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**CANCER MORTALITY AND SURVIVAL AFTER CANCER  
DIAGNOSIS BY MIGRATION BACKGROUND AND  
SOCIOECONOMIC POSITION IN SWEDEN**

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# **Cancer mortality and survival after cancer diagnosis by migration background and socioeconomic position in Sweden**

THESIS FOR DOCTORAL DEGREE (Ph.D.)

## **ACADEMIC DISSERTATION**

This thesis will be defended in public at Lecture hall Rockefeller, Nobels väg 11, Karolinska Institutet, Solna.

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*In the name of God the Merciful the Compassionate*

**To my mother and the memory of my father  
&  
To my sibling**

تقدیم به مادرم

به مرحوم پدرم

وبه برادران و خواهرانم



## ABSTRACT

**Aims:** The overall aim of this thesis was to investigate the risk of cancer mortality and survival after cancer diagnosis based on migration background and socioeconomic position in Sweden. We studied the effects of country of birth and level of education, as a proxy for socioeconomic position, on mortality due to all-site cancer (and some common specific cancers), trends in overall survival after cancer diagnosis (all sites and selected cancer sites), and all-cause and excess mortality in breast cancer patients by stage at diagnosis.

**Materials and methods:** The data used in this thesis are from a nationwide dataset, the Migration and Health Cohort, which was specifically designed to address health status among immigrants and among socially and economically deprived population in Sweden. In this cohort, information was retrieved through linkage between several national Swedish registers (Studies I–III). Based on country of birth, we followed individuals from the total population in the years 1961–2009 (Study I), cancer patients 45 years of age and older in the years 1961–2009 (Study II), and breast cancer patients by stage at diagnosis in the years 2004–2009 (Study III). The outcomes were cancer mortality (Study I) and survival (Studies II and III). We calculated mortality rate ratios (MRRs) (Study I), age-standardized rates (ASRs) (Study I), hazard ratios (HRs) (Studies II and III), relative risk ratios (RRRs), and relative excess rate (RER) (Study III) with 95% confidence intervals (CIs) using Poisson (for MRR and RER), Cox, and multinomial logistic regression models, respectively.

**Results:** We observed a downward trend in all-site ASRs over the past two decades in men but no change in women regardless of country of birth (Study I). In comparison with Sweden-born men, all-site cancer mortality was slightly higher in foreign-born men, with men born in Angola, Laos, and Cambodia having the highest risk. Among women, a similar risk was observed in foreign-born and Sweden-born individuals (Study I). However, the findings varied across different cancer sites; foreign-born individuals had lower risks of colon, prostate, and breast cancer mortality but higher risks of lung and cervical cancer mortality compared with Sweden-born individuals (Study I). All-site cancer mortality increased with decreasing level of education (Study I). A similar pattern of level of education was observed with regard to all-cause mortality in breast cancer patients (Study III). Overall, after the year 2000, overall survival was lower in foreign-born cancer patients, who were on average 4 years younger at the time of diagnosis, compared with cancer patients born in Sweden (Study II). The results were almost the same independent of sex, duration of residence, and age at diagnosis. The overall survival trends for prostate and breast cancers were also similar to the trend for all-site cancers (Study II). Not surprisingly, survival decreased with increasing tumor size, number of lymph nodes involved, presence of metastasis, comorbidity, and anatomic stage in breast cancer patients, particularly among foreign-born patients (Study III). We observed a higher risk of stage II tumor (stage I as baseline) among all foreign-born breast cancer patients and patients born in Asia compared with those born in Sweden (Study III). In addition, a poorer survival was observed among all foreign-born breast cancer patients with stages III–IV cancer and also patients born in Asia and Southern Europe with stages III and IV cancer, respectively, compared with breast cancer patients born in Sweden (Study III). Analyses taking into account reason for migration showed that refugee patients with breast cancer had a higher risk of both all-cause and excess mortality, compared with Sweden-born patients. In the stratified analysis by stage, the risks were prominent in advanced stages (III–IV) of disease. The higher risks of all-cause and excess mortality were not statistically significant. Furthermore, compared with non-refugee patients, we found non-significantly higher risks of both all-cause and excess mortality among refugee women with advanced-stage cancer.

**Conclusions:** Country of birth is an important determinant of risk of cancer mortality and survival after cancer diagnosis. Increased mortality risk with decreasing level of education, remains a major risk indicator for these events. The decreased overall survival among foreign-born patients after the year 2000 and poor prognosis among foreign-born breast cancer patients with advanced stages of the disease need further investigation to fully understand the reasons behind these disparities.



## LIST OF SCIENTIFIC PAPERS

- I. **Gholamreza Abdoli**, Matteo Bottai, Tahereh Moradi.  
Cancer mortality by country of birth, sex, and socioeconomic position in Sweden, 1961-2009.  
PLoS One. 2014 Mar 28;9(3):e93174.
  
- II. **Gholamreza Abdoli**, Matteo Bottai, Anna Sidorchuk, Tahereh Moradi.  
Trends in mortality after cancer diagnosis: A nationwide cohort study over 45 years of follow-up in Sweden by country of birth.  
Cancer Epidemiol. 2015 Aug; 39(4):633-40.
  
- III. **Gholamreza Abdoli**, Matteo Bottai, Kerstin Sandelin, Tahereh Moradi.  
Breast cancer diagnosis and mortality by tumor stage and migration background in a nationwide cohort study in Sweden.  
Breast. 2017 Feb;31:57-65.



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## LIST OF ABBREVIATIONS

ASR	Age-standardized rate
CCI	Charlson's comorbidity index
CI	Confidence interval
HR	Hazard ratio
HPV	Human papillomavirus
ICD	International Classification of Disease
LISA	Longitudinal integration database for health insurance and labor market
OR	Odds ratio
M	Metastasis
MRR	Mortality rate ratio
M&H Co.	Migration and Health Cohort
N	Number of lymph nodes involved
PIN	Personal identity number
RER	Relative excess rate
RRR	Relative risk ratio
RSR	Relative survival ratio
SAS	Statistical analysis system
SEP	Socioeconomic position
T	Tumor size
TPR	Total Population Register



# 1 INTRODUCTION

## 1.1 MIGRATION

### *Definition*

Migration is any movement of an individual or a group of individuals from one place to another. There is no clear universal definition for the term ‘migrant’ but it generally applies to a person moving from one country to another country or region temporarily or permanently [1, 2]. Depending on the reasons for migration and the legal status of the migrants in the host country, migrants are classified into different groups.

### *Types of migrants*

#### *Asylum seekers and refugees*

Refugees include persons who have left their countries of origin as their lives and security are threatened for political, social, religious, or ethnic reasons. An asylum seeker is a person who is seeking to be identified as a refugee, but has not yet received formal refugee status [1]. Worldwide there were 19.5 million refugees at the end of 2014 (about 7% of all international migrants) and it is estimated that half of all refugees are under 18 years of age [3, 4].

#### *Labor migrants*

Labor migration refers to movement of persons across countries or within one country for the purpose of work [1]. In 2014, approximately 50% (105 million) of international migrants worldwide were labor migrants [5].

#### *Documented versus undocumented migrants*

Documented migrants are individuals who have entered a country legally and have the right to remain according to the admission regulations. Conversely, undocumented migrants are those who do not have a legal permit or authorization to reside, work, or study in the host country [1, 6]. According to a report from the International Organization for Migration, about 10% to 15% of the world’s international migrants were undocumented in 2010 [7].

In this thesis, we first defined migrants as individuals living in Sweden legally who were born abroad, without considering the reasons for their migration. We then performed additional analysis taking into account the reason for migration.

## **1.2 MIGRATION WORLDWIDE**

According to the World Health Organization (WHO), there are an estimated 1 billion migrants in the world of whom 232 million are international migrants (3.2% of the global population) and 740 million are domestic migrants [8-10]. International migration has increased, particularly in the past three decades. The number of international migrants increased from 75 million in 1965 to 105 million in 1985 (2.3% to 2.7% of the global population). Between 1990 and 2013, the number of international migrants increased from 154 to 232 million (2.9% to 3.2% of the global population) with the largest growth rate in Europe. In 2013, European countries hosted more than 72 million international migrants (9.8% of the European population) [9, 11-15]. Recently, at least 7 million persons have fled the ongoing conflict in Syria and around 3 million have been displaced [16]. More than 51% of international migrants worldwide were living in 10 countries in 2013. The USA hosted the largest number of international migrants (46 million) followed by the Russian Federation (11 million), Germany (10 million), Saudi Arabia (9 million), and the UK and the United Arab Emirates (8 million each) [13]. It is estimated that the number of international migrants will reach 405 million worldwide by 2050 [17].

## **1.3 MIGRATION IN SWEDEN**

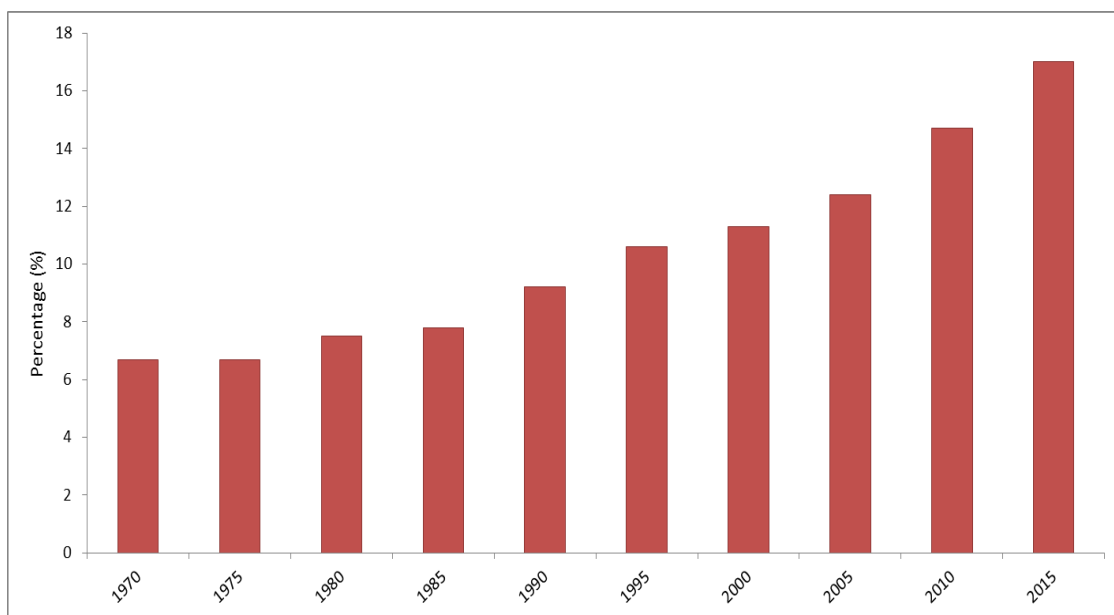
The immigrant population has increased in Sweden over time, dramatically influencing population growth (Figures 1 and 2). In 2015, 17% (1,676,264) of the total population of Sweden was born outside the country compared to 6.7% in 1970 [18]. This figure does not include undocumented migrants, such as asylum seekers and other migrants without a residence permit, who are not included in any registry or in population statistics [19].

Sweden has experienced several waves of migration over time. Before 1930, Sweden was a country of net emigration, mainly to North America. After 1930, the net flow of migration in Sweden changed from emigration to immigration [20], with immigration to Sweden increasing due to several causes including social, labor, religious, and political factors. In the 1940s, there was an increase in net flow of immigration, mostly from Europe, including refugees after the Second World War. In the 1950s and 1960s, large numbers of labor migrants arrived in Sweden from the Nordic countries, Southern Europe, and Turkey [19, 20]. During the 1970s and 1980s, the immigration pattern changed: refugees mainly arrived

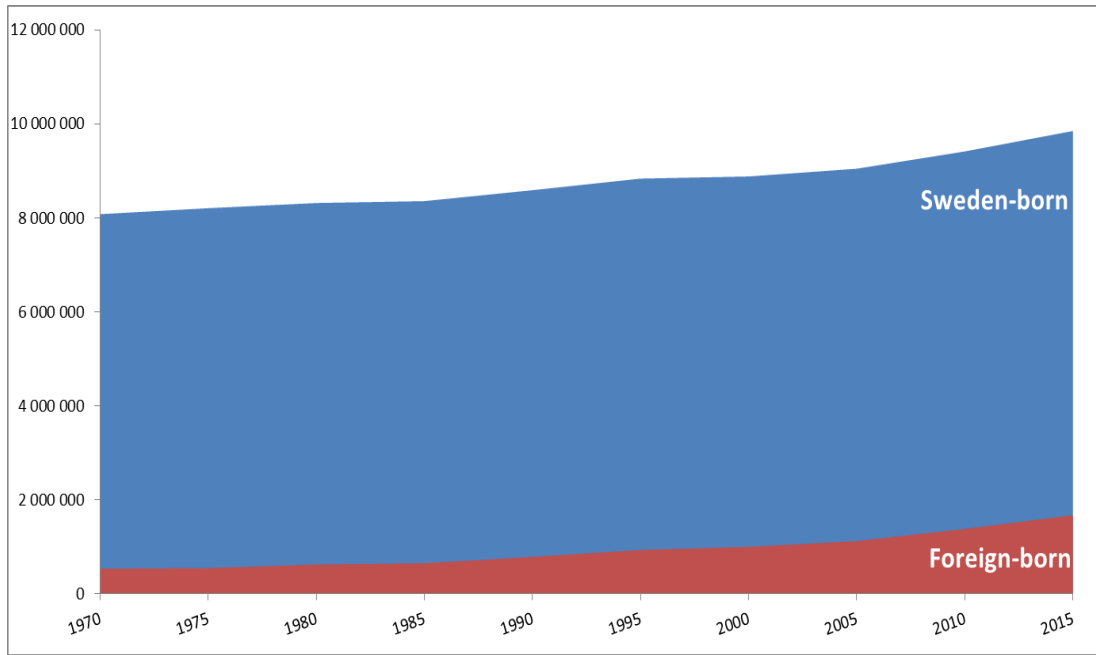


from Asian countries and Latin America because of unemployment and economic difficulties. Political factors have also led to a rise in immigration; high numbers of refugees arrived in Sweden fleeing from Latin American dictatorships and the Islamic revolution in Iran in the 1970s, and the disintegrating former communist countries, including Yugoslavia and the Soviet Union, and civil war in Iraq and Somalia during the 1990s and early 2000s [19, 20]. Recently there has been a new wave of migration to Sweden from Syria due to civil war [21]. Since 2010, the majority of asylum seekers have come from Middle Eastern and African countries, including Syria, Somalia, Eritrea, Iraq, Afghanistan, and Serbia [22].

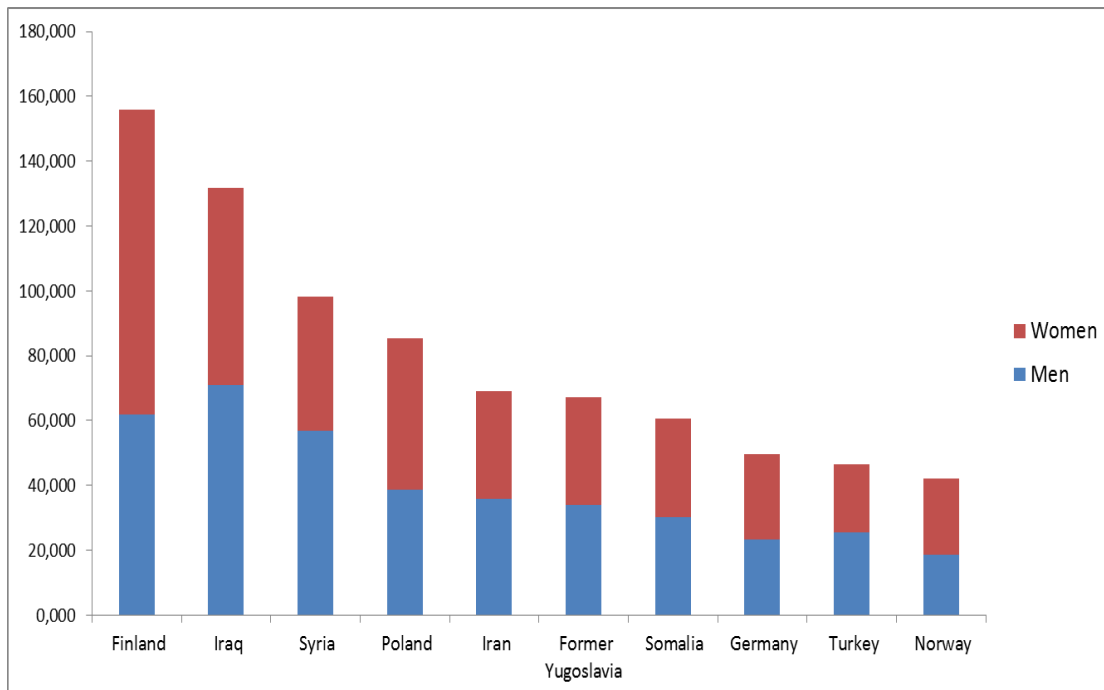
The 10 largest immigrant populations (first generation) in Sweden in 2015 were from Finland, Iraq, Syria, Poland, Iran, the former Yugoslavia, Somalia, Germany, Turkey, and Norway (Figure 3) [23].



**Figure 1:** Proportion of the foreign-born population in Sweden between 1970 and 2015 (Source: Statistics Sweden).



**Figure 2:** The Swedish population between 1970 and 2015 by migration status (Sweden-born and foreign-born individuals) (Source: Statistics Sweden).



**Figure 3:** The 10 largest groups of foreign-born populations by sex in Sweden in 2015 (Source: Statistics Sweden).

## 1.4 MIGRANT HEALTH

With increasing numbers of migrants worldwide, migrant health has become an important global public health issue [24]. Migration itself has become an interesting topic worldwide in terms of population projection and the disparities in the distribution of diseases between migrants and the native population in the host country. The effect of immigration on health status is controversial. Some studies have shown that migrants, despite poorer access to healthcare, have better health compared to the native population [25, 26]. This has been termed the “healthy immigrant” effect. According to several epidemiological studies, some immigrants have better economic status and are healthier, in comparison to the general population in their country of origin [27, 28]. On the other hand, there have been reports that some groups of immigrants experience much higher rates of disease and poorer health status than that of natives [29, 30]. In Sweden, the rate of diseases among immigrants compared with native Swedes varies by country of origin and type of disease. Compared with native Swedes most immigrant groups have higher risk for coronary heart disease [31-34], post-traumatic stress disorder [35], depression and psychotic disorders [36] and lower risk for cancers of breast, endometrium, ovary, prostate [37-39] and child and young adult type 1 diabetes [40, 41].

The complex issue of migrant health is an important public matter related not only to the ethical implications of unequal access to healthcare but also to healthcare costs. Health problems are often directly linked to deprivation and poor living conditions [30]. A society’s social cohesion in terms of economic sustainability and political cooperation is affected to large extent on the health of its members and its healthcare system [11, 42]. Because migrants generally live in poor areas and have economic difficulties, they may be most vulnerable to health problems. The health profiles, values, and beliefs of migrants often differ from those that prevail in the host country. These factors often have an impact on the usage of health-related services by migrants [43].

Displacement and migration are critical phases in an individual’s life. In addition to its influence on health, migration has both short- and long-term social and economic effects. These effects have been extensively investigated and many studies highlight their complexity and variation between and among individuals/groups. Some of the social effects of migration are briefly discussed below. These effects can have an indirect impact on an individual’s life and health.

### ***Language barriers and the role of the authorities***

Proficiency in the local language is a crucial factor for social engagement in the community. Access to translators and professionals acting as cultural mediators is essential for ensuring good understanding and communication [44, 45]. Language courses and interracial social activities are important in the process of integration and belonging, both at work and in the community as a whole [46]. Difficulty in communicating due to poor language skills has been associated with acculturation problems and mental health issues [47-49]. Evidence suggests that immigrants holding a permanent residence permit have significantly better language skills compared to those with a temporary permit [47]. Communication problems between health providers and patients have been associated with unnecessary consumption of resources, difficulty in following providers' instructions and understanding various side effects, decreased use of primary care with increased focus on the emergency department, and insufficiently regular follow-ups [50-53]. Furthermore, immigrants with poor language skills are less able to seek and gain other sources of health information such as from the media or internet which may have a negative effect on their health status in terms of both prevention and treatment [54, 55]. Poor language skill can affect utilization of health care system. Immigrants in Sweden have been reported to utilize health care system less frequently than native Swedes [56-58]. In absence of suitable communication, their access to wider care is often hindered [59].

The feeling of belonging and improvement of mental health conditions have been shown to be proportional to the degree of support from the local authorities [60, 61]. Healthcare providers' lack of knowledge of cultural differences in health-related issues can be another factor that negatively affects immigrants' health [55]. In a Canadian study, immigrant women from several countries defined health and health-related issues very differently compared to providers. They felt that providers were unaware and disrespectful of these differences, and were therefore dissatisfied with the care provided [62]. Taking these differences into consideration, healthcare providers should aim to actively create a healthcare environment based on mutual respect and understanding [55].

### ***Sense of discrimination***

It has been shown that migrants from developing countries are more vulnerable to discrimination after entry to the host country [63]. In a report about racial discrimination, it

was highlighted that up to 80% of Afro-Americans have experienced discrimination based on their race/ethnicity [64]. Further, in the USA and Canada, discrimination has been reported to be common in educational centers, both in schools and English language centers [65]. Discrimination and harassment have a negative impact on psychological health. At an individual level, a person's self-confidence and ability to interact with others can be reduced. At the societal level, discrimination has a direct negative impact on integration and acculturation [65-67]. The incidence of discrimination toward immigrants is argued to be much higher due to underreporting [68]. Immigrants in Sweden are identified to have a poorer mental health conditions than natives [69, 70]. Factors such as racial discrimination [71], unemployment [72], and lack of access to skills training programs [73] have been shown to be associated to the poor health among immigrants.

### ***Length of residence and acculturation***

During and shortly after the process of migration, poorer health conditions have been observed in some migrant groups, compared with the local-born population [55], however this difference decreases with time until conditions reach the same level as in natives after around 8 years of residence [74]. Integration of immigrants has also been shown to affect access to healthcare. The individual's capacity to adapt to the new sociocultural structure in the host country, and to reflect on self-identity [75-77], are factors that can influence health-related issues. Some immigrants groups in Sweden has been shown to have a greater difficulties for a psychological adaptation in Sweden, and that is shown to affect their health condition negatively [78, 79].

Lifestyle and living conditions differ between labor migrants and refugees. Labor migrants may integrate more easily than refugees, because they already have an occupation when they arrive in the host country. They have also already chosen a host country which they believe will benefit them in some way. There are factors that might be less favorable to labor migrants with respect to health conditions compared to refugees. Labor migrants are exposed to less work-related stress and occupational environmental hazards [11, 80-82]. However, access to healthcare is lower among refugees compared with labor migrants [74, 83]. Further, there are clear differences in terms of psychological conditions. The prevalence of mental distress and depression has been shown to be higher among refugees compared with labor migrants [84, 85], especially among women and those who are older, lack social support, or have experienced previous trauma or more stress since migration [86].

## 1.5 MIGRATION AND CANCER

### *Background*

According to the WHO, cancer is a growing global problem with increasing incidence and mortality. Cancer is a leading cause of death worldwide. Despite the fact that more than 30% of cancers are potentially preventable, there were approximately 14 million new cases of cancer, 8.2 million deaths, and 32.6 million persons living with cancer within 5 years of diagnosis in 2012 [87, 88]. Those numbers were additionally increased during 2015 with 17.5 million cancer cases worldwide and 8.7 million deaths [89]. It is expected that the number of annual cancer cases will further rise to 22 million within the next two decades [87]. Deaths due to cancer worldwide are projected to increase continuously, to an estimated 11 million in 2030. Cancers of the lung, liver, stomach, colon, and breast are the leading causes of cancer deaths [87, 88]. In 2012, the five most common types of cancer diagnosed among men were lung, prostate, colorectal, stomach, and liver cancers and among women were breast, colorectal, lung, cervical, and stomach cancers [87]. Overall, 20% of deaths in Europe are due to cancer with more than 1.7 million deaths annually [90]. Of note, 57% of new cancer cases, and 65% of cancer deaths occur in low- and middle-income countries [91] with few or no resources for prevention, diagnosis, or treatment of the disease [90].

In Sweden the annual number of cancer cases reported to the Cancer Registry has increased during the last two decades. The average annual increase is 1.9% for men and 1.3% for women [92]. Prostate, female breast, skin (except melanoma), colon, and lung cancers are the most common types of cancer in Sweden [25]. Cancer is the second most common cause of mortality in Sweden (26% of deaths among men and 22% among women) [93] and contributes to 60% of the total burden of disease [94].

Survival is a key measure of the efficiency of healthcare systems and is defined as the time between cancer diagnosis and death [95]. Survival trends can help both in the formulation of strategies for cancer control and in the assessment of their effectiveness [96]. An increasing trend in cancer survival with calendar time for most types of cancers and in most countries is well documented [88, 96-98]. Despite increasing survival trends, substantial and persistent differences exist within and between countries. A goal of the World Cancer Declaration is to achieve major improvements in survival worldwide by 2020 [96].

Regardless of resource level, all countries can implement the four basic components of cancer control: prevention, early detection, diagnosis and treatment, and palliative care [90]. A national cancer strategy for Sweden was proposed in 2009 with the aim of improving survival and quality of life, and reducing geographical differences, among cancer patients [96]. Among European countries, Sweden has a relatively high overall cancer survival rate for both men and women [99].

### ***Migration and cancer incidence***

#### *All-site cancer*

Compared with the host population, lower all-cancer incidence rates have been observed among migrants from Southern Europe living in the Netherlands [100], Middle Eastern migrants living in Denmark [101], North Africans living in the Netherlands and Denmark [100, 101], Asians living in the UK [102], South-East Asians living in the UK and in the Netherlands [100, 103-105], and South American migrants and migrant men from Africa in the Netherlands [100]. However, no differences in all-cancer incidence have been observed among migrant men from Eastern Europe living in Germany [106], compared with German-born men.

#### *Stomach cancer*

Studies of stomach cancer incidence comparing migrants with the host population have shown higher incidence rates of stomach cancer among migrants from Scandinavia living in the USA [107] and Eastern European migrants and men-born in Southern Europe and Turkey living in Germany [106, 108], compared with US-born and German-born populations, respectively. However, a lower risk of stomach cancer has been observed among migrants from South-East Asia living in the UK and the Netherlands [100, 104], from Southern Europe and Turkey living in Germany [109], and Asian men living in the UK [102], compared with the host populations. In another study, no statistically significant differences in stomach cancer incidence were observed between migrant men from Asia and UK-born men [110].

#### *Colon cancer*

The majority of studies investigating the incidence of colon cancer have shown a lower risk among migrants compared to the host population in different countries. A lower colon

cancer incidence has been reported among migrants from Southern Europe and Turkey living in Germany and the Netherlands [100, 109], from Eastern Europe living in Denmark [101], Africa, North Africa, and South America living in the Netherlands [100], the Middle East living in Denmark [101], and South-East Asia living in the UK and the Netherlands [103, 104], and also among Chinese men and Filipino living in the USA [111] and men born in Eastern Europe living in Germany [106], compared with the host populations. However, no statistically significant differences in colon cancer incidence have been observed among migrants from Asia in the Netherlands [100] and women born in Eastern Europe living in Germany [106], compared with the host population.

#### *Lung cancer*

Lung cancer incidence comparing immigrants with the host populations has been shown to be lower among migrants from South-East Asia living in the UK [103, 104], from South America and North Africa in the Netherlands [100], and Scandinavia in the USA [107], as well as among men born in South-East Asia living in the UK and the Netherlands [100, 105] and women from Eastern Europe living in Germany [106] and from Southern Europe and Turkey living in Germany and the Netherlands [100, 109]. However, a higher lung cancer incidence has been observed among migrant men from Southern and Eastern Europe living in Germany [106, 109], compared with German-born men.

#### *Breast cancer*

Female breast cancer incidence rates among immigrants compared with the host populations have frequently been shown to be lower among migrant women from Southern and Eastern Europe living in Germany [106, 109], from Southern Europe and Turkey living in the Netherlands [100, 112], from the Middle East and Eastern Europe living in Denmark [101], from China and the Philippines living in the USA [113], from Africa living in the Netherlands [100], from North Africa living in the Netherlands and Denmark [100, 101, 112], from Asia living in the UK [102], from South America living in the Netherlands [100, 112], and from South-East Asia living in the UK [103-105]. However, no statistically significant differences in breast cancer incidence have been observed among Japanese migrant women living in the USA [113] and African and South American migrant women in the UK [114], compared with the host population.



### *Cervical cancer*

Compared with Dutch-born women, higher cervical cancer incidence was found among migrant women from South America and North Africa in the Netherlands [100, 115]. However, a lower risk of cancer of the cervix has been observed among Asian and South-East Asian women in the UK [102, 104], compared with UK-born women.

### *Prostate cancer*

Prostate cancer incidence among immigrants compared with the host population has been shown to be lower among migrant men from Southern Europe and Turkey living in Germany and the Netherlands [100, 109], from Asia and North Africa living in the Netherlands [100], and from South-East Asia living in the Netherlands and the UK [100, 103, 104]. However, higher risk of prostate cancer has been observed among migrant men from South America in the Netherlands [100], compared with Dutch-born men.

## ***Migration and cancer incidence in Sweden***

### *All-site cancer*

Studies in Sweden indicated lower all-cancer incidence rates among all migrants [116], migrants from Africa, Asia, and South America [116], and the Middle East [117], compared with Sweden-born individuals.

### *Stomach cancer*

Studies of stomach cancer incidence comparing migrants with Sweden-born individuals have shown a higher incidence among all migrants as well as specifically among migrants from Asia [116], South America [118], and Estonia [119] and among migrant women from East and South-East Asia [120], whereas lower risks of stomach cancer have been observed among migrant men from the Middle East [117] and women from Turkey [118].

### *Colon cancer*

Lower incidence of colon cancer have been reported among migrants from Asia [116], South America [118], and the Middle East [117], and among Turkish women [118], compared with Sweden-born individuals.

### *Lung cancer*

Lower lung cancer incidence rates have been reported among migrants from the Middle East [117], women born in South America [116], and Asian Arab women [121], compared with Sweden-born individuals. Higher lung cancer risk has been observed among all migrant men [116], migrant men from Estonia [119] and Eastern Europe [118, 121], and women from Turkey [118, 120], Denmark, Norway, and Finland [121]. However, in another study, no difference in lung cancer incidence was observed between Asian and Sweden-born men [116].

### *Breast cancer*

Female breast cancer incidence rates among migrant women compared with Sweden-born women have frequently been shown to be lower among all migrants [37, 116, 122-124], migrant women from Africa, Europe, and Northern Europe [37], Latin America [37, 122], Asia [37, 116], South America [116, 122, 124], East Asia and South-East Asia [122, 124], the Middle East [117, 122], Estonia [119], the Baltic countries, Poland, Russia, Greece, Finland, Norway [122], and Turkey [122, 124].

### *Cervical cancer*

Compared with women born in Sweden, a higher cervical cancer incidence was found among all migrants [39, 116], migrant women from Poland, Bosnia [39], Eastern Europe [120, 125, 126], South-East Asia, South and Central America [120, 126], and Denmark and Norway [120, 125, 126]. However, a lower risk was observed among migrants from Africa [39, 116], Turkey, Southern Europe [39], East Africa and South-Central and Western Asia [126], the Middle East [39, 117, 126], Asia [116, 125, 126], South America [116], and Finland [39, 125], compared with women born in Sweden.

### *Prostate cancer*

A lower prostate cancer incidence has been shown among all migrants [38, 116, 127, 128] and migrants born in Africa [116], the Middle East [117, 127], Asia [116, 127], Turkey, and Chile [127], compared with native Swedes. However, migrants born in Central Africa and the Caribbean had higher risks of prostate cancer [38], compared with Sweden-born men. Moreover, no differences in prostate cancer incidence have been observed between South American migrants and men born in Sweden [116].

The cause of the observed differences in cancer incidence between immigrants and natives is multifactorial and could be explained by several factors including barriers to healthcare access [101, 114, 116, 129], environmental [37, 38, 102, 117] and genetic factors [38, 100], dietary habits [104, 105, 109, 114], lifestyle patterns [37, 100-102, 104, 105, 115, 126, 130], smoking [101, 105, 109, 116], alcohol consumption [102, 105], screening uptake [101, 104, 105, 112, 114-116, 126, 129, 131-133], reproductive behavior [39, 109, 112, 117, 126], human papillomavirus (HPV) prevalence [39, 115, 126], socioeconomic factors [104, 105, 116, 117], and the healthy migrant effect [126].

### ***Migration and cancer mortality***

Cancer mortality rates among migrants differ from those of the host population [25, 106, 134] and, similar to cancer incidence, show large variability across cancer sites, country of origin, and host country [135].

#### *All-site cancer*

Compared with the host population, lower all-cancer mortality rates have been observed among migrants from Southern Europe living in the Netherlands [134, 136], from Eastern Europe living in Germany, Italy, and the UK [106, 137-140], from North Africa living in France, the Netherlands, and Italy [134, 136, 140, 141], from West [142] and East Africa living in the UK [137, 143, 144], from Asia living in the UK and Spain [137, 145], from South Asia living in Canada [146], from South-East Asia living in France and the UK [137, 144, 147], from South and Central America living in the Netherlands and the UK [134, 136, 143, 144], from Suriname living in the Netherlands [148], and from Turkey living in Belgium, Denmark, France, and the Netherlands [149]. On the other hand, higher mortality rates due to all cancers were observed among migrants from South Eastern Europe and Eastern Europe living in Australia [150], and migrant men from West Africa living in the UK [137, 143] and from Eastern Europe living in Spain [145], compared with the native populations. No differences in all-cancer mortality have been observed among migrants from the Middle East living in the UK, compared with UK-born individuals [137].

#### *Stomach cancer*

Studies of mortality due to stomach cancer comparing migrants with the host population in the USA [151] and Australia [150] have reported a higher risk among immigrant groups.

This is also the case among Turkish migrants in France and the Netherlands [149]. A higher mortality rate was also reported among migrant men from Eastern Europe living in Germany [106, 138, 152] and from South and Central American countries living in the UK [144], as well as among migrant women from Southern European countries in the Netherlands [136] and from Asia in the UK [110]. Nevertheless, there have been reports of lower stomach cancer mortality among migrant men from North Africa living in France [141] and from East Africa living in the UK [143], compared with the host population.

### *Colon cancer*

The majority of studies investigating mortality due to colon cancer have shown a lower risk among migrants compared to the host population in different countries. The lower mortality risk due to colon cancer has been reported among Southern European migrants living in the Netherlands [134], North African migrants in the Netherlands and France [134, 141, 153], South-East Asian migrants in France and the UK [147, 154], South and Central American migrants in the Netherlands and the UK [134, 143], and all migrants in Australia [150, 155]. Migrant men from West Africa living in France [142], from East Africa and the Middle East living in the UK [137], and from Eastern Europe living in Germany [106], and foreign-born women from East Africa living in the UK [143] also have lower colon cancer mortality rates compared with the host population. However, a higher colon cancer mortality rate was observed among migrant men from China compared with their US-born counterparts [156].

### *Lung cancer*

Results from the majority of studies of lung cancer mortality have also shown lower mortality rates among immigrants compared with the host populations. Mortality risk has been shown to be lower among migrants in the USA [151], migrants from Southern Europe living in the Netherlands [134, 136], from West and East Africa [137, 143] and Asia [137] in the UK, from South and Central America in the Netherlands and the UK [134, 143], from Turkey in the Netherlands and France [149], and Cuba in the USA [157], compared with the host populations. Lower lung cancer mortality rates have also been reported among all migrant women in Australia [155] and women from Eastern Europe living in Germany and the UK [106, 137], from North Africa living in the Netherlands and France [134, 136], and from the Middle East living in the UK [137], as well as migrant men from North Africa living in the Netherlands and France [134, 136, 141, 153], and foreign-born men from West

Africa living in France [142] compared with the host populations. However, a higher risk has been reported among migrant men from Southern Europe living in Spain [145], from Eastern Europe in Germany [106, 139], and from China in the USA [156], as well as migrant women from North Africa living in France [153], compared with the host populations.

#### *Breast cancer*

Female breast cancer mortality risk among migrants compared with the host population has been shown to be lower among migrant women from Southern Europe living in the Netherlands [134, 136], from Eastern Europe living in Germany and the UK [106, 137, 139], from North Africa in the Netherlands and France [134, 136, 141, 153], from Asia in the UK [110], from South-East Asia in France and the UK [147, 154], from South America in the Netherlands and the UK [134, 143], and from Turkey in the Netherlands and France [149]. Among migrant women from West Africa, a higher mortality risk due to breast cancer was observed in studies from the UK [137, 143], but a lower mortality risk was found in France [142], compared with the host populations.

#### *Cervical cancer*

Compared with the host population, a higher mortality risk due to cancer of the cervix was found among migrant women in Italy [140] and South and Central American countries living in the UK [143], and among South-East Asian migrants in France and the UK [147, 154]. However, a lower cervical cancer mortality risk has been reported among migrant women from Southern Europe living in the Netherlands [134], from South and Central America in the Netherlands [134], and from North Africa in the Netherlands and France [134], and among foreign-born women from East Africa in the UK [143], compared with the host populations.

#### *Prostate cancer*

Mortality risk due to prostate cancer among migrants compared with the host population has been shown to be lower among migrants from the British Isles and continental Europe living in Australia [155], from Eastern Europe living in Germany and the UK [106, 137, 139], from North Africa in the Netherlands and France [134], from East Africa, the Middle East, and Asia living in the UK [137], from South-East Asia in France and the UK [147, 154], and from Cuba in the USA [157]. However, a higher mortality risk has been reported

in the UK among migrants from West Africa [137, 143] and from South and Central America [143, 144], compared with UK-born men.

### ***Migration and cancer mortality in Sweden***

Studies of cancer mortality among immigrants in Sweden have been limited to two studies, one of all-site cancer [158] and the other of cancer of the cervix [125].

#### *All-site cancer*

Higher cancer mortality risks among foreign-born immigrant men from Bosnia, Somalia, Yugoslavia, Denmark, and Finland have been reported in Sweden, compared with native Swedes [158]. The results have been less consistent among women. Higher mortality was only observed among women from Denmark, whereas some immigrant populations such as women from Iran and Germany had lower cancer mortality [158].

#### *Cervical cancer*

Higher cervical cancer mortality among foreign-born women from Denmark and Norway was observed in Sweden. However, a lower risk among foreign-born women from Iran and no differences among all immigrants in Sweden were found [125].

Differences in cancer mortality among migrants compared with the host population have been considered to be related to various factors such as the healthy migrant effect [108, 134, 136, 141, 142], the return of migrants in poor health to their country of origin prior to death (“salmon bias”) [108, 141, 142], pre-migration risk factors (country of origin effect) [139], living conditions [108, 138], differences in diets [108, 134, 136-139, 141, 142, 150, 152, 153], smoking habits (particularly for lung cancer) [106, 108, 134, 136, 137, 139, 141-145, 150, 154], alcohol consumption [106, 138, 139, 141-144, 153, 154], genetic factors [139, 143, 147, 153], viral causes [139, 144, 153], cultural factors [141, 153], the prevalence of *Helicobacter pylori* infection (for stomach cancer) [106, 108, 138], reproductive behavior (for breast and cervical cancers) [139, 141, 150, 154], birth rates (for breast cancer) [106], access to healthcare and improved treatment options [152], earlier detection [152], health-seeking behavior [138], physical activity [139], sociocultural barriers (affecting uptake and quality of clinical treatment) [108], and cancer screening (for breast, prostate and cervical cancers) [137].

### ***Migration and mortality after cancer diagnosis (survival)***

The increasing trend in cancer survival with calendar time for most cancer types has been shown in many countries [88, 96-98, 159], although clear differences have been observed within [160] and between countries [96, 161].

#### *All-site cancer*

A study in Denmark showed no significant differences in overall survival for all cancer patients between migrant and Danish-born women [162].

#### *Stomach cancer*

One-year survival was higher in all migrant patients [163], but mortality for stomach cancer patients was lower among migrants from Morocco, Suriname, and Turkey, compared with local-born Dutch [163, 164].

#### *Colon cancer*

A US study demonstrated poorer overall survival among foreign-born patients with colon cancer, compared with those born in the USA [165]. However, studies in Denmark [162] and the Netherlands [166] have shown no significant differences in survival for colon cancer patients among migrants compared with native Danish and Dutch, respectively.

#### *Lung cancer*

No significant differences in overall survival for patients with lung cancer were observed between migrants and native Danes [162].

#### *Breast cancer*

Most migration studies in breast cancer patients have been limited to specific ethnic groups in the USA, and have shown that, for each disease stage, survival is poorer among Afro-American compared with Caucasian women [167]. After adjustment for covariates including stage, the results of a study conducted in the USA indicated that Native Americans and migrants of Asian or Central and South American ethnicity had higher risks of mortality after a breast cancer diagnosis compared with non-Hispanic white women [168]. Other studies in the USA showed better survival for patients with breast cancer among foreign-born Hispanic women, compared with US-born Hispanic women [169]. Studies in the Netherlands indicated lower 5-year survival for patients with breast cancer

among all migrants, compared with native-born Dutch [163]. However, mortality among patients with breast cancer was higher in women from Morocco [163] and lower in those from Surinamese and Indonesia [163, 164], compared with local-born Dutch women. A study in Norway has demonstrated poorer survival after breast cancer diagnosis for migrant women from Sri Lanka, Pakistan, and Somalia compared with Norwegian women [170].

#### *Cervical cancer*

Compared with native Dutch women, survival for patients with cervical cancer was improved among migrant women in the Netherlands [166].

### ***Migration and mortality after cancer diagnosis (survival) in Sweden***

#### *Breast cancer*

Lower 5-year survival for female breast cancer patients was observed among Estonian women compared with the total Swedish population [171]. Case fatality of breast cancer was also lower in patients diagnosed after 50 years of age among migrants compared with Sweden-born women [37]. Specifically, poor survival was found for lobular breast cancer among foreign-born patients from low-risk non-European countries (Indians, East Asians, Latin Americans, and Africans) [124].

#### *Prostate cancer*

For prostate cancer patients, no differences in survival have been shown among all immigrants in Sweden [127], but immigrant men from Estonian [171] and from the Middle East, Asia, North Africa, and Chile had higher survival rates [120, 127].

#### *Other cancers*

Lower 5-year survival was observed for cancers of the colon among Estonian women, and of the lung among Estonian men, compared with the Swedish patients. However, higher rates were observed for cancers of the stomach and colon among men [171].

To explain why there is variation in cancer survival among migrants compared to host populations, one needs to understand the complexity of the disease. Cancer survival is reflected by several hallmarks, important for both development and treatment of cancer. Access to high-quality healthcare affects cancer survival. To be able to survive cancer, both prevention and detection are important, and are directly linked to access to healthcare which may differ between these groups [135, 162, 164, 170-172]. Poor access to the local



healthcare system has been reported in foreign-born patients compared to the host population and this factor has been correlated with poorer cancer survival [161, 165].

Early detection, which often corresponds to detection of tumors at an early stage, is an important prognostic factor [88, 96, 97, 160, 168]. When a cancer is detected at early stage, the patient has a much higher chance of responding to treatment and thereby increased probability of survival [161, 163, 169, 171, 173]. Racial differences in detection of breast cancer have been reported. It is known that Afro-American women are generally diagnosed with breast cancer at a later stage and thus have a poorer prognosis [167, 174].

Various screening programs have been recognized as important tools for successful and early detection and thus better prognosis (for breast, cervical, and prostate cancers) [120, 124, 160, 163, 164, 166, 169, 170, 173, 175-178]. Differences in screening program attendance have been reported. Migrants have been shown to attend screening calls in a smaller extend compared to the host population [115, 133, 168, 177-184]. Reduced awareness and sociocultural differences are factors, among many others, associated with lower screening program attendance [96, 177, 178, 185].

It is known that comorbidities affect overall differences in survival [88, 96, 165, 173]. Comorbidity differences between immigrants and natives, if present, may explain the differences in cancer survival between these groups [97]. An individual's socioeconomic position (SEP) is a crucial factor for promoting better survival [159]. Lower SEP unavoidably affects lifestyle factors important for improved survival [168, 170]. Genetic variation is another important factor for both cancer incidence and survival [186], and partly explains the differences in incidence and survival between groups of different genetic background through factors such as mutation pattern and response to treatments [164]. Finally, the occurrence of salmon bias can also lead to an overestimation of survival rate among immigrants, which does not reflect the reality [166, 187].

### ***Conclusion***

The incidence of cancer among immigrants has been extensively studied by a number of researchers and the available literature is comprehensive. The vast majority of studies investigating the incidence of cancer have shown that migrants are less likely to develop cancer compared to the host population in several countries. This is especially true for cancers of the colon, breast, and prostate. For other cancer sites, the pattern is unclear and a

large variability across cancer sites and studies is observed.

For cancer mortality, a large variability across cancer sites, country of origin, and host countries has been shown. The majority of studies investigating mortality have shown that migrants have lower risks of mortality due to cancers of the colon, lung, breast, and prostate. The results of very few studies in Sweden indicate higher all-sites cancer mortality among male migrants, whereas no clear pattern has been observed among women.

Studies investigating cancer survival among migrants are also limited. The results show no differences in overall survival for all-site cancer patients between migrants and their local-born counterparts. This is especially true for lung cancer patients due to the short survival period after diagnosis. For colon and breast cancer patients, the majority of studies have demonstrated lower survival among migrants, whereas improved survival has been observed among migrants with cervical cancer compared to the host population. In Sweden, the few studies that have been conducted show poorer survival for cancers of the breast and colon among migrant women and of the lung among migrant men, compared with Sweden-born women and men respectively. However, better survival is observed for cancers of the prostate, stomach, and colon among migrant compared with Sweden-born men.

### ***Limitations of previous studies concerning cancer mortality and survival of migrants in Sweden***

Although the medical system in Sweden is suitable for carrying out epidemiological studies focusing on cancer mortality and survival among immigrants, few such studies had been conducted at the time of the start of our study. Furthermore, such previous studies had several limitations.

In studies of cancer mortality, either SEP or duration of residence in the new environment, or both, has often not been taken into consideration. Other weaknesses include age limited and a short follow-up period. Moreover, some previous studies on cancer mortality used the indirect method for standardization of mortality ratios (SMRs) to compare rates between migrants and Swedes. The use of this method was based on a small number of cases in the migrant groups. The main limitation of SMR is that it must be consistent across all ages. If the studied group is not consistent, the values will not be comparable. In addition, there has been a lack of information concerning cancer mortality in Sweden. Several studies have been conducted but either focusing on all-site cancer or cervical cancer alone. To our knowledge,

none of the other types of cancer that have been studied in our project have yet been investigated by others.

Previous cancer survival studies did not perform separate analyses with respect to year of diagnosis, age at diagnosis, sex, and time since immigration to Sweden. We evaluated trends in mortality after cancer diagnosis for cancers at any site and at the leading cancer sites in Sweden (colon, lung, stomach, prostate, female breast, and cervix). In addition, survival for cancers (at studied sites (Study II)) in respect to country of birth is relatively new approach that has not been studied earlier in a comprehensive way, only partly.

To our knowledge, our study of breast cancer diagnosis and mortality by tumor stage and migration background (Study III) is the first to evaluate breast cancer risk and mortality by tumor characteristics and country of birth taking into consideration the effect of comorbidity.

Our knowledge regarding the effects of immigration on cancer mortality and survival at all and any leading sites in Sweden, namely colon, lung, stomach, prostate, female breast, and cervix, is limited. One way to determine the effect of environmental and lifestyle factors on diseases is to study the disease occurrence among immigrants and compare it to that of the residents in the host country.

## **2 AIMS**

### **2.1 GENERAL AIM**

The overall aim of this thesis was to investigate the trends in cancer mortality and survival for all-site cancer and some common specific cancer types (colon, lung, stomach, prostate, breast, and cervical cancers) in Sweden, with particular reference to country of birth and level of education.

### **2.2 SPECIFIC AIMS**

#### **2.2.1 Mortality (Study I)**

- To evaluate the risk of mortality due to all-site cancer and cancer of selected sites by country of birth in women and in men (Study I).
- To investigate the effect of level of education on all-site cancer mortality by country of birth and sex (Study I).

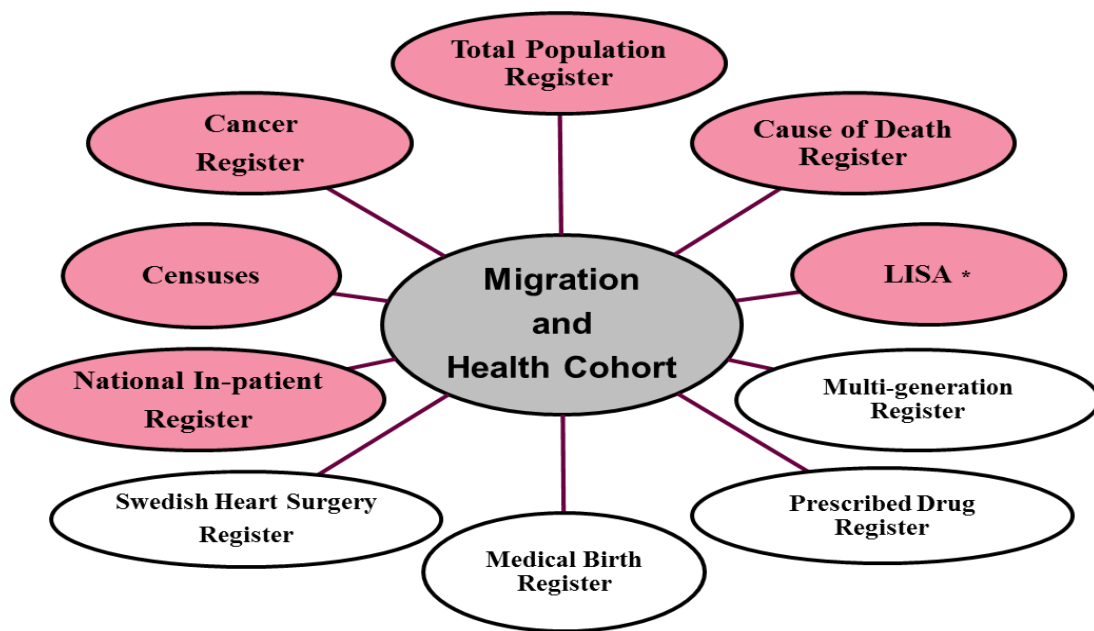
#### **2.2.2 Survival (Studies II and III, and extra analysis)**

- To investigate the effect of country of birth on trends in all-cause mortality after cancer diagnosis (all-site cancer and cancer of selected sites) by year of diagnosis, age at diagnosis, and time since immigration to Sweden in women and men (Study II).
- To detect disparities in survival after breast cancer diagnosis among female breast cancer patients by disease stage at the time of diagnosis, country of birth (Study III), and reasons for migration (extra analysis).

### 3 MATERIALS AND METHODS

#### 3.1 DATABASES

The data used in these three studies were available from a nationwide dataset, the Migration and Health Cohort (M&H Co.) [188], which was built by linkage of several Swedish national demographic and health registers through the 10-digit unique Swedish personal identity number (PIN). The M&H Co. is provided by the National Tax Board for all individuals who have resided in Sweden for more than 1 year since 1947. The PIN has been replaced by serial numbers and the key code is kept by Statistics Sweden to ensure confidentiality. The M&H Co. was created to specifically address health status among immigrants and their offspring to facilitate studies on diabetes, cancer, and cardiovascular and psychiatric diseases in Sweden (Figure 4).



- \* Longitudinal integration database for health insurance and labor market studies
- Registers used in studies I-III

**Figure 4:** The Migration and Health Cohort.

Parts of the M&H Co. that are used in this thesis were obtained from the following registries.

### 3.1.1 The Total Population Register (TPR)

Population registration in Sweden was originally started by the Church of Sweden with continuous information dating back to the 17th century [189]. Between 1961 and 1967 population registration was based on printed cards sent from the county administrative boards to Statistics Sweden [190]. The TPR in Sweden was officially established in 1968 by Statistics Sweden, which contains demographic information, country of birth, and data on emigration and immigration [190]. Most persons (who were born in or who moved to Sweden) are registered in the TPR and their details are updated continuously until the date they emigrate or die [191].

The register includes the following variables:

- Name
- Address
- PIN and co-ordination number
- Country of birth
- Citizenship
- Civil status
- Spouse, children, parents, legal guardians, and adoption
- Property, parish, and municipality of registration
- Immigration to Sweden including date of immigration, country of origin, and reasons for migration (with incomplete information for a large number of immigrants)
- De-registration information (emigration from Sweden and address abroad, or death and burial site)
- Sex
- Age

The TPR in Sweden covers the entire population and is updated on a daily basis. Although there is still both under-coverage (lack of information about birth and immigration) and over-coverage (lack of information about death and emigration), the exact magnitude of these is unknown [189].

### 3.1.2 The Swedish Cancer Register

The Cancer Register from the Swedish National Board of Health and Welfare contains data on diagnoses of cancers since 1958 and covers the whole population. Malignant diseases are coded using the seventh and ninth revisions of the International Classification of Diseases (ICD-7 and ICD-9 respectively). The ICD-7 codes are available for whole period of time from 1958 by the National Board of Health and Welfare. "According to Regulations by the National Board of Health and Welfare (SOSFS 2006:15) all physicians in hospitals and other establishments for medical treatment under public or private administration in Sweden must report all malignant and certain benign tumors to the Cancer Register. Furthermore, pathologists and cytologists separately report every tumor diagnosed from surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates, and autopsies. Thus, the majority of cases are notified twice, in separate reports. Only persons that have official residency in Sweden are included in the Cancer Register" [192]. Since the mid-1980s, six regional registries have been associated with the oncology centers in each medical region of Sweden (Stockholm, Gothenburg, Linköping, Lund–Malmö, Umeå, and Uppsala) where registration, coding, and major check-up and correction are performed. This regionalization implies close contact between the registry and the reporting physician, which in turn simplifies the task of correcting and checking the material [192].

There are three different types of information:

- Patient data including PIN, sex, age, and place of residence.
- Medical data including site of tumor (ICD-7 codes available for the entire period from 1958 to 2009), histological type, basis of diagnosis, date of diagnosis, stage (collected since 2004), reporting hospital and department, reporting pathology/cytology department, and identification number for the tissue specimen.
- Follow-up data, date of death, cause of death, and date of migration.

Diagnosis was based on clinical diagnosis and x-ray or autopsy examination [193] and all cases were histologically verified [127, 193]. The completeness of this registry regarding verified cases is considered to be close to 100% [194, 195].

### **3.1.3 The Cause of Death Register**

The Cause of Death Register (from the Swedish National Board of Health and Welfare) contains data on the date and the main cause of death from 1961 onwards, and is updated annually [196, 197]. This register is based on seventh, eighth, ninth, and tenth revisions of the ICD [198]. The Cause of Death Register includes data for all deceased persons who at the time of death were registered in Sweden, whether the death occurred within or outside Sweden. Persons who had not yet received a residence permit or those who died during a temporary stay in Sweden, stillbirths, and emigrants from Sweden who are no longer registered in the country are not included in the register.

The register contains:

- PIN
- Place of death
- Main and contributing cause of death
- Date of death
- Sex, age, and marital status

Autopsies provide valuable information regarding cause of death, however the proportion of autopsies has decreased from 50% during the 1970s to 12% in recent years [199, 200]. The non-reporting rate for the Cause of Death Register has been estimated to be less than 2% [93, 98].

### **3.1.4 The Swedish National Inpatient Register**

The Swedish National Inpatient Register, also known as the Hospital Discharge Register, contains data on comorbid diseases in hospitalized patients. The register contains data on the main diagnosis and up to eight secondary diagnoses, coded according to ICD-9 during the years 1987–1996, and 10th version of ICD from 1997. The National Inpatient Register was established in 1964 with nationwide coverage in 1987. The Swedish National Board of Health and Welfare check the quality and completeness of data available in the National Inpatient Register on a regular basis. The diagnoses for most diseases included in this register are valid in 85–95% of cases [201].



### **3.1.5 The National Population and Housing Censuses**

The National Population and Housing Censuses collected data on sociodemographic variables such as education level in Sweden between 1960 and 1990. The information was updated every 5 years from a questionnaire delivered by post to every household in Sweden. In addition to demographic and socioeconomic data, household information was collected including information on housing, employment, number of residents, and overcrowding [202].

### **3.1.6 LISA**

The longitudinal integration database for health insurance and labor market studies (LISA) from Statistics Sweden provides information on the highest attained level of education; since 1990 the information is updated annually. The LISA includes all persons aged  $\geq 16$  years what were registered in Sweden at the end of each year. The database includes demographic, occupational, and socioeconomic variables such as individual, family, and capital income, level of education and marital status [198, 203]. The level of education is updated annually from many different sources, most of which are other registers from Statistics Sweden or other authorities. Since 2000, a questionnaire has been sent to foreign-born residents with an unknown level of education to request this information [204].

## **3.2 ETHICAL ISSUES**

The studies in this thesis were approved by the regional boards of the Ethics Committee in Stockholm, Sweden (reference no. 2005/726-31 and amendment 2009/2033-32). Linkages have been completed via the PIN by Statistics Sweden and the National Board of Health and Welfare. To ensure that data anonymity and confidentiality for research are maintained, the PINs have been replaced by serial numbers with the code held at Statistics Sweden.

## **3.3 METHODS**

The data for all three studies are derived from the M&H Co. and there are two main groups in all studies; cohort members born outside Sweden are referred to as foreign-born individuals and those born in Sweden are referred to as Sweden-born individuals. The analyses were stratified by sex.

### 3.3.1 Study cohorts and follow-up

#### *Study I*

The study cohort consisted of all individuals (7,109,327 men and 6,958,714 women) living in Sweden at any time between January 1, 1961 and December 31, 2009. The cohort was followed from the beginning of 1961, the date of birth for Sweden-born individuals, or the date of immigration for foreign-born individuals, whichever occurred last, until the date of death due to cancer (see Table 1 for ICD codes), the date of first emigration, or the end of follow-up (December 31, 2009), whichever occurred first.

**Table 1:** International Classification of Diseases (ICD) codes for cancer death according to calendar period of study.

	ICD-7 (1961–1968)	ICD-8 (1969–1986)	ICD-9 (1987–1996)	ICD-10 (1997–2009)
All-site cancers	140–209	140–209	140–208	C00–C97
Lung cancer	162–163	162–163	162–163	C33–C34
Colon cancer	153	153	153	C18
Stomach cancer	151	151	151	C16
Breast cancer	170	174	174	C50
Cervical cancer	171	180	180	C53
Prostate cancer	177	185	185	C61

ICD-7, -8, -9, and -10, seventh, eighth, ninth, and tenth revisions of the International Classification of Diseases, respectively.

#### *Study II*

The study cohort consisted of all cancer patients (787,751 men and 768,357 women), aged 45 years or older, living in Sweden at any time between January 1, 1961 and December 31, 2009. The cohort members were followed from the date of cancer diagnosis (see Table 1 for ICD-7 codes), until the date of death due to any cause, the date of first emigration, or the end of follow-up (December 31, 2009), whichever occurred first.

#### *Study III*

The study cohort consisted of 35,268 female patients with a first primary diagnosis of invasive breast cancer (see Table 1 for ICD-7 code) after excluding non-melanoma skin cancer (ICD-7 code: 191) among women living in Sweden at any time between January 1, 2004 and December 31, 2009. The women were followed from the date of breast cancer

diagnosis, until the date of death due to any cause, the date of first emigration, or the end of follow-up (December 31, 2009), whatever occurred first.

### **3.3.2 Exclusion criteria**

In Studies II and III, foreign-born cancer patients residing in Sweden for <5 years before diagnosis were excluded from the study cohort for the following two reasons: to avoid including patients who had been diagnosed prior to immigration, and to minimize detection bias resulting from patients' possibly limited access to healthcare.

### **3.3.3 Outcome variables**

In Study I, the main outcome of interest was death due to cancer (see Table 1) as an underlying cause. In Studies II and III, the main outcome of interest was death due to any cause. In Study III, anatomic stage of breast cancer at the time of diagnosis was also an outcome; staging of breast cancer is based on three components, the size of the tumor (T), the number of lymph nodes involved (N), and the presence of metastasis (M). According to the TNM classification, invasive breast cancer is divided into four main anatomic stages (I–IV) [205]. Stage at diagnosis is classified as missing if information any of the variables T, N, or M are missing or unidentifiable.

### **3.3.4 Exposure variables**

The main exposures of interest in this thesis were country of birth (for all three studies) and level of education (for Studies I and III). For Studies I and III, place of birth for foreign-born patients was classified into six continents, which were further subdivided into 19 world regions, as defined by the United Nations Population Division as follows: Africa (East, Central, North, Southern, and West Africa), Asia (East, South-Central, South-East, and Western Asia), Europe (Eastern, Northern, Southern, and Western Europe), Latin America (Caribbean, Central America, and South America), North America, and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia) [206]. Only countries with five or more cases of deaths (cancer death for Study I and all-cause death for Studies II and III) were reported in order to ensure enough statistical power. In Studies I and III, the association was also investigated between the highest attained education level as a proxy for SEP and the outcome, when applicable, using census data before 1990 and the LISA

from 1990 onwards. The level of education was divided into four categories: 0–9 years (compulsory school education), 10–12 years (upper secondary school), more than 12 years (post-secondary school), and unknown. In Study II, the analysis was stratified by duration of residence for foreign-born individuals, the age at diagnosis, and the calendar year of diagnosis. For duration of residence of 5 years or more, foreign-born patients were categorized into three groups (5–14, 15–29, and 30+ years). Age at cancer diagnosis was categorized into nine groups of 5-year intervals (45–49, 50–54, ..., 80–84, and 85+ years). The calendar year of diagnosis was categorized into five groups (1961–1969, 1970–1979, 1980–1989, 1990–1999, and 2000–2009). In Study III, for patients diagnosed with breast cancer, the association was also investigated between the T, N, M, stage (I–IV), comorbidity and the outcome among foreign-born and Sweden-born patients. Using an updated version of the Charlson’s comorbidity index (CCI), comorbidity burden was assessed [207, 208]. We categorized patients according to comorbidity burden through information on diagnosis of diseases other than breast cancer using the index. We further calculated the CCI score at least 7 years before the date of breast cancer diagnosis to assess patient comorbidity (Table 2). The CCI scores were grouped into four categories (0, 1, 2 and  $\geq 3$ ).

**Table 2:** Specification of Charlson comorbidities, International Classification of Disease 10th revision (ICD-10) codes, and Charlson weight.

Comorbidities	ICD-10	Charlson weight
Myocardial infarction	I21-I22, I252	1
Congestive heart failure	I099, I110, I130, I132, I255, I420, I425-I429, I43, I50, P290	1
Peripheral vascular disease	I70-I71, I731, I738-I739, I771, I790, I792, K551, K558-K559, Z958-Z959	1
Cerebrovascular disease	G45-G46, H340, I60-I69	1
Dementia	F00-F03, F051, G30, G311	1
Chronic pulmonary disease	I278-I279, J40-J47, J60-J67, J684, J701, J703	1
Rheumatic disease	M05-M06, M32- M34, M315, M351, M353, M360	1
Peptic ulcer disease	K25-K28	1
Mild liver disease	B18, K700-K703, K709, K713-K715, K717, K73-K74, K760, K762-K764, K768-K769, Z944	1
Diabetes without chronic complication	E100-E101, E106, E108-E111, E116, E118-E121, E126, E128-E131, E136, E138- E141, E146, E148-E149	1
Diabetes with chronic complication	E102-E105, E107, E112- E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	2
Hemiplegia/paraplegia	G041, G114, G801-G802, G81-G82, G830-G834, G839	2
Renal disease	I120, I131, N032-N037, N052-N057, N18-N19, N250, Z490- Z492, Z992	2
Any malignancy including lymphoma and leukemia, excluding melanoma of skin	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	2
Moderate or severe liver disease	I850, I859, I864, I982, K704, K711, K721, K729, K765-K767	3
Metastatic solid tumor	C77-C80	6
HIV/AIDS	B20-B22, B24	6

### **3.3.5 Explanatory variables**

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

Age at follow-up, education level, and calendar period at baseline were considered as confounders in the analysis in Study I, when applicable. Age at follow-up was divided into 19 groups of 5-year intervals (0–4, 5–9, ..., 85–89, and 90+ years). Calendar period at baseline was divided into 10 groups of 5-year intervals (1961–1965, ..., and 2006–2009). In all three studies the highest attained level of education was used as an indicator of SEP and level of education was divided into four categories: 0–9 years, 10–12 years, >12 years, and unknown.

#### ***Study II***

Education level was divided into four categories as described above.

#### ***Study III***

Age at breast cancer diagnosis, educational level, medical county of residence, and comorbidity were considered as confounders in the analysis in Study III, when applicable. Age at breast cancer diagnosis was categorized into 14 groups (<25, 25–29, 30–34, ..., 75–79, 80–84, and 85+ years). Educational level was divided into four categories as described above. Medical county of residence was geographically divided into the six healthcare regions in Sweden: Stockholm, Gothenburg, Linköping, Lund–Malmö, Umeå, and Uppsala [192]. The CCI is described above.

## **3.4 STATISTICAL ANALYSIS**

### **3.4.1 Age-standardized rate**

Age-standardized rates (ASRs) of cancer mortality between 1961 and 2009 stratified by country of birth and sex (Study I) were calculated from the numbers of new cases divided by the estimated numbers of person-years at risk. To adjust for age (age distribution differences between immigrants and Sweden-born individuals) in the study population, ASRs were directly calculated using weighted averages based on the world population as the standard, assuming equal distribution in each age group. ASRs are reported per 100,000 person-years.

### **3.4.2 Poisson regression**

In Study I, mortality rate ratios (MRRs) and 95% confidence intervals (CIs) were calculated to assess the association between country of birth or level of education and cancer mortality as a measure of relative risk using Poisson regression models. In Study III, relative survival ratio (RSR) was calculated to estimate breast cancer-specific survival. In addition, we modeled relative excess rate (RER) of death and 95% CIs by stage at breast cancer diagnosis and country of birth, based on collapsed data using exact survival times [209]. In Poisson regression the outcome variable is assumed to follow the Poisson distribution, which describes a discrete probability distribution for the counts of events that occur randomly in a given interval of time. Follow-up time is separated into time intervals and a separate rate is measured for each interval, thereby allowing for the probability that the rate is changing over time, but the assumption of Poisson regression is that the rate is constant within each time interval. As in Poisson distribution, the mean is equal to its variance.

### **3.4.3 Cox proportional hazards regression**

The multivariable Cox proportional hazard regression model was used to calculate the hazard ratios (HRs) and 95% CIs of all-cause mortality after cancer diagnosis in Studies II and III. The Cox proportional hazards model is the most commonly applied model in medical time-to-event studies. It assumes a multiplicative association between the underlying hazard functions and a log-linear function of the covariates. The model further assumes proportionality of hazards; the hazard curves are assumed to be parallel on a log scale and the hazards for patient subgroups are proportional over the follow-up period. The validity of the proportional hazards assumption was visually assessed across different groups of patients by plotting the log (-log (survival)) against log (time) by group.

### **3.4.4 Multinomial logistic regression**

Relative risk ratios (RRRs) and 95% CIs of risk of anatomic breast cancer stage at the time of diagnosis were calculated using the multinomial logistic regression model (study III). In the analysis, anatomic stage I was considered as baseline (stages II, III, and IV vs. I). Multinomial logistic regression is a method that is useful to model the probability with categorical outcome variables. One of the possible categories of the categorical outcome is considered as baseline, and the model allows any other category to be compared with the baseline category.

## 4 RESULTS

### 4.1 STUDY I: CANCER MORTALITY BY COUNTRY OF BIRTH, SEX, AND SOCIOECONOMIC POSITION IN SWEDEN, 1961–2009

We followed a cohort of all individuals (7,109,327 men and 6,958,714 women) living in Sweden at any time between January 1, 1961 and December 31, 2009. Among this group, 1,950,551 (13.9%) were born outside Sweden. During the study period (1961–2009), there were 464,690 deaths due to cancer among men (29,142 foreign-born men) and 417,258 deaths due to cancer among women (29,537 foreign-born women).

All-site cancer mortality declined with increasing education level independent of sex and country of birth ( $p$  for trend  $<0.0001$ ).

Compared with Sweden-born men, foreign-born men had an overall 5% higher all-site cancer mortality risk after adjustment for age and calendar period at baseline (MRR=1.05, 95% CI 1.04–1.07), whereas similar risks were found for foreign-born and Sweden-born women (MRR=1.0, 95% CI 0.98–1.01). Among foreign-born men from Europe, the highest MRR was observed among those born in Bosnia followed by men born in the Netherlands, Finland, Denmark, Estonia, Hungary, and the former Yugoslavia with a 10% higher risk, and only a 5% higher risk was observed for those born in Norway. Men born in other parts of Europe had similar MRRs to Sweden-born men (except for men born in Greece with a 26% reduced risk). By contrast, the all-site cancer mortality risks were 15% and 10% lower in men born in Asia and North America, respectively, compared with Sweden-born men. The lowest MRRs with 35% reduced risk were observed among men born in Iran and India. The only immigrant groups with an increased MRR from these continents were men born in Laos and Cambodia with more than a 3-fold and 2-fold increased risk, respectively. Overall, men born in Africa had a similar MRR to men born in Sweden whereas African men born in Angola had a 5-fold higher risk.

Overall, foreign-born women had lower or similar MRRs compared to Sweden-born women. Women born in Iceland, Mexico, Denmark, Norway, and Romania had higher MRRs compared to women born in Sweden. The lowest mortality risk was observed among women born in Iran, Greece, Spain, Switzerland, Turkey, and Syria.

### *Specific cancer types*

#### *Colon cancer*

In comparison to Sweden-born individuals, men and women born outside Sweden had a 9% lower risk of colon cancer mortality. In all studied countries of birth, we observed lower or similar risks of colon cancer mortality among men and women, except men born in Latvia (40% elevated risk) and women born in Denmark (30% elevated risk).

#### *Lung cancer*

Lung cancer mortality was higher in foreign-born individuals of both sexes compared with Sweden-born individuals. At the country level, we observed higher or similar risks among men born in all studied countries except for those born in Iran (55% reduced risk). Women born in almost all countries in Europe had higher risks of lung cancer but women born in Asian, African, and Latin American countries had similar or lower risks.

#### *Stomach cancer*

Overall foreign-born individuals had similar risks of stomach cancer mortality compared with Sweden-born men and women. In the analysis by specific birth country, compared with Sweden-born men, we observed higher risks of stomach cancer among men born in Estonia, the former Soviet Union, Chile, Bosnia, Poland, and the former Yugoslavia, and lower or similar risks among men born in the remaining countries studied. Women in most parts of Asia and Northern Europe had higher risks of stomach cancer mortality whereas women born in the rest of the world had similar risks compared with Sweden-born women.

#### *Prostate cancer*

Foreign-born men overall had a 30% lower risk of prostate cancer mortality, in comparison with men born in Sweden. At the country level, we observed lower risks in almost all countries studied.

#### *Breast cancer*

Compared with Sweden-born women, foreign-born women had an overall 8% lower risk of breast cancer mortality. A decline in risk was also observed among women born in all studied countries except Canada, Iraq, Mexico, Belgium, and the USA, in whom the risks were higher.



### *Cervical cancer*

The risk of cervical cancer mortality was higher in foreign-born women compared to women born in Sweden. In the analysis by specific birth country, we observed higher risks in women born in almost all studied countries with the highest risk in those born in Vietnam, followed by India, Romania, Latvia, Denmark, Norway, and the former Czechoslovakia.

## **4.2 STUDY II: TRENDS IN MORTALITY AFTER CANCER DIAGNOSIS: A NATIONWIDE COHORT STUDY OVER 45 YEARS OF FOLLOW-UP IN SWEDEN BY COUNTRY OF BIRTH**

We followed a cohort of all cancer patients (787,751 men and 768,357 women), aged 45 years or older, living in Sweden at any time between January 1, 1961 and December 31, 2009. Among this group, 109,915 (7.06%) were born outside Sweden. During the study period (1961–2009), there were 604,035 deaths due to any cause among men and 540,138 all-cause deaths among women (33,593 and 34,174 foreign-born men and women, respectively).

In the analysis stratified by calendar year of diagnosis, age at diagnosis, and duration of residence, for the period between 1970 and 1990, all-cause mortality was lower among foreign-born cancer patients compared with those born in Sweden. Similar results were observed for both sexes regardless of duration of residence and age at diagnosis. After 1990, the all-cause mortality risk disparity between patients born inside and outside Sweden started to increase gradually over time, though the patterns were inconsistent among foreign-born groups with different durations of residence, until 2000 when the increase became more evident, particularly among men. We observed an almost identical pattern for cancer-specific mortality among all cancer patients. Furthermore, the all-cause mortality trend for prostate and breast cancers were similar as all-site cancer patients.

## **4.3 STUDY III: BREAST CANCER DIAGNOSIS AND MORTALITY BY TUMOR STAGE AND MIGRATION BACKGROUND IN A NATIONWIDE COHORT STUDY IN SWEDEN**

We followed a cohort of all 35,268 patients with a first primary diagnosis of invasive breast cancer after excluding non-melanoma skin cancer among women living in Sweden at any time between January 1, 2004 and December 31, 2009. Among this group, 4,232 patients

(12.0%) were born outside Sweden. During the study period (2004–2009), there were 4,178 deaths due to any cause (418 foreign-born women).

Among patients with breast cancer, all-cause and excess mortality decreased with increasing level of education regardless of country of birth ( $p$  for trend  $<0.05$ ). All-cause and excess mortality for breast cancer patients increased with increasing tumor size, level of lymph node involvement, and CCI score ( $p$  for trend  $<0.0001$ ) but with a more pronounced increased excess mortality. All-cause mortality was higher about 6-fold and 11-fold in Sweden-born and foreign-born patients with metastatic disease, respectively, compared with patients without metastatic disease. In the excess mortality analyses the pattern was even more pronounced.

After adjusting for age at diagnosis, education level, county of residence and CCI score, and considering stage I as baseline, the entire group of foreign-born patients and those born in Asia specifically had a 9% and 25% higher risk of stage II tumor, respectively, compared with Sweden-born patients. Regarding anatomic stage, we observed that all-cause and excess mortality for breast cancer patients increased with increasing anatomic stage both among Sweden-born and foreign-born women ( $p$  for trend  $<0.0001$ ). We found a higher risk of dying among foreign-born women overall if their tumor was diagnosed at advanced stages III–IV (HR=1.25, 95% CI 1.00–1.56 and RER=1.30, 95% CI 1.03–1.64), compared with Sweden-born patients. Adjustment for age at diagnosis, education, county of residence, and CCI score reduced the risk of dying to 20% (HR=1.20, 95% CI 0.95–1.51 and RER=1.21, 95% CI 0.95–1.55). The risk was highest among women born in Southern Europe (HR=1.36, 95% CI 0.77–2.40 and RER=1.36, 95% CI 0.76–2.46) and Asia (HR=1.50, 95% CI 0.87–2.63 and RER=1.47, 95% CI 0.83–2.63).

The 1- and 2-year RSRs of breast cancer patients were decreased by increasing tumor stage regardless of country of birth. The RSRs were lower for foreign-born patients if the tumor was diagnosed at stages III or IV. In addition, the 1- and 2-year RSRs for patients with missing information about stage were similar to those for patients with stages I and II cancer regardless of country of birth.

#### **4.4 ANALYSIS OF REASON FOR MIGRATION IN BREAST CANCER PATIENTS**

We further performed an extra analysis of survival based on reasons for immigration among foreign-born (refugee, non-refugee, and unknown) in comparison to Sweden-born breast cancer patients. The definition of a refugee was based on the classification of the Swedish Migration Board: “a person who has applied for asylum and can stay in Sweden on refugee grounds”. A non-refugee immigrant was defined as a person accepted by Sweden on humanitarian grounds, family of a refugee, a worker, family of a worker, family not of refugee or worker and other non-refugee [210-212]. Missing information for reasons for immigration was defined as unknown. Among foreign-born patients with the first primary diagnosis of breast cancer, 1,037 (24.5%) had information about reasons for immigration, and 87 died due to any cause. A total of 249 refugee patients were included in the analysis; there were 23 deaths due to any cause in this group. Among foreign-born patients, information about stage was missing for 1,717 (40%). While 88 refugee patients (35,3%) also lacked this information (Tables 3 and 4).

After adjustment for age at diagnosis, education, county of residence and CCI, we observed 46% and 41% higher all-cause and excess mortality, respectively, for refugee women with stage III–IV disease (HR=1.46, 95% CI 0.68–3.15 and RER=1.41, 95% CI 0.64–3.12), compared with Sweden-born patients (Tables 3 and 4). In a later analysis including women with all stages and missing information together, the all-cause and excess mortality risks were decreased to 23% and 13%, respectively, for refugee women (Table 5).

Refugee patients with stage III–IV cancer had 17% and 16% higher risk of all-cause and excess mortality, respectively, compared with non-refugee patients (HR=1.17, 95% CI 0.40–3.40 and RER=1.16, 95% CI 0.39–3.48) (Tables 6 and 7).

**Table 3:** Hazard ratio (HR) of all-cause mortality and 95% confidence interval (CI) among foreign-born, based on reasons for migration, and Sweden-born breast cancer patients by tumor stage, in Sweden in 2004–2009.

Country of birth	Breast cancer stage														
	Stage I			Stage II			Stage III–IV			All stages			Missing		
	NO <sup>a</sup>	D <sup>b</sup>	HR* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95%CI)
<b>Sweden-born</b>	8234	266	1 (Referent)	7635	847	1 (Referent)	1621	665	1 (Referent)	17490	1778	1 (Referent)	13546	1982	1 (Referent)
<b>Foreign-born</b>	1136	24	0.67 (0.44-1.04)	1147	96	0.86(0.69-1.08)	232	93	1.20 (0.95-1.51)	2515	213	0.92 (0.79-1.06)	1717	205	1.03 (0.89-1.19)
Reasons for migration															
<b>Refugee</b>	64	1	1.08 (0.15-7.84)	80	7	1.16 (0.55-2.47)	17	7	1.46 (0.68-3.15)	161	15	1.43 (0.86-2.39)	88	8	1.05 (0.52-2.12)
<b>Non-refugee</b>	200	6	0.93 (0.37-2.35)	244	19	0.92 (0.56-1.50)	48	16	1.16 (0.67-1.99)	492	41	0.93 (0.67-1.30)	296	23	0.81 (0.53-1.23)
<b>Unknown</b>	872	17	0.61 (0.37-1.01)	823	70	0.83 (0.65-1.07)	167	70	1.19 (0.92-1.53)	1862	157	0.89 (0.75-1.05)	1333	174	1.06 (0.91-1.24)

\*Adjusted for age at diagnosis, education, county of residence, and comorbidity.

<sup>a</sup> Number of women diagnosed with breast cancer.

<sup>b</sup> Number of deaths.

**Table 4:** Relative excess risk (RER) and 95% confidence interval (CI) among foreign-born, based on reasons for migration, and Sweden-born breast cancer patients by tumor stage, in Sweden in 2004–2009.

Country of birth	Breast cancer stage														
	Stage I			Stage II			Stage III–IV			All stages			Missing		
	NO <sup>a</sup>	D <sup>b</sup>	RER* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95%CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95%CI)
<b>Sweden-born</b>	8234	266	1 (Referent)	7635	847	1 (Referent)	1621	665	1 (Referent)	17490	1778	1 (Referent)	13546	1982	1 (Referent)
<b>Foreign-born</b>	1136	24	0.14 (0.01-1.83)	1147	96	0.75 (0.53-1.06)	232	93	1.21 (0.94-1.55)	2515	213	0.84 (0.67-1.04)	1717	205	1.05 (0.86-1.29)
Reasons for migration															
<b>Refugee</b>	64	1	NA	80	7	1.09 (0.47-2.53)	17	7	1.41 (0.64-3.12)	161	15	1.28 (0.70-2.33)	88	8	0.93 (0.40-2.16)
<b>Non-refugee</b>	200	6	NA	244	19	0.81 (0.42-1.55)	48	16	1.14 (0.64-2.01)	492	41	0.83 (0.53-1.28)	296	23	0.82 (0.49-1.36)
<b>Unknown</b>	872	17	NA	823	70	0.70 (0.46-1.05)	167	70	1.21 (0.92-1.59)	1862	157	0.82 (0.64-1.05)	1333	174	1.12 (0.89-1.39)

\*Adjusted for age at diagnosis, education, county of residence, and comorbidity.

<sup>a</sup> Number of women diagnosed with breast cancer.

<sup>b</sup> Number of deaths.

**Table 5:** Hazard ratio (HR) and relative excess risk (RER) and 95% confidence interval (CI) among foreign-born, based on reasons for migration, and Sweden-born breast cancer patients, in Sweden in 2004–2009.

Country of birth	Breast cancer patients			
	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)	RER* (95% CI)
<b>Sweden-born</b>	31036	3760	1 (Referent)	1 (Referent)
<b>Foreign-born</b>	4232	418	0.99 (0.89-1.11)	1.02 (0.88-1.17)
<b>Refugee</b>	249	23	1.23 (0.81-1.86)	1.13 (0.71-1.79)
<b>Non-refugee</b>	788	64	0.92 (0.71-1.20)	0.91 (0.66-1.25)
<b>Family of refugee</b>	168	2	0.73 (0.41-1.29)	0.76 (0.39-1.49)
<b>Family not of refugee or worker</b>	382	30	0.78 (0.54-1.13)	0.77 (0.47-1.24)
<b>Humanitarian grounds</b>	204	20	1.48 (0.95-2.31)	1.34 (0.79-2.23)
<b>Worker</b>	15	0	NA	NA
<b>Others</b>	19	2	1.96 (0.48-8.00)	1.99 (0.40-9.80)
<b>Unknown</b>	3195	331	1.00 (0.89-1.12)	1.03 (0.88-1.21)

\*Adjusted for age at diagnosis, education, county of residence, tumor stage, and comorbidity.

<sup>a</sup>Number of women diagnosed with breast cancer.

<sup>b</sup>Number of deaths.

**Table 6:** Hazard ratio (HR) of all-cause mortality and 95% confidence interval (CI) among foreign-born breast cancer patients, based on reasons for migration, by tumor stage in Sweden in 2004–2009.

Reasons for migration	Breast cancer stage														
	Stage I			Stage II			Stage III–IV			All stages			Missing		
	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	HR* (95% CI)
<b>Refugee</b>	64	1	0.71 (0.08-6.58)	80	7	0.98 (0.40-2.42)	17	7	1.17 (0.40-3.40)	161	15	1.33 (0.72-2.44)	88	8	1.21 (0.54-2.74)
<b>Non-refugee</b>	200	6	1 (Referent)	244	19	1 (Referent)	48	16	1 (Referent)	492	41	1 (Referent)	296	23	1 (Referent)
<b>Unknown</b>	872	17	0.37 (0.11-1.22)	823	70	0.47 (0.25-0.89)	167	70	1.01 (0.48-2.12)	1862	157	0.75 (0.50-1.13)	1333	174	1.31 (0.79-2.17)

\*Adjusted for age at diagnosis, education, county of residence, and comorbidity.

<sup>a</sup> Number of women diagnosed with breast cancer.

<sup>b</sup> Number of deaths.

**Table 7:** Relative excess risk (RER) and 95% confidence interval (CI) among foreign-born breast cancer patients, based on reasons for migration, by tumor stage in Sweden in 2004–2009.

Reasons for migration	Breast cancer stage														
	Stage I			Stage II			Stage III–IV			All stages			Missing		
	NO <sup>a</sup>	D <sup>b</sup>	RER* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95% CI)	NO <sup>a</sup>	D <sup>b</sup>	RER* (95% CI)
<b>Refugee</b>	64	1	NA	80	7	1.04 (0.37-2.88)	17	7	1.16 (0.39-3.48)	161	15	1.42 (0.69-2.94)	88	8	1.04 (0.38-2.80)
<b>Non-refugee</b>	200	6	1 (Referent)	244	19	1 (Referent)	48	16	1 (Referent)	492	41	1 (Referent)	296	23	1 (Referent)
<b>Unknown</b>	872	17	NA	823	70	0.41 (0.18-0.95)	167	70	0.97 (0.44-2.14)	1862	157	0.83 (0.48-1.45)	1333	174	1.25 (0.66-2.37)

\*Adjusted for age at diagnosis, education, county of residence, and comorbidity.

<sup>a</sup> Number of women diagnosed with breast cancer.

<sup>b</sup> Number of deaths.

## **5 DISCUSSION**

### **5.1 MAIN FINDINGS**

#### **5.1.1 Study I**

In this nationwide cohort study in Sweden between 1961 and 2009, we observed a higher risk of all-site cancer mortality among persons with a low level of education compared with those who were highly educated regardless of sex and country birth. Compared with Sweden-born men, all-site cancer mortality was slightly higher among foreign-born men, whereas women born outside Sweden had a similar risk for all-site cancer mortality compared with Sweden-born women. The results varied for site-specific cancers. Compared with Sweden-born individuals, those born outside Sweden had lower risks of colon, breast, and prostate cancer mortality but higher risks of lung and cervical cancer mortality.

#### **5.1.2 Study II**

In general, in this nationwide cohort study of all cancer patients aged over 45 years between 1961 and 2009 in Sweden, we found a reduction in overall survival among foreign-born patients diagnosed with all types of cancer after the year 2000 compared with Sweden-born patients. The results were almost identical for both sexes regardless of duration of residence and age at diagnosis. Furthermore, the mortality trend was similar for prostate and breast cancer patients.

#### **5.1.3 Study III**

In this nationwide cohort study of breast cancer patients with regard to stage at diagnosis between 2004 and 2009 in Sweden, we found that all-cause and excess mortality decreased with increasing level of education regardless of country of birth. All-cause and excess mortality increased with increasing tumor size, number of lymph nodes involved, anatomic stage, presence of metastasis, and comorbidity particularly among foreign-born breast cancer patients. The risk of stage II tumor (stage I as baseline) was higher in all foreign-born patients and those born in Asia specifically compared with Sweden-born patients. The risk of all-cause and excess mortality was higher in all foreign-born patients and also those born in Southern Europe and Asia with advanced cancer (stages III–IV), compared with Sweden-born patients.

#### **5.1.4 Reason for migration**

Refugees with breast cancer had higher (but not statistically significant) risks of both all-cause and excess mortality, compared with Sweden-born patients. In the stratified analysis by stage, the risks were greatest at stages III–IV. In addition, compared with non-refugees, refugee patients had non-significantly higher risks of both all-cause and excess mortality with advanced cancer stages III–IV.

## **5.2 INTERPRETATION OF FINDINGS**

### **5.2.1 Migration background and mortality**

#### *All-site cancer*

Our finding of a higher risk of all-site cancer mortality among foreign-born men was in contrast with the findings of some previous studies [25, 134] but in line with others from the UK [137, 143]. The lower risk in our study among men born in Asia and in South-East Asia has been reported previously [137, 144, 145]. The higher risk among men born in Eastern and Southern Europe in our study is in contrast to results reported from Spain [134, 136, 145]. Among women, the finding of a similar risk of all-site cancer mortality among foreign-born and Sweden-born individuals in our study is in line with some previous results [25], but in contrast to others [134, 136, 213]. Similar lower risks among women born in Turkey, Asia, South-East Asia, Italy, East and North Africa, Southern Europe, and South America have been reported in some studies [134, 136, 137, 141, 143, 144, 147, 149, 214].

The lower all-site cancer mortality among some migrants might be associated with factors such as the healthy migrant effect [92, 108, 134, 136, 141, 142]. Migrants who had a long duration of stay would have higher cancer mortality compared with those with a shorter duration of stay, which has been correlated with the healthy migrant effect [134, 215]. However, to our knowledge, there has been no precise data of the healthy migrant effect in Sweden. It is known that many migrant groups maintain their cultural habits and previous lifestyle. If these habits are a risk for various health conditions, they will increase the risk for many years in the host country [153]. In general, cultural background and lifestyle habits are associated with cancer mortality [216]. Traditional habits related to religion or to other cultural factors among migrants, such as lower consumption of alcohol, have been shown to be related to lower cancer mortality [141, 142, 153]. On the other hand, some groups have a



higher capacity for adoption of various forms of unhealthy behaviors as well as general risks related to life in urbanized environments [217]. As mentioned earlier, cancer is a very complex disease, known to be associated with many factors. Both genetic and environmental factors (including diet, obesity, physical activity, socioeconomic status, etc.) have been shown to effect both cancer incidence and mortality [134, 137, 139, 143, 144, 150].

### *Specific cancer types*

#### *Colon cancer*

The lower risk of colon cancer mortality among foreign-born men and women from Southern Europe and Turkey in our study was consistent with the results of another study [134]. By contrast, a higher risk was observed among foreign-born men and women from Middle Eastern countries in a study in California [218]. The differences in colon cancer mortality risk might be due to differences in lifestyle-related factors including alcohol consumption and diet [134, 219, 220].

#### *Lung cancer*

In our study, lung cancer mortality was higher among foreign-born men from Southern Europe and the former Soviet Union, in line with the results of previous studies [106, 145], and lower among foreign-born women from Asia and South America, which is also in agreement with reported results from the Netherlands [134, 136, 137, 143]. In contrast to our results, lower lung cancer mortality risks among foreign-born men from Asia, West Africa, and Turkey and among foreign-born women from Eastern Europe were observed in other studies [106, 137, 142, 143, 149]. The most probable explanations for the observed differences in lung cancer mortality among foreign-born compared with Sweden-born men and women are prevalence of smoking, the causal risk factor for lung cancer [106, 108, 134, 136, 137, 139, 141-145, 150, 154, 221], and genetic factors [220]. Smoking varies by geographical region and sex. Unfortunately, reliable data on smoking among immigrants in Sweden are lacking. However, the results of a health survey in Stockholm County showed a lower prevalence of daily smoking among migrants born in Canada, USA, Britain, and Ireland, and a higher prevalence among migrants born in Eastern Europe, Iraq, Finland, Iran, Poland, the former Yugoslavia, Southern Europe, Bosnia, North Africa, Chile, and Turkey, compared with Sweden-born individuals (personal communication).

Moreover, the same health survey showed a higher prevalence of smoking among men born

in Finland, the former Yugoslavia, Denmark, Chile, Iran, Southern Europe, North Africa, Iraq, Poland, Norway, Iceland, and Turkey, compared with Sweden-born men (personal communication). Of interest, we found higher cancer mortality among migrant men from several countries highlighted in the survey, including Finland, the former Yugoslavia, Denmark, Southern Europe, and Norway. Furthermore, the health survey showed a lower prevalence of daily smoking among women born in Central and Southern Africa and a higher prevalence among women born in the former Yugoslavia, Eastern Europe, Finland, Bosnia, Chile, and Turkey [39, 222]. The higher prevalence of daily smoking among migrant women born in Bosnia was correlated with our finding of higher cancer mortality among migrant women.

In Malmo County, the prevalence of daily smoking was higher among both men and women born in Denmark/Norway, and men born in Poland and Arabic-speaking countries, than among Swedish men and women. The prevalence of smoking was lower in women born in Arabic-speaking countries [223]. Studies of prevalence of unhealthy behaviors and risk factors for coronary heart disease carried out among migrants in Sweden showed that prevalence of smoking was higher among immigrant men (in all subgroups) than Swedish men [224, 225]. A higher prevalence of smoking was observed in immigrant women from the Organization for Economic Cooperation and Development (OECD), Chile, and Poland, compared to Swedish women [224], whereas the prevalence was lower in women from Iran [224, 225].

#### *Stomach cancer*

The observed higher stomach cancer mortality risks among men born in South America and Eastern Europe and women born in most countries in Asia are supported by previous studies [106, 110, 138, 144, 147, 149, 152, 220]. The higher stomach cancer mortality risk among immigrants could be due to an increased incidence of stomach cancer as a result of a higher prevalence of *Helicobacter pylori* infection, genetic variation, and different dietary habits such as a higher consumption of salty foods [106, 149].

#### *Prostate cancer*

A lower risk of prostate cancer mortality among foreign-born men has previously been demonstrated [106, 134, 137, 139, 219, 220, 226, 227]; this might be due to a true lower prostate cancer incidence [38, 143], genetic factors [155, 228], or to undetected prostate

cancer among immigrants as a result of a lack of awareness among this group of the prostate-specific antigen test. In contrast to our findings, a higher risk of prostate cancer mortality was observed previously among men born in South America [143, 144]. Screening is one of the main factors that affect the incidence of prostate cancer [38]. Of note, evidence shows that the decreased prostate cancer mortality does not appear to be a result of a prostate cancer screening [229, 230]. Lower prostate cancer risk in migrants is consistent with the fact that the countries they come from have lower incidence and mortality compared with the host country [147, 226, 231-233].

Family history and race/ethnicity are other risk factors that are strongly linked to development of prostate cancer [228, 232, 234-241]. Men with family history for prostate cancer are known to have higher rate of mortality due that [242-244]. Men with two or more diagnosed relatives and/or men whose relatives were diagnosed with prostate cancer before the age of 65 years had a considerably increased mortality rate due prostate cancer [243]. However, findings differed for prostate cancer mortality among different racial/ethnic groups [245, 246]. A recent study indicated that black men in the UK have a poor awareness of prostate cancer risk [247]. Race disparities were also found for mortality rates, which were markedly higher in Afro-American men compared with white American men [238, 241, 248, 249]. Conversely, Puerto Rican, Asian-American, Pacific Island, American Indian, native Alaskan, and Hispanic men all had lower mortality rates compared with white American men [241, 250, 251]. However, according to our calculation based on data from Statistics Sweden, the proportion of African migrant men among all foreign-born men in Sweden is low (about 8% in 2009) [252]. Therefore we believe the effect of racial factors on prostate cancer mortality cannot be excluded but, due the low number of African emigrants, such an effect may not be obvious.

### *Breast cancer*

The observed lower risk of breast cancer mortality among foreign-born women has previously been reported including in women born in Asia, East Asia, South America, Chile, and Turkey migrating to other parts of the world [110, 134, 136, 137, 143, 144, 149, 154, 219-221, 226, 253]. The observed lower risk of breast cancer mortality could be explained partly by a decreased breast cancer incidence in this group [37] or by death from other diseases such as cardiovascular disorders [254, 255]. However, the results of a previous study

in Sweden [37] indicate that the risk of mortality among immigrant breast cancer patients was higher after the year 2000, compared with patients born in Sweden.

### *Cervical cancer*

The higher risk of cervical cancer mortality in our study has previously been observed among immigrant women compared with white women in the USA [256]. By contrast, immigrant women in the Netherlands had a lower risk of cervical cancer mortality [134]. The higher cervical cancer mortality among foreign-born women could be due to late detection of HPV infection among immigrant women (thus late diagnosis of cervical cancer) [133, 220, 257-259], early life exposures in the country of origin, and disparities in the access to care.

In the case of HPV infection, there are more than 100 types of HPV, of which at least 13 have been associated with increased risk of several types of cancer including cervical cancer [260-263]. In particular two HPV types, HPV16 and 18, are most strongly related to risk of cancer [264, 265]. HPV 16 and 18 are also recognized as inducers of approximately 70% of all cervical cancer cases [263]. Higher rates of HPV infection have been found in immigrant women, and this group has also been reported to have lower rates of participation in screening programs [258, 266]. In Sweden, the healthcare system has systematically developed effective screening strategies as an attempt toward cancer prevention. Immigrants from low and middle income countries had limited access to screenings in their home countries which unavoidably affects early diagnosis and thus mortality [263]. It is known that the cascade of cervical cancer development starts with dysplasia (cellular abnormalities and formation of precancerous lesions) [263, 267]. HPV infection can also induce dysplasia which is primarily mild which later often leads to fatal, invasive cervical cancer [268-274].

### **5.2.2 Level of education and mortality**

During the study period (1961– 2009), we observed a higher risk of all-site cancer mortality in Sweden among individuals with a low level of education, except in the years between 1961 and 1970; this was consistent with the results of studies conducted in Australia and Spain [193, 275]. This association between all-site cancer mortality and education level could be explained by different health-seeking behavior leading to late-stage cancer at diagnosis, less favorable lifestyle factors [276], and death from cancers with a poor prognosis and a higher prevalence among individuals with a low SEP, such as stomach cancer [275, 277] that leading to increased cancer mortality among individuals with low level of education. The

decreased mortality with decreasing level of education observed during the 1960s was supported by the findings of studies from Barcelona, Spain and from Puerto Rico [278, 279]. However, this should be interpreted with caution as the percentage of missing information on level of education was higher during the 1960s compared with other periods.

### **5.2.3 Migration background and overall survival**

#### *All-site cancer*

Next we focused on cancer patients aged over 45 years between 1961 and 2009 in Sweden to investigate the effect of migration background on all-cause mortality. Compared with Sweden-born patients, we observed higher overall survival among foreign-born patients between 1970 and 1990, which could be partly due to the composition of migrant populations in Sweden, with differences in terms of ethnicity and reasons for migration in different time periods [280]. In the 1940s the majority of immigrants were refugees from the Second World War, whereas in the 1950s and 1960s the labor market migrants from the Nordic countries and later from parts of Southern Europe and Turkey moved to Sweden [19]. Other reasons for the higher overall survival among foreign-born patients between 1970 and 1990, may be the result of the “healthy migrant effect” [28] and “salmon bias” [92] as well as the degree of acculturation and healthcare accessibility and utilization, mostly among those resident in Sweden for at least 15 years.

Unclear trends in overall survival in our cohort between 1990 and 2000 may be explained by the huge diversity in ethnic status among those who immigrated to Sweden after the 1970s; the reasons for immigration changed from labor migration to asylum-seeking and fleeing from Iran and Latin America during the 1970s and 1980s [19]. Moreover, in the 1990s and at the beginning of the 2000s the largest groups of immigrants in Sweden were from the former communist countries in Eastern Europe and from Somalia and Iraq [18, 19].

Lower levels of integration might account for a part of the overall increased risk of all-site mortality among foreign-born cancer patients in the period after the year 2000. Other reasons that might contribute to poor survival are detrimental health changes among migrants from war-torn regions [281] and low participation rates in screening programs [179, 180].

Previous studies have shown that low physical activity [282], high intake of total fat [283],

high alcohol intake [284], smoking [285, 286], or any individual cancer-related risk factor and its distribution between immigrants and the local-born population might underlie the differences in survival.

### ***Breast cancer***

Overall survival for patients with breast cancer varies between foreign- and Sweden-born, after year 2000 this difference increases in worsen survival for migrants. This could partially be explained by lower participation in mammography screening program among foreign born women [183], similar findings have been documented in Australia and Netherlands [177, 287].

In our study, we observed later-stage disease presentation in foreign-born women. This is in agreement with findings in ethnic minorities in the USA [288, 289], New Zealand [290], Canada [291], and in some European studies conducted in England [114], Denmark [129], and Norway [170]. This delay might be due to low adherence to mammographic screening programs [292, 293], or cultural and behavioral aspects such as language and integration difficulties. In migrant populations, accesses to healthcare and SEP might also explain this delay [178, 294, 295]. Other factors involving poor access to medical services, delay in seeking healthcare, individual awareness of personal risk, lack of communication with healthcare professionals, and insufficient health promotion strategies [295] can also play a role in delayed diagnoses and further have an impact on the duration between diagnosis and treatment [296]. Moreover, a combination of differences in risk factors and biology [291, 297] and age at diagnosis in foreign-born women might partly explain this. Differences in the clinical and biological characteristics between young and older patients with breast cancer as well as across different racial/ethnic groups have been demonstrated. In comparison to older patients, in younger patients diagnosed with breast cancer the tumor is more aggressive and presents with a more advanced tumor stage, larger tumor size, and higher tumor grade [298-301]. Similar clinical characteristics have also been found among African-American and Hispanic patients with breast cancer living in the USA [302, 303], and patients living in Africa, Eastern Europe, Middle East, South America, Mexico, and Caribbean [304].

It has been suggested that differences in the distribution of stage at diagnosis for patients with breast cancer and subsequent disparity in mortality between immigrants and native populations may be partly due to low commitment to mammography screening [168, 181, 182].

We observed higher all-cause and excess mortality among foreign-born compared with Sweden-born patients with the same tumor stage, therefore poorer prognosis among migrant patients with advanced tumor stages III–IV cannot be explained by low participation in mammography screening. This observation has also been reported previously in several ethnic groups living in the USA, including Afro-Americans, Native Americans, and migrants from Asia and Central and South America [167, 168].

Comorbidity has previously been associated with both lower survival [305–307] and less aggressive treatment [173, 308] in patients with breast cancer. In this study, we observed lower survival in breast cancer patients with comorbid diseases, although the poorer prognosis in foreign-born patients with stage III–IV tumors could not be attributed to comorbidity (as this was adjusted for in the multivariable analysis). Furthermore, factors such as obesity [309], physical inactivity [310, 311], and weight gain after breast cancer diagnosis [312] have also been associated with high mortality in patients with breast cancer.

#### **5.2.4 Level of education and overall survival**

Reduced all-cause and excess mortality associated with a higher level of education among patients with breast cancer regardless of country of birth has previously been demonstrated in Sweden [313, 314] and other countries [310]. The use of preventive healthcare such as mammography screening may be related to educational level [315]. Late stage at diagnosis of breast cancer and worse prognosis may be due to non-participation in mammography screening [316]. However, in our project, the opposite association between education and all-cause and excess mortality remained after adjustment for tumor stage.

#### **5.2.5 Reason for migration in breast cancer patients**

Among women diagnosed with breast cancer, we found non-significantly higher risks of both all-cause and excess mortality in refugee women, compared with Sweden-born patients. In the stratified analysis by stage, the increase in risk was greatest in advanced disease (stages III–IV). Furthermore, compared with non-refugee patients, we found non-significantly higher risks of both all-cause and excess mortality among refugee women with stage III–IV cancer. The reason the risk increases were not significant may be related to low power and number of patients among refugees especially in the subgroup with stage III–IV cancer (17 patients and

seven deaths). It is noteworthy that there is a lack of knowledge about survival for breast cancer patients by stage in subpopulations of migrants (such as refugees), therefore further research is needed in this area. A lack of statistically significant findings may also indicate efficiency and availability of the Swedish healthcare system. In Sweden, adult refugees have access to healthcare for urgent conditions from the day they seek asylum [317]. All breast cancer patients are treated in a similar manner.



## **6 METHODOLOGICAL CONSIDERATIONS**

### **6.1 STRENGTHS**

The main strength of present thesis is that all included studies are cohort studies based on several unique and high-quality Swedish registers including all individuals and cancer cases in Sweden. The Cause of Death Register ensured complete follow-up for all individuals including patients with cancer. Almost complete information was available on the main exposure of the study (country of birth) including foreign-born and Sweden-born individuals in Sweden. In addition, because of the cohort design with a long follow-up period and the large sample size in our studies, we were able to either adjust for some potential confounding factors between exposures (country of birth and education level) and outcomes (cancer mortality and all-cause mortality of patients with cancer) or perform a multidimensional stratified analysis.

### **6.2 LIMITATIONS**

An important limitation is the lack of clinical data such as stage of cancer for the whole study period for Studies I and II and treatment for all studies. Moreover, we also lacked genetic data and information on environmental factors, such as social support, access to healthcare services, dietary habits, smoking, alcohol consumption, physical activities, degree of acculturation, or any individual cancer-related risk factors, which may have affected the observed results. In addition, we did not have access to other indicators of SEP such as occupation and income for whole study period in the three studies in this thesis.

### **6.3 BIAS**

In statistics, bias occurs when the estimator's expected value is not equal to the true value of the parameter. In an epidemiological study, bias is defined as any systematic error that distorts the estimate of the association between exposure and outcome that cannot be controlled for in the analysis stage. The three main forms of bias in epidemiological studies are selection bias, information bias and salmon bias.

### **6.3.1 Selection bias**

Selection bias is defined as a systematic error in the selection of samples in the population. This occurs when an unrepresentative group is selected in the study population. Immigrants are most likely a self-selected subgroup of the original population and might not represent the whole population in their home countries. Thus, the interpretation of findings in immigrant groups can be limited and might not be generalizable to the whole population in their countries of birth.

Loss of follow-up is a problem particularly associated with cohort studies. If there is a difference between participants lost to follow-up with regards to the exposure and outcome compared to those who remain in the study, this may lead to bias. Register-based follow-up among immigrants is another issue that needs to be considered if they leave Sweden without reporting to the authorities. This leads to over-coverage in the TPR and subsequently underestimation of the outcome under study. Statistics Sweden estimated that there is as much as 10% over-coverage of immigrants in the TPR [23].

### **6.3.2 Information bias**

Information bias is a systematic error that occurs as a result of incorrect or inaccurate classification of exposure or outcome and this may result in either non-differential or differential misclassification. Non-differential misclassification means that the frequency of errors in either exposure or outcome is approximately the same in the comparison groups. Otherwise the misclassification will be differential. Non-differential misclassification is generally less problematic because it can only lead to a dilution of the real association. However, differential misclassification may lead to underestimation or overestimation of the real association. Differential misclassification of the outcome among an exposed group and an unexposed group is more likely to lead to overestimation and underestimation, respectively, and similarly for a misclassified exposure.

### **6.3.3 Salmon bias**

According to the salmon bias hypothesis, immigrants in poorer health may return to their country of birth prior to death [92, 318-321]. This is more likely to apply to older migrants for whom health problems may be more prevalent [318, 319]. In the case of return migration,

deaths are thus recorded in the country of birth rather than the host country [320]. Return migration might be due to family support and the cultural importance of family ties, and lower cost of living, greater access to healthcare, or to other factors in the country of birth [92, 319, 321].

Swedish immigrants who undergo salmon bias are often registered as deceased in the Cancer Death Register. However, the cause of death is not always registered for immigrants. Therefore in Study I, because the outcome is mortality due to cancer and death might be due to other causes, it is possible that cause of death was in fact due to cancer but we may have considered the death due to other causes. This would lead to differential misclassification of outcome as this problem is not encountered among Sweden-born individuals. However, we believe that it is unlikely that this would have affected our results in Study I, because the percentage of immigrants who left Sweden before death was very small. Regarding misclassification of country of birth, to our knowledge there is no evidence indicating any major problems related to being registered either as born inside or outside Sweden in our studies regardless of outcome.

It is unlikely that misclassification of either exposure or outcome occurred because of the register-based nature of data in our studies, virtually complete information on country of birth (foreign-born and Sweden-born), and completeness of the Swedish health registers.

According to the salmon bias hypothesis, foreign-born patients who return to their country of birth are exposed to higher mortality risks than those who stay in the host country. The results of some studies were consistent with this notion [319]. In addition, after repatriation, the mortality rate may be increased in their native country [92]. Return migration leads to an underestimation of the mortality rates among foreign-born individuals in the host country [92, 142, 322]. Death rates are calculated using all events observed during a given period divided by the baseline population. However, regardless of the health condition of the return migrants, a bias in the estimated mortality rates will result, because the return migrants have generally poorer health in comparison with those who remain in the host country [92, 318]. However, the finding of lower mortality among Latin Americans in the USA does not support the salmon bias hypothesis [92].

In our project, differences in cancer mortality among migrants compared with the host population might be related to the return of migrants in poor health to their country of

origin prior to death [108, 141, 142]. Compared to our results (Study I), a lower risk of all-site cancer mortality has been reported among Mexican women in the USA [323]. Lack of reporting about reverse emigration (back to the home country) among elderly and ill individuals prior to death might be associated with the observed decrease in all-site cancer mortality in this group [141, 142, 153]. However, the opposite findings of a higher risk in foreign-born men and similar risk in foreign-born women do not support this hypothesis. Furthermore, the higher overall survival among foreign-born patients between 1970 and 1990 (Study II) may be explained by the salmon bias hypothesis [92]. However, studies have found that immigrants who return to their country of birth actually have lower survival rates [166, 187].

It is important to note that we cannot determine the impact of salmon bias on our findings. Salmon bias may have led to an underestimation of the mortality rates and/or overestimation of the survival rates. This is an important issue that must be considered. Because we do not have access to precise data on return migration of foreign-born individuals, the impact of salmon bias in Sweden cannot be excluded. To obtain an estimation of the effect we analyzed 5-year survival for breast cancer patients older than 60 years of age diagnosed between 1961 and 2005 and followed from 1961 to 2009 by country of birth in Sweden. We found that women from Chile, Greece, and Iran had higher rates of survival (86%, 79%, and 77%, respectively) than both Sweden-born (62%) and all foreign-born (69%) women. Of interest, we found that cancer mortality was lowest in migrants (both sexes) born in Iran and Greece compared with those born in Sweden (Study I). We assume that salmon bias may have had an effect on our results in these migrant groups. In the longer term, the results of the sensitivity analysis showed that the proportion of individuals who were 100 years of age and older was very low and similar among Sweden-born and foreign-born groups, thus further refuting the hypothesis of non-reported emigration of older foreign-born men and women.

#### **6.4 CONFOUNDING**

The purpose of epidemiological studies is to find a real association between an exposure and an outcome. However, in practice, it is uncommon to find a real association and usually the association is distorted by another factor, known as a confounder. This occurs when another exposure or risk factor is associated with both the exposure and the outcome (but is not part of the causal pathway between them) and is able to distort their association.

Uncontrolled confounding leads to a misleading association between the exposure and outcome and should be controlled. The usual ways to control for confounding are either in the study design; randomization, matching, and restriction, or in the analysis; stratification and as adjustments in the regression model. The benefit of using regression models is to be able to control for more than one confounder simultaneously [324].

In this thesis, which includes three studies, we identified and controlled for several possible confounders based on previous literature and knowledge of the field. For association between country of birth as the main exposure and cancer mortality and survival after cancer diagnosis as outcomes, we identified several potential confounding factors to control by adjustment in the analyses and also by stratification.

The most important confounders in epidemiological studies are non-modifiable variables such as age and sex. Differences in age distribution between immigrants and Sweden-born individuals (older age among those born in Sweden), especially for the cancers studied, might confound the comparison of cancer mortality and survival after cancer diagnosis in our studies. Thus, in Study I, age at follow-up as a potential confounder was controlled in the analyses and sex as another potential confounder was controlled by stratification. Further, ASRs were calculated using the world population as the standard in Study I to adjust only for age. In Study II, age at diagnosis for patients with cancer as a potential confounder was controlled in the analyses and sex was controlled by stratification. In Study III, age at breast cancer diagnosis as a potential confounder was controlled in the analyses.

Level of education is one of the most basic indicators of SEP; health awareness that could affect health outcome and lifestyle is more related to literacy and level of education than occupation and income [325, 326], especially in Sweden with a good healthcare system. Furthermore, attained level of education is a more stable and standard indicator of SEP that is comparable between different studies. We indicated the effect of SEP on the risks by stratification of exposure; the risks decreased with increasing level of education however this effect was more evident for foreign-born men and for Sweden-born women. Thus, as another potential confounder, we adjusted for the highest level of education as an indicator of SEP when applicable in all analyses in this thesis.

Moreover, there were other potential confounders in the studies such as calendar period at

baseline in Study I (which was controlled in the analyses as adjustment), duration of residence for foreign-born individuals and the calendar year of diagnosis in Study II (controlled by stratified analysis), and medical county of residence, comorbidity and anatomic stage, when applicable, in Study III (controlled in the analyses as adjustments, because distribution differences of these variables between immigrants and Sweden-born patients might confound the comparison of the risks).

Finally, we lacked information on environmental factors, such as social support, access to healthcare services, dietary habits, smoking, alcohol consumption, and physical activities, which might have had an impact on the association between country of birth as the main exposure and cancer mortality and survival after cancer diagnosis as outcomes.

## 7 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

- The decreasing overall cancer mortality trend in men but not women over the past two decades, regardless of country of birth, suggests the need for studies to identify the factors that influence this gender disparity in mortality.
- The slight higher overall cancer mortality among foreign-born men compared with Sweden-born men indicates that studies are needed to investigate the mechanism(s) underlying the differences in cancer mortality among immigrants and Sweden-born men.
- The association between low level of education and increased overall cancer mortality as well as poor survival after breast cancer diagnosis might be reduced by educating cancer patients and systematically improving care for patients with a low level of education.
- Further studies with detailed clinical data are needed to understand the reasons behind the higher all-cause mortality after the year 2000 among foreign-born patients with all-site, breast and prostate cancers need these inequities.
- The observed poor prognosis among foreign-born breast cancer patients with advanced-stage disease at diagnosis suggests that further studies with detailed patient and clinical data are needed.
- As the power for results of refugees was low, further studies with appropriate power and longer follow-up are needed.





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