From the Division of Epidemiology
Department of Environmental Medicine
Karolinska Institutet, Stockholm, Sweden

Cancer and Migration:

Epidemiological studies on relationship between country of birth, socio-economic position and cancer

Omid Beiki

Stockholm 2010

Published by Karolinska Institutet. Printed by Universitetsservice US-AB.

ISBN 978-91-7409-825-9

In the name of God, the beneficent, the merciful

To my family
Najmeh, Yasaman, Ida

Abstract

Background: Migrant studies offer a unique opportunity to analyze variation in disease occurrence due to background factors. The role of environmental and lifestyle exposures are of particular interest in cancer research, and migrant studies can be considered as “natural experiments” in epidemiological research. Large numbers of immigrants from different regions of the world and the availability of comprehensive demographic and health-related registers in Sweden have prompted us to conduct migrant studies on the epidemiology of cancer. Breast cancer and genital tract cancers were selected for study since the role of environmental and lifestyle risk factors are debated for these disorders.

Objectives: To compare the risk and survival of the female breast, cervical, ovarian and endometrial cancers and male prostate and testicular cancers among immigrants to those among Swedish-born individuals to elucidate the importance and the potential timing of environmental and genetic factors in cancer etiology.

Methods: We established different cohorts by linkages between Swedish national registers, including Cancer and Cause of Death registers, through personal identity number. The main exposure variable was country of birth with Swedish-born persons with both parents born in Sweden as reference group. Each cohort was followed from start date of follow-up period, date of birth or first immigration date, whichever occurred last, until exit date from the cohort, which was diagnosis of primary outcomes of interest, first emigration, or end of follow-up, whichever came first. We calculated incidence rate ratios and hazard ratios with 95% confidence intervals adjusted for age and calendar period of follow-up using Poisson and Cox proportional hazards regression models.

Results: First-generation immigrants in Sweden had an overall lower risk of cancers studied compared with Swedish-born people. However, we found remarkable variations in cancer risks and survival by country of birth. Age at immigration and duration of residence of first-generation immigrants were important factors affecting risk of cervical, breast, prostate, and testis seminomas. An increasing trend in incidence of prostate cancer among first-generation immigrants similar to either Sweden or country of birth was observed. Second-generation immigrants showed a risk converging toward the risk in Sweden for testicular and breast cancers. Education, as an indicator of socio-economic position, differentially affected the risk of cervical cancer among first-generation immigrants and Swedish-born women. Among both immigrants and Swedish-born women, breast cancer risk increased, while its mortality decreased with increasing level of education.

Conclusions: Country of birth was a major determinant for cancer risk. Variation of risk by age at immigration or duration of residence highlights the effect of environmental and lifestyle factors on cancer risk. The observed patterns of prostate cancer risk imply the importance of both genetic and environmental factors in the etiology of this cancer. Patterns of testicular cancer risk indicate the importance of early environmental risk factors acting even after the intrauterine period.

Keywords: country of birth, immigrants, breast neoplasm, uterine cervical neoplasm, endometrial neoplasm, ovarian neoplasm, prostatic neoplasm, testicular neoplasm, socio-economic position, incidence, survival, Sweden

List of Publications

This thesis is based on the following papers, which in the text will be referred to by their roman numerals (**I**-**IV**):

I. **Beiki O.**, Allebeck P., Nordqvist T., Moradi T.
Cervical, endometrial and ovarian cancers among immigrants in Sweden: importance of age at immigration and duration of residence.
Eur J Cancer 2009; 45(1): 107-18.

II. **Beiki O.**, Ekbom A., Allebeck P., Moradi T.
Risk of prostate cancer among Swedish-born and foreign-born men in Sweden, 1961-2004.
Int J Cancer 2009; 124(8): 1941-53.

III. **Beiki O.**, Granath F., Allebeck P., Akre O., Moradi T.
Subtype-specific risk of testicular tumors among immigrants and their descendants in Sweden, 1960-2007.
Cancer Epidemiol Biomarkers Prev 2010; 19(4): 1053–65.

IV. **Beiki O.**, Moradi T.
Breast cancer risk and survival among immigrants and their descendants in Sweden, 1961-2007.
Manuscript.

Contents

List of abbreviations

AACR	International Association of Cancer Registries
APC	Annual Percent Change
ASR	Age Standardized Incidence Rate (per 100,000 World Population)
CDR	Cause of Death Register
CI	Confidence Interval
CI5	Cancer Incidence in Five Continents
DRE	Digital Rectal Examination
HPV	Human Papillomavirus
HR	Hazard Rate Ratio
HRT	Hormone Replacement Therapy
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IRR	Incidence Rate Ratio
LISA	Longitudinal Integration Database for Health Insurance and Labour Market
NSAID	Non-steroidal Anti-inflammatory Drug
OECD	Organization for Economic Cooperation & Development
PID	Personal Identity Number
PSA	Prostate Specific Antigen
SEI	Socio-economic Index
SEP	Socio-economic Position
SIR	Standardized Incidence Ratios
TPR	Total Population Register
TURP	Transurethral Resection of the Prostate
UK	United Kingdom
US	The United States

1 Introduction

Cancer is a major public health problem in many parts of the world and its incidence and mortality is projected to double by 2020 (1). A profound variation in the geographical pattern of cancer is present in terms of its risk and mortality (2). The reasons for these differences are largely unknown. In Sweden, cancer is currently one of the three dominating groups of diseases which account for more than 60% of the total burden of disease in Sweden (3).

Today, international migration is occurring in greater numbers, in a faster rate than before and over greater distances (4). Immigration has increased in Sweden. In 2008, 13.8% of the population or over 1.2 million persons were born outside Sweden (5), with 200 different nationalities represented within this group of immigrants. Adding persons born in Sweden with two parents born outside Sweden, referred to as second-generation, immigrants accounted for about 18% of total population of Sweden.

During the last decades, analytical epidemiological studies focusing on the comparison of cancer risk and mortality among different populations have been an approach to shedding further light on the unknown aspects of cancer etiology. In addition, epidemiologic approaches studying cancer care and health services for immigrants help to identify health inequalities and can thus contribute to improve health care. In Sweden, the high proportion of foreign-born residents, the vast majority coming from other Nordic countries, as well as a well-established system of population-based registers provide a unique opportunity to conduct migrant studies on cancer.

This thesis aimed to compare the risk and survival of the most common male and female genital cancers among immigrants and their descendants to those among Swedish-born persons in order to elucidate the importance of genetic and environmental factors in cancer etiology and the potential timing of exposures.

2 Background

2.1 Immigrants in Sweden

In the 19th and the early 20th century, Sweden was an emigration country. Many migrated to other countries, primarily the United States but also to Canada, Australia and Argentina. At the same time, there was also a labor migration to Germany, to Denmark especially from the southern part of Sweden and to Norway from other parts of Sweden.

Sweden has now been an immigration country for many decades. As Sweden was the only Nordic country that was not involved in the war, with the war an increasing number of refugees came to Sweden. The large flow of refugee immigrants during the Second World War changed Sweden from being an emigration country to an immigration country. The majority of the refugees returned but many also stayed in Sweden. The number of foreign citizens staying in Sweden was much higher after the war than before the war. In the years after 1945 the net immigration was around 10,000 and increased steadily throughout the 1950s and 1960s (6-8).

Refugees from the neighboring countries dominated immigration from 1940 to 1948. In 1946, more than 70,000 foreign citizens lived in Sweden, four times more than in 1940. This was also associated with an increase in the number of people from other Nordic countries (6-8).

Between 1949 and 1971, migrants from southern Europe dominated the influx of foreign nationals. From 1954, the first common Nordic labor market was established, and citizens from Sweden's neighbors were free to work and live in Sweden. This resulted in a considerable increase in number of immigrants especially from Finland but also from Denmark and to some extent Norway. Employers recruited from abroad and many workers arrived spontaneously to Sweden looking for a job (6-8).

During the period between 1972 and 1989, immigration was characterized by refugee immigration. The migration of family members of refugees that arrived earlier and labor migrants also grew. Predominantly during the 1970s, refugees fleeing Chile after the military coup of 1973 constituted the largest part of immigrants. Asylum seekers from the Middle East then superseded this flow of Latin American refugees at the beginning of the 1980s. The Iran-Iraq war was the main reason for this new inflow of refugees. By the end of the 1980s, migration of non-Nordic citizens accounted for 70% and that of non-European citizens for half of the total immigration to Sweden .

In the last decade of the twentieth century, political events in the Balkans led to increased numbers of asylum seekers from the former Yugoslavia. There was also an influx of immigrants from Africa, and the Middle East in the 2000s (6-8).

In Sweden, 13.8% of the population or over 1.2 million persons were foreign-born in 2008 (5). Among this group of immigrants, 200 different nationalities were represented (**Figure 1**). There were 379,422 persons, accounting for 4.1% of the registered population born in Sweden but with both parents born outside of Sweden. Most foreign-born immigrants, nearly 60%, have an origin in Europe. In 2008, one-seventh of Sweden's foreign-born population originally comes from Finland followed

by Iraq, former Yugoslavia, Poland, Iran, Bosnia and Herzegovina, Germany, Denmark, Norway and Turkey.

The gender distribution was uneven for each of the ten largest countries of birth except Bosnia-Herzegovina and former Yugoslavia, while there were far more women than men are. Nearly 60% of immigrants originating from Finland and Poland were women. In contrast, there was much larger proportion of men, 55% against 45% women among those who were born in Iraq (9). In **Table 1**, we presented summary statistics including the number of immigrants, age at immigration, duration of residence, and age at diagnosis for any cancer among immigrants who were registered in Sweden at any time between 1960 and 2007.

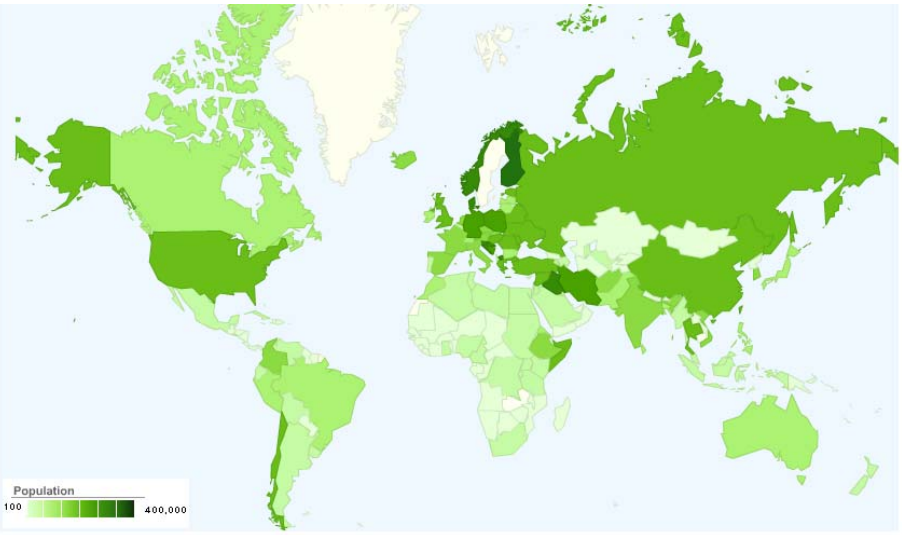

Figure 1: Distribution of immigrants registered anytime between 1960 and 2007 in Total Population Register in Sweden by countries of birth. (Created by *Google Visualization API*)

2.2 Studies of cancer in immigrant populations

2.2.1 Migrant studies

Migration of a population from one to another environment has been considered as a "natural experiment" (10). Most migrant studies address cancer incidence or mortality. This allows for a comparison of the risk of cancer either in populations of similar genetic background living in different environments or in populations of different genetic background living in similar environment. Cancer studies among immigrants are based on the assumption that immigrants carry a risk of cancer that to some extent reflects that of their country of origin rather than the host country.

Table 1- Age at immigration, duration of residence and age at diagnosis of any cancer among immigrants registered in Sweden between 1960 and 2007.

Birth Region	No. Population	AAM[1]	DOR[2]	No. Cancer	AAD[3]	Birth Region	No. Population	AAM[1]	DOR[2]	No. Cancer	AAD[3]
Africa	110,162	24.4	7.3	1,230	50.6	Ex-Soviet Union	36,842	27.2	6.9	2,499	69.2
Northern Africa	22,637	26.7	8.9	442	54.6	other	6,972	27.5	7.9	210	59.6
Western Africa	17,205	25.7	7.7	171	49.1	***Northern Europe***	677,037	23.0	11.0	59,152	64.7
Other Africa	70,320	22.8	6.6	617	47.6	Denmark	103,222	25.7	5.3	9,887	66.3
Ethiopia	14,851	22.5	15.7	195	44.7	Estonia	26,006	24.4	10.5	5,512	70.6
Somalia	29,942	21.0	4.8	127	45.9	Finland	372,160	21.7	25.6	30,819	62.1
other	25,527	24.9	4.8	295	49.7	Iceland	13,491	22.9	3.9	220	55.5
Asia	463,162	24.2	8.6	6,863	53.4	Norway	111,704	24.5	5.5	10,556	67.9
Eastern Asia	46,902	23.4	5.4	614	58.1	UK	35,266	26.5	5.4	1,142	61.9
China	24,680	25.4	3.9	368	65.6	other	15,188	25.9	2.9	1,116	71.1
Korea (Republic)	11,845	23.0	23.4	104	35.3	***Southern Europe***	238,492	25.5	13.4	9,789	59.2
other	10,377	28.0	3.7	142	55.1	Bosnia	62,050	29.0	13.7	2,049	60.4
South-Central Asia	127,935	24.7	12.9	1,944	53.1	Greece	25,503	24.8	12.3	923	55.8
Afghanistan	11,977	21.0	5.1	65	51.8	Italy	16,036	26.2	8.0	1,115	63.3
India	19,935	22.2	11.2	243	58.1	Spain	12,453	25.6	7.1	440	59.6
Iran	68,974	25.8	16.3	1,428	53.1	Ex-Yugoslavia	116,358	24.4	13.3	5,040	58.2
other	27,049	24.7	5.9	208	49.1	other	6,092	25.1	11.2	222	58.7
South-Eastern Asia	60,702	24.3	7.1	676	47.2	***Western Europe***	135,832	24.9	7.3	12,092	66.7
Thailand	28,013	25.0	4.3	182	41.1	Austria	11,889	23.2	33.9	1,433	66.1
Viet Nam	14,934	21.5	15.3	213	53.2	France	14,859	24.6	4.2	511	64.6
other	17,755	25.1	7.5	281	47.4	Germany	86,530	25.2	9.7	9,049	67.1
Western Asia	227,623	24.0	8.0	3,629	54.1	Netherlands	12,988	27.0	3.6	667	63.1
Iraq	114,933	25.0	5.7	1,034	51.8	other	9,566	23.4	5.0	432	66.5
Lebanon	26,542	22.5	16.2	442	49.6	**Latin America**	89,378	24.0	14.6	1,966	55.3
Syria	20,215	25.3	15.3	477	53.1	***South America***	76,406	23.7	15.7	1,780	55.1
Turkey	46,703	23.0	16.3	1,418	58.7	Colombia	11,083	5.2	13.2	100	48.7
other	19,230	24.0	4.3	258	55.9	Chile	34,731	24.3	18.8	1,003	5.3
Europe	1,232,752	24.2	12.2	92,998	64.4	other	30,592	25.2	9.5	677	55.8
Eastern Europe	181,391	27.0	11.7	11,965	64.7	***Central/Caribbean***	12,972	25.3	9.1	186	57.3
Ex-Czechoslovakia	14,280	25.7	20.8	1,550	65.3	**Northern America**	47,412	24.5	4.4	3,141	70.6
Hungary	23,297	25.9	25.1	2,524	63.4	Canada	5,742	24.9	4.2	197	66.4
Poland	79,228	27.0	11.9	4,273	63.1	USA	41,601	24.4	4.5	2,943	70.9
Romania	20,772	28.5	12.1	909	62.1	**Oceania**	8,631	25.6	3.8	96	53.2

[1]**Median age at migration;** [2] **Median duration of residence;** [3] **Median age at diagnosis of first malignant cancer.**

Migrant studies can be used for generating hypotheses or confirming hypotheses derived from etiologic studies of environmental risk factors associated with cancer occurrence. They can also be used to study of the health status of minorities in host country. Migrant studies can be grouped into different categories as follows (11):

2.2.1.1 Single-comparison studies:

In this category, the researcher compares the risk in immigrants versus that in the host country. These are the least informative, showing differences in cancer risk between immigrants and the locally-born, but providing no information on the populations from which the immigrants came from. However, lack of data from the country of origin may result from the non-existence of appropriate sources.

