Ethnic Heterogeneity of Cancer in Europe

Lessons from registry-based studies in migrants

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Ethnic Heterogeneity of Cancer in Europe
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Etnische heterogeniteit van kanker in Europa
Lessen uit registratie-gebaseerde studies bij migranten

Thesis

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born in Vorwerk, Germany

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Contents

Every man is more than just himself; he also represents the unique, the very special and always significant and remarkable point at which the world's phenomena intersect, only once in this way, and never again.

That is why every man's story is important, eternal, sacred; that is why every man, as long as he lives and fulfils the will of nature, is wondrous, and worthy of consideration.

Hermann Hesse (1877-1962)

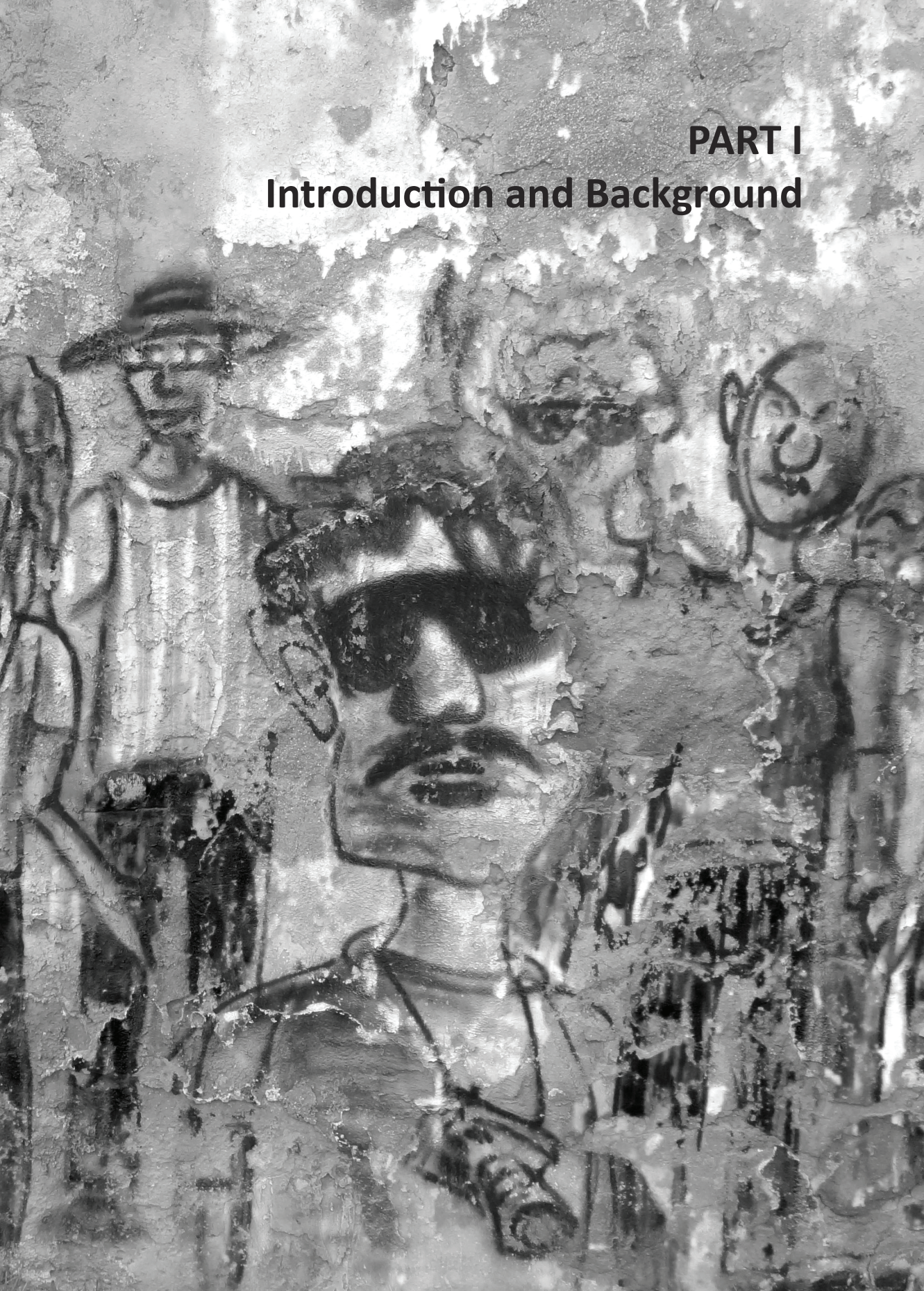
Preface

Hermann Hesse used to sketch life as steps, where one's heart must always be prepared for sudden farewells and new beginnings. New steps in life bear a certain kind of magic, protecting us from disappointments and helping us to look ahead. Those are also the moments that make our lives exciting, revive our spirits and keep us moving.

Migration, especially immigration, is neither a new phenomenon to Europe nor to public health. Quite the contrary, it has become a hot topic in terms of demographic trends, labour markets and social coexistence. Migration by itself is not a risk factor for disease or inequality. It is human, the consequence of globalization and rapidly changing needs of a growing global society. However, ethnic disparities exist on several levels. Policymakers are therefore asked to meet the social, cultural and health care needs of a growing number of multi-ethnic societies in many Western countries. Assessing and monitoring the health of migrant and ethnic groups can benefit the whole population by contributing to a better understanding of disease patterns and aetiology. Cancer represents a whole range of diseases with different underlying risk factors and clinical courses. Just like migration, cancer is characterized by a high degree of complexity, heterogeneity and relevance to society. In fact, we can learn a lot by combining the two in research.

The scope of this thesis is

- to summarise current knowledge of cancer occurrence and mortality in migrant populations in Europe.
- to present new findings from studies on cancer in migrants in different European countries, with a focus on Turkish migrants and studies in the Netherlands.
- to outline limitations of such studies and to discuss methodological remedies.
- to suggest new targets for research, considering the expected demographic developments in Europe in the future.



PART I
Introduction and Background

1

Introduction

Introduction

Immigration to Europe and the Netherlands

Europe has long since laid off its image as a primarily emigration-dominated continent and has transformed into a coveted destination of immigrants from all over the world. Immigration has substantially characterized the European society and has ensured a positive migration balance as well as a rejuvenating influence in many countries since mid-1900s (2).

In Europe, there have been three major migration waves since World War II. Immigration to the Netherlands is closely interrelated with those developments and exemplary for several other Western European countries, such as Germany, France and the Scandinavian countries. Shortages on the lower labour market caused by the economic growth in the post-war era resulted in vigorous labour migration from the south of Europe, Turkey and the Maghrebian countries. The recruitment of *guest-workers* stopped with the recession in 1973 (in the Netherlands in 1975) and was followed by family reunification, representing the most common immigration type to the Netherlands. Many Turks and Moroccans residing in the Netherlands and other Western European countries called for their families in order to settle permanently. In the 1980s, the Netherlands faced a post-industrial immigration wave, which mainly consisted of asylum seekers, highly educated migrant workers and illegal immigrants. Next to those developments affecting large parts of Western Europe, some countries, including the Netherlands, experienced substantial postcolonial immigration. The decolonization of the Dutch East Indies caused considerable migration to the Netherlands in the 1950s and 60s (3). Similarly, the independence of Suriname in 1975 contributed to persistent immigration. Today, about 350,000 Surinamese people live in the Netherlands while Suriname itself hosts about less than half a million inhabitants.

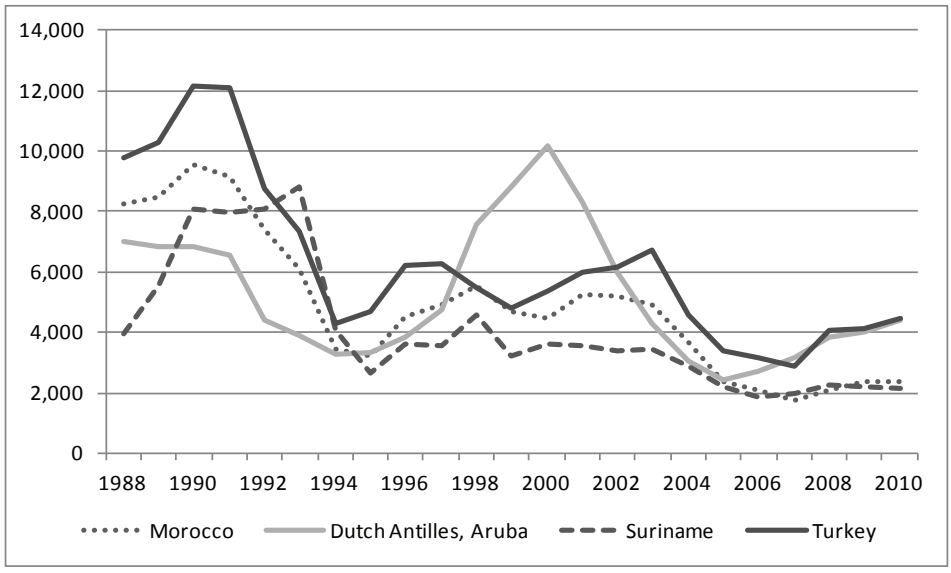


Figure 1 Immigrants to the Netherlands by country of origin, 1988-2010
(Source: Statistics Netherlands)

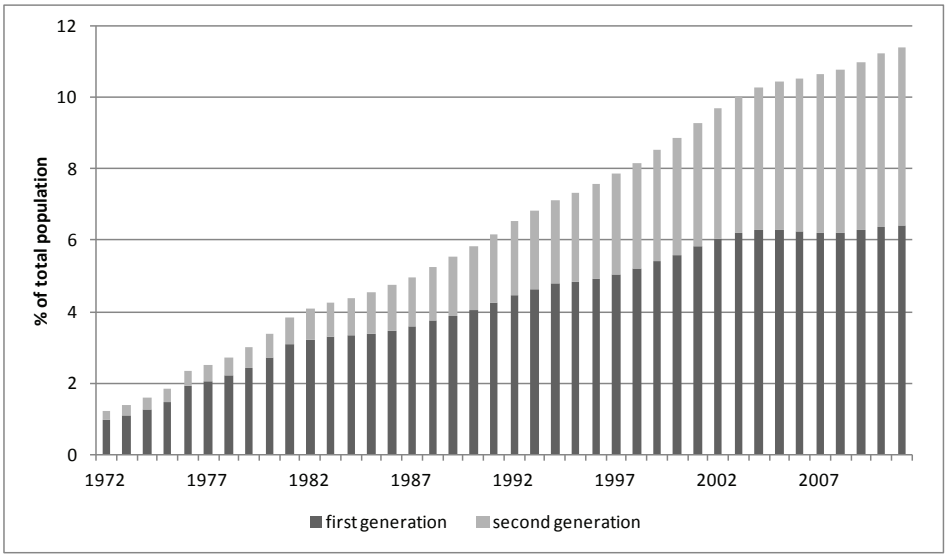


Figure 2 Percentage of non-western immigrants in the Dutch population by generation, 1972-2010 (Source: Statistics Netherlands)

Figure 1 displays the development of absolute immigration of the most important non-Western groups to the Netherlands. As a result of the bad economic situation, there were substantial job cuts on the Dutch Antilles in the late 1990s which also caused a remarkable immigration wave in subsequent years. Immigration from Turkey, Morocco and Suriname has been decreasing since the early 1990s, which is in accordance with policy regulations that limit immigration and family reunification from those countries. Since the enlargements of the EU in 2004 and 2007, there is also a growing number of East Europeans residing in the Netherlands, especially from Poland, Bulgaria and Romania. According to the Statistics Netherlands, in 2011, every fifth Dutch citizen had a migration background of either first or second degree (4). Whereas, until the late 90s, migration from Western countries dominated and has further increased by 44% since 1972, currently, migrants from non-Western (see **box 1**) countries represent about 55% of all migrants residing in the Netherlands and increased ten-fold since 1972. The ratio of first- and second generation (see **box 1**) migrants has been relatively stable in Western migrant groups, where second-generation migrants prevail since decades. In non-Western migrants, however, the second generation has been growing steadily since the early 1990s (**Figure 2**). In the European comparison, the percentage of foreign-born residents in the Netherlands is above the EU average (11.1% vs. 9.4%). On an absolute scale, the Netherlands belong to the nine EU member states with more than one million foreign-born residents (5-6). The biggest groups of non-EU foreigners come from Turkey and Morocco, followed

Box 1

- A **first-generation** migrant is someone who was born abroad with at least one parent born abroad and a **second-generation** migrant is defined as someone who was born in the Netherlands with at least one parent born abroad. (Statistics Netherlands definition)
- **Non-Western migrants** are defined as persons from Africa, Latin-America and Asia (except Indonesia and Japan) and Turkey. **Western migrants** are persons from another EU-country (except Turkey), North America, a, Indonesia and Japan. (Statistics Netherlands definition)

by Albania and China. However, big differences exist at member state level. The choice of country of residence can be very heterogeneous and often depends on employment opportunities, language, geographical proximity, historical links and national policies.

Immigrant, migrant or ethnic group?
There is a great variety of terms and definitions used in the field of migration research. They mostly differ with regard to their accuracy and specificity as well as the context in which they are used. Commonly used terms are *immigrant* ('a non-national who moves into a country for the purpose of settlement') and *migrant* ('persons and family members, moving to another country or region to better their material or social conditions and improve the prospect for themselves or their family'), usually a broader and more varying definition, whereas a *refugee* ('a person who owing to a well founded fear of being persecuted for reasons of race, ethnicity, nationality, membership of a particular social group, a political opinion, is outside the country of his nationality, and is unable to or, owing to such fear, is unwilling to avail himself of the protection of that country') is an internationally more recognized term (7-8).
Ethnicity, on the other hand, reflects shared cultural characteristics, including religion, ancestry, dietary habits and language. It refers to the social group to which a person belongs and with which he shares his identity (9). Migration and ethnicity are thus closely interrelated terms, both reflecting differences in environment, culture and ancestry (10). Unlike *race*, which has strong ties with the history of the US and slowly seems to be dismissed in science (11), ethnicity does not make any assumptions with regard to perceived differences in biology, physical appearance and behaviour (12). The differences and similarities between the measures are discussed in more detail in **chapter 2**.
In this thesis, the term 'migrant' is used in a broad manner and is understood to cover persons that have migrated to another country different from their country of birth. This (inevitably) also implies differences with regard to ethnicity when compared to the native population of their new host country. Although they did not migrate actively themselves, the offspring of migrants are referred to as second generation migrants, as they face health challenges that are related to the migration of their (grand)parents.
Populations from a similar geographic origin, for example Western populations, often share not only sociocultural and socioeconomic backgrounds but also ancestry and risk profiles. As migrant studies can only provide useful results when there are differences in underlying risks in migrants (or their country of origin) and the comparison group (most of the times the population of their host country), the studies presented in this thesis focus on migrants of non-Western origin.

Ethnicity in public health research and policy
When presenting health data, ethnicity and migrant status have become key variables in epidemiologic and public health research (13-14). Its use implies expected differences in the characteristics of ethnic groups and their experience of disease and aims to explain disease variation. Europe slowly follows a trend that has long since been enrooted in the research culture of the United States.
However, there is no standard approach, and there is still a long way to go to achieve comprehensive and standardized measures in this field. This is crucial in order to monitor health, to learn about existing inequalities, and to set priorities for targeted prevention measures. In particular, the understanding that the study of ethnic variation in disease risk may benefit the whole population still needs to be promoted (10). A clear policy commitment can help promoting this understanding and forwarding research.

During the course of the sixty-first World Health Assembly in 2008, the WHO member states endorsed a resolution on migrant health, including four basic principles of a public health approach (15):

1. to ensure migrant's health rights
2. to avoid disparities in health status and access
3. to reduce excess mortality and morbidity
4. to minimize the negative impact of the migration process

Two years later, in 2010, the global consultation on migrant health was held in Madrid, initiated by WHO, the International Organization for Migration (IOM) and the Ministry of Health and Social Policy of Spain. All member states were asked to develop and implement migrant sensitive health policies and practices. The resolution identified four key themes and corresponding actions to be tackled in the near future (16):

1. monitoring migrant health
2. integrating policy and legal frameworks
3. promoting migrant sensitive health systems
4. encouraging international collaborations

The aim is to develop a basis for policy frameworks in order to define public health strategies for migrants. However, health policy can only respond adequately if there is a clear understanding of the underlying factors that cause health disparities. And in fact, evidence and data infrastructure is still poor, starting with the (basic) problem of finding and implementing a uniform definition of migrants. All those aspects query the practicability of these statements and will be discussed in more detail in **chapters 2 and 10**.

The influence of immigration on cancer in the Netherlands was for the first time addressed in a scenario report commissioned by the steering committee on future health scenarios in 1984 and published in 1988 (17). A more than average increase in the number of newly diagnosed migrant cancer patients was predicted, given the expected increase in cancer incidence in general and the expected relatively rapid aging in this group. In 2003, the Dutch Cancer Society (DCS), then responsible for such future explorations, recognized the need for migrant-sensitive research and installed a working group Migrants and Cancer ('Allochtonen & Kanker'). Subsequently, an alert report was published in 2006 (18). The aim of the quantitative part of the report was to provide an idea on how big the burden for the Dutch health care system will be in terms of an increasing proportion of migrant cancer patients. On an absolute scale, common cancers such as tumours of the lung, prostate and colon are expected to rise in migrants by the year 2030. As most migrants are residing in the urban areas of the Netherlands, the proportion of migrants among all cancer cases is expected to be substantially higher and increase faster in cities like Amsterdam, Rotterdam and The Hague. Whereas the proportion of migrants among all cancer cases is estimated to be 3% in 2015 and 6% in 2030 for the country as a whole, it is expected to amount up to 11% and 20% in bigger cities, respectively. The report furthermore highlighted lower cancer mortality among migrants as well as different risk factor patterns in this group. This especially accounts for less smoking and alcohol consumption, but also for higher risks to carry infections. The convergence of risks towards the level of native Dutch persons was found to be slow process that is mainly influenced by age at migration. In view of the limited availability of incidence data, DCS recommended to include more migration-related variables in cancer registration data and/or data linkage with the population register in order to improve monitoring. The qualitative part of the report provided insights into the needs and expectations of migrant cancer patients based on the literature and focus group

interviews. According to DCS, in the future more detailed in-depth studies are necessary that will serve to increase awareness of the topic among policy makers and care givers, to direct new research initiatives and prevention. In their concluding recommendations, DCS emphasised the need for quantitative research into health care utilization of migrant groups and quantitative studies into socio-cultural backgrounds of participation in the health care sector as well as migrants' quality of care and quality of life.
The Flemish League against Cancer (VLK) focused on the need to support health care providers in dealing with migrant cancer patients and published a detailed guide in 2010 (19). Results from open interviews with migrant cancer patients and their families were thereby translated into 21 areas of action, such as cancer as a taboo, language barriers and communication problems with clinicians.
At present, several patient organisations are operating on the Dutch level with the aim to improve culture-sensitive health care, like the '*Stichting Allochtonen en Kanker*' (20) and '*Mammarosa*' (21). The latter provides specific information for migrant women with breast cancer in various languages. In addition, the PHAROS institute (22), a knowledge and advisory centre, works in close collaboration with migrants and refugees, health care providers, health insurers, municipalities and many other stakeholders since more than 30 years. Their main aim is to improve migration-sensitive prevention and health care on the national and regional level and support the implementation of methods and interventions that are tailored to the needs of migrants.

Cancer in Migrants
The rationale of studying cancer in migrants is the description of a natural, uncontrolled, large-scale experiment of human populations with two main goals: gaining insights into the relative contribution of environmental factors and inherited predisposition in cancer aetiology and developing and evaluating corresponding cancer prevention measures that may also serve to optimise care among migrant groups (23). Several types of comparisons are conceivable in this context. Most prominently, comparing disease rates between migrants (i) and the (remaining) population in their country of origin (persons with a similar genetic and cultural background residing in different environments) or (ii) the population of their host country (persons with a different genetic and cultural background residing in the same geographic environment). Changes in differences in rates between the groups are often interpreted as proof of convergence (with host population rates) and divergence (from country of origin rates) and as an indication of a predominant role of extrinsic factors in carcinogenesis. Changing risks can ideally be measured in relation to age at migration and duration of residence (assuming a greater change in cumulative exposure to relevant risk factors, acculturation with increasing duration of residence) as well as comparisons between generations (assessing the importance of genetic susceptibility and persistent characteristics). Thus, in terms of causality, both the magnitude and the rate of change are considered very informative. Ideally, in order to fully understand disease patterns in migrants, a life course approach should be used, covering pre-, peri- and post-migration periods and/or birth cohorts (24).

Studies from countries with long immigration histories and large immigrant populations, such as the United States (25-26), Australia (27), Canada (28) and Israel (29) reach back to the 1960s. Some decades later, studies from Britain (30-31) and later from other countries of Western Europe followed (32-35). Through studies on migrant populations, evidence for a predominant role of environmental factors in the causation of cancer accumulated, and recent studies have identified critical periods of exposure to decisive risk

factors during a life course (36-37). Specifically, early-life exposures are important in the risk of developing stomach cancer, whereas 'new' exposures, typically after migration, in adult life, are more meaningful for the development of colon and breast cancer. One of the core issues in migrant studies is also to what extent socioeconomic circumstances contribute to health differentials in ethnic groups (38), reasoned by the fact that migrants tend to be of lower socioeconomic status than the majority population of their host country (39). And people of lower socioeconomic status are often affected by poorer health and lower life expectancy (40).

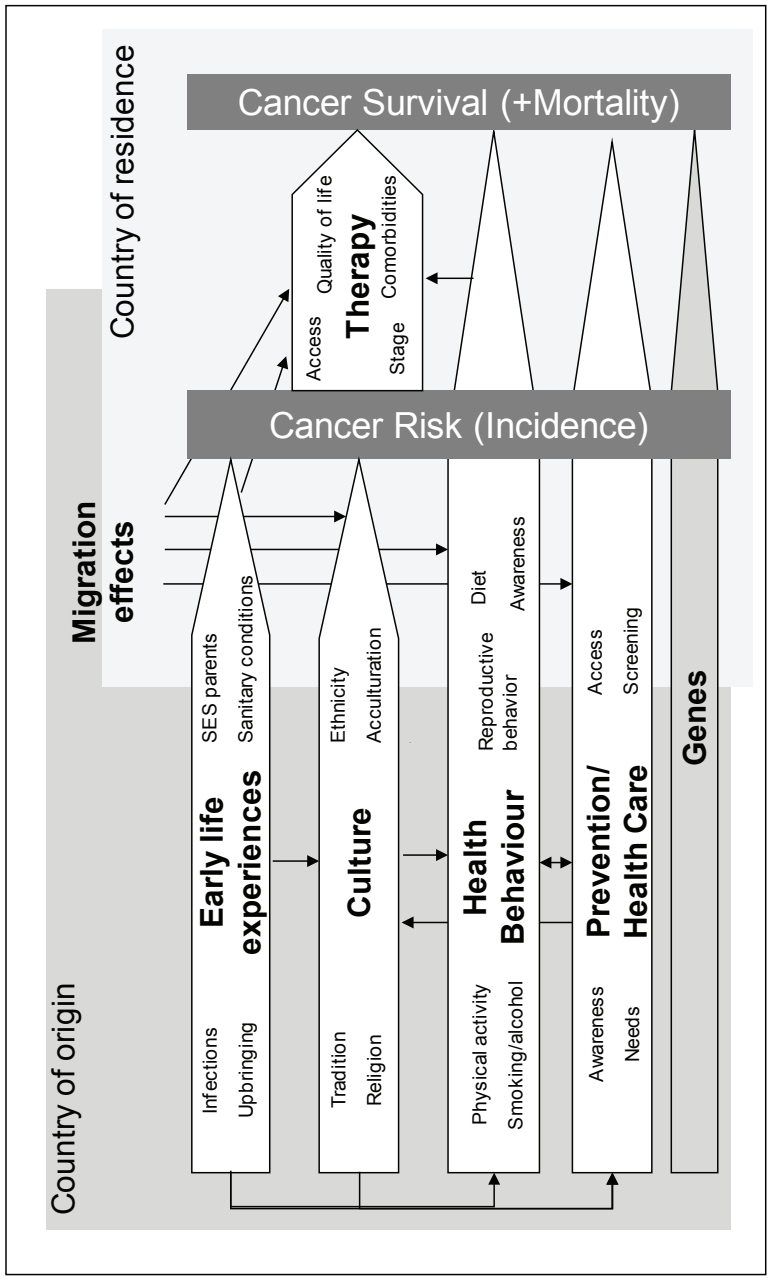


Figure 3 Conceptual model of ethnic heterogeneity and migration influences in cancer risk and survival

Figure 3 describes a conceptual model that aims to explain ethnic heterogeneity influenced by migration in cancer risk and survival. Similar models have been developed for the prevalence of diabetes by Agyemang and colleagues (41) and for health of migrants during life course by Spallek and colleagues (24). Before migration, in the country of origin, there are several important determinants that may have an impact on cancer risk in later life. Particularly, early life experiences have been found to have an important impact on cancer development, to an extent that even a paradigm shift in cancer research towards earlier rather than later periods in life has recently been proposed (42). In addition to an underlying, genetically predetermined cancer risk, the interaction of health beliefs and behaviours as well as culture-related aspects and the availability of (adequate) prevention and health care are additional important factors affecting cancer risk. Migration effects, due to drastic changes in environment (geographically and socially), can potentially modify all these factors (apart from genetics), creating heterogeneous cancer risks.
Of course this is not meant to be a static figure. Quite the contrary, it implies dynamic changes in exposures and risks over time from different angles (country of origin/ country of residence) and at different doses (dependent on age at migration/ duration of residence). Migration effects also persist after cancer diagnosis and can have a major influence on (access to) treatment, disease perception and quality of life. This may result in different cancer survival and cancer mortality patterns between migrant and non-migrant groups, respectively and may even persist across generations.

In migrant studies, the greatest share of data on cancer is registry-based and usually comes from cancer registration or death certification, together with population data. Migrant studies are, however, often subject to specific biases which mostly relate to misclassification and selection effects, but also sometimes to inconsistencies in data quality (and availability) between different data sources. In addition, many potential confounders and effect modifiers (for example socioeconomic position, religion or general health) may hamper a straightforward interpretation of such studies.
Most of the in depth studies in this thesis are based on data from the Netherlands Cancer Registry (NCR). In the Netherlands, a nationwide cancer registration covering the whole Dutch population was formed in 1989 fed by 9 CCC's ('Comprehensive Cancer Centre Netherlands'). Regional registries, especially IKZ in the south of the country, have operated since the 1950s. The NCR gets notifications of all newly diagnosed malignancies at regional level by the automated national pathology archive (PALGA). Additional sources are the national registry of hospital discharge (LMR), haematology departments and laboratories and radiotherapy institutes. Completeness is estimated to be at least 95% (43). Yet, there are also patients with only a clinical diagnosis of cancer who were never admitted to a hospital or who decided not to undergo a recordable treatment who are not recorded in the cancer registry. Country of birth is routinely recorded in the NCR and represents a standard proxy for ethnicity in health research in the Netherlands (44). Its completeness however varies by region and tumour site, being more complete for cancers with a relatively high fatality.
Previously, only regional studies have been conducted on cancer incidence of migrants in the Netherlands (45-47). Cancer mortality patterns of migrants residing in the Netherlands have recently been studied by Stirbu and colleagues (48), as well as Bos and colleagues (49-50).
There has been progress against many cancers in terms of decreasing and/or improving survival followed by declining mortality in the Netherlands since recent years for

many cancer sites (51). Overall, Europe carries a disproportionate share of cancer in the world. Whilst only 7.5% of the World population lives in Europe, more than 25% of the global cancer burden and approximately 22% of all cancer deaths currently take place in Europe. This pattern can in large part be ascribed to its population's higher average age and lifestyle factors that foster common Western cancers such as breast, colorectal, lung and prostate cancer. While breast, prostate and colorectal cancer incidence is still increasing in most European countries, mortality rates in general declined in recent years (52). Central and Eastern European countries still carry a high risk and mortality from lung cancer; both however decreased in males in other parts of Europe but kept rising in females. Stomach cancer incidence and mortality declined across Europe. The same is true for mortality from cervical cancer, however remarkable contrasts exist between member states (53) and trends in incidence suggest the same, but are more difficult to judge due to heterogeneous screening and registration practices across countries (54). Undoubtedly, (global)migration can have an influence on disease and cancer patterns across Europe. By making use of it in epidemiological studies, it can help shaping the fight against cancer and developing corresponding prevention measures.

This thesis

Part I focuses on the theoretical and methodological background of studies on cancer in migrant populations in Europe, starting with a summary of strengths and limitations of migration-sensitive cancer registration in Europe (**chapter 2**). Subsequently, a comprehensive overview of cancer risk and mortality in non-Western migrants in presented in **chapter 3**.

Studies on cancer incidence, survival and mortality in migrant groups in several European countries are the core of **part II**. The first two studies focus on Turkish immigrants, starting with a study on cancer risks in Turkish migrants in Hamburg, Germany (**chapter 4**), followed by a study on cancer mortality patterns among Turkish immigrants in four European countries with respect to their home country (**chapter 5**). In the latter study, the potentials of multinational study approaches are being explored. Subsequently, three studies on cancer patterns in migrants using Dutch cancer registry data are presented. First, breast and stomach incidence and survival are being explored in **chapter 6**. Second, **c**ervical, oesophageal and colon cancer incidence and survival have been analysed in **chapter 7.** And third, differential trends in smoking- and immigration-related incidence and mortality from nasopharyngeal cancer in the Netherlands have been studied in **chapter 8**.

In **part III**, a critical reflection and explanatory approach on the concept of migration as a high-speed health transition is presented (**chapter 9**). The general discussion (**part IV, chapter 10**) summarises priorities for care and research prospects.

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2

Migration-sensitive cancer registration in Europe

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*This chapter is a summary of the book 'Migration-sensitive cancer registration in Europe' (1).

Establishing migration-sensitive cancer registration in Europe would mean establishing a routine monitoring of cancer occurrence in migrant and ethnic minority groups within and between European countries. It is a basic requirement for describing their health status and revealing cancer risk disparities, both between similar migrant groups in different European countries, as well as between migrants and autochthonous populations, in order to develop adequate strategies to prevent or reduce health inequalities between migrants and non-migrants.
The majority of European countries has to face a growing diversity of its populations especially due to heterogeneous groups migrating to Europe or staying there in the second or third generation. Migrants in Europe are quite heterogeneous with respect to origin, age, socioeconomic status, reason of migration, migrant generation as well as health risks and resources. So far, in many European countries, there is a lack of information and data that are collected on these groups. Data are not collected routinely or systematically and hence these countries are not able to obtain an overview of the health situation of the migrants residing there.

One of the basic problems regarding the lack of health reporting in migrant groups in Europe is the difficulty of defining migrants or ethnic groups. There is no standardised definition available in most EU countries and comparisons between countries are hardly possible. Migration background or ethnicity are often described by approximating measures, e.g. by country of birth, language or origin (2). In some countries, nationality is the only indicator for migration background. Before it will be possible to monitor and describe cancer patterns (and other health risks and outcomes) among migrants across countries, it has to be agreed on a uniform migrant definition.
Developing migration-sensitive health indicators for monitoring constitutes one of the major aims of the EU-funded Migrant and Ethnic Health Observatory" (MEHO)-project (3). Some of the results presented in this chapter are part of MEHO, funded by the European Commission and conducted between 2006 and 2009. The coordination of the project was headed by the Erasmus Medical Center at Rotterdam University. The project comprised nine work packages with associated partners in other European countries and focussed on the lack of routinely collected information on migrant status in health databases and encouraged the EU member states to share experiences regarding this topic.

Specific objectives of the work package cancer and cancer registration were:
- to identify existing databases in European cancer registries with information on cancer cases/incidence according to migrant status,
- to identify the different ways in which information on migrant status is collected in European cancer registries,
- to assess data on the coverage and completeness of the registries,
- to develop indicators for cancer patterns among immigrants in Europe,
- to develop recommendations for a uniform definition of migrant status in EU cancer registrations and for further improvements of "migrant sensitivity".

Migration-sensitive cancer registration: A survey
In order to obtain an overview of migration-sensitive data collection in the cancer setting, a survey among all European cancer registries was carried out with the support of the European Network of Cancer Registries (ENCR), Lyon (4). A questionnaire comprising 22 questions was sent to all European cancer registries (n = 191). The questionnaire had two parts. The first part dealt with data sources, data quality (completeness, death certificate only) and the information that is collected on patient, tumour details, methods

of initial treatment and outcome. The second part included questions on available data on ethnicity, nationality or migration background, data on the catchment area of the registry as well as possible or planned studies concerning immigrants.
A pre-test of the questionnaire was conducted in 11 German cancer registries of the federal states and the National Finnish Cancer Registry. In November 2007 the questionnaire was sent electronically (or as a paper version if the email address was not available) to all European cancer registries. After sending reminders the response rate was 41%.
The data quality of all registries fits international standards based on completeness and DCO (Death Certificate Only) rate. Nearly every registry which answered reported a completeness of more than 94% and a DCO rate of less than 5%. Cancer registries from all Scandinavian countries and at least one from nearly every Western Europe country answered. In addition, the majority of Eastern European countries in returned questionnaires, e.g. Belarus, Bosnia-Herzegovina, Croatia, Estonia, Latvia, Lithuania and Poland.
According to the used indicator of migrant background, the registries were classified either as "exemplary" or "less exemplary" or as "registry without any migrant-specific data." "Exemplary" cancer registries use the individual's ethnic group (self-reported/self-assigned) or country of birth as indicator of migration background. "Less exemplary" registries use an individual's nationality or other indicators like name, religion, parents' country of birth, or the ethnic group assigned by another person, e.g. by the reporting doctor.
Several countries e.g. Italy, France and Spain maintain region-based registries instead of a nationwide registry. It turned out that no uniform method is used to assign migrant status among the respective registries.

Results
Nearly half of the responding cancer registries (44.9 %) collect information on country of birth routinely (exemplary), six registries collect nationality and three collect race (less exemplary). Other information on migration background that was mentioned is the status of naturalisation.
Although a considerable proportion of surveyed cancer registries collect information on country of birth, merely 14 cancer registries reported having the possibilities to conduct migrant-specific analyses. Among them, several registries explained that migrant-specific analyses would need extra resources, e.g. in terms of time and budget, but these are not available. Among the responders, merely one registry carries out routine analyses by migrant status. Additional research such as surveys or studies is carried out in 6 exemplary registries and 1 less than exemplary registry. Also, two German registries conduct additional research e.g. by record linkage procedures, because they do not obtain any migrant specific variables in their data. Several registries indicated that descriptive analyses or case only/proportional analyses (e.g. Proportional Cancer Incidence Ratios, PCIRs) would be possible. For example, Turkish immigrants could be identified with the help of a name recognition software.
To summarise these results it is remarkable that nearly half of the cancer registries responded to have exemplary data, but only few conduct migrant-specific analyses. Only one register conducts such analyses routinely. The analysis of the survey shows that currently there is a lack of data on migration status in European cancer registration and widely differing definition approaches are used. Moreover, the survey showed that even when migration status is collected, utilisation and analysis of migrant data may still be insufficient. Thus, it will be a long way to implement routine analyses. Furthermore there is still a high non-response among the European cancer registries.

Migration-sensitive health indicators in cancer research

Health reporting is essential in assessing and monitoring (global) health and serves as a basis for policy making. In this context, specific health indicators are helpful tools in measuring the state of (global) health, but also in recognizing trends as well as existing inequalities. In order to adequately describe the health of migrant groups, migration-sensitive health indicators need to be developed and implemented respectively.

Two major steps need to be taken in order to pave the way for migration-sensitive health and cancer research. Firstly, aiming at global comparisons, consistent definitions and identification methods in health (and cancer registration) data need to be pointed out and implemented. Secondly, by evaluating existing/recommended health indicators (in the cancer setting), ways to integrate migration-specific components and to conduct migration-sensitive cancer research are being suggested, also drawing attention to specific biases that may occur in migrant studies. Lastly, an overall bottom line of the both challenging and promising implementation of migration-sensitive health indicators is being delineated.

Ethnicity is a social construct, referring to one's sense of identity in a cultural group or society that is sometimes hard to grasp. Unlike race, ethnicity is not restricted to phenotypes and is motivated by sharing certain views, lifestyles and cultural habits. Migrants often represent ethnic minority groups in their countries of residence and share cultural identities as well as common ideals and goals. Due to their various origins, migrant groups are often characterized by a high degree of heterogeneity which makes their adequate identification and consideration in research even more challenging. Not only the lack of consistent definitions of the migrant status, but also often missing information in most routine data sources emphasize the necessity of changing practice. Migration and cultural diversity is gaining social importance and therefore makes monitoring culturally diverse health care needs indispensible in order to ensure the supply of high quality and appropriate health care.(5)

Different concepts of ethnicity, race and migration inevitably lead to different research angles and also have an impact on how to acquire and analyse data respectively. Whereas race is mostly used to investigate the association between genetic differences and outcomes, the concept of a migration background is often applied in the course of etiologic research questions. Ethnicity on the other hand is more related to disease perception and health behaviours. Nevertheless, most countries have their own tradition of collecting the one or the other and researchers are often forced to work with what they get.

Yet, the most accepted ways of identifying and describing a migration background are to collect data on (self-assigned) ethnicity or country of birth, which also has its pitfalls but is – according to the MEHO project (see chapter 3.2) – considered exemplary. Alternatively, other ethnicity proxies such as nationality, name, religion, parental country of birth or ethnicity assigned by another person (e.g. by the doctor) can be applied to take culturally related aspects into account. The latter approaches are – again, based on our survey – considered less than exemplary and are often used when other information on ethnicity is missing.

Ethnicity (self-assigned)

Using self-assigned ethnicity as the defining indicator represents the most valid way of investigating the impact of ethnicity on health. Its concept emphasises the common sense of identity and allows conclusions regarding cultural and lifestyle-related factors.

However, this approach is also coupled with limitations that mainly refer to the test-retest reliability. Self-perceived ethnicity may vary over time and may be dependent on

the level of integration in the host country. In addition, the assessment of this variable may be extremely challenging: whether to use predefined categories or an open question is dependent on the study question and the degree of heterogeneity that is aimed at. Furthermore, the exact wording of a question on ethnic identification is essential for the reliability of the answers. It is also important to take multiple generations of migrants into consideration. A migrant background may go far back in time and generation assignment may not always be possible. Defining migrants on the basis of their self-perceived ethnicity is exemplary and an already adopted method in some countries (e.g. the United Kingdom), although it can sometimes be difficult to grasp and may range from biological concepts through the national origin (of the persons or ancestors to cultural affiliation. It can thus make international comparisons challenging (2, 5-6).

Country of birth (own or parental)
The usage of country of birth as a proxy for ethnicity is widespread and emphasises the aspect of descent or common geographical origin. It is often routinely collected for administrative purposes and therefore likely to be available in many registries. It is an objective and unchanging attribute, but remains a crude measure that does not allow for distinctions with regard to ethnic diversity within migrant groups. Many countries host more than one ethnicity: Surinamese Creoles (with descendants from West Africa) and Hindoestanen (with descendants from South Asia), two very different groups, mostly born in Suriname and of Dutch nationality, can for instance not be distinguished using the country of birth approach. The lack of heterogeneity and validity (no gold standard available) plays an important role in this case. An advantage of this approach is that migrants can clearly be distinguished from their direct offspring (sometimes called “second generation”) if the individual and parental country of birth is available. However, this method becomes inaccurate over the generations, and already the “third generation” cannot be identified using this method (as long as the country of birth of the grandparents is not available). Yet its application in research settings is simple and can be done by an outsider. It is therefore considered to be more objective and constant than self-perceived ethnicity (6-7).

Nationality
Nationality as a proxy for migrant status is probably the most simple, objectively assessable and convenient method because it is universally available and applicable. It is though a very crude measure, and in many countries it is not reliable anymore. Nationality is a characteristic that may change over time (uptake of citizenship of host country, marriage, etc), and it has only a weak link to the ethnic background. Since the legislation to obtain a new nationality is different between countries, the comparability of data can be problematic. Moreover, many people originating from former European colonies hold European citizenships, but have different ethnic origins. Also, the rate of naturalization among former labour migrants is increasing. All these issues make nationality a crude proxy for ethnicity, although it is in many countries the only available identifier.

Name
Name-based approaches are can be applied needing no other information but names and have for instance been used for Turks in Germany (8-9) and South Asians in the United Kingdom (10). It is only feasible with a limited number of migrant groups and does not provide any information regarding actual migration, generation and ethnic identity. Using this method, identification of migrants is carried out based on a set of family and first names that need to be distinct and unique for the country of origin.

For example, Turkish names (in Turkey) usually have a meaning in the Turkish language and are free of religious content. They can therefore easily be distinguished from Arabic names (9). After a automatic part of the applied algorithm, experts need to be involved in the analysis in order to verify the results. However, this method slowly loses its validity due to intercultural marriages, increasing naturalization and rapidly growing ethnic diversity that cannot be appreciated by using the name as an ethnicity proxy. Data privacy regulations may also inhibit this method since very sensitive information in clear text is needed to for the conduct.

Other (additional) indicators
Other common proxies for ethnicity are religion, language spoken, migration history and ethnicity assigned by another person. However, these most often serve as additional discrimination factors in order to compensate for the limitations of other identifiers or to improve their validity respectively. Spoken language can for example be used in order to amend the country of birth identifier and thus to improve the way of appropriately capturing a complex migration background.

Which approach to chose is mostly based on the availability of data and the actual research question respectively. For this reason, it is highly context- and country-dependent when it comes to the use of an identifier variable for migration and its validity. Prospectively, in order to achieve comparability and to allow for cross-country analyses, it is important to implement comprehensive, exemplary and unique identifiers, such as a standardized definition of ethnicity or consistent usage of country of birth.

Health quality indicators in cancer research
In order to increase and ensure accessibility and quality of cancer care, irrespective of socioeconomic position or ethnic background, effective health information and monitoring are essential. Several organisations acting on the European and international level are dedicated to systematic data gathering, analysis, interpretation and dissemination, eventually being shared for evidence-based health policies and in order to develop comparative health information.
Standardized health indicators are vital for national as well as international comparisons and may explain cross-country variations in outcomes. Health indicators are based on (future) needs and aims and are mostly defined on what is available in the specific country. After drafting a long-term framework and developing country-specific implementation plans, evidence-based measures can be launched.
ECHIM (European Community Health Indicators and Monitoring), a project initiated by the European Commission, built on the work of ECHI (European Community Health Indicators), aims at helping countries to implement, collect and disseminate health indicators, based on the ECHI shortlist of 88 indicators. In cancer research, important indicators that reflect quality of care have been developed in the course of various projects. Most prominent, apart from those of ECHIM, are the Health Care Quality Indicators (HCQI) by the Organisation for Economic Co-operation and Development (OECD) and the European Cancer Health Indicator Project (EUROCHIP). **Table 1** provides an overview of all health quality indicators in cancer research recommended and developed during the course of the above mentioned projects. Furthermore, migration-related research questions underline the relevance of each indicator. Promoting the comprehensive collection of these indicators is the basis for developing ways to involve migration-sensitive components.
Conducting migration-sensitive cancer research

Most cancer registries do not routinely collect data on ethnicity or they have insufficient completeness of this variable. This has also been confirmed by the MEHO survey (see chapter 3.2). But even if migrant-sensitive data is not directly available in the registries, other methods can be applied to conduct migrant-sensitive research such as linkage procedures given that (a proxy of) ethnicity is included in other databases (like population data from statistical offices or medical records) or by using name based approaches. In order to be able to analyse health quality indicators in a migration-sensitive setting, the following steps help exploring ways for their implementation. How to construct the numerator (identifying migrants)

The numerator comprises (incident) cancer cases according to sex, age, geographical area and period. Of course, migrants need to be identified using a variable indicating ethnicity or a proxy respectively. Ways to identify migrants in cancer registry data and their validity have been discussed previously.

How to construct the denominator (choosing the reference population)

The denominator, defining the background population under risk, has to cover the same catchment area as the numerator (population or regional level) and needs to take into account the same time period. Furthermore, exactly the same definition of ethnicity needs to be applied as well as matching data quality, completeness, sensitivity and specificity of the used method. Data on the background population can in most cases be obtained from statistical offices or population registries. A common problem is that the definitions of migrant status in the numerator and in the denominator do not match.

How to merge numerator and denominator and perform migrant-specific analyses

Different methods can be applied in order to merge numerator and denominator, strongly depending on the availability, conceivableness and type of data obtained.

Direct methods

The most straight-forward way to perform migrant-specific analyses is to identify migrants directly in the data of the cancer registry (nominator) and to acquire data on the background population (denominator) based on the same definitions and categories. This simple record linkage is possible for instance on the basis of names, date of birth or even more convenient using a personal identifier or health service number that has already been introduced in some countries.

Indirect methods: linkage

Technically more complex options are linkage procedures that can be applied if no information on ethnicity is available in cancer registry data. Given that ethnicity is included in other databases such as population census data, data from general register offices or (cause of) death databases, these records can be linked to health data (like hospital discharge or cancer registry data) using probability matching procedures. An advantage is the availability of a personalised identifier like the Community Health Index (CHI) in Scotland (11) or the Citizen Service Number (CSN) that has been introduced in the Netherlands and is obligatory as well as unique for every person making use of the national health care system. Using this approach, anonymised data merging can be achieved by applying data encryption methods. In a recent study, Bhopal and colleagues (12) successfully demonstrated that linking databases can provide solid migration-sensitive cancer data without recourse to cohort studies. Furthermore, this method is in principal internationally applicable, although data privacy regulations may vary and always deserve strict adherence.

Indirect methods: name-based approaches

An additional indirect method to conduct migrant-sensitive analyses are name-based

Table 1 Health quality indicators in cancer research

Indicator	Suggested by	Description
Cancer mortality (rates, trends, projections, person-years-of-life-lost)	ECHIM, HCQI, EUROCHIP	All-cancer mortality and mortality of the most important cancers (breast, cervical, colon, lung and prostate cancer), per 100.000 population, in a given year (crude and age-standardized). Calculated as the number of patients that died of cancer during the given calendar year divided by person-years at risk (stratified by sex, geographical area, period and age group).
Cancer incidence (rates, trends and projections)	ECHIM item 20, EUROCHIP	Corresponds to the all-cancer incidence and incidence of the most important cancers (per 100.000 persons) in a given year. The numerator is the number of patients with newly diagnosed cancer during the given calendar year, divided by the denominator (background population), person-years at risk (per sex, geographical area, period and age group), expressed as per 100.000 population.
Breast, cervical, colorectal cancer screening	ECHIM items 58-60, HCQI	Proportion of persons in the screening age group (breast cancer: 50-69; cervical cancer: 20-69; colorectal cancer: 50-74) reporting to have undergone a cancer screening test within the past two (breast and colorectal cancer) or three (cervical cancer) years.
Cancer (relative) survival rates (breast, cervix, colorectal)	ECHIM item 78, HCQI, EUROCHIP	Relative cancer survival corresponds to the proportion of patients who survive at least five years after diagnosis, after correction for background mortality.
Cancer treatment quality	ECHIM item 83, EUROCHIP	Compliance with best oncology practice
Stage at cancer diagnosis	EUROCHIP	Extension of tumour at diagnosis, usually indicated with clinical and pathological TNM status. Percentage of cases with early diagnosis and cases with a metastatic test.
Palliative cancer therapy	EUROCHIP	Use of morphine in cancer patients, percentage of patients receiving palliative radiotherapy
Cancer treatment delay	EUROCHIP	The average time (in days) between the date of first treatment and the pre-diagnostic date, by cancer site (breast, colon and rectal cancer).
Coverage/ completeness of cancer registration	EUROCHIP	Population covered by high quality cancer registries

Data source(s)	Migration–related research questions
Population-based cancer and cause of death registries; secondary data sources (GLOBOCAN)	Do cancer mortality patterns differ between migrants and non-migrants? Are there changes over time/ across migrant generations?
Population-based cancer registries; secondary data sources (GLOBOCAN)	Is there a difference in underlying risk factor patterns that causes disparities in cancer incidence? Are there changes over time/across migrant generations?
EUROSTAT and OECD (available every five years)	Does uptake/attendance of preventive measures differ between migrant and indigenous populations? What are the main problems/barriers?
EUROCARE, cancer registries (delay of 2-5 yrs)	Does survival differ between migrants and non-migrants? Which factors play a role?
Hospitals	Are migrants treated differently and does that have an impact on their survival/mortality?
Population-based cancer registries	Is there a difference at stage at diagnosis, resulting in differences in mortality/survival?
Hospitals	Do therapy measures differ?
Cancer registries – still to be developed.	Is there a difference in the time span between actions/ treatments in migrants and non-migrants (possibly resulting in differences in mortality/survival)?
IARC	How complete is the registration of variables needed to identify migrant populations?

approaches where the same procedure of identifying migrants is applied to both the numerator (cancer registry data) and the denominator population (reference population). This has for instance been performed in Germany (13), the Netherlands (14) and the United Kingdom (15-16).

Numerator-only migrant-specific analyses
Alternatively, given that linkage is not feasible or possible, numerator-only based analyses/measures can be used to perform migrant-specific analyses. Options are for example Proportional Cancer Incidence Ratios (PCIR) (17-19) or calculating relative survival using the corresponding background mortality (life tables) (20).

Bias in migrant studies on cancer

Identification methods
The method of identifying migrants can lead to substantial bias with regard to ethnic identity and variations within migrant groups. Country of birth, the currently most accepted proxy for ethnicity (7), does not address these issues and can therefore lead to considerable misclassifications as well as underestimations of mortality differences. Ideally, risk variations within migrant groups can be taken into account by stratification for additional culturally-related factors such as mother tongue and exact birth place. In some cases, adjustments for socioeconomic position may also help distinguishing certain groups. (21-22) In this context, one should also give special attention to matching numerator and denominator figures when identifying migrant groups. It is essential that migrant status is defined in an identical manner in both cases and reference population
Selection effects
Migrants are often likely to be a non-random, self-selected group of the population of their country of origin (23). This can for instance be reflected in particular (limited) geographical areas of origin or certain cultural or social groups with own distinctive cancer patterns (6). Seeking a new life requires energy and resources, leading to selective migration of particularly healthy individuals and resulting in favorable health outcomes in the new host country. This health selection effect (healthy migrant effect), accountable for an initial advantage in health, only affects first generation migrants from specific countries (primarily low-income countries) and has been reported to decrease over time (24). Work-related selection (healthy worker effect) might be another explanation for lower incidence and mortality figures (25).
In studies, this bias can be explored by investigating cancer risk according to duration of stay in the host country and taking into account age at migration. Significant changes in cancer risk between the population of the host country and recent migrant groups may be precipitated by this form of bias. Yet, it can be questionable how strong the healthy migrant effect is, because most migrants migrate at an age at which symptoms of the major causes of death/ chronic conditions are rarely present. (6)
A second important selection effect concerns the selective remigration of a diseased or unhealthy subgroup of migrants, leaving a healthier selection of their population in the host country. This so called salmon bias assumes that migrant groups are more likely to return to their country of origin when they become elderly or chronically ill and therefore quantifies the impact of deaths abroad. This often unregistered remigration leads to inaccurate denominator figures, resulting in a seemingly better survival and lower mortality of migrants in the host country (25-27).
However, there is evidence for remaining health and mortality advantages after accounting for the above mentioned selection effects, remaining a paradox but pointing to the concept of health transition (28). As migrants from less developed regions migrate

to more affluent countries, they retain the disease risk patterns typical for their country of origin, where infectious diseases often still dominate and chronic conditions such as cancer are only slowly in the ascendant. It may therefore take many years till mortality patterns diverge towards those of the population of the host country respectively. (29)

Social and behavioral factors (confounding)

In the United States, ethnicity is often used as a socioeconomic indicator, whereas in other countries, socioeconomic circumstances are used to approximate ethnicity. The problems of these approaches are obvious and the need to analyze ethnicity and socioeconomic position as separate variables in health studies has been recognized (30). Socioeconomic position is a strong determinant for cancer risk and can also potentially explain some aspects of ethnic variation in cancer risk. A certain degree of interaction between low socioeconomic status (SES) and ethnicity has been proven (migrants tend to be socially disadvantaged in the host country), but what exactly the separate effect of ethnicity on cancer risk is, often remains unclear. SES is often taken into account using ecological measures which are sometimes limited with regard to their validity for all ethnic groups. Some studies found that the size of socioeconomic inequalities varies between ethnic groups, but that socioeconomic differences are larger in the population of the host country (22, 30). SES should thus – if possible – be included as an important covariable in any analysis. In any case, one should be aware and carefully distinguish ethnic and socioeconomic inequalities and find a way to disentangle the two concepts.

Differences in cancer risk may also partly be attributable to ethnic variation with respect to social support and social gradients in behavioral risk factor patterns. Social support can in some ethnic groups be a key factor, determining socioeconomic disparities within ethnic groups. High levels of support, e.g. close family ties and strong group cohesions, may partly avert adverse effects of a low socioeconomic background.

Lifestyle and behavioral risk factors may persist or change over time. Migration especially entails completely new, compelling exposures, often leading to an adoption of unhealthy Western lifestyles in migrant groups. The currently high prevalence of smokers among mainly male migrants residing in more affluent countries for instance reflects their tendency to adopt behavior common in the host country. (31)

Migrants tend to settle in certain (often urban) areas. It thus needs to be considered carefully which comparisons between migrants and the population of the host country are appropriate and most reasonable.

Many cancer registries already routinely collect a broad range of demographic variables that can also be considered important determinants (confounders) in migration-sensitive cancer research (e.g. date of diagnosis/death, marital status, place of residence, ethnic group/ country of birth, occupation, SES). Nevertheless, data on behavioral patterns is often missing or incomplete.

Data quality

There is often considerable disparity between countries in the accuracy of the coded underlying cause of death (differences in access to diagnosis facilities, manners of completing and coding death certificates, etc.) and often also in the quality, completeness and coverage of cancer registry data.

When including data from the migrants' country of origin and conducting comparisons with the host country, differences in the ascertainment of some cancers, especially those with diagnostic difficulties, can be even more grave. It can lead to a so called "overshoot", a phenomenon giving rise to higher rates in migrants compared with the host country, but lower rates compared with the country of origin. Furthermore, rates in the host country can be influenced by the detection of asymptomatic cancers during screening, surgery or autopsy. (6)

The quality of cancer registry data can be assessed by comparing certain indices e.g. proportions of deaths certified with non-specific causes, cancer deaths at ill-defined sites and other traditional quality indicators (e.g. percentage histologically verified, death-certificate-only cases or the ratio of mortality to incidence) (32).

Country Reports

After having conducted the survey among all European cancer registries, in-depth reports for five European countries were written in close collaboration with local experts from every country. Every country report contained a description of the specific situation with regard to (i) cancer registration, (ii) conducted studies on cancer among migrant populations, (iii) possibilities of analysing routine data or conducting dedicated studies on the cancer risks of migrants and (iv) factors impeding the implementation of routine migrant specific analyses. These findings enabled us to derive conclusions with regard to the present situation of migrant-specific cancer registration in Europe (as a whole) and its future potentials and role.

Germany, The Netherlands and Sweden are typical immigration countries with more than 10% of the entire population having some kind of migration background and a large fraction of migrant from non-Western countries such as Turkey, Morocco, the Caribbean, Eastern Europe, the Middle East. Given those facts, one should actually assume some degree of adaptation of (health) data acquisition procedures to a changing composition of societies with changing needs and expectations. In cancer registration, The Netherlands and Sweden have adapted most with regard to the relevance and importance of migration-sensitive data collection, being evident in sophisticated data gathering, linkage and targeted utilization for scientific purposes. This requires highly developed technical solutions and funds allowing for the inclusion of migration-sensitive variables in the course of routine analyses as well as the handling of directed research questions. However, lacking or incomplete information on ethnicity, especially in respect of the limitations accompanied by the use of country of birth as identification method for migrants, still appears to be a barrier.

The Netherlands introduced unique personal identification numbers in their health care systems, in order to facilitate networking and linkage. This procedure promises further analysis options in future and would also lead to a high degree of completeness in data. Due to a region-based cancer registration (at the cost of lacking data comparability between the federal states) and no migrant identification options in official longitudinal population or health data in Germany, research on cancer in migrants is only possible in very limited and laborious ways, e.g. by means of name-based approaches or historical cohorts. In addition, often insufficiently clarified data protection regulations prevail.

In Finland, migrants represent only a small fraction of the population and mainly originate from Russia and Estonia. Although country of birth, citizenship and spoken language are included in population data, the cancer registry does not routinely collect those variables. The assumed small number of cancer cases at a rather high expenditure of costs and time, does not seem to counterbalance the value that could be achieved with introducing such research and for instance the inclusion of country of birth in cancer registry data. However, also data linkage procedures using the personal identity code (PID), automatically assigned to every Finnish citizen, promise further options for conducting migration-sensitive cancer (and health) research in future.

Scotland also only hosts a relatively small number of migrants most often coming from Western countries as well as South Asian origins. The Scottish population census is being conducted on a decadal basis and includes a categorization of ethnic group. Scottish cancer registry data principally also include ethnic group, whereas the exact distinction of groups may vary between cancer and population data due to inconsistent coding. To

overcome those difficulties, an attempt has been made using the personal identification number (PIN), facilitating linkage procedures and making all kinds of migration-sensitive analyses possible. A summary of all findings is presented in **table 2**.

Migration-sensitive cancer registration: Main challenges

One of the major challenges in the conduct of migration-sensitive cancer research is the definition and identification of migrant groups as migrant background or ethnicity is a social construct that is hard to grasp. The understanding of "migrants" or "ethnic minority groups" can however vary strongly between countries, in each case associated to the history, dimension and cognition of migration in research and public respectively. This makes it difficult to develop and implement a uniform definition for all European countries. Furthermore, ethnologic and epidemiologic views on the concept "migration" or "culture" can deviate from each other in a sense that in most instances the chosen definition to identify migrants in population-based migration research is based on variables in routine health data that already exist, rather than on the most comprehensive concept for migrant status. The latter often require disproportional effort (new data gathering, setup of studies) while being very specific with regard to characteristics of certain migrant groups in the (restricted) catchment area of the cancer registry respectively and are thus often not applicable using routine data. At present, the most accepted concept for identification of migrants is country of birth, when applicable refined with more profound/detailed variables such as religion or spoken language, allowing for clear demarcations on the one hand, but lacking the possibility to make distinctions regarding ethnic diversity within migrant groups and to identify the offspring of migrants.

A further challenge is the development and implementation of migration-sensitive health (cancer) indicators. They can be seen as a valuable method to provide important insights into existing cancer disparities just like into differences in underlying risk factor patterns and possible starting points for public health and prevention strategies. Yet, as we also found in our survey, routine data sources and cancer registries may not include a person's ethnicity or country of birth at all. When direct methods to perform migration-sensitive analyses (migrants are equally identified in both numerator – cancer registry data – and denominator – the reference population –) are hence not possible, indirect methods (based on linkage procedures) can serve as good alternatives although they involve quite some technical effort and may be impeded in connection with data privacy regulations that demand strict adherence. Linkage procedures require a proxy of ethnicity in any population-based data source (e.g. population census data or data from statistical offices) and can be applied either based on probability matching or personalized identifiers used in some countries.

Migrant studies are often subject to specific biases that should always be taken into account when conducting research in this field. Most prominent are biases with regard to selection effects ("healthy migrant effect", "salmon bias"), identification methods (as discussed above) and confounding effects (especially the effects of socioeconomic circumstances and their interaction with migrant status). Furthermore, differences in data quality between countries (e.g. disparities in the coding of causes of death, availability/implementation of cancer screening and diagnostic procedures) can lead to considerable bias.

Table 2 Migration-sensitive cancer registration in selected European countries

Country	(1) Migrants in general population, (2) largest migrant groups	Indicators available in (1) Population data, (2) Cancer registry data
Finland: Finnish Cancer Registry (population-based, national level)	(1) 4.4% (foreign country of birth) (2) Russia, Estonia	(1) Country of birth, Citizenship, Language (2) None
Germany: Regional registries (all 16 federal states covered in 2011, completeness fits international standards in 14 federal states)	(1) ~20% (migration background) (2) Eastern Europe (re-settlers), South and South Eastern Europe (Turkey)	(1) None (Country of birth in Mikrocensus data) (2) None
Netherlands: Netherlands Cancer Registry (population-based, national level)	(1) 19.5% (foreign background) (2) Turkey, Morocco, Western Europe, Suriname, Netherlands Antilles, Indonesia	(1) Country of birth (2) Country of birth
Scotland: Scottish Cancer Registry (population-based, national level)	(1) 3.8% (foreign country of birth) (2) UK, US, Western Europe, Pakistan, India, Bangladesh, China	(1) Ethnic group (category classification, predefined in Scottish census) (2) Ethnic group (classification varies)
Sweden: Swedish Cancer Register (population-based, national level)	(1) 13.8% (foreign country of birth) (2) Europe (mostly Scandinavia), Iraq, Iran, Former Yugoslavia, Poland	(1) Country of birth, foreign background (2) None.

* latest data available, CHI = Community Health Index; CR = Cancer Registry/Registration; CSN = Citizen

Routine analyses? Studies on cancer in migrants (key references)	Main barriers	Current/Future Potentials
No. Using linkage procedures [22]	Time consuming permission procedures Costs of additional data extraction Small number of cancer cases among migrants	Data linkage through personal identity code PID Inclusion of country of origin in CR data
No. Using a name-based approach to identify Turkish cancer cases (13, 17-18) Setting up a historical cohort of resettlers from the FSU (33-34)	Data protection not officially clarified German history (prosecution of ethnic minorities) Organisation of CRs on federal state level by federal state law (lacking data comparability) Lacking of migrant indicators in population data	Indirect methods (e.g. name-based approaches) Numerator-only analyses Data linkage procedures
No. Using linkage procedures (24, 26, 35)	No resources for routine analyses Lacking completeness of country of birth variable in incidence analyses	Introduction of citizen service number (CSN) will facilitate linkage
No. Using name-based approaches for migrants from India, Pakistan and China (36-38) First attempts using linkage with CHI (11-12)	Existing data often incomplete Inconsistent coding of ethnic groups between data sources Only small ethnic minority groups	Linkage procedures using CHI are promising and can in future overcome most barriers
Yes. Using the Health and Migration Cohort (39-41) Using the Family-Cancer Database (42-46)	Lack of information on ethnicity (variation within the same country of origin) Technical solutions are still under development	PIN facilitates linkage of registers and enables all kinds of analyses (incidence, mortality, survival) and covariates (e.g. SES)

Service Number; FSU = Former Soviet Union; PID/PIN = Personal Identity/ Identification Number

Recommendations for the next steps towards a migration-sensitive cancer registration

In this work, we identified barriers as well as potentials of migration-sensitive cancer registration in Europe. We demonstrated the challenges related to migration-sensitive cancer registration when it comes to the identification of migrants, the integration of migration-sensitive components into existing health indicators as well as the conduct of analyses with possible threats to validity due to biases that may emerge and need to be kept in mind. Furthermore, ways to overcome those difficulties by selecting alternative approaches or making use of (new) linkage options were presented and have already exemplarily been implemented in some European countries. In summary, migration-sensitive cancer registration and monitoring is at different stages in different European countries. Its implementation is highly dependent on the (i) national context, (ii) the relevance of migrant groups within a country, (iii) the availability of corresponding resources as well as (iv) the backup from politics. Most importantly and in view of an increasing culturally diverse European society, the necessity for migration-sensitive cancer registration first of all deserves awareness on various levels. Existing heterogeneities in data infrastructure between and within countries require some overlap, i.e. a minimal set of consistent definitions and indicators in order to ensure a certain degree of data comparability. Until the implementation of routine monitoring, a essential prerequisite is to perform additional research and analytical studies in terms of within and cross-country analyses to study the feasibility and problems of migrations-sensitive cancer registration across Europe. Furthermore, results from such research can help gain further insight into explanations for different cancer patterns and give rise to directed prevention strategies in ethnic minority groups. On this account, migration-sensitive health research needs to be vitalized and augmented by intensive networking between (and sometimes firstly even within) countries in future.

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3

Cancer risk diversity in non-Western migrants in Europe: An overview of the literature

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Abstract

Background: Cancer risk varies geographically and across ethnic groups that can be monitored in cancer control to respond to observed trends as well as ensure appropriate health care. The study of cancer risk in immigrant populations has great potential to contribute new insights into aetiology, diagnosis and treatment of cancer. Disparities in cancer risk patterns between immigrant and autochthonous populations have been reported many times, but up to now studies have been heterogeneous and may be discordant in their findings.
The aim of this overview was to compile and compare studies on cancer occurrence in migrant populations from non-western countries residing in Western Europe in order to reflect current knowledge in this field and to appeal for further research and culturally sensitive prevention strategies.

Methods: We included 37 studies published in the English language between 1990 and April 2010 focussing on cancer in adult migrants from non-western countries, living in the industrialised countries of the European Union. Migrants were defined based on their country of birth, ethnicity and name-based approaches.We conducted a between-country comparison of age-adjusted cancer incidence and mortality in immigrant populations with those in autochthonous populations.

Findings: Across the board migrants from non-western countries showed a more favourable all-cancer morbidity and mortality compared with native populations of European host countries, but with considerable site-specific risk diversity: Migrants from non-western countries were more prone to cancers that are related to infections experienced in early life, such as liver, cervical and stomach cancer. In contrast, migrants of non-western origin were less likely to suffer from cancers related to a western lifestyle, e.g. colorectal, breast and prostate cancer.

Discussion: Confirming the great cancer risk diversity in non-western migrants in and between different European countries, this overview reaffirms the importance of exposures experienced during life course (before, during and after migration) for carcinogenesis. Culturally sensitive cancer prevention programmes should focus on individual risk patterns and specific health care needs. Therefore, continuously changing environments and subsequently changing risks in both migrant and autochthonous populations need to be observed carefully in the future.

Background

Studies on cancer risk in migrant populations have recently gained increased recognition, but still have rather heterogeneous study populations and methods applied. However, insights into risk diversity deduced from such studies contribute to our understanding of carcinogenesis and might help answer unclear aetiology questions.

Migration has become an important phenomenon in Western Europe in terms of population changes and the composition of society during the past decades. In 2005, Western and Central Europe hosted 44.1 million migrants, defined as foreign-born persons. (1) Many of them originate from non-western countries, seeking social security, employment opportunities and a better future. European societies characterised by an increasing degree of heterogeneity pose major challenges to health care systems and policies. Evidence-based research is therefore a prerequisite for appropriate and individual health care of high quality and effectiveness as well as the implementation of culturally sensitive measures of prevention.(2,3)

Health is closely related to global movements. The transition of disease and risk patterns over time and across countries have been the scope of many epidemiological research questions. Accordingly, infectious diseases become less important as populations advance in terms of westernisation and the role of chronic health conditions, such as cancer and cardio-vascular diseases, becomes predominant.(4) Hence,migrants fromnon-western countries are equipped with a unique constellation of risk factors that are determined by exposure and disease patterns experienced in both their home as well as their host country. (5,6) This sudden change in the stage of epidemiological transition as well as environmental determinants has a major impact on an individual's lifetime disease risk. Many theories have been developed to explain differences in mortality and morbidity between migrants and the population of their host andhomecountries, respectively, one of them being the healthymigrant effect. Thus, migrants are subject to selection processes that initially underlie good physical and mental health. Those health advantages after migration are thought likely to disappear with advancing duration of residence and generations. As suggested in some studies, no evidence of quickly diminishing health advantages could be observed, challenging this concept and allowingroomfor other explanations.(7) Nonetheless, the change in risk patterns over time is of special interest in epidemiological research. Multi-causality and geographical variation make cancer in migrant populations highly suitable for research, especially in cancerswhose main causes are still not attributable to either environmental('nurturecomponents') orgenetic ('naturecomponents') risk factors.(8) In this context, the individual life course and particularly early life experiences (as the first step in carcinogenesis) have a great impact and play a major role in the effects of exposure and their association with cancer risks.(9,10) Investigating the occurrence of cancer in migrant populations may allow for a better understanding of cancer aetiology and of biological factors that can be integrated into prevention and treatment programmes.

The purpose of this article is to compile and compare results from studies conducted all over Europe dealing with cancer in non-western migrant populations. The resulting overview can serve as a guide, reflecting the present state of knowledge in this field, and as an appeal for further research and prevention.

Methods

Inclusion criteria of studies

We included studies focussing mainly or partly on cancer incidence and mortality in adult migrants from non-western countries, living in the industrialised countries of the European Union, published in English between 1990 and April 2010. Studies were identified by searching pubmed and other established scientific databases in combination with the following keywords: cancer + ethnicity/ethnic minority/(im)migrant(s)/foreign(ers)/ country of birth. A further inclusion criterion was a comparison of the migrant population with the native population of the country of the study (no studies conducted within migrant populations).

Study descriptions

We identified 37 studies conducted in the following seven countries: Denmark (3), France (4), Germany (6), Spain (1), Sweden (7), The Netherlands (5) and the United Kingdom (11). In 51% of the studies (19/37) incidence data were analysed, in 41% (15/37) mortality data and in 8% (3/37) both. All studies were based on the retrospective cohort design. Owing to the heterogeneous measures of association applied in the studies, we described tendencies instead of combined rate ratios (RRs) or odds ratios (ORs) to indicate differences in risks as follows: significantly elevated, elevated, no difference, decreased and significantly decreased. Ageadjustment procedures had been carried out in all the studies included. Other covariables are listed in Table 1.

In general 70% of the studies (26/37) involved all-cancer comparisons and 24% of the studies (9/37) focused on only one specific cancer site. The most commonly investigated sites were breast (28 studies) and lung cancer (26 studies) as well as stomach and colorectal cancer (24 studies each).

Defining the migrant status, generations involved and pooling of migrant origins

The indicator for defining the migrant population under study ranged from country of birth (of the patient or in combination with the parental country of birth) in 73% (27/37), name-based approaches in 14% (5/37), (self-assigned) ethnicity in 11% (4/37) and a combination in one study. The applied indicator or proxy for ethnicity is highly dependent on the availability and completeness of potential variables in the particular host country. However, country of birth is the most widely used and accepted proxy although it has some validity limitations with regard to cultural and ethnic identity.(11*)*

Only one study focused entirely on second-generation migrants (12) (based on the patient's own and parental country of birth) and two other studies included this group explicitly in addition to first-generation migrants.(13,14) Seven studies included descendants indirectly, owing to the method used for identifying migrants. (15–21) For instance, the name-based approach does not allow a distinction between generations, which can only be estimated vaguely based on age. There were 27 studies that were aimed at first-generation migrants only.

For reasons of clarity, migrant origins have been pooled into the following categories: Eastern Europe [Former Soviet Union (FSU), Russia], Africa (North,West and East Africa), Middle East (most frequently referring to Iran, Iraq and adjacent countries), Southern Europe/Turkey, Asia [divided into general Asia (mostly China and Vietnam) and South Asia (including India, Bangladesh, Indonesia, Ceylon and Pakistan)] and Southern and

Central America. Owing to inconsistent definitions between the studies, some overlap cannot be excluded.

Applied methods
Studies investigating cancer incidence used mainly cancer registry data (21/37). Studies assessing cancer mortality drew mostly on vital statistics such as mortality or cause of death registries and databases or surveys (17/37). Population data were obtained from population registers/statistical bureaux (17/37), census data (13/37) – which were primarily used in studies from France and the United Kingdom (UK) – or a population sample (7/37). Most studies were population-/registry-based. In many studies linkage procedures had been performed using a unique identifier such as the 'Personal Identity Number' in Sweden and the 'National Health Service (NHS) number' in the UK. Two studies used numerator-only analyses. Some studies adjusted for a socioeconomic proxy and also took important covariables such as duration of stay, age at immigration and calendar year into account. Table 1 summarises the methodological features, explanations and limitations of the studies included.

Findings

Table 2 provides an overview of all findings according to country of study, population of interest and cancer site, expressed in tendencies. The all-cancer comparison of most studies showed in particular on average a lower cancer risk for first-generation migrants from non-western countries in terms of incidence and mortality, although there were some studies that did not reveal significant differences, sometimes obviously due to small study cohorts. However, male subjects originating from West Africa exhibited significantly elevated cancer mortality in two studies from the United Kingdom.22,23 Ambiguous results were attained for migrants from Eastern Europe: Many studies revealed advantageous risks, although in several cases they were not significant.
Since all-cancer morbidity reflects a summary of site-specific results, the aim is to point out cancers with significantly elevated or lowered risks among migrants and to investigate these results according to migrant origin.

Migrants from Southern Europe
In 35% of all studies (13/37) included from five different countries, migrants from Southern Europe, mostly Turkey, were investigated. According to these studies, all malignant neoplasms together tended to occur significantly less often in this group compared with the general population of the host country.
Significantly elevated risks for this migrant group could be observed for cancers of the stomach, liver, lung among males and thyroid gland. In addition, increased risks were reported for Hodgkin's disease and lymphomas. In contrast, significantly lower risks were found for cancers of the oesophagus, colorectum, lung among females, skin, breast, prostate and testis and bladder.

Table 1 Methodological features of the studies included

Country, authors and year of study		Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
Denmark	Myrup et al. 2008 (13)	The aetiology of testicular cancer risk	Study population: civil registration system linked to Danish Cancer Registry through unique personal identification number (population-based)	1968–2003	Incidence RR (Age, calendar year, parental birthplace, duration of stay, age at immigration)	Males born between 1930 and 2003; residents of Denmark between 2nd April 1968 and 31st December 2003, born between 1st January 1930 and 31st December 2003; known place of birth; exclusion of individuals born in Greenland
	Norredam et al. 2008 (29)	Differences in cancer stage at diagnosis between migrant women and native Danish women	Study population: Statistical Department at The Danish Immigration Service; linkage of civil registration numbers of the study cohort with Danish Cancer Registry (population-/registerbased cohort)	1993–1999 (cohort)/ 2002 (cases)	Incidence OR (matching procedure, age group, cancer type at first diagnosis)	Women aged 18+; migrants with residence permit as refugees or through family reunification in Denmark between 1st January 1993 and 31st December 1999; only first diagnosis cancers; only cancer types allowing categorisation of stage; exclusion criteria: missing civil registration number; duplicates; unclear or missing data on nationality
	Norredam et al. 2007 (30)	Incidence of cancer among 1st generation migrants compared with native Danes, including time trends	Statistical Department at The Danish Immigration Service; linkage of civil registration numbers of the study cohort with Danish Cancer Registry (population-/registerbased cohort)	1993–2003	Incidence RR (age, region of origin, migrant type, duration of residence)	Men and women aged 30–80; residence permit as refugees or through family reunification in Denmark between 1st January 1993 and 31st December 1999; exclusion criteria: missing civil registration number; duplicates; unclear or missing data on nationality; non-melanoma skin cancers
France	Bouchardy et al. 1996 (31)	Cancer mortality in North African migrants to France	Population data: 'Institut National de la Statistique et des Etudes Economiques' (INSEE), derived from the French 1982 census; mortality data: 'Institut National de la santé et de la recherche médicale' (INSERM)	1979–1985	Mortality RR (age, gender, social class, area of residence)	Men and women of all ages; records of deaths in resident population of France from 1979 to 1985 (provided by INSERM)
	Bouchardy et al. 1995 (32)	Cancer mortality in sub-Saharan African migrants to France	Population data: 'Institut National de la Statistique et des Etudes Economiques' (INSEE), derived from the French 1982 census; mortality data: 'Institut National de la santé et de la recherche médicale' (INSERM)	1979–1985	Mortality RR (age, gender, social class, area of residence)	Men and women of all ages; records of deaths in resident population of France from 1979 to 1985 (provided by INSERM)
	Khlat 1995 (33)	The cancer profile of Maghrebian and Near Eastern migrants	Two large migrant studies	1979–1991	Mortality RR (age, area of residence, social class)	Men and women of all ages; French mortality data

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Adjustments for maternal and paternal birthplace in different strata; trend analyses for duration of stay and age at immigration	(Parental) Country of birth (collected by civil registration system from index cards in municipality registration offices)	Men born in Denmark of parents born in Denmark	Cohort: n = 2,109,459 Cancer cases in cohort: n = 4216 (1st generation migrants: n = 166 (3.9%), 2nd generation migrants: n = 13 (0.3%)	Early environmental exposures/period in uteri; salmon bias	Small number of cases in second-generation immigrants
1:6 matching on age and sex on population level; 1:4 matching on an individual level on age and sex through a random sampling procedure; comparison of local with non-local stages of tumours; migrant status as proxy for pre- and post-migration circumstances	Nationality according to WHO's classification system	Danish-born residents with Danish-born parents (identified through Statistics DK)	Study cohort: Cases (1st generation Migrants) n = 62461; Controls (Danish-born) n = 249,839; Cancer cohort: Cases n = 269; Controls n = 1608	Differences in tumour biology between migrants and host populations; barriers in access to healthcare (language, culture, health care system); poor screening uptake; salmon bias	Small number of cases; high number of cases with unknown stage; nationality as poor socio-cultural proxy of ethnicity; no SES adjustments possible
1:6 matching on age and sex upon arrival in Denmark and 1:4 matching on an individual level on age and sex through a random sampling procedure in the study cohort; migrant status as proxy for pre- and post-migration circumstances	Nationality according to WHO's classification system	Danish-born residents with Danish-born parents (identified through Statistics DK)	Study cohort: cases (1st generation migrants) n = 62461; controls (Danish-born) n = 249,899; Cancer Cases n = 3366 (16% migrants	Lifestyle patterns (breast and colorectal cancer), smoking; decline in incidence over time in migrant women related to increased cancer diagnostic activities such as screening and better access to healthcare services	Small number of cases; no SES adjustments possible; trend analysis irrespective of duration of stay which may dilute effects
Stratified analyses by socioeconomic subgroup	Country of birth	Individuals born in metropolitan France (native French)	Cancer deaths among migrants: n = 27,352 (3.4% of all cancer deaths)	Return of ill migrants to country of origin prior to death; healthy-migrant effect; lower consumption of alcohol and higher tobacco intake; dietary differences; reproductive behaviour; cultural factors related to Islam	Poor quality of French mortality data; small numbers of cancer deaths among Egyptian migrants; heterogeneity within migrant groups
Stratified analyses by socioeconomic subgroup	Country of birth	Individuals born in metropolitan France (native French)	Migrant study population: n = 288,060; Cancer deaths among migrants: n = 1126 (0.1%)	Return of ill migrants to country of origin; healthy migrant effect; protective lifestyle factors (tobacco, alcohol consumption, lower meat/fat intake, high fibre diets); infection with hepatitis B virus during childhood/ chronic persistent hepatitis (liver cancer); Schistosoma haematobium infections (bladder cancer); Burkitt's lymphoma (NHL)	Poor data quality; heterogeneity within migrant groups
Review of studies	Country of birth	Native French population	Cancer deaths among Moroccan migrants: n = 2062	Genetic factors, diet, alcohol consumption, childbearing patterns, cultural factors, viral causes	

Table 1 (continued)

Country, authors and year of study		Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
France	Bouchardy et al. 1994 (34)	Cancer patterns in Chinese and South East Asian migrants to France	Population data: 'Institut National de la Statistique et des Etudes Economiques' (INSEE), derived from the French 1982 census; mortality data: 'Institut National de la santé et de la recherche médicale' (INSERM)	1979–1985	Mortality RR (age, gender, social class, area of residence)	Men and women of all ages; records of deaths in resident population of France from 1979 to 1985 (provided by INSERM)
Germany	Spallek et al. 2009 (16)	Cancer incidence in Turkish immigrants in Hamburg	Study cohort: Hamburg Cancer Registry; Reference population: population registry	1990–2004	Incidence RR (year of birth)	Men and women of all ages; identification of cases of Turkish origin by use of name-based algorithm
	Winkler et al. 2009 (35)	Cancer mortality and incidence in FSU migrants in Germany	Cancer mortality: sample of migrant cohort in North Rhine-Westphalia; cancer incidence: sample of migrant cohort in Saarland; Linkage with local population registries, local reception centres, Saarland Cancer Registry, NRW statistical office and local health offices	1990–2005	SMR, SIR (age, calendar year)	Cancer mortality: arrival in Germany between 1st January 1990 and 31st December 2001; aged 15+; Cancer incidence: arrival between 1990 and 2005; exclusion: missing data, cancer diagnosis in country of origin
	Ronellenfitsch et al. 2009 (36)	Stomach cancer mortality in FSU migrants in Germany	Study population: sample of migrants from FSU to German federal state North Rhine Westphalia, identified in municipal population registries; linkage with mortality data (cause of death database) through sex, dates of birth and death, last residence as identifiers (registry-based)	1990–2005	SMR (age, calendar year)	Arrival in Germany between 1st January 1990 and 31st December 2001; aged 15+; successfully identified in electronic municipal population registries
	Ott et al. 2008 (37)	Mortality of cancers of possibly infectious origin in migrants from FSU to Germany	Study population: sample of migrants from FSU to German federal state North Rhine Westphalia, identified in municipal population registries; linkage with mortality data (cause of death database) through sex, dates of birth and death, last residence as identifiers (registry-based)	1990–2005	SMR (sex, 5-year age group, calendar year, length of stay, immigration period), Mortality RR	Arrival in Germany between 1st January 1990 and 31st December 2001; aged 15+; successfully identified in electronic municipal population registries

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Computation of differences in risk between migrants using a case-control approach	Country of birth	Metropolitan-born population in France	Migrants in population data: 3.2%; Cancer deaths among migrants: n = 8708	Consumption of salted and preserved foods (nasopharyngeal cancer); genetic susceptibility; high and early exposure to infection with hepatitis-B virus and aflatoxin, chronic infection with liver flukes (liver cancer)	Poor quality of French mortality data; Small number of deaths in Chinese-born migrants
Stratification by birth cohorts to adjust for age and to investigate the life course perspective	Name-based algorithm	Representative population sample of Hamburg	Cancer cases in Turkish migrants: n = 1346	Different nutritional patterns (cancer of digestive, urinary tract and prostate); early life experiences and infections (e.g. HPV and EBV); higher smoking prevalence among Turkish males; different reproductive behaviour	Misclassification and incomplete identification cannot be ruled out due to namebased approach; small number of Turkish cases; possible underestimation due to remigration
Date of arrival approximated by passport issue date; person-year estimation using German mortality rates	Resettlers from FSU of German ethnicity	The entire population of Germany	Mortality: Study (migrant) cohort: n = 34,393, Deaths in cohort: n = 2580, Cancer deaths: n= 708; Incidence: Study (migrant) cohort: n = 18,619, Cancer cases: n = 586	Similar SIR and SMR patterns (presumably no survival differences); big impact of smoking prevalence (similar to country of origin); H. pylori prevalence (stomach cancer); alcohol consumption and hepatitis infection (liver cancer); higher birth rates (breast cancer)	Slightly different populations used for standardisation; follow-up estimation
Follow-up assurance through electronic record linkage with municipal population registries and a state cause of death database; vital status ascertainment; cause of death retrieval	Resettlers from FSU of German ethnicity	The entire population of Germany	Study (migrant) cohort: n = 34,393, deaths in cohort: n = 2580; stomach cancer deaths: n = 68	Long latency after exposure to risk factors in early life (e.g. HP infection; continuation of lifestyles and behaviours (e.g. dietary habits); change in hygiene conditions, earlier detection, better treatment options, improved access to healthcare	Restricted data availability; differences in study populations; no information on exact tumour location
Age-, sex-, cause- and calendar year specific mortality rates of the German population obtained using WHO's Mortality Database; Effect of length of residence analysis	Resettlers from FSU of German ethnicity	The entire population of Germany	Study cohort: n = 34,393, deaths in cohort: n = 2580	H. pylori and hepatitis virus infection, nutritional factors (low fruit/vegetable consumption, high intake of nitrite-containing foods), high alcohol consumption (gastric and liver cancer); living conditions; differences in health-seeking behaviour	Results not adjusted for prevalence of risk factors; only limited interpretation of results possible owing to absence of ethnicspecific mortality data in studies using administrative data

Table 1 (continued)

Country, authors and year of study		Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
Germany	Kyobutungi et al. 2006 (38)	Differences in cancer mortality between ethnic German immigrants and the native German population	Study population: sample of migrants from FSU to German federal state North Rhine Westphalia, identified in municipal population registries; linkage with mortality data (cause of death database) through sex, dates of birth and death, last residence as identifiers (registry-based)	1990–2001/ 2002	SMR (age, calendar year, arrival period), Mortality RR	Arrival in Germany between 1st January 1990 and 31st December 2001; aged 15+; successfully identified in electronic municipal population registries
	Zeeb et al. 2002 (21)	The transition in cancer mortality patterns among Turkish migrants residing in Germany	Mortality data: death registration records (former) West Germany; Incidence data: Saarland cancer registry	Incidence: 1970–1998 Mortality: 1980–1997	ASMR, PCIR (age)	Men and women aged 0–64; use of name-based approach (based on Turkish first and surnames) as proxy for ethnicity
Spain	Regidor et al. 2008 (39)	Whether mortality in immigrants in the region of Madrid differs from mortality in Spanish in-country migrants	Mortality data: mortality register; Population data: Municipal Population Register, census data (both sources provided by Madrid Institute of Statistics); unlinked study	2000–2004	Mortality RR (age, per capita income, area of residence)	Men aged 20–64
Sweden	Hemminki et al. 2010 (40)	Liver and gallbladder cancer in immigrants to Sweden	Study cohort: Swedish Family Cancer Database; linkage of administrative family register at Statistics Sweden to The Swedish Cancer Registry	1958–2006	SIR (5-year age group, sex, period)	Foreign-born men and women of all ages; primary liver cancer
	Mousavi et al. 2010 (41)	Cancer incidence in Iranian immigrants to Sweden	Study cohort: Swedish Family Cancer Database (created by linkage of administrative family register at Statistics Sweden to The Swedish Cancer Registry	1958–2006	SIR (5-year age group, sex, region, time period)	Men and women of all ages
	Mousavi et al. 2010 (42)	Nasopharyngeal and hypopharyngeal cancer risk in immigrants to Sweden	Study cohort: Swedish Family Cancer Database (created by linkage of administrative family register at Statistics Sweden to The Swedish Cancer Registry	1958–2006	SIR (5-year age group, sex, time period)	Men and women of all ages

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Age-, sex-, cause- and calendar year specific mortality rates of the German population obtained using WHO's Mortality Database; analysis of secular trends and effect of length of residence; directly standardises death rates calculated for all-cancers and lung cancer	Resettlers from FSU of German ethnicity	The entire population of Germany	Person-years of FU in migrant study cohort: n = 247,143; Cancer deaths in cohort: n = 469	Differences in risk factor distribution: smoking, alcohol consumption, diet, physical activity, reproductive history, health care utilisation, genetic factors, viral infections; cancer mortality mainly influenced by pre-migration risk factors (country of origin effect)	Assessment of current or pre-migration individual risk profiles of migrants impossible; incomplete FU for some cohort members
Time trends for ASMRs analysed in three equal intervals; missing information on ethnicity in incident denominator population remedied by calculation of PCIRs (nominator only), expected proportions obtained by use of stratified random sample of the entire registry	Nationality (mortality analysis); namebased algorithm (incidence analysis)	Native German population	Cancer deaths among migrants: n = 6054; incident cancer cases among migrants: n = 163	Potential risk factors: unfavourable living conditions in childhood, high prevalence of H. pylori infections among Turks (stomach cancer); high dietary energy intake (breast cancer); smoking trends; hepatitis B infection (liver cancer); healthy migrant effect; re-migration of ill migrants (salmon bias); lifestyle changes; socio-cultural barriers affecting uptake and quality of clinical treatment	Study restricted to persons below 65; small number of cases because of young age distribution of Turkish migrants in Germany; no generation assignment possible and subject to bias (e.g. intercultural marriages)
Per capita income estimated based on income tax returns for the year 2000, quartiles of distribution assigned to each individual based on census tract of residence	Country of birth	Spanish in-country migrants; population born in Madrid	Cancer deaths among migrants: n = 335	Healthy-migrant effect; differences in demographics; stage of smoking epidemic	Heterogeneity within migrant groups; information on population and deaths from different sources (numerator/ denominator information bias); no information on duration of residence
	Country of birth	Native Swedish population	Cancer cases in migrants: n = 1428	Chronic HBV infection, often transmitted at birth; liver fluke infections; poor living conditions; unavailability of medical care	
	Country of birth	Native Swedish population	Cancer cases in migrants: n = 1293	Environmental, reproductive and socioeconomic factors; Hepatitis infection in country of origin; smoking (bladder cancer)	
	Country of birth	Native Swedish population	Cancer cases in migrants: n = 243	EBV infection in early life; differences in smoking and dietary patterns; chewing tobacco	

Table 1 (continued)

Country, authors and year of study		Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
	Azerkan et al. 2008 (43)	Risk of invasive cervical cancer among immigrant women	Study population: Swedish Total Population Register; linkage with Swedish Cancer, cause of death and migration registers through national registration numbers	1968–2004	Incidence ASR, RR (age, calendar period, SES)	Women aged 13–79; exclusion criteria: death, emigration, history of cervical cancer before entry into cohort; missing place of birth or migration date; women older than 100 years during FU
	Moradi et al. 2008 (44)	The occurrence of thyroid cancer among Swedish residents born in Iran compared with that of Swedish-born residents	Study cohort: total Population Register held by Statistics Sweden; reference cohort: National censuses 1960–1990, longitudinal integration database for health insurance and labour market studies 1990–2003; linkage with Cancer Register through national registration number	1969–2004	Incidence RR (age, calendar year, education)	Men and women of all ages; known date of immigration, free of thyroid cancer at start of FU
	Hemminki et al. 2002 (45)	Cancer risks in adult immigrants to Sweden	Study cohort: Swedish Family Cancer Database (created by linkage of administrative family register at Statistics Sweden to The Swedish Cancer Registry); mortality data: death notification data; additional population data: national censuses of 1960, 1970, 1980 and 1990; linkage through unique technical identification number	1961–1998	SIR (5-year age group, sex, region, period, tumour type)	Adult men and women; having children born in Sweden (member of Family Database)
	Hemminki and Li 2002 (12)	Cancer risks in Sweden-born descendants of immigrants from European and North American countries	Study cohort: Swedish Family Cancer Database (created by linkage of administrative family register at Statistics Sweden to The Swedish Cancer Registry through unique technical identification number)	1961–1998	SIR (5-year age group, sex, region, period, tumour type)	Men and women aged 0–66
The Netherlands	Visser and van Leeuwen 2007 (46)	Cancer risk in first generation migrants	Population data: annual population data from Statistics Netherlands; linked with Study Cohort: Amsterdam Cancer Registry (covering the provinces North Holland and Flevoland); population-based	1995–2004	SIR (age, gender)	Men and women of all ages; primary invasive cancers; exclusion criterion: unknown country of birth

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Categorisation of migrant origins into low-, medium- and high-risk areas for cervical cancer, accounting for inter-country variations; SES obtained from 1960, 1970, 1980 and 1990 censuses, categorised into five groups; effect of duration of stay (more or less than 10 years); stratification by age at immigration	Birth regions	Swedish-born women	Cervical cancer cases: n = 19,542, Cases among migrants: n = 1991 (10.2%)	Changes in lifestyle, sexual behaviour; establishment of cervical cancer screening programmes; healthy migrant effect; persistent HPV infection or precancerous lesions before immigration	Re-migration without recording, leading to underestimation of risks; young migrant populations; higher proportion of unclassified SES among immigrants
Data on parental place of birth through linkage with multigeneration register; stratification of results by age at immigration, duration of stay and calendar year of migration (before or after 1990)	Country of birth	Native Swedish population	Incident cancer cases: n = 9826; among migrants: n = 50 (0.5%)	Exposure to environmental risk factors during early life; iodine deficiency; hyperplastic lesions of the thyroid gland	No information on prevalence of risk factors; no information on histological classification
	Country of birth	Native Swedish population	Cancer cases: n = 673,424, cancer cases among immigrants: n = 32,722 (4.9%)	Marital status; young age distribution of immigrants; tobacco consumption (lung, urinary bladder); pigmentation, behavioural differences (melanoma); reproductive histories (breast); diagnostic activity; medical services	Multiple comparison problem
Separate analysis by father's birth country,mother's birth country, for compatriot parents	Parental country of birth	Offspring of Swedish natives	Cancer cases by father's birth country: n = 3460; cancer cases by mother's birth country: n = 4473	Long-lasting environmental and heritable effects (e.g. skin pigmentation); immune response	Small number of cases; multiple comparisons
Country of birth (if possible) verified with information from national population network (e.g. screening participants)	Residents born outside the Netherlands	Native Dutch population of North Holland/ Flevoand	Cancer cases: n = 106,415; Cancer cases among migrants: n = 9271 (9%)	Exposure to infectious diseases before migration; healthy lifestyle habits protecting against cancer; genetic factors (e.g. higher prostate cancer risk in Surinamese males)	Selective (re-) migration

Table 1 (continued)

Country, authors and year of study		Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
	Stirbu et al. 2006 (14)	Differences in cancer mortality between migrants and the native Dutch population	Population data: municipal population registers; linked through personal identification numbers to mortality data: cause of death registry (population-based)	1995–2000	Mortality RR (age, sex, marital status, urbanisation level, area income)	Men and women of all ages; legal residents of the Netherlands
	Bos et al. 2004 (47)	Factors causing a higher or lower mortality in migrants compared with the native population	Population data: municipal population registers; linked through personal identification numbers to mortality data: cause of death registry (population-based)	1995–2000	Mortality RR (age, marital status, region, degree of urbanisation, SES by sex)	Men and women of all ages; legal residents of the Netherlands
	Visser et al. 2004 (48)	Breast cancer incidence in migrants in the Netherlands	Population data: annual population data obtained from Statistics Netherlands; study cohort: Amsterdam Cancer Registry and Cancer Centre West (covering the provinces North Holland and The Hague) linked to screening data	1989–1998	SIR	Women of all ages
	Visser et al. 2003 (49)	Incidence of cervical cancer in North Holland by country of birth	Population data: annual population data obtained from Statistics Netherlands; study cohort: Amsterdam Cancer Registry (covering the provinces North Holland and Flevoland)	1988–1998	ASIR, O/E ratio (age)	Women of all ages with invasive cervical cancer
United Kingdom	Harding et al. 2009 (28)	Trends in cancer mortality in migrants living in England and Wales	Anonymised death records; population data from the 1981, 1991 and 2001 censuses for England and Wales	1979–2003	Mortality RR (age)	Men and women aged 30–69; consistent country of birth definition in both deaths and census data
	Jack et al. 2009 (17)	Breast cancer incidence, stage, treatment and survival in ethnic groups in South East England	Study cohort: Thames Cancer Registry; National Health Service Central Register; population data: Office for National Statistics (matching on NHS number); registry- and population-based study	1998–2003	Incidence RR, HR (age, socioeconomic deprivation, stage at diagnosis, treatment)	Women of all ages; known ethnicity, complete registration information; exclusion criteria: patients registered by death certificate only excluded from analyses on stage, treatment and mortality

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Age at immigration and duration of residence based on latest known date of immigration; degree of urbanisation and mean household equivalent used to approximate SES calculated based on postal code	Residents or parents of residents born abroad (predominant role of country of birth of mother)	Native Dutch population	Cancer deaths: n = 173,461; Deaths among migrants n = 1454 (0.8%)	Healthy-migrant/unhealthyremigrant effect; uptake of western lifestyle (smoking, changes in diet and reproductive behaviour); hepatitis B surface antigens (risk factor for liver cancer); importance of life-course perspective	Limited statistical power owing to small numbers and relatively young (and highly different) age distributions of migrants
	Country of birth of subject and both parents (non-Dutch if at least one parent born abroad)	Native Dutch population	All deaths in Dutch population during study period: n = 750,148	Healthy-migrant/unhealthyremigrant effect; smoking, dietary habits (adaptation of unhealthy western lifestyle)	No information on within-migrant group variations; risk underestimation in some groups; unregistered remigration
Validation of country of birth information with breast cancer screening programmes to Cancer registry data; if data in cancer registry discrepant or missing, country of birth information from screening data used	Country of birth	Native Dutch women	Cancer cases: n = 20,016 (among migrants: n = 1699 (8.5%)	Screening attendance; change in reproductive risk factors such as lower parity	
	Dutch resident born abroad	Native Dutch women	Cancer cases: n = 1530 (among migrants: n = 232 (15.2%)	HPV infection; changes in lifestyle; screening programmes in host country; selection effects	Missing country of birth in 10% of cases; incompleteness of mortality registration; no information on prevalence of risk factors and differences in SES
Trend analysis (changes in death rates among three time intervals	Country of birth	English -and Welshborn		Changes in risk behaviour (convergence in rates to those of England and Wales); rising smoking trends among immigrants; alcohol consumption; delayed uptake and poorer quality of clinical management; poor cancer awareness; comorbidities; historic (viral) infections	Possible misclassification of country of birth between census data and death certificates; healthy-migrant effect (selection bias)
Socio-demographic deprivation based on income domain of Index of Multiple Deprivation 2000, divided into quintiles, assigned to records using postcode of residence at diagnosis	Self-assigned ethnicity (using codes from 1991 and 2001 censuses)	White women	Cancer cohort: n = 33,024	Screening uptake; treatment differences; reproductive, socio-economic, anthropometric and dietary factors; differences in disease perception and resulting access to healthcare services	Ethnicity information not available for large proportion of patients (36%); representativeness of ethnic groups; within ethnic group variation

Table 1 (continued)

Country, authors and year of study	Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
Wild et al. 2006 (22)	Cancer mortality in England and Wales by country of birth	Population data: National Statistics, 2001 Census of England and Wales; mortality data: Office of National Statistics	2001–2003	SMR (age)	Men and women aged 20+
Smith et al. 2003 (18)	Recent trends in cancer incidence among UK South Asians	Population data: estimates from 1991 census of England and Wales; Study cohort: Trent Cancer Registry	1990–1999	Incidence RR (age, deprivation)	Men and women of all ages (for all-cancer)/aged 30+ (for site-specific analyses)
Harding and Rosato 1999 (50)	Incidence of cancers among foreign-born residents of England and Wales	Study cohort: 1% sample of the population of England and Wales; linked to Cancer registrations: NHS Central Register	1971–1989	SIR (sex, age, year of diagnosis)	Men and women aged 15+
Haworth et al. 1999 (51)	Mortality from cirrhosis of the liver and primary liver cancer in first-generation migrants to England and Wales	Population data: estimates from 1991 census of England and Wales; mortality data: Office for National Statistics	1988–1992	SMR (age, sex)	Men and women aged 20–69
Winter et al. 1999 (20)	Cancer incidence in the South Asian population of England	Population data: estimates from 1991 census of England and Wales; study cohort: Cancer Registries of Thames, Trent, West Midlands and Yorkshire	1990–1992	ASIR (age)	Men and women of all ages
Swerdlow et al. 1995 (19)	Cancer risks in British ethnic and Indian ethnic migrants to England and Wales	Mortality data: Office of Population Censuses and Surveys	1973–1985	Mortality RR (MH OR) (age)	Men and women of all ages; exclusion criterion: unknown ethnicity

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
	Country of birth	England and Wales as a whole	Cancer deaths: n = 398,515; among non-western migrants: n = 13,161 (3.3%)	Complex combination of genetic and environmental factors (diet, lifestyle, socio-economic status); smoking habits (lung cancer); poor uptake of cancer screenings; unexplained high risks in West Africans	No information on environmental and demographic factors; limited reliability of country of birth as ethnicity proxy; numerator/denominator bias; accuracy of cause of death information; possible misclassification of country of birth
Level of deprivation of the patient's area of residence (SES proxy) using Townsend Index	Sur- and forename	English non-South Asians	Cancer cases: n = 12,128; among migrants: n = 862 (7.1%)		
Stratification of results by religion	Country of birth, enhanced by name analysis, classified by religion	All members of the study	Cancer cases among non-western migrants: n = 167	Differences in socioeconomic status; smoking and alcohol consumption; dietary habits; uptake of screening services; lifestyle; occupation	Unknown emigrations; higher loss of FU among migrants; self-selection processes; no information on social distribution of risk factors
	Country of birth	Native population of England and Wales	Cancer deaths: n = 3237; Cancer deaths among migrants from non-western countries: n = 238 (7.4%)	Culture; Religion; Socioeconomic differences; Alcohol intake; Chronic hepatitis B and C infections; lifestyle	Small numbers of deaths (especially among females)
South Asian names identified using a computer programme; two comparisons: South Asian versus. non-South Asian (England) and South Asians in England versus data from the Indian subcontinent	Ethnic origin determined based on names	Non-South Asian English population of study region; Indian registry data	Incident cancer cases: n = 356,555; Cases among migrants: n = 3845 (1.1%)	Lifestyle; diet; access and uptake of health services (screenings); chewing of tobacco with betel-quid (risk factor for cancer of tongue, mouth and hypopharynx); hepatitis B infection (liver)	Within-group differences with regard to lifestyle, diet etc; possible misclassification of names; very limited validity of comparison between English South Asian rates and Indian Asian rates
No suitable denominator information: calculation of odds ratios, risk of death from each cancer site in each migrant group/ risk of death from the same cancer site in English- and Welsh-born residents (relative risk of mortality); Information on social class, marital status and parity from 1971 census	Country of birth and ethnic group (determined on the basis of names)	Native English and Welsh natives	Cancer deaths among migrants: n = 8282	Differences in exposures (occupation); differences in social class; betel-quid chewing (oral and pharyngeal cancers); smoking and alcohol consumption (oesophageal and laryngeal cancer); hepatitis B infection (liver); obesity (gallbladder); reproductive factors (breast)	Numerator only measure; reliability of ethnic coding; misrecording of death certificates; no information on distribution of risk factors

Table 1 (continued)

Country, authors and year of study	Study aim: to explore	Data source	Period	Outcome/ measure of association (covariables)	Cohort acquisition/ in- and exclusion criteria
Grulich et al. 1992 (23)	Site-specific cancer mortality in West African-, East African- and Caribbean-born immigrants	Population data: 1971 population census of England and Wales; mortality data: Office of Population Censuses and Surveys	1970–1985	Mortality RR (age, calendar period, social class)	Men and women of all ages
Swerdlow 1991 (52)	Cancer incidence and mortality in Vietnamese refugees in England and Wales	Study population: National Health Service Central Register	1979–1989	SMR, SRR (age)	Male and female Vietnamese refugees born before 1950 and with NHS registrations from 24 May 1979 to 16 July 1985; exclusion criteria: unknown sex, death during FU
Barker and Baker 1990 (15)	Incidence of cancer in Asians living in Bradford, England	Population data: 1981 census (University of Leeds); study population: Yorkshire Regional Cancer Registry	1979–1984	Incidence SRR (age)	Men and women of all ages

ASMR, age-standardised mortality rate/ratio; ASIR, age-standardised incidence rate/ratio; ASR, age-standardised rate; EBV, Epstein–Barr virus; FSU, Former Soviet Union; FU, follow-up; HPV, Human Papilloma Virus; NHL, non-Hodgkin's lymphoma; NHS, National Health Service; O/E-ratio, observed/expected ratio; OR, odds ratio; PCIR, proportional cancer incidence ratio; RR, risk/rate ratio; SES, socioeconomic status; SIR, standardised incidence rate/ratio; SMR, standardised mortality rate/ratio; SRR, standardised registration rate/ratio.

Migrants from Eastern Europe

In 32% of studies from five countries (12/37) migrants came from the Eastern part of Europe, mostly parts of the former Soviet Union. Lower all-cancer morbidity and mortality were confirmed by the majority of these studies. The site-specific results were ambiguous, but strongly concurred on the elevated risks for stomach and lung cancer in males, whereas consistently decreased risks could be observed for breast cancer in females and melanoma.

Migrants from Africa

Migrants originating fromthe African continent had to be categorised into 'Africa' (if no subgroups were available), 'North Africa', 'West Africa' and 'East Africa'. In 16% of studies from four countries (6/37) migrants from Africa without further regional classifications were investigated. However, only three studies covered all-cancer morbidity which resulted in advantageous risks for migrants. The most striking similarities in the study results could be observed for liver cancer due to strongly elevated risks and colorectal cancer as well as cancer of male and female genital organs due to decreased risks.

North African migrants were studied in 12 studies (32%) from five countries (Denmark, France, Sweden, Netherlands and the UK). All-cancer morbidity was lower or not significant in all studies. Elevated risks were observed for cancers of the nasopharynx, liver, gallbladder and cervix uteri. Significantly decreased risks were found for almost all other cancer sites, especially for colorectal, lung and breast cancer as well as melanoma.

Migrants from the western part of Africa represent an exceptional group among migrants from non-industrialised countries. Only 4 out of 37 studies (11%) from France

Methodological pecularities	Definition of ethnicity	Reference population	Size and composition of study population	Discussed explanations for risk differences	Study limitations
Social class recorded on death certificates (only available for subjects aged 15–64), only performed for Caribbean	Country of birth	England and Wales natives	Cancer deaths among migrants: n = 5407	Viral origins; differences in social class; western lifestyle; genetic disposition; hepatitis B infection (liver); diagnostic facilities; betelchewing (oral cancer)	
Observed mortality and cancer registrations compared with age-, sex-, and year-specific expectations derived from application of England and Wales national mortality and cancer registration rates to the person-years at risk	Refugees born abroad	Mortality and cancer incidence in England and Wales (cancer registration data)	Migrant study cohort: n = 3327; Total mortality: n = 187; Cancer incidence: n = 49	High prevalence of tuberculosis and hepatitis B	Incomplete death registration; selection bias
Census data restricted to heads of households; Cancer risk among Asians in Bradford compared with non-Asians in Bradford and with cancer registry data from Bombay	Ethnic origin determined on the basis of names	Rates of non-Asian population/ the Bombay cancer registries	Cancer cases among migrants: n = 178	Change in environmental and behavioural influencescing, heavy alcohol consumption, betel chewing, consumption of spiced foods (hypopharynx, pharynx); uptake of cancer screenings	Small number of cases; limited validity of comparison with Bombay rates; misclassification of ethnicity

and the UK looked at this group but all of them presented quite detailed results that allowed us to look at many possible parallels. All cancer mortality was significantly elevated among males residing in the United Kingdom, but the opposite was the case for males living in France. The studies coincide in increased risks for cancers of the liver, pancreas and prostate as well as lymphomas. Other cancer sites showed ambiguous results, for example, significantly elevated mortality due to breast cancer in the studies from the UK as opposed to study results from France, which showed a significantly decreased risk among West African women. This implies important regional risk diversity in similar migrant groups across European countries and is certainly an interesting subject for further research. Another four studies fromSweden and the UK focussed on East African migrants. The three British studies agreed on lower all-cancer mortality in this group and revealed elevated risks for cancer of the oral cavity and leukaemia. All other cancer sites showed continuously decreased risks, most remarkably for cancers of the colon and rectum, lung and genital organs. The Swedish study yielded a significantly decreased risk of cancer of the cervix uteri in this migrant group.

Migrants from the Middle East

In 24% of the studies (9/37) migrants originating from the Middle East were investigated, investigating only few cancer sites. All-cancer occurrence appeared to be significantly less frequent in three studies. Moreover, decreased risks could be observed for colorectal, lung, prostate, testis and breast cancer in studies carried out in Denmark, the United Kingdom and Sweden, where an increased risk of cancer of the thyroid gland was also revealed.

Table 2 Site-specific cancer occurrence in male and female migrants from different

Migrant Origin	Host Country	ICD Codes (C...)		00-97		00-06		11		15		16		18-21		22		23		25		33 34
		Reference	Ratio based on Inc./Mort.	All malignant neoplasms		Mouth, oral cavity		Naso-pharynx		Oeso-phagus		Stomach		Colon and rectum		Liver		Gallbladder		Pancreas		Lung
				F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Southern Europe/ Turkey	DK	(13)	Inc.																			
	GE	(16)	Inc.			--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
		(21)	Inc.	-	-							0	++		+							
	NL	(46)	Inc.	--	--	-	-	++	++	--	--	+	+	--	--	++	++	+	+	-	-	--
		(14)	Mort.	--	--					--	--	+	+	--	--	++	++			-	-	--
		(47)	Mort.	--	--							++	+									--
		(48)	Inc.																			
		(49)	Inc.																			
	SP	(39)	Mort.		0																	
	SW	(40)	Inc.													+	++	0	-			
		(42)	Inc.					+	+													
		(43)	Inc.																			
		(45)	Inc.	--	--							+	++	-	+							+
Eastern Europe	DK	(30)	Inc.	0	+									--	--							-
	GE	(35)	Mort.	--	0	-	--					+	++	-	--	+	+			0	0	--
		(35)	Inc.	-	0	-	-					++	++	0	--	+	-			0	-	--
		(36)	Mort.									+	++									
		(37)	Mort.	--	0							+	++			++	++					
		(38)	Mort.	--	0					-	-	0	+	-	-	-	0			-	-	-
	SP	(39)	Mort.		--																	
	SW	(40)	Inc.													+	+	--	+			
		(42)	Inc.					+	+													
		(43)	Inc.																			
		(45)	Inc.	--	0							++	++	0	++							0
		(12)	Inc.	0	0							0	0	-	-							0
	UK	(22)	Mort.	--	-									0	0							--
Africa	NL	(46)	Inc.	-	--	-	-	+	+			-	-	--	--	++	++	++	++	-	-	-
	SP	(39)	Mort.		0																	
	SW	(40)	Inc.													++	++	+				
		(45)	Inc.	--	--								+	-	-							-
	UK	(17)	Inc.																			
		(51)	Mort.													+	++					
North Africa	DK	(30)	Inc.	--	--									--	--							
	FR	(31)	Mort.	--	--	-	--	+	++	--	--	-	--	--	--	0	0	+	+	0	-	-
		(33)	Mort.	0	--					0	--	+	-	--	--							++
	NL	(46)	Inc.	--	--	--	--	++	++	--	--	+	+	--	--	++	++	+	+	-	-	--
		(14)	Mort.	--	--					--	--	-	-	--	--	+	+			--	--	--
		(47)	Mort.	--	--							-	-									--

regions residing in selected European countries[*,#]

33 34	43/44		50	53	54	56	60	61	62	64		65-68		69-72		73		81		82-85		91-95	
Lung	Melanoma		Breast	Cervix Uteri	Corpus Uteri	Ovary	Penis	Prostate	Testis	Kidney		Bladder & Urinary tract		Brain, CNS		Thyroid Gland		Hodgkin's Disease		Lymphoma		Leukaemia	
M	F	M	F	F	F	F	M	M	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
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+	--	--	--	+	--	-		--	--	-	-	--	--	-	-	++	++	++	++				
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Table 2 (continued)

Migrant Origin	Host Country	ICD Codes (C...)		00-97		00-06		11		15		16		18-21		22		23		25		33 34
		Reference	Ratio based on Inc./Mort.	All malignant neoplasms		Mouth, oral cavity		Naso-pharynx		Oeso-phagus		Stomach		Colon and rectum		Liver		Gallbladder		Pancreas		Lung
				F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
North Africa	NL	(48)	Inc.																			
		(49)	Inc.																			
	SW	(40)	Inc.														++		+			
		(42)	Inc.					++	++													
		(43)	Inc.																			
	UK	(22)	Mort.	0	0									+	0							-
West Africa	FR	(32)	Mort.	-	--		--				--	-	0	-	--	++	++			+	-	0
	UK	(28)	Mort.																			
		(22)	Mort.	0	++									+	-							--
		(23)	Mort.	+	++	++	-	+	+	-	++	+	+	+	0	++	++	+	+	+	++	--
East Africa	SW	(43)	Inc.																			
	UK	(28)	Mort.	--	--																	
		(22)	Mort.	--	--									-	--							--
		(23)	Mort.	--	--	++	++	+	-	++	-	-	--	--	-	+	0	-	-	-	--	--
Middle East	DK	(13)	Inc.																			
		(30)	Inc.	--	--									--	--							
	SW	(40)	Inc.													-	-	-				
		(41)	Inc.	--	--	-	--			+	--	+	--	--	--	--	--	--	--	--	--	--
		(42)	Inc.					+	++													
		(43)	Inc.																			
		(44)	Inc.																			
		(45)	Inc.	--	--							+	-	-	-							-
	UK	(22)	Mort.	0	0									-	--							--
Asia	DK	(13)	Inc.																			
	FR	(34)	Mort.	-	--		-			+	-	-	+	0	-	++	+		+		-	+
	NL	(46)	Inc.	--	-	-	-	++	++	+	+	+	+	0	0	++	++	+	+	-	-	--
	SP	(39)	Mort.		--																	
	SW	(43)	Inc.																			
		(45)	Inc.	--	--							++	++	--	--							-
		(12)	Inc.	0	0									0	0							
	UK	(17)	Inc.																			
		(22)	Mort.	--	--									-	0							--
		(52)	Mort.	-	-				++		0	++	+				++					0
		(52)	Inc.	-	-	+	0	+	++		+	+	0	-	-		+					-
		(15)	Inc.	--	--		+		+		-	0	--	-	-	-		++	-	-	-	--
	FR	(34)	Mort.	--	--	-	--		++	-	0	++	+	--	--	++	++		++	0	0	++
	NL	(46)	Inc.	--	--	--	--	+	+	--	--	--	--	-	-	++	++	+	+	--	--	-
		(48)	Inc.																			

33 34	43/44		50	53	54	56	60	61	62	64		65-68		69-72		73		81		82-85		91-95	
Lung	Melanoma		Breast	Cervix Uteri	Corpus Uteri	Ovary	Penis	Prostate	Testis	Kidney		Bladder & Urinary tract		Brain, CNS		Thyroid Gland		Hodgkin's Disease		Lymphoma		Leukaemia	
M	F	M	F	F	F	F	M	M	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
			--																				
				++																			
				-																			
-			+					-															
--	0	-	--			+		0	-		--	+	++	-	--			-	-	-	+	-	-
			+																				
--			++					++															
--	+	-	++	-	+	-	+	++	-	+	+		-	-	-			-	-	+	++	+	+
				--																			
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--		-	--	++	0	-		--		-	-	--	--	-	--			+	-	+	+	-	-
--	--	--	-	+	-	+		--	-	--	--	--	--	-	-	+	+	+	+				
			-																				

Table 2 (continued)

Migrant Origin	Host Country	ICD Codes (C...)		00-97		00-06		11		15		16		18-21		22		23		25		33 34
		Reference	Ratio based on Inc./Mort.	All malignant neoplasms		Mouth, oral cavity		Naso-pharynx		Oeso-phagus		Stomach		Colon and rectum		Liver		Gallbladder		Pancreas		Lung
				F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
South East Asia	NL	(49)	Inc.																			
	SW	(40)	Inc.													++	++	+				
		(42)	Inc.					++	++													
		(43)	Inc.																			
	UK	(28)	Mort.	--	--									--	--						--	
		(17)	Inc.																			
		(22)	Mort.	--	--									--	--							--
		(18)	Inc.	--	--	++	++	++	++					--	--							--
		(50)	Inc.	--	--		+			+	-	+	-	-	-	+	+			-	-	-
		(51)	Mort.													+	++					
		(20)	Inc.	--	--	++	+	-	+	+	--	--	--	--	--	++	++	++	++	-	--	--
		(19)	Mort.			++	++	+	0	++	++	-	--	--	--	++	++	++	++	++	++	--
South America	DK	(13)	Inc.																			
	NL	(46)	Inc.	--	--	-	-	++	++	--	--	+	+	--	--	++	++	++	++	0	0	--
		(14)	Mort.	--	--					-	-	+	+	--	--	++	++			--	--	--
		(47)	Mort.	--	--							+	+									--
		(48)	Inc.																			
		(49)	Inc.																			
	SP	(39)	Mort.		--																	
	SW	(40)	Inc.													-	+					
		(42)	Inc.					+	+													
		(43)	Inc.																			
		(45)	Inc.	--	--							+	+	-	-							--
	UK	(28)	Mort.	--	--								++									
		(17)	Inc.																			
		(51)	Mort.													+	++					
		(23)	Mort.	--	--	0	-	+	++	--	--	0	0	--	--	++	++	++	0	--	-	--

"-" = lower risk (more than 10% risk reduction); "--" = significantly lower risk; 0 = no difference in risk
"+" = higher risk (more than 10% risk elevation); "++" = significantly higher risk

F = Female; M = Male; Inc. = Incidence; Mort. = Mortality
DK = Denmark; FR = France; GE = Germany; NL = Netherlands; SP = Spain; SW = Sweden; UK = United Kingdom

* if only a total risk was reported in studies (no distinction between males and females), the tendencies for F/M correspond to the total
# if only combined diagnosis groups were provided in studies, the same results were repeated over the separate diagnoses

33 34	43/44		50	53	54	56	60	61	62	64		65-68		69-72		73		81		82-85		91-95	
Lung	Melanoma		Breast	Cervix Uteri	Corpus Uteri	Ovary	Penis	Prostate	Testis	Kidney		Bladder & Urinary tract		Brain, CNS		Thyroid Gland		Hodgkin's Disease		Lymphoma		Leukaemia	
M	F	M	F	F	F	F	M	M	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
				0																			
				++																			
--			--			--		--													0		0
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--	--	--	--	++		--		+	--	-	-	-	--	-	-	+	++	0	++	++	++	++	++
									-														
--	--	--	--	++	-	--		++	--	-	-	--	--	--	--			++	++				
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			0																				
--	--	--	--	++	+	--	+	++	--	-	--	--	--	--	--			0	0	++	++	0	0

Migrants from Asia

Many studies took migrants from Asia into account. With regard to the vastness of this continent, it made sense to distinguish between Asia in general, mostly referring to China and Vietnam, and South East Asia, which included India, Ceylon, Bangladesh, Indonesia and sometimes Pakistan (depending on the definition).

Cancer risks among migrants from Asia in general were examined in 30% of the studies from six different European countries (11/37), all of them exhibiting lower all-cancer mortality and morbidity rates. Consistent findings of elevated risks were found for cancers of the nasopharynx, stomach, liver and endocrine glands as well as lymphomas. Parallel, decreased risks could in particular be observed for colorectal, lung, breast and bladder cancer as well as for melanoma and cancers of the cervix, ovary, prostate and testis. Migrants from South East Asia showed surprisingly similar results between the studies for many cancers. In total, 41% of all studies included (15/37), performed in France, Sweden, The Netherlands and the UK focused on this migrant group, varying little in the definition of South East Asian countries. All-cancer mortality and morbidity risks appeared to be consistently lower in all studies that covered this general comparison. Uniformly elevated riskswere revealed for migrants with cancers of the oral cavity, nasopharynx, liver, gallbladder and thyroid gland. Moreover, a higher risk of lymphomas and leukaemiawas observed in several studies, whereas lowered risks were found for stomach, colorectal, lung, breast, ovary, prostate, testis, kidney and bladder cancer as well as melanoma.

Migrants from South and Central America

In 41% of all studies included in this overview (15/37) cancer risks were determined for migrants coming from South and Central American countries, most frequently Caribbean countries that used to be European colonies. All-cancer mortality and morbidity risks were consistently lower for migrants from this part of the world. Particularly elevated risks could be observed for cancers of the nasopharynx, liver, cervix uteri, prostate and lymphomas. In contrast, notably lowered risks were revealed for cancers of the oesophagus, colon and rectum, lung, breast, skin, ovary and bladder.

Second-generation migrants

Studies on cancer risk in second-generation migrants are still scarce and were included in this overview for the sake of completeness only. However, a convergence of risks towards the rates of the host population as well as less extreme risks was revealed by Hemminki and Li.(12) In addition, studies assessing the effects of duration of residence or age at migration indicate an adaptation of rates, which also indicates a change of risk over time, i.e. after migration. Investigating cancer occurrence in second-generation migrants will become more relevant in future, due to the increasing age and size of this population group.

Discussion

Our findings suggest that migrants from non-western countries were more likely to develop cancers that are related to infectious diseases, compared with the general population of their industrialised host country. This is especially true for cancers of the oral cavity, nasopharynx, stomach, liver, gallbladder, cervix uteri, prostate and lymphomas.

In contrast, almost all studies found lower risks for cancers that are strongly related to a 'western' lifestyle (poor diet, physical inactivity, reproductive factors, etc.), irrespective of the migrant origin. This is in particular the case for colorectal cancer and cancers of the pancreas, lung, breast, ovary, kidney and bladder. Some elevated risks could also be explained partly by important covariables such as socioeconomic status, especially for migrants originating from West Africa. We also found that in most studies, migrants show cancer risks that are in between the corresponding risk of the native populations in their home and their host country. The majority of the findings tend to be in accordance with the rates, visualised in Fig. 1.

Whereas all-cancer incidence in the more developed countries amounts to 314 [age-standardised rate (ASR(W)) per 100,000] among males and 228 among females, less welldeveloped countries show an average of 159 for males and 129 for females.(24)

It can be observed that cancer sites with a comparatively high incidence in less well-developed regions also exhibit a high incidence for migrant populations from non-western countries residing in industrialised countries. This applies particularly for cancers of the liver, oesophagus, stomach and nasopharynx among males and cervix, stomach, liver, oesophagus and nasopharynx among females. In the same manner, low incidences in less well-developed regions are reflected by low incidences among migrant groups originating from these countries. This pattern could be confirmed in a recent study by Zanetti and colleagues,(25) who analysed cancer incidence in North Africa.

Mortality data show a similar picture, although the differences are less clear, which is-mainly attributable to disparities in access to care and suboptimal communication on the dilemmas of treatment. Our findings also concur with those of others from non-European countries and continents that host non-western migrants. McCredie and colleagues (26) for instance observed lower cancer incidences for migrants from various non-western origins in Australia and McDonald and Neily (27) could confirm similar results for migrant women in the United States. A close relationship with individual exposure experienced during a life span could be confirmed for migrants of various origins. In addition to individual factors and health behaviour, the causal roles of exposure in the home country, i.e. before migration, during migration itself and in the host country, as well as the influence of social factors, certainly represent key factors in carcinogenesis.

Exposure to risk factors and adaptation to changing environments evolve over time and therefore cancer risk diversifies with the duration of residence, new exposures and new generations. Prospectively, a convergence of cancer risk (a simultaneous decrease in cancers with high incidence in migrants and an increase in those with a currently low incidence) towards the level of the rates in the native population of the host country can be expected over time and across migrant generations.(6,14,16,28)

Of course there are limitations to the comparisons conducted in this overview. Firstly, the definitions of the migrant groups and the study populations varied among studies and countries. Ethnicity proxies, such as 'self-assigned ethnicity' and name-based approaches, are in particular prone to misclassification bias, since a distinction between generations or for example intercultural marriages is not possible. Second, the comparability of studies is also limited with regard to the size, composition and time window of the study populations. It is also important to note that in some studies population data from censuses or surveys were used (instead of population-based registers), which is always a biased underestimate of the population at risk because as a rule only the head of the household is considered.

Third, migrant origins may sometimes have been collected in an inconsistent way, which was unavoidable in some cases (e.g. the allocation of Pakistan or Turkey).
Fourth, studies investigating both mortality and morbidity have been included, given the assumption of parallel effects, although mortality is mainly driven by (access to) treatment
and the varying fatality rates of different cancers. Consequently, different measures of association have been pooled and compared on the basis of tendencies. The comparisons therefore lack amagnitude and only provide a rough estimation of risk disparities. Meta-analysis was not the aim of this overview.
The healthy migrant effect could partly explain the advantageous risks of migrants, but since effects seem to persist, its influence is probably marginal. Several studies also discussed the possible effects of the so-called salmon-bias, which assumes that migrants tend to return to their roots when they become ill. This is in most instances unlikely due to the fact that health services and treatment are often better in the host country and many migrants have already been joined by and settled with their families.
This is to our knowledge the first direct comparison of studies on cancer occurrence in migrant populations in Europe. Despite the limitations mentioned above, broad comparisons are feasible and will gain importance in the future. Prospectively, a transnational study of cancer occurrence in migrant populations could surmount many of these difficulties. This primarily concerns the definition of migrant groups requiring close networking between countries. In doing so, the results would be more reliable and the magnitude of the risk diversity could be studied in more detail. In order to appreciate the change in risk after migration, a comparison with data from the country of birth would be ideal.

Conflict of interest statement
None declared.

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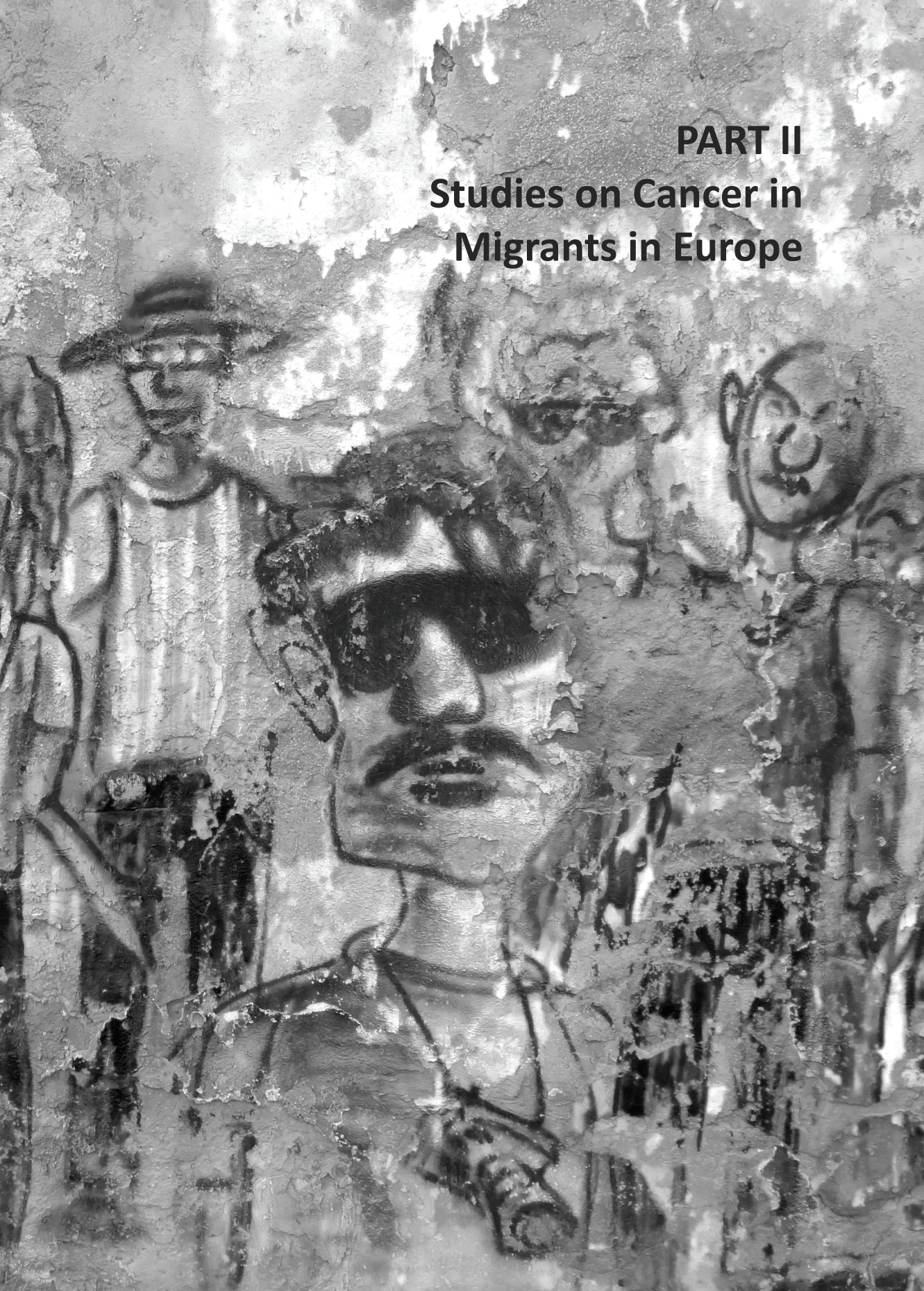

PART II
Studies on Cancer in Migrants in Europe

4

Cancer incidence rate ratios of Turkish immigrants in Hamburg, Germany: A registry-based study

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Abstract

The aim of this study was to estimate cancer incidence rate ratios for Turkish migrants in Hamburg, Germany.We used a name-based approach and identified 1346 cases with Turkish names (as a proxy of Turkish origin) among 140,249 cases of cancer registered in the cancer registry Hamburg during 1990–2005. To estimate the size of the denominator population, we applied the name-based approach to the population of Hamburg as well. The cancer incidence of specific cancer sites was compared between Turkish and non-Turkish cases using incidence rate ratios (IRR), stratified by gender and birth cohort. Our main findings are that cancer of the respiratory organs is diagnosed less frequent among Turkish men in older birth cohorts but with higher frequency in the younger birth cohorts. Malignant neoplasms of lymphoid, haematopoietic and related tissues are slightly higher in mostmale Turkish men birth cohorts, and even considerably higher for the birth cohort 1961 to <1971 (IRR = 1.8). Among women, incidence rates for Turkish women are lower than for non-Turkish women for cancer of the respiratory system, skin cancer and cancer of genital organs. Also, breast cancer incidence rates of Turkish women are lower than for non-Turkish women, especially in older birth cohorts. Incidence rate ratios of neoplasms of lymphoid, haematopoietic and related tissues are low in the 1931 to <1941 cohort (IRR = 0.71) but increase in younger birth cohorts. In conclusion, we found differences in cancer risks between cases with and without Turkish names for specific cancer sites. These results are consistent with the findings of studies from other countries.

Introduction

The absolute number of migrants in western countries as well as their proportion of the respective populations have increased substantially during the last decades and are still increasing. Germany has become a popular destination for immigrants in terms of employment opportunities, social security and future prospects. Currently the number of people with a migration background exceeds 15 million, corresponding to approximately 19% of the total German population. The majority of immigrants originate from eastern and southern parts of Europe, and Turkey. In 2005, about 2.4 million people of Turkish origin were living in Germany, forming the largest ethnic minority group [1,2]. Most of them had migrated from Turkey to Germany during the 1960s in the course of labour migration. A large proportion of migrant workers took permanent residence to Germany, followed by their families [3]. Today, the first generation of Turkish immigrants has reached retirement age, and consequently their health status as well as their health care issues is taking on greater importance. Studies of cancer in migrants are of special scientific and epidemiological interest [4]. They allow comparing a population with a similar genetic background living in a different physical and social environment. Differences in cancer patterns between migrant and non-migrant populations may thus lead to further insights into the aetiology of the disease. Furthermore, important knowledge regarding target-group-specific cancer prevention may be gained [5].

Previous studies on cancer risks in migrants showed significant variation between the allochthonous (migrant) and autochthonous (native) populations of several countries. Studies analysing cancer patterns in migrants in the UK [6,7], the Netherlands [8], Sweden [9–11], Australia [12], Israel [13], and Germany [14,15] draw more or less identical conclusions: there are differences in mortality and morbidity, mostly favouring the migrants. Moreover, the results imply that migrants from non-western countries are in general more prone to cancers in sites that are related to infectious diseases experienced in youth/childhood (e.g. liver, cervical and stomach cancer), but are less likely to suffer from cancers related to a ''western lifestyle'' (e.g. colorectal, breast and prostate cancer). In addition, a convergence (decrease or increase of risks over time) towards the level of the rates in the native population could be observed across migrant generations [16]. This would mean that the frequency of cancers with currently low occurrence rates in the migrant population is expected to increase over time and cancers with high incidences in migrants will most probably decrease simultaneously, converging towards the rates of the host population. Since this phenomenon is estimated to take many years, this study uses several birth cohorts to assess this hypothesis.

Up to this point, knowledge about the cancer risk in people with a migrant background in Germany is scarce [17–19]. This project aims at investigating cancer incidences among Turkish immigrants in Hamburg.

Methods

The cancer registry of Hamburg (HKR)

Hamburg is the second largest city of Germany with a total population of approx. 1.8 million, among them 15% (or approximately 257,000) foreign residents. The largest ethnic group is Turks (approx. 58,000) [20]. In Hamburg, cancer documentation and registration has a long tradition dating back to 1926. After a break in the 1970s, the population-based

cancer registry of Hamburg started reporting again in 1985 and reached a high degree of completeness of registration in the 1990s, which is documented over many years [21]. In Germany, most routine health data does not contain valid and complete information on migrant status. Information on citizenship is insufficient because it excludes the large and increasing number of immigrants with German nationality. Therefore, identification with the sole variable nationality would only be appropriate for approximately two thirds of the study population and may introduce bias. In contrast, the variable country of birth has been shown to be one of the best available proxies for ethnicity in health research [22].

The HKR does not routinely collect information relevant to migration status of registered cases. The underlying reasons are that the notifying physician or pathologist is often unaware of the migrant status of the diagnosed patient. There is no legal requirement concerning in- or exclusion of variables of migrant status in a case report to the cancer registry. As a result, migrantspecific analyses of cancer patterns or cancer risks are not available. To overcome this challenge, we used a name-based algorithm which had proved performance and effectiveness in previous studies—explicit details are described in the referenced literature [23,24]. The aim of this approach is to identify all cases with a Turkish migration background in the cancer registry on the basis of their names. The purpose-developed and computerized algorithm works with lists containing common Turkish first names and surnames. After a reform in 1934, all Turkish names had to have a meaning in the Turkish language, which makes Turkish names unique and categorically separates them from names in other languages. The name-based algorithm consists of two phases: first an automatic phase and then a manual one, in which cases that could not be classified in the automatic phase are reviewed by an expert. The statistical analysis was done using a completely anonymized dataset.

Results after application of the name-algorithm

In the period 1990–2004, 140,249 incident cases were registered in the database of the cancer registry of Hamburg (**Figure 1**). The automatic phase of the name-algorithm identified 992 cases with Turkish names, 944 cases with possible Turkish names and 138,313 cases with names that were not identified as Turkish. In a second step, the manual phase, a review of the cases with possible Turkish names resulted in 354 additional cases with Turkish names while 590 cases were judged not to be Turkish. In total 1346 cases with and 138,903 cases without Turkish names could thus be identified. At analysis date, the registration of cases for 2005 was still incomplete. Due to this, only 12 cases with Turkish names and 1243 cases with non-Turkish names that were registered in 2005 could be included into the study population. These cases were added to the diagnosis year 2004, sensitivity analysis showed no differences between cases registered in 2004 and 2005.

Denominator

To calculate incidence rates, a denominator for the incident Turkish and non-Turkish cases was needed. No comparable population data of persons with Turkish names in the background population is available. Due to the high number of naturalized Turkish migrants, the data on the number of Turkish migrants in Hamburg based on citizenship, which are available from the statistical office, would have introduced a numerator denominator bias and could not be used. The number of Turkish migrants in the background population – the resident population of Hamburg (ca. 1.8 million residents) – had

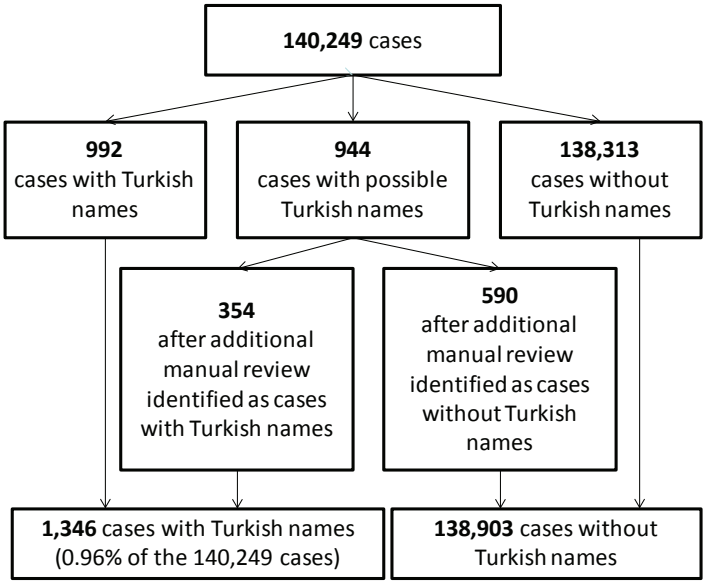

Figure 1 Identified cases with and with non-Turkish names after application of the name algorithm on all collected cancer cases of the cancer registry Hamburg, 1990–2005.

to be estimated in the same way as the number of Turkish cases in the cancer registry. Therefore, the name-algorithm was used to identify the number of Turkish migrants in a representative 5% random sample (n = 155,270) by gender and age group of all people living in Hamburg from 1990–2004 (N = 3,105,401). This population included people who were born, died, moved away from Hamburg or came to Hamburg during this period. 6531 persons (4.21%) with a Turkish name were identified in this population. The number from the 5% sample was extrapolated to the whole population of Hamburg. To adjust for the different age distribution of the migrant population (**Table 1**), the population was stratified by birth cohorts. Birth cohorts were used instead of age because persons in the background are ageing 15 years from 1990 to 2004. The numbers of cancer cases and background population stratified by birth cohorts and gender were used to calculate incidence rates (number of cancer cases 1990–2004/number of persons in the background population 1990–2004). The incidence rates cannot be compared to common incidence rates, e.g. incidence rates for lung cancer per 100,000, which are usually calculated on an annual basis. Calculation of incidence rates for specific years was not possible in this study due to the small number of Turkish cases. Because of the small number of Turkish cases for specific diagnosis, cancer, diagnoses were grouped in diagnosis groups based on ICD-10. Incidence rate ratios were calculated by dividing incidence rate of persons with Turkish names by incidence rate of persons with non-Turkish names. Additionally, we conducted a Poisson regression to model gender specific rate ratios adjusted for year of birth.
All analyses were conducted using SAS software (Version 9.1).

Results

1346 cases with a Turkish name and 138,903 cases with a non-Turkish name were identified in the cancer registry (1990–2004). The proportion of Turkish cases increased from 1990 to 2004, reflecting the increasing number and ageing of Turkish migrants in the background population. Nevertheless, the population of Turkish migrants in Germany is still younger than the nonmigrant population, and the number of Turkish cases aged 70 and above is low.

The cancer sites with the highest number of cases among Turkish men are cancer of the respiratory and intrathoracic organs. The incidence rates are lower for Turkish men than for non-Turkish men for skin cancer, cancer of the digestive organs, cancer of the urinary tract and cancer of the male genital organs in all birth cohorts. Cancer of the respiratory organs is diagnosed less frequent among Turkish men in older birth cohorts but with higher frequency in the younger birth cohorts (IRR = 1.39, 1951 to <1961 cohort). Malignant neoplasms of lymphoid, haematopoietic and related tissues are slightly higher in most male Turkish men birth cohorts, and even considerably higher for the birth cohort 1961 to <1971 (IRR = 1.8); exception is the birth cohort 1951 to <1961 (IRR = 0.9) (**Table 2**).

Table 1 Characteristics of the cases (HKR 1990–2004)

	Cases with non-Turkish names No. (%)	**Cases with Turkish names No. (%)**
Females (F)	71,093 (51.2)	493 (36.6)
Males (M)	67,810 (48.8)	853 (63.4)
Mean age (F/M)	68.6/67.6	50.4/55.0
Age (years)		
0-10	282 (0.2)	20 (1.5)
11-20	324 (0.2)	26 (1.9)
21-30	1,436 (1.0)	63 (4.7)
31-40	3,893 (2.8)	144 (10.7)
41-50	9,208 (6.6)	217 (16.1)
51-60	22,745 (16.4)	413 (30.7)
71-80	35,473 (25.5)	346 (25.7)
81-90	36,709 (26.4)	97 (7.2)
>90	24,570 (17.7)	3 (0.2)
Total	138,903 (100)	1346 (100)

Among women, breast cancer accounts for the highest number of Turkish cases. The incidence rates for Turkish women are lower than for non-Turkish women for cancer of respiratory system, skin cancer and cancer of female genital organs. Incidence rates for breast cancer of Turkish women are lower in older birth cohorts but appear to increase in younger cohort, with an incidence rate ratio of 1.31 in 1961 to <1971 cohort. Similarly, cancer of digestive organs is decreased in females born between 1931 and 1950 but increased in females of birth cohort 1951 to <1961 (IRR = 1.49). Incidence rate ratios of

Table 2 Incidence rate ratios of male Turkish and non-Turkish cases by birth cohort and diagnosis group, 1990-2004.

Birth cohort	Respiratory and intrathoracic organs (C30-C39)		Urinary tract (C64-C68)		Skin (C43-C44)		Malignant neoplasm of lymphoid, hematopoietic and related tissue (C81-C96)		Male genital organs (C60-C63)		Digestive organs (C15-C26)	
	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases
<1931	0.4 (0.28-0.57)	29	0.33 (0.19-0.56)	14	0.23 (0.12-0.42)	10		[b]	0.15 (0.09-0.27)	12		[b]
1931 to <1941	0.83 (0.68-1.01)	100	0.77 (0.55-1.08)	34	0.16 (0.09-0.29)	12	1.15 (0.84-1.58)	40	0.42 (0.31-0.56)	44	0.5 (0.39-0.65)	59
1941 to <1951	1.13 (0.91-1.41)	80	0.97 (0.62-1.49)	21	0.34 (0.20-0.58)	14	1.06 (0.71-1.58)	25	0.7 (0.47-1.03)	26	0.73 (0.54-0.97)	47
1951 to <1961	1.39 (0.89-2.18)	20		[b]		[b]	0.9 (0.50-1.65)	11		[b]	0.73 (0.39-1.37)	10
1961 to <1971		[b]		[b]		[b]	1.8 (1.17-2.78)	22		[b]		[b]
1971 to <1981		[b]		[b]		[b]	1.07 (0.60-1.93)	12		[b]		[b]
1981 to <1991		[b]		[b]		[b]	1.27 (0.64-2.52)	9		[b]		[b]
1991+		[b]		[b]		[b]		[b]		[b]		[b]

[a] 95% confidence interval; [b] Number of Turkish cases = 8 or less.

neoplasms of lymphoid, haematopoietic and related tissues are low in the 1931 to<1941 cohort (IRR = 0.71) but increasing in younger birth cohorts. Younger Turkish females of the birth cohort 1961 to <1971 and 1981 to <1991 have increased incidence rate ratios of 1.7 and 1.99, respectively (**Table 3**).

Results of multivariate analysis (**Table 4**), adjusting for year of birth, show increased risks for Turkish men for cancer of respiratory and intrathoracic organs, cancer of the breast and lymphatic cancers. Incidence rates are lower for cancer of the skin, lip, oral cavity and pharynx, cancer of digestive organs and male genital organs. Turkish women have increased risks for cancer of thyroid and other endocrine glands and lower risks for several cancer sites, including cancer of the breast, skin and digestive organs.

Discussion

We present for the first time incidence rate ratios of persons of Turkish origin living in Germany. Previous studies on cancer among Turkish migrants focused on proportional case-only and survival analyses [17,18,25]. Strengths of our study are the fairly large population, the good quality of data in the cancer registry and the representativeness. In our study, we analysed the cancer risks of persons of Turkish origin in Hamburg and compared them to the general German population in Hamburg. The most common cancer among men of Turkish origin in Hamburg is cancer of the respiratory system, and among Turkish women, cancer of the breast. These results are

Table 3 Incidence rate ratios of female Turkish and non-Turkish cases by birth cohort and diagnosis group, 1990-2004.

Birth cohort	Respiratory and intrathoracic organs (C30-C39)		Breast (C50)		Skin (C43-C44)		Malignant neoplasm of lymphoid, hematopoietic and related tissue (C81-C96)		Gynaecological cancers (C50-C53)		Digestive organs (C15-C26)	
	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases	IRR (CI)[a]	Turk. cases
<1931		[b]	0.23 (0.12-0.90)	9	0.49 (0.27-0.88)	11		[b]		[b]		[b]
1931 to <1941	0.47 (0.24-0.90)	9	0.41 (0.28-0.59)	29	0.32 (0.17-0.62)	9	0.71 (0.37-1.36)	9	0.85 (0.55-1.28)	22	0.37 (0.22-0.64)	13
1941 to <1951	0.39 (0.22-0.70)	12	0.38 (0.29-0.50)	49	0.22 (0.12-0.43)	9	1.03 (0.63-1.66)	17	0.57 (0.37-0.89)	20	0.55 (0.36-0.84)	21
1951 to <1961		[b]	0.76 (0.55-1.06)	36		[b]	1.29 (0.66-2.50)	9	0.63 (0.35-1.15)	11	1.49 (0.87-2.53)	14
1961 to <1971		[b]	1.31 (0.87-1.97)	24		[b]	1.7 (0.97-2.98)	13	0.91 (0.47-1.76)	9		[b]
1971 to <1981		[b]		[b]		[b]		[b]		[b]		[b]
1981 to <1991		[b]		[b]		[b]	1.99 (0.99-4.00)	9		[b]		[b]
1991+		[b]		[b]		[b]		[b]		[b]		[b]

[a] 95% confidence interval; [b] Number of Turkish cases = 8 or less.

consistent with those of a study on the most common cancer sites in Turkey [26] and comparable with the findings on the most common cancer sites in the German population [27].

We found lower incidence rate ratios for skin cancer among Turkish men and women than among non-Turkish men and women. This is consistent with the findings by Visser and van Leeuwen [8], who found low skin cancer risks among Turkish migrants in North-Holland, a part of the Netherlands. It is also consistent with the lower skin cancer risks found among Turkish migrants in Australia [28]. A likely explanation for these lower risks for skin cancer is the darker skin color of persons from Mediterranean countries, compared to Western-Europeans. The lower risks for cancer of the genital organs among Turkish men and women compared to non-Turkish men and women are also comparable to the findings of Visser's and van Leeuwen's [8] study among Turkish migrants in the Netherlands. Among others, they discussed early life experiences as a possible explanation for low rates of testicular cancer. Furthermore, prostate cancer is known to be correlated with different nutritional patterns (fat intake) and also appeared to be low in Turkish men in their study. The lower risks of Turkish men for cancer of the digestive system and cancer of the urinary tract could also be explained with nutritional differences. Wild et al. found lower mortality for colorectal cancer for immigrants from the Middle East [6], thus supporting our results that cancer incidence of digestive organs might be lower

Table 4 Rate ratios of Turkish versus non-Turkish cases by gender, adjusted for year of birth, 1990-2004.

Cancer site	Men		Women	
	RR[a]	CI[b]	RR[a]	CI[b]
Lip, oral cavity and pharynx (C00-C14)	0.47	(0.33-0.68)	0.29	(0.11-0.78)
Digestive organs (C15-C26)	0.74	(0.62-0.87)	0.65	(0.51-0.84)
Respiratory and intrathoracic organs (C30-C39)	1.20	(1.06-1.37)	0.51	(0.34-0.74)
Bone and articular cartilage (C40-C41)	0.96	(0.35-2.64)	1.00	(0.31-3.20)
Skin (C43-C44)	0.34	(0.25-0.45)	0.45	(0.33-0.61)
Mesothelial and soft tissue (C45-C49)	0.92	(0.60-1.41)	1.63	(0.93-2.85)
Breast (C50)	3.11	(1.35-7.16)	0.69	(0.59-0.81)
Gynaecological cancers (C51-C58)	-	-	0.89	(0.70-1.12)
Male genital organs (C60-C63)	0.54	(0.45-0.67)	-	-
Urinary tract (C64-C68)	1.09	(0.88-1.35)	1.13	(0.75-1.69)
Eye, brain and other parts of CNS (C69-C72)	1.16	(0.80-1.67)	0.73	(0.39-1.37)
Thyroid and other endocrine glands (C73-C75)	1.27	(0.65-2.48)	2.14	(1.33-3.45)
Unspecified sites (C76-C80)	1.03	(0.64-1.64)	0.44	(0.16-1.17)
Malignant neoplasm of lymphoid, hematopoietic malignancies and related tissue	1.26	(1.05-1.50)	1.19	(0.93-1.52)

[a] Rate ratios estimated with Poisson regression; [b] 95% confidence interval.

among immigrants from this region.

The lower risks for gynaecological cancers among Turkish women are comparable to two recent Swedish studies. One Swedish study found lower risks for cervical cancer among women from Southwestern Asia, discussing different prevalence of infections with human papilloma virus as possible explanation for lower risks of women from this region [10]. In another Swedish study immigrant women with a Turkish background were found to have lower risk ratios for cervical and ovarian cancer [11]. The increased incidence rate ratios for cancer of the respiratory system among Turkish men reflects a higher smoking prevalence among male Turkish migrants compared to the general German population [29] and is consistent with the findings of a study among Turkish migrants in Sweden [9]. The smoking prevalence of female Turkish migrants in Germany is lower than that of German women. This might explain the lower incidence rate ratios for cancer of the respiratory system among Turkish women compared to non-Turkish women in our study.

The incidence rate ratios for cancer of lymphoid, hematopoietic and related tissue are increased for Turkish men and Turkish women in nearly all birth cohorts. This increase was also found in a study by Zeeb and Razum [19], who measured proportional cancer incidence ratios in a population of Turkish migrants in Saarland, a federal state of Germany. It is assumed that infection with Epstein–Barr virus (EBV) is a risk factor for this cancer. EBV prevalence is assumed to be high in Turkey.

The lower risk for breast cancer in older Turkish women corresponds to the results from other studies [8,9,12,16,30]. The underlying reasons could be a different reproductive behavior of Turkish migrants, characterized by a higher number of children and a younger age of mothers at first birth compared to the autochthonous German population [19]. It is remarkable that in most diagnosis groups there are fewer differences in the cancer

rates between Turkish and non-Turkish persons in the younger birth cohorts than in the older birth cohorts. This can be an indicator for a convergence of cancer risks in younger birth cohorts. The reason for this convergence of cancer risks could be an increasing adaption of the ''western lifestyle'' among younger Turkish migrants and exposure to the environment in Germany. A recent study of Ronellefitsch et al. showed a convergence of stomach cancer rates among immigrants from the former Soviet Union in Germany [15]. Further studies should analyse convergence of cancer risks, incorporating the duration of stay of immigrants and data from the country of origin.

Our study has several limitations. The identification of Turkish cases based on a name-algorithmcan never be complete. But in the cancer registry, no other valid information about migrant status is available, and an identification based on citizenship would have excluded the large and increasing number of naturalized migrants. Other studies that used the name-algorithm showed that close to 97% of Turkish persons in a registry can be identified with this method [31]. The selection bias, inherent to this method, is non-differential, affecting both the number of cases identified (numerator) and background population (denominator) to the same extent. Another limitation is the small number of Turkish cases which might lead to chance findings. Therefore, we only present incidence rate ratios for diagnosis groups and strata that have at least nine cases. The lower incidence rate ratios of Turkish cases in the oldest birth cohort (<1931) in all diagnosis groups could be the expression of an underestimation of Turkish cases due to remigration of sick Turkish migrants to Turkey (also called ''salmon bias''). However, this bias is more probable for the outcome mortality than for incidence: if the diagnosis of cancer triggers return migration, the affected person will still have been registered as an incident case in the cancer registry. Additionally, Turkish migrants could benefit from the health care system in Germany if they stay.

Overall, we found differences in the cancer risks of a migrant population relative to that of the autochthonous population that are consistent with the findings from other studies. Most proposed explanations for these differences relate to lifestyle factors like reproductive behavior, smoking and nutrition. Several models were developed to explain such differences [32]. Cancer is known to be multifactorial. In the development of most cancer sites, nature (or genetic predispositions) and nurture (or environmental factors) seem to interact on different periods of the life course. This, and the findings of our study that for some cancer sites the incidence rate ratios change over the birth cohorts, imply that the appropriate model for the study of cancer in migrants may be a ''life course perspective''. A life course perspective would take several factors in different life periods into account, for instance social deprivation, living conditions or different patterns of health behaviour and health awareness. Results from life course epidemiology studies may in future be used to gain further insight into the aetiology of various cancers and to improve target-group-specific prevention [33].

Conflict of interest statement

All authors declare that there is no conflict of interests. They all disclose any financial and personal relationships with other people or organizations that could inappropriately influence the work.

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Cancer mortality patterns among Turkish immigrants in four European countries and in Turkey

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Abstract

Aim of the study: For the first time, traditional comparisons in migrant health research have been extended in two ways. First, data on cancer mortality from the immigrants' country of origin were included and second, cancer mortality among Turkish immigrants across four European countries (Belgium, Denmark, France and the Netherlands) was compared.

Methods: Population-based cancer mortality data from these countries were included. Age-standardized mortality rates were computed for the local-born and Turkish population of each country. Relative differences in cancer mortality were examined by fitting country-specific Poisson regression models. Globocan data on cancer mortality in Turkey were used in order to compare mortality rates of Turkish immigrants with those from their country of origin.

Results: Turkish immigrants had lower all-cancer mortality than the local-born populations of their host countries, comparable to the lower all-cancer mortality in Turkey. In the Netherlands and France breast cancer mortality was consistently lower in Turkish immigrants women than among local-born women. Lung cancer mortality was slightly lower in Turkish immigrants in the Netherlands and France but varied considerably between the countries. In contrast, stomach cancer mortality was significantly higher in Turkish immigrants than in local-born French and Dutch persons and even exceeded mortality risks in Turkey itself.

Conclusion: The results indicate the presence of health effects due to migration and due to the situation in the country of residence on cancer mortality of immigrants. Despite limitations affecting any cross-country comparison of mortality, the innovative multi-comparison approach is a promising way to gain insights into determinants of cancer of migrants.

Introduction

Many studies have been conducted exploring cancer incidence and mortality in migrant populations from low and middle-income countries in comparison to the local-born population of their host country. A recent literature overview on this topic revealed largely consistent patterns between studies, confirming lower all-cancer risks but substantial variation and heterogeneity by cancer site, country of residence and the origin of immigrants (1). Whereas breast cancer risk was found to be low in immigrants from low-incidence countries compared to the native population of their host country, lung cancer risk strongly depended on the country of origin and the prevalence of driving risk factors in the host country. Furthermore, a transition of risks has been observed over time and with subsequent generations, approaching risks of high-income countries (2). Immigrants thus retain parts of their risk profile typical for their region of origin, while changing physical and socio-cultural environments in the host countries entail the gradual change in disease patterns (3). However, cancer incidence and mortality often show contrasting patterns, precipitated by different underlying factors. The latter has often been reported to be poorer in immigrant populations when compared to the local-born population of their host country, presumably due to inferior access to health services and adequate treatment (4). On the other hand, improving structural conditions and health care services after migration to high-income countries can also have a positive influence on cancer mortality (5).

Yet, the magnitude of changing cancer risks and mortality rates – and thus the influence of environmental and other extrinsic risk factors – can only fully be measured by comparing corresponding parameters (such as standardized cancer incidence and mortality rates) in immigrant populations with those of the population of their country of origin and with the same immigrant group residing in other host countries, respectively (6). In doing so, studies can help determining the impact of the national context on disparities in cancer risk and mortality in immigrant groups (7). Thus, if living conditions in the host countries would exert strong effects, cancer rates of same-origin immigrants would be expected (a) to be "caught in the middle", i.e. between home and host country and (b) to differ across host countries.

Nevertheless, to date, both approaches have stayed on the side-line, particularly comparisons involving more than one host country, and those with respect to migrants from low- and middle-income countries. Immigrants of Turkish origin form a considerable ethnic group in many Western European countries, mostly attributable to large labour migration waves during the 1960s and 1970s. After settling permanently, many were followed by their families and stayed ever since (8). Today, this group has reached retirement age and their health situation has become an important aspect of public health.

In this study, we aim to be the first to extend traditional comparisons in two ways: first, we include data on cancer mortality from their country of origin (Turkey) and second, we compare cancer mortality in Turkish immigrants across four European countries (Belgium, Denmark, France and the Netherlands). Our broader aim was to introduce the idea of cross-country comparisons of cancer mortality among immigrants and to discuss strengths, potentials and methodological limitations of this approach.

Material and Methods

Data sources

Nationwide data on cancer mortality in Turkish immigrants were available for four European countries: Belgium (1991-1995), Denmark (1992-2001), France (2005-2007) and the Netherlands (1996-2006). This study partly used the same data as Vandenheede et al. 2011 and Bhopal et al. 2011 (9-10), who described differences in mortality from diabetes and circulatory diseases among immigrants. The data from all countries refer to the complete national population and cover the entire territory of each country. French data however excluded the overseas departments (Guadeloupe, Martinique, Guyane, La Réunion). Data from longitudinal, record linkage studies were used in three countries (Belgium, Denmark, the Netherlands). In these studies, people enumerated at the population census were followed through a linkage between the census and the mortality register. For Belgium, the study cohort was semi-closed. Nobody could enter the study cohort during the follow-up period, but people could leave the population by emigration or death. In Denmark and the Netherlands an open cohort design was used. Participants could enter or exit the study at any point in time during the follow-up period. For France, cross-sectional data were used. The number of deaths according to country of birth provided by this study was derived from the national mortality registers, whereas the person-years at risk (PY) were based on population census information. Mortality data were centred around the latest population censuses.

Variables

Depending on the country and years of the studies, either the 8th, 9th or 10th revision of the International Classification of Disease (ICD) was used in order to determine mortality from cancer. The relevant codes for ICD-9 were 161-163 and 165 for lung cancer, 174-175 for breast cancer and 151 for stomach cancer. In ICD-10, C30-34 and C39 were used for lung, C50 for breast, and C16 for stomach cancer. In the Danish dataset ICD-8 codes were applied until 1993.

Country of birth was used to determine immigrant origin. Consequently, all people who migrated from Turkey to Belgium, Denmark, France or The Netherlands, were considered 'Turkish immigrants'. Non-residents, such as asylum seekers, were excluded from the analyses.

Age was stratified into 5-year age bands. The recorded age corresponded to age at time of the population census in linked studies and to age at death in the unlinked study. Consequently, persons from the census linked studies were slightly older than persons from the unlinked study (and whom we allocated to the same age group).

Statistical analysis

Age-specific mortality rates were computed for the local-born and Turkish population of each country, using person-years at risk (PY) as the denominator. Next, age-standardised mortality rates (ASMRs) were calculated based on the direct method of age-standardization, using the WHO World Standard Population (11). To examine relative differences in cancer mortality, country-specific Poisson regression models were fitted using number of deaths as the dependent variable, person-years at risk as the offset variable, and country of birth as the independent variable. Due to the low number of cases, site-specific comparisons were carried out with the Dutch and French datasets only. All analyses

were performed stratified by sex and adjusted for age.
Data on cancer mortality from Turkey was obtained from Globocan 2000 (12), a year close to the period covered by the included studies. It represents an estimation of rates for Turkey as a whole but is based on data from the Izmir cancer registry. Cancer mortality from Globocan is directly age-standardized to the WHO world population. Ratios of the age-standardized mortality rates comparing Turkey to the corresponding host country were calculated as an indicator for the difference in cancer mortality between the country of birth and the host countries.
All regression analyses were performed using SAS 9.2.

Results

Turkish immigrants had a substantially lower all-cancer mortality than the local-born populations of the host countries included (**table 1**). Mortality rate ratios (MRR) were significantly lower in Turkish immigrants when compared with the populations of all four host countries. In addition, all-cancer mortality in Turkey (in relation to that of the four host countries) was equal or lower than that of Turkish immigrants (when compared to their host country). This implies that all-cancer mortality in Turkish immigrants was in between that of their country of origin and their host country, respectively.
The magnitude of the advantage in cancer mortality varied according to cancer site (**table 2**). Breast cancer mortality was considerably lower in Turkish immigrant women than among local-born French and Dutch women. In addition, their mortality risks were in between that of Turkey and their host country.
Lung cancer mortality among Turkish immigrant women showed contrasting patterns in those residing in France (where rates converged to the mortality level of native French) and in the Netherlands (where mortality was even lower than in Turkey). Lung cancer mortality among Turkish immigrant men in France and The Netherlands was slightly lower than that of local-born men. Turkish immigrant men in the Netherlands had slightly higher age-adjusted lung cancer mortality compared to the lung cancer mortality in Turkey.
Stomach cancer mortality was significantly higher in Turkish immigrants when compared to local-born French and Dutch. Furthermore, it also exceeded stomach cancer mortality in Turkey.

Discussion

Our results showed that Turkish immigrants tend to have a lower overall cancer mortality and lower cancer-specific mortality rates for breast and lung cancer when compared to local-born populations in the host countries. The results on breast cancer mortality are in line with results from several national studies on cancer risks among Turkish immigrants Europe (1, 13); however a study from Germany showed a convergence of breast cancer incidence among Turkish immigrant women towards the risks of women without immigrant background of younger ages in Hamburg, Germany (14).
Mortality from lung cancer varied considerably between Turkish immigrants in the Netherlands and France, and among women and men. Despite the higher smoking prevalence in the general population, Turkish immigrants in the Netherlands seem to have a lower lung cancer mortality than Turkish immigrants in France. The reason for these

Table 1 Crude and age-standardized all-cancer mortality rates among Turkish immigrant and local-born populations in Belgium, Denmark, France and The Netherlands and age-adjusted all-cancer mortality rate ratios (MRR) among Turkish-born immigrants and in Turkey in comparison to the local-born populations

		Person-years at risk (PY)		Absolute cancer deaths (n)		Crude mortality rate		Age-standardized mortality rate (per 100,000 PY)		Age-adjusted mortality rate ratios (MRRs)*		
	Country	Local-born population	Turkish population	Local-born population	Turkish population	Local-born population	Turkish population	Local-born population	Turkish population	MRR Turkish population vs. local-born population	95% CI	MRR Turkey** vs. country of residence
Males	Belgium	19,856,738	218,556	70,751	100	356.3	45.8	273.8	157.2	**0.65**	0.53-0.79	0.58
	Denmark	25,996,864	182,399	80,217	69	308.6	37.8	139.2	96.6	0.85	0.67-1.08	0.57
	France	78,719,481	381,402	240,949	492	306.1	129.0	219.3	166.0	**0.69**	0.63-0.75	0.57
	Netherlands	71,247,835	1,859,854	213,579	916	299.8	49.3	201.3	126.8	**0.71**	0.67-0.76	0.63
Females	Belgium	20,982,893	202,450	51,790	43	246.8	21.2	140.0	60.7	**0.51**	0.38-0.68	0.47
	Denmark	26,655,302	162,014	78,447	37	294.3	22.8	113.0	56.2	**0.57**	0.41-0.78	0.54
	France	83,852,076	330,721	163,750	282	195.3	85.3	102.4	81.7	**0.83**	0.74-0.93	0.54
	Netherlands	72,988,509	1,704,834	176,380	431	241.7	25.3	127.1	63.8	**0.49**	0.45-0.54	0.44

Bold number are statistically significant at the p<0,05 level

* MRRs and 95% CIs were derived from a Poisson regression model with local-born populations as reference category and adjusted for age

** Ratio of age-standardized mortality rates from Turkey and the corresponding country of residence; estimates from globocan 2000 (12)

Table 2 Crude and age-standardized lung, breast and stomach cancer mortality rates among Turkish immigrant and local-born populations in France and the Netherlands and age-adjusted cancer mortality rate ratios (MRR) among Turkish-born immigrants and in Turkey in comparison to the local-born populations

		Absolute cancer deaths (n)		Crude mortality rate		Age-standardized mortality rate (per 100,000 PY)		Age-adjusted mortality rate ratios (MRRs)*		
	Country	Local-born population	Turkish population	Local-born population	Turkish population	Local-born population	Turkish population	MRR Turkish population vs. local-born population	95% CI	MRR Turkey** vs. country of residence
Lung cancer										
Males	France	57,985	156	73.7	40.9	54.5	52.8	**0.81**	0.69-0.95	0.76
	Netherlands	66,595	329	93.5	17.7	62.3	42.7	**0.83**	0.74-0.93	0.62
Females	France	12,426	29	14.8	8.8	9.0	9.5	0.98	0.68-1.41	0.55
	Netherlands	24,028	29	32.9	1.7	19.8	4.2	**0.19**	0.13-0.28	0.25
Breast cancer										
Females	France	30,019	50	35.8	15.1	21.4	11.8	**0.67**	0.51-0.89	0.43
	Netherlands	33,988	95	46.6	5.6	26.5	11.1	**0.45**	0.37-0.55	0.33
Stomach Cancer										
Males	France	8,074	32	10.3	8.4	7.2	11.9	**1.44**	1.02-2.04	1.13
	Netherlands	9,949	76	14.0	4.1	9.3	11.1	**1.35**	1.07-1.69	0.96
Females	France	5,077	16	6.1	4.8	2.7	5.1	**1.69**	1.03-2.76	1.33
	Netherlands	6,389	37	8.8	2.2	4.1	6.3	**1.61**	1.17-2.23	1.04

Bold number are statistically significant at the p<0,05 level

* MRRs and 95% CIs were derived from a Poisson regression model with local-born populations as reference category and adjusted for age

** Ratio of age-standardized mortality rates from Turkey and the corresponding country of residence; estimates from globocan 2000 (12)

variations might be related to different durations of stay or migration histories of the immigrants, acculturation mechanisms, selection effects or misclassification. Influencing factors could be differences in smoking prevalence and smoking policy, e.g. smoking laws and the availability of cigarettes, in these countries. In the Netherlands, prevalence of smoking in the general population is higher than in France (15), which is also reflected in a higher lung cancer mortality in the general population of the Netherlands as compared to France. These factors might interact with the beliefs and smoking behaviours that immigrants bring from their country of birth and retain in their ethnic communities over time (3). The results indicate the presence of specific effects that can be related to the situation in the host country on lung cancer mortality among Turkish immigrants.
Stomach cancer mortality in Turkish immigrants was not only higher than in local-born French and Dutch but also exceeded mortality rates from Turkey itself. The higher stomach cancer mortality among Turkish immigrants compared to the local-born population is in line with several national studies on cancer risks among Turkish immigrants in Europe (1, 13-14). In Turkey, stomach cancer represents one of the leading causes of death and varies greatly according to geographical region (16). This is mainly due to a higher prevalence of infection with Helicobacter pylori and differences in diet, e.g. more salty foods. Our results on stomach cancer mortality among Turkish immigrants therefore suggest the presence of factors that are related to the situation in their country of origin. Higher stomach cancer mortality of Turkish immigrants when compared to mortality in Turkey might also be explained by the fact that Globocan data from Turkey are estimated based on data from one region, covered by the Izmir cancer registry. Data from this mainly urban region in West-Turkey might not be representative for rural regions with a higher prevalence of H. pylori infections and possibly higher stomach cancer mortality. This especially applies to rural East-Turkey, where the majority of Turkish immigrants in Europe originates from.

Feasibility and potentials of multinational studies on cancer mortality in immigrants
The study showed that immigrant-specific data on cancer mortality were available from several European countries and that cross-country comparisons of immigrant cancer mortality were possible, while suffering from several methodological limitations. Lag time, i.e. the time between the exposure to risk factors and cancer mortality, played a major role in the interpretation of our results. Since the included studies covered divergent observation periods, time since migration is different in Turkish immigrants across the four host countries. This, together with different study designs, limits the comparability of mortality rates across countries and represents a weakness of our research design. Globocan data on cancer mortality from Turkey are an extrapolation of data from one single cancer registry and can therefore only provide a limited point of reference regarding cancer mortality in Turkey as a whole.
The large difference between the crude and the age-adjusted estimates in the immigrant group emphasized substantial differences in age structure between immigrant populations and the local-born populations in the host countries. The difference in age between cross-sectional and longitudinal data may have resulted in an underestimation of mortality in France as opposed to the other countries. This especially applied to data from the Netherlands and Denmark, which were based on a ten-year observation period and where age at census time was used. Yet, these differences did not have an influence on the mortality rate ratios as the method for observation was the same for local-born

and immigrant populations in each country. It may, however, limit the comparability across countries.

The number of deaths among immigrants was rather small, in particular for stomach cancer and when stratified for age and sex. For this reason, to date only studies focussing on common cancers in sufficiently large population subgroups are possible. However, as the absolute number and proportion of immigrants and ethnic minorities in Europe increases, the number of cases will increase in the future.

The registration of deaths of immigrants is challenging for several reasons. Mortality among older immigrants is often underestimated due to unregistered remigration (and death outside of the country of residence). For instance, of all immigrants of Turkish origin, who permanently settled in the Netherlands, about 22% die abroad, i.e. in their country of birth (17). While the death itself is in most cases registered with the Dutch authorities, the cause of death often remains unknown, leading to a considerable proportion of deaths that cannot be attributed. Future studies on cancer mortality of European populations, in particular on cancer mortality among specific sub-populations such as immigrants and ethnic minority groups, will benefit from improvements in the standardization of mortality registration across Europe.

Conclusions

Overall, studying the potentials of multinational comparisons of cancer mortality among immigrants yielded promising results. This applies to both methodological considerations that were challenged and new insights that could be gained by conducting such multi-way comparisons. Prospectively, our approach can potentially be extended to other immigrants groups, host countries and cancer sites. We recommend using this approach for the study of effects of national-level conditions on the health of population subgroups. In a similar manner, a recent study by Agyemang (18) analysed the association between metabolic syndrome and type II Diabetes in ethnic groups in The Netherlands and the UK.

Cancer is known to be multifactorial. In the development of most cancer sites nature (or genetic predispositions) and nurture (or environmental factors) seem to interact at different time points during life course. Aim of future studies based on multinational databases could be to distinguish 'country of origin'-related from 'country of residence'-related factors in more detail. The approach we tested in this study is a promising step forward to such studies, which should ideally include data from different host countries and from the country of origin.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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Diverging breast and stomach cancer incidence and survival in migrants in the Netherlands, 1996-2009

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Abstract

Background: Migrant populations usually experience a health transition with respect to their cancer risk as a result from environmental changes and acculturation processes. We investigated breast and stomach cancer risk and survival in migrants to the Netherlands in a retrospective cohort study.

Methods: Invasive breast (n=96,126) and stomach cancer cases (n=24,496) diagnosed 1996-2009 were selected from the population-based Netherlands Cancer Registry. Standardised Incidence Ratios (SIRs) were computed as the ratio of observed and expected cancers. Differences in survival were expressed as Hazard Ratios (HRs) using Cox regression and relative survival rates (RSR).

Results: Women from Morocco, Suriname and Turkey exhibited a significantly lower risk for breast cancer than native Dutch women (SIR range: 0.5-0.9), 5-year RSR being slightly lower in premenopausal (range 74-83%) and slightly higher in postmenopausal migrant women (range 83-92%) when compared to Dutch natives (83% and 82% respectively). Hazards of death were significantly increased in premenopausal Moroccan (HR=1.4, 95% CI: 1.0-2.0) and Surinamese (HR=1.3, 1.0-1.7) patients.
The incidence of non-cardia stomach cancer was significantly elevated in all migrants, except in Indonesians, being highest in Turkish males (SIR=2.2, 1.9-2.6). Cardia stomach cancer appeared to be less frequent in all migrants, being lowest in Surinamese males (SIR=0.3, 0.2-0.5). One-year RSR for stomach cancer were significantly better in migrants from Morocco, Suriname and Turkey in comparison with native Dutch. Correspondingly, hazards of death were significantly reduced in patients from the Antilles (HR=0.7, 0.6-1.0), Suriname (0.7, 0.6-0.8), Turkey (0.7, 0.6-0.8) and Morocco (0.8, 0.6-0.9).

Conclusion: The lower incidence rates of breast and cardia stomach cancer in migrants as well as their higher non-cardia stomach cancer rates reflect most likely early life exposures including pregnancy and/or dietary patterns during life-course. The favourable cancer risks in migrants might also be useful for cancer prevention in the Dutch population and worthwhile to sustain.

Introduction

Migration has substantially characterized the societies of Western European countries, which especially holds for the Netherlands with every fifth citizen having a foreign background of first or second degree (1). Increasing ethnic diversity in populations demands new orientation of social services and health care. In particular the aging of relatively young migrant groups in the Netherlands entails new challenges regarding health care supply, appropriateness and equality. Social gradients in cancer burden need to be addressed and monitored carefully since especially the concomitance of low socioeconomic position and foreign ethnicity has been observed to increase health inequalities.
Cancer incidence varies greatly across and within countries and populations (2). Although migrants from low-income countries usually experience lower all-cancer risks, substantial site-specific disparities develop in comparison with the populations of their home and their host countries: whereas cancers associated with a Western lifestyle (such as breast, colorectal and prostate cancer) occur significantly less in most migrant groups, contrasting cancers with viral or bacterial origins (like stomach, liver or oral cancers). This pattern has been confirmed by studies conducted in many industrialized countries, including the Netherlands (3). Moreover, cancer risk differences between the native population and migrants were found to diminish over time and with upcoming migrant generations (4). This process of converging cancer risks, likely to be induced by acculturation processes, is an interesting phenomenon and may help solving unclear aetiology questions. Cancer survival not only reflects the incidence patterns but also accessibility and participation to early detection programs and possibly differences in treatment across population groups. Elucidating these differences is essential for providing adequate, culturally sensitive health care and for assuring high quality of preventive measures.
Breast cancer represents the most common malignancy among women world-wide and has become most frequent in developed regions of the world, especially since mass screening evolved. In particular reproductive patterns and to some extent lifestyle-related exposures are known to be key risk factors (5). If detected at an early stage, survival rates for breast cancer are high (6). Thus, population-based survival differences in breast cancer can partly be attributed to screening attendance, i.e. an early stage diagnosis, and to a lesser extent by treatment quality and the presence of co-morbidities (7). Stomach cancer, however, is predominantly caused by chronic infection with the helicobacter pylori bacterium, being endemic in many less-developed regions of the world (8). Stomach cancer typically develops several decades after infection - exposure is most frequently experienced during childhood, in first generation migrants typically in the country of birth. As survival from stomach cancer is low (6), disparities are more likely due to differences in genetic predisposition or still unknown factors rather than treatment and detection.
We selected two very different and contrasting cancer sites – breast cancer occurring less and stomach cancer being more prominent in migrants compared to the local-born population of their host country – to demonstrate the effect of migration-related risk factors on cancer risk and survival in later life. The recently changed multicultural character in combination with the population-based cancer registry since 1989 make the Netherlands a unique place to conduct migrant studies on cancer. Following regional analyses, this is to our knowledge the first analysis of cancer incidence and cancer sur-

vival in the largest migrant groups in the Netherlands.

Material and Methods

Cancer Cohort

Invasive stomach (ICD9 (1510) and ICD10 (C16), excluding lymphomas) and female breast (ICD9 (1740) and ICD10 (C50)) cancer cases diagnosed between 1996 and 2009 were acquired from the population-based Netherlands Cancer Registry (NCR). We distinguished cardia from non-cardia stomach cancers, since they are known to be caused by different mechanisms and exhibit a different prognosis (5). In breast cancer, pre- (below age 50) and postmenopausal (age 50 and older) patients were distinguished.

The nationwide Dutch pathology laboratory network and registry for histo- and cytopathology (PALGA), regularly reports all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, from the patient files using the registration and coding manual of the NCR. Stage at diagnosis was taken into account using the tumour-node-metastasis (TNM) classification at the year of diagnosis (9). Hereby, pathological and clinical TNM were combined into one variable, primarily referring to the pathological stage unless missing.

We identified migrants based on their country of birth (COB) which is routinely collected in the NCR and supplemented with data from the nationwide database of all municipal population registries in case of death or emigration. Patients with unknown COB were excluded. The largest migrant groups, originating from Turkey, Morocco, Suriname, the Netherlands Antilles/Aruba as well as Indonesia, were analysed separately. We applied an ecological proxy for SES by using four-digit postal code at the time of diagnosis, obtained from the Netherlands Institute for Social Research (a governmental organisation). SES was based on mean income per household, the percentage of households with a low income and the percentage of households with a low education. SES was analysed in deciles (1=first-third decile, 2=fourth-seventh decile, 3=eighth-tenth decile), resulting in three SES levels: high, intermediate and low.

Incidence analyses

Incidence rates were calculated per age group (0-14, 15-29, 30-44, 45-64 and 65 years and older), sex and year of diagnosis with cancer incidence rates of the entire Dutch population as reference, acquired from Statistics Netherlands (1). Population data of all legal residents of the Netherlands contained country of birth as a proxy for migration background and were available for the period 1996-2009. Expected numbers of cancer cases in each migrant group were derived from annual population data as well as age- and sex-specific cancer incidences and were compared with the observed numbers of cases in our data. Standardized incidence ratios (SIRs) were computed as the ratio between observed and expected numbers of cases between 1996 and 2006 with their 95% confidence intervals (CIs), calculated after log transformation.

Survival analyses

Vital status was established either directly from the patient's medical record or through

linkage of cancer registry data with the (automated) municipal population registries which record information on their deceased inhabitants (follow-up until December 31st, 2010). Not all of these regional cancer registries (which together constitute the NCR) had complete registration of COB. In case of cancers with low lethality, patients being alive at the end of follow up may have missing COB. For breast cancer (low lethality), we therefore only included data of cancer registries with complete registration of COB for the survival analyses and stage distribution. These data were gathered from the former areas (both rural and urban) of the comprehensive cancer centres Amsterdam, West and Stedendriehoek Twente all together covering about 40% of the Dutch population. Biannual organized mass screening for breast cancer was gradually introduced since 1991 at age 50-69, being extended to 75 years since 1998.
Survival analyses were performed for patients diagnosed from 1996 onwards. First, hazard ratios (HRs) for all-cause mortality were computed using Cox regression analysis, adjusting for all relevant covariables, i.e. age (continuously), sex (female versus male), country of birth, SES (high, intermediate vs. low), stage and cancer site (stomach: cardia vs. non-cardia).
Second, cohort-based relative survival (RSRs) was calculated. In order to account for different competing risks and comorbidities among most migrants, we incorporated country of birth-specific death rates in the background mortality. This approach had been used earlier to correctly measure socioeconomic differences in cancer survival (10). In order to correct for low numbers of deaths in some groups, we used log-linear regression with interaction terms for period, age and sex to smooth the mortality rates. All analyses were generated using SAS 9.3 software.

Results

Table 1 summarizes the main characteristics of the study cohort. During the study period 96,126 invasive breast cancer cases and 25,496 stomach cancer were included. All migrants, except Indonesians, were on average much younger at cancer diagnosis compared to Dutch natives and came from lower socioeconomic backgrounds, especially migrants from Turkey and Morocco. The aging of originally relatively young migrant groups in the Netherlands was reflected in the increasing numbers of cancer cases over this 10-year period, especially among women from Turkey and Morocco. Substantial increases were also observed for stomach cancer in all migrant groups, except for Indonesians. Dutch natives showed an absolute decrease in breast cancer cases and a decrease in stomach cancer cases over time (data not shown).

Breast cancer
Migrants also had a slightly disadvantageous stage distribution in breast cancer when compared to Dutch natives (table 1). Migrant women from Turkey (SIR=0.5), Morocco (SIR=0.6) and Suriname (SIR=0.7) exhibited significantly lower breast cancer risks than native Dutch women (table 2).
The risk of dying was significantly higher in premenopausal women from Morocco (HR=1.4; 95%CI: 1.0-2.0) and Suriname (HR=1.3; 95%CI: 1.0-1.7) in comparison with native Dutch women (table 3). Additional adjustment for stage at diagnosis reduced these survival disparities in premenopausal women, being no longer statistically significant. In this age group five-year relative survival ranged from 74% in Moroccan to 83% in

Table 1 Description of cohort of newly diagnosed breast and stomach cancer cases in the Netherlands according to country of birth (1996-2009)

	Country of birth					
	Native Dutch	Antilles/Aruba	Indonesia	Morocco	Suriname	Turkey
Breast cancer						
Total (n)	92,197	366	1964	325	888	386
Mean age (yrs)	63	53	67	46	54	49
SES high (%)	29	25	37	12	22	12
SES mid (%)	34	25	26	17	16	13
SES low (%)	37	49	37	71	62	75
SES unknown (%)	0.1	0.8	0.3	0.0	0.2	0.3
Stage* (n included)	45,927	221	1,253	196	664	242
Stage 1 (%)	38	38	36	21	33	27
Stage 2 (%)	44	46	44	49	49	47
Stage 3 (%)	11	11	11	21	11	19
Stage 4 (%)	5.6	4.1	6.0	4.6	5.6	5.0
Stage unknown (%)	1.9	1.4	2.8	3.1	1.5	2.5
Median FU (yrs)	4.6	4.1	4.7	3.9	4.5	4.5
Stomach cancer						
Total (n)	24,443	83	279	154	263	274
Females (%)	36	46	37	32	41	30
Mean age (yrs)	71	57	70	57	61	56
Cardia (%)	16	38	13	28	11	14
Non-cardia (%)	84	62	87	72	89	86
SES high (%)	24	19	35	8	15	5
SES mid (%)	35	16	28	19	16	13
SES low (%)	41	65	37	72	68	81
SES unknown (%)	0.0	0.0	0.0	0.0	0.4	0.0
Stage cardia (n included)	6,869	13	105	20	30	38
Stage 1 (%)	9.0	0.0	6.7	20	6.7	13
Stage 2 (%)	12	0.0	16	0.0	3.3	18
Stage 3 (%)	16	31	16	10	27	11
Stage 4 (%)	41	46	31	50	33	45
Stage unknown (%)	22	23	30	20	30	13
Stage non-cardia (n included)	17,574	70	174	134	233	236
Stage 1 (%)	13	7.1	10	16	17	17
Stage 2 (%)	11	5.7	7.5	14	9.4	13
Stage 3 (%)	15	14	11	19	16	19
Stage 4 (%)	38	57	38	41	39	37

Table 1 (continued)

	Country of birth					
	Native Dutch	Antilles/Aruba	Indonesia	Morocco	Suriname	Turkey
Stage unknown (%)	23	16	33	10	18	13
Median FU (yrs)	0.5	0.9	0.6	0.7	0.9	1.0
Cardia	0.6	0.9	0.6	0.5	0.6	0.7
Non-cardia	0.5	0.9	0.5	0.9	1.0	1.1

SES = Socioeconomic Status; FU = Follow Up; *data on stage distribution of breast cancer are based on the former regions of Comprehensive Centres Amsterdam, West and Stedendriehoek Twente.

Table 2 Standardised Incidence Ratios (SIRs) for breast and stomach cancer with 95% confidence intervals (CI) for Males (M) and Females (F) according to country of birth (1996-2009)*

		Country of birth									
		Antilles/Aruba		Indonesia		Morocco		Suriname		Turkey	
		SIR	95%CI	SIR	95%CI	SIR	95%CI	SIR	95%CI	SIR	95%CI
Breast Cancer	F	1.0	(0.9-1.1)	**0.9**	(0.9-1.0)	**0.6**	(0.5-0.6)	**0.7**	(0.7-0.8)	**0.5**	(0.4-0.5)
Stomach cancer	F	**1.6**	(1.2-2.3)	**0.5**	(0.4-0.5)	**1.5**	(1.1-2.0)	**1.3**	(1.1-1.6)	**1.8**	(1.5-2.3)
	M	1.2	(0.9-1.7)	**0.5**	(0.4-0.5)	0.9	(0.8-1.1)	**1.2**	(1.0-1.4)	**1.7**	(1.4-1.9)
Cardia	F	1.3	(0.6-2.9)	**0.6**	(0.4-0.9)	0.5	(0.1-1.4)	0.9	(0.5-1.5)	0.8	(0.4-1.6)
	M	0.5	(0.2-1.0)	**0.6**	(0.5-0.8)	**0.4**	(0.3-0.7)	**0.3**	(0.2-0.5)	0.7	(0.5-1.0)
Non-cardia	F	**1.7**	(1.2-2.4)	**0.4**	(0.3-0.5)	**1.7**	(1.3-2.3)	**1.4**	(1.2-1.7)	**2.1**	(1.7-2.6)
	M	**1.7**	(1.2-2.4)	**0.4**	(0.3-0.4)	1.2	(1.0-1.5)	**1.7**	(1.5-2.0)	**2.2**	(1.9-2.6)

*Native Dutch = Reference (SIR=1.0); bold blue numbers are significant at p≤0.05 level

Indonesian and Dutch women. In postmenopausal women, 5-year relative survival of invasive breast cancer was 82% in Dutch and ranged from 83% in Indonesian to 92% in Antillean women.

Stomach cancer

Stomach cancer risk was significantly lower in migrants from Indonesia (SIR=0.5) and higher in (male and female) migrants from Turkey (1.7 and 1.8, respectively) and Suriname (1.2 and 1.3) as well as in males from the Antilles/Aruba (1.6) and Morocco (1.5). The risk for cancer of the cardia was lower in all migrant groups as compared to native Dutch patients, but only significantly in migrants from Indonesia and males from Morocco and Suriname. In contrast, non-cardia stomach cancer risk was significantly elevated in all groups except Indonesians and Moroccan females (table 2).

Hazard of death was reduced in migrants from the Antilles (HR=0.7), Suriname (HR=0.7), Turkey (HR=0.7) and Morocco (HR=0.8) was relative to Dutch natives (table 3). One-year relative survival rates was 36% in Dutch natives, but ranged between 39% in Indonesian to 54% in Turkish migrants, holding for both cardia and non-cardia stomach cancer (except for Moroccan cardia patients), however more pronounced in the latter.

Table 3 Survival estimates for breast and stomach cancer according to country of birth (1996-2009)

	Country of birth											
	Native Dutch		Antilles/Aruba		Indonesia		Morocco		Suriname		Turkey	
Breast cancer*												
% alive at end of FU	65		67		59		76		72		74	
Age < 50 yrs	75		61		70		73		72		72	
Age ≥ 50	62		70		58		83		72		77	
HR^{crude} (95%CI)	1.0	(Ref)	**0.7**	(0.5-0.9)	**1.1**	(1.0-1.2)	0.8	(0.6-1.0)	**0.8**	(0.7-0.9)	**0.7**	(0.5-0.9)
HR^{adjusted†}	1.0	(Ref)	1.1	(0.8-1.4)	0.9	(0.9-1.0)	**1.4**	(1.0-1.9)	**1.2**	(1.0-1.4)	1.1	(0.9-1.5)
Age < 50‡	1.0	(Ref)	1.4	(0.9-2.2)	1.1	(0.8-1.6)	**1.4**	(1.0-2.0)	**1.3**	(1.0-1.7)	1.2	(0.8-1.7)
Age < 50$^{(+stage)†}$	1.0	(Ref)	1.3	(0.8-2.0)	1.2	(0.9-1.7)	1.2	(0.9-1.7)	1.2	(0.9-1.5)	1.0	(0.7-1.4)
Age ≥ 50‡	1.0	(Ref)	1.1	(0.7-1.5)	1.0	(0.9-1.1)	1.1	(0.6-2.0)	1.1	(0.9-1.3)	0.9	(0.6-1.3)
Age ≥ 50$^{(+stage)†}$	1.0	(Ref)	1.0	(0.7-1.5)	1.0	(0.9-1.0)	0.9	(0.5-1.6)	1.1	(0.9-1.3)	0.9	(0.6-1.3)
5-year RSR (95%CI)	82	(82-82)	87	(81-93)	83	(80-86)	78	(71-85)	82	(78-86)	83	(77-89)
Age < 50	83	(82-84)	78	(67-89)	83	(76-90)	74	(65-83)	80	(75-85)	76	(68-84)
Age ≥ 50	82	(81-83)	92	(86-98)	83	(80-86)	89	(79-99)	83	(78-88)	91	(84-98)
10-year RSR (95%CI)	71	(70-72)	71	(61-81)	71	(66-76)	65	(54-76)	70	(65-75)	70	(61-79)
Age < 50	73	(72-74)	67	(52-82)	70	(61-79)	62	(50-74)	64	(56-72)	66	(55-77)
Age ≥ 50	71	(70-72)	73	(60-86)	71	(66-76)	-	-	76	(68-84)	74	(56-92)
Stomach Cancer												
% alive at end of FU	6		15		10		18		17		21	
HR^{crude} (95%CI)	1.0	(Ref)	**0.7**	(0.6-0.9)	0.9	(0.8-1.9)	**0.6**	(0.5-0.7)	**0.6**	(0.5-0.8)	**0.7**	(0.6-0.7)
HR§	1.0	(Ref)	**0.7**	(0.6-1.0)	1.0	(0.8-1.1)	**0.8**	(0.6-0.9)	**0.7**	(0.6-0.8)	**0.7**	(0.6-0.8)
Cardia$	1.0	(Ref)	0.8	(0.4-1.4)	1.0	(0.8-1.2)	0.7	(0.5-1.2)	0.9	(0.6-1.3)	**0.7**	(0.5-1.0)
Non-cardia$	1.0	(Ref)	**0.7**	(0.6-1.0)	0.9	(0.8-1.1)	**0.8**	(0.6-0.9)	**0.7**	(0. 6-0.8)	**0.7**	(0.6-0.9)
1-year RSR (95%CI)	36	(35-37)	47	(36-58)	39	(33-45)	48	(40-56)	51	(45-57)	54	(48-60)
Cardia	36	(35-37)	45	(18-72)	38	(28-48)	25	(6-44)	41	(23-59)	49	(33-65)
Non-cardia	36	(35-37)	47	(35-59)	38	(31-45)	51	(42-60)	52	(45-59)	55	(49-61)
5-year RSR (95%CI)	11	(11-11)	-	-	18	(13-23)	22	(15-29)	24	(18-30)	25	(19-31)

FU=Follow-Up; HR=Hazard Ratio; RSR=Relative Survival Rate; CI=Confidence Interval; Ref=Reference

* for the breast cancer survival analyses 48,503 patients were included.

† adjusted for age, socioeconomic status, stage and country of birth

‡ adjusted for age, socioeconomic status and country of birth

§ adjusted for age, sex, socioeconomic status, stage, country of birth and stomach site (cardia/non-cardia)

$ adjusted for age, sex, socioeconomic status, stage and country of birth

bold numbers are significant at p≤0.05 level

Discussion

Migrants carried significantly lower risks of breast and cardia stomach cancer, contrasting higher non-cardia stomach cancer risks relative to patients from the native Dutch population. High mortality among migrant breast cancer patients could largely be explained by stage at diagnosis. Stomach cancer survival was significantly better in migrants from Morocco, Suriname and Turkey compared to Dutch natives and with only little variation by subsite (cardia, non-cardia). Contrary to our expectations, relative breast and stomach cancer survival was generally better in migrants as compared to native Dutch cancer patients.

The reasons for lower breast cancer risks in migrant women compared to native women of Western countries can partly be explained by differences in reproductive and lifestyle patterns. More specifically, reproductive indicators such as the early age at menarche and higher age at first birth as well as the number of children, breastfeeding behaviours and the use of hormonal therapies in postmenopausal women represent key risk factors in the carcinogenesis of breast cancer (5). Migrant women from less developed countries often exhibit many protective risk factors that subsequently lower their breast cancer risk (11). Low breast cancer incidences in migrant women of non-Western origin residing in the Netherlands have also been reported by several studies from the Netherlands (12-13) and other Western European countries (14-16). Breast cancer is curable if detected at an early stage and treated adequately. Similar or better breast cancer survival rates appeared in migrant women in contrast to lower rates in studies from the US and New Zealand (17-18). These disparities in breast cancer survival may reflect differences in screening attendance which has often been observed to be significantly lower in migrant women in the Netherlands (19) but also in other countries (20-21). Important barriers in migrant women residing in the Netherlands are lacking knowledge and awareness as well as socio-cultural aspects as important inhibiting factors influencing screening uptake. Nevertheless, considering the very low breast cancer risk in migrant women, low attendance rates in breast cancer screening programmes are presently not worrisome. To the contrary, a higher screening uptake might even be unfavourable in these groups, entailing a high 'number needed to screen' and thereby risking a high number of false positive.

High risks of non-cardia stomach cancer in migrant populations are likely to be associated with helicobacter pylori (H. pylori), typically acquired during early childhood, i.e. before migration. H. pylori incidence is highest in developing countries, but also in southern and eastern Europe, and transmission is fostered by poverty associated factors such as unhygienic and crowded living conditions (5, 8). Thus, migrants from low-income countries experience a relatively high stomach cancer incidence when compared to the population of their host country, which is also evident in our data. Differences between cardia (proximal tumours, close to the gastro-oesophageal junction) and non-cardia (distal tumours) stomach cancer incidence may be due to different underlying risk factor patterns. Whilst the association to H. pylori infection seems to be confined to non-cardia stomach cancers, risk factors for cardia stomach cancer are more similar to those of oesophageal cancers, thus lifestyle related factors such as diet, smoking and alcohol consumption (22). In fact, adenocarcinomas of the distal oesophagus and cardia

stomach cancer were found to be one clinical entity (23). This explains the high rates for non-cardia but low rates for cardia stomach cancer among migrants that we found in our study. Yet, possible modification of the carcinogenicity of H. pylori in concurrence with environmental factors cannot be excluded and still needs to be investigated.
Contrary to our expectations, the study revealed favourable stomach cancer survival rates in most migrant groups, irrespective of the exact tumour location and even though stage distribution at diagnosis was worse than among Dutch natives (table 1). Several other studies, however, found that stomach cancer survival was especially poor in migrants (3). Due to the high fatality of stomach cancer in general, differences in survival are unlikely to be influenced by early detection measures or possible treatment inequalities. As a result, the observed differences are likely to be driven by other causes that are beyond the currently known risk factors. Differences in genetic predisposition might for instance play a causal role. Another explanation for the observed survival advantage might be the so called salmon bias. The remigration of diseased persons back to their country of origin without de-registering with the Dutch authorities, renders them statistically immortal and results in low survival rates (24).

Our results are limited with regard to the validity of the migrant definition we used in our study. Country of birth is currently the most accepted proxy for ethnicity, although it has limitations with regard to cultural and ethnic identity (25). This limitation resulted in different results for migrants originating from Indonesia, formerly Dutch Indies, a Dutch colony, when compared to the other migrant groups. On the one hand, most people who were born in Indonesia and migrated to the Netherlands had Dutch ancestors and were ethnic Dutch, and on the other hand, their migration history to the Netherlands reaches back much longer than that of 'newer' migrants. Moreover, there was missing COB information for many individuals still alive at the end of follow-up. Due to generally low survival rates, this hardly affected stomach cancer survival in our study. However, for breast cancer with on average better survival, data from only three regional cancer registries with sufficient completeness could be included. Only by doing this, we were able to calculate reliable estimates of survival rates according to COB. We assumed that the completeness of registration of COB affects migrants and natives similarly, although registration clerks might have been more likely to register COB in case of a non-Dutch patient.
Due to lacking data availability in the reference population, we could not apply the SES proxy in the incidence analyses. This leaves uncertainty of how much of the effect may be attributable to socioeconomic circumstances. Yet, the survival analyses showed significant effects after adjusting for potentially confounding socioeconomic factors. As age at migration and duration of residence are not available in NCR data (as in few other cancer registries in the world) , we were not able to assess the impact of these factors. On the other hand, we were able to accurately estimate relative survival using country of birth-specific background mortality provided by Statistics Netherlands.

Especially by the cancer experience of Indonesian migrants (most of whom reside in the Netherlands for more than 60 years), our results emphasize the importance of life course in the analysis of cancer risks in migrant populations. Exposures before, during and after migration underscore key hints for causal inferences in carcinogenesis. In particular, early life exposures (non-cardia stomach cancer) and acculturation processes

(breast cancer) play important roles in the change of cancer risks over time and across generations.
Survival disparities require careful monitoring and counteraction with preventive means as well as improved access to healthcare. This is especially relevant for access to care for upper gastrointestinal section complaints and symptoms. Migrant-specific risk profiles should complement guidelines for the detection and management of stomach cancer.

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Conflict of interest.
None to declare.

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7

Investigating cervical, oesophageal and colon cancer risk and survival in migrants in the Netherlands

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Abstract

Background: Studies on cancer in migrants can shed light on grey areas in cancer aetiology and help assessing the effectiveness of prevention measures. In this study, we aim to determine the impact of migration and different ethnic backgrounds on cervical, colon and oesophageal cancer risk and survival.

Methods: Cancers diagnosed 1996-2009 were selected from the Netherlands Cancer Registry. Besides standardized incidence ratios, differences in survival were explored using Cox regression and relative survival analysis.

Results: All migrant women had increased risks for cervical cancer when compared to Dutch native women, ranging from SIR=1.8 (95%CI: 1.6-2.2) in Surinamese women to 1.2 (0.9-1.5) in Turkish women. Relative survival was better among Moroccan, Surinamese and Antillean migrants (5-yr RSR range: 71-73%) compared to that of native Dutch (66%), however poorer in Indonesians (51%). While oesophageal cancer risk was lower in all migrants with SIRs ranging from 0.1 to 0.6, survival was slightly lower relative to Dutch natives (1-yr RSR 21-32% compared to 37%, Turkish: 42%). Colon cancer was less common among migrants, particularly among Moroccans and Turkish. 5-yr RSR from colon cancer was equal or better in all migrants (range: 48% in Indonesians to 62% in Turkish) compared to Dutch natives (48%).

Conclusion: Risk of cervical, oesophageal and colon cancer in migrants mainly reflects the risks in their countries of origin. Almost similar cancer survival in migrants and native Dutch points toward successful and comprehensive healthcare in the Netherlands. Primary cancer prevention should target high-risk groups and involve migration-sensitive approaches.

Introduction

Studies on cancer in migrant populations may provide valuable insight into carcinogenesis and be helpful in exploring the contributions of environmental and genetically determined risk factors as well as their interaction (1).
Cervical cancer is the second most common female cancer worldwide and varies greatly on a global scale, being most prevalent in developing countries. Studies from Sweden reported increased risks of cervical cancer in immigrant women (2-3), especially among those who originate from Central America and Middle Africa (2-3). The opposite was true for women from Eastern Africa and Asia, who had lower risks than Swedish-born women (2). The heterogeneous geographical and ethnic distribution of cervical cancer has been found to be strongly linked to human papillomavirus (HPV) infection.
Oesophageal cancer was reported was reported to be less common in various migrant groups (4), however particularly high in African American males and immigrants from East/Central Asia and East Africa (5-6). Heavy alcohol use, tobacco smoking as well as low consumption of fruits and vegetables, obesity and gastro-oesophageal reflux is related to oesophageal cancer (7).
The incidence of colon cancer has also been reported to vary substantially among ethnic groups. Globally, the highest rates have been observed among African Americans and Japanese Americans (8). Low physical activity, a positive family history, high meat and alcohol intake as well as smoking are considered the most important risk factors while high consumption of vegetables and dairy foods (calcium) as well as a low BMI are known to be protective (9).
Ethnic background was found not only to influence cancer risk, but also stage of disease at diagnosis and prognosis (10). However, to date, studies on cancer survival among migrants remain scarce and especially the link between cancer incidence and survival in migrant populations has so far been paid little attention. The Netherlands represent a unique setting for such studies given its obligatory health insurance for all inhabitants and its nation-wide cancer registry.
The aim of this study was to investigate the impact of migration on the incidence and survival of cervical, oesophageal and colon cancer in different migrant groups in the Netherlands. These cancers were selected because of their relevance to the migrant groups under study (particularly low or high risk, figure 1). We hypothesised that due to manifold environmental influences before, during and after migration, the various groups differ with regard to their risk factor patterns and their cancer risk.

Methods

Cancer Cohort
We obtained invasive cancers of the oesophagus (C15), colon (C18) and cervix uteri (C53), diagnosed between 1996 and 2009, from the population-based Netherlands Cancer Registry (NCR). For oesophageal and cervical cancer we only included squamous cell carcinomas (SCC) and adenocarcinomas (AC).
Stage at diagnosis was taken into account using the tumour-node-metastasis (TNM) classification at the year of diagnosis (11-13). Hereby, pathological and clinical TNM were combined into one variable, primarily referring to the pathological stage unless missing for colon and oesophagus. FIGO (International Federation of Gynaecology and Obstet-

rics) stage for cervical cancer was derived from clinical TNM stage (11-13), using pTNM in case of an unknown cTNM. Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the (automated) municipal population registries which record information on their inhabitant's vital status (follow-up until December 31, 2009).
We identified migrants based on their country of birth (COB) which is collected in the NCR and supplemented with data from the nationwide database of all municipal population registries in case of death or emigration. Besides native Dutch cancer patients, the largest migrant groups, originating from Turkey, Morocco, Suriname, the Netherlands Antilles/Aruba as well as Indonesia, were included and analysed separately. Patients with another (n=3092) or unknown COB (n=31,714) were excluded. Not all regional cancer registries (which together form the NCR) have complete registration of COB. In case of cancers with low lethality, patients being alive at the end of follow up may have missing COB. For colon and cervical cancer (which both have low lethality), we therefore only included data of cancer registries with complete registration of COB for the analyses on survival and stage distribution. These data were gathered from the former areas (both rural and urban) of the comprehensive cancer centres Amsterdam, West and Stedendriehoek Twente which cover approximately 40% of the Dutch population.
We applied an ecological proxy for socioeconomic status (SES) by using four-digit postal code at the time of diagnosis, provided by the Netherlands Institute for Social Research. SES was based on mean income per household, the percentage of households with a low income, low education and unemployed inhabitants. The variable SES was analysed in tertiles, resulting in three SES levels: high, intermediate and low. A more detailed explanation is described elsewhere (14).

Statistical Analysis
Oesophageal, colon and cervical cancer were analysed separately. Incidence rates were calculated per age group (0-14, 15-29, 30-44, 45-64 and 65 years and older), sex and year of diagnosis with cancer incidence rates of the entire Dutch population as reference, acquired from Statistics Netherlands (15). Population data of all legal residents of the Netherlands contained country of birth as a proxy for migration background and were available for the period 1996-2009. Expected numbers of cancer cases in each migrant group were derived from annual population data as well as age- and sex-specific cancer incidence and were compared to the observed numbers of cases in our data. Standardised incidence ratios (SIRs) were computed as the ratio between observed and expected numbers of cases between 1996 and 2009 with their 95% confidence intervals (CIs), calculated after log transformation (16).
For survival analysis, first, hazard ratios (HRs) were computed using Cox regression, adjusting for sex, age, morphology, SES, COB and stage of disease at diagnosis. Second, cohort-based relative survival was calculated. In order to account for the fact that migrants may experience different competing risks and comorbidities, we incorporated country of birth-specific death rates in the background mortality. This approach had been used earlier to correctly measure socioeconomic differences in cancer survival (17-18). In order to correct for low numbers of deaths in some groups, we used log-linear regression with interaction terms for period, age and sex to smooth the mortality rates. In all analyses, all-cause mortality was used as the outcome measure. All analyses were performed with SAS 9.1.

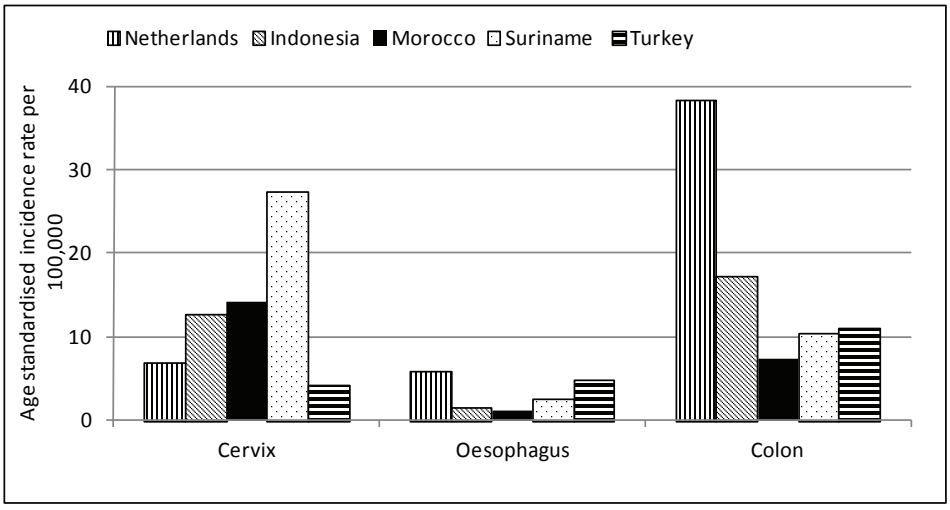

Figure 1 Age-standardized incidence rates per 100,000 of cervical, oesophageal and colon cancer in the Netherlands, Indonesia, Morocco, Suriname and Turkey (source: Globocan 2008 (5))

Results

In total, 5,546 patients with invasive cervical, 16,217 patients with oesophageal and 67,479 patients with colon cancer were included in the study. Cancer patients with a foreign background were on average younger at diagnosis than cancer patients from the Netherlands, with the exception of migrants originating from Indonesia (table 1). There were statistical significant differences ($p<0.05$) in SES between the groups for all three cancer types and for cervical and colon cancer in stage at diagnosis.

Cervical cancer

The risk for cervical cancer was increased in all migrant women when compared to Dutch native women and ranged from SIR=1.8 (95%CI: 1.6-2.2) in Surinamese women to 1.2 (0.9-1.5) in Turkish women (figure 2). This pattern was more pronounced for SCCs where migrant women from all origins exhibited significantly increased risks, being highest in Surinamese women (2.1; 1.7-2.4) (data not shown). Significantly increased risks for ACs of the cervix were only found in Moroccan women (1.7; 1.1-2.6).

The risk of dying after cervical cancer was increased, however non-significantly, for patients from Antilles/Aruba (HR=2.0, 95%CI: 1.0-4.0) and Turkey (1.2; 0.7-2.0). Risks for Indonesians, Moroccans and Surinamese women were similar to those of native Dutch. 1- and 5-year relative survival was better in migrants from the Antilles/Aruba and Turkey, but also for Morocco and Suriname (ranging from 91 to 96% for 1-yr RSR and 66 to 73% for 5-yr RSR) compared to that of native Dutch cancer patients (1-yr RSR: 84%; 5-yr RSR: 66%), however significantly only for 1-yr RSR in Moroccan and Surinamese women (table 2).

Oesophageal cancer

All migrant groups exhibited lower risks for oesophageal cancer as compared to Dutch

Table 1 Description of cohort of newly diagnosed patients with cervical, colon and oesophageal cancer in the Netherlands according to country of birth (1996-2009)

	Country of birth					
	Native Dutch	Antilles/ Aruba	Indonesia	Morocco	Suriname	Turkey
Cervix Uteri (C53)						
Total (n)	5,072	39	129	81	151	74
Mean age (yrs)	55	48	62	48	54	47
AC (%)	22	15	17	24	13	15
SCC (%)	78	85	83	77	87	85
SES high (%)	27	18	36	11	19	4
SES mid (%)	30	15	18	14	15	11
SES low (%)	43	67	46	75	66	85
SES unknown (%)	0	0	1	0	1	0
p-value (chi²)						<0.0001
Stage* (n included)	2,406	22	83	49	103	41
Stage 1 (%)	55	73	37	57	66	59
Stage 2 (%)	24	9	28	33	11	29
Stage 3 (%)	15	18	23	10	20	5
Stage 4 (%)	5	0	12	0	2	7
Stage unknown (%)	2	0	0	0	1	0
p-value (chi²)						0.0028
Oesophagus (C15)						
Total (n)	15,865	32	232	20	43	25
Females (%)	28	22	29	10	19	44
Mean age (yrs)	68	64	70	64	64	60
AC (%)	62	31	56	70	21	24
SCC (%)	38	69	44	30	79	76
SES high (%)	26	22	35	5	14	12
SES mid (%)	35	16	26	20	19	16
SES low (%)	40	63	39	75	67	72
SES unknown (%)	0	0	0	0	0	0
p-value (chi²)						<0.0001
Stage (n included)	15,865	32	232	20	43	25
Stage 1 (%)	5	6	4	5	0	4
Stage 2 (%)	14	16	14	15	12	8
Stage 3 (%)	21	19	19	25	26	48
Stage 4 (%)	35	44	37	30	42	28
Stage unknown (%)	25	16	26	25	21	12
p-value (chi²)						0.564

Table 1 (continued)

	Country of birth					
	Native Dutch	Antilles/ Aruba	Indonesia	Morocco	Suriname	Turkey
Colon (C18)						
Total (n)	65,011	153	1,548	135	461	171
Females (%)	51	54	52	26	54	36
Mean age (yrs)	72	61	73	59	62	59
SES high (%)	27	28	38	13	20	8
SES mid (%)	34	16	26	13	20	13
SES low (%)	39	56	36	75	60	80
SES unknown (%)	0	1	0	0	1	0
p-value (chi^2)						<0.0001
Stage* (n included)	27,528	83	902	75	321	77
Stage 1 (%)	13	12	15	11	12	6
Stage 2 (%)	32	25	31	31	29	42
Stage 3 (%)	24	24	25	24	31	26
Stage 4 (%)	23	35	23	29	23	25
Stage unknown (%)	7	4	7	5	5	1
p-value (chi^2)						0.0358

AC = Adenocarcinoma; SCC = Squamous Cell Carcinoma; SES = Socioeconomic Status;
*data on stage distribution of cervix and colon cancer are based on the former regions of Comprehensive Centres Amsterdam, West and Stedendriehoek Twente.

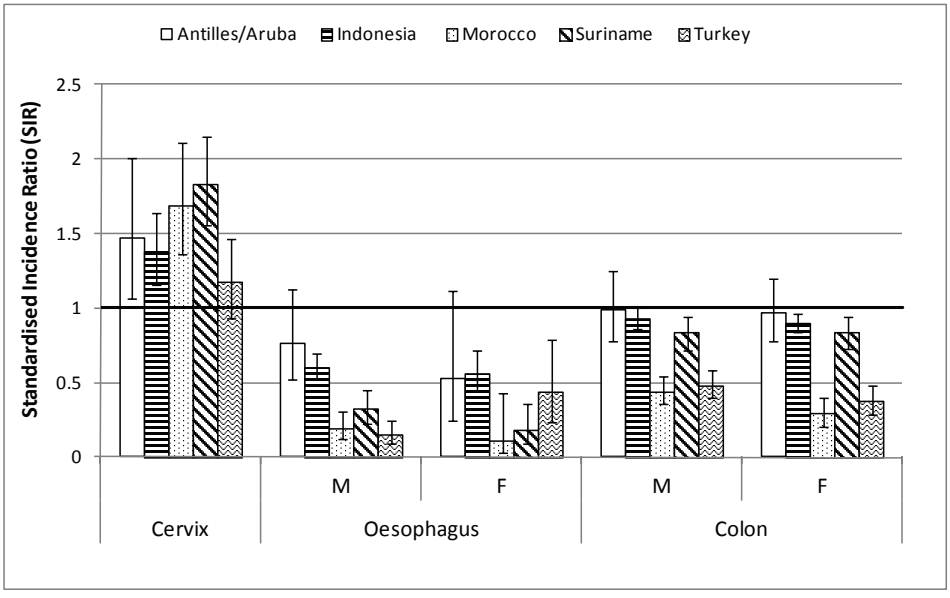

Figure 2 Standardised Incidence Ratios (SIRs) with 95% CIs for cervical, oesophageal and colon cancer for males (M) and females (F) according to country of birth compared to the native Dutch population (ref=1) 1996-2009.

natives (figure 2), being significantly lower for males from Indonesia (SIR=0.6; 95%CI: 0.4-0.7), Morocco (0.1; 0.0-0.4), Suriname (0.2; 0.1-0.4) and Turkey (0.4; 0.3-0.8). Similarly, risks were also significantly reduced in female migrants from Indonesia (0.6; 0.4-0.7), Morocco (0.1; 0.0-0.4), Suriname (0.2; 0.1-0.4), and Turkey (0.4; 0.3-0.8). Those patterns also held after stratification for SCC and AC, however being more pronounced in the latter (data not shown).
The risk of dying after oesophageal cancer among migrant patients was similar to that of native Dutch patients, regardless of the histological type (table 2). Low SES independently increased the risk of dying when compared to high SES (data not shown). 1-yr RSR was worse in most migrant groups (ranging from 21% in Surinamese and 32% in Indonesians; however statistically significant only in Surinamese) with the exception of migrants from Turkey (42%) as compared to Dutch natives (37%) (table 2).

Colon cancer
Colon cancer was less common among most migrant groups in comparison to Dutch natives. Particularly migrants from Suriname (SIR males: 0.8; 95%CI: 0.7-0.9, female: 0.8; 0.7-0.9), Morocco (males: 0.4; 0.4-0.5, females: 0.3; 0.2-0.4) and Turkey (males: 0.5; 0.4-0.6, females: 0.4; 0.3-0.5) showed significantly lower risks, whereas migrants from the Antilles as well as Indonesia exhibited risks close to that of Dutch natives (figure 2).
Migrants exhibited death risks after colon cancer that were similar to those of native Dutch (table 2). Being of low or intermediate SES significantly increased the risk of dying when compared to the high SES group while adjusting for COB in the same model (data not shown). 5-yr relative survival for patients with colon cancer was equal or better in all migrant groups, although not statistically significant (ranging from 48% in Indonesian to 62% in Turkish) in comparison with native Dutch (48%) (table 2).

Table 2 Hazard Ratios (HRs)* with 95% Confidence Intervals (95% CI) and Relative Survival Rates (RSRs)† for cervical, oesophageal and colon cancer according to country of birth compared to the native Dutch population, 1996-2009.

	Country of birth					
	Native Dutch	Antilles/ Aruba	Indonesia	Morocco	Suriname	Turkey
Cervix Uteri (C53)						
HR‡ (95%CI)	1.0	2.0 (1.0-4.0)	1.0 (0.7-1.3)	0.9 (0.5-1.6)	0.9 (0.7-1.3)	1.2 (0.7-2.0)
1-yr RSR	84 (82-86)	91 (78-104)	78 (69-87)	**96** (90-102)	**93** (88-98)	93 (85-101)
5-yr RSR	66 (64-68)	70 (46-94)	**51** (39-63)	73 (59-87)	72 (62-82)	66 (50-82)
Oesophagus (C15)						
HR‡ (95%CI)	1.0	0.9 (0.6-1.3)	1.1 (0.9-1.2)	0.8 (0.5-1.3)	1.1 (0.8-1.5)	0.9 (0.6-1.4)
1-yr RSR	37 (36-38)	29 (13-45)	32 (26-38)	27 (7-47)	**21** (8-34)	42 (22-62)
Colon (C18)						
HR§ (95%CI)	1.0	1.0 (0.8-1.4)	1.0 (0.9-1.1)	1.0 (0.7-1.4)	0.9 (0.8-1.1)	1.0 (0.7-1.4)
5-yr RSR	48 (47-49)	49 (36-62)	49 (45-53)	53 (39-67)	56 (49-63)	61 (47-75)

Discussion

The purpose of this study was to investigate the impact of migration on the risk and survival of oesophageal, colon and cervical cancer among migrants in the Netherlands. The findings suggest that migrants are on average at higher risk of developing cervical cancer but at lower risk of developing oesophageal and colon cancer. Furthermore, we found that the risk of dying of cancer was similar to that of the native Dutch population, pointing towards a great success in health care in the Netherlands.

Cervical cancer

The major cause of cervical cancer is HPV infection, showing a close association with the incidence of SCCs. Obesity and other lifestyle-related factors are more common in the development of ACs (19). The high incidence of cervical cancer in (most, but not all) migrant women found in our study reflects the situation in their country of origin with the highest SIR found among Surinamese women (figure 1 and 2). This might be due to a higher HPV prevalence in developing countries and/or the variation of different carcinogenic subtypes (20-21). It should however be noted that not all countries have a cancer registry or have good quality data, making international comparisons difficult.

Our results are in line with other studies from Europe, confirming increased risks among migrant women who migrated at older age and who originated from Central America and Middle Africa (2-3). In our study, risks were even more pronounced for SCCs, suggesting a predominant role for HPV-infection. A study on cervical cancer in Suriname found that besides high incidence rates also advanced stages at presentation and a strong correlation with socioeconomic conditions (i.e. higher incidence among socially disadvantaged) were typical for the disease (22). The correlation of lower SES with higher FIGO stage, fewer ACs and younger age at diagnosis has also been confirmed, in a study partly using the same database (14).

Relative survival from cervical cancer was better among migrant women than in native Dutch women. Geographic and ethnic differences in cervical cancer survival can partly arise due to screening. Nationwide screening was established in 1996 in the Netherlands, contributing to an ongoing decrease in mortality from cervical cancer since a few decades (23). Visser and colleagues (24) found that the participation of migrant women in cervical cancer screening was below target, especially in women originating from Morocco and the Antilles. Similarly, studies from the UK (25) and Sweden (26) reported lower uptakes for cervical cancer screening in various ethnic groups as compared to local-born women. Accordingly, we expected worse stage distribution and outcomes in migrant women with cervical cancer. However, screening for disease in pre-invasive stages not only leads to the removal of pre-malignant lesions and decreasing cancer incidence, but may also leave more aggressive, fast-growing tumours with worse survival. Unscreened populations may therefore have better survival as compared to screened populations (27), possibly explaining the better survival among migrant women in our study.

Oesophageal cancer

Oesophageal cancer is one of the most deadly malignancies. Squamous cell carcinoma (SCC) is the dominant type, however decreasing in many European countries, and mainly attributable to heavy alcohol use, tobacco smoking and low consumption of fruits and

vegetables. In contrast, adenocarcinoma (AC) is strongly linked to obesity as well as severe gastro-oesophageal reflux and is increasing in Western countries (7). In our study, we found proportionally more SCCs among migrants and more ACs among native Dutch cancer patients (table 1).
In accordance with our expectations, we found significantly lower risks for oesophageal cancer among all migrant groups. Risks were particularly low in migrants from Morocco and Turkey, reflecting lower incidences in their countries of origin (figure 1), most likely due to the retention of more favourable risk factor patterns, i.e. higher prevalence of alcohol abstinence and lower prevalence of tobacco smoking (28). Similarly, a study from Sweden (4) found decreased risks in migrant groups from low-incidence regions, however socioeconomic status was not taken into account. In our study, survival was equal or worse in all migrant groups compared to native Dutch whereby there was no indication for these findings considering the stage distribution at diagnosis (table 1). A possible explanation is the strong inverse link with socioeconomic determinants and poverty, potentially leading to worse access to and utilization of care.
At this stage, the most effective means in order to prevent oesophageal cancer is lifestyle change, i.e. smoking cessation and moderation of alcohol intake.

Colon cancer
Countries like Morocco, Turkey, Suriname and Indonesia are characterised by much lower rates of colon cancer than the Netherlands (figure 1) (5, 29-30). The same pattern was reflected in our data: migrants from low-incidence countries apparently carried their risk patterns forward to their new host country. Mortality from colon cancer is decreasing in many developed countries due to screening, surveillance practices and more effective treatments both surgically and systemically. No significant differences in colon cancer survival were found in our data, even though relative survival was slightly better, although not significantly, in all migrant groups as compared to native Dutch. In another study from the Netherlands, slightly higher survival rates were found for the Dutch population as a whole (31).

Discussion of methods
There were three main methodological limitations related to our study. Firstly, the validity of COB as indicator for ethnicity is impeachable. Yet, it is currently the most widely used proxy in health research, mainly because of the limited availability of migration-sensitive health/cancer data in many European countries (32-33). In our study, there was missing COB information for many individuals still alive at the end of follow-up. To overcome this problem, survival analyses were limited to only 3 regional cancer registries, covering approximately 40% of the Dutch population. Only by doing this, we were able to calculate reliable estimates of survival rates according to COB. However, incidence rates were calculated with nation-wide cancer registry data. This might have been affected by incomplete registration of COB. Due to generally low survival rates, this hardly affected oesophageal cancer incidence in our study. However, for cervical and colon cancer with on average better survival, incidence rates might have been incorrectly estimated. We assumed that the completeness of registration of COB affects migrants and natives similarly, although registration clerks might have been more likely to register COB in case of a non-Dutch patient.
Secondly, we cannot entirely exclude selective remigration ('salmon bias') due to severe

illness and death. However, because survival of colon and oesophageal cancer in migrants in our study even came below that of the Dutch population as a whole (cf. colon 5-yr-RSR: 59%; cervix 5-yr-RSR: 66%; oesophagus 1-yr-RSR: 42% (1999-2008) (34)) the impact is considered negligible. Migrants are often referred to as a highly (self-)selected group, comprising on average healthier persons (35). Yet, due to the population-based approach and the type of migrants we studied, the possible impact of the so called "healthy migrant effect" is considered minor. Migrants from Indonesia took a distinct role relative to the other migrant groups, being older at diagnosis and having the highest SES. Moreover, their cancer incidence and survival were close to that of the native Dutch. Since Indonesia was the first Dutch colony that claimed independence (in 1949), Indonesian migrants have the longest history in the Netherlands compared to other migrant groups. Length of stay is related to higher degrees of acculturation, which would explain the patterns we found (36). Besides, the majority of migrants from Indonesia are ethnic Dutch. Unfortunately, (linked) data on age at immigration and duration of residence of immigrants are not available in Dutch cancer registry data.

Thirdly, the applied SES measure in this study is ecological and reflects the socioeconomic background at the time of diagnosis (or preceding diagnosis). We thus cannot rule out that the effects for SES would be different if individual SES was used.

Conclusion

We conclude that risks of cervical, oesophageal and colon cancer in migrants in large parts reflect the risks in their countries of origin. Early childhood experiences before migration (cervical cancer) and the retention of favourable health patterns with regard to smoking, alcohol consumption and diet (oesophageal and colon cancer) determine their cancer risks in the new host country. Especially in combination with corresponding cancer survival measures, the findings of this study can serve as important starting points for cancer prevention in disadvantaged groups, respectively.

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Key points

- Analysis of cancer patterns in high risk migrants in low risk host countries (and of low risk migrants in high risk host countries) may lead to important insight into carcinogenesis.
- To date, insight into the combined picture of cancer incidence and survival in migrant populations is much-needed but remains scarce.
- Ethnic differences in cervical, oesophageal and colon cancer incidence in large part reflect underlying risk factor patterns in the countries of origin, however, survival, in the presence of socioeconomic disadvantages, appears to be similar to that of native Dutch.
- Equal cancer survival points toward equal access, quality and utilization of cancer care - a great success for the Dutch healthcare system.
- Prospectively, potential cancer inequalities should be measured and monitored by taking both incidence and survival (and mortality) into account.

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8

Lower mortality from nasopharyngeal cancer in the Netherlands since 1970 with differential incidence trends in histopathology

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Abstract

Objective: Nasopharyngeal carcinoma (NPC) is rare in Western countries although related to common and unrelated phenomena, smoking and immigration from China and North Africa. We studied trends in NPC incidence, tumour morphology, survival and mortality in order to assess progress against this cancer.

Material and Methods: Nationwide incidence and mortality data covering the periods 1989-2009 and 1970-2009 were analysed. According to the WHO classification we distinguished keratinizing SCC (WHO-I), differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma. Changes in rates were evaluated by calculating the estimated percentage of change (EAPC).

Results: NPC incidence significantly decreased since 1989, especially in males (EAPC 1989-2009: -1.3; 95% CI: -2.5, -0.2) and in patients with keratinizing SCC (WHO-I) (EAPC: -3.6; 95%CI: -5.3, -1.8). In contrast, the incidence of differentiated non-keratinizing tumours (WHO-IIA) significantly increased in the same period (EAPC: 9.6; 95% CI: 5.6, 13.5). One- and three-year relative survival, used to estimate disease-specific survival, showed a slight increase from 79 to 81% and from 57 to 65% between 1989 and 2009 respectively. NPC mortality significantly decreased since 1970 (EAPC: -1.2; 95%CI: -1.8, -0.5), more pronounced since 1989 (EAPC: -3.0; 95%CI: -4.3, -1.6).

Conclusion: During the past two decades, the incidence of NPC in the Netherlands decreased mainly by less keratinizing, supposedly smoking-related NPC (WHO-I). However, the incidence of non-keratinizing NPC (WHO-IIA, B) increased, most likely due to EBV infection and thus related to higher immigration levels of people from high-incidence areas.

Introduction

Nasopharyngeal carcinoma (NPC) has a substantial geographic and demographic variation. In western countries, NPC is an orphan disease with incidence rates below one per 100,000. NPC is endemic in Southern China and North Africa (1-3) and it is thus most prevalent in the Netherlands among immigrants from high incidence countries like China, Indonesia and Morocco (4).
The World Health Organization (WHO) distinguishes three major histological forms: keratinizing squamous cell carcinoma (SCC) (WHO-I) – highly differentiated tumours with characteristic epithelial cell shape, growth patterns and keratin filaments – as well as differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma, that retain epithelial cell shape and growth patterns and are distinguished based on light microscopy (5-7). While WHO-I is a more common tumour in low-incidence populations, WHO-IIA and B usually occur more frequently in high-incidence populations (8-9).
A well-established risk factor for NPC is infection with Epstein-Barr virus (EBV), an ubiquitous herpes virus and confined to non-keratinizing carcinomas (WHO-IIA and B). Tobacco smoking and alcohol consumption are likely to contribute to SCCs of the nasopharynx (WHO-I) (10-11).
Nasopharyngeal carcinoma is highly sensitive to radiotherapy, the standard treatment for NPC patients without distant metastases. In cases with more advanced disease usually a combination of chemo-radiation is standard of care (12). Important prognostic factors for survival are stage, WHO type and age at diagnosis. Recently, EBV-related markers for diagnosis and prognosis of NPC became available (13-16) including molecular defined EBV (IgA) serology, which is characteristic for undifferentiated carcinomas (WHO-IIB), detection of EBV DNA load and oncogenic mRNA in nasopharyngeal brushings, reflecting local tumour presence and EBV DNA load in blood reflecting disease activity, clinical response after therapy and predicting distant metastases (17).
The aim of this study was to assess progress against NPC by investigating population- and behaviour-related trends in incidence and tumour sub-classification, together with survival and mortality since 1970/89 in the Netherlands, a low incidence country.

Material and Methods

Incidence data on NPC from 1989 to 2009 were extracted from the population-based Netherlands Cancer Registry (NCR). Only malignant tumours were included. Sarcomas in the nasopharynx were excluded. Mortality data from 1970 to 2009 were acquired from Statistics Netherlands (18). Information on the vital status of diagnosed cancer patients was initially obtained from municipal registries and from 1995 onward from the nationwide database of all municipal population registries, providing virtually complete coverage of all deceased Dutch citizens. Follow-up was complete until 1 January 2010. For most analyses, males and females were grouped and stratified into three age groups (<60, 60-74 and ≥75 years). Three main histological types according to the WHO classification (5) were distinguished: keratinizing SCC (WHO-I) as well as differentiated (WHO-IIA) and undifferentiated (WHO-IIB) non-keratinizing carcinoma. Neuroendocrine carcinoma, adenocarcinoma and tumours without pathological confirmation were combined as 'other carcinoma'. Stage was registered according to the UICC TNM Classification. Cases diagnosed 1989-1998 were classified according to the 4th TNM edition and

diagnosed 1999-2009 according to later editions, as those are equal for NPC. Additional information on country of birth, that was not included in the original dataset, was provided in hindsight and upon request from the NCR. It thus marginally deviates from the patient group included in the original study but still represents a valid comparison.

Incidence and mortality rates were standardized to the European standard population. Changes in rates were evaluated by calculating the estimated percentage of change (EAPC) and the corresponding 95% confidence interval (CI). This was done by performing a linear regression analysis where a regression line is fitted to the natural logarithm of the rates, using calendar year as regressor variable. The trend was considered significant when the p-value was below 0.05. Changes in NPC occurrence were identified by performing joinpoint regression analysis (National Cancer Institute, Bethesda, Maryland) (19).
One-, three- and five-year relative survival was used to estimate disease-specific survival. Relative survival reflects the survival of cancer patients, adjusted for competing causes of death in the general population with the same age and gender distribution. Traditional cohort-based relative survival analysis was performed for the period 1989-2009. All statistical analyses were performed using SAS (version 9.2).

Results

The main characteristics of all 1,411 patients diagnosed with NPC between 1989 and 2009 are summarized in table 1. Among the patients were 1,005 (71%) males and 406 (29%) females. The male-to-female incidence ratio was 2.5:1 in the period 1989-1993 and gradually equalized in more recent years. About 59% of the patients were below age 60 at diagnosis.
During 1989-1998, 5% of the cases were diagnosed in stage I, 6% in stage II, 14% in stage III and 69% in stage IV. Stage distribution changed to 5% stage I, 20% stage II, 29% stage III and 40% stage IV during 1999-2009.
With 621 cases (44%), undifferentiated non-keratinizing carcinoma (WHO-IIB) was the predominant histological type, followed by 555 (39%) keratinizing squamous cell carcinomas (WHO-I) and 115 (8%) differentiated non-keratinizing carcinomas (WHO-IIA). Radiotherapy was most commonly administered to these patients. While 715 patients (51%) received radiotherapy only, another 429 patients (30%) were treated in combination with systemic and/or chemotherapy. Merely 76 patients (5%) received additional surgery and in 99 patients (7%) treatment was abandoned. About 69% of all newly diagnosed NPC patients were born in the Netherlands, 10% in Morocco, 5% in China, 4% in Indonesia and 3% in Turkey.

Histological variation
Patients with WHO-I tumours were on average older, diagnosed at later stages and received surgery more often than patients with other tumour histology. WHO-I was the predominant NPC type in patients born in the Netherlands (47%), whereas in patients born in most non-western countries, WHO-IIB was the most common histological variant (53-66%; Tab. 1).

Table 1 Characteristics of incident NPC cases according to WHO histology classification 1989-2009 (source: NCR)

	WHO-I keratinizing squamous cell carcinoma		WHO-IIA differentiated, non-keratinizing carcinoma		WHO-IIB undifferentiated, non-keratinizing carcinoma		Other carcinoma		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*
Period of diagnosis									
1989-1993	162	47	13	4	143	41	28	8	346
1994-1998	128	42	10	3	134	44	32	11	304
1999-2003	122	35	29	8	164	47	34	10	349
2004-2009	143	35	63	15	180	44	26	6	412
Age at diagnosis									
0-14	3	9	1	3	17	50	13	38	34
15-29	10	14	4	6	50	71	6	9	70
30-44	58	27	23	11	122	56	15	7	218
45-59	218	43	43	8	219	43	27	5	507
60-74	197	45	34	8	164	38	39	9	434
75+	69	47	10	7	49	33	20	14	148
Sex									
Male	412	41	82	8	451	45	60	6	1,005
Female	143	35	33	8	170	42	60	15	406
Stage at diagnosis (1989-1998)									
1	20	63	1	3	6	19	5	16	32
2	21	54	3	8	12	31	3	8	39
3	46	52	0	0	39	44	3	3	88
4	190	43	19	4	211	47	27	6	447
unknown	13	30	0	0	9	20	22	50	44
Stage at diagnosis (1999-2009)									
1	16	41	6	15	12	31	5	13	39
2B	48	32	19	13	78	52	4	3	149
3	69	31	32	14	113	51	7	3	221
4A	78	40	23	12	76	39	16	8	193
4B	31	44	7	10	32	45	1	1	71
4C	14	36	3	8	20	51	2	5	39
unknown	9	18	2	4	13	27	25	51	49
Country of birth*									
Netherlands	444	47	72	8	364	38	70	7	950
Other Western	13	54	0	0	10	42	1	4	24
Indonesia	18	30	9	15	32	53	1	2	60
Suriname/ Dutch Antilles	12	35	2	6	18	53	2	6	34

Table 1 (continued)

	WHO-I keratinizing squamous cell carcinoma		WHO-IIA differentiated, non-keratiniz-ing carcinoma		WHO-IIB undifferentiated, non-keratinizing carcinoma		Other carcinoma		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*
Turkey	17	40	1	2	24	57	0	0	42
Morocco	29	21	17	13	88	65	1	1	135
China	16	25	5	8	43	66	1	2	65
Other non-Western	20	31	9	14	35	55	0	0	64

* Data on country of birth originate from a separate dataset provided upon request by the Netherlands Cancer Registry

Trends in incidence

Among males, the age-standardized incidence rate of NPC significantly decreased over time from 0.8 per 100,000 in 1991 to 0.5 in 2007 (EAPC 1989-2009: -1.3; 95% CI: -2.5, -0.2), whereas the incidence among females remained stable at about 0.2 per 100,000 (Tab. 2, Fig. 1). The age-specific incidence rose after the age of 30 and peaked at the age 55-65 years, being highest in the period 1989-1991 (Fig. 2). A decline in incidence was observed in almost all age groups, however only significant in patients aged 75 and over (EAPC: -3.5; 95% CI: -6.3, -0.8). The incidence of WHO-I tumours decreased significantly between 1989 and 2009 (EAPC: -3.6; 95%CI: -5.3, -1.8), whereas the incidence of non-keratinizing differentiated tumours significantly increased in males (EAPC: 6.6; 95%CI: 2.5, 10.8) (Tab. 2).

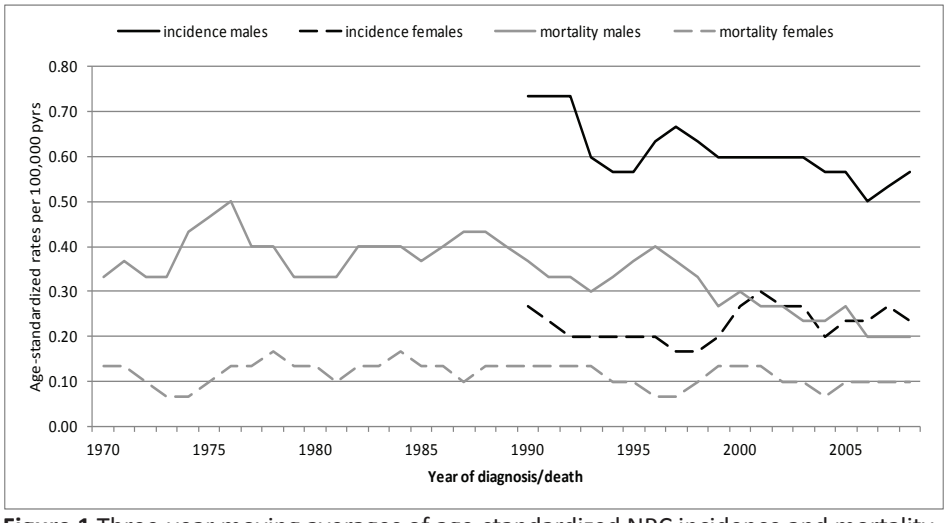


Figure 1 Three-year moving averages of age-standardized NPC incidence and mortality rates per 100,000 person-years (ESR) in the Netherlands 1970/1989-2009 (source: NCR, Statistics Netherlands)

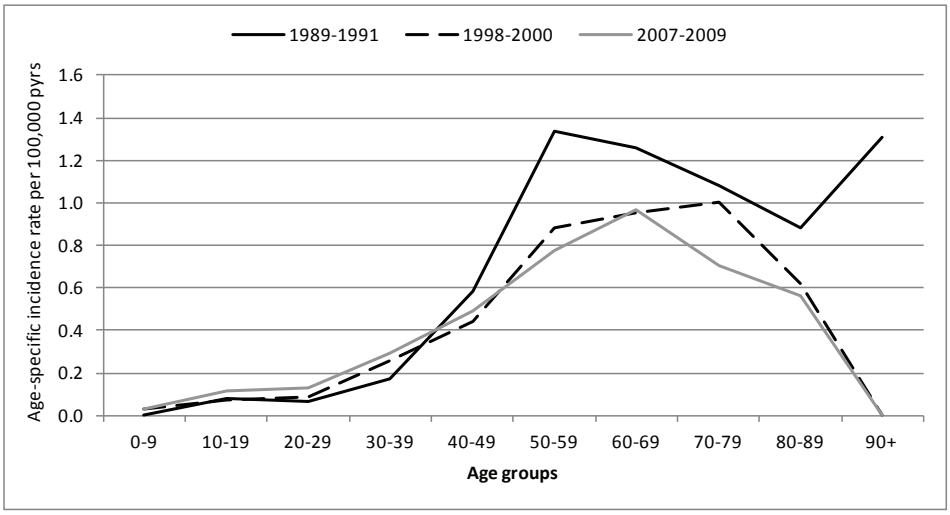


Figure 2 Age-specific NPC incidence per 100,000 person-years, 1989-2009 (source: NCR)

Trends in survival

One- and three-year relative survival slightly increased during the study period and amounted to 81% and 65% in 2009 as compared to 79% and 57% in 1989, respectively (Fig. 3). Five-year relative survival rose from 50% in 1989-1993 to 55% in 2004-2009. No sex-specific differences were found, however, relative survival was clearly worse for patients of higher age and stage. Whilst patients with non-keratinizing tumours (WHO-IIA and B) had the highest survival rates which slightly increased over time (1-year relative survival ranging from 91 to 98%), survival of patients with keratinizing SCCs (WHO-I) was lower (1-year relative survival ranging from 65 to 78%) and slightly decreased over time (Fig. 4). Similarly, 3-year relative survival increased in patients with non-keratinizing tumours (ranging from 64 to 78%) and decreased in patients with WHO type I tumours (ranging from 53% to 44%) (data not shown).

Trends in mortality

Between 1970 and 2009, 1,275 persons died from NPC in the Netherlands (683 between 1989 and 2009). The mortality-to-incidence ratio, an approximation measure for survival (20), is thus 0.48 for the period 1989-2009. Most deaths (39%) occurred in the age group 60-74 years. About 41% of all deaths were younger than age 60 and 21% in patients aged 75 and over.

The overall mortality from NPC significantly decreased between 1970 and 2009 from 0.3 per 100,000 in 1971 to 0.1 per 100,000 in 2008 (EAPC 1970-2009: -1.2; 95%CI: -1.8, -0.5), however even stronger since 1989 (EAPC: -3.0; 95%CI: -4.3, -1.6) (Tab. 2, Fig. 1). The decrease during the latter period was more pronounced in males than in females and was observed across all age groups, however particularly in females aged 75 and over (Tab. 1).

Table 2 Trends in NPC incidence and mortality according to sex, age group, stage at diagnosis and histology in the Netherlands 1970/89-2009* (source: NCR, Statistics Netherlands)

	Incidence (1989-2009)			Mortality (1970-2009)			Mortality (1989-2009)		
EAPC	Males	Females	Total	Males	Females	Total	Males	Females	Total
Overall (95%CI)	**-1.3** (-2.5, -0.2)	-1.0 (-3.2, 1.3)	**-1.2** (-2.3, -0.2)	**-1.5** (-2.2, -0.8)	-0.5 (-1.7, 0.6)	**-1.2** (-1.8, -0.5)	**-3.7** (-5.3, -2.0)	-1.3 (-4.6, 2.1)	**-3.0** (-4.3, -1.6)
Age <60	-0.9 (-2.2, 0.5)	-1.7 (-4.7, 1.4)	-1.0 (-2.4, 0.3)	**-1.5** (-2.3, -0.6)	-0.4 (-1.8, 1.0)	**-1.1** (-1.8, -0.5)	**-2.2** (-4.1, -0.4)	-2.6 (-6.5, 1.4)	**-2.4** (-3.8, -1.0)
Age 60-74	-1.3 (-3.2, 0.7)	1.1 (-2.8, 5.0)	-0.8 (-2.7, 1.1)	**-1.5** (-2.6, -0.5)	-0.2 (-2.0, 1.6)	**-1.0** (-1.9, -0.1)	**-4.7** (-6.9, -2.4)	0.4 (-4.5, 5.3)	-3.4 (-5.4, -1.4)
Age ≥75	-3.4 (-8.0, 1.3)	-3.0 (-7.8, 1.7)	**-3.5** (-6.3, -0.8)	**-1.3** (-2.6, -0.1)	**-3.1** (-4.7, -1.5)	**-1.6** (-3.0, -0.2)	-3.0 (-6.3, 0.3)	0.8 (-3.1, 4.7)	**-3.2** (-6.3, -0.2)
WHO-I	**-3.2** (-5.0, -1.3)	**-3.7** (-6.7, -0.7)	**-3.6** (-5.3, -1.8)						
WHO-IIA	**6.6** (2.5, 10.8)	3.0 (-8.5, 14.5)	**9.6** (5.6, 13.5)						
WHO-IIB	-0.7 (-2.3, 0.9)	-0.5 (-2.7, 1.8)	-0.7 (-1.8, 0.5)						

EAPC= Estimated Annual Percentage Change; 95% CI= 95% Confidence Interval

*Bold numbers are significant at p<0.05 level

Discussion

We found a decrease in NPC incidence, especially in males and in patients with keratinizing SCCs (WHO-I). The incidence of differentiated non-keratinizing NPC (WHO-IIA) concurrently increased significantly. The decline of cases with the poorest survival (WHO-I) in combination with slowly improving survival rates led to decreasing mortality from NPC in the Netherlands in recent years. This insight into NPC trends was possible by evaluating NPC incidence, survival and mortality at the same time.

Between 1989 and 2009, the age-standardized incidence of NPC decreased significantly in males and a downward tendency was also observed in females. According to 'Cancer Incidence in Five Continents – volume VI, VIII and IX', NPC risk is slowly decreasing in many European countries (1-2). Overall, our findings are largely consistent with other European studies (21), which exhibit a marked South-North gradient in NPC risk with the highest rates in Malta (figure 5, appendix). A similar study from Scotland (22) did not show a clear trend in overall incidence, although it declined in males below age 50. However, in the same study, people from lower socio-economic backgrounds exhibited increased NPC risks, also of dying. Studies from China also confirmed an inverse relationship of NPC incidence and social class (10). Bray and colleagues (11) recently suggested a bimodal pattern in age-specific incidence curves of NPC in low-risk populations with a first peak in late adolescence/early adulthood (ages 15-24 years), a subsequent decline and a second

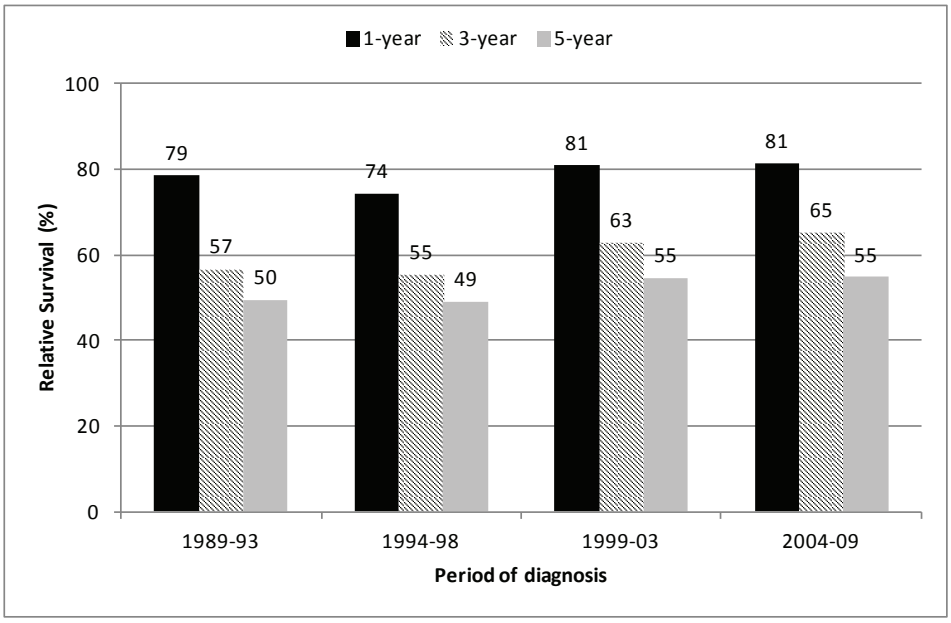


Figure 3 Trends in 1-, 3- and 5-year cohort-based relative survival from NPC, 1989-2009 (source: NCR)

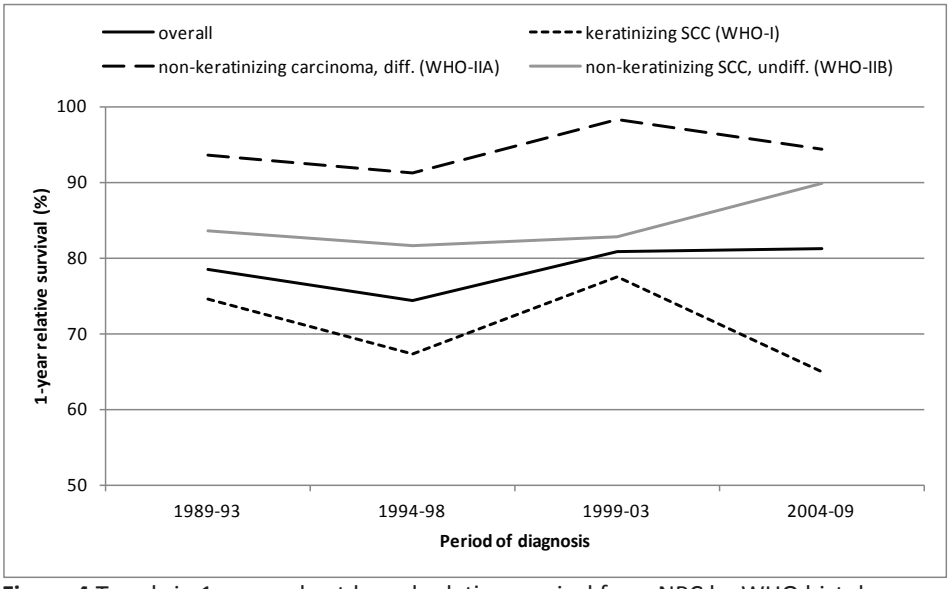


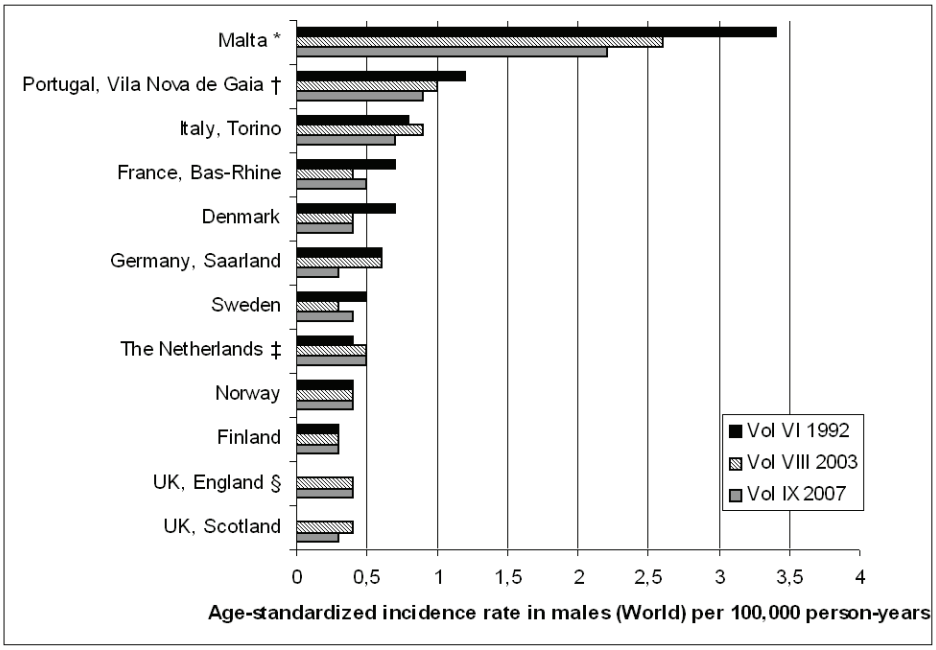
Figure 4 Trends in 1-year cohort-based relative survival from NPC by WHO histology classification, 1989-2009 (source: NCR)

peak in later life (ages 65-79 years), which was not evident in high-risk populations. In our data, however, we could not confirm this pattern, possibly due to low numbers.
The observed trends in our study are most likely due to variation and changes in exposure to carcinogenic risk factors as well as increasing immigration from high-incidence regions of NPC. Even though the contribution of environmental, viral and genetic risk

factors in the causation of NPC has long been controversial, the role of EBV in the development WHO-IIA and B tumours is clearly established (23). The association between tobacco smoking, alcohol drinking and NPC risk, however, seems to be confined to SSCs of the nasopharynx (WHO-I) (24). More than two-thirds of differentiated squamous cell NPC cases arising in older persons were due to smoking and, to a lesser degree, to alcohol in a study from the US (9). The role of alcohol in the causation of NPC is, however, often considered an interactive effect with smoking (24). In our study, we found a higher and increasing incidence of non-keratinizing tumours as opposed to a lower and slowly decreasing incidence of (smoking-related) keratinizing SCCs. This might be related to the decrease in smoking in the Netherlands from 59% in 1970 to 28% in 2009 (25). Similarly, a decreasing incidence in WHO-I tumours has been observed in high-incidence areas like Southern China and Hong Kong in recent years and is most probably also due to the decline in smoking (26). In contrast, the increasing incidence of non-keratinizing tumours suggests a driving role of EBV and other environmental risk factors. The consumption of salted fish and preserved foods has also been found to play important etiologic roles (10).

Earlier studies found that NPC incidence is particularly high in migrants from high-incidence regions. For instance, a recent study from Sweden revealed elevated risks for NPC among immigrants from Former Yugoslavia, Asian Arab countries, Southeast Asia and North Africa, being up to 35-fold the risk of Native Swedes (27). Accordingly, the histological types of NPC varied by patient origin in our study: whereas WHO-I was the predominant NPC type in patients born in the Netherlands, it was WHO-IIB in patients born in most non-western countries. This pattern has also been described previously among Japanese and Chinese in comparison with Caucasians NPC patients (28). Thus, the increase in the incidence of EBV-related tumours (WHO-IIA and B) might be explained by recent migration waves to the Netherlands. For example, the number of immigrants from China nearly tripled between 1996 (16 000) and 2011 (45 000) (18). Given the latest immigration figures and assuming that Chinese, South-East Asian and North-African migrants carry higher NPC risks, especially for WHO-IIA and B tumours, the observed trends in this study are in line with expectations. This also implies that immigrant groups deserve special attention from health care professionals with regard to NPC risk and that EBV-based NPC diagnostics might be considered for risk-assessment and treatment monitoring in this group (13-15).

In recent years, survival from NPC has increased steadily due to refined and earlier staging as well as treatment in many countries, including the Netherlands (29). This can partly be attributed to the introduction of more advanced technologies like intensity-modulated radiation therapy (IMRT). In addition, the enhanced imaging of the nasopharyngeal region by magnetic resonance imaging (MRI) instead of CT-imaging and the adjustment of radiotherapy doses have considerably refined treatment options in recent years. Five-year relative survival increased from 50% in 1989-93 to 55% in 2004-09 in our study, compared to 48% found in an earlier study from the Netherlands of 129 NPC patients diagnosed between 1977 and 1993 (30). A Europe-wide study found even lower NPC survival; one- and five-year relative survival rates were 75% and 34% for males and 72% and 32% for females, respectively (31). The most important prognostic factors are stage of disease at diagnosis, tumour histology and, to a lesser extent, age at diagnosis. Still, more than two thirds of all newly diagnosed NPC cases are stage 3 or 4 tumours with a reduced chance for cure. The late presentation might be due to often non-specific



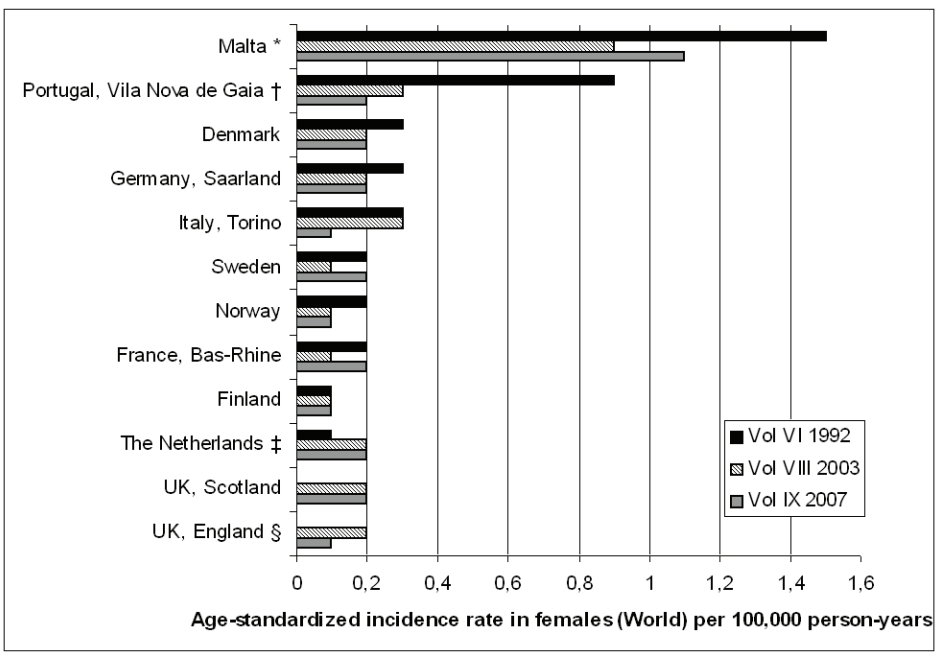


Figure 5 Trends in NPC incidence in males (A) and females (B) in selected European countries according to Cancer Incidence in Five Continents, Volumes VI, VIII and IX (1-2)

* for Volume VI, data from Volume III was used as substitute

† for Volume IX, data for Portugal, Porto was used as substitute

‡ for Volume VI, data from the Netherlands, Eindhoven was used as substitute

§ for Volume IX, data from the UK, East of England was used as substitute

and flu-like symptoms, resulting in delayed diagnoses. In addition, low numbers of cases seen by Dutch clinicians per year may limit their familiarity with the diagnosis of NPC. Specialists in non-endemic regions, like the Netherlands, should be more aware of the symptoms of NPC and a higher incidence among immigrants, especially from North Africa and South East Asia. Low awareness is also present in health care workers working in high incidence regions like Indonesia where NPC is one of the most common tumours (32).

We found the poorest survival among patients with keratinizing SCC (WHO-I), probably due to a higher incidence of locally advanced tumours and loco-regional failure. This results in poorer survival as compared to non-keratinizing tumours (16, 33). A similar picture and even lower survival among WHO-I patients was found in a study from Switzerland (8). As migrants of non-western origin are more often affected by non-keratinizing tumours, they probably have a better survival from NPC when compared to native Dutch patients.

Our results also emphasize the need for more 'tumour-customized' treatment plans for different WHO types of NPC, in particular WHO-I tumours may require a more aggressive or adjusted treatment.

Limitations

We explored the combined picture of NPC incidence, survival and mortality, but the final effect of declining incidence and increasing survival since 1989 will only fully be reflected in mortality in the next few years, even though NPC fatality is rather high and mortality often occurs within few years after diagnosis. However, NPC continues to be a rare disease and trends subject to random variation, entailing difficult interpretations. Besides, changes in pathological practice in the classification of NPC may have contributed to the observed trends and made it impossible to investigate time trends according to stage. Although the correct differentiation of WHO types has advanced in recent years, a small degree of misclassification cannot be ruled out.

Conclusion

Since 1989, the incidence of NPC in the Netherlands decreased, mainly of smoking-related, keratinizing NPC (WHO-I). Contrastingly, the incidence of non-keratinizing NPC (WHO-IIA and B) increased, most likely due to changes in the classification of NPC tumours and immigration of persons from high-incidence countries. Increased awareness among clinicians and the use of EBV-related markers may improve detecting and monitoring NPC in this group. As patients with WHO-I tumours have a poor survival, the decrease in incidence of this NPC type may have contributed to the small overall increase in survival, albeit still far from ideal.

Acknowledgements

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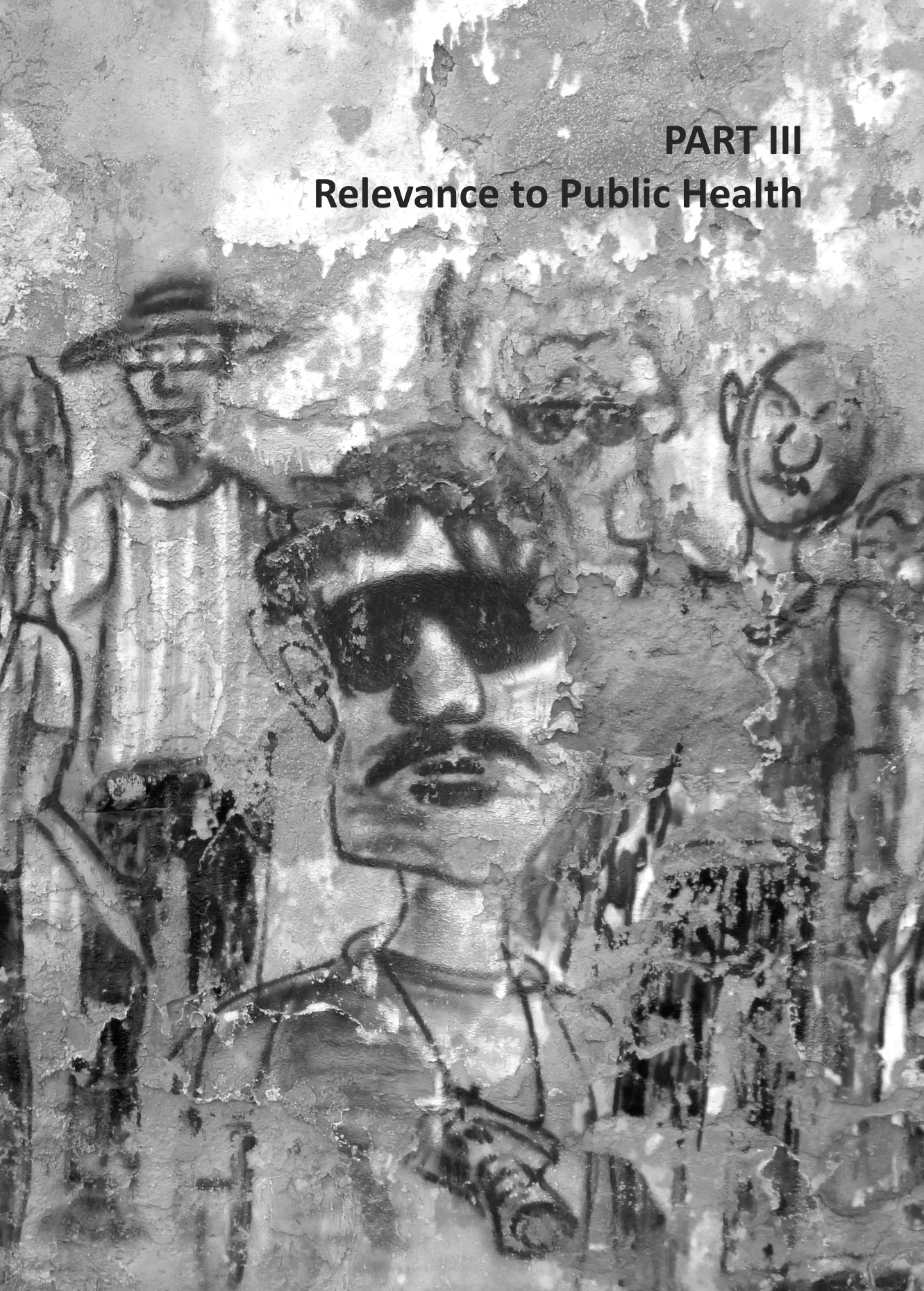

PART III
Relevance to Public Health

9

Migration conceptualized as high-speed health transition: Do new data support this hypothesis?

M. Arnold, O. Razum

Submitted for publication

Abstract

Introduction: Stage and pace of the health transition vary greatly between countries and populations. Low-income countries only recently started to experience the increasing burden of non-communicable diseases (NCDs) and associated modern risks while the burden of infectious diseases is still high and decreasing only slowly. Migration from low- to high-income countries thus has been conceptualized as high-speed health transition: while treatment options and access to care are improved, modern risks remain low for long lag periods. We investigate whether recent data support this hypothesis. We argue that contradicting findings provide insights into the relative strength of environmental and genetic determinants on disease risk.

Methods: A total of 23 studies on disease risk and mortality in immigrant populations were reviewed with regard to the concept of migration as health transition.

Results: Immigrants often exhibit paradoxically low and long-lasting advantages in morbidity and mortality relative to the native population of their host country. This might be due to better access to health care in their host countries and the retention of more favourable health behaviours from their country of origin. In some immigrant groups, however, disease rates were not only found to converge towards, but to exceed those of Western populations and remained high, even years after migration. Thus, immigrants were found to experience significantly slower declines and excess mortality as compared to the native population of their host country.

Conclusion: Recent findings partly support the conceptualization of migration as high-speed health transition. However, immigrants from low-income countries do not necessarily benefit to the same extent to the general decline in NCD mortality in high-income countries, increasing existing disparities and showing adverse trends that largely remain unexplained. Substantial context- and acculturation-dependent variations in disease risk and mortality between and within immigrant groups confirm strong links between exposures and determinants in both the country of origin and the host country.

Background

Migration from low- to high-income countries has been conceptualized as 'time travel' in terms of a high-speed health transition in our previous work (1). Ten years later, this concept demands an update and revalidation. We argue that while treatment, access to care and sanitary conditions improve almost instantaneously after migration, the health effects of "western" risk factors such as diet and smoking will become evident only after long lag periods in immigrants from low-income countries. This should result in (albeit temporary) advantages in morbidity and mortality in immigrants from low-income countries when compared to host populations of high-income countries. Our concept thus helps to explain why the 'healthy migrant effect' (2) may last for years or even decades after migration, in spite of socioeconomic disadvantage and discrimination faced by immigrant populations in many host countries.
The reasons behind this phenomenon are twofold. First, there are differences with regard to the stage of health transition between the immigrant's country of origin (CO) and their Western host countries (HC). And second, the pace at which morbidity and mortality patterns change after migration differs greatly between countries. Health transition describes a complex change in disease patterns and burden over time, shifting from infectious diseases toward non-communicable, degenerative diseases (NCDs) (3). This phenomenon is the consequence of increasing urbanization, globalization, affluence and associated lifestyle changes. Advancements in medical care and public health foster higher standards of living, increasing hygiene and better health in many countries. Compared with their HC, the immigrant's CO are often in an earlier phase of this health transition. Accordingly, disease patterns of the HCs differ from that of immigrant's COs. Compared to the population in the HC, immigrants initially have lower cardiovascular risks and also lower risks form lifestyle-induced cancers; the higher risk for infectious and maternal conditions declines quickly and substantially due to better medical care. Conceptualizing migration as a high-speed health transition could help to explain the persistence over time of the 'healthy migrant effect', which would thus constitute more than merely a (self-)selection of particularly healthy persons into migration. The advantages of immigrants in terms of morbidity and mortality would thus not only result from being a highly selected group in terms of health, education, skills and ambition (2).
In order to analyse the effects of health transition on disease patterns in immigrants and to test whether this can substantiate the healthy migrant effect, three main assumptions need to be examined (see also figure 1).

Assumption 1: Immigrants moving from low- to high-income countries should instantaneously experience a declining burden from treatable communicable conditions due to better access to health care and better treatment in the HC as compared their counterparts in the CO. This entails immediate morbidity and mortality advantages upon migration in comparison with the population of the CO.

Assumption 2: The exposure and adaptation to modern health risks - such as physical inactivity, obesity as well as tobacco and alcohol-related risks - in the HC should be followed by slowly increasing chronic disease morbidity in immigrants from low-income countries. However, long lag periods exist between increases in the exposure to risk factors such as obesogenic nutritional habits and an increased risk for NCDs. This lag time

ensures prevailing advantages in NCD morbidity in immigrants when compared to the population of their HC for many years.

Assumption 3: Due to the health transition, first-generation immigrants may initially exhibit lower morbidity and mortality from various NCDs than the native population of their HC. However, with increasing duration of stay and greater degree of acculturation in the HC, health behaviors and disease patterns in immigrants are likely to converge to levels close to those of the HC population. This is mainly driven by strong declines in morbidity and mortality from infectious diseases due to reduced exposure to communicable conditions (assumption 1) and a slow increase in NCDs due to exposure to modern risks (assumption 2). In addition, persisting risks from conditions related to childhood deprivation, such as infection-related cancers occurring in later life, represent important supplementary risks and are due to the unfinished agenda of the health transition experienced by immigrants.
In this paper, we investigate whether recent data support these assumptions. In addition, we argue that findings from recent international migration studies provide insights into the relative strength of environmental and genetic determinants on disease risk as well as its context-dependence.

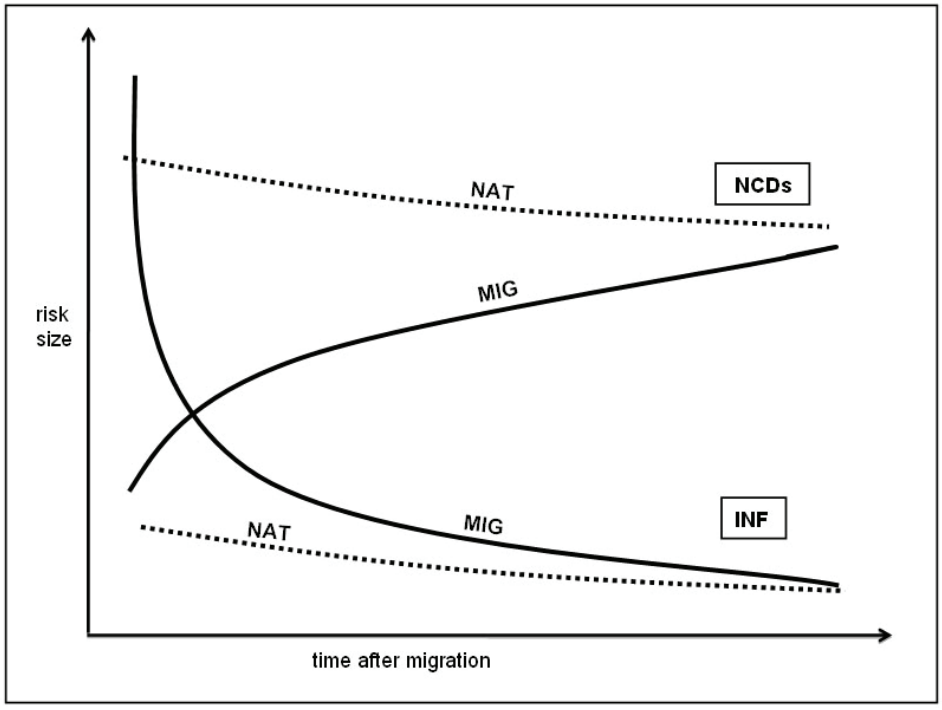

Figure 1 Model illustrating the effects of migration from low- to high-income countries on morbidity from noncommunicable (NCDs) and infectious diseases (INF). MIG=Immigrant populations (solid lines); NAT=Native populations of high-income countries (dashed lines)

Methods

Search strategy and selection criteria

We obtained data for this review from searches of Pubmed, using the terms "(im)migrant", "transients & migrants", "ethnic(ity)", "nativity", "country of birth", "foreign(-born)" AND "mortality", "health status", "survival" and specific searches for every condition. Snowballing was used to track down additional references. Studies published since 2002 were included, as this was the year of the publication of our previous study on this topic. We focussed on studies comparing morbidity and mortality risks between immigrants and the population of their HC, preferably including information on duration of stay and/or age at migration. In order to determine the 'position' and the degree of convergence toward the risks in the local-born population of the immigrant's HC, information on disease patterns in those remaining in the CO, is crucial, however only rarely available.

In total, results from 23 studies from various countries, of which twelve contained information on duration of stay or age at migration, were included. By the term (im)migrants, we mean a population group that temporarily or permanently moved into a new country. Since we aim to assess the impact of immigration on (long-term) disease patterns, we draw on studies exploring disease patterns in first-generation immigrants only. We note that our definition of immigrants needs to be distinguished from other ethnicity-related constructs that are discussed in the literature.

Results

Cardiovascular diseases

Overall, age-adjusted cardiovascular disease (CVD) mortality is today higher in some low and middle income countries than in developed countries where slow but gradual declines have been observed since years (4). This can be explained with better prevention and treatment management (5). However, CVD epidemics are not all the same and great geographical variation exists (6). Singh and Hiatt (7), for example, found a continuously lower and more rapidly decreasing mortality from major cardiovascular diseases in all foreign-born groups except Non-Hispanic whites and Asian females when compared with US-born persons.

Stroke

A high mortality from stroke was found in Surinamese immigrants residing in the Netherlands which also substantially contributed to an elevated CVD mortality when compared to native Dutch (8). While significantly increased risks of dying from hypertension and stroke were found in recent male immigrants when compared to immigrants residing in the Netherlands for 15 years or longer, the opposite was true for female immigrants (9). In a later study, no systematic relation between duration of residence and CVD was observed in Turkish and Moroccan immigrants while Surinamese and Antillean immigrants showed mortality levels that were closer to the Dutch population with increasing duration of residence (10). In the UK, an increasing mortality from stroke with increasing duration of residence and age at migration was found among immigrants from the Caribbean to England and Wales (11). This was later also confirmed for immigrants of African and South Asian backgrounds, strongly exceeding that of UK natives (12). Higher risks

for stroke were also found in foreign-born (when compared with native-born) females in the US (13).

Ischemic heart disease (IHD)
Significantly lower mortality rates from ischemic heart disease (IHD) were found in Moroccan males and Turkish females residing in the Netherlands (8), whereas studies from Sweden found that immigrants from Turkey and South Asia were at greater risk of acute myocardial infarction (14) and IHD (15) as compared to native-born Swedes, even after adjustment for socioeconomic position (SEP). Similarly, foreign-born females in the US were at greater risk of death from IHD (13) and disproportionally high (and increasing) mortality from IHD was also found in immigrants of South Asian (India, Pakistan and Bangladesh) and East African origin residing in the UK. Contrastingly, IHD mortality in immigrants from the Caribbean was lower, however, gradually converged toward the rate of UK natives (12).

Diabetes
In recent years, the prevalence of type 2 diabetes has nowhere in the world increased as rapidly as in native and migrant Asian populations (16). Persons leaving those high-prevalence regions and migrating to other parts of the world should experience stable, probably slowly decreasing risks as opposed to the population staying in their region of origin. Most immigrants from low-income countries have a higher burden of diabetes mortality than the native population of their country of residence. A recent study, exploring data from several European countries, revealed that these patterns were most pronounced in immigrants from North Africa, the Caribbean, South Asia or low-GDP countries (17). In the Netherlands, this pattern could be confirmed for Surinamese and Antillean immigrants, with risks for dying from diabetes more than 3 times of that of the native Dutch population (9). Concurrently, higher and increasing diabetes prevalence after migration was found among Indian and African-Caribbean immigrants residing in the Netherlands and in the UK, with more pronounced patterns among both groups residing in the Netherlands (18). Foreign-born immigrants in the US exhibit a higher diabetes prevalence with great variation according to origin (19).

Cancer
Still, most cancer occurs in high-income countries; however the burden is expected to increase substantially in low- and medium-income countries in the next decades. In contrast, mortality from cancer has already become a leading cause of death and disability in poor countries. Globally, there are strong site-specific differences in cancer morbidity and mortality that become evident when studying immigrant populations. Whereas immigrants from most low-income countries are more prone to cancers of infectious origin such as liver or stomach cancer, at the same time experience much lower risks from cancers associated with a western lifestyle (20).
Avoidable mortality from cancer is consistently lower in all immigrants in the Netherlands than in Dutch natives, ranging from 16% lower in Antillean immigrants and 56% in Moroccan immigrants (9). No significant difference was found between recent immigrants (residing longer than 15 years in the HC) and immigrants that arrived less recently. For a large number of cancers, immigrants had 50% or lower risk of death when compared to the native Dutch population (21). Significantly lower lung, colorectal and breast

cancer mortality was found (8, 21), while immigrants that migrated at a younger age and longer duration of residence in the HC had higher death rates from cancer than more recent immigrants (21). Clear convergence patterns were, however, only observed in Surinamese immigrants while in other immigrants groups no clear change with increasing duration of residence was found (10, 21). Similarly, breast cancer risk remained more or less constant with increasing length of stay in immigrants to Sweden, irrespective of age at migration (22).

In Australia, rapidly increasing risks for colorectal cancer in immigrants from low-risk areas were found (23). A study from Sweden specified that immigration at older ages had no effect on colorectal cancer risk whereas persons who migrated at younger ages reached risk levels close to that of native Swedes (22). The same study also reported a decreasing lung cancer and increasing prostate cancer incidence in immigrants from high-incidence countries that migrated at older age. In Germany, consistently lower prostate cancer incidence and mortality was found in immigrants from the Former Soviet Union since more than two decades (24). Singh and Hiatt found lower and decreasing risks for dying of lung cancer in immigrants to the US when compared with their US-born counterparts (28% lower in 1979-81; 42% lower in 1999-2001) (7). Similar results were also found for colorectal, prostate, breast, kidney, and brain cancers as well as non-Hodgkin's lymphoma.

A recent study from Sweden (25) reported high incidence of liver cancer among immigrants from Asian and Asian Arab countries. In the Netherlands, elevated risks in immigrants were confined to non-cardia stomach cancer only (26). In line with these findings, substantial elevations in risk of death from liver and stomach cancer were found in immigrants, increasing with younger age at migration in the Netherlands (21). Similar patterns were also found for stomach and liver cancers in the US, where excess mortality was 52% among immigrants in 1989-91 and grew significantly till 2001. The highest stomach cancer mortality rates were found among foreign-born Asians, where risks were more than three times higher than in US-whites and two times higher than among US-born Asians. Similarly, higher stomach and liver cancer mortality was found in black and non-Hispanic white immigrants as compared to US-born whites (7).

Infectious diseases

Higher mortality from infectious diseases in immigrants was found in studies from Denmark (27) and the Netherlands (8-9), were patterns were most distinct in immigrants from North Africa and the Caribbean. Furthermore, avoidable mortality from infectious diseases was found to be considerably higher in immigrants when compared to Dutch natives; in particular for tuberculosis (TB), hepatitis and HIV/Aids (8-9). Risks were particularly high in recent immigrants, residing less then 15 years in the Netherlands and were more pronounced in females. An increasing incidence of TB in immigrant and non-immigrant HIV-infected patients has recently been reported in a study from France (28). Similarly, a persistently high incidence of TB has been reported in studies from the Netherlands (29), Denmark (30) and Canada (31). Incidence rates gradually decreased as time since immigration increased, however, rates remained high even a decade after migration. On the contrary, significantly lower and slower increasing mortality from TB, viral hepatitis and HIV/Aids diseases has been observed among foreign-born immigrants as compared to their US-born counterparts (7).

Discussion

Many important aspects of our previous work on migration as a high-speed health transition could be confirmed by new evidence. This especially applies to a higher and increasing mortality from stroke and lower breast cancer incidence and mortality in immigrants. In this regard, the concept of health transition can help explaining the healthy migrant effect. However, we also found counterexamples, in particular, when looking at time trends of health outcomes after migration.

Persistently higher and increasing mortality from IHD among South Asians and East Africans residing in the UK entailed significantly smaller declines in mortality than in local-born persons (11-12). This excess mortality from IHD, especially in immigrants of South Asian origin, may reflect a rapid change in lifestyle, entailing high disease burdens (32). The adoption of risk behaviors such as smoking and decreasing physical activity, in concomitance with greater socioeconomic disadvantage in their HC, may be responsible for this development. The prevalence of obesity and diabetes – strong predictors for IHD – is increasing faster in many Asian countries than elsewhere in the world (33). Genetic predisposition to insulin resistance and other metabolic disturbances in South Asians are, in turn, also discussed as possible explanations for this phenomenon (16, 34). Higher and increasing prevalence of diabetes was also evident in immigrants of Indian and African-Caribbean origin. The risk size varied substantially by HC, underling the context-dependence and the impact of difference in speed of transition and acculturation across immigrant groups (9, 18). Rapid socioeconomic change may also be the main reason for excess immigrant diabetes mortality, which is also likely to be mediated by increasing urbanization and drastic lifestyle changes, such as a decrease in physical activity and a high-fat, energy-dense diet (17). Since diabetes-related death is strongly associated with differences in access to and quality of diabetes care, metabolic control and complications, case fatality could also explain differences in diabetes mortality between immigrants and local-born populations.

In cancer mortality, few consistent trends with regard to duration of stay in the HC have been observed in immigrant groups. This might be explained by slow adaptation of health-related behaviors that are common in the local-born population of the HC. This pattern, however, differed substantially by immigrant origin and was, for example, more consistent in Turkish and Moroccan than in Surinamese and Antillean immigrants in the Netherlands. Stable risks can, on the other hand, also point towards a greater role of genetic predisposition rather than environmental influences. Lower risks of death from lung cancer were found in several studies, despite a steeply increasing smoking prevalence, respectively (8, 21). However, since there usually is a long delay between increase in smoking and developing lung cancer and other chronic conditions related to smoking, currently low rates of lung cancer among immigrants imply that older immigrants (especially males) are less likely to have been heavy smokers at younger ages than older natives (men). This corresponds with the course of the smoking epidemic in less-developed countries (35). The increasing uptake of smoking among immigrants seen in many countries also suggests that the peak of smoking-related mortality in this group is yet to come (36).

Growing excess mortality from stomach and liver cancers, especially among Asian immigrants in the US, might reflect higher incidence of hepatitis-B virus infection, helicobacter pylori infection and greater consumption of salted, pickled and smoked foods

in the countries of origin (37). Vertical transmission of hepatitis (mother to child) can possibly explain the high liver cancer incidence even in subsequent immigrant generations (38). High risks for TB in immigrants have been reported to persist even decades after migration. This is possibly due to the reactivation of latent infections, multi-drug resistant forms of TB and infections acquired during visits to the CO (29).

According to our assumptions, a rapid transition in terms of treatment encounters a slow(er) transition in terms of NCD risk accumulation, entailing (temporary) health advantages. However, our findings show that the outcome is not always in line with this hypothesis. Due to an 'unfinished agenda' of health transition in their CO, immigrants from low-income countries often remain at higher risk for infectious diseases in the HC, while suffering from an excessive burden of NCDs in later life. Persistently high rates of TB and excess mortality from IHD challenge the health transition hypothesis. Variations in underlying disease patterns in the CO as well as context-dependent, acculturation-related factors in the HC are important factors to be considered, leading to manifold paths of health transition across immigrant groups. In addition, socioeconomic circumstances play an important role as immigrants are often more likely to be affected by poverty and social deprivation when compared to the local-born population of their HC. This often translates into greater disadvantages in health for immigrant groups. However, social disadvantages do not fully explain health disparities and smaller declines in mortality observed in many high-income countries (12), and despite lower socioeconomic position, immigrants often retain higher overall health levels. Thus, if immigrants and natives had a similar socioeconomic position, the immigrant advantage might even be larger.

Methodological considerations

Earlier studies reporting low immigrant mortality often dismissed this finding as due to bias (39). In fact, selection bias is a well-known methodological challenge in migration research. However, unregistered remigration ('salmon bias') and, as a consequence, the underestimation of mortality if sicker immigrants return to their CO prior to their death cannot fully explain the mortality advantage observed among immigrants (1-2, 40). Remigration has in many counties become rare among immigrants, and medical care is often more advanced and of higher quality in their home countries (1, 40).

Immigrants are a heterogeneous group, potentially becoming even more heterogeneous over time. Hence, addressing ethnic and other variations within immigrant groups is extremely complex. Categorizing immigrants and using proxies for ethnicity always bears the risk of misclassification (41). Due to a shortness of reliable cause-specific mortality and morbidity data in some COs, it often remains unclear whether mortality in immigrants diverges from that of persons who remain in the CO. Studying the effects of duration of stay in the HC is also not always feasible but it is crucial to assess whether outcomes in immigrants converge toward that of the local-born population of their HC. Both approaches have the potential to provide important insights into the relative contribution of genetic versus environmental factors, e.g. in carcinogenesis.

Conclusion

Over the past ten years, new evidence has been created that partly supports our earlier work conceptualizing migration as a high-speed health transition (1). For example, new studies confirmed higher mortality from stroke, infection-related cancers and sequelae of infectious diseases among immigrants. However, substantial evidence shows that some immigrant groups are, for example, affected by excess mortality from IHD and

persistently high risks for TB. Hence, additional processes need to be considered when conceptualizing migration as a high-speed health transition. Among these, the effects of socio-economic factors and discrimination are likely candidates.

We pointed out that immigrants from low-income countries do not necessarily benefit to the same extent from the general decline in mortality from NCDs in high-income countries and are at high risk of a double disease burden due to 'unfinished agendas' of health transition. Temporary advances in health might be the result of both selection effects and long lag time between increased exposure to risk factors and disease onset. Accordingly, NCDs are expected to become more common diseases and causes of death in immigrants residing in high-income countries. Disparities in disease risk and mortality seem to widen over time, with substantial variation by origin and HC. The reasons for these developments are not yet fully understood. However, the comparatively smaller declines in NCD mortality observed among immigrants are likely to increase existing disparities in health. Disease and risk factor patterns in the CO as well as socioeconomic circumstances play important but not all-embracing roles in the explanation of mortality and morbidity differentials between immigrants and non-immigrants.

Trends in disease patterns in immigrants provide insights into disease aetiology and should be assessed using a life course approach. However, many methodological problems are not yet solved and comprehensive studies are still - and will, for the near future remain - scarce. By taking, for example, age at migration and duration of stay into account, critical ages of migration and associated risk factors can be identified more accurately. Ideally, prospective studies, covering the whole migration process (pre-, peri- and post-migration influences on health), are needed in order to increase our understanding of the dynamics of health transition in immigrant populations.

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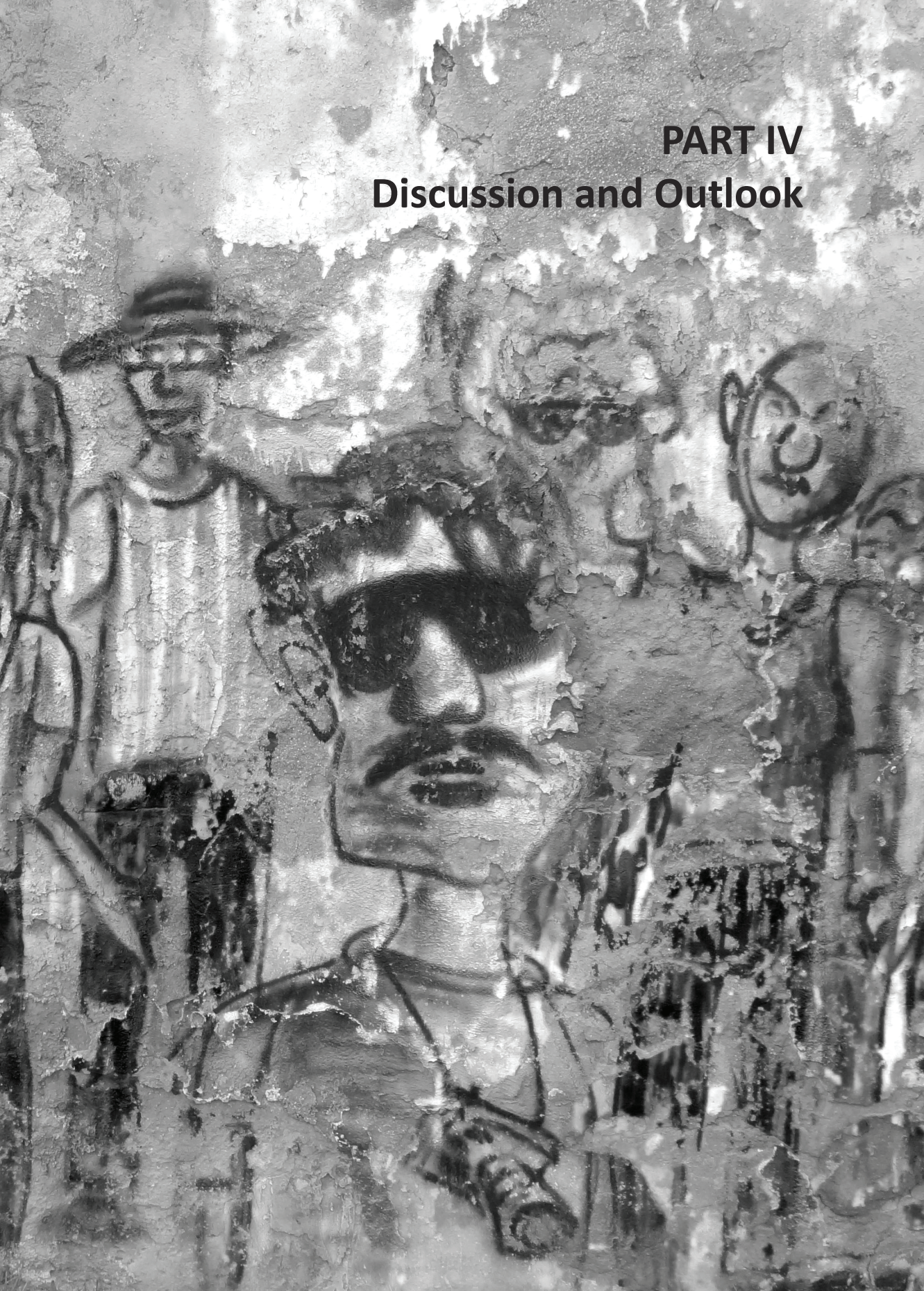

PART IV
Discussion and Outlook

Discussion

Europe has become a remarkable multicultural and multiethnic society, characterised by a common vision on democracy, welfare, social inclusion and protection of its citizens. In the age of globalisation, most European countries are however increasingly facing problems with regard to the sustainability of their social models. This especially applies to low and decreasing birth rates, population aging and effects of migration on Europe's population composition. This development inevitably raises the question whether the European social construct is flexible enough to defy these changes and whether social equality is still a realistic aim across all segments of society. This line of reasoning also represents the scientific and public health rationale of making migrant health a core theme at EU-level consultations and in health programmes. Besides, from an epidemiological point of view, migration can be seen as a big-scale natural experiment that has the potential to teach us about the power of cancer prevention and grey areas that still exist in aetiological cancer research.
In this final chapter, first the results and implications of the studies in this thesis are being summarised. Subsequently, methodological considerations and the interplay between ethnicity and socioeconomic determinants and their effects on disease, especially cancer, are being discussed. Finally, priorities for further research are derived based on what is already known on ethnicity as a self-evident variable in cancer research and what this thesis adds to this knowledge. In the conclusion and outlook, short- and long-term targets for prospective research on cancer in migrants are presented.

Ethnic heterogeneity of cancer in Europe

Cancer incidence and mortality
A variety of studies from Europe has shown that ethnic disparities in the burden of cancer exist (1). In **chapter 3**, we explored cancer patterns in non-Western migrants in Europe based on the literature. We found that in Europe, non-Western migrants were more prone to infection-related cancers but had lower risks for cancers associated with a more western lifestyle, such as colon, breast and prostate cancer. Risks in migrants were often in between the corresponding risks in their home and in their host country. This pattern largely reflects the retention of more favourable risk factors that are common in the migrants' countries of origin parallel to a slow adaptation and acculturation to the risk profiles of the majority population of the country of residence. A close interrelationship with individual doses of exposure experienced during life span and health effects of social determinants could be identified as additional key factors in development of cancer.

Our study among Turkish migrants residing in Hamburg (Germany), revealed lower risks for cancer of the respiratory organs among Turkish males than in the non-Turkish population, particularly in the older birth cohorts (**chapter 4**). Younger birth cohorts had increasingly similar risks to the non-Turkish population. The risk for malignant neoplasms of lymphoid, haematopoietic and related tissues was slightly higher in most male Turkish birth cohorts. Incidence rates in Turkish women were lower than in non-Turkish women for cancer of the respiratory system, skin and the genital organs.
In a multinational study including data from France, Belgium, Denmark and the Nether-

lands (**chapter 5**), all cancer mortality was consistently lower in Turkish migrants than among the local-born population of their host countries, irrespective of their current country of residence. Cancer mortality in Turkey in relation to that of the four host countries was, however, equal or lower than that of Turkish immigrants relative to the local-born population of their host country. This implies that all-cancer mortality in Turkish immigrants was in between that of their country of origin and their host country. The same applied for breast cancer in Turkish migrant women in relation to Dutch- and French-born women. For lung cancer, contrasting patterns in Turks residing in France and in the Netherlands were found. Whereas in France lung cancer mortality in Turkish migrants converged towards that of French natives, mortality rates of Turkish migrants residing in the Netherlands were even lower than in Turkey itself. The reason for this variation between host countries might be related to different durations of stay, migration histories, acculturation mechanisms, selection effects or misclassification. Moreover, differences in smoking prevalence and smoking policies could cause considerable variation in risks between countries. The impact of the national context on smoking prevalence has previously been established in the comparison of English and Dutch South Asian and African migrant groups (2).

Data from the Netherlands confirmed the earlier findings from Germany (**chapter 4**) and suggested a significantly lower incidence of breast cancer among migrant women in comparison with native Dutch women (**chapter 6**). This pattern persisted while screening uptake among migrant women in the Netherlands remained considerably lower than among the majority population (3). The main reasons for lower breast cancer risks among migrant women could be different underlying risk factor patterns, most importantly younger age at first birth, higher parity and more and longer breastfeeding. In the Generation R study, Mediterranean first generation mothers were for example more likely to start and to continue breastfeeding as opposed to native Dutch women (4). Besides breast cancer, the incidence of stomach cancer among migrants in the Netherlands was explored in **chapter 6**. Here we found increased risks for non-cardia stomach cancer in migrants (especially in Turks), which is often attributable to an infection with helicobacter pylori (H. pylori) and a high consumption of salt-preserved foods. The higher risk of non-cardia stomach cancer in migrants probably reflects a higher prevalence of infection in the regions where the migrants originate from, for example east Turkey (5-6).
A higher incidence of stomach cancer also affects stomach cancer mortality, which was found to be significantly elevated in Turkish migrants residing in France and in the Netherlands (**chapter 5**). Interestingly, stomach cancer mortality among Turkish migrants in our study was even higher than in Turkey itself. This finding is most likely related to the limited validity of Globocan data that were used for the comparison with Turkish cancer mortality data. Globocan 2000 data for Turkey are based on one cancer registry only, the Izmir Cancer Registry, covering a mainly urban region of West-Turkey which is potentially unrepresentative for rural regions with a higher prevalence of H. pylori infection and possibly higher stomach cancer mortality.

In a subsequent study, risks for cervical, oesophageal and colon cancer were investigated among migrants from five different countries in the Netherlands (**chapter 7**). Migrant women exhibited elevated risks for cervical cancer, in particular migrant women from Suriname (1.8-fold risk) when compared to native Dutch women. Elevated risks were

more pronounced for squamous cell carcinomas (SCCs). Human Papilloma Virus (HPV) infection is one of the main causes for cervical cancer and is in particular associated with the development of SCCs. Lifestyle-related factors such as obesity are on the contrary more common in the development of adenocarcinomas of the cervix. In the same study, lower risks were found for both colon and oesophageal cancer in all migrant groups, reflecting lower risks in their countries of origin and more favourable lifestyle patterns, i.e. higher prevalence of alcohol abstinence and lower prevalence of tobacco smoking.
How migration can affect national cancer rates has been exemplified by exploring trends of nasopharyngeal cancer (NPC) in the Netherlands (**chapter 8**). NPC is relatively rare in Western countries and mortality from this cancer has been decreasing since decades. In terms of tumour histology, two main types of NPC are being distinguished: keratinizing tumours (WHO type I) and non-keratinizing tumours (WHO types IIA and IIB), which followed different incidence trends in recent years. While the incidence of mainly smoking-related, keratinizing NPC decreased, the incidence of non-keratinizing NPC increased. A close relationship exists between infection with the Epstein-Barr Virus (EBV) and development of non-keratinizing NPC, which is most prevalent in China and North Africa. Increasing migration from high-incidence countries in recent years is likely to have contributed to the rising incidence of non-keratinizing, EBV-related NPCs in the Netherlands and demands special attention and awareness among health care professionals.

Cancer survival
In contrast to other studies on breast cancer survival (7-8), we found slightly lower survival for premenopausal migrant women, but higher for postmenopausal women when compared to native Dutch women. Among stomach cancer patients, death rates were on average 30% lower in migrants than among native Dutch. Similarly, one-year relative survival from stomach cancer was more favourable in migrant stomach cancer patients (**chapter 6**). Other studies reported poorer stomach cancer survival among migrants (9-10). We argue that different tumour histology as well as genetic predisposition could possibly underlie this result or that methodological issues might be involved in artificially causing this effect, for example by selective remigration (salmon bias), which will also be addressed later in this chapter.
Relative survival from cervical and colon cancer was slightly better in all migrants, except Indonesians, and oesophageal cancer survival was slightly poorer than among Dutch natives (**chapter 7**). As oesophageal cancer is one of the most fatal malignancies, differences in survival can primarily be ascribed to differences in access to and utilization of care as well as treatment, potentially amplified by a strong inverse link with socio-economic determinants. The results for cervical cancer survival seem, similar to breast cancer, somehow contradicting a lower screening participation among migrant women. However, in the case of breast cancer, this is also underlying a significantly lower risk to develop breast cancer in the first place. Thus, screening might not yet be that relevant in this group and lower attendance no reason to worry. Better survival from cervical cancer, on the other hand, could be explained by the fact that in some instances, unscreened populations have a more favourable survival than screened populations, because more aggressive and fast-growing tumours with a poorer prognosis are left in the latter group (11).

Clinical aspects

Disease burden and symptoms presented at GP practices differ between migrants and native Dutch persons (12). This 'ethnic factor' in health care also persists after adjusting for other important determinants such as education, occupation and marital status and suggests a genetically, lifestyle- and/or communication-related origin. Besides, migrants often exhibit a different pattern of healthcare utilisation; whereas an increased use of GP care and prescribed drugs prevails especially among Turkish and Moroccan migrants, more specialised care is often underutilised by this group (13-15). The latter cannot be explained by socioeconomic determinants. Furthermore, lower utilisation of physical therapy and home care among elderly immigrants could solely be ascribed to language barriers rather than socioeconomic factors (16). In internal medicine, first-generation migrants made significantly more use of outpatients' care and were more likely to be referred for analysis and treatment of gastro-intestinal complaints and liver diseases, which was also independent of socioeconomic factors (17). This pattern reflects their higher risks for those conditions and is also evident in the occurrence of cancer at those sites (**chapters 3, 6**).

Public Health aspects

Migration from low- to high-income countries has been conceptualized as 'time travel' in terms of a high-speed health transition (18). In our update study (**chapter 9**), we argued that while treatment, access to care and sanitary conditions improve almost instantaneously after migration, health effects of "western" risk factors such as diet and smoking will become evident only after long lag periods in immigrants from low-income countries. Interestingly, this should entail (temporary) advantages in morbidity and mortality in immigrants from low-income countries when compared to local-born host populations of high-income countries. With this approach, we aimed to explain why the 'healthy migrant effect' may last for years or even decades after migration, in spite of socioeconomic disadvantage and discrimination faced by immigrant populations in many host countries. We found that immigrants from low-income countries do not necessarily benefit to the same extent from the general decline in mortality from non-communicable diseases (NCDs) in high-income countries and are at high risk of a double disease burden due to 'unfinished agendas' of health transition. Temporary advances in health might be the result of both selection effects and long lag times between increased exposure to new risk factors and disease onset. Accordingly, NCDs are expected to become more common diseases and causes of death in immigrants residing in high-income countries. Hence, disparities in disease risk and mortality between migrants and local-born persons seem to widen – hopefully only temporarily – over time, with substantial variation by origin and host country. The reasons for these developments are not yet fully understood. However, the comparatively smaller declines in NCD mortality observed among immigrants are likely to increase existing disparities in health. Socioeconomic gradients in the tobacco epidemic for example reverse earlier in immigrants, being more pronounced in low SES groups in males and in high SES groups in females, and point towards ways to implement tailored prevention measures (19).

Methodological considerations

Studies on cancer in migrants are often subject to many methodological limitations related to the availability, quality and consistency of data as well as to migration-specific biases. These depend on the type of comparison that is being made and the populations under study (**figure 1**). The 'healthy migrant effect' and the 'salmon bias' are commonly discussed biases in migrant studies that most often result in an underestimation of morbidity and/or mortality in migrants. Due to their time-varying nature, these phenomena are however assumed to wear off with time (20). In particular mortality among older immigrants is often underestimated due to salmon bias, implying unregistered remigration and death outside of the country of residence. For instance, of all immigrants of Turkish origin who permanently settled in the Netherlands, about 22% die abroad, most of the times in their country of birth (21). While the death itself is often registered with the Dutch authorities, the cause of death generally remains unknown, leading to a considerable proportion of deaths that cannot be attributed and as a consequence to biased cause-specific mortality and survival estimates.
Three possible types of comparisons in migrant studies and their rationales are presented in **figure 1**, all of them potentially subject to confounding by diagnosis/death, marital status, place of residence, ethnic group and socioeconomic position. When comparing population, death and cancer registration data from the migrants' host country with that of their country of origin, often substantial differences in data quality, accuracy and completeness exist. Globocan data (22) on cancer incidence and mortality in low- and middle-income countries, for example, often represent extrapolations from a few cancer registries, hospitals or death statistics and can therefore only provide a limited point of reference regarding cancer burden in those countries as a whole (**chapter 5**). Of course, differences in data quality and validity cannot be changed but imply that comparisons have to be interpreted with caution. Another important issue in this context is a mismatching numerator/denominator bias that can occur if, for example, migrant status is not identically defined in both population and cancer or death data (23).

A uniform definition of 'migrants' within Europe would facilitate comparisons across countries and databases. Many countries do not yet routinely handle variables related to migration in their registries, and it is probably still a long way to go in order to achieve this (**chapter 2**). The WHO consultation has highlighted the need for a standardised approach and a minimal standard for data collection (24). A recent review on data collection practices of migrant health in Europe revealed that most member states still lack information on the health of migrants, impeding monitoring and improvements in migrant health (25).
Apart from this, in epidemiology it is quite common to work with proxies for complex social constructs. This approach in itself is not reprehensible, however, sometimes misleading. Both socioeconomic and ethnic determinants should ideally not only be measured on an individual basis but also require adequate categorization in order to minimize misclassification (26). To date, often if there is data on migration available, it enforces black and white thinking in a way that a person can either be a migrant or not. However, this is an unrealistic and even unethical distinction. Migration should rather be seen as a continuous process that is not completed upon the moment of settlement in the new host country. To the contrary, it represents an ethnic transition whose effects can last for

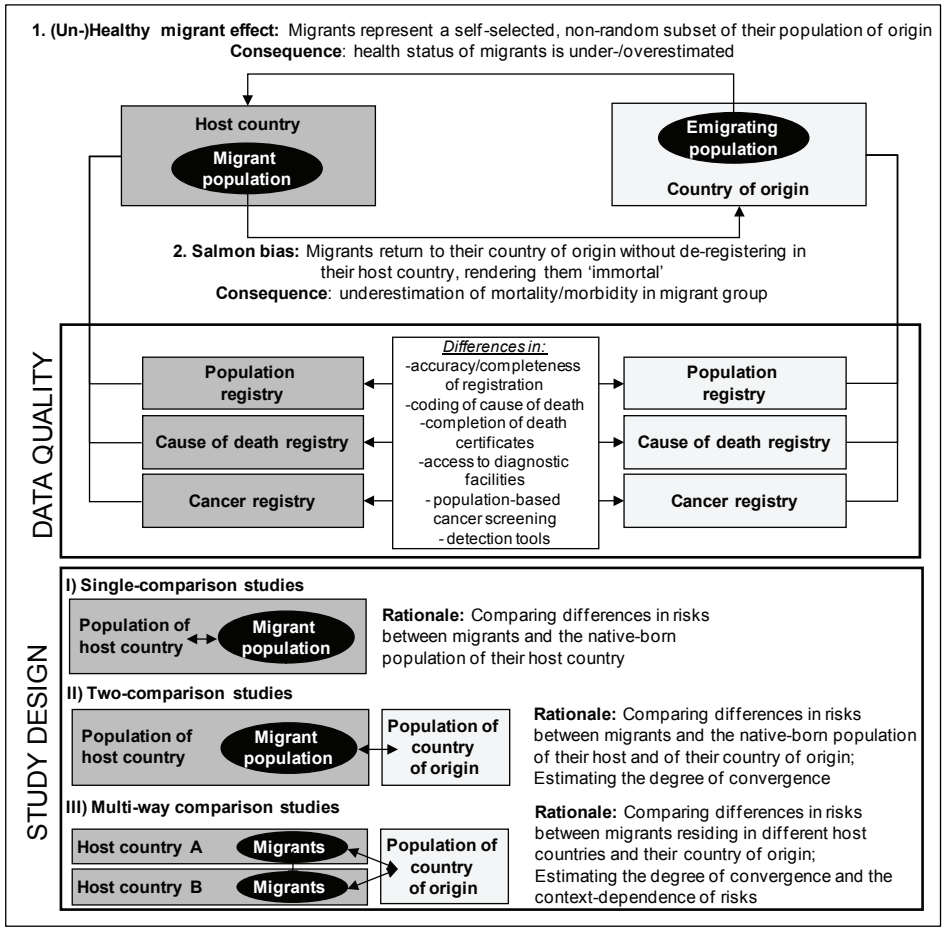

Figure 1 Outline of the most common biases, methodological challenges and study designs in studies on cancer in migrant populations

decades and even operate across generations. Reflecting this concept in epidemiological practice is extremely complex and often not possible, in particular in register-based studies. In, the end, we need to find a way to live with this complexity (27).

In the Netherlands, country of birth is the most commonly used indicator for migrant status, despite its substantial drawbacks when it comes to ethnic variation within one country of birth and the identification of third generation migrants. Another limitation has for example become obvious in our studies involving migrants from Indonesia, a former Dutch colony (**chapter 6 and 7**). Many people who were born in Indonesia and migrated to the Netherlands about 60 years ago have Dutch ancestors or are ethnic Dutch. This fact not only explains similar results for Dutch and Indonesians in cancer risk, but also underlines the pitfalls attached to using country of birth as a proxy for ethnicity. Stronks and colleagues therefore suggested including additional indicators next to country of birth in biomedical research in order to overcome these limitations (28-29). The validity of for example geographical origin of ancestors, language or self-assigned ethnic group may, however, vary by migrant group and research question.

In Germany, to date, only name-based approaches can be used in order to identify Turkish migrants (**chapters 2 and 4**) (30-31). This is partly due to the fact that there is no national cancer registry, covering the entire country and no routine registration of migration-sensitive indicators yet.

Measuring ethnic cancer disparities in a comprehensive way is crucial to the correct interpretation of data. When choosing the right summary measure such as cancer risk, one can in general distinguish absolute from relative measures. There has been some debate on their use and interpretation (32-33). When using relative measures, the reference group must be chosen with great care and needs to fit the research question. Since cause of death is often more likely to be unknown in migrants than in the local-born population of their host country (due to the fact that a greater proportion of deaths occur abroad), cause-specific mortality and survival analyses can be subject to considerable bias. For comparisons of cancer survival, relative survival analysis or excess mortality modelling is therefore the preferable method, given that appropriate and valid background mortality data are available for the corresponding (ethnic) groups. This has been done for the first time in two of the included papers in this thesis (**chapters 6 and 7**) and can serve as a model for future studies in different settings and on different cancers. Subgroup-specific background mortality had previously been used to correctly measure differences in cancer survival across socioeconomic groups in Sweden and Finland (34-35).

The UK and the Scandinavian countries are pioneers when it comes to ethnically disaggregated morbidity surveillance data in Europe (36) (**chapter 2**). Their excellent data infrastructure and information systems have great potential, especially in terms of data linkage. Scotland, in particular, achieved many successes in promoting and facilitating migration-sensitive research in recent years. Amongst other measures, by introducing ethnicity on death certificates (37) and the 'Scottish Health and Ethnicity Linkage Study', allowing for various kinds of analyses on ethnic variations in a cohort of 4.65 million people (38-39). This approach not only facilitates the analysis of health care procedures and treatment paths, but also removes uncertainties related to potentially confounding factors that can now more easily be adjusted for. Internationally, linkage can fill the information gap on health data by ethnic group, given that there is standardised information on ethnicity available across databases. Its use is most effective and accurate when it is based on a unique, personal identification number. The Burgerservicenummer (BSN) is such a number which was originally meant to be a fiscal identifier, but has been introduced to the Dutch health care system in 2009. Until today, it is being used exclusively by governmental authorities for fraud prevention and not (yet) approved for research. Provided that its abuse can be excluded, the BSN could be an extremely valuable instrument for studies in migrants. The comprehensive information on migration available in the population register could potentially, through linkage, be studied in many different settings, including register-based studies on cancer.

Johnman and colleagues recently outlined the potentials of record linkage studies on ethnic inequalities in health outcomes in Scotland, New Zealand and the Netherlands (40). They concluded that this methodology allows for large-scale studies that can be conducted at relatively low costs and provide insights into ethnic inequalities at a global level.

The interplay of ethnicity and socioeconomic determinants

The association between socioeconomic determinants and health is well-known. Ethnic inequalities in health are in parts attributable to socioeconomic circumstances, making them closely interrelated but not equivalent concepts (27, 41). Both are independently associated with cancer incidence, survival and mortality. Their interplay is multidimensional and still poorly understood.

In the Netherlands, an ecological proxy serves as the standard approach to measure socioeconomic differences in health. In brief, it is based on four-digit postal code at the time of diagnosis and reflects mean income per household, the percentage of low income households and the percentage of households with a low education (42).
In table 1, cancer incidence in non-western migrants in the Netherlands is compared to that of Dutch persons with low socioeconomic status (SES) (43) in order to see similarities and discrepancies in risk profiles. Especially advantageous patterns for colon, skin, breast and prostate cancer coincide between the groups. The same is true for higher risks for cancers of the head and neck, cervix uteri and Hodgkin's lymphoma. Yet, whereas persons with a low SES have higher risks for other mainly lifestyle-related cancers such as tumors of the upper GI and lung, the opposite is true for non-western migrants. Unlike low SES groups, non-western migrants exhibit a higher burden of infection-related tumours (like nasopharyngeal, liver and non-cardia stomach cancer). These patterns imply overlapping, but not congruent cancer risk profiles between migrants and persons of low socioeconomic status. It is important to note that both migrants and persons of low SES may represent very heterogeneous groups with different priorities in terms of cancer risk and prevention (for example substantially elevated risks for nasopharyngeal and liver cancer among Chinese migrants).
Higher risks and increasing detection rates among persons with a high SES seem to result from greater awareness and knowledge of cancer and the willingness to seek medical advice. Typically, this entails an earlier stage at diagnosis and a better prognosis among cancer patients with a high SES as opposed to low SES patients who often exhibit worse survival (43). In the most deprived women with breast cancer for example, poorer survival persisted even after adjustment for common factors related to prognosis such as grade, stage and treatment (44). This might be due to lower attendance rates in mass screening for breast cancer among low SES women (45) that is also characteristic for migrant women (3, 46). Lacking awareness and knowledge as well as organizational determinants and other socio-cultural aspects could be responsible for this (47). Most migrant women, however, not only carry considerably lower risks to develop (especially postmenopausal) breast cancer, they also exhibit equal or slightly better survival when compared with native Dutch women (**chapters 3 and 6**). This is why low attendance of migrant women in mass screening is, at the moment and opposed to low SES women, not necessarily a reason for concern or immediate action. Screening in low-incidence populations can produce many false positive outcomes and harm related to unnecessary treatment (48-49). Even so, the expected increase in burden from breast cancer in migrant women demands regular cancer surveillance in this population group (50). Re-evaluation of cancer risks should ideally be done by means of follow-up studies, in future potentially also based on known data on age at menarche and at first birth.

Table 1 Comparing cancer sites with low and high incidence between non-western migrants and persons with low SES in the Netherlands

	Non-western migrants*	**Males with low SES****	**Females with low SES****
Low incidence	*All cancer* Oesophagus Stomach (cardia) *Colon* Lung *Skin, melanoma* *Non-melanoma skin* *Breast* *Prostate*	*All cancer*[#] *Colon* Pancreas *Skin, melanoma* *Skin, basal cell carcinoma* *Skin, squamous cell* *Prostate* Urinary bladder	*Skin, melanoma* *Skin, basal cell carcinoma* *Breast*[§]
High incidence	Nasopharynx *Stomach (non-cardia)* Liver Kaposi's sarcoma *Cervix uteri* Thyroid gland *Hodgkin's lymphoma*	Oropharynx Larynx Oesophagus *Stomach (non-cardia)* Lung	All cancer Oropharynx Larynx Oesophagus *Stomach (non-cardia)* Colon Rectum Lung Skin, squamous cell *Cervix uteri* Kidney Urinary bladder Mature B-cell including *Hodgkin's lymphoma*

Congruent sites in terms of a high or low incidence across the groups are marked in *italic*
* Non-western migrants in comparison with native Dutch (based on chapters 6, 7, 8 and (51));
**Low SES in comparison with high SES in the South of the Netherlands in 2008 (based on (43));
[#] this was the reverse in the late 1990s; [§] especially below age 45

Can the interrelationship between socioeconomic and ethnic inequalities in health be further disentangled in order to improve the understanding of their separate effects? It has been suggested to use different socioeconomic indicators for ethnic and/or migrant groups as opposed to the majority population of the host country. Especially first generation migrants may have experienced a different form of education (often in their country of origin) and other acculturation- and integration-related factors that can influence their socioeconomic position and cannot easily be compared to the majority population (41). The lack of adequate formal education before migration can be one of the most important factors that determine their socioeconomic position in later life.
Furthermore, the impact of socioeconomic status may differ by ethnic group; socioeconomic inequalities in mortality appeared to be smaller within ethnic groups than in the general Dutch population (52). This is why the effects on health can possibly take different directions among migrant and ethnic groups as opposed to socially disadvantaged groups. However, given its multiple dimensions and strong interdependence, socioeconomic and ethnic determinants on health should always be addressed jointly in order to refine policies for prevention and surveillance.

Cancer in migrants: priorities for the future

Policy and public awareness

Demographic developments will inevitably further increase ethnic diversity and complexity in Europe in the near future. A mix of first to fourth generation migrants will become characteristic for many European societies. Also the number of absolute cancer cases among persons with a migration background will undoubtedly rise, largely driven by aging, but also by increased acculturation and the adaptation of Western lifestyle patterns. This also implies that this group will constitute a growing proportion of all cancer patients in the Netherlands and in most other European countries (50). The position of (elderly) migrant cancer patients in many societies and health systems is however still to be determined. The adaptation and reorientation of social and health systems and above all, a clear and realistic policy commitment, are only slowly gaining ground.

The WHO consultation clearly stated the necessity for raising awareness about health needs of migrants among policy makers and the media (24). Within migrant-inclusive (and migrant-sensitive, that is taking cultural, religious, linguistic needs of migrants into account) health systems, accurate data on the health status of migrants and their utilization of health care services are needed to develop targeted interventions and improve health outcomes. In order to achieve this, migrant health needs should become part of national plans and resources, respectively. Along with the general need for adequate health insurance coverage, the day to day problems of doctors, nurses and other caregivers needs to be given a voice in policy making.

Building partnerships and networks

European and international partnerships represent key venues in promoting migrant health and can be used as a basis for the exchange of practices, policies, knowledge and data (24). Country-specific activities can be supplemented by regional and global strategies and pooling of migrant-specific data across European countries will increase the power of such studies. In addition, as migrants are facing similar problems in various European countries, joint multinational approaches and studies will be most effective and cost-efficient.

In research on cancer in migrants, two-comparison (including information from both the country of origin and the host country) and multi-way comparison studies (including more than one host country) are still scarce (figure 1). This is because those kinds of comparisons can involve many limitations (**chapters 2, 3 and 5**). Surmounting these limitations requires high data quality within countries and close networking between countries. Multinational studies would make results more reliable and would allow studying the magnitude and trends of cancer risk diversity among migrants residing in Europe in more detail. In order to appreciate changes in risks after migration and during life course, data from the country of origin should ideally be incorporated in studies, same as details on the migration process itself (especially age at and time of migration). Multi-way comparisons can also allow for insights into the context-dependence of cancer risks. Differences in exposure to risk factors, health systems and policies may produce variation in cancer risk and mortality between countries. Studies among migrants have the potential to reveal the driving factors for these differences. And in fact, it matters where you have migrated to (53).

The comparison of cancer mortality in Turkish migrants across four different host coun-

tries has been the first of this kind (**chapter 5**), following the example of mortality from circulatory diseases (54) and diabetes (55-56). Although limited with regard to heterogeneous study designs and data inconsistencies between countries, those types of studies may possibly disclose important reasons for differences in cancer burden across Europe. In addition, scenario studies on avoidable cancer burden and mortality are a promising setting for migrant studies. Following examples such as: if socioeconomic inequalities were eliminated (57) or if risk profiles of one country would equalize that of the country with the lowest risks (58), or if the majority population would have the same, low but apparently feasible cancer incidence of certain migrant groups.
Building partnerships is important, especially to actively engage key-migrants in the process of designing and conducting research. Maximizing their awareness and participation will further increase validity and comprehensiveness of studies and knowledge on cancer in migrants in general. This could, for example, be achieved by creating interactions through social media. In addition, recognizing migrants as a very heterogeneous and ethnically diverse group represents one of the main challenges for future research and health care provision. Another interesting aspect for future studies is the measurement of preferences and satisfaction with health care among migrants, possibly by means of discrete choice experiments. In the provision of health care, ethnic background of the health care advisor has been found to play a key role in addressing and communicating with ethnic groups (59).

Combining disciplines
There is evidence that social conditions and deprivation experienced during life course can have a cumulative effect on all cause mortality, in particular on cardiovascular diseases and smoking-related cancers (60). This is one of the reasons why life course epidemiology of chronic diseases is a promising field that deserves more attention in the context of migrant studies and in combination with other disciplines. The patterns found in our studies (**chapters 3, 4, 5, 6, 7 and 8**) point towards a strong link between environmental exposures and/or behavioural patterns and the development of cancer during life course. To gain further insight into acculturation processes, studies should most importantly include a time variable, ideally age at migration or duration of residence, constituting a proxy for exposures before migration, i.e. in the country of origin. This also asks for longitudinal study designs and measurements at patient level, i.e. not using aggregated data or ecological proxies (applying to both ethnic and socioeconomic determinants) (61-62). One of the most prominent examples in this field has been published by McCredie and colleagues in the late 1990s, investigating cancer mortality in migrants in Australia over long follow up periods (63). They found persistently low mortality for cancers of the prostate and mouth/pharynx in European migrants relative to the Australian-born even 30 years after migration.

Culture plays a central role in medical anthropology and influences patients' views on their disease and their expectations regarding care (64). The core of medical anthropology is the relation between culture and health/disease as well as its communication in a setting where health care provider and patient come from different ethnic backgrounds (65). Integrating this approach in epidemiological studies could enrich them by moving beyond the one-sidedness of current approaches, generating little understanding of the roots of disparities. The reconceptualization of social and cultural dimensions of ethnic-

ity and its measurement as well as models that emphasize both psychological and sociocultural factors in the emergence of health disparities are needed in order to achieve this (66). For example, in view of the central role of food in the culture of Turkish and Moroccan migrants, how does acculturation influence dietary patterns and possibly future cancer risk? And what are the generational effects of those lifestyle changes?
In aging societies, there is a growing need to explore co-morbidities in order to develop more comprehensive routes to treatment (67). Recent evidence of a positive relationship between diabetes and cancer (68) might point towards a double disease burden in some migrant groups that are at an increased risk for (mortality from) diabetes (56), for example South Asians and Africans (69). Similarly, the protective effect of vitamin D on osteoporosis, diabetes, cardiovascular disease and some common cancers can serve as a starting point for more comprehensive and interdisciplinary studies, also among migrants (70). Furthermore, vitamin D status has been found to be poorer in Surinamese migrants in the Netherlands, partly explaining their higher blood pressure and higher risks for hypertension (71).

Priorities for care
The provision of care in migrant cancer patients should focus on their actual needs and research should aim to help preparing health systems and health care providers for this growing challenge. Insights into differences in disease perception and coping mechanisms are necessary in order to respond and treat responsibly. Although some quantitative questionnaires on quality of life have recently been evaluated for the use in culturally diverse settings (72-74), this branch is still in its infancy. The EORTC quality of life questionnaires have been developed to assess the quality of life of cancer patients and have been translated to various languages. They are however not culturally sensitive. Differential functioning for several items across ethnic groups have suggested caution when comparing quality of life scores (75-76).
Racial and ethnic disparities in cancer care have also been addressed by the American Society of Clinical Oncology (ASCO). ASCO committed to improving access to health care, increasing the awareness of existing disparities and supporting research on ethnic disparities in cancer (77). In their policy statement, they especially emphasize the need for diversification and training of oncology workforce and the diversification of clinical trials as well as the patient's involvement in their own care. The reduction of economic barriers and the improvement of policies such as insurance reforms belong to their most recent commitments (78). The European counterpart of the ASCO, the European Cancer Organisation (ECCO), has no corresponding, culture-specific guidelines or statements for cancer care among migrants in Europe yet. However, good practices in health care in immigrants are currently being assessed by the multinational EUGATE project (79) and a broad consensus exists among experts about major principles of good practice that should be implemented across Europe (80). The report on cancer in migrants for caregivers by the Flemish League against Cancer (VLK) also provides some valuable starting points for migration- and culture-sensitive cancer care (81).

Future research (and some dreaming beyond)
Accurate information on migrants' health care needs and health-seeking behaviours is essential in order to respond with targeted interventions and to improve outcomes. Qualitative studies can explore those aspects and serve as a basis for hypothesis devel-

opment that can in turn stimulate and complement quantitative studies. Qualitative approaches also represent important means to acquire insight into the patients' perspective on the disease, including related fears, hopes and preferences towards care givers.

Next to multinational studies, there are visions for a longitudinal migrant cohort, taking into account behavioural and socioeconomic variables at the individual level (62). In order to appreciate the full effect of migration on health in a broader sense, this could ideally be done by enrolling the study participants before they migrate and following them, no matter where they settle, move or return. By this means, it could be determined in what manner and to which degree the migration experience and acculturation set off the convergence of health risks. A minimal set of important extrinsic and intrinsic determinants as well as physical characteristics related to the disease under study should be collected and studied in order to shed light on causal mechanisms. For breast cancer, this would for example comprise information on age at menarche and at first birth, oral contraceptive use but possibly also on dietary patterns, physical activity and measurements of breast density. The adequate measurement of ethnicity- and migration-related variables such as self-assigned ethnicity, religion, (parental) country of birth and age at migration would further increase the meaningfulness of such an approach. In terms of outcomes, a cohort study with a long follow-up would allow to measure cancer incidence, survival and mortality in a valid and comprehensible way. A sufficient number of study participants could be achieved by anticipating migration waves that involve numerous migrating people to a few host countries, for example when former colonies obtain independence. This approach would however only be realistic for common cancers and would involve major challenges with regard to data quality, protection and resources.
Another vision for future migration research are randomised controlled trials (RCT). Evidence from random migration lottery in New Zealand for example showed that experimental study designs may represent a promising new tool in migration research (82). The study among randomly chosen families from Tonga revealed significantly decreased stunting, increasing height but also increasing overweight and obesity in young children shortly after migration. Due to their special character in terms of feasibility and applicability per country, these kind of studies will remain limited. Yet, RCTs represent the methodological golden standard in clinical research and epidemiology as they can overcome selection bias that is usually present (but often not measurable) in migrant studies.

Conclusion and Outlook

Many cancers are preventable (83-84). The contribution of environmental and behavioural determinants in the development of various cancer types has been estimated to be larger than previously thought (85). While biological determinants (like reproductive factors, viruses and medication) are likely to represent 18% of all cancers causes, 39% can be ascribed to social (behavioural) factors (like diet, tobacco smoking and alcohol consumption) and another 31% to our physical environment (like sun/radiation, obesity, sedentary lifestyle and environment). Hence, personal lifestyle choices have been identified as the main cause for the development of cancer and the main key to cancer prevention.
Although cancer mortality is on the decline in almost all Western countries since two to three decades, crude cancer incidence is still rising. This is largely due to demographic

aging, but can potentially also be ascribed to the suboptimal implementation of (effective) prevention programmes and persisting grey areas in the knowledge on cancer aetiology (86). Migrant studies have the potential to help both refining the understanding of causes and translating this knowledge into directed prevention strategies.
In addition, the growing group of culturally and ethnically diverse elderly in Western European societies requires reconsideration of current practices towards more migrant-inclusive and –sensitive health care.

Most cancer types occur less frequently in migrants and their survival can be better than in the general population. However, some tumours occur more often in migrants and deserve special attention among health care professionals. In practice, favourable risks in migrants should be sustained as long as possible while unfavourable risks should be reduced by means of adequate and target-group specific prevention. As it can be difficult to change lifestyle, the main focus should be on increasing cancer awareness and ensuring early detection and targeted care in migrants and other ethnic groups. But also further efforts to reduce the increased prevalence of overweight/obesity (87-88) and smoking (19, 89) among immigrants and disadvantaged groups represent solid starting points for cancer prevention. The heterogeneity of cancer risk among migrants demands subgroup-specific recommendations and guidelines for care. Increasing cultural and ethnic sensitivity, rather than equality, should be the main aim in the provision of care.
But how can Europe contribute to these aims? The Framework Programme of the European Commission can help establishing and strengthening a sustainable network of experts throughout Europe. Sufficient resources need to be provided to initiate long-term studies, complementing the work of the 'Migrant and Ethnic Health Observatory' (MEHO, 2003-2008) during the course of which indicators for monitoring the health status of migrants have been developed (**chapter 2**) (90). As healthcare professionals from various European countries experience similar problems in the provision of care in migrants, good practices in healthcare need to be pooled into a common strategy, which is the scope of the DG SANCO funded EUGATE project (79) and has also been suggested by Devillé and colleagues in their Delphi study among country experts (80).
While the need for more specific research on cancer in migrants has already been acknowledged by the Dutch Cancer Society (DCS) in their 2006 alert report (50), six years later all sorts of efforts are still needed to further establish this topic in research and care. This particularly applies to improvements in migration-sensitive cancer registration and qualitative studies on socio-cultural aspects that influence health care utilisation, quality of care and quality of life among migrant cancer patients. Migrant-specific information needs to be included in training and education of health care professionals, addressing the impact of socio-cultural differences on disease perception and care-seeking as well as epidemiological profiles of the various groups (24).

To conclude, short- and long-term targets for research on cancer in migrants are given below. Short-term goals mostly refer to improvements in the organisation of health services, infrastructure and communication within and across countries that can theoretically be achieved within a few years. Long-term goals focus on establishing culture- and migration-sensitive cancer surveillance and care as well as its long-term evaluation and the initiation of multidisciplinary research approaches.

Short-term targets

- **Increase awareness on ethnic heterogeneity in cancer**
  Awareness of the benefits of monitoring migrant health needs to be increased among the public, policy makers and the media by targeted campaigns and support from higher level entities such as EU and WHO in order to drive the topic forth and to mobilise funds.
- **Learn from each other through networking**
  More intense partnerships between research and policy entities on the national and international level can serve to share experiences, copy good practices and, possibly, combine data on cancer in migrants multinationally.
- **Find common denominators and elaborate methods**
  Approaches to identify and define migrants within and across European countries need to be elaborated and standardised. Knowledge and experiences with various methods need to be exchanged among experts of all countries.
- **Foster qualitative research**
  Qualitative studies on the needs and expectations of migrant cancer patients need to be increasingly launched in order to reveal priorities for care and to develop new clinical strategies. This especially applies to disease perception, coping, quality of life and health care utilization. The results will generate new hypotheses for quantitative research.
- **Involve the various groups of migrants in research**
  Migrants and members of ethnic groups need to actively be involved in the planning and conduct of research in order to maximize its meaningfulness.
- **Involve and sensitise health care providers**
  (Prospective) health care professionals need to be educated and trained in dealing with ethnically and culturally diverse patients. This can for example be achieved by providing epidemiological risk profiles and by addressing culture-specific needs and expectations with regard to treatment. This again requires knowledge from comprehensive (qualitative) studies.

Long-term targets

- **Establish culture- and migration-sensitive cancer surveillance**
  Comprehensive migration-sensitive surveillance of cancer risks and mortality needs to be implemented and regularly evaluated.
- **Make use of new study approaches and disciplines**
  Study designs need to become more interdisciplinary in order to make results more meaningful and reliable. This especially applies to life course approaches (i.e. cohort studies with a long follow-up), linkage studies, scenario studies and possibly experimental study designs.
- **Refine the distinction and identification of ethnic groups**
  We need to learn from other disciplines, for instance anthropology, to find ways to do justice to the interplay of social, ethnicity- and culture-related determinants in epidemiology. This also concerns a more comprehensive distinction of ethnic groups (and generations) which will prospectively allow for more refined aetiological inferences.

- **Establish culture- and migration-sensitive guidelines for cancer care**
  Guidelines for culturally-sensitive (cancer) care need to be developed and established in order to tackle the challenge of increasing ethnic diversity in aging European societies.

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Summary

Europe has become a remarkable multicultural and multiethnic society, characterised by a common vision on democracy, welfare, social inclusion and protection of its citizens. In the age of globalisation, most European countries are however increasingly facing problems with regard to the sustainability of their social models. This especially applies to low and decreasing birth rates, population aging and effects of migration on Europe's population composition. This development inevitably raises the question whether the European social construct is flexible enough to defy these changes and whether social equality is still a realistic aim across all segments of society. This line of reasoning also represents the scientific and public health rationale of making migrant health a core theme at EU-level consultations and in health programmes. Besides, from an epidemiological point of view, migration can be seen as a big-scale natural experiment that has the potential to teach us about the power of cancer prevention and grey areas that still exist in aetiological cancer research.

Cancer incidence and mortality

A variety of studies from Europe has shown that ethnic disparities in the burden of cancer exist. In **chapter 3**, we explored cancer patterns in non-Western migrants in Europe based on the literature. We found that in Europe, non-Western migrants were more prone to infection-related cancers but had lower risks for cancers associated with a more western lifestyle, such as colon, breast and prostate cancer. Risks in migrants were often in between the corresponding risks in their home and in their host country. This pattern largely reflects the retention of more favourable risk factors that are common in the migrants' countries of origin, parallel to a slow adaptation and acculturation to the risk profiles of the majority population of the country of residence.

Our study among Turkish migrants residing in Hamburg (Germany), revealed lower risks for cancer of the respiratory organs among Turkish males than in the non-Turkish population, particularly in the older birth cohorts (**chapter 4**). Younger birth cohorts had increasingly similar risks to the non-Turkish population. The risk for malignant neoplasms of lymphoid, haematopoietic and related tissues was slightly higher in most male Turkish birth cohorts. Incidence rates for Turkish women were lower than among non-Turkish women for cancer of the respiratory system, skin and the genital organs.

In a multinational study including data from France, Belgium, Denmark and the Netherlands (**chapter 5**), all-cancer mortality was consistently lower in Turkish migrants than among the local-born population of their host countries, irrespective of their current country of residence. Cancer mortality in Turkey in relation to that of the four host countries was, however, equal or lower than that of Turkish immigrants relative to the local-born population of their host country. Besides we found that all-cancer mortality in Turkish immigrants was in between that of their country of origin and their host country. The same applied for breast cancer in Turkish migrant women in relation to Dutch- and French-born women. For lung cancer, contrasting patterns in Turks residing in France and in the Netherlands existed. Whereas in France lung cancer mortality in Turkish migrants converged towards that of French natives, mortality rates of Turkish females residing in the Netherlands were even lower than in Turkey. The reason for this variation between host countries might be related to different durations of stay, migration histories, acculturation mechanisms, selection effects or misclassification.

Data from the Netherlands confirmed the earlier findings from Germany (**chapter 4**)

and suggested a significantly lower incidence of breast cancer among migrant women in comparison with native Dutch women (**chapter 6**). The main reasons for lower breast cancer risks among migrant women could be different underlying risk factor patterns, most importantly younger age at first birth, higher parity and more and longer breast-feeding. Next to breast cancer, the incidence of stomach cancer among migrants in the Netherlands was explored in **chapter 6**. Here we found increased risks for non-cardia stomach cancer in migrants (especially in Turks). This type of cancer is in most cases attributable to an infection with helicobacter pylori (H. pylori) and a high consumption of salt-preserved foods. The higher risk of non-cardia stomach cancer in migrants reflects a higher prevalence of infection in the regions where the migrants originate from, for example east Turkey. A higher incidence of stomach cancer also affects stomach cancer mortality, which was found to be significantly elevated in Turkish migrants residing in France and in the Netherlands (**chapter 5**).

In a subsequent study, risks for cervical, oesophageal and colon cancer were investigated among migrants from five different countries in the Netherlands (**chapter 7**). Migrant women exhibited elevated risks for cervical cancer, in particular migrant women from Suriname (1.8-fold risk) when compared to native Dutch women. Elevated risks were more pronounced for squamous cell carcinomas, which is caused by Human Papilloma Virus (HPV) infection. In the same study, lower risks were found for both colon and oesophageal cancer in all migrant groups, reflecting lower risks in their countries of origin and more favourable lifestyle patterns, i.e. a higher prevalence of alcohol abstinence and a lower prevalence of tobacco smoking.

How migration can have an effect on national cancer rates has been explored by analysing trends of nasopharyngeal cancer (NPC) in the Netherlands (**chapter 8**). NPC is relatively rare in Western countries and mortality from this cancer type is decreasing since decades. However, we found differential incidence trends across tumour histologies: while the incidence of mainly smoking-related, keratinizing NPC decreased, the incidence of non-keratinizing NPC increased. A close relationship exists between infection with the Epstein-Barr Virus (EBV) and development of non-keratinizing NPC, which is most prevalent in China and North Africa. Increasing migration from high-incidence countries in recent years is likely to have contributed to the rising incidence of non-keratinizing, EBV-related NPC in the Netherlands and demands special attention and awareness among health care professionals.

Cancer survival

Most migrant women, however, not only carry considerably lower risks to develop (especially postmenopausal) breast cancer, they also exhibit equal or slightly better survival when compared with native Dutch women (**chapters 3 and 6**). In contrast to other studies on breast cancer survival, we found slightly lower survival for premenopausal migrant women, but higher for postmenopausal women relative to native Dutch women. Low attendance of migrant women in mass screening is therefore at present not necessarily a reason for concern or immediate action. Screening in low-incidence populations can produce many false positive outcomes and even harm related to unnecessary treatment. However, since the burden from breast cancer in migrant women is expected to increase in the coming years, more regular monitoring and re-evaluation by means of follow-up studies in the future is required. Potentially known data on age at menarche and at first birth would make these studies even more meaningful and could provide

extremely valuable insights into the causal factors responsible for changes in risk among migrant women.
Among stomach cancer patients, death rates were on average 30% lower in migrants than among native Dutch. Similarly, one-year relative survival from stomach cancer was more favourable in migrant stomach cancer patients (**chapter 6**). We argue that different tumour histology as well as genetic predisposition could possibly underlie this result or that methodological issues might be involved in artificially causing this effect, for example by selective remigration (salmon bias). Survival from cervical and colon cancer was slightly better in all migrants, except Indonesians, and oesophageal cancer survival was slightly poorer than among Dutch natives (**chapter 7**).

Public Health aspects
Migration from low- to high-income countries has been conceptualized as 'time travel' in terms of a high-speed health transition. In our update study (**chapter 9**), we argued that while treatment, access to care and sanitary conditions improve almost instantaneously after migration, health effects of "western" risk factors such as diet and smoking will become evident only after long lag periods in immigrants from low-income countries. Interestingly, this should entail (temporary) advantages in morbidity and mortality in immigrants from low-income countries when compared to local-born host populations of high-income countries. We found that immigrants from low-income countries do not necessarily benefit to the same extent from the general decline in mortality from non-communicable diseases (NCDs) in high-income countries and are at high risk of a double disease burden due to 'unfinished agendas' of health transition. Temporary advances in health might be the result of both selection effects and long lag times between increased exposure to new risk factors and disease onset. Accordingly, NCDs are expected to become more common diseases and causes of death in immigrants residing in high-income countries and the comparatively smaller declines in NCD mortality observed among immigrants are likely to increase existing disparities in health.

Methodological considerations
Studies on cancer in migrants are often subject to many methodological limitations related to the availability, quality and consistency of data as well as to migration-specific biases. This particularly hampers cross-country comparisons (**chapter 5**). A uniform definition of 'migrants' within Europe would facilitate comparisons across countries and databases. Many countries do not yet routinely handle variables related to migration in their registries, and it is probably still a long way to go in order to achieve this (**chapter 2**). In the Netherlands, country of birth is the most commonly used indicator for migrant status, despite its substantial drawbacks when it comes to ethnic variation within one country of birth and the identification of third generation migrants. This limitation has for example become obvious in migrants originating from Indonesia, a former Dutch colony. Many people who were born in Indonesia and migrated to the Netherlands about 60 years ago have Dutch ancestors or are ethnic Dutch. This fact not only explains similar results for Dutch and Indonesians in cancer risk, but also underlines the pitfalls attached to using country of birth as a proxy for ethnicity (**chapters 2, 6 and 7**). In Germany, to date, name-based approaches are the only way to identify Turkish migrants in health data (**chapters 2 and 4**). This is partly due to the fact that there is no national cancer registry, covering the entire country and no routine registration of migration-sensitive

indicators yet.
The UK and the Scandinavian countries are pioneers when it comes to ethnically disaggregated morbidity surveillance data in Europe (**chapter 2**). Internationally, data linkage can fill the information gap on health data by ethnic group, given that there is standardised information on ethnicity available across databases. Its use is most effective and accurate when it is based on a unique, personal identification number. The Burgerservicenummer (BSN) is such a number that is, however, not (yet) approved for research. Provided that its abuse can be excluded, the BSN could be an extremely valuable instrument for studies in migrants. The comprehensive information on migration available in the population register could potentially, through linkage, be studied in many different settings, including register-based studies on cancer.

The association between socioeconomic determinants and health is well-known. Ethnic inequalities in health are in parts attributable to socioeconomic circumstances, making them closely interrelated but not equivalent concepts. Both are independently associated with cancer incidence, survival and mortality. In the Netherlands, an ecological proxy based on four-digit postal code is the standard approach to measure socioeconomic differences in health and in cancer. This proxy reflects the mean income per household, the percentage of households with a low income and the percentage of households with a low education at the time of diagnosis. Migrants and people of low SES share certain cancer risks. Especially lower risks for colon, skin, breast and prostate cancer as well as higher risks for cancers of the head and neck, cervix uteri and Hodgkin's lymphoma coincide between the groups. Whereas persons with a low SES show higher risks for other mainly lifestyle-related cancers such as of the upper GI and lung, the opposite is true for non-western migrants. Unlike low SES groups, non-western migrants exhibit a higher burden of infection-related tumours (like nasopharyngeal, liver and non-cardia stomach cancer). These patterns imply overlapping, but not congruent cancer risk profiles between migrants and persons of low socioeconomic status. It is important to note that both migrants and persons of low SES may represent very heterogeneous groups with different priorities in terms of cancer risk and prevention (for example substantially elevated risks for nasopharyngeal among migrants from South Asia, **chapter 8**).

Conclusion and Outlook
There is evidence that many cancers are preventable. The contribution of environmental and behavioural determinants in the development of various cancer types is estimated to be larger than previously thought and studies among migrants have substantially contributed to this knowledge. Hence, personal lifestyle choices have been identified as the main cause for the development of cancer and the main key to cancer prevention.
Although cancer mortality is on the decline in almost all Western countries in the last two to three decades, crude cancer incidence is still rising. This is largely due to demographic aging, but can potentially also be ascribed to the suboptimal implementation of (effective) prevention programmes and persisting grey areas in the knowledge on cancer aetiology. Migrant studies have the potential to help both refining the understanding of causes and translating this knowledge into directed prevention strategies. In addition, a growing proportion of elderly persons with a migration background (or foreign ethnicity) in Western European societies requires reconsideration of current practices towards more migrant-inclusive and -sensitive health care.

Most cancer types occur less frequently in migrants and cancer survival in migrants is equal or better than in the general population. However, some tumours occur more often in this group, especially those with an infectious origin, and deserve special attention among health care professionals. In practice, favourable risks in migrants should be sustained as long as possible while unfavourable risks should be reduced by means of adequate and target-group specific prevention. As it is difficult to change lifestyle behaviours or even stop acculturation, the focus should be on increasing cancer awareness and ensuring early detection and targeted care in migrants and other ethnic groups. Further efforts to reduce the increased prevalence of overweight/obesity and smoking among immigrants and disadvantaged groups are solid starting points for cancer prevention. The heterogeneity of cancer risk among migrants demands subgroup-specific recommendations and guidelines for care. Increasing cultural and ethnic sensitivity, rather than equality, should be the main aim. All sorts of efforts are still needed to achieve this and to further establish this topic in research and care in the Netherlands. This particularly applies to improvements in migration-sensitive cancer registration and qualitative studies on socio-cultural aspects that influence health care utilisation, quality of care and quality of life among migrant cancer patients. Migrant-specific information needs to be included in training and education of health care professionals, addressing the impact of socio-cultural differences on disease perception and care-seeking as well as epidemiological profiles of the various ethnic and migrant groups.

Samenvatting

Europa is in de afgelopen decennia gegroeid tot een opmerkelijke multiculturele en multietnische samenleving, gekenmerkt door een gemeenschappelijke visie op democratie, welzijn, sociale integratie en de bescherming van burgers. In dit tijdperk van globalisering ondervindt het merendeel van de Europese landen echter steeds vaker problemen met betrekking tot de duurzaamheid van hun sociale modellen. Dit betreft met name lage en dalende geboortecijfers, vergrijzing van de bevolking en de effecten van migratie op de samenstelling van de Europese bevolking. Uit deze ontwikkeling rijst onvermijdelijk de vraag of de sociale constructie van Europa flexibel genoeg is om deze veranderingen te trotseren en of sociale gelijkheid nog steeds een realistisch doel voor de samenleving is. Deze redenering houdt ook verband met de kerngedachte uit het wetenschappelijk onderzoek en de maatschappelijke gezondheidszorg om de gezondheid van migranten een hoofdthema binnen overleggen op EU niveau en in zorgprogramma's te maken. Bovendien kan migratie vanuit epidemiologisch oogpunt gezien worden als een grootschalig, natuurlijk experiment met het potentieel om ons te leren over de kracht van kankerpreventie en de hiaten die nog steeds bestaan in de kennis van de oorzaken van deze ziekte.

Kanker incidentie en sterfte
Een aantal studies uit Europa heeft aangetoond dat er etnische verschillen bestaan in de draaglast van kanker. In **hoofdstuk 3** hebben we op basis van de literatuur patronen in het voorkomen van kanker bij niet-westerse migranten in Europa onderzocht. We vonden dat niet-westerse migranten in Europa vatbaarder waren voor infectie-gerelateerde vormen van kanker, maar dat zij een lager risico hadden op vormen van kanker gerelateerd aan een westerse levensstijl, waaronder darm-, borst- en prostaatkanker. Het risico op kanker bevond zich bij migranten vaak tussen het risico in hun land van herkomst en hun land van verblijf. Dit patroon weerspiegelt grotendeels het behoud van gunstiger risicofactoren die gangbaar zijn in het land van herkomst van migranten, parallel aan een langzame aanpassing en acculturatie van de risicoprofielen van de meerderheid van de bevolking in het land van verblijf.

Onze studie bij Turkse migranten in Hamburg (Duitsland), toonde lagere risico's voor kanker van de ademhalingsorganen onder Turkse mannen dan bij de niet-Turkse bevolking, in het bijzonder in de oudere geboortecohorten (**hoofdstuk 4**). Turken uit jongere cohorten leken qua risico op kanker steeds meer op de niet-Turkse bevolking. Het risico voor carcinomen in lymfoïde, hematopoëtische en verwante weefsels was iets hoger in de meeste mannelijke Turkse geboortecohorten. Bij Turkse vrouwen kwam minder vaak kanker van de luchtwegen, de huid en de geslachtsorganen voor dan bij niet-Turkse vrouwen.
In een multinationale studie met gegevens uit Frankrijk, België, Denemarken en Nederland (**hoofdstuk 5**), was de kankersterfte bij Turkse immigranten constant lager dan onder de lokaal geboren bevolking van het gastland, ongeacht hun huidige land van verblijf. Verder ontdekten wij dat alle kankersterfte bij Turkse immigranten zich bevond tussen die van hun land van herkomst en het gastland. Hetzelfde was van toepassing op borstkanker bij Turkse vrouwen in vergelijking met in Nederland en Frankrijk geboren vrouwen. Voor longkanker werden contrasterende patronen gevonden bij Turken, die in Frankrijk en in Nederland wonen. Terwijl de sterfte aan longkanker onder Turkse migranten in Frankrijk samenvalt met die van de in Frankrijk geboren personen, waren

sterftecijfers van Turkse migranten in Nederland zelfs lager dan in Turkije zelf. Deze variaties tussen de gastlanden kunnen worden verklaard door verschillen in duur van verblijf, migratie geschiedenissen, acculturatie mechanismen, selectie-effecten of misclassificatie.

Gegevens uit Nederland hebben eerdere bevindingen uit Duitsland (**hoofdstuk 4**) bevestigd en toonden een significant lagere incidentie van borstkanker onder allochtone vrouwen in vergelijking met autochtone Nederlandse vrouwen (**hoofdstuk 6**). De belangrijkste redenen voor de lagere risico's op borstkanker onder allochtone vrouwen zijn jongere leeftijd bij de eerste geboorte, meer kinderen en het veelvuldiger en langer geven van borstvoeding. Naast borstkanker, werd de incidentie van maagkanker bij migranten in Nederland onderzocht in **hoofdstuk 6**. Hier vonden we een verhoogd risico op non-cardia carcinomen in de maag bij migranten (vooral bij Turken), hetgeen vaak te wijten is aan een infectie met Helicobacter pylori (H. pylori) en een hoge consumptie van sterk gezouten voedsel. Het hogere risico van non-cardia maagkanker bij migranten weerspiegelt een hogere prevalentie van infectie in de regio's waar de migranten vandaan komen, bijvoorbeeld Oost-Turkije.

Een hogere incidentie van maagkanker heeft ook invloed op maagkanker sterfte. Deze bleek sterk verhoogd in Turkse migranten die in Frankrijk en in Nederland wonen (**hoofdstuk 5**).
In een volgende studie werden risico's op baarmoederhals-, slokdarm- en darmkanker onderzocht onder migranten uit vijf verschillende landen woonachtig in Nederland (**hoofdstuk 7**). Vrouwelijke migranten hadden een verhoogd risico op baarmoederhalskanker, in het bijzonder allochtone vrouwen uit Suriname (1,8-voudig risico) in vergelijking met autochtone Nederlandse vrouwen. Verhoogde risico's waren meer uitgesproken voor plaveiselcelcarcinomen, die vaak worden veroorzaakt door een infectie met het Humaan Papillomavirus (HPV). In dezelfde studie werden ook lagere risico's gevonden voor zowel darm- en slokdarmkanker in alle migrantengroepen, als gevolg van lagere risico's in hun land van herkomst en een gunstiger levensstijl, door bijvoorbeeld minder roken en minder drinken van alcohol.
Hoe migratie de kankercijfers van een land kan beïnvloeden, wordt duidelijk wanneer we naar trends van het nasofarynxcarcinoom (NPC) in Nederland kijken (**hoofdstuk 8**). Deze tumor is relatief zeldzaam in westerse landen en komt tegenwoordig het meest voor in China en Noord-Afrika. De sterfte aan deze vorm van kanker daalt sinds decennia, ook in Nederland. Afhankelijk dan de histologie van de tumor, hebben wij echter diverse incidentietrends waargenomen. Terwijl de incidentie van het, aan roken gerelateerde, keratiniserende type sinds 1989 is gedaald, is de incidentie van niet-keratiniserende tumoren toegenomen. Er blijkt een nauwe relatie tussen de infectie met het Epstein-Barr Virus (EBV) en de ontwikkeling van niet-keratiniserende tumoren in de nasofarynx te bestaan. Waarschijnlijk draagt de toenemende migratie vanuit hoog-incidentie landen bij aan de stijgende incidentie van dit type kanker in Nederland. Deze bevinding vraagt speciale aandacht en bewustwording onder specialisten in de gezondheidszorg.

Kankeroverleving
De meeste vrouwelijke migranten hebben niet alleen een aanzienlijk lager risico op borstkanker (in het bijzonder na de menopauze), ze vertonen ook dezelfde of een iets betere

overleving in vergelijking met autochtone Nederlandse vrouwen (**hoofdