearly have the same potential to adopt these liberal attitudes as the Swedish-born population, immigrants may be more or less inclined to retain the culturally-defined sexual behaviour of their country of birth. The sexual attitudes in Sweden and other Nordic countries are known to be relatively liberal and open (256). But although the attitude toward sexual matters is a notably open feature of Swedish society, there are different degrees of openness and it is mainly the biological side of sexuality that is openly discussed (257).

The Swedish tradition of a supportive approach towards adolescent sexual relations, including the existence of a network of youth health clinics, needs to be evaluated in view of the changing epidemiology of sexual health in Sweden. The increase in the incidence of STIs such as chlamydia and gonorrhoea, and the spread of HPV and herpes simplex virus type 2, in combination with the decrease in condom sales, might be an indication that the practice of safe sex is decreasing (258).

A population-based, cross-sectional study reported a median age at first sexual intercourse of 16 years for women in Sweden, Denmark, Norway and Iceland, and noted that many women in these countries have had more than 10 sexual partners in their lifetime (259). This is of significance as both early age at first sexual intercourse and high lifetime number of sexual partners are considered risk factors for cervical cancer. The relatively high sexual activity among women living in the Nordic countries may partly explain the comparatively high incidence of cervical cancer observed among Nordic immigrants in Sweden, as presented in the results from Study I. The risk of cervical cancer has been reported to be high in Denmark (260,261); this has also been shown to be the case among immigrant women from Denmark in Sweden in other studies (127,128). Sexual behaviour after immigration has been suggested to play an important role in the risk of cervical cancer. In addition, differences in the prevalence of HPV infection between immigrant women and the population of the host country may be influenced by sexual behaviour (129). The prevalence of HPV among women

with normal cervical cytology in Denmark is around three times higher than among women in Sweden (130).

Immigrant status has been linked to later age at first sexual intercourse (262-265), lower number of sexual partners, and lower rates of contraceptive use (266,267) among Hispanics in the United States. Variations in age at first sexual intercourse by immigrant status are substantial, and the nature of these differences varies by country according to the culture and values of the particular minority or immigrant group (265). The age-specific IRs (Study II) presented in Figure 2 increased and peaked at an older age (5-10 years later) among immigrant non-attenders compared to Swedish-born non-attenders. This may indicate that the first sexual intercourse is occurring later among immigrant women than among Swedish-born women. HPV infection is essential in cervical cancer development. The effect of risk factors such as age at first sexual intercourse and lifetime number of sexual partners, is mediated via exposure to HPV or by affecting susceptibility to the carcinogenic effects of HPV (268). It has been shown that the high prevalence of HPV infection among immigrant women residing in Italy (132) correlates very well with the risk of invasive cervical cancer in these women. Crocetti et al (146) recently evaluated the risk of invasive and *in situ* cervical cancer, during the period 2000-2004 among immigrant women aged 25-59 living in central Italy. The incidence of invasive cervical cancer among women born in Central and South America and the Caribbean (60.5 per 100 000) and among women born in Central and Eastern Europe (38.3 per 100 000) was statistically and significantly higher than that of Italian-born women (33).

The high HPV prevalence and cervical cancer incidence in Africa compared to Eastern African immigrants in Sweden, who had an 80% decreased RR compared to Swedish-born women, needs further investigation. One study found no significant difference among African immigrants in France compared to French-born women (139). In another study, cervical cancer mortality was observed to be 60% lower among Eastern African immigrants in England and Wales compared to that in the English- and Wales-born population (140). In both these studies (139,140) it was suggested that the results may be due to the relatively higher socioeconomic status of these African immigrants. The variation in sensitivity and specificity of HPV testing methods may underlie some of the variability in HPV prevalence from different studies, but it is also worth

considering possible differences in surveillance and detection. Another plausible explanation is that this might indicate a larger selection mechanism (the healthy migrant effect).

Tobacco use has been shown to be associated with geographical variations in lung cancer incidence (148), and has also been shown to increase the risk of cervical cancer (65). A study on the risk of lung cancer among immigrants to Sweden reported that ASRs (World) from 1993-2008 for lung cancer by histology among women in Sweden were 14.3 per 100 000 and among all immigrants combined 13.4 per 100 000. However, there was a large variation, with Danish (23.3), Norwegian (19.5) and Finnish (14.5) immigrant women having the highest IRs of lung cancer, and Asian and Arab women having the lowest IR (5.8). Consequently, smoking behaviour in the host country is a likely explanation for the preservation of IRs of lung cancer in the country of birth. It has been reported that immigrant women from other European countries in Sweden smoke more than Swedish-born women, while those who are born outside Europe smoke the least (269,270).

The higher risk of cervical cancer found among women who were older at immigration may be due to persistent HPV infection, or the presence of precancerous lesions before immigration, in combination with a lower adherence to cervical screening. In addition, women are not invited to organised screening after 60 years of age in Sweden.

In this thesis an excess risk of cervical cancer mortality was observed among both Swedish-born and immigrant women with low education level, independent of history of cervical screening attendance. One study in Sweden showed statistically significantly higher survival rates for the highest group of socioeconomic status (271). It has also recently been shown that the odds of cervical cancer morbidity and mortality in Sweden are higher among women residing in deprived neighbourhoods than among women living in wealthy neighbourhoods. Adjustment for individual-level sociodemographic variables and comorbidities did not alter this difference (272). The pronounced hierarchy among different immigrant groups and Swedish-born women is a striking feature in Sweden that exists both in the labour market and in housing. This is further characterized by the distinct multi-ethnic character of all immigrant-dense neighbourhoods. In Sweden, immigrants are often young adults, and households comprised of young adults are

overrepresented in rental housing. Demography as well as income could be factors that explain immigrants' positions in the housing market. Although housing location might be the result of immigrants' preferences, their labour market position is not (273). However, neither the causal pathways between neighbourhood socioeconomic deprivation and poor health outcomes nor socioeconomic status and prognosis are fully understood.

In summary, there is a close association between an individual's lifetime exposure to various risk factors and carcinogenesis. Other important factors in cancer development and the causal roles of exposures in the country of birth are represented by the time before and after immigration, as well as the influence of social factors in the country of birth (274-277). However, this kind of information is rarely available, and this thesis is no exception. A main reason for the diversity of cancer risk with duration of residence in the host country, which in this thesis refers to the effect of follow-up time, is that exposure to risk factors and adaptation to changing environments evolve over time. Cancer risk among immigrants can be expected to converge towards the rates of the population in the host country over time and across generations, which can be seen as a consequence of a simultaneous decrease among immigrants with high cancer incidence and increase in those with a formerly low cancer incidence (274-277).

The persistence of cervical cancer risk across generations, i.e., among first- and second-generation immigrant women, was not investigated in this thesis. However, a Swedish study has shown that both risk of cervical cancer and cervical cancer mortality were fairly unchanged in second-generation compared to first-generation immigrant women. The authors (128) suggested that the risk factors and protective factors of cervical cancer, which were mainly behavioural aspects, were retained after immigration and across generations and/or that it could represent an aetiological factor by familial aggregation.

Despite the many similarities between Denmark, Norway and Sweden with regard to the way of life, history, language and social structure, including the existence of an organised cervical screening programme (278,279), immigration to Sweden *per se* seemed to influence our participating Danish and Norwegian immigrant women not to attend to cervical screening according to the recommendations of the Swedish National Board of

Health and Welfare. Consistent with previous research, competing needs have been shown to be major obstacles to cervical screening attendance among immigrant women (280). However, the competing needs evoked by immigrant women in the United States were essential needs, such as food, shelter and clothing (280). The Danish and Norwegian immigrant women in our study discussed specifically how their energy and focus were consumed by the change of environment, attempts to learn how different societal systems worked in the new country, and to their resettlement efforts, all of which are related to competing needs due to the immigration. This may indicate that the process of transitioning to life in a new country can be difficult and stressful for immigrant women even if the new host country is a neighbouring country with many similarities. Danish and Norwegian immigrant women who took part in this qualitative study revealed views that can be summarised into one main theme: “Women have a comprehensive rationale for postponing cervical screening, yet do not view themselves as non-attenders”. This view was apparent even when the delay had been up to a decade. The main finding indicates that postponement of cervical screening attendance was based on the women’s rationale, which was partially explained by factors related to immigration, but was also influenced by other aspects, such as previous experiences, psychological and individual factors, childbearing-related factors, social support and social network, and risk perception. The women’s reasoning thereby revealed no active stance against attending cervical screening (defined as attendance according to the recommendations of the Swedish National Board of Health and Welfare). The women’s reasoning of postponement was rather due to a comprehensive rationale.

While human papillomavirus vaccination will probably play a major role in the primary prevention of cervical cancer for young birth cohorts in the future, cervical screening will remain the principal strategy to prevent cervical cancer for many decades. The public health benefits of newly introduced HPV vaccines offer an opportunity to address cervical cancer disparities, but a substantial decrease in cervical cancer burden will only be attained if the new technology is also accepted and used by high-risk groups, including high-risk immigrant groups (161). If HPV vaccination was offered to younger birth cohorts of immigrant groups who do not participate in screening, it could have a long-lasting impact and reduce the risk of cervical cancer substantially in the future. For immigrant women who are beyond the age at which HPV vaccination is recommended or is effective, efforts to improve access to cervical screening should

continue, especially for immigrant groups with a high risk of cervical cancer. Overall, the results presented in this thesis demonstrate that immigrants in Sweden bring their own unique health characteristics with them. These characters may be quite different from those of the general Swedish population and are also likely to differ according to their country of birth.

#### **7.4 IMPLICATIONS OF FINDINGS**

Health care providers should be aware of immigrant women from regions where there is a high risk of cervical cancer. Clinicians who care for women who have immigrated from these regions should obtain a careful medical history to determine whether a Pap smear was performed prior to immigration, or after their arrival in Sweden, and should offer them an additional Pap smear unless their previous results were normal. Furthermore, clinicians should seize the opportunity to discuss cervical screening attendance with newly immigrated women, including where and how to get screened, which could be highly influential in their decision to attend cervical screening.

Though the organised cervical screening programme in Sweden invites all women 23-60 years of age, it would be justified to have a more prompt approach to screen older female immigrants at least once after their arrival in Sweden. Immigration at older ages seems to infer a higher risk of cervical cancer and should be considered an important barrier to cervical screening, which in turn infers a high risk of cervical cancer.

A good cervical cancer prevention programme must determine the demands that will be placed on high-quality organised cervical screening in the future. This should include reaching women who are most in need of screening through targeted prevention and identification of risk factors and high-risk groups. In order to reduce cervical cancer mortality, the importance of increasing the coverage of cervical screening programmes among patients with low socioeconomic status, regardless of whether they are immigrant or Swedish-born women, should be emphasised in public health programmes.

Despite a higher risk of cervical cancer among certain immigrant groups compared to others, and a lower degree of cervical screening attendance among immigrant women compared to Swedish-born women, cervical cancer prognosis is still 20% better among

non-Nordic immigrants, whereas no significant differences were observed among Nordic immigrants. This seems to indicate that as long as women diagnosed with cervical cancer have access to high-quality care and treatment, there is a chance for a good prognosis, regardless of their country of birth.

## **7.5 CONCLUSIONS**

In Study I the incidence of cervical cancer among immigrant women was generally lower than that among women in their country of birth. However, immigrants from Finland, Denmark and Norway had considerably higher ASRs compared to women in their country of birth. Compared to Swedish-born women, the risks of cervical cancer among women from Northern Europe, Middle Africa and Central America were higher, while the opposite was true for women from Eastern Africa and South Central Asia. It was concluded that age at immigration and follow-up time were important effect modifiers for the risk of cervical cancer among immigrant women in Sweden; those who immigrated at an older age ( $\geq 50$  years) had a higher risk than those who immigrated at a younger age ( $< 30$  years), and the risk of cervical cancer decreased in many groups of immigrant women after living 10 years in Sweden. The decreasing trend in the risk of cervical cancer by follow-up time also indicates that the immigrants benefit more from the cervical screening programme the longer they live in Sweden. However, the increasing trend among immigrants from the Baltic States and Western Asia indicates that exposure to risk factors for cervical cancer in Sweden has probably increased over time for these women. Therefore targeted prevention programmes should be recommended for high-risk immigrant women, specifically those who immigrate at older ages ( $\geq 50$  years).

In Study II the mean cervical screening attendance among Swedish-born women was higher than among immigrant women in Sweden, and there was a higher proportion of immigrants who did not attend cervical screening at all. Cervical screening attendance showed large variations between immigrant groups, and attendance was lowest among those who immigrated at older ages. The risk of cervical cancer increased at least five-fold both among immigrant and Swedish-born non-attenders. After adjustment for cervical screening attendance, only two immigrant groups showed an excess RR for cervical cancer, namely women from Norway and the Baltic States. We therefore conclude that adherence to recommended screening intervals is very effective in

preventing cervical cancer, although other factors, e.g., socioeconomic status and risk factor prevalence, should also be taken into consideration. In addition, immigration at older ages seems to be an important barrier to cervical screening attendance, which infers a high risk of cervical cancer.

In Study III, the main theme generated from the data was “Women have a comprehensive rationale for postponing cervical screening, yet do not view themselves as non-attenders”. Investigation of women’s rationale for non-attendance after being invited to cervical screening revealed, amongst the factors discussed, some complex reasons related to immigration itself, including competing needs, organisational and structural factors and differences in mentality. The rationale used to postpone cervical screening, in combination with the fact that women do not consider themselves to be non-attenders, indicates that they have not actively taken a stance against cervical screening, and reveals an opportunity to motivate these women to attend.

In Study IV certain immigrant groups had a higher risk of cervical cancer than Swedish-born women, but their prognoses were rather equal. Prognosis of cervical cancer was better among non-Nordic immigrants than Swedish-born women, indicating their equal access to health care in Sweden. Both Swedish-born and immigrant women showed a three- to four-fold, non-differential excess risk of mortality among symptomatic cases, with or without a history of cervical screening attendance, compared to screening-detected cases. An excess risk of cervical cancer mortality was observed among both Swedish-born and immigrant women with low education level, independent of history of cervical screening attendance. This was also the case for Swedish-born women with low manual household occupational class, women from households not in the labour force and women with missing information on occupational class. The findings emphasise the importance of increasing the coverage of cervical cancer prevention programmes such as cervical screening among high-risk groups and patients with low socioeconomic status, be they immigrant or Swedish-born women, to reduce cervical cancer mortality.

## **7.6 FUTURE RESEARCH**

One important area that remains unclear is whether differences in sexual behaviour by country of birth are consistent across the age spectrum, and the extent to which age at



immigration has an impact on high-risk sexual behaviour. Future studies will benefit from assessing partnership-level characteristics in addition to individual-level high-risk sexual behaviour. The investigation of the risk of cervical cancer among immigrants by HPV variants and other environmental factors is another important area of future research.

There is also a need for more research regarding women's views about health and disease, and their knowledge about cervical cancer and its prevention, which may also influence cervical screening attendance. Future studies on the identification of possible lifestyle and clinical factors that may account for apparent advantages and disadvantages in prognosis of immigrant groups and how they influence cervical cancer prognosis may further shed light on the aetiology of cervical cancer. This knowledge may improve opportunities from a public health perspective to adopt broad-based interventions that could produce substantial health benefits for women.

There is still little understanding of how social determinants are affected by immigrant status, or how social determinants operate in conjunction with immigrant status to influence cervical cancer survival in a country with universal access to health care. One reason may be that socioeconomic status is a culturally sensitive variable, and that the tools to measure socioeconomic status need to be further developed and improved. Thus a part of the research agenda for the future is to develop a greater understanding of the joint and separate functioning of social determinants and immigrant status in influencing the risk of cervical cancer and its prognosis.

Findings are important for further research on cancer aetiology, policy development and health service planning. Improved health promotion and disease prevention strategies could be further investigated, including primary and secondary prevention programmes, to encourage use of available health services (e.g. cervical screening programmes and HPV vaccination programme) and to meet the health needs of immigrants.

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## 9 REFERENCE LIST

- (1) Parkin DM, Khlat M. Studies of cancer in migrants: rationale and methodology. *Eur J Cancer* 1996 May;32A:761-71.
- (2) Bosch FX, de Sanjosé S. Chapter 1: Human papillomavirus and cervical cancer--burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003;(31):3-13.
- (3) Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-9.
- (4) Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518-27.
- (5) Clifford GM, Gallus S, Herrero R, Muñoz N, Snijders PJ, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet* 2005;366:991-8.
- (6) Arbyn M, Raifu AO, Autier P, Ferlay J. Burden of cervical cancer in Europe: estimates for 2004. *Ann Oncol* 2007;18:1708-15.
- (7) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer incidence and mortality worldwide: IARC CancerBase No. 10 [Internet]. Lyon; International Agency for Research on Cancer; 2010 [cited May 2013]. Available from <http://globocan.iarc.fr>
- (8) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
- (9) Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007;370:890-907.
- (10) Thomas DB, Karagas MR. Migrant studies. In: Schottenfeld D, Fraumeni JF, Jr., editors. *Cancer epidemiology and prevention*. 2nd edition. New York: Oxford University Press; 1996. p. 236-54.
- (11) Singh GK, Miller BA, Hankey BF, Edwards BK. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival, 1975-2000. *Cancer* 2004;101:1051-7.

- (12) Johnson M, Coker A, Moore CG, Bolick-Aldrich S. Poverty and cervical cancer survival among South Carolina women. *Am J Epidemiol* 2004;159(11 Suppl):S69.
- (13) Shelton D, Paturzo D, Flannery J, Gregorio D. Race, stage of disease, and survival with cervical cancer. *Ethn Dis* 1992;2:47-54.
- (14) Brooks SE, Baquet CR, Gardner JF, Moses G, Ghosh A. Cervical cancer--the impact of clinical presentation, health and race on survival. *J Assoc Acad Minor Phys* 2000;11:55-9.
- (15) Invasive cervical cancer among Hispanic and non-Hispanic women--United States, 1992-1999. *MMWR Morb Mortal Wkly Rep* 2002;51:1067-70.
- (16) Breen N, Figueroa JB. Stage of breast and cervical cancer diagnosis in disadvantaged neighborhoods: a prevention policy perspective. *Am J Prev Med* 1996;12:319-26.
- (17) del Carmen MG, Montz FJ, Bristow RE, Bovicelli A, Cornelison T, Trimble E. Ethnic differences in patterns of care of stage 1A(1) and stage 1A(2) cervical cancer: a SEER database study. *Gynecol Oncol* 1999;75:113-7.
- (18) United Nations Population Fund. State of world population 2006. A passage to hope - Women and international migration. New York: United Nations Population Fund; 2006.
- (19) Statistics Sweden. Utrikes födda efter region, ålder i tioårsklasser och kön. År 2001-2012. Stockholm: Statistics Sweden; 2013 [cited May 2013]. Available from:  
[http://www.scb.se/Pages/SSD/SSD\\_SelectVariables\\_\\_\\_\\_340487.aspx?rxid=82ae3e5a-0917-40d9-a188-7866e08a1a99&px\\_tableid=ssd\\_extern%3aUtrikesFoddaTotNK](http://www.scb.se/Pages/SSD/SSD_SelectVariables____340487.aspx?rxid=82ae3e5a-0917-40d9-a188-7866e08a1a99&px_tableid=ssd_extern%3aUtrikesFoddaTotNK).
- (20) Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. *Eur J Cancer* 2010;46:2647-59.
- (21) IARC. IARC handbooks of cancer prevention. Volume 10: Cervix cancer screening. Lyon: International Agency for Research on Cancer; 2005.
- (22) Tota JE, Chevarie-Davis M, Richardson LA, Devries M, Franco EL. Epidemiology and burden of HPV infection and related diseases: implications for prevention strategies. *Prev Med* 2011;53 (Suppl 1):S12-S21.
- (23) Lax S. Histopathology of cervical precursor lesions and cancer. *Acta Dermatovenerol Alp Panonica Adriat* 2011;20:125-33.



- (24) Castle PE, Schiffman M, Bratti MC, Hildesheim A, Herrero R, Hutchinson ML, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. *J Infect Dis* 2004;190:458-67.
- (25) Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine* 2006;24 (Suppl 3):S3-11-S3/25.
- (26) de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. *Virology* 2004;324:17-27.
- (27) Gillison ML, Alemany L, Snijders PJ, Chaturvedi A, Steinberg BM, Schwartz S, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. *Vaccine* 2012;30 (Suppl 5):F34-F54.
- (28) Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 2007;121:621-32.
- (29) Stanley M. HPV - immune response to infection and vaccination. *Infect Agent Cancer* 2010;5:19.
- (30) Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003;157:218-26.
- (31) Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol* 1998;91:92-6.
- (32) Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32 (Suppl 1):S16-S24.
- (33) Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006;354:2645-54.
- (34) Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *Int J Cancer* 2003;107:811-6.
- (35) Richardson H, Abrahamowicz M, Tellier PP, Kelsall G, du BR, Ferenczy A, et al. Modifiable risk factors associated with clearance of type-specific cervical human papillomavirus infections in a cohort of university students. *Cancer Epidemiol Biomarkers Prev* 2005;14:1149-56.

- (36) Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12:186-92.
- (37) Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol* 2007;127:805-15.
- (38) McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;9:425-34.
- (39) Chang AR. Carcinoma in situ of the cervix and its malignant potential. A lesson from New Zealand. *Cytopathology* 1990;1:321-8.
- (40) Franceschi S, Rajkumar R, Snijders PJ, Arslan A, Mahe C, Plummer M, et al. Papillomavirus infection in rural women in southern India. *Br J Cancer* 2005;92:601-6.
- (41) Pham TH, Nguyen TH, Herrero R, Vaccarella S, Smith JS, Nguyen Thuy TT, et al. Human papillomavirus infection among women in South and North Vietnam. *Int J Cancer* 2003;104:213-20.
- (42) Sukvirach S, Smith JS, Tunsakul S, Muñoz N, Kesararat V, Opatatian O, et al. Population-based human papillomavirus prevalence in Lampang and Songkla, Thailand. *J Infect Dis* 2003;187:1246-56.
- (43) Shin HR, Lee DH, Herrero R, Smith JS, Vaccarella S, Hong SH, et al. Prevalence of human papillomavirus infection in women in Busan, South Korea. *Int J Cancer* 2003;103:413-21.
- (44) Molano M, Posso H, Weiderpass E, van den Brule AJ, Ronderos M, Franceschi S, et al. Prevalence and determinants of HPV infection among Colombian women with normal cytology. *Br J Cancer* 2002;87:324-33.
- (45) Matos E, Loria D, Amestoy GM, Herrera L, Prince MA, Moreno J, et al. Prevalence of human papillomavirus infection among women in Concordia, Argentina: a population-based study. *Sex Transm Dis* 2003;30:593-9.
- (46) Ferreccio C, Prado RB, Luzoro AV, Ampuero SL, Snijders PJ, Meijer CJ, et al. Population-based prevalence and age distribution of human papillomavirus among women in Santiago, Chile. *Cancer Epidemiol Biomarkers Prev* 2004;13:2271-6.

- (47) Jacobs MV, Walboomers JM, Snijders PJ, Voorhorst FJ, Verheijen RH, Franssen-Daalmeijer N, et al. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer* 2000;87:221-7.
- (48) Ronco G, Ghisetti V, Segnan N, Snijders PJ, Gillio-Tos A, Meijer CJ, et al. Prevalence of human papillomavirus infection in women in Turin, Italy. *Eur J Cancer* 2005;41:297-305.
- (49) Lazcano-Ponce E, Herrero R, Muñoz N, Cruz A, Shah KV, Alonso P, et al. Epidemiology of HPV infection among Mexican women with normal cervical cytology. *Int J Cancer* 2001;91:412-20.
- (50) Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, Oh JK, et al. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis* 2004;190:468-76.
- (51) Thomas JO, Herrero R, Omigbodun AA, Ojemakinde K, Ajayi IO, Fawole A, et al. Prevalence of papillomavirus infection in women in Ibadan, Nigeria: a population-based study. *Br J Cancer* 2004;90:638-45.
- (52) de Sanjosé S, Almirall R, Lloveras B, Font R, Diaz M, Muñoz N, et al. Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis* 2003;30:788-93.
- (53) de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis* 2007;7:453-9.
- (54) Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, De SS. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010;202:1789-99.
- (55) Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. *Virus Res* 2002;89:229-40.
- (56) Strickler HD, Palefsky JM, Shah KV, Anastos K, Klein RS, Minkoff H, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. *J Natl Cancer Inst* 2003;95:1062-71.
- (57) Shepherd JJ, Peersman G, Napuli I. Interventions for encouraging sexual lifestyles and behaviours intended to prevent cervical cancer. *Cochrane Database Syst Rev* 2009; CD001035.

- (58) Louie KS, de Sanjosé S, Diaz M, Castellsagué X, Herrero R, Meijer CJ, et al. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *Br J Cancer* 2009;100:1191-7.
- (59) Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst* 2010;102:315-24.
- (60) Edelstein ZR, Madeleine MM, Hughes JP, Johnson LG, Schwartz SM, Galloway DA, et al. Age of diagnosis of squamous cell cervical carcinoma and early sexual experience. *Cancer Epidemiol Biomarkers Prev* 2009;18:1070-6.
- (61) Biswas LN, Manna B, Maiti PK, Sengupta S. Sexual risk factors for cervical cancer among rural Indian women: a case-control study. *Int J Epidemiol* 1997;26:491-5.
- (62) Leval A, Sundstrom K, Ploner A, Dahlstrom LA, Widmark C, Sparén P. Assessing perceived risk and STI prevention behavior: a national population-based study with special reference to HPV. *PLoS One* 2011;6:e20624.
- (63) International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and sexual behavior: collaborative reanalysis of individual data on 15,461 women with cervical carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies. *Cancer Epidemiol Biomarkers Prev* 2009;18:1060-9.
- (64) Castellsagué X, Bosch FX, Muñoz N, Meijer CJ, Shah KV, de Sanjosé S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002;346:1105-12.
- (65) International Collaboration of Epidemiological Studies of Cervical Cancer. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer* 2006;118:1481-95.
- (66) Castellsagué X, Muñoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *J Natl Cancer Inst Monogr* 2003;(31):20-8.
- (67) Khan MJ, Partridge EE, Wang SS, Schiffman M. Socioeconomic status and the risk of cervical intraepithelial neoplasia grade 3 among oncogenic human

- papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. *Cancer* 2005;104:61-70.
- (68) Garcia-Closas R, Castellsagué X, Bosch X, Gonzalez CA. The role of diet and nutrition in cervical carcinogenesis: a review of recent evidence. *Int J Cancer* 2005;117:629-37.
- (69) Potischman N, Freudenheim JL. Biomarkers of nutritional exposure and nutritional status: an overview. *J Nutr* 2003;133 (Suppl 3):873S-4S.
- (70) Zhang X, Dai B, Zhang B, Wang Z. Vitamin A and risk of cervical cancer: a meta-analysis. *Gynecol Oncol* 2012;124:366-73.
- (71) Statistics Sweden. Tables on population in Sweden 2006. Örebro: Statistics Sweden; 2007 [cited May, 2013]. Available from: [http://www.scb.se/statistik/publikationer/BE0101\\_2006A01\\_BR\\_BE0107TAB.pdf](http://www.scb.se/statistik/publikationer/BE0101_2006A01_BR_BE0107TAB.pdf).
- (72) Statistics Sweden. To measure and monitor internal migration based on national population register. IAOS Conference Ottawa, Canada. Örebro: Statistics Sweden; 2006.
- (73) Jorde LB, Watkins WS, Bamshad MJ, Dixon ME, Ricker CE, Seielstad MT, et al. The distribution of human genetic diversity: a comparison of mitochondrial, autosomal, and Y-chromosome data. *Am J Hum Genet* 2000;66:979-88.
- (74) Hinds DA, Stuve LL, Nilsen GB, Halperin E, Eskin E, Ballinger DG, et al. Whole-genome patterns of common DNA variation in three human populations. *Science* 2005;307:1072-9.
- (75) Chaturvedi N, McKeigue PM. Methods for epidemiological surveys of ethnic minority groups. *J Epidemiol Community Health* 1994;48:107-11.
- (76) McKenney NR, Bennett CE. Issues regarding data on race and ethnicity: the Census Bureau experience. *Public Health Rep* 1994;109:16-25.
- (77) Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. *BMJ* 1994;309:327-30.
- (78) Williams DR, Lavizzo-Mourey R, Warren RC. The concept of race and health status in America. *Public Health Rep* 1994;109:26-41.
- (79) Kressin NR, Chang BH, Hendricks A, Kazis LE. Agreement between administrative data and patients' self-reports of race/ethnicity. *Am J Public Health* 2003;93:1734-9.

- (80) Hutchinson J, Smith AD, editors. *Ethnicity*. New York: Oxford University Press; 1996.
- (81) Cornell S, Hartmann D. *Ethnicity and race: making identities in a changing world*. Thousand Oaks: Pine Forge Press; 1998.
- (82) The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet* 2005;77:519-32.
- (83) Hayes-Bautista DE, Chapa J. Latino terminology: conceptual bases for standardized terminology. *Am J Public Health* 1987;77:61-8.
- (84) Oppenheimer GM. Paradigm lost: race, ethnicity, and the search for a new population taxonomy. *Am J Public Health* 2001;91:1049-55.
- (85) Foster MW, Sharp RR. Beyond race: towards a whole-genome perspective on human populations and genetic variation. *Nat Rev Genet* 2004;5:790-6.
- (86) Integrating ethics and science in the International HapMap Project. *Nat Rev Genet* 2004;5:467-75.
- (87) Mays VM, Ponce NA, Washington DL, Cochran SD. Classification of race and ethnicity: implications for public health. *Annu Rev Public Health* 2003;24:83-110.
- (88) Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. *Ethn Health* 2009;14:255-69.
- (89) Helman CG. *Culture, health and illness*. 5th edition. New York: Oxford University Press; 2007.
- (90) Skegg DC, Corwin PA, Paul C, Doll R. Importance of the male factor in cancer of the cervix. *Lancet* 1982;2:581-3.
- (91) United Nations Department of Economic and Social Affairs Population Division. *International migration report 2006*. New York: United Nations; 2006.
- (92) World Health Organization. *Sexual determinants of sexual and reproductive health. Informing future research and programme implementation*. Geneva: World Health Organization; 2010.
- (93) [www.migrationsinfo.se](http://www.migrationsinfo.se). Historical [Internet]. [Place unknown]: [www.migrationsinfo.se](http://www.migrationsinfo.se) [updated: 11 February 2013;April 2013]. Available from: <http://www.migrationsinfo.se/migration/sverige/historiskt/>.

- (94) SOPEMI (Continuous Reporting System on Migration). Trends in international migration: annual report. Paris: Organization for Economic Cooperation and Development; 2001.
- (95) Aral SO, Ward H. Modern day influences on sexual behavior. *Infect Dis Clin North Am* 2005;19:297-309.
- (96) Wellings K, Collumbien M, Slaymaker E, Singh S, Hodges Z, Patel D, et al. Sexual behaviour in context: a global perspective. *Lancet* 2006;368:1706-28.
- (97) UNDESA. World population monitoring, focusing on international migration and development: Report of the Secretary-General. New York: United Nations; 2006.
- (98) Gonzalez C, Ortiz M, Canals J, Muñoz L, Jarrin I, de la Hera MG, et al. Higher prevalence of human papillomavirus infection in migrant women from Latin America in Spain. *Sex Transm Infect* 2006;82:260-2.
- (99) del Amo J, Gonzalez C, Losana J, Clavo P, Muñoz L, Ballesteros J, et al. Influence of age and geographical origin in the prevalence of high risk human papillomavirus in migrant female sex workers in Spain. *Sex Transm Infect* 2005;81:79-84.
- (100) Adrien A, Leane V, Remis RS, Boivin JF, Rud E, Duperval R, et al. Migration and HIV: an epidemiological study of Montrealers of Haitian origin. *Int J STD AIDS* 1999;10:237-42.
- (101) Rangel MG, Martinez-Donate AP, Hovell MF, Santibanez J, Sipan CL, Izazola-Licea JA. Prevalence of risk factors for HIV infection among Mexican migrants and immigrants: probability survey in the North border of Mexico. *Salud Publica Mex* 2006;48:3-12.
- (102) Mercer A, Khanam R, Gurley E, Azim T. Sexual risk behavior of married men and women in Bangladesh associated with husbands' work migration and living apart. *Sex Transm Dis* 2007;34:265-73.
- (103) Yang X, Derlega VJ, Luo H. Migration, behaviour change and HIV/STD risks in China. *AIDS Care* 2007;19:282-8.
- (104) Zuma K, Lurie MN, Williams BG, Mkaya-Mwamburi D, Garnett GP, Sturm AW. Risk factors of sexually transmitted infections among migrant and non-migrant sexual partnerships from rural South Africa. *Epidemiol Infect* 2005;133:421-8.
- (105) International Coalition on AIDS and Development. International Migration and HIV/AIDS. Ottawa: International Coalition on AIDS and Development; 2004. Available from: [http://icad-cisd.com/pdf/e\\_Migration\\_FINAL.pdf](http://icad-cisd.com/pdf/e_Migration_FINAL.pdf).

- (106) International Organization for Migration. Migration and HIV/AIDS in Europe. Geneva: International Organization for Migration; 2000.
- (107) International Organization for Migration. IOM position paper on HIV/AIDS and migration. Geneva: International Organization for Migration; 2002.
- (108) Ezzati M, Hoorn SV, Rodgers A, Lopez AD, Mathers CD, Murray CJ. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet* 2003;362:271-80.
- (109) Slaymaker E. A critique of international indicators of sexual risk behaviour. *Sex Transm Infect* 2004;80 (Suppl 2)::ii13-ii21.
- (110) Collumbien M, Gerressu M, Cleland J. Non use and use of ineffective methods of contraception. In: Ezzati M, Lopez A, Rodgers A, Murray C, editors. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization; 2004. p. 1255-320.
- (111) National Center for Health Statistics. Health, United States, 1998: Socioeconomic status and health chartbook. Hyattsville: National Center for Health Statistics; 1998.
- (112) Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood)* 2002;21:60-76.
- (113) Ross CE, Wu C. The links between education and health. *American Sociological Review* 1995;719-45.
- (114) Kaplan GA, Pamuk ER, Lynch JW, Cohen RD, Balfour JL. Inequality in income and mortality in the United States: analysis of mortality and potential pathways. *BMJ* 1996;312:999-1003.
- (115) Backlund E, Sorlie PD, Johnson NJ. A comparison of the relationships of education and income with mortality: the National Longitudinal Mortality Study. *Soc Sci Med* 1999;49:1373-84.
- (116) Ross CE, Mirowsky J. Does employment affect health? *J Health Soc Behav* 1995;36:230-43.
- (117) Wilson SH, Walker GM. Unemployment and health: a review. *Public Health* 1993;107:153-62.
- (118) Gregorio DI, Walsh SJ, Paturzo D. The effects of occupation-based social position on mortality in a large American cohort. *Am J Public Health* 1997;87:1472-5.



- (119) de Sanjosé S, Bosch FX, Muñoz N, Shah K. Social differences in sexual behaviour and cervical cancer. *IARC Sci Publ* 1997;(138):309-17.
- (120) Segnan N. Socioeconomic status and cancer screening. *IARC Sci Publ* 1997;(138):369-76.
- (121) Roine J, Waldenström D. The evaluation of top incomes in an egalitarian society: Sweden 1903-2004. *Journal of Public Economics* 2008;92:366-87.
- (122) Swedish Association of Local Authorities and Regions. Swedish health care in international context - a comparison of care needs, costs and outcomes. Stockholm: Swedish Association of Local Authorities and Regions; 2005.
- (123) Micheli A, Coebergh JW, Mugno E, Massimiliani E, Sant M, Oberaigner W, et al. European health systems and cancer care. *Ann Oncol* 2003;14 (Suppl 5):v41-v60.
- (124) National Board of Health and Welfare. [Guidelines for cervical screening]. Stockholm: National Board of Health and Welfare; 1998. Swedish.
- (125) Social and Cultural Planning office of the Netherlands (SCP). Public sector performance 2004. An international comparison of education, health care, law and order, and public administration. The Hague: SCP Publications; 2004.
- (126) Report of the commission of inquiry on a national cancer strategy. Swedish Government Official Reports. A national cancer screening strategy for the future - summary. Stockholm, Edita Sverige AB; 2009.
- (127) Hemminki K, Li X. Cancer risks in Nordic immigrants and their offspring in Sweden. *Eur J Cancer* 2002;38:2428-34.
- (128) Mousavi SM, Sundquist K, Hemminki K. Morbidity and mortality in gynecological cancers among first- and second-generation immigrants in Sweden. *Int J Cancer* 2012;131:497-504.
- (129) Hemminki K, Li X. Cancer risks in second-generation immigrants to Sweden. *Int J Cancer* 2002;99:229-37.
- (130) WHO/ICO Information Centre on HPV and Cervical Cancer. HPV and cervical cancer in the 2007 report. *Vaccine* 2007 Nov 1;25 Suppl 3:C1-230.
- (131) Kirschner B, Junge J, Holl K, Rosenlund M, Collas de Sanjosé S, Quint W, et al. HPV genotypes in invasive cervical cancer in Danish women. *Acta Obstet Gynecol Scand* 2013 Jun 13 [Epub ahead of print].

- (132) Tornesello ML, Cassese R, De RN, Buonaguro L, Masucci A, Vallefucio G, et al. High prevalence of human papillomavirus infection in Eastern European and West African women immigrants in South Italy. *APMIS* 2011;119:701-9.
- (133) Menczer J, Barchana M, Chetrit A, Liphshitz I, Sadetzki S. Incidence rates of cervical carcinoma among first- and second-generation women of North African origin in Israel. *Int J Gynecol Cancer* 2009;19:1606-9.
- (134) Jee SH, Won SY, Yun JE, Lee JE, Park JS, Ji SS. Polymorphism p53 codon-72 and invasive cervical cancer: a meta-analysis. *Int J Gynaecol Obstet* 2004;85:301-8.
- (135) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893-917.
- (136) Hemminki K, Jiang Y. Life style and cancer: effect of divorce. *Int J Cancer* 2002;98:316-9.
- (137) Kvikstad A, Vatten LJ, Tretli S, Kvinnsland S. Widowhood and divorce related to cancer risk in middle-aged women. A nested case-control study among Norwegian women born between 1935 and 1954. *Int J Cancer* 1994;58:512-6.
- (138) Bjorge T, Kravdal O. Reproductive variables and risk of uterine cervical cancer in Norwegian registry data. *Cancer Causes Control* 1996;7:351-7.
- (139) Bouchardy C, Wanner P, Parkin DM. Cancer mortality among sub-Saharan African migrants in France. *Cancer Causes Control* 1995;6:539-44.
- (140) Grulich AE, Swerdlow AJ, Head J, Marmot MG. Cancer mortality in African and Caribbean migrants to England and Wales. *Br J Cancer* 1992;66:905-11.
- (141) Taylor VM, Jackson JC, Schwartz SM, Tu SP, Thompson B. Cervical cancer among Asian American women: A neglected public health problem? *Asian Am Pac Isl J Health* 1996;4:327-42.
- (142) McCracken M, Olsen M, Chen MS, Jr., Jemal A, Thun M, Cokkinides V, et al. Cancer incidence, mortality, and associated risk factors among Asian Americans of Chinese, Filipino, Vietnamese, Korean, and Japanese ethnicities. *CA Cancer J Clin* 2007;57:190-205.
- (143) Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al., editors. *SEER cancer statistics review, 1975-2000*. Bethesda: National Cancer Institute; 2003.

- (144) Jacobs EA, Lauderdale DS. Receipt of cancer screening procedures among Hispanic and non-Hispanic health maintenance organization members. *Cancer* 2001;91(1 Suppl):257-61.
- (145) Patel DA, Barnholtz-Sloan JS, Patel MK, Malone JM, Jr., Chuba PJ, Schwartz K. A population-based study of racial and ethnic differences in survival among women with invasive cervical cancer: analysis of Surveillance, Epidemiology, and End Results data. *Gynecol Oncol* 2005;97:550-8.
- (146) Crocetti E, Manneschi G, Visioli CB, Zappa M. Risk of invasive cervical cancer and cervical intraepithelial neoplasia grade III in central Italy by area of birth. *J Med Screen* 2010;17:87-90.
- (147) Kobetz E, Kish JK, Campos NG, Koru-Sengul T, Bishop I, Lipshultz H, et al. Burden of human papillomavirus among Haitian immigrants in Miami, Florida: Community-based participatory research in action. *J Oncol* 2012;2012:728397.
- (148) Boyle P, Levin B, editors. *World Cancer Report 2008*. Lyon: International Agency for Research on Cancer; 2008.
- (149) Moscicki AB, Shiboski S, Hills NK, Powell KJ, Jay N, Hanson EN, et al. Regression of low-grade squamous intra-epithelial lesions in young women. *Lancet* 2004;364:1678-83.
- (150) Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. *Obstet Gynecol* 1998;91:973-6.
- (151) Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskeva E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367:489-98.
- (152) Cox JT. Management of cervical intraepithelial neoplasia. *Lancet* 1999;353:857-9.
- (153) Plante M, Renaud MC, Hoskins IA, Roy M. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. *Gynecol Oncol* 2005;98:3-10.
- (154) Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev* 2005;(3):CD002225.

- (155) World Health Organization Department of Reproductive Health and Research. Strengthening cervical cancer prevention and control. Report of the GAVI-UNFPA-WHO meeting on 1 December 2009, Geneva, Switzerland. Geneva: World Health Organization; 2010.
- (156) Denny L. Cervical cancer: prevention and treatment. *Discov Med* 2012 Aug;14:125-31.
- (157) Bates JH, Hofer BM, Parikh-Patel A. Cervical cancer incidence, mortality, and survival among Asian subgroups in California, 1990-2004. *Cancer* 2008;113(10 Suppl):2955-63.
- (158) Federico C, Alleyn J, Dola C, Tafti S, Galandak J, Jacob C, et al. Relationship among age, race, medical funding, and cervical cancer survival. *J Natl Med Assoc* 2010;102:199-205.
- (159) Robin L, Dittus P, Whitaker D, Crosby R, Ethier K, Mezzoff J, et al. Behavioral interventions to reduce incidence of HIV, STD, and pregnancy among adolescents: a decade in review. *J Adolesc Health* 2004;34:3-26.
- (160) European Centers for Disease Prevention and Control. Introduction of HPV vaccines in EU countries - an update. Stockholm:ECDC; 2012.
- (161) Scarinci IC, Garcia FA, Kobetz E, Partridge EE, Brandt HM, Bell MC, et al. Cervical cancer prevention: new tools and old barriers. *Cancer* 2010;116:2531-42.
- (162) Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. *Cancer Epidemiol Biomarkers Prev* 2005;14:2191-9.
- (163) Bergstrom R, Sparén P, Adami HO. Trends in cancer of the cervix uteri in Sweden following cytological screening. *Br J Cancer* 1999;81:159-66.
- (164) Shepherd JP, Frampton GK, Harris P. Interventions for encouraging sexual behaviours intended to prevent cervical cancer. *Cochrane Database Syst Rev* 2011;(4):CD001035.
- (165) Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Moller H, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;14:677-86.
- (166) Dillner J. Cervical cancer screening in Sweden. *Eur J Cancer* 2000;36:2255-9.

- (167) Dillner L, Pagliusi S, Bray F, Lorincz A, Kjaer SK, Anttila A, et al. Strengthening prevention programs to eliminate cervical cancer in the Nordic countries. *Acta Obstet Gynecol Scand* 2008;87:489-98.
- (168) Socialstyrelsen. Cancer incidence in Sweden 2005. Stockholm: National Board of Health and Welfare; 2007.
- (169) Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening. Europe against cancer programme. *Eur J Cancer* 1993;29A (Suppl 4):S1-38.
- (170) National Cervical Cancer Screening Register. National cervical screening in Sweden, report 2007 with data until 2006. Stockholm: National Cervical Cancer Screening Register; 2008. Swedish.
- (171) National Quality Register for Cervical Screening. Cervical screening in Sweden. Annual report 2011 from the National Quality Register for Cervical Screening. Stockholm: National Quality Register for Cervical Screening; 2011. Swedish.
- (172) Franco EL, Harper DM. Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. *Vaccine* 2005;23:2388-94.
- (173) Camilloni L, Ferroni E, Cendales BJ, Pezzarossi A, Furnari G, Borgia P, et al. Methods to increase participation in organised screening programs: a systematic review. *BMC Public Health* 2013;13:464.
- (174) Hakama M, Chamberlain J, Day NE, Miller AB, Prorok PC. Evaluation of screening programmes for gynaecological cancer. *Br J Cancer* 1985;52:669-73.
- (175) Mitchell H, Hirst S, Cockburn J, Reading DJ, Staples MP, Medley G. Cervical cancer screening: a comparison of recruitment strategies among older women. *Med J Aust* 1991;155:79-82.
- (176) Sparén P. Gynekologisk cellprovskontroll I Sverige. Stockholm: Nationellt kvalitetsregister för Gynekologisk Cellprovskontroll; 2006. Swedish.
- (177) Strander B. Cervical cancer prevention, studies on possible improvements. Göteborg: Intellect DocuSys AB; 2008.
- (178) Casamitjana M, Sala M, Ochoa D, Fuste P, Castells X, Alameda F. Results of a cervical cancer screening programme from an area of Barcelona (Spain) with a large immigrant population. *Eur J Public Health* 2009;19:499-503.
- (179) Woltman KJ, Newbold KB. Immigrant women and cervical cancer screening uptake: a multilevel analysis. *Can J Public Health* 2007;98:470-5.

- (180) Harlan LC, Bernstein AB, Kessler LG. Cervical cancer screening: who is not screened and why? *Am J Public Health* 1991;81:885-90.
- (181) McDonald JT, Kennedy S. Cervical cancer screening by immigrant and minority women in Canada. *J Immigr Minor Health* 2007;9:323-34.
- (182) Latif E. Recent immigrants and the use of cervical cancer screening test in Canada. *J Immigr Minor Health* 2010;12:1-17.
- (183) Goel V. Factors associated with cervical cancer screening: results from the Ontario Health Survey. *Can J Public Health* 1994;85:125-7.
- (184) Goel MS, Wee CC, McCarthy EP, Davis RB, Ngo-Metzger Q, Phillips RS. Racial and ethnic disparities in cancer screening: the importance of foreign birth as a barrier to care. *J Gen Intern Med* 2003;18:1028-35.
- (185) Samuel PS, Pringle JP, James NW, Fielding SJ, Fairfield KM. Breast, cervical, and colorectal cancer screening rates amongst female Cambodian, Somali, and Vietnamese immigrants in the USA. *Int J Equity Health* 2009;8:30.
- (186) Swan J, Breen N, Coates RJ, Rimer BK, Lee NC. Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey. *Cancer* 2003;97:1528-40.
- (187) Tangka FK, O'Hara B, Gardner JG, Turner J, Royalty J, Shaw K, et al. Meeting the cervical cancer screening needs of underserved women: the National Breast and Cervical Cancer Early Detection Program, 2004-2006. *Cancer Causes Control* 2010;21:1081-90.
- (188) Lofters AK, Moineddin R, Hwang SW, Glazier RH. Low rates of cervical cancer screening among urban immigrants: a population-based study in Ontario, Canada. *Med Care* 2010;48:611-8.
- (189) National Institutes of Health. Consensus statement: cervical cancer. Bethesda: National Institutes of Health; 1996.
- (190) Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst* 2008;100:622-9.
- (191) Rodvall Y, Kemetli L, Tishelman C, Tornberg S. Factors related to participation in a cervical cancer screening programme in urban Sweden. *Eur J Cancer Prev* 2005;14:459-66.

- (192) McDougall JA, Madeleine MM, Daling JR, Li CI. Racial and ethnic disparities in cervical cancer incidence rates in the United States, 1992-2003. *Cancer Causes Control* 2007;18:1175-86.
- (193) Schleicher E. Immigrant women and cervical cancer prevention in the United States. Baltimore, MD: Women's and Children's Health Policy Center. Johns Hopkins Bloomberg School of Public Health; 2007.
- (194) Juon HS, Seung-Lee C, Klassen AC. Predictors of regular Pap smears among Korean-American women. *Prev Med* 2003;37:585-92.
- (195) Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ* 1995;311:42-5.
- (196) Barbour RS. The case for combining qualitative and quantitative approaches in health services research. *J Health Serv Res Policy* 1999;4:39-43.
- (197) Forman J, Creswell JW, Damschroder L, Kowalski CP, Krein SL. Qualitative research methods: key features and insights gained from use in infection prevention research. *Am J Infect Control* 2008;36:764-71.
- (198) Cronbach LJ. Beyond the two disciplines of scientific psychology. *Am Psychol* 1975;30:116-27.
- (199) Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;24:659-67.
- (200) Swedish Tax Agency. Population registration in Sweden. SKV 717B. Edition 4. Stockholm: Swedish Tax Agency; 2007.
- (201) Weitoft GR, Gullberg A, Hjern A, Rosen M. Mortality statistics in immigrant research: method for adjusting underestimation of mortality. *Int J Epidemiol* 1999;28:756-63.
- (202) World Health Organization. International Classification of Diseases. Geneva: World Health Organization; 2013 [cited May 2013]. Available from: <http://www.who.int/classifications/icd/en/>.
- (203) Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2008.
- (204) Bonita R, Beaglehole BR, Kjellström T. Basic epidemiology, 2nd edition. Geneva: WHO Press; 2006.
- (205) Morgan DL. Focus groups as qualitative research. 2nd edition. London: SAGE Publications; 1997.

- (206) Barbour R. Doing focus groups. The SAGE qualitative research kit. London: Sage Publications; 2007.
- (207) Statistics Sweden. Örebro: Statistics Sweden; 2013 [cited April 2013]. Available from: [http://www.scb.se/default\\_\\_\\_\\_30.aspx](http://www.scb.se/default____30.aspx).
- (208) Socialstyrelsen. Swedish Cancer Registry. Stockholm: Socialstyrelsen; 2001 [cited June 2013 Available from: <http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/inenglish>.
- (209) National Board of Health and Welfare Center for Epidemiology. Causes of death 2004. Stockholm: National Board of Health and Welfare; 2007.
- (210) Socialstyrelsen. Cause of Death Register. Stockholm: Socialstyrelsen; 2001 [cited June 2013]. Available from: <http://www.socialstyrelsen.se/register/dodsorsaksregistret>.
- (211) Nationellt Kvalitetsregister för Cervixcancerprevention. Förebyggande av livmoderhalscancer i Sverige. Verksamhetsberättelse och Årsrapport 2012 med data tom 2011. Stockholm: Nationellt Kvalitetsregister för Cervixcancerprevention; 2012. Swedish.
- (212) Statistics Sweden. Registerbaserad arbetsmarknadsstatistik (RAMS) [Internet]. Stockholm: Statistics Sweden; 2001 [cited June 2013] Available from: [http://www.scb.se/Statistik/AM/AM0207/\\_dokument/AM0207\\_BS\\_2001.pdf](http://www.scb.se/Statistik/AM/AM0207/_dokument/AM0207_BS_2001.pdf).
- (213) Statistics Sweden. Population and housing census 1990. Örebro: Statistics Sweden; 1992.
- (214) Statistics Sweden. Census of the population in 1960 part VII. Economically active population, by occupation and sex, in the whole country. Stockholm: Statistics Sweden; 1967.
- (215) Statistics Sweden. Population and housing census 1980. Stockholm: LiberFörlag; 1985.
- (216) Statistics Sweden. The Swedish Register of Education [Internet]. Stockholm: Statistics Sweden; 2004 [cited June 2013]. Available from: [http://www.scb.se/statistik/UF/UF0506/Produktbeskrivning\\_short\\_English\\_UF0506\\_20040101r.doc](http://www.scb.se/statistik/UF/UF0506/Produktbeskrivning_short_English_UF0506_20040101r.doc).
- (217) Statistics Sweden. Background facts, population and welfare statistics. Evaluation of the Swedish Register of Education. Stockholm: Statistics Sweden; 2006.
- (218) dos Santos Silva I. Cancer epidemiology: principles and methods. Lyon: International Agency for Research on Cancer; 1999.



- (219) International Agency for Research on Cancer. GLOBOCAN 2002 database [CD-ROM]. Lyon: International Agency for Research on Cancer; 2002.
- (220) Rothman KJ, Greenland S. Modern epidemiology. 2nd edition. Philadelphia: Lippincott; 1998.
- (221) Andrae B, Andersson TML, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: a population-based cohort study. *BMJ* 2012;344:e900.
- (222) Erikson R. Social-class of men, women and families. *Sociology* 1984;18:514.
- (223) Fitzmaurice G. Adjusting for confounding. *Nutrition* 2004;20:594-6.
- (224) Age-standardization. In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, editors. Cancer incidence in five continents. Volume VIII. Lyon: International Agency for Research on Cancer; 2002. p. 87-9.
- (225) Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004;24:105-12.
- (226) Downe-Wamboldt B. Content analysis: method, applications, and issues. *Health Care Women Int* 1992;13:313-21.
- (227) Coffey A, Attfield KR. Making sense of qualitative data. Complementary research strategies. London: Sage Publications, Inc.; 1996.
- (228) Krueger RA. Focus groups. A practical guide for applied research. 2nd edition. Thousand Oaks: Sage Publications, Inc.; 1994.
- (229) Cain KC, Harlow SD, Little RJ, Nan B, Yosef M, Taffe JR, et al. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. *Am J Epidemiol* 2011;173:1078-84.
- (230) Azerkan F, Zendehdel K, Tillgren P, Faxelid E, Sparén P. Risk of cervical cancer among immigrants by age at immigration and follow-up time in Sweden, from 1968 to 2004. *Int J Cancer* 2008;123:2664-70.
- (231) Khan FA, Zia E, Janzon L, Engstrom G. Incidence of stroke and stroke subtypes in Malmo, Sweden, 1990-2000: marked differences between groups defined by birth country. *Stroke* 2004;35:2054-8.
- (232) Helgesson O, Bengtsson C, Lapidus L, Merck C, Sparén P. Malignant disease observed in a cohort of women. A validation of Swedish Cancer Registry data. *Scand J Soc Med* 1994;22:46-9.

- (233) National Board of Health and Welfare Center for Epidemiology. Causes of death 2000. Stockholm: National Board of Health and Welfare; 2002.
- (234) Johansson LA, Bjorkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. *J Clin Epidemiol* 2009;62:1202-9.
- (235) The National Board of Health and Welfare, Center for Epidemiology. Causes of death 2007. Stockholm: The National Board of Health and Welfare, Center for Epidemiology; 2009.
- (236) Statistics Sweden. Migrations- och integrationsstatistik vid SCB – nuläge och utveckling. Örebro: Statistics Sweden; 2005. Swedish.
- (237) Nilsson Å. Migrationsstatistikens kvalitet. In: Nilsson Å, editor. Immigration and emigration in the postwar period. Örebro: Statistics Sweden; 2004. p. 99-121.
- (238) Statistics Sweden. Migration 2003. Immigration, emigration and asylum seekers. April 2013: Statistics Sweden; 2003. Available from: [http://www.scb.se/statistik/BE/BE0101/2004M02/BE0101\\_2004M02\\_SM\\_BE68SM0401.pdf](http://www.scb.se/statistik/BE/BE0101/2004M02/BE0101_2004M02_SM_BE68SM0401.pdf).
- (239) Lundholm C, Forsgren C, Johansson AL, Cnattingius S, Altman D. Hysterectomy on benign indications in Sweden 1987-2003: a nationwide trend analysis. *Acta Obstet Gynecol Scand* 2009;88:52-8.
- (240) Plummer M, Peto J, Franceschi S, for the International Collaboration of Epidemiological Studies of Cervical Cancer. Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer* 2012;130:2638-44.
- (241) Arnheim DL, Andersson K, Luostarinen T, Thoresen S, Ogmundsdottir H, Tryggvadottir L, et al. Prospective seroepidemiologic study of human papillomavirus and other risk factors in cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:2541-50.
- (242) Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 2006;17:5-19.
- (243) Rolfe G. Validity, trustworthiness and rigour: quality and the idea of qualitative research. *J Adv Nurs* 2006;53:304-10.
- (244) Morgan DL. Successful focus groups. Newsbury Park: Sage; 1993.
- (245) Blomberg K, Tishelman C, Ternstedt BM, Tornberg S, Leval A, Widmark C. How can young women be encouraged to attend cervical cancer screening?

- Suggestions from face-to-face and internet focus group discussions with 30-year-old women in Stockholm, Sweden. *Acta Oncol* 2011;50:112-20.
- (246) Martin LM, Calle EE, Wingo PA, Heath CW, Jr. Comparison of mammography and Pap test use from the 1987 and 1992 National Health Interview Surveys: are we closing the gaps? *Am J Prev Med* 1996;12:82-90.
- (247) Asbury J-E. Overview of focus group research. *Qual Health Res* 1995;5:414-20.
- (248) Jootun D, McGhee G, Marland GR. Reflexivity: promoting rigour in qualitative research. *Nurs Stand* 2009;23:42-6.
- (249) Karwalajtys TL, Redwood-Campbell LJ, Fowler NC, Lohfeld LH, Howard M, Kaczorowski JA, et al. Conducting qualitative research on cervical cancer screening among diverse groups of immigrant women: research reflections: challenges and solutions. *Can Fam Physician* 2010;56:e130-e135.
- (250) Kuper A, Reeves S, Levinson W. An introduction to reading and appraising qualitative research. *BMJ* 2008;337:a288.
- (251) Patton MQ. Enhancing the quality and credibility of qualitative analysis. *Health Serv Res* 1999;34:1189-208.
- (252) Long T, Johnson M. Rigour, reliability and validity in qualitative research. *Clinical Effectiveness in Nursin* 2000;4:30-7.
- (253) Tobin GA, Begley CM. Methodological rigour within a qualitative framework. *J Adv Nurs* 2004;48:388-96.
- (254) Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. *BMJ* 2008;337:a1035.
- (255) Maxwell JA. *Qualitative research design: an interactive approach*. Thousand Oaks, CA: Sage Publications, Inc.; 1996.
- (256) Bender S, Geirsson RT, Kosunen E. Trends in teenage fertility, abortion, and pregnancy rates in Iceland compared with other Nordic countries, 1976-99. *Acta Obstet Gynecol Scand* 2003;82:38-47.
- (257) Danielsson M, Rogala C, Sundstrom K. *Teenage sexual and reproductive behavior in developed countries: country report for Sweden*. New York: The Alan Guttmacher Institute; 2001.
- (258) Edgardh K. Adolescent sexual health in Sweden. *Sex Transm Infect* 2002;78:352-6.
- (259) Jensen KE, Munk C, Sparén P, Tryggvadottir L, Liaw KL, Dasbach E, et al. Women's sexual behavior. Population-based study among 65,000 women from

- four Nordic countries before introduction of human papillomavirus vaccination. *Acta Obstet Gynecol Scand* 2011;90:459-67.
- (260) Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN: cancer incidence, mortality, prevalence and prediction in the Nordic Countries, Version 3.6. Copenhagen: Association of Nordic Cancer Registries. Danish Cancer Society; 2010. Available from: <http://www-dep.iarc.fr/NORDCAN/english/frame.asp>.
- (261) Kjaer SK, Dahl C, Engholm G, Bock JE, Lynge E, Jensen OM. Case-control study of risk factors for cervical neoplasia in Denmark. II. Role of sexual activity, reproductive factors, and venereal infections. *Cancer Causes Control* 1992;3:339-48.
- (262) Harris KM. The health status and risk behaviors of adolescents in immigrant families. In: Hernandez J, editor. *Children of immigrants: health, adjustment, and public assistance*. Washington, DC: National Academy Press; 1999. p. 286-347.
- (263) Gilliam ML, Berlin A, Kozloski M, Hernandez M, Grundy M. Interpersonal and personal factors influencing sexual debut among Mexican-American young women in the United States. *J Adolesc Health* 2007;41:495-503.
- (264) Kaplan CP, Erikson PI, Juarez-Reyes M. Acculturation, gender role orientation, and reproductive risk-taking behavior among Latina adolescent family planning clients. *Journal of Adolescent Research* 2002;17:103-21.
- (265) Singh S, Darroch JE, Frost JJ. Socioeconomic disadvantage and adolescent women's sexual and reproductive behavior: the case of five developed countries. *Fam Plann Perspect* 2001 Nov;33:251-8, 289.
- (266) Faulkner SL. Good girl or flirt girl: Latinas' definitions of sex and sexual relationships. *Hispanic Journal of Behavioral Sciences* 2003;25:174-200.
- (267) Marin BV, Tschann JM, Gomez CA, Kegeles SM. Acculturation and gender differences in sexual attitudes and behaviors: Hispanic vs non-Hispanic white unmarried adults. *Am J Public Health* 1993;83:1759-61.
- (268) Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137-50.
- (269) Stockholm County. [Child health care in Stockholm County. Annual report 2006]. Stockholm: Stockholm County; 2007. Swedish.

- (270) Johansson A. Passive smoking in children. The importance of parent's smoking and use of protective measures [doktorsavhandling]. Linköping: University of Linköping; 2004.
- (271) Vagero D, Persson G. Cancer survival and social class in Sweden. *J Epidemiol Community Health* 1987;41:204-9.
- (272) Li X, Sundquist J, Calling S, Zoller B, Sundquist K. Neighborhood deprivation and risk of cervical cancer morbidity and mortality: a multilevel analysis from Sweden. *Gynecol Oncol* 2012;127:283-9.
- (273) Schönwälder K. Residential segregation and the integration of immigrants: Britain, the Netherlands and Sweden. Discussion Paper Nr. SP IV 2007-602. Berlin: Social Science Research Center Berlin; 2007.
- (274) Razum O, Twardella D. Time travel with Oliver Twist--towards an explanation foa a paradoxically low mortality among recent immigrants. *Trop Med Int Health* 2002;7:4-10.
- (275) Stirbu I, Kunst AE, Vlems FA, Visser O, Bos V, Deville W, et al. Cancer mortality rates among first and second generation migrants in the Netherlands: Convergence toward the rates of the native Dutch population. *Int J Cancer* 2006;119:2665-72.
- (276) Spallek J, Arnold M, Hentschel S, Razum O. Cancer incidence rate ratios of Turkish immigrants in Hamburg, Germany: A registry based study. *Cancer Epidemiol* 2009;33:413-8.
- (277) Harding S, Rosato M, Teyhan A. Trends in cancer mortality among migrants in England and Wales, 1979-2003. *Eur J Cancer* 2009;45:2168-79.
- (278) Sigurdsson K. [The Nordic cervical screening programmes through 1995. Evaluation of incidence and mortality rates, targeted age groups and screening intervals]. *Laeknabladid* 1999;85:862-72.
- (279) The Nordic Council of Ministers. Nordic statistical yearbook Vol. 49. Copenhagen: The Nordic Council of Ministers; 2011.
- (280) Owusu GA, Eve SB, Cready CM, Koelln K, Trevino F, Urrutia-Rojas X, et al. Race and ethnic disparities in cervical cancer screening in a safety-net system. *Matern Child Health J* 2005;9:285-95.

**Table A1. Definition of birth regions used in Paper I**

Country of birth, region or risk-region	Country of birth
Sweden(L)	Swedish-born women
Eastern Africa(H)	Burundi, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, Somalia, Tanzania, Uganda, Zambia, Zimbabwe, Seychelles
Middle Africa(H)	Angola, Cameroon, Chad, Congo, Congo Brazzaville,
Northern Africa(M)	Algeria, Egypt, Libya, Morocco, Sudan, Tunisia
Other Low risk areas(L)	Egypt, Tunisia
Other Medium risk areas(M)	Algeria, Libya, Morocco, Sudan
Southern Africa(H)	Botswana, Lesotho, Namibia, South African Republic
Western Africa(H)	Benin, Burkina Faso, Cape Verde, Cote d'Ivoire, The Gambia, Ghana, Guinea, Guinea- Bissau, Liberia, Mali, Mauritania, Nigeria, Senegal, Sierra Leone, Togo
Caribbean(H)	Barbados, Cuba, Dominican Republic, Haiti, Jamaica, Trinidad and Tobago, S.T Lucia, Dominica
Central America(H)	Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Grenada
South America(H)	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela
Chile(H)	Chile
Other High risk areas(H)	Argentina, Bolivia, Brazil, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela
USA and Canada(L)	United States of America, Canada
Eastern Asia(L)	China, Hong Kong, Taiwan, Japan, Korea Democratic Republic, Korea Republic, Mongolia
Other Low risk areas(L)	China, Hong Kong, Japan
Other Medium risk areas(M)	Taiwan, Korea Democratic Republic, Korea Republic, Mongolia
South Eastern Asia(M)	Cambodia, Indonesia, Lao, Malaysia, Myanmar, Philippines, Singapore, Thailand, Viet Nam
Other Medium risk areas(M)	Indonesia, Lao, Malaysia, Singapore, Thailand
Other High risk areas(H)	Cambodia, Myanmar, Philippines, Viet Nam
South Central Asia(H)	Afghanistan, Bangladesh, India, Iran Islamic Republic, Kazakhstan, Kyrgyzstan, Nepal, Pakistan, Sri Lanka, Tajikistan, Turkmenistan, Uzbekistan
Iran(L)	Iran
Other Low risk areas(L)	Afghanistan, Pakistan, Tajikistan
Other Medium risk areas(M)	Sri Lanka, Turkmenistan, Uzbekistan
Other High risk areas(H)	Bangladesh, India, , Kazakhstan, Kyrgyzstan, Nepal
Western Asia(L)	Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen, Palestine
Iraq(L)	Iraq
Turkey(L)	Turkey
Other Low risk areas(L)	Azerbaijan, Bahrain, Israel, Jordan, Kuwait, Qatar, Saudi Arabia, Syrian Arab Republic, United Arab Emirates, Yemen, Palestine
Other Medium risk areas(M)	Armenia, Cyprus, Georgia, Lebanon
Central and Eastern Europe(M)	Belarus, Bulgaria, Czech republic, Hungary, Moldova, Poland, Romania, Russian Federation, Slovakia, Ukraine, Soviet Union, Czechoslovakia,
Romania(H)	Romania
Poland(M)	Poland
Other Medium risk areas(M)	Belarus, Bulgaria, Czech republic, Hungary, Moldova, Russian Federation, Slovakia, Ukraine, Soviet Union, Czechoslovakia,
Northern Europe (excl Sweden) (M)	Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom
Denmark(M)	Denmark
Estonia, Lithuania, Latvia(M)	Estonia, Lithuania, Latvia
Finland(L)	Finland
Norway(M)	Norway
Iceland, Ireland, UK(L)	Iceland, Ireland, United Kingdom

Country of birth, region or risk-region	Country of birth
Southern Europe(M)	Albania, Bosnia Herzegovina, Croatia, Greece, Italy, Macedonia, Malta, Portugal, Slovenia, Spain, Yugoslavia
Greece, Italy, Malta, Spain(L)	Greece, Italy, Malta, Spain
Yugoslavia(M)	Bosnia Herzegovina, Croatia, Macedonia, Slovenia, Yugoslavia
Portugal(M)	Portugal
Western Europe(M)	Austria, Belgium, France, Germany, Luxembourg, The Netherlands, Switzerland
Austria(M)	Austria,
Germany(M)	Germany
Other Low risk areas(L)	Belgium, France, Luxembourg, The Netherlands, Switzerland
Australia and New Zealand(L)	Australia, New Zealand
Melanesia(H)	Fiji, Papua New Guinea, Oceania, Tonga

(L) Low risk region (<10 ASR); (M) Medium risk region (10-20 ASR); (H) High risk region (>20 ASR)