2.2.1.2 Two-comparison studies:

These are the most common types of migrant studies reported. Cancer risks among immigrants are compared with the risk in the host country and with the country of origin. The results can be interpreted as the degree to which the risk for cancer changes among immigrants away from that in the country of origin and towards that in host country.

2.2.1.3 Studies with a time dimension:

In this kind of migrant study; in addition to single or two comparisons studies, the effect of duration of residence of immigrants in the host country, age at immigration on the risk, or the risk among subsequent generations of immigrants is evaluated.

2.2.1.4 Studies with information on exposures in immigrants and host countries:

In this type of study, data on the prevalence of exposure to possible etiological factors are available for the immigrants and the population of the host country, and sometimes for country or origin. Studies of Japanese immigrants to Hawaii and studies of European immigrants to Australia are examples of studies of this kind, which showed that changes in cancer risk could be linked to the changes in the dietary habits (12-14).

2.2.2 A glance at literature

Migrant studies have been of most interest for those cancers for which a large fraction of unknown environmental or genetic risk factors is attributable. For cancers such as oral cancer that is clearly linked to chewing habits (15, 16) or lung cancer that is linked to tobacco smoking (17), the risk in immigrants will be almost entirely determined by past chewing and smoking habits. Thus, evaluation of the contributions of other environmental factors will be quite impossible in the absence of detailed knowledge of exposure to these known risk factors. However, the changes of risk for cancers, such as breast and prostate cancers in which the known risk factors explain only a small proportion of the incidence, migrant studies have been useful in delineating the relative importance of environmental risk factors in the etiology of cancer.

In this thesis, our focus is on female breast cancer, the most common female (cervical, ovarian and endometrial) and male (prostate and testicular) genital cancers. For these cancers, we will present a summary of previous studies that were carried out among immigrants.

2.2.2.1 Cervical Cancer

Worldwide, cervical cancer is the second most common malignant disease among women, with more than 500,000 new cases diagnosed each year (18, 19). Although cervical cancer is associated with a broad age range, the peak is at a mean age of 54 years (20). Cervical cancer is one of the cancers with higher rates in many low- and middle-income countries than in high-income countries, with nearly 80% of new cases occurring in low- and middle-income countries (19). Being the most common gynecological cancer in the low- and middle-income world, it accounts for two-thirds of cases and continues to be a serious health problem. Of cervical cancers worldwide, 90% are squamous cell carcinomas. Human papillomavirus (HPV) acts as the necessary cause in the development of cervical cancer and more than 90% of squamous cervical cancers contain HPV DNA. This virus is acquired mainly through sexual activity. Other factors associated with development of cervical cancer, such as smoking, early sexual debut, a high total number of sexual partners, multi-parity, and oral contraceptive use probably act as risk modifiers of HPV-associated cervical cancer (21, 22).

There is an 8-fold variation in the incidence of cervical cancer worldwide. The highest rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia, and South-East Asia (23). The incidence is generally low in high-income countries, with age-standardized rates less than 14 per 100,000 women. The low risk in such countries is due to effective screening programs. Before the introduction of screening programs, the incidence rates in most high-income countries were similar to those found in low- and middle-income countries today (24).

Several studies have been performed on the risk of cervical cancer among different immigrant groups in different countries including Sweden (25), Australia (26), the Netherlands (27), United States (28), France (29), and United Kingdom (30). Unfortunately, in many studies, carcinomas of the cervix and corpus uteri were combined and little information on rates in second-generation immigrants is available. Overall, previous studies showed that cervical cancer incidence or mortality is lower among immigrants than among those in countries of origin.

2.2.2.2 Endometrial cancer

Worldwide, endometrial cancer is the seventh most common malignant disorder, but incidence varies among regions. Endometrial cancer ranks as the most common gynecologic cancer in high-income countries while it has low incidence in low- and middle-income countries (18, 31). The highest incidences are observed in North America, and in Europe. Incidence rates in South America are intermediate, whereas rates are low in Southern and Eastern Asia and most of Africa. In Sweden, the incidence of endometrial cancer is one of the highest in Europe (19). The incidence of endometrial cancer has been increasing in Europe, United States and other regions of the world in the past several decades.

Endometrial cancer is a post-menopausal cancer with 90% of cases occurring in women over 50 years of age (32). Known risk factors associated with endometrial cancer are nulliparity, hormone replacement therapy (HRT), diabetes, age at menarche and menopause, obesity and physical activity (33-35).

Endometrial cancers have been poorly studied in immigrant populations. In some studies, it has not been possible to distinguish endometrial cancers from cervix uteri cancers. The results of studies mostly performed in US showed considerably lower incidence of malignant tumors of the uterine corpus among blacks compared with whites; however, blacks had less favorable survival and mortality rates (36). Another study on Asian immigrants in the US showed that the annual incidence of primary endometrial cancer was lower among Chinese-American and Japanese-American women born in Asia than among their counterparts who were born in the United States (37). The distribution of known risk factors of endometrial cancer could not explain the observed reduced risk among different ethnic populations in the US (38). Overall, a lower risk of endometrial cancer has been observed among immigrants in Sweden compared with Swedish-born women (25).

2.2.2.3 Ovarian cancer

Epithelial ovarian cancer is the deadliest gynecologic cancer, with the 5-year survival less than 50% (23). Ovarian cancer is the second most common gynecological cancer. It accounts for 19% of all gynecological cancers in low- and middle-income countries and 29% in high-income countries (23). Incidence rates are highest in high-income countries, with rates in these areas exceeding 10 per 100,000 women, except for Japan. The incidence in South America is relatively high compared with many regions in Asia and Africa. The incidence rate has been slowly increasing in many high-income countries over the last two decades. In Sweden, the incidence of ovarian cancer is one of the highest in Europe (19).

A number of epidemiological studies have evaluated a variety of risk factors for ovarian cancer. However, contrary to cervical and endometrial cancers, little is known about the etiology of ovarian cancer. To date, these risk factors include age (39), non-steroidal anti-inflammatory drug (NSAID) use (40), diet (41), ethnicity, HRT (42), hysterectomy, infertility drug use, obesity, smoking, and talc use (43).

Several studies have reported the risk of ovarian cancer among immigrants in UK and US (30, 44-47). Haenszel was not able to show significant difference in ovarian cancer mortality among immigrants in the US in 1960 except for the higher mortality for women from Italy (46). Later, he observed that mortality from ovarian tumors had risen among Japanese migrants and their descendants (47). Japanese, Chinese, Hispano, and Black women had lower rates of epithelial ovarian tumors than those of White women in the US (45). A lower incidence of ovarian cancer has been reported among first-generation migrants from Africa and Caribbean compared with White native women in Britain, even after correction for reproductive factors and menstrual history (30, 44). In Sweden, a lower risk has been observed among all immigrants as a whole and immigrants from Asia and Yugoslavia compared with Swedish-born women (25).

2.2.2.4 Breast cancer

With one million new cases each year, breast cancer is the most common malignancy in women in the world. It comprises 18% of all female cancers (48). Breast cancer is also the most common cause of cancer-related mortality among women, which is approximately 15% of all cancer-related deaths, representing 1.7% of all female deaths (48, 49). In terms of absolute numbers of death, the figure is now higher in low- and middle-income countries compared with high-income countries.

Both incidence of, and mortality from breast cancer vary about five-fold across countries around the world (50). The difference between Far Eastern and Western countries is diminishing but is still about five-fold. Countries with high risk of breast cancer i.e. world age-standardized rates (ASR) greater than 80 new cases per 100,000 women years, include the US, Canada, Australia, New Zealand, Sweden, and Uruguay in South America (18).

Estrogens are connected to many of the established risk factors of breast cancer (50). Early menarche (51, 52), late menopause (51-53), obesity in postmenopausal women (54), alcohol (55), oral contraceptives (56), hormonal therapy for menopause (57) and mutations in certain genes (58-60) are associated with an increase in risk. Childbearing (61), early first birth (62, 63), a larger number of births; breastfeeding (51, 62-64), low socio-economic position (65) and physical activity (66) reduce the risk.

Potential explanations for the large geographical differences in breast cancer incidence may either be genetics, lifestyle and environment or most likely the interaction between gene and environment. Results from studies on migrants from low-risk to high-risk countries have shown that the rates increase and eventually become similar to those among the rest of the population in the new country. The study of Chinese migrating to Hong-Kong and then to the United States showed that it took more than one generation for the risk to converge towards the high risk of breast cancer of Caucasian American women (53). Studies of migrants from Japan to Hawaii showed that the rates of breast cancer in migrants reached the rate in the host country within one or two generations, indicating that environmental factors are of greater importance than genetic factors (47, 67).

2.2.2.5 Prostate cancer

Prostate cancer is the second most common cancer diagnosed among men worldwide (68). Reported prostate cancer incidence rates vary considerably worldwide (19). It was the most common type of cancer diagnosed among men in many high-income countries; however, in low- and middle-income countries, prostate cancer was the sixth most common cancer among men (69). In 2002, there was about a six-fold difference between the prostate cancer incidences in high-income countries compared with low- and middle-income countries. Rates among African-Americans are the highest in the world, followed by Caucasian-Americans. Rates in the Caribbean and in Brazil, where there are large populations of African descent, are comparable to the rates among Caucasian-Americans. In contrast, in Central America and other parts of South America, rates are much lower. Rates within Europe vary almost 7-fold, and are highest in Western Europe in particular Austria, and lowest in Eastern Europe. Although rates in Canada, Oceania, Western Europe, and Scandinavia are generally lower than the rates reported in the US, they are 2-3 times higher than those reported in Eastern

Europe. Asia, the continent having the lowest incidence of prostate cancer, also has considerable variation in reported incidence, with more westernized countries such as Japan, and the Philippines showing markedly higher rates than Thailand, India, Pakistan, Shanghai, and China. Prostate cancer incidence data from Africa are sparse.

Despite its high morbidity, the etiology of prostate cancer remains largely unknown. Age, race, and a family history of prostate cancer are the only established risk factors (69, 70). Other risk factors, including androgens (71-73), diet (74, 75), physical activity (76-78), sexual activity and numbers of sexual partners (79), inflammation (80), and obesity (81), have been suspected, but their roles in prostate cancer etiology remain unclear. It is estimated that a large proportion of the prostate cancer risk may be accounted for by genetic influences (69).

Ethnicity has consistently been observed as a risk factor for prostate cancer. African-Americans have the highest incidence rates in the world. Prevalence of latent disease at autopsy and proportion of localized tumors among all prostate cancers indicate that differences in detection cannot explain all of the observed variability in prostate cancer risk between populations (82, 83). This supports the results of migrant studies suggesting that ethnic factors, including genetic, lifestyle, or environmental factors, may affect prostate cancer risk and explain much of the differences in risk between high and low-risk populations (26, 27, 84-89).

In a study on immigrants in Sweden, researchers found that prostate cancer rate was statistically significantly lower among immigrants that among Swedish-born men. The lowest rate was found for Turkish, Yugoslavs, Italian, and Greek men (25).

2.2.2.6 Testicular cancer

Although testicular cancer remains an uncommon malignancy in men, it is the most common malignancy in young men (90, 91). There is marked geographical variation in the incidence of testicular cancer, with the highest incidence among men in the Nordic countries and the lowest incidence among men in the Middle East and Asia. Even in the Nordic region, there is a 4-fold difference in the incidence of testicular cancer. Denmark and Norway have the highest incidences and have about twice the risk of Swedish men, while the Finnish incidence is half of the incidence in Sweden. In many high-income countries, the incidence of testicular cancer has increased over the past 50 years (91-93). Reasons for this increase in incidence are less understood.

The only risk factors consistently reported to be associated with testicular cancer are cryptorchidism, past individual history and family history of testicular cancer (94, 95). A birth cohort pattern has been found for the testicular cancer (96-98) plus carcinoma in situ found in embryonic testes (99) indicating that exposures very early in life can play a role in the development of testicular cancer. Results of testicular cancer studies are often inconsistent mostly because of small sample size. A recently published systematic review and meta-analysis has found associations of maternal bleeding, birth order, sibship size and possibly caesarean section with the risk of testicular cancer (100).

A decreased risk of testicular cancer has been reported among immigrants in Sweden compared with the natives, with a tendency for this risk to disappear in next generation (25, 101). The risk among second-generation immigrants from Finland in Sweden has been shown to be double compared with that of their fathers (102, 103).

None of these studies explored the effect of age at immigration and duration of residence on the risk of subtype-specific testicular cancer.

2.2.3 Limitations of previous migrants studies in Sweden

Though there is a unique opportunity to perform migrant studies in Sweden, there were a limited number of studies on cancer morbidity and mortality among immigrant in Sweden at the start of our study. A couple of limitations are recognized in these studies:

- Most of these studies (25, 101, 104) used "Family-Cancer Database" created by linkages between Swedish National Registers. However, the focus of this register was to study familial cancer risk in Sweden. Thus, this database included only individuals who were parents of children born in Sweden. Later, researchers used this database to perform migrant studies. Since the probability of having a child might not be the same for native Swedes and immigrants (105) and because it has been shown that the risk of some cancers are affected by reproductive factors, this kind of selection might be a source of bias in migrant studies based on this register.
- They utilized the indirect method for standardization of cancer incidence rates (SIR, Standardized Incidence Ratios) to compare rates between immigrants and Swedes. These summary statistics are of value when there are small numbers of cases in the migrant groups. However, the major disadvantage of these ratios is that they are assumed to be constant across all ages, and if they are not, the values for the various groups are not comparable.
- Social class and occupation are also known to be strong determinants of cancer risk, and it is often clear from census data that migrants are over-represented in specific occupational categories, and are atypical of the general population in their socio-economic profile. Even though it is well known that certain cancers have shown clustering in groups with different socioeconomic position (SEP), previous studies have not taken SEP into consideration in their analysis.
- Previous studies did not take age at immigration and duration of residence into consideration as proxies for the acculturation in the new environment.
- In studies on testicular cancer, lack of power hampered analysis on the effect of age at immigration and duration of residence and did not allow researchers to perform histology-specific analysis.

3 Aims of this thesis

3.1 General aim

The general objective of this thesis was to delineate the effect of country of birth and socio-economic position on incidence and survival for female breast cancer and the most common female (cervical, ovarian, and endometrial) and male (prostate and testicular) genital cancers in Sweden.

3.2 Specific aims

The specific aims of the studies described in this thesis were:

Incidence (Study I-IV):

- To compare incidence of the selected cancers among first-generation immigrants to those among Swedish-born men and women (Study **I-IV**);
- To study the effect of age at immigration and duration of residence on the risk of the selected cancers among first-generation immigrants in Sweden (Study **I-IV**);
- To study the effect of socio-economic position (SEP) on the risk of the selected cancers among first-generation immigrants in Sweden (Study **I**, **II** and **IV**);
- To compare trends in incidence of prostate cancer among first-generation immigrants to that in country of origin (Study **II**);
- To compare incidence of testicular and breast cancers among second-generation immigrants to that among first-generation immigrants and Swedish-born people (Study **III-IV**).

Survival (Study IV):

- To compare survival of female breast cancer among first- and second-generation immigrants to that among Swedish-born women;
- To study the effect of age at immigration and duration of residence on the survival of female breast cancer among first-generation immigrants in Sweden;
- To study the effect of socio-economic position (SEP) on the survival of female breast cancer among first-generation immigrants in Sweden;
- To compare incidence of female breast cancer among second-generation immigrants to that among first-generation immigrants and Swedish-born people.

4 Materials and methods

From 1947 and onwards, every individual that has resided in Sweden on a permanent basis i.e. been recorded in the Total Population Register (TPR) has been assigned a 10-digit personal identity number (PIN). In health care, the PIN is used for vital statistics but it is also the key variable for linkages between different demographic and health registers including the Total population register, Cancer Register, and Cause of Death Register (106). Several authorities handle register linkages for health research purposes, but the two major operators are Statistics Sweden and the National Board of Health and Welfare. At present, PIN consists of date of birth, a three-digit birth number which is sex-specific, and a check digit (107).

Every new born in Sweden will receive a unique PIN that must be reported to the Tax Board. Immigrants without a PIN will also receive a PIN if they intend to stay in Sweden for at least one year.

4.1 Materials

We used Health and Migration Cohort, designed specifically to address health status among immigrants and their descendants in Sweden. This database was created by linkages between more than fifteen Swedish national registers through the PIN to study cancer, cardiovascular and psychiatric diseases among these groups. Part of the H&M Co data that was used in this thesis is listed below.

4.1.1 Total Population Register (TPR)

Statistics Sweden's Total Population Register was established in 1968 when a large amount of data from the registers at the country administrative boards was copied and sent to Statistics Sweden. Simultaneously, the control digit was officially introduced into personal identity numbers in 1968 when the population registration system was computerized and county-based population registers were introduced.

The TPR contain information on the population as well as population changes and should reflect the content of the population registration. The National Tax Board is the central authority with the overall responsibility for population registration. Notifications on changes in the population register are reported on a continuous basis from the National Tax Board to Statistics Sweden and the TPR. The notifications contain data on births, deaths, migrations, changes of address, changes in civil status, immigrations and emigrations.

TPR is primarily used as a basic register to produce statistics on population size and composition by variables such as sex, age, marital status in counties and municipalities. Reports on changes in the population register are used for statistics on migration, births, deaths, marriages and divorces.

The information that is registered in the population register includes:

- Name
- Address
- Personal identity number
- Country of birth
- Citizenship

- Civil status
- Spouse, children, parents, guardian(s) and adoption
- Population registration circumstances (county, municipality and parish, plus property designation)
- Immigration to and emigration from Sweden
- Address abroad
- Death and place of burial.

TPR should cover the whole population registration in Sweden; however, both undercoverage (persons who should be registered but who are not) and overcoverage (persons who should not be registered but who are) occur. Currently, no exact measurements of the size of these deficiencies are available (108).

Deficiencies in the reporting of births and immigration introduce undercoverage, while gaps in the reporting of deaths and emigrations results in overcoverage. Due to fast reporting of routines, births and deaths will introduce only very small errors. However, long intervals between the time of arrival to Sweden and the time of being entered into the population register make immigration a potential factor for undercoverage. In 1996, the median time from the registration of application for persons with citizenship of a non-Nordic country to the time they were entered into the population register was 21 weeks. This lag is shorter for immigrants since Nordic citizens stay in Sweden without a residence permit. Emigration also causes overcoverage because it is not always reported.

Probably the most serious quality deficiency in TPR is that it contains a considerable number of persons who no longer live in Sweden. Studies showed that overcoverage among foreign-born persons can be as large as 10%; however, a recently published study indicated that overcoverage among non-Nordic immigrants lies within the interval of 25,000-50,000 persons, equivalent to 4-8 % of non-Nordic immigrants (108).

4.1.2 Swedish Cancer Register

The Swedish Cancer Register was founded in 1958 and covers total population in Sweden. It is compulsory for every health care provider to report newly detected cancer cases diagnosed at clinical, pathological, or other laboratory examinations as well as cases diagnosed at autopsy to the registry.

Regional cancer registries were established in the country in the mid-1970s. Since the early 1980s, there have been six regional registries associated with oncologic centers in each medical region of Sweden, where the registration, coding, and major check-up and correction work is performed. After verification of the material, it is then sent annually to the National Board for inclusion in the Swedish Cancer Registry.
There are different types of information:

- Data on the patient, including personal identity number, sex, age, and place of residence;
- Medical data, including site of tumor (the codes are available as ICD-7 codes for the whole period from 1958), histological type, stage (has been collected since 2004), basis of diagnosis, date of diagnosis, reporting hospital and department, reporting pathology/cytology department, and identification number for the tissue specimen;

- Follow-up data, including date and cause of death, as well as date of migration.

Collected information passes through the different steps. First, personal identity number is checked against the total population register of Sweden. Second, duplicate cases and information by, for example sex and site are checked in order to preserve the validity and logical contents of the codes. A couple of studies aiming to evaluate quality of the cancer register were published (109-111). In the most recent article, the coverage rate was evaluated in comparison to the inpatient registry. The underreporting was then estimated to approximately 4%. Researchers concluded that the overall completeness of the registry is high and available underreporting will be without major impact for most uses in epidemiological or public health surveillance.

Since the Swedish Cancer Register does not accept notifications from death certificates, an estimation of the underreporting of cancers was also done by comparing the Cancer Register data with the Cause of Death Register. They found that underreporting is highly dependent on the cancer site; for example, breast cancer, female genital cancer, and urologic cancers have very low underreporting while there are a larger number of pancreatic and lung cancer that are not reported to the cancer registry (109).

4.1.3 Cause of Death Register

The Cause of Death Register (CDR) is administered by The Swedish Board of Health and Welfare (Socialstyrelsen) and contains data from 1952 onward. A medical doctor issues death certificates and cause of death certificates when a person dies in Sweden. The death certificate is sent to the local tax authority and the cause of death certificate is sent to the Swedish Board of Health and Welfare. Information in the CDR is mainly retrieved from the cause of death certificates.

The register includes all deaths, including deaths of persons registered in Sweden but occurring outside Sweden. Stillborn babies, persons who died during temporary stay in Sweden or persons without a residence permit are not included in the register. The register is updated yearly and contains personal identity number, place of death (county and municipality), underlying cause of death, nature of the injury, contributing causes of death, date of death, sex, marital status, and age. The international classification code for diseases (ICD) is used for classification of the causes of death.

Quality of Cause of Death Register is influenced by a variety of factors. The loss is small, and information about the cause of death is missing in a maximum of 0.5% of all deaths. There have been no loses since 1997, because the data collected from population statistics also include that for the deceased persons but without indicating the cause of death. A major source of uncertainty is the doctors' determination and reporting of cause of death. New legislation to give families greater ability to refuse an autopsy, and the changing rules for forensic death investigation have gradually reduced the number of autopsies for more than 50% of the deceased autopsies since the mid-1970s, compared with 14% in 2003s (5, 112).

The quality of cause of death in the register also varies mainly with age and diagnosis of the deceased. Cause of death data is more precise for young people than for older people. Old people often suffer from many diseases and it can be difficult for the physician to determine which condition was critical to the death. Similarly, data on

violent deaths and diseases with an acute nature are more reliable than data on chronic conditions. When reporting ambiguous or poorly specified causes of death, the Swedish authority requests additional information. Each year, additional information is requested in more than 4,500 cases of death.

4.1.4 Multi-generation Register

A Multi-Generation Register has been created focusing on the child-parent (biological and adoptive) relationship. The register, which contains all persons born since 1932, makes it possible to study biological relationships, which for example is of great interest for medical research (113). When data on country of birth is missing in the TPR, this information is taken from the Multi-Generation Register.

4.1.5 The National Population and Housing Censuses

The National Population and Housing Censuses cover demographic, occupational, and socioeconomic factors, such as income, occupation, and education for each household member. Variables related to SEP i.e. education, is obtained from this register. The register contains data on the total population of Sweden between 1960 and 1990. Since 1960, census information has been obtained in Sweden approximately every five years using questionnaires mailed to every Swedish household. This practice ended in 1990.

4.1.6 LISA

The Longitudinal Integration Database for Health Insurance and Labor Market (LISA) presently holds annual registers since 1990 and includes all individuals 16 years of age and older that are registered in Sweden as of December 31 each year. The database integrates existing data from the labor market, educational and social sectors and is updated each year with a new annual register. LISA includes several demographic, occupational, and socioeconomic factors, such as individual income, family income, capital income, education, and marital status.

4.1.7 GLOBOCAN 2002

The GLOBOCAN 2002 database was built up using data available in the Descriptive Epidemiology Group of International Agency for Research on Cancer (IARC). It presents estimates of the incidence, prevalence, and mortality of 27 cancers for all countries in the world in 2002 (114). It used five different methods to estimate the sex and age-specific incidence rates of cancer based on the optimal information available from each country; National Incidence data, Mortality Data, Local (regional) incidence data, Frequency data, No data. This means that estimated ASRs are not always based on data from the entire population or high quality cancer registers and indicates that the ASRs for most low and medium resource countries might be underestimated (18). In Study **III**, stratified analysis based on testicular cancer risk in parental country of birth was performed using age-standardized rates in countries of origin, derived from GLOBOCAN2002.

4.1.8 Cancer Incidence in Five Continents (CI5)

The Cancer Incidence in Five Continents series, published every five years, has become the reference source of data on the international incidence of cancer. This project is the result of collaboration between the International Agency for Research on Cancer and the International Association of Cancer Registries (AACR). The aim of the Cancer Incidence in Five Continents series was understanding disease etiology from the study of disease frequency in different communities, in different areas, and over time. The Cancer Incidence in Five Continents presents incidence data from populations all over the world for which good quality data are available (high-quality registers).

We obtained standardized rates, age-adjusted to the world population, for prostate cancer between 1963 and 2002 in the countries of origin from volumes II-IX of Cancer Incidence in Five Continents (115, 116). The criteria used to select countries were the availability of population-based data from five consecutive volumes of IARC publications.

4.2 Methods

As shown in **Table 2**, we established different cohorts consisted of men or women with known individual country of birth (and known parental country of birth for Study **III** and **IV**). All cohorts consisted of at least two groups: persons born outside of Sweden, called foreign-born (first-generation), and persons born in Sweden with both parents born in Sweden, called Swedish-born as reference group. In study **III** and **IV** we also had another group of people who were born in Sweden with at least one parent born outside of Sweden called the second-generation immigrants.

Each cohort was followed either from start date of follow-up period, date of birth or first immigration date for immigrants, whichever occurred last, until they exited from the cohorts, which were the date of diagnosis of cancer, first emigration date, death, or end of follow-up, whichever came first.

In survival analysis (Study **IV**), the primary outcomes of interest were death due to any cause and death due to breast cancer as main cause. The final cohort was followed from date of cancer diagnosis, until they exited from the cohort which was the date of death, first emigration date, or end of follow-up, whichever came first. In cause-specific survival analysis, patient's follow-up was considered censored if either death for other reasons or emigration took place.

4.2.1 Outcome variable

In the analysis of incidence (Study **I-IV**), the primary outcome of interest was diagnosis of the first malignant cancer of interest for each person. We used International Classification of Diseases (ICD-7) to identify cancer cases during the follow-up from the Swedish Cancer Registry (**Table 2**).

In survival analysis (Study **IV**), the primary outcomes of interest were death due to any cause and death due to breast cancer as main cause obtained from the Cause of Death Register.

Table 2- Characteristics of studies included in this thesis

Study	I	II	III	IV
Data source	**Health and Migration Cohort**			
Follow-up Period	**1969-2004**	**1961-2004**	**1960-2007**	**1961-2007**
Study Design	**Follow-up Study**	**Follow-up Study**	**Follow-up Study**	**Follow-up Study** **Survival Study**
Population				
Swedish-born	**4,751,448**	**3,385,160**	**3,597,708**	**3,297,353**
Foreign-born	**600,078**	**372,663**	**732,228**	**760,214**
Second-generation	-	-	**312,275**	**495,917**
Age span (years)	**15+**	**45+**	**15-54**	**All ages**
Exposure variable	**Country of birth** **(13 groups)**	**Country of birth** **(Classification by United Nations Population Division)**		
Outcome variable	**Cervical Cancer Incidence** **(ICD-7 Code; 171)** **Endometrial Cancer Incidence** **(ICD-7 Code; 172)** **Ovarian Cancer Incidence** **(ICD-7 Code; 175)**	**Prostate Cancer Incidence** **(ICD-7 Code; 177)**	**Testicular Cancer Incidence** **(ICD-7 Code; 178)**	**Breast Cancer Incidence** **(ICD-7 Code; 170)** **All-cause Mortality** **Breast Cancer Mortality**
Explanatory variable	**Age,** **Calendar period of follow-up** **Education,** **Age at immigration,** **Duration of residence**	**Age,** **Calendar period of follow-up** **Education,** **Age at immigration,** **Duration of residence**	**Age,** **Calendar period of follow-up** **Age at immigration,** **Duration of residence**	**Age,** **Calendar period of follow-up** **Education,** **Age at immigration,** **Duration of residence,** **Residence place at diagnosis**
Risk Measures	**Incidence Rate Ratio (IRR)**	**Incidence Rate Ratio (IRR)**	**Incidence Rate Ratio (IRR)**	**Incidence Rate Ratio (IRR)** **Hazard Ratio (HR)**

4.2.2 Exposure variable

In this thesis, the main exposure variable was country of birth; being an immigrant or Swedish-born person living in Sweden, obtained from the Swedish Total Population Register. Many studies on immigrants' health use ethnicity as exposure but since this term refers to a complex phenomenon including both objective and subjective criteria that is difficult to measure, country of birth is used as the more straightforward variable. Since one country may include several ethnic groups and one ethnic group may be presented in several countries, it was not possible to infer a person's ethnicity from their country of birth.

Despite the recurrence of the term immigrant in the official statistics of Sweden, there is no generally accepted definition of the word in use. The broadest definition includes all persons born in another country, as well as their children. The term 'First-generation' immigrant usually refers to persons born outside of the country, regardless of whether they are foreign citizens or have acquired Swedish citizenship. Persons born in Sweden, but with one or both parents born abroad comprise second-generations immigrants.

In study **I**, we used classification as follows:

- OECD countries (Organization for Economic Cooperation & Development) not specified in other groups (US, Canada, Australia, New Zealand, Western Europe except for Finland);
- Finland;
- South Europe (Portugal, Spain, Italy, Cyprus, Greece and the former Yugoslavia);
- Eastern Europe (Estonia, Latvia, Lithuania, Romania, Slovakia, the Czech Republic, Hungary, Albania, Bulgaria, Croatia, Macedonia, Moldavia, Slovenia, Russia, the Soviet Union, Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirgizstan, Tadzhikistan, Turkmenistan, Ukraine, Uzbekistan);
- Poland;
- Bosnia;
- South America (Chile and other Latin American countries);
- Asia (except Turkey, Iran, Iraq and Arabic-speaking countries);
- Turkey;
- Iraq and other Arabic countries;
- Iran;
- Africa (except Arabic-speaking countries of North Africa).

For studies **II-IV**, we classified foreign-born individuals into six continents according to their country of birth. We further subdivided continents into 19 world regions (**Figure 2**), as defined by the United Nations Population Division (114, 117). We reported the results in a pooled format at the level of regions or countries whenever we encountered statistical lack of power.

To evaluate the change in risk of cancer in the new environment, we performed analyses among first-generation immigrants stratified by age at immigration and duration of residence in Sweden. Tests for homogeneity and for trend were performed as likelihood ratio tests. To assess the homogeneity, we calculated *p*-values for the interaction between country of birth, duration of stay and age at immigration. Tests for trend were performed with the median in each category used as the continuous variable.

4.2.3 Explanatory variables

4.2.3.1 Socio-economic Position

We selected educational level as an indicator for socio-economic position (SEP), which has been shown to be a preferable surrogate factor for SEP (118). Furthermore, among other available variables for use as possible indicators of SEP, such as the Swedish socio-economic index (SEI), employment status, and income, education was the variable with the most complete coverage and that was largely unaffected by retirement. We obtained individual information on highest attained level of education from censuses and LISA. We classified educational level into low (<9 years), middle (10-12 years), high (college and university, 13+ years), and unknown education.

4.2.3.2 Area of residence at diagnosis

Since the early 1980s, there have been six regional registries associated with the oncologic centers in each medical region of Sweden, where the registration, coding, as well as major check-up and correction work are performed. After verification of the material, it is sent to the National Board of Health and Welfare annually for inclusion in the National Cancer Registry. We studied the effect of place of residence at diagnosis on breast cancer risk and survival (Study **IV**) by stratifying our analysis by geographical place at diagnosis into six regions (Gothenburg, Linkoping, Lund-Malmo, Stockholm, Umea, and Uppsala).

4.2.3.3 Attained age

We adjusted for attained age in 5-year (Study **I**, **III**, **and IV**) and 2-year (Study **II**) intervals in all models we fitted. We also stratified our analysis based on the attained age as below:

- Study **I**: 15-34, 35-49, 50-59, and 60+;
- Study **II**: 45-54, 55-64, 65-74, 75-84, and 85+;
- Study **IV**: 0-34, 35-49, 50-64, and 65+.

4.2.3.4 Calendar period of follow-up

We adjusted for calendar period of follow-up in all fitted statistical models as follows:

- Study **I**: 1969-1978, 1979-1988, and 1989-2004;
- Study **II**: 1961-1975, 1976-1990, and 1991-2004;
- Study **III**: 2-year intervals;
- Study **IV**: 1961-1985, 1986-1995, 1996-2000, and 2001-2007.

Figure 2: World regions classification recommended by United Nations Population Division (Source: Wikipedia)

4.2.4 Statistical methods

4.2.4.1 Poisson regression

We calculated incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using Poisson regression models. All analyses were adjusted for attained age (age at follow-up) and calendar period of follow-up (Study **I-IV**).

In Poisson regression models, the outcome variable is assumed to come from a Poisson distribution, a distribution of the number of events in a fixed time interval, if the events occur randomly at a constant rate. The multiplicative Poisson regression models were fitted as a log-linear regression with an offset equal to the natural logarithm of person-time. With this multiplicative model, the exponents of coefficients are equal to the incidence rate ratio (relative risk). These baseline relative risks give values relative to covariates for the whole population.

A characteristic of the Poisson distribution is that its mean is equal to its variance. In certain circumstances, the observed variance is greater than the mean; this is known as overdispersion and indicates that the model is not appropriate. A common reason for this is the omission of relevant explanatory variables.

4.2.4.2 Cox proportional hazard regression

Hazard ratios (HR) with 95% confidence intervals (CIs) for breast cancer patients (Study **IV**) were calculated using stratified Cox proportional hazards regression model. Point estimates and 95% confidence intervals were produced using the maximum partial likelihood for the effect estimates. The validity of the proportional hazards assumption was evaluated using a martingale residual-based graphical and numerical approach.

The proportional hazard model is not based on any assumptions concerning the nature or shape of the underlying survival distribution. The model assumes that the underlying hazard rate is a function of the independent variables; no assumptions are made about the nature or shape of the hazard function. However, the model requires fulfillment of two assumptions. The first is the proportionality assumption that specifies a multiplicative relationship between the underlying hazard function and the log-linear function of the covariates. The second assumption of course, is that there is a log-linear relationship between the independent variables and the underlying hazard function.

4.2.4.3 Joinpoint regression

The Joinpoint regression models were used (Study **III**) to find the best-fit line for trends of prostate cancer incidence rates (119, 120). The software takes trend data (e.g. cancer rates) and fits the simplest joinpoint model that the data allow. This analysis involves fitting a series of joined straight lines on a log scale to the trends in the age-adjusted rates. Line segments were joined at points called joinpoints. Each joinpoint denotes a statistically significant change in trend. The program starts with the minimum number of joinpoint and tests whether more joinpoints are statistically significant and must be added to the model (up to the maximum number defined by user). Once the line segments are established, the estimated annual percent change (APC) was used to describe and test the statistical significance of the trends. The null hypothesis in this analysis is that the trend in incidence rates is neither increasing nor decreasing. The

software also allows viewing one graph for each joinpoint model with the minimum number of joinpoints to the model with maximum number of joinpoints.

4.3 Ethical consideration

Epidemiological research using registers constitutes a special case regarding selection of appropriate information and consent procedures. Several national registers have been established in Sweden and elsewhere without individual consent through decisions by the national parliament on behalf of its citizens (e.g. patient registers, cancer and death cause registers). An individual has the legal right to know what kind of information the register contains but has no legal right to withdraw information from the register. Linkage of different registers is intrinsic to epidemiological research. However, protection of privacy through strict coding measures and restricted access to data is of paramount ethical interest.

To avoid violation of personal integrity; researchers need to make sure that it is not possible to link sensitive personal information to individuals. In our studies, Statistics Sweden and Centre for Epidemiology at the National Board of Health and Welfare have completed the linkages. To ensure confidentiality, the personal identity numbers are replaced with serial numbers and the codes kept by Statistics Sweden in order to preserve the possibility to perform future linkage requests by researchers. No contacts with the individuals are allowed.

This study was approved by the Regional Board of The Ethical Committee, Stockholm (Dnr: 2005/726-31 and amendment 2009/587-32).

5 Results (Table 3)

5.1 Cervical cancer (Study I)

In general, we observed a significantly lower risk for cervical cancer among foreign-born women compared with Swedish-born women after adjusting for attained age, and calendar period of follow-up. At country level, analyses revealed statistically significantly higher risk of cervical cancer among women born in Poland and Bosnia. Observed excess risk of cervical cancer among women born in Bosnia and Poland was confined to women aged 35-49 that had a doubled risk compared with Swedish-born women. We also found an increased risk among women older than 50 who were born in South America.

Overall, the risk of cervical cancer increased with increasing age at migration; however, no variation in cervical cancer risk was observed by duration of residence among all immigrant groups combined. The risk was reduced by 30% among women who immigrated at younger ages and increased by 60% among women who immigrated at older ages. Women born in Iraq and Africa who immigrated before 35 years of age had the lowest risk for cervical cancer while women born in South America, Asia, and Poland who immigrated in their fifties or later showed the highest risk for cervical cancer. A significant excess risk was apparent among women born in Bosnia and Eastern Europe within the first 5 years since immigration compared with the Swedish-born women, which converged toward the risk of the host country thereafter.

We found a slight attenuation in the risk of cervical cancer after adjustment for education, while the adjustment did not affect the risk for endometrial or ovarian cancer.

5.2 Endometrial cancer (Study I)

We observed an overall lower risk, age and calendar-adjusted, for endometrial cancer that was similar in all age strata among foreign-born women compared with Swedish-born women. Additional adjustment for education did not affect the risk for endometrial cancer.

Contrary to the risk for cervical cancer, we observed a slight decrease in the risk for endometrial cancer with increasing age at migration that was significant in women born in Asia and Turkey. Incidence rate ratios for endometrial cancer in foreign-born women were not affected by duration of residence and were lower than or similar to that for Swedish-born women, regardless of the time since immigration.

5.3 Ovarian cancer (Study I)

We observed an overall lower IRR for ovarian cancer among foreign-born women compared with Swedish-born women after adjusting for attained age, and calendar period of follow-up. Additional adjustment for education did not affect the risk.

In all age strata, the risk of ovarian cancer was the same or lower among foreign-born women compared with Swedish-born women.

The risk of ovarian cancer was 10% to 80% lower in all immigrant groups than in women born in Sweden. The lowest risk was observed among women born in Asia, South America and Turkey. Overall, ovarian cancer risk did not vary by age at migration and duration of residence.

5.4 Breast cancer (Study IV)

5.4.1 Incidence

First-generation immigrants had an overall lower risk of breast cancer. However, the overall risk among second-generation immigrants was similar to that of Swedish-born women. When stratifying the results by age at exit, calendar period of year, education, and place of residence at diagnosis, we found no variation in breast cancer risk among first- and second-generation immigrants compared with Swedish-born women. However, the risk statistically significantly decreased with increasing age at immigration among first-generation immigrants. This variation in risk by age at immigration was prominent among immigrants from low-risk countries in Africa, Asia and Eastern Europe.

There was a 20-50% statistically significantly lower risk of breast cancer observed among first-generation immigrants born in different regions in Asia, Africa, and Latin America. At the country level, IRR of breast cancer was 5% to 55% significantly lower among immigrants born in Finland, Ex-Yugoslavia, Norway, Bosnia, Poland, Ex-Czechoslovakia, China, Chile, Thailand, Turkey, and Viet Nam compared with Swedish-born women.

Women with lowest educational level had statistically significantly decreased risk of breast cancer. The decreased risk varied between 15% among women born in Sweden and second generation immigrants to 20% among first generation immigrants in the lowest compared with the highest educational level.

5.4.2 Survival

5.4.2.1 All-cause mortality

Overall, first-generation and second-generation immigrants had similar all-cause mortality compared with Swedish-born women. However, first-generation immigrants who were born in Ethiopia, Poland, and Portugal as well as second-generation immigrants whose parents, either one or both, were born in Latvia, France, and the Netherlands had statistically significantly higher risk of all-cause mortality, while women born in Asia had significantly lower risk of all-cause mortality compared with Swedish-born women.

5.4.2.2 Cause-specific mortality

We did not find statistically significant differences in cause-specific mortality either among first- or among second-generation migrants compared with Swedish-born women. However, cause-specific mortality increased significantly with increasing age at immigration. Post-menopausal breast cancer mortality was statistically significantly

higher among first-generation immigrants than among Swedish-born women, while breast cancer mortality was significantly lower if cancer was diagnosed pre-menopausal.

We observed a clear socioeconomic gradient in the breast cancer mortality. Regardless of country of birth, women with lowest educational level had statistically significantly around 50% higher risk of dying of breast cancer compared with women with highest level of education.

5.5 Prostate cancer (Study II)

In general, foreign-born men had a 40% lower risk of prostate cancer compared with Swedish-born men after adjusting for attained age and calendar period of year. Additional adjustment for education did not change the risk of prostate cancer.

At the level of World regions, men born in the Caribbean had a non-significant elevated risk and men born in Middle Africa had a borderline increased risk. The risk among immigrants from Democratic Republic of the Congo, who constituted the majority of immigrants from Middle Africa, was about 3 times higher than the risk for men born in Sweden.

Overall, the risk adjusted for attained age, calendar period of year and education was lower in both strata of age at immigration and duration of residence compared with the Swedish-born men. After additional adjustment for birth country, we observed a significantly higher risk among immigrants who immigrated at ages younger than 40 years compared with those who immigrated at ages older than 40 years, and among foreign-born men who stayed longer than 35 years compared with those who stayed for shorter periods.

In analyzing the incidence trend by joinpoint regression, prostate cancer incidence among Swedish-born men increased significantly by 2.0% per year for the period 1964-1995 and by 8.0% per year for the period of 1996-2004. Rates among immigrants from Estonia also increased by 1.6% and 9.0% per year for the periods of 1961-1993 and 1994-2004, respectively. Incidence rates were relatively stable for 1961 through 1995 among immigrants from Denmark, Germany and Finland, whereas their more recent rates (1996-2004) increased by around 9% per year.

5.6 Testicular cancer (Study III)

First-generation immigrants showed remarkably different IRRs by country of birth. In general, IRRs among first-generation immigrants reflected to some extent, the risk in the countries of birth. Compared with Swedish-born men, first-generation immigrants from low-risk countries had a lower risk of testicular cancer, while those from high-risk countries had a higher risk. At the country level, IRR of testicular cancer was 40% to 85% significantly lower among immigrants born in Ex-Yugoslavia, Lebanon, Finland, Iran, Turkey, and Iraq compared with Swedish-born men. The risk was 40% to 240% significantly higher among men born in Germany, Norway, Denmark, Chile, and Switzerland compared with Swedish-born men.

Overall risk of testicular cancer among second-generation immigrants was similar to that of Swedish-born men, but varied by parental country of birth. An apparent

convergence toward the risk of Swedish-born men was observed among most second-generation groups.

Among first-generation immigrants with both parents born outside Sweden, those from high-risk areas had 60% higher risk, while those from low-risk areas showed about 60% lower risk compared with the Swedish-born men.

Among second-generation immigrants, there was no significant difference across parental categories of origin (mother foreign-born, father foreign-born or both foreign-born). However, second-generation immigrants with both parents born outside Sweden had higher risk compared with Swedish-born men if parents were from high-risk areas and lower risk if parents were from low-risk areas.

Compared with the first-generation immigrants, testicular cancer risk was lower among second-generation immigrants with parents from high-risk areas, while the risk was two times higher among second-generation immigrants with parents from low-risk areas. When the data was stratified by histopathological subtypes, the overall results were basically the same but more prominent for seminomas than non-seminomas. At the country level, the risk was significantly higher among second-generation immigrants with at least one parent born in former Soviet Union, Turkey, and Finland compared with the corresponding first-generation immigrants.

In general, the risk decreased by increasing age at immigration and increased by increasing duration of residence regardless of the risk in country of birth. When stratifying the results by histopathological subtypes, the risk of testicular seminomas was statistically significantly modified by age at immigration and duration of residence among immigrants from high-risk areas, but not among those from low-risk areas. The risk patterns in the analysis of the risk of non-seminomas were less regular and without statistically significant trend or heterogeneity.

Table 3- Summary of results of studies included in this thesis

	Female Cancers				Male Cancers	
	Cervical	Endometrial	Ovarian	Breast	Prostate	Testicular
Cancer cases						
Swedish-born	17,070	33,658	31,070	60,249	187,675	4,733
First-generation	1,177	1,632	1,157	8,315	8,244	530
Second-generation	-	-	-	1,513	-	538
Risk: immigrants vs. Swedish-born; IRR (95% CI)						
First-generation	0.88 (0.83-0.94)	0.78 (0.74-0.82)	0.59 (0.55-0.62)	0.90 (0.88-0.92)	0.57 (0.56-0.58)	Low-risk area: 0.43 (0.38-0.49) High-risk area: 1.61 (1.42-1.83)
Second-generation	-	-	-	1.04 (0.99-1.09)	-	1.02 (0.93-1.12)
Risk: lowest vs. highest level of education; IRR (95% CI)						
Swedish-born	-	-	-	0.84 (0.82-0.86)	-	-
First-generation	-	-	-	0.78 (0.74-0.83)	-	-
Second-generation	-	-	-	0.85 (0.76-0.95)	-	-
Effect modification by:						
Age at Immigration	Yes	No	No	Yes	No	Yes seminomas
Duration of Residence	No	No	No	No	Yes	Yes seminomas
Socio-economic Position	Yes	No	No	No	No	-
Survival: Immigrants vs. Swedish-born; HR (95% CI)						
First-generation	-	-	-	1.00 (0.93-1.06)	-	-
Second-generation	-	-	-	0.92 (0.82-1.03)	-	-
Survival: lowest vs. highest level of education; HR (95% CI)						
Swedish-born	-	-	-	1.55 (1.47-1.63)	-	-
First-generation	-	-	-	1.42 (1.22-1.66)	-	-
Second-generation	-	-	-	1.43 (1.06-1.95)	-	-

6 Methodological considerations

The major strengths of our studies are the unprecedented statistical precision and the nation-wide design with a long follow-up of all Swedish-born and foreign-born men during the study period. We had almost complete records about our main exposure, country of birth. Misclassification with regard to exposure, if any, is most likely independent of cancers and thus non-differential since information on exposure was collected before the diagnosis of any cancer. It is obviously essential that migrant status should be defined in an identical manner in the censuses as sources of exposure variable and population at risk data, as well as cancer and death registers as sources of outcome variables. We used Total Population Register as the source for country of birth in our studies and linked that to the National Cancer and Cause of Death Registers. Thus, there is virtually no concern about consistency in definition of migrant status in our studies.

Power to stratify the risk among immigrants by age at immigration and duration of residence, by histopathological subtypes and by risk in parental country of birth (Study **III**) and among second-generation immigrants (Study **III** and **IV**) together with the completeness and reliability of registers in Sweden are other strengths. These factors allowed us to evaluate further the importance of exposure timing on epidemiology of selected cancers among immigrants.

6.1 Selection bias

Interpretation of migrant studies is not straightforward as migrant populations are most likely a self-selected and non-random sample from the population of their countries of origin. Immigrants may often come from very limited sub-areas within the country of origin or from special religions, socio-economic positions, occupations, or ethnic groups. When comparing disease risk among immigrants to that in country of origin, one should take into account that immigrants may differ from non-migrants according to different factors. This selection may influence health and disease risk, although this effect is likely to disappear with time and in the second generation.

It often assumes that migrants are healthier than the average population in the country of origin, the “healthy migrant effect” (121). For example, this kind of effect has been reported in studies on mortality among Turkish immigrants in Germany but not in Sweden (122, 123). One reason might be that migration needs energy and enough resources. Another reason, not applicable to Sweden, might be the exclusions for ill or disabled persons introduced by authorities of host countries. Researchers have also reported an “unhealthy migrant effect”.

To reduce the effect of selection bias in migrant studies, researchers can make comparisons between similar groups, immigrants vs. source population in country of origin. This comparison is usually impossible for the country of origin except for immigrants from distinct geographical regions within the country of origin when health data, and in our case cancer data is available. In some situations, where there is considerable variation in rates of cancer within various parts of the country of birth, such as testicular cancer in Denmark (124), more defined measures for place of birth within country of origin is needed. We had no such information in Swedish national

registers. However, it is possible to check for these effects, healthy or unhealthy, if risk according to duration of residence in the country of origin can be estimated. A significant change in rates from those in the host country in recent migrants suggests this form of bias (11). In our study on testicular cancer (Study **III**), we used cancer rates in countries of origin extracted from GLOBOCAN to categorize immigrants into high-risk and low-risk. When analyzing the effect of duration of residence on cancer risk (Study **I-IV**), we excluded cancer cases diagnosed within two years of arrival. Similar to some of other studies, we found no sign of any such effect among immigrants in Sweden regarding selected cancer risks (125).

6.2 Confounding

Exploring the effect of birthplace on cancer risk, several variables related to both cancer risk and exposure can be considered as confounders. Two most important demographic factors with such possible effect are age and calendar year of diagnosis. Different age distribution between immigrants and population of host country might be a strong confounder in the comparison of cancer risk. Controlling for age, either by age-standardization or by adjustment, has commonly been used to control for the effect of this potential confounder. In our studies, we adjusted for attained age in all our analyses. However, residual confounding may still be of concern due to older age among Swedish-born residents compared with immigrant population and especially for cancers with peak incidence at older ages. Temporal trends in cancer incidence may also be different in both migrant and host populations, especially if, like in our studies, historical data is used. This should be considered, especially when studying the effect of duration of residence. In this case, an adjustment for period is necessary because data from more recent periods will contain more migrants with long periods of residence than those from earlier years. All statistical models in our studies included calendar period of year as a probable confounder.

Geographical variation in cancer risk within host country is also considered as a possible source for confounding, given that immigrants are rarely distributed homogeneously in the host country. In Sweden, researchers reported variation in breast and prostate cancer risk by geographical regions within the country (126, 127). We performed the stratified analysis by area of residence at diagnosis of breast cancer (Study **IV**). We did not find any effect modification of place of residence on the incidence rate ratio of breast cancer among immigrants compared with Swedish-born women.

Socio-economic position (SEP) is known to be a strong determinant of cancer risk. It is often clear from census data that migrants are over-represented in specific occupational categories, and are atypical of the general population in their socio-economic profile. To have meaningful comparisons, one should therefore take SEP into account. Besides the adjustment of risk for SEP, we tried to study the effect of SEP on the risk of cancers by stratification in this thesis.

Several risk factors have been suggested for the cancers that were studied in this thesis. We could not adjust for these potential confounders because such information was not available in the Swedish registers. However, because most of these factors can only account for a small fraction of the total incidence of malignant tumors such as

testicular cancer, differences found in risks among immigrants might not be explained by these factors.

6.3 Data quality

Variation in the quality of data from different sources is a source of problem when cancer rates in one country are compared with those from another country i.e. country of origin for immigrants vs. host country. Comparisons within a country are less likely to suffer from systematic biases in data quality. However, biases might result from inequalities in access to healthcare facilities for immigrants compared with the native population of the host country.

Some cancer sites are prone to misclassification at registration. A well-known example is cancer of the uterus, for which cause-specific death records varies considerably between countries, leading to large international variation in the death rates of cervical and endometrial cancer. However, to our knowledge, there is no evidence indicating differences of cancer registration between immigrants and native Swedes in Sweden.

Calculation of incidence rates requires an estimate of person-years at risk. This calculation is normally made from census data. However, censuses are usually infrequent, and interpolations are needed to derive person-years at risk. This might introduce some practical difficulties in using population-at-risk data, especially when active migration is still occurring during the study period. In our analyses for age at immigration and duration of residence, we found an overall 12% missing data for first immigration date. The degree in which immigration date was missing varied considerably by country of birth; ranging from less than 5% among immigrants from Asia and Latin America to 67% among immigrants from Estonia. Immigrants from Nordic and European countries had between 10 and 30% missing data in first immigration date. To overcome the problem, some researchers used first date of appearance in censuses in Sweden as a proxy for immigration date. To preserve accuracy, we analyzed age at immigration and duration of residence only among immigrants with known immigration date. On the other hand, when calculating person-years at risk we used first date of appearance in censuses as entry date to cohort for immigrants with unknown immigration date.

A source of bias that is more difficult to detect is the failure to report re-migration. The problem arises if immigrants return to their country of origin due to critical status of their health and the probability of passing away there. This overcoverage in the population statistics leads to overestimation of person-years at risk and, subsequently to underestimation of the incidence of the health outcome under study. One study on mortality among immigrants in Sweden found significantly lower death rates among residents born in Turkey, Southern Europe, Latin America, Asia, and Africa compared with native Swedes. However, when the income criterion was introduced as an indicator for residence in Sweden, the reduced relative death risks was no longer significant for males born in Southern Europe, former Yugoslavia, and Turkey as well as women born in Asia and Africa (123). However, in a study in Germany researchers found comparatively low mortality among Turkish immigrants that was not explained by over-registration alone (122). Overcoverage in Sweden is estimated to range from 4 to 8% for non-Nordic immigrants (128). No overcoverage

has been observed for immigrants from Nordic countries because since 1969 Nordic countries have coordinated their population changes with each other. Further studies are required to rule out probable biases due to selective re-migration of critically ill individuals to their home countries.

7 Interpretation of findings

7.1 Cervical cancer (Study I)

We found that foreign-born women had an overall lower risk of cervical cancer than Swedish-born women (129). Our findings are in line with the results from studies on first-generation immigrants in New South Wales and the Netherlands (26, 27), and in contrast to the results of a Swedish study (25). Lack of power due to restriction of cohort to women who gave birth after immigration to Sweden in the latter Swedish study may explain the contrasting results with our study (25). We did not compare the risk of cervical cancer among immigrants to that in the countries of origin. However, other studies on immigrants in the United States, France, Netherlands, and Australia as well as a recently published study in Sweden consistently showed that cervical cancer risk is lower among immigrants than that in their countries of origin (27, 29, 30, 130-133).

The risk of cervical cancer was higher among older immigrants especially those from high-risk regions, such as Asia, Bosnia, Eastern Europe, Poland and South America. This risk modification by age at immigration may be due to the fact that older immigrants have had undetected persistent human papillomavirus (HPV) infection or pre-cancerous lesions before immigration (134). The finding of increased risk among these older immigrants is in accordance with available data on cancer rates in the respective countries of origin in GLOBOCAN (135). The observed risk after the age of 50 years at immigration reflects a rate corresponding reasonably to the rate of the birth country of these immigrants.

Another explanation might be lower probability of access to screening because in Sweden women are not invited for screening after the age of 60 years. In addition, from the decreasing trend in the risk of cervical cancer by duration of residence among immigrants from Bosnia and Eastern Europe, it can also be hypothesized that the immigrants live longer because they benefit from the cervical cancer screening program in Sweden. Similarities in HPV prevalence between Eastern Europe and Sweden (136, 137), and differences in attitudes toward pre-marital and extramarital sex, sex before the age of 16, and homosexuality between Poland and Sweden (138) cannot explain the observed increased risk among women immigrating at the age of 50 years and older. Further studies on attendance to cervical cancer screening and occurrence of carcinoma *in situ* would help to clarify this hypothesis.

The decreased risk of cervical cancer among immigrant women born in Africa, Iran, Iraq/Arab countries and Turkey might be explained by exposure related to different sexual behaviors, which is reflected by the dominant religion among these women, Islam (139). Prohibited extramarital sexual activities might lead to later age at first intercourse and fewer sexual partners (140).

The incidence rates of cervical cancer vary considerably in the world. They are much higher in low- and middle-income countries than in high-income countries and highest in sub-Saharan Africa and Melanesia (135).The estimated RR among immigrants from Africa in our study was unexpectedly low and might be explained by

the "healthy migrant effect" (11), or by misclassification due to the pooling of African countries due to lack of power.

Socioeconomic position (SEP) has an important implication on cervical cancer risk and screening practices (141, 142). We adjusted for years of education, which has been shown to be a preferable surrogate factor for SEP (118). We found a slight attenuation of the risk of cervical cancer after adjustment for education. This is in line with the known confounding effect of SEP on the risk of cervical cancer, which might be explained by different sexual behaviors and higher prevalence of HPV prevalence in women with low SEP (143).

7.2 Endometrial cancer (Study I)

All foreign-born women had a lower risk of endometrial cancer compared with the Swedish-born women, with no effect modification by age at migration, duration of residence or socioeconomic position (129).

According to the available information, endometrial cancer incidences are low in southern and eastern Asia, and the highest incidences are observed in North America and Europe (18). Sweden has one of the highest rates in the world (144). Our results indicate that the immigrant women retained their lower risk without convergence to the risk in the host country. Poorer medical surveillance of immigrants than that among native residents might also partially explain this finding.

Epidemiologic data are consistent with a model system for hormonal effects in women, which indicate that estrogens induce endometrial proliferation and carcinomatous change, whereas progestins counteract these effects. We had no information on individual risk factors, such as parity, use of oral contraceptives and menopausal estrogen therapy, age at menarche and menopause, or obesity (33). However, a study on different ethnic groups in the USA showed that the distribution of known risk factors of endometrial cancer could not explain the observed reduced risk among different ethnic populations (38). Furthermore, findings from a recently performed health survey in Stockholm County (145) and results from other studies (146, 147) showed that the prevalence of obesity is higher among women born in Turkey, Iraq, Chile and South America, Bosnia, South Europe, Finland and Iran than among Swedish-born women. On the other hand, obesity has been associated with increased risk of endometrial cancer by increasing peripheral production of estrogen (33), which is in contrast to the observed decreased risk of endometrial cancer found among immigrant women in our study.

Increased risk of endometrial cancer caused by exposure to unopposed estrogen among Swedish women could explain the increased risk of endometrial cancer among Swedish-born women (148). The use of unopposed estrogen was common in Sweden in the 1970s among postmenopausal women (148).

One study on childless women aged 20-41 years showed a higher first birth rate in most foreign-born women compared with native Swedish women (105). The highest rates were found among women from Iraq and other Arabic-speaking countries, Bosnia, Turkey and Somalia. If first birth rate is an indicator of multi-parity, then decreased risk of endometrial cancer among migrants might be explained by higher first birth rates.

7.3 Ovarian cancer (Study I)

We found an overall lower risk of ovarian cancer among immigrants in Sweden compared with the Swedish-born women (129). We did not find any effect modification by age at migration, duration of residence or socioeconomic position. Overall, observed lower risk of ovarian cancer among foreign-born women is in agreement with available data on ovarian cancer rates in countries of origin. Incidence of ovarian cancer is lower in Africa and Asia compared with Western countries and it is highest in Northern Europe (18). Our findings are also in line with studies on black women, Japanese and Chinese immigrants in the United States and on immigrants from Africa and Caribbean in Britain, which showed consistently lower risk among immigrants compared with the host country (30, 44, 45).

Findings of no affect of age at migration or duration of residence on ovarian cancer risk in our study indicate that protective factors for ovarian cancer, if any, seem to be retained upon migration.

Contrary to cervical and endometrial cancers, little is known about the etiology of ovarian cancer. Older age, nulliparity, talc use, early menarche, late menopause, obesity, endometriosis, being Caucasian, and family history of ovarian cancer have been shown to be positively associated with ovarian cancer, while the inverse association has been observed for oral contraceptive use and parity (149, 150). Foreign-born women in our study were younger than Swedish-born women. The observed lower risk of ovarian cancer among immigrants cannot be explained by age, as decreased risk was consistently observed in all strata of attained age. Prevalence of obesity was higher among many immigrant groups compared with Swedish-born women in previous studies, which is in contrast with observed lower risk among immigrants in our study (146, 147, 151). On the other hand, higher first birth rate, as a probable indicator of multi-parity, could explain part of the observed decreased risk of ovarian cancer among foreign-born women (105). None of these studies were population-based; thus, one should be careful to draw any conclusions based on these results.

7.4 Breast cancer (Study IV)

7.4.1 Incidence

We observed an overall lower risk of breast cancer among first-generation immigrants, but a risk among second-generation immigrants similar to that of Swedish-born women. Age at immigration significantly modified the risk among first-generation immigrants. Previous studies on cancer among immigrants in Sweden neither focused on breast cancer *per se* nor considered age at immigration and duration of residence (25, 152-154).

Previous migrants studies on breast cancer incidence have shown that adult immigrant women from low-risk areas retain their low risk, while younger migrants had an increased risk (155). This highlights the importance of early exposures such as diet. In our study we examined changes in risk with respect to three indicators of acculturation i.e. age at immigration, duration of stay and generation in Sweden. Our findings of risk modification by age at immigration, but not by duration of residence, in

line with studies on Italian migrants and US Hispanics (156-158), suggest that the timing of migration might be a stronger predictor of breast cancer risk than duration of residence and highlights the importance of early-life exposures.

The low incidence in women born in Finland, Ex-Yugoslavia, Norway, Bosnia, Poland, Ex-Czechoslovakia, China, Chile, Thailand, Turkey, and Viet Nam found in our study might be due to different distribution of risk factors in comparison to native Swedes. We had no information on individual risk factors in this study.

In agreement with the results of studies among immigrants from Asia and Latin America in the US and immigrants from Ireland in the UK (53, 159-161), we observed convergence of risk toward the risk in Sweden among second-generation immigrants particularly among those whose parents were from low-risk areas such as Asia and Latin America.

The finding of our study of protective effect of low social position on breast cancer risk was expected and was consistent with the results from numerous previous studies (162-168).

7.4.2 Survival

Overall, cause-specific and all-cause mortality were similar between first- and second-generation immigrants compared with Swedish-born women. However, at country level some groups of immigrants, either among first- or among second-generation immigrants, showed statistically significantly higher all-cause mortality compared with Swedish-born women. Cause-specific mortality was statistically significantly higher among older first-generation immigrants, or if cancer was diagnosed post-menopausal or in most recent years.

Evidence from different epidemiological studies including our study and other studies from Sweden with believed equal access to a uniform health care system, indicate that breast cancer survival is poorer among socio-economically disadvantaged women (169-173). Despite the observed socioeconomic gradient, we did not find a significant variation in survival by education among immigrants compared with Swedish-born women, indicating similar poorer breast cancer prognosis among immigrants and Swedes in less advantaged social group.

It is known that breast cancer survival is better in Sweden than in Denmark (174). We found a similar survival rate among immigrants from Denmark and among Swedish-born women. Our finding is in agreement with the results of a previous study that concluded that the early detection in Sweden has a significant impact of breast cancer survival (175).

Swedish researchers have earlier shown that young women affected by breast cancer have a high risk of mortality even if diagnosed early and receiving intensive treatment. In older women, however, less diagnostic activity, less aggressive treatment, and later diagnoses were associated with poorer survival (176, 177). In our study, we found a disparity in survival for postmenopausal breast cancer among immigrants and Swedish-born women but not for premenopausal cancer. It might be explained by differences in management and diagnosis of breast cancer in older immigrant women (178-180).

7.5 Prostate cancer (Study II)

We found that foreign-born men had an overall lower risk of prostate cancer compared with Swedish-born men that was not affected by education, and was similar in all strata of attained age (181). Duration of residence was an effect modifier for prostate cancer risk among the immigrants. The observed differences in risk of prostate cancer among foreign-born compared with Swedish-born men may be related to a number of factors. These factors include diagnosis by prostate specific antigen (182, 183), access to health care and different diagnostic procedures including digital rectal examination (DRE) and transurethral resection of the prostate (TURP)(184), genetic susceptibility, and exposure to environmental and lifestyle risk factors.

Although, the risk of prostate cancer among first-generation immigrants was modified by duration of residence, it remained statistically lower than that among Swedish-born men in both strata of duration of residence. This might suggest that either genetic factors are more influential than environmental factors in the susceptibility to prostate cancer, or more likely that it takes more than one generation for environmental factors to act.

In general, the observed high risk of prostate cancer among immigrants from Middle Africa and the Caribbean that have common ancestors in Africa, may suggest a strong influence of genetics or, less likely, shared lifestyle risk factors in the etiology of prostate cancer. Our findings are in agreement with the consistently observed high risk of prostate cancer among African immigrants in the USA and the UK and among immigrants from the Caribbean in the UK (185-187). The data is also suggestive of higher rates of prostate cancer in Africa and the Caribbean than that presented in international data, indicating the possibility of unreported cases in these countries (18).

The observed lower risk of prostate cancer among immigrants from Asia compared with Swedish-born men is similar to other studies on Asian migrants in the USA, the UK and Australia (26, 187, 188). We found a tendency of convergence of the risk among Asian immigrants who immigrated at younger ages or among those who stayed longer toward the risk among Swedish-born men. Unknown risk factors associated with western lifestyle in this group, especially diet could partly explain this convergence (70, 189).

The incidence of prostate cancer is more affected by screening than any other cancer. In addition, the prevalence of microscopic latent tumors has been shown to be quite high and similar among the elderly in most populations (190). A more rapid increase in incidence of prostate cancer, which started around 1995 among immigrants from Denmark, Estonia, Germany, and Finland, and for the same period among Swedish-born men, can be attributed to the introduction of diagnostic PSA test in Sweden around 1990 (191).

Migrants from Denmark had similar trends of incidence to their counterparts in Denmark. We also found that the risk of prostate cancer among immigrants from Denmark remained lower compared with Swedish-born men in all strata of attained age, age at immigration and duration of residence. This might be explained by genetic factors or persistent lifestyle risk factors in the etiology and progression of prostate cancer within this population; however, the effect of diagnostic density should also be taken into account.

Migrants from Estonia, known as the most integrated immigrants into the Swedish society (153), had a trend in incidence of prostate cancer more similar to the Swedish-born men than to their counterparts in Estonia. We found a higher risk among Estonians who immigrated at younger ages and among those who stayed longer. These observations indicate the importance of modifiable environmental factors in the etiology of prostate cancer.

High SEP has been shown to be associated with increased incidence of prostate cancer (192, 193). These differences in SEP have often been explained by differences in diagnostic activity, and are at least partly due to greater use of diagnostic PSA test among higher educated men. In our study, however, adjustment for education did not affect the risk. Although, education is one of the best indicators of SEP, there might be a residual confounding regarding social position. Diagnostic activity may also vary by occupation due to available occupational health services.

7.6 Testicular cancer (Study III)

The incidence of testicular cancer has doubled in the past decades in the USA, Canada, Europe and Australia (92, 93, 194, 195). Such a rapid increase indicates environmental and lifestyle factors are crucial in the development of testicular cancer. Our findings of a clear maintenance of the risk of the country of origin by first-generation immigrants and convergence of risk towards that among native Swedes in second-generation immigrants (196) are in line with results of previous studies (102, 152, 197), and provide further evidence of the effect of environmental and life style factors on the risk of testicular cancer.

There is a reasonably large amount of epidemiological and experimental data supporting the hypothesis that factors acting *in utero*, namely excess estrogens play a role in the development of testicular cancer (198, 199). Our findings of risk modification of seminomas by age at immigration and duration of residence among first-generation immigrants from high-risk areas, in contrast to the results of previous studies (102, 152, 197), indicate however, that the risk of testicular cancer is affected by environmental and life style factors acting postnatal. Unfortunately, previous studies supporting the importance of postnatal factors in developing testicular cancer (200, 201) have not reported risk of testicular cancer separately for seminomas and non-seminomas.

Several risk factors, such as birth weight, maternal age and parity, have been suggested for testicular cancer (202-204). These data were not available in our study. However, since these factors only account for a small fraction of the total incidence, and because of very similar population in the Nordic countries of such factors, differences found among immigrants from Nordic countries might not be explained by these factors (205).

Second-generation immigrants with both parents born in low-risk areas had a doubled risk as compared with first-generation immigrants, while those with at least one parent born in high-risk areas showed similar risk to that among their fathers. Differences in genetic susceptibility cannot explain doubling of the risk and might indicate existence of a gene-environment interaction in testicular cancer etiology. There have been some indications of a link between genetic factors and ethnic differences in

testicular cancer (206, 207). Further investigation is needed to combine exposure data with genetic predisposition of testicular cancer.

We found no or modest change in the risk for non-seminomas compared with seminomas. It is possible that the two types do not entirely share risk factors, and as suggested by previous studies, non-seminomas may be worth further investigation for genetic susceptibility (98, 208-215).

Our results for first-generation immigrants from the countries with better cancer registration showed similar or even lower risk compared with the risk in country of birth. However, the risk among immigrants from countries with no or poor quality registers showed a higher risk compared with country of birth, indicating that testicular cancer risk in these countries is likely to be underestimated by GLOBOCAN 2002 (19, 114).

8 Concluding remarks

- First-generation immigrants in Sweden have an overall lower risk of all cancers studied compared with Swedish-born people. However, there are considerable variations in cervical, prostate, and testicular cancer risks among first-generation immigrants by country of birth. Thus, country of birth is a major determinant for cancer risk. More importantly, immigrants should not be considered as a homogeneous group and thus, should not be treated as one group in research and preventive programs.

- Age at immigration and duration of residence are important factors affecting risk of cervical, breast, prostate, and testicular (seminomas) cancers among first-generation immigrants, which illustrate the effect of environmental and lifestyle factors on cancer risk. Risk of ovarian and endometrial cancer remains low even after long stay in the host country, indicating that protective factors for these cancers are retained upon migration.

- Education, as an indicator of socio-economic position, differentially affected the risk of cervical cancer among first-generation immigrants and Swedish-born women. Education either had no effect or non-differentially affected the risk of other cancers among immigrants and Swedes.

- The observed increasing trend in prostate cancer incidence among first-generation immigrants similar to the trend in either Sweden or country of birth implies the importance of both genetic and environmental factors in the etiology of prostate cancer.

- Similar patterns of testicular cancer risk among second-generation immigrants and Swedish-born men indicate the importance of early environmental risk factors that probably act after the intrauterine period. These factors appear to influence the risk of seminomas more than other cancer types.

- Individual country of birth, parental country of birth and age at diagnosis are important effect modifiers in the analysis of breast cancer survival among first- and second-generation immigrants compared with Swedish-born women.

- Among both immigrants and Swedish-born women, breast cancer risk increased, while, its survival decreased with increasing level of education.

9 Future perspective

- Sweden is an excellent country to perform migrant studies on cancer because of its uniform health care system, high-quality cancer registration and the large and increasing number of immigrants from many parts of the world. Many immigrant groups in Sweden originate from countries with no cancer registration. Swedish cancer data among immigrants may provide reasonable estimates of the cancer rates for countries with no registration.

- Our established Health & Migration Cohort is an ideal resource to carry out migrant studies on cancer incidence and survival in almost all types of cancers. It will help to estimate an unbiased data on cancer risks, to stimulate the formulation of new etiological hypotheses, and to find appropriate ways to reduce mortality from cancer.

- Individual-based data on risk factors, diagnoses, treatments, and outcomes of cancers are valuable for drawing conclusions from migrant studies. A system of national quality registries has been established in the last decade in Sweden and contains individual data on diagnoses, treatments, and outcomes. Linkage to these resources may shed further light on etiology of cancer and in the interpretation of the survival studies; it also can help to find inequalities, if any, in access to health care for cancers among immigrants.

- Data on disparity in diagnostic activities and screening behavior by country of birth in Sweden is scarce. Such differences may help to explain part of the differences in cancer risk among immigrant groups compared with Swedish-born individuals. Also for public health reasons it is important to increase uptake of screening also in immigrants group.

- The results of our studies provide useful information for authorities involved in the management of health care and cancer prevention programs relating to immigrant population. Culturally- and linguistically-adapted educational and research materials may enhance access of immigrants to health care and screening programs and increase participation rates in studies. All of which are of importance to policy makers, health care professionals and obviously to the public.

- Further studies on pitfalls of migrant studies, such as selection bias, effect of return migration and over-coverage in population registration are needed.

- Socio-economic position (SEP) is an important factor associated with risk and survival of many cancer types. Unfortunately, there is a lack of a reliable indicator of SEP, especially among immigrants. Further studies focusing on selection of the most precise indicators of SEP are necessary.

10 Acknowledgements

My first thanks are to the Almighty God for making all things possible in life. This thesis is the result of the support and encouragement of many excellent people from the beginning to the end. I would like to give my sincere thanks to everyone who has contributed directly or indirectly to this thesis and everyone that has inspired me through the different stages of my work. Thank you very much every body.

Without any special order, I would like to give special thanks to:
Tahereh Moradi, my outstanding supervisor, for introducing a new world of PhD studentship to me, for all the great scientific discussions, and your endless support during these years. In particular, I am thankful for the amount of time you spent with your PhD students and for always keeping your door open. I wish to also thank you for introducing me to a challenging and interesting field of research. Your support led me to become an independent researcher with teamwork skills. Thank you also for reading and correcting my thesis draft.

Peter Allebeck, an excellent co-supervisor, for helping me to see the wider picture of research, always with a careful approach. Thank you so much for your support and encouragement during these years. I particularly appreciate your efforts in getting me a job as managing editor of the European Journal of Public Health, which has showed me the hidden world of scientific publishing. Thank you also for your comments on my thesis draft.

Reza Mohammadi, my mentor, for your invaluable guidance from start to finish. You and your family were always supportive of me as well as being supportive of my wife during her studies in the master of public health program. Thank you!

I wish to also thank all the co-authors that have contributed immensely to this thesis and shared their expertise with me. I wish to especially mention **Anders Ekbom**, for great discussions about science and history. I am very thankful that you shared your profound knowledge in cancer epidemiology with me, all your ideas that led to great publications and for all the input that made our publications even better; **Fredrik Granath**, for your incredible knowledge of study design, data analysis and SAS programming, which were fundamental to completing this work; **Olof Akre**, for further enriching my experience in epidemiological research by your constructive input into my third article on testicular cancer; **Tobias Nordquist**, for contributing with analysis of data for my first paper in this thesis; and **Sara Wedrén**, for your excellent comments on my first paper.

I would also like to thank other members of our group: **Anna Sidorchuk**, **Diddy Antai**, **Dashti Dzayee**, **Dong Yang**, and **Soudabeh Radpoor** for endless talks about everything during coffee breaks and lunch meetings and lots of fun moments together; **Mohammad Mohammadi** for your constructive comments on my thesis. Special thanks to **Diddy** for your time and patience in English editing of my thesis draft.

To everyone at the **Unit of Cardiovascular Epidemiology, Institute of Environmental Medicine**, thank you for so much fun during lunch meetings. I've learnt a lot from your presentations and discussions. I would like to particularly thank **Lars Alfredsson**, head of the unit of cardiovascular epidemiology and head of doctoral program in Epidemiology at Karolinska Institutet for your support, your wise advices and sustaining my interest about epidemiology by designing the excellent program; **Ulf de Faire**, former head of unit of cardiovascular epidemiology and **Anders Ahlbom**, chairman and director of the Institute of Environmental Medicine for maintaining a pleasant and enthusiastic environment at IMM.

To everyone at the **Department of Public Health Sciences** for a lot of fun times during coffee breaks and meetings, thanks a lot for your nice present, a mug with your pictures on it, when I was leaving the department! I particularly thank **Imre Janszky**, and **Rickard Ljung**, for teaching me how to critically read articles and for welcoming me as a teacher in the course "Problem-based overview of medical statistics".

Rino Bellocco, for your enthusiasm in teaching biostatistics and for welcoming me as a teaching assistant during course "**Biostatistics II: Multivariate methods for epidemiology** ".

Editorial office of European Journal of Public Health - **Karin Guldbrandsson**, **Emilie Agardh**, and **Sara Sjölund**, for being informative, helpful and flexible when performing assignments for the journal; and especially **Edison Manrique-Garcia** for being an excellent roommate when we shared our office at Norrbacka discussing about similarities and differences of Iranian, Colombian and Swedish cultures.

This thesis was made possible by access to the Swedish national registers including Cancer and Cause of Death Registers, and other data maintained at the **Swedish National Board of Health and Welfare** and **Statistics Sweden.** I would like to thank **Peter Allebeck** and **Stockholm County Council** for their support in having access to these registers.

All PhD students attending postgraduate courses for your kind and informative discussion during group assignments and nice comments on my study plan, grant applications, presentations and several others. I learnt a lot from you all. Thank you everybody!

Administration, without you my work would have been much more difficult. In particular, I wish to thank **Gunmaria Löfberg**, **Annika Himmelstrand**, and **Eva Undsén** for helping me organize everything around my admission seminar, half-time seminar, and my thesis defense as well as for providing many friendly advices.

The IT group, for maintaining the IT system; especially **Sten Thorold** at IMM and **Anders Lundström** at the department of public health with whom I had the most contact. Thank you for all your support.

Kermanshah University of Medical Sciences and the Scholarship office at the **Ministry of Health and Medical Education of Iran**, for awarding me a full scholarship to pursue my PhD degree in epidemiology. I would especially thank Dr. **Babak Izadi**, Dr. **Samad Noorizad**, Dr. **Mohammadreza Abbasi**, Dr. **Hadi Kharrazi**, Dr. **Masoumali Masoumi**, Dr. **Mohammad Reza Saidi**, Dr. **Farid Najafi**, and Dr. **Mansour Rezaee** for all your support before I started my PhD and afterwards. Special thanks to Dr. **Alireza Ahmadi** for helping me bring my knowledge about online journal publishing systems into practice by starting the **Journal of Injury and Violence Research**. Special thanks to Dr. **Hamid Akbari**, Miss **Nafissi**, Miss **Bavanpour** and Miss **Aminhashemi** for their kind support in administrative work, and thanks to Dr. **Abdollahi**, Scientific Representative of Islamic Republic of Iran in the Schengen Area, for all administrative assistance during these years.

Dr. **Seyed Mahmood Sadr** and Dr. **Seyed Khalil Foroozannia**, my teachers at **Shaheed Sadoughi University of Medical Sciences of Yazd**, for all your support, wise advice during my study in medicine and afterwards, and for keeping my interest about medical research. Special thanks to Dr. **Seyed Mehdi Kalantar** and Dr. **Arya** for your kind advice and support when I was competing to get the scholarship.

Dr. **Mohammad Reza Mohammadi**, former director of the National Research Centre in Medical Sciences in Iran, for accepting me as a research fellow and for supporting me towards the award of a prize in the **RAZI Research Festival on Medical Sciences.**

I would like to thank all Iranian students and friends in Sweden and Europe for all the gathering ceremonies, for the memorable weekends and support from you and your families as well as for sharing happy times with us: **Majid Baghaei Nejad**, **Ali Davodi**, **Alireza Baghbanan**, **Mohsen Karimi**, **Omid Faridani**, **Siamak Akbari**, **Abbas Nikravesh**, **Bahman Koroji**, **Masoud Yusefi**, **Fatemeh Sadeghifar**, **Saeed Rahimi**, **Behrooz Hamzeh**, **Davood Khorasani**, **Seyed Isaac Hashemi**, **Afshin Mohammadi**, **Parviz Kokhaei, Shahram Bahmanyar**, **Mehdi Bahrekazemi**, **Seyed Majid Mohseni**, and **Ali Soroush.** Special thanks to **Kazem Zendehdel,** I will never forget your help prior to my coming to Sweden. You were always ready to answer my questions. Thank you for all the discussions around cancer epidemiology, and particularly for the study of cancer among Iranian immigrants in Sweden.

I would like to express my sincere thanks to **my parents** for teaching me the importance of setting high standards for oneself. Without your kind support and guidance I would never have been where I am today. My dear **father** for his constant concern and extremely generous attitude during my school years; he is unfortunately not among us anymore, God bless him! I wish to thank my **mother** for understanding me, having faith in me and always putting my needs first. Without you, this would not have been possible! I would like to thank my brothers and my sister; **Davood**, **Saeed**, **Hamid**, **Majid**, and **Nahid**. **Davood**, lots of thanks for being such a nice and caring brother especially during our trips to Iran, and for lots of paper work I had for you. I have missed you a lot during these years. I wish you the best and success in your life and career. And thanks to my other relatives for supporting and taking care of my parents when I was far away from home.

Many thanks to my parents-, brothers- and sisters-in-law for all of your supports, calls and warm hospitality during our trips to Iran. All your calls refreshed our energies. Najmeh, Yasaman and recently, Ida were happy to hear your kind voices.

And most importantly I express my extreme gratitude and thanks to my wife, **Najmeh**, for your endless love, support, and care. If I could marry you twice I would do so without blinking an eye. Words cannot describe what I feel for you! You have brought love into my life in such a way I never thought was possible. Thanks for your patience in listening to my issues. I know how difficult it is to be a wife at the same time as being a mother of two children and a master student. Undoubtedly, without your constant support, encouragement, guidance and care, I would not have been able to make any meaningful achievement in my life, including this work. I also wish you a successful thesis defence!

To my daughters, **Yasaman** and **Ida**, you both have brought joy, pleasure and real happiness into my life in ways that are impossible to describe. When people described how it felt to be a father, I never truly understood until now. **Yasaman**, you have lost a lot during these years. I was always busy and I didn't spend enough time with you. I hope I will have more time to be with you from now on. **Ida,** I feel a consolation when you show me your cheerful smile!

For all misspellings in the names of those I mentioned above and for all those who I may have unintentionally not mentioned, please forgive me! I am always aware in my heart of the very important people who supported me in different ways and at different stages. Thank you for all your help!

Omid Beiki
May 2010, Stockholm, Sweden

11 References

1. Jones SB. Cancer in the developing world: a call to action. Bmj1999 Aug 21;319(7208):505-8.
2. Parkin DM. International variation. Oncogene2004 Aug 23;23(38):6329-40.
3. Moradi T, Allebeck P, Jacobsson A, Mathers C. [The burden of disease in Sweden measured with DALY. Neuropsychiatric diseases and cardiovascular diseases dominate]. Lakartidningen2006 Jan 18-24;103(3):137-41.
4. United Nations, Department of Economic and Social Affairs, Population Devision (2009): Trends in International Migrant Stock: The 2008 Revision.
5. Statistics Sweden. Population Statistics. 2010 [cited 2010 January 20]; Available from: www.scb.se.
6. Vollmer B. MigPol. Immigration Policy in Sweden.2002.
7. Vollmer, B. (2005) Immigration Policies in Sweden, in Blaschke, J. (ed.), Immigration Policies in the European Union, Berlin: Edition Parabolis.
8. Westin, C. 1996. Immigration to Sweden – An Overview. Stockholm: Centrum för Invandrarforskning.
9. Statistics Sweden, Population Statistics Unit, Description of the Population in Sweden 2008.
10. Parkin DM. Studies of cancer in migrant populations. IARC Sci Publ1993(123):1-10.
11. Parkin DM, Khlat M. Studies of cancer in migrants: rationale and methodology. Eur J Cancer1996 May;32A(5):761-71.
12. Stemmermann GN. Gastric cancer in the Hawaii Japanese. Gann1977 Oct;68(5):525-35.
13. Kolonel LN, Hankin JH, Nomura AM. Multiethnic studies of diet, nutrition, and cancer in Hawaii. Princess Takamatsu Symp1985;16:29-40.
14. McMichael AJ, McCall MG, Hartshorne JM, Woodings TL. Patterns of gastro-intestinal cancer in European migrants to Australia: the role of dietary change. Int J Cancer1980 Apr 15;25(4):431-7.
15. Thomas S, Kearsley J. Betel quid and oral cancer: a review. Eur J Cancer B Oral Oncol1993 Oct;29B(4):251-5.
16. Winn DM. Tobacco chewing and snuff dipping: an association with human cancer. IARC Sci Publ1984(57):837-49.
17. Miller YE. Pathogenesis of Lung Cancer: 100 Year Report. Am J Respir Cell Mol Biol2005 September 1, 2005;33(3):216-23.
18. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin2005 Mar-Apr;55(2):74-108.
19. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al. Cancer Incidence in Five Continents, Vol. IX: IARC Scientific Publications No. 160, Lyon, IARC.; 2007. Available from: www-dep.iarc.fr.
20. Cannistra SA, Niloff JM. Cancer of the uterine cervix. N Engl J Med1996 Apr 18;334(16):1030-8.
21. Kjellberg L, Hallmans G, Ahren AM, Johansson R, Bergman F, Wadell G, et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. Br J Cancer2000 Apr;82(7):1332-8.
22. Daling JR, Madeleine MM, McKnight B, Carter JJ, Wipf GC, Ashley R, et al. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. Cancer Epidemiol Biomarkers Prev1996 Jul;5(7):541-8.
23. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol2006 Apr;20(2):207-25.

24. Gustafsson L, Ponten J, Bergstrom R, Adami HO. International incidence rates of invasive cervical cancer before cytological screening. Int J Cancer1997 Apr 10;71(2):159-65.
25. Hemminki K, Li X, Czene K. Cancer risks in first-generation immigrants to Sweden. Int J Cancer2002 May 10;99(2):218-28.
26. McCredie M, Coates M, Grulich A. Cancer incidence in migrants to New South Wales (Australia) from the Middle East, 1972-91. Cancer Causes Control1994 Sep;5(5):414-21.
27. Visser O, van Leeuwen FE. Cancer risk in first generation migrants in North-Holland/Flevoland, The Netherlands, 1995-2004. Eur J Cancer2007 Mar;43(5):901-8.
28. Seeff LC, McKenna MT. Cervical cancer mortality among foreign-born women living in the United States, 1985 to 1996. Cancer Detect Prev2003;27(3):203-8.
29. Bouchardy C, Parkin DM, Wanner P, Khlat M. Cancer mortality among north African migrants in France. Int J Epidemiol1996 Feb;25(1):5-13.
30. Grulich AE, Swerdlow AJ, Head J, Marmot MG. Cancer mortality in African and Caribbean migrants to England and Wales. Br J Cancer1992 Nov;66(5):905-11.
31. Parazzini F, La Vecchia C, Bocciolone L, Franceschi S. The epidemiology of endometrial cancer. Gynecol Oncol1991 Apr;41(1):1-16.
32. Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat2001;6(1):47-86.
33. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet2005 Aug 6-12;366(9484):491-505.
34. Moradi T, Nyren O, Bergstrom R, Gridley G, Linet M, Wolk A, et al. Risk for endometrial cancer in relation to occupational physical activity: a nationwide cohort study in Sweden. Int J Cancer1998 May 29;76(5):665-70.
35. Moradi T, Weiderpass E, Signorello LB, Persson I, Nyren O, Adami HO. Physical activity and postmenopausal endometrial cancer risk (Sweden). Cancer Causes Control2000 Oct;11(9):829-37.
36. Sherman ME, Devesa SS. Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus. Cancer2003 Jul 1;98(1):176-86.
37. Liao CK, Rosenblatt KA, Schwartz SM, Weiss NS. Endometrial cancer in Asian migrants to the United States and their descendants. Cancer Causes Control2003 May;14(4):357-60.
38. Setiawan VW, Pike MC, Kolonel LN, Nomura AM, Goodman MT, Henderson BE. Racial/ethnic differences in endometrial cancer risk: the multiethnic cohort study. Am J Epidemiol2007 Feb 1;165(3):262-70.
39. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J Natl Cancer Inst1983 Oct;71(4):717-21.
40. Cramer DW, Harlow BL, Titus-Ernstoff L, Bohlke K, Welch WR, Greenberg ER. Over-the-counter analgesics and risk of ovarian cancer. Lancet1998 Jan 10;351(9096):104-7.
41. La Vecchia C, Decarli A, Negri E, Parazzini F, Gentile A, Cecchetti G, et al. Dietary factors and the risk of epithelial ovarian cancer. J Natl Cancer Inst1987 Oct;79(4):663-9.
42. Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. Fertil Steril2004 Jul;82(1):186-95.
43. McLemore MR, Miaskowski C, Aouizerat BE, Chen LM, Dodd MJ. Epidemiological and genetic factors associated with ovarian cancer. Cancer Nurs2009 Jul-Aug;32(4):281-8; quiz 9-90.
44. John EM, Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of seven U.S. case-control studies. Epithelial ovarian cancer in black women. Collaborative Ovarian Cancer Group. J Natl Cancer Inst1993 Jan 20;85(2):142-7.

45. Weiss NS, Peterson AS. Racial variation in the incidence of ovarian cancer in the United States. Am J Epidemiol1978 Feb;107(2):91-5.
46. Haenszel W. Cancer mortality among the foreign-born in the United States. J Natl Cancer Inst1961 Jan;26:37-132.
47. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst1968 Jan;40(1):43-68.
48. Sasco AJ. Epidemiology of breast cancer: an environmental disease? APMIS2001 May;109(5):321-32.
49. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: II. Results for the global burden of disease 2000. BMC Cancer2002 Dec 26;2:37.
50. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol2001 Mar;2(3):133-40.
51. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev1993;15(1):36-47.
52. Hunter DJ, Spiegelman D, Adami HO, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Non-dietary factors as risk factors for breast cancer, and as effect modifiers of the association of fat intake and risk of breast cancer. Cancer Causes Control1997 Jan;8(1):49-56.
53. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst1993 Nov 17;85(22):1819-27.
54. Hunter DJ, Willett WC. Diet, body size, and breast cancer. Epidemiol Rev1993;15(1):110-32.
55. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA1998 Feb 18;279(7):535-40.
56. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet1996 Jun 22;347(9017):1713-27.
57. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int J Cancer1999 May 5;81(3):339-44.
58. Thorlacius S, Struewing JP, Hartge P, Olafsdottir GH, Sigvaldason H, Tryggvadottir L, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet1998 Oct 24;352(9137):1337-9.
59. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst1999 Jun 2;91(11):943-9.
60. Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Res1999;1(1):14-7.
61. Beral V, Reeves G. Childbearing, oral contraceptive use, and breast cancer. Lancet1993 Apr 24;341(8852):1102.
62. Layde PM, Webster LA, Baughman AL, Wingo PA, Rubin GL, Ory HW. The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. Cancer and Steroid Hormone Study Group. J Clin Epidemiol1989;42(10):963-73.
63. Ewertz M, Duffy SW, Adami HO, Kvale G, Lund E, Meirik O, et al. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer1990 Oct 15;46(4):597-603.
64. Lipworth L, Bailey LR, Trichopoulos D. History of breast-feeding in relation to breast cancer risk: a review of the epidemiologic literature. J Natl Cancer Inst2000 Feb 16;92(4):302-12.

65. Moradi T, Nyren O, Zack M, Magnusson C, Persson I, Adami HO. Breast cancer risk and lifetime leisure-time and occupational physical activity (Sweden). Cancer Causes Control2000 Jul;11(6):523-31.
66. Moradi T, Adami HO, Ekbom A, Wedren S, Terry P, Floderus B, et al. Physical activity and risk for breast cancer a prospective cohort study among Swedish twins. Int J Cancer2002 Jul 1;100(1):76-81.
67. Parkin DM. Cancers of the breast, endometrium and ovary: geographic correlations. Eur J Cancer Clin Oncol1989 Dec;25(12):1917-25.
68. Baade PD, Youlden DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. Mol Nutr Food Res2009 Feb;53(2):171-84.
69. Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci2006;11:1388-413.
70. Gronberg H. Prostate cancer epidemiology. Lancet2003 Mar 8;361(9360):859-64.
71. Stattin P, Lumme S, Tenkanen L, Alfthan H, Jellum E, Hallmans G, et al. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. Int J Cancer2004 Jan 20;108(3):418-24.
72. Hsing AW. Hormones and prostate cancer: what's next? Epidemiol Rev2001;23(1):42-58.
73. Hsing AW. Hormones and prostate cancer: where do we go from here? J Natl Cancer Inst1996 Aug 21;88(16):1093-5.
74. Kolonel LN, Nomura AM, Cooney RV. Dietary fat and prostate cancer: current status. J Natl Cancer Inst1999 Mar 3;91(5):414-28.
75. Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies. Nutr Cancer2008;60(4):421-41.
76. Lee IM, Sesso HD, Chen JJ, Paffenbarger RS, Jr. Does physical activity play a role in the prevention of prostate cancer? Epidemiol Rev2001;23(1):132-7.
77. Norman A, Moradi T, Gridley G, Dosemeci M, Rydh B, Nyren O, et al. Occupational physical activity and risk for prostate cancer in a nationwide cohort study in Sweden. Br J Cancer2002 Jan 7;86(1):70-5.
78. Orsini N, Bellocco R, Bottai M, Pagano M, Andersson SO, Johansson JE, et al. A prospective study of lifetime physical activity and prostate cancer incidence and mortality. Br J Cancer2009 Dec 1;101(11):1932-8.
79. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology2002 Jan;13(1):72-9.
80. Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer. J Urol2004 Feb;171(2 Pt 2):S36-40.
81. Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, et al. Body size and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev2000 Dec;9(12):1335-41.
82. Cook LS, Goldoft M, Schwartz SM, Weiss NS. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. J Urol1999 Jan;161(1):152-5.
83. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer1991 Jun;63(6):963-6.
84. Winkler V, Ott JJ, Holleczek B, Stegmaier C, Becher H. Cancer profile of migrants from the Former Soviet Union in Germany: incidence and mortality. Cancer Causes Control2009 Jun 20.
85. Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. Ethn Dis2004 Summer;14(3):431-9.
86. Harding S, Rosato M. Cancer incidence among first generation Scottish, Irish, West Indian and South Asian migrants living in England and Wales. Ethn Health1999 Feb-May;4(1-2):83-92.

87. Moradi T, Delfino RJ, Bergstrom SR, Yu ES, Adami HO, Yuen J. Cancer risk among Scandinavian immigrants in the US and Scandinavian residents compared with US whites, 1973-89. Eur J Cancer Prev1998 Apr;7(2):117-25.
88. Khlat M. Cancer in Mediterranean migrants--based on studies in France and Australia. Cancer Causes Control1995 Nov;6(6):525-31.
89. Grulich AE, McCredie M, Coates M. Cancer incidence in Asian migrants to New South Wales, Australia. Br J Cancer1995 Feb;71(2):400-8.
90. Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: an overview. Int J Cancer2005 Sep 1;116(3):331-9.
91. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review. J Urol2003 Jul;170(1):5-11.
92. Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Moller H. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer2006 Jun 15;118(12):3099-111.
93. Purdue MP, Devesa SS, Sigurdson AJ, McGlynn KA. International patterns and trends in testis cancer incidence. Int J Cancer2005 Jul 10;115(5):822-7.
94. McGlynn KA. Environmental and host factors in testicular germ cell tumors. Cancer Invest2001;19(8):842-53.
95. McGlynn KA, Cook MB. Etiologic factors in testicular germ-cell tumors. Future Oncol2009 Nov;5(9):1389-402.
96. Bray F, Ferlay J, Devesa SS, McGlynn KA, Moller H. Interpreting the international trends in testicular seminoma and nonseminoma incidence. Nat Clin Pract Urol2006 Oct;3(10):532-43.
97. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, et al. Testicular cancer incidence in eight northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev2004 Dec;13(12):2157-66.
98. Bray F, Richiardi L, Ekbom A, Forman D, Pukkala E, Cuninkova M, et al. Do testicular seminoma and nonseminoma share the same etiology? Evidence from an age-period-cohort analysis of incidence trends in eight European countries. Cancer Epidemiol Biomarkers Prev2006 Apr;15(4):652-8.
99. Jacobsen GK, Henriques UV. A fetal testis with intratubular germ cell neoplasia (ITGCN). Mod Pathol1992 Sep;5(5):547-9.
100. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer--experiences of the mother. Int J Epidemiol2009 Dec;38(6):1532-42.
101. Hemminki K, Li X. Cancer risks in second-generation immigrants to Sweden. Int J Cancer2002 May 10;99(2):229-37.
102. Ekbom A, Richiardi L, Akre O, Montgomery SM, Sparen P. Age at immigration and duration of stay in relation to risk for testicular cancer among Finnish immigrants in Sweden. J Natl Cancer Inst2003 Aug 20;95(16):1238-40.
103. Montgomery SM, Granath F, Ehlin A, Sparen P, Ekbom A. Germ-cell testicular cancer in offspring of Finnish immigrants to Sweden. Cancer Epidemiol Biomarkers Prev2005 Jan;14(1):280-2.
104. Hemminki K, Li X. Cancer risks in childhood and adolescence among the offspring of immigrants to Sweden. Br J Cancer2002 May 6;86(9):1414-8.
105. Eggert J, Sundquist K. Socioeconomic factors, country of birth, and years in Sweden are associated with first birth fertility trends during the 1990s: a national cohort study. Scand J Public Health2006;34(5):504-14.
106. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol2009;24(11):659-67.
107. Swedish Tax Agency. Population registration in Sweden. 2007 [cited 2010 January 20]; Edition 4:[Available from: http://www.skatteverket.se/download/18.5cbdbba811c9a768f0c80002830/717b04.pdf?posid=1&sv.search.query.allwords=717b04.pdf.

108. Statistics Sweden, Background Facts, Historic population register.
109. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol2009;48(1):27-33.
110. Holmang S, Amsler-Nordin S, Carlson K, Holmberg E, Johansson SL. Completeness and correctness of registration of renal pelvic and ureteral cancer in the Swedish Cancer Registry. Scand J Urol Nephrol2008;42(1):12-7.
111. Turesson I, Linet MS, Bjorkholm M, Kristinsson SY, Goldin LR, Caporaso NE, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. Int J Cancer2007 Nov 15;121(10):2260-6.
112. Lindstrom P, Janzon L, Sternby NH. Declining autopsy rate in Sweden: a study of causes and consequences in Malmo, Sweden. J Intern Med1997 Aug;242(2):157-65.
113. Statistska Centralbyrån. Bakgrundsfakta till befolknings-ochvälfärdsstatistik (The Multi-Generation Registry). Örebro: Statistska Centralbyrån; 2001.
114. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. Lyon, France: IARC CancerBase No.5, Version 2.0. Lyon, France: IARC Press.; 2004 [January 10, 2010]; Available from: www-dep.iarc.fr.
115. Cancer Incidence in Five Continents, Vol. I to VIII [database on the Internet]. International Agency for Research on Cancer, IARC CancerBase No. 7, Lyon. 2005.
116. Cancer Incidence in Five Continents, Vol. IX [database on the Internet]. IARC Scientific Publications No. 160, Lyon, IARC. 2007.
117. United Nations publication, Standard Country or Area Codes for Statistical Use, Revision 4.
118. Devesa SS, Diamond EL. Association of breast cancer and cervical cancer incidence with income and education among whites and blacks. J Natl Cancer Inst1980;65(3):515.
119. Statistical Research and Applications Branch NCI. Joinpoint Regression Program. Version 3.3.1. edApril 2008.
120. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med2000 Feb 15;19(3):335-51.
121. Marmot MG, Adelstein AM, Bulusu L. Lessons from the study of immigrant mortality. Lancet1984 Jun 30;1(8392):1455-7.
122. Razum O, Zeeb H, Rohrmann S. The healthy migrant effect'-not merely a fallacy of inaccurate denominator figures. Int J Epidemiol2000 February 1, 2000;29(1):191-2.
123. Weitoft GR, Gullberg A, Hjern A, Rosen M. Mortality statistics in immigrant research: method for adjusting underestimation of mortality. Int J Epidemiol1999 Aug;28(4):756-63.
124. Myrup C, Wohlfahrt J, Oudin A, Schnack T, Melbye M. Risk of testicular cancer according to birthplace and birth cohort in Denmark. Int J Cancer2010 Jan 1;126(1):217-23.
125. Swerdlow A. Mortality and cancer incidence in Vietnamese refugees in England and Wales: a follow-up study. Int J Epidemiol1991 Mar;20(1):13-9.
126. Rutqvist LE, Carstensen J, Mattsson B, Mardsjo G. Geographic variations of breast carcinoma incidence in Sweden. Are the differences real? Acta Radiol Oncol1986 Mar-Apr;25(2):99-104.
127. Stattin P, Johansson R, Lodnert R, Andren O, Bill-Axelsson A, Bratt O, et al. Geographical variation in incidence of prostate cancer in Sweden. Scand J Urol Nephrol2005;39(5):372-9.
128. Qvist J. [Problems of coverage in the register of total population (RTB). Estimation of overcoverage with an indirect method]. Örebro, Sweden: Statistics Sweden1999.

129. Beiki O, Allebeck P, Nordqvist T, Moradi T. Cervical, endometrial and ovarian cancers among immigrants in Sweden: importance of age at migration and duration of residence. Eur J Cancer2009 Jan;45(1):107-18.
130. Tyczynski J, Parkin D, Zatonski W, Tarkowski W. Cancer mortality among Polish migrants to France. Bull Cancer1992;79(8):789-800.
131. Swerdlow AJ, Cooke KR, Skegg DC, Wilkinson J. Cancer incidence in England and Wales and New Zealand and in migrants between the two countries. Br J Cancer1995 Jul;72(1):236-43.
132. Bouchardy C, Wanner P, Parkin DM. Cancer mortality among sub-Saharan African migrants in France. Cancer Causes Control1995 Nov;6(6):539-44.
133. Azerkan F, Zendehdel K, Tillgren P, Faxelid E, Sparen P. Risk of cervical cancer among immigrants by age at immigration and follow-up time in Sweden, from 1968 to 2004. Int J Cancer2008 Dec 1;123(11):2664-70.
134. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol2002 Apr;55(4):244-65.
135. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. Lyon, 2004.: IARCPress; 2004.
136. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis2007 Jul;7(7):453-9.
137. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer2003 Jan 13;88(1):63-73.
138. Widmer ED, Treas J, Newcomb R. Attitudes toward nonmarital sex in 24 countries. Journal of Sex Research1998;35:349-58.
139. Drain PK, Holmes KK, Hughes JP, Koutsky LA. Determinants of cervical cancer rates in developing countries. Int J Cancer2002 Jul 10;100(2):199-205.
140. Coleman LM, Testa A. Sexual health knowledge, attitudes and behaviours: variations among a religiously diverse sample of young people in London, UK. Ethn Health2008 Jan;13(1):55-72.
141. Liu L, Deapen D, Bernstein L. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). Cancer Causes Control1998 Aug;9(4):369-80.
142. Hemminki K, Zhang H, Czene K. Socioeconomic factors in cancer in Sweden. Int J Cancer2003 Jul 10;105(5):692-700.
143. Hildesheim A, Gravitt P, Schiffman MH, Kurman RJ, Barnes W, Jones S, et al. Determinants of genital human papillomavirus infection in low-income women in Washington, D.C. Sex Transm Dis1993 Sep-Oct;20(5):279-85.
144. Parkin, D.M., Whelan, S.L., Ferlay, J., and Storm, H. Cancer Incidence in Five Continents, Vol. I to VIII IARC CancerBase No. 7, Lyon, 2005.
145. Public health in Stockholm County 2007. Report from Centre for Public Health. ISBN 978-91-975889-3-5. Stockholm2007.
146. Lahmann PH, Lissner L, Gullberg B, Berglund G. Differences in body fat and central adiposity between Swedes and European immigrants: the Malmo Diet and Cancer Study. Obes Res2000 Dec;8(9):620-31.
147. Koochek A, Mirmiran P, Azizi T, Padyab M, Johansson SE, Karlstrom B, et al. Is migration to Sweden associated with increased prevalence of risk factors for cardiovascular disease? Eur J Cardiovasc Prev Rehabil2008 Feb;15(1):78-82.
148. Persson I, Schmidt M, Adami HO, Bergstrom R, Pettersson B, Sparen P. Trends in endometrial cancer incidence and mortality in Sweden, 1960-84. Cancer Causes Control1990 Nov;1(3):201-8.
149. La Vecchia C. Epidemiology of ovarian cancer: a summary review. Eur J Cancer Prev2001 Apr;10(2):125-9.

150. Hulka BS. Epidemiologic analysis of breast and gynecologic cancers. Prog Clin Biol Res1997;396:17-29.
151. Gadd M, Sundquist J, Johansson SE, Wandell P. Do immigrants have an increased prevalence of unhealthy behaviours and risk factors for coronary heart disease? Eur J Cardiovasc Prev Rehabil2005 Dec;12(6):535-41.
152. Hemminki K, Li X. Cancer risks in Nordic immigrants and their offspring in Sweden. Eur J Cancer2002 Dec;38(18):2428-34.
153. Nilsson B, Gustavson-Kadaka E, Rotstein S, Hakulinen T, Rahu M, Aareleid T. Cancer incidence in Estonian migrants to Sweden. Int J Cancer1993 Sep 9;55(2):190-5.
154. Mousavi SM, Brandt A, Weires M, Ji J, Sundquist J, Hemminki K. Cancer incidence among Iranian immigrants in Sweden and Iranian residents compared to the native Swedish population. Eur J Cancer2009 Feb;46(3):599-605.
155. Andreeva VA, Unger JB, Pentz MA. Breast cancer among immigrants: a systematic review and new research directions. J Immigr Minor Health2007 Oct;9(4):307-22.
156. Coates MS, Kaldor JM, Hayes D. Cancer in Italian migrant populations. New South Wales, Australia. IARC Sci Publ1993(123):138-48.
157. Bouchardy C, Mirra AP. Cancer in Italian migrant populations. Sao Paulo, Brazil. IARC Sci Publ1993(123):103-16.
158. John EM, Phipps AI, Davis A, Koo J. Migration history, acculturation, and breast cancer risk in Hispanic women. Cancer Epidemiol Biomarkers Prev2005 Dec;14(12):2905-13.
159. Stanford JL, Herrinton LJ, Schwartz SM, Weiss NS. Breast cancer incidence in Asian migrants to the United States and their descendants. Epidemiology1995 Mar;6(2):181-3.
160. Menck HR, Henderson BE, Pike MC, Mack T, Martin SP, SooHoo J. Cancer incidence in the Mexican-American. J Natl Cancer Inst1975 Sep;55(3):531-6.
161. Harding S, Rosato M, Teyhan A. Trends in cancer mortality among migrants in England and Wales, 1979-2003. Eur J Cancer2009 Aug;45(12):2168-79.
162. Pukkala E, Weiderpass E. Time trends in socio-economic differences in incidence rates of cancers of the breast and female genital organs (Finland, 1971-1995). Int J Cancer1999 Mar 31;81(1):56-61.
163. Carlsen K, Hoybye MT, Dalton SO, Tjonneland A. Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003. Eur J Cancer2008 Sep;44(14):1996-2002.
164. Baquet CR, Commiskey P. Socioeconomic factors and breast carcinoma in multicultural women. Cancer2000 Mar 1;88(5 Suppl):1256-64.
165. Geyer S. Social inequalities in the incidence and case fatality of cancers of the lung, the stomach, the bowels, and the breast. Cancer Causes Control2008 Nov;19(9):965-74.
166. Shack L, Jordan C, Thomson CS, Mak V, Moller H, Registries UKAoC. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. BMC Cancer2008;8:271.
167. Vainshtein J. Disparities in breast cancer incidence across racial/ethnic strata and socioeconomic status: a systematic review. J Natl Med Assoc2008 Jul;100(7):833-9.
168. Yabroff KR, Gordis L. Does stage at diagnosis influence the observed relationship between socioeconomic status and breast cancer incidence, case-fatality, and mortality? Soc Sci Med2003 Dec;57(12):2265-79.
169. Lagerlund M, Bellocco R, Karlsson P, Tejler G, Lambe M. Socio-economic factors and breast cancer survival--a population-based cohort study (Sweden). Cancer Causes Control2005 May;16(4):419-30.
170. Downing A, Prakash K, Gilthorpe MS, Mikeljevic JS, Forman D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. Br J Cancer2007 Mar 12;96(5):836-40.

171. Kogevinas M, Porta M. Socioeconomic differences in cancer survival: a review of the evidence. IARC Sci Publ1997(138):177-206.
172. Rutqvist LE, Bern A. Socioeconomic gradients in clinical stage at presentation and survival among breast cancer patients in the Stockholm area 1977-1997. Int J Cancer2006 Sep 15;119(6):1433-9.
173. Eaker S, Halmin M, Bellocco R, Bergkvist L, Ahlgren J, Holmberg L, et al. Social differences in breast cancer survival in relation to patient management within a National Health Care System (Sweden). Int J Cancer2009 Jan 1;124(1):180-7.
174. Tulinius H, Storm HH, Pukkala E, Andersen A, Ericsson J. Cancer in the Nordic countries, 1981-86. A joint publication of the five Nordic Cancer Registries. APMIS Suppl1992;31:1-194.
175. Jensen AR, Garne JP, Storm HH, Engholm G, Moller T, Overgaard J. Does stage at diagnosis explain the difference in survival after breast cancer in Denmark and Sweden? Acta Oncol2004;43(8):719-26.
176. Eaker S, Dickman PW, Bergkvist L, Holmberg L, Uppsala/Orebro Breast Cancer G. Differences in management of older women influence breast cancer survival: results from a population-based database in Sweden. PLoS Med2006 Mar;3(3):e25.
177. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PLoS One2009;4(11):e7695.
178. Vermeer B, Van den Muijsenbergh ME. The attendance of migrant women at the national breast cancer screening in the Netherlands 1997-2008. Eur J Cancer Prev May;19(3):195-8.
179. Coughlin SS, Wilson KM. Breast and cervical cancer screening among migrant and seasonal farmworkers: a review. Cancer Detect Prev2002;26(3):203-9.
180. Islam N, Kwon SC, Senie R, Kathuria N. Breast and cervical cancer screening among South Asian women in New York City. J Immigr Minor Health2006 Jul;8(3):211-21.
181. Beiki O, Ekbom A, Allebeck P, Moradi T. Risk of prostate cancer among Swedish-born and foreign-born men in Sweden, 1961-2004. Int J Cancer2009 Apr 15;124(8):1941-53.
182. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. Jama1995 Feb 15;273(7):548-52.
183. Lu-Yao GL, Greenberg ER. Changes in prostate cancer incidence and treatment in USA. Lancet1994 Jan 29;343(8892):251-4.
184. Merrill RM, Feuer EJ, Warren JL, Schussler N, Stephenson RA. Role of transurethral resection of the prostate in population-based prostate cancer incidence rates. Am J Epidemiol1999 Oct 15;150(8):848-60.
185. Ben-Shlomo Y, Evans S, Ibrahim F, Patel B, Anson K, Chinegwundoh F, et al. The risk of prostate cancer amongst black men in the United Kingdom: the PROCESS cohort study. Eur Urol2008 Jan;53(1):99-105.
186. Odedina FT, Ogunbiyi JO, Ukoli FA. Roots of prostate cancer in African-American men. J Natl Med Assoc2006 Apr;98(4):539-43.
187. Platz EA, Rimm EB, Willett WC, Kantoff PW, Giovannucci E. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals. J Natl Cancer Inst2000 Dec 20;92(24):2009-17.
188. Chinegwundoh F, Enver M, Lee A, Nargund V, Oliver T, Ben-Shlomo Y. Risk and presenting features of prostate cancer amongst African-Caribbean, South Asian and European men in North-east London. BJU Int2006 Dec;98(6):1216-20.
189. Hsing AW, Devesa SS, Jin F, Gao YT. Rising incidence of prostate cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev1998 Jan;7(1):83-4.

190. Breslow N, Chan CW, Dhom G, Drury RA, Franks LM, Gellei B, et al. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. Int J Cancer1977 Nov 15;20(5):680-8.
191. Sennfalt K, Carlsson P, Varenhorst E. Diffusion and economic consequences of health technologies in prostate cancer care in Sweden, 1991-2002. Eur Urol2006 Jun;49(6):1028-34.
192. Liu L, Cozen W, Bernstein L, Ross RK, Deapen D. Changing relationship between socioeconomic status and prostate cancer incidence. J Natl Cancer Inst2001 May 2;93(9):705-9.
193. Hemminki K, Li X. Level of education and the risk of cancer in Sweden. Cancer Epidemiol Biomarkers Prev2003 Aug;12(8):796-802.
194. Weir HK, Marrett LD, Moravan V. Trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, 1964-1996. Cmaj1999 Jan 26;160(2):201-5.
195. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. Cancer2003 Jan 1;97(1):63-70.
196. Beiki O, Granath F, Allebeck P, Akre O, Moradi T. Subtype-specific risk of testicular tumors among immigrants and their descendants in Sweden, 1960 to 2007. Cancer Epidemiol Biomarkers Prev2010 Apr;19(4):1053-65.
197. Myrup C, Westergaard T, Schnack T, Oudin A, Ritz C, Wohlfahrt J, et al. Testicular cancer risk in first- and second-generation immigrants to Denmark. J Natl Cancer Inst2008 Jan 2;100(1):41-7.
198. Grotmol T, Weiderpass E, Tretli S. Conditions in utero and cancer risk. Eur J Epidemiol2006;21(8):561-70.
199. Sharpe RM. The 'oestrogen hypothesis'- where do we stand now? Int J Androl2003 Feb;26(1):2-15.
200. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med2007 May 3;356(18):1835-41.
201. Akre O, Pettersson A, Richiardi L. Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis. Int J Cancer2009 Feb 1;124(3):687-9.
202. Richiardi L, Akre O, Bellocco R, Ekbom A. Perinatal determinants of germ-cell testicular cancer in relation to histological subtypes. Br J Cancer2002 Aug 27;87(5):545-50.
203. Cook MB, Graubard BI, Rubertone MV, Erickson RL, McGlynn KA. Perinatal factors and the risk of testicular germ cell tumors. Int J Cancer2008 Jun 1;122(11):2600-6.
204. Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. Int J Cancer2000 Aug 1;87(3):438-43.
205. Silventoinen K, Lahelma E, Lundberg O, Rahkonen O. Body height, birth cohort and social background in Finland and Sweden. Eur J Public Health2001 Jun;11(2):124-9.
206. Giwercman A, Lundin KB, Eberhard J, Stahl O, Cwikiel M, Cavallin-Stahl E, et al. Linkage between androgen receptor gene CAG trinucleotide repeat length and testicular germ cell cancer histological type and clinical stage. Eur J Cancer2004 Sep;40(14):2152-8.
207. Giwercman A, Rylander L, Hagmar L, Giwercman YL. Ethnic differences in occurrence of TDS-- genetics and/or environment? Int J Androl2006 Feb;29(1):291-7; discussion 304-6.
208. Liu S, Semenciw R, Waters C, Wen SW, Mery LS, Mao Y. Clues to the aetiological heterogeneity of testicular seminomas and non-seminomas: time trends and age-period-cohort effects. Int J Epidemiol2000 Oct;29(5):826-31.
209. Stang A, Rusner C, Eisinger B, Stegmaier C, Kaatsch P. Subtype-specific incidence of testicular cancer in Germany: a pooled analysis of nine population-based cancer registries. Int J Androl2007 Dec 30;32(4):306-16.

210. Aschim EL, Haugen TB, Tretli S, Daltveit AK, Grotmol T. Risk factors for testicular cancer--differences between pure non-seminoma and mixed seminoma/non-seminoma? Int J Androl2006 Aug;29(4):458-67.
211. Ferlin A, Pengo M, Selice R, Salmaso L, Garolla A, Foresta C. Analysis of single nucleotide polymorphisms of FSH receptor gene suggests association with testicular cancer susceptibility. Endocr Relat Cancer2008 Jun;15(2):429-37.
212. Purdue MP, Sakoda LC, Graubard BI, Welch R, Chanock SJ, Sesterhenn IA, et al. A case-control investigation of immune function gene polymorphisms and risk of testicular germ cell tumors. Cancer Epidemiol Biomarkers Prev2007 Jan;16(1):77-83.
213. Cook MB, Graubard BI, Quraishi SM, Yeager M, Chanock SJ, Crenshaw A, et al. Genetic variants in the 8q24 locus and risk of testicular germ cell tumors. Hum Genet2008 May;123(4):409-18.
214. Figueroa JD, Sakoda LC, Graubard BI, Chanock S, Rubertone MV, Erickson RL, et al. Genetic variation in hormone metabolizing genes and risk of testicular germ cell tumors. Cancer Causes Control2008 Nov;19(9):917-29.
215. Purdue MP, Graubard BI, Chanock SJ, Rubertone MV, Erickson RL, McGlynn KA. Genetic variation in the inhibin pathway and risk of testicular germ cell tumors. Cancer Res2008 Apr 15;68(8):3043-8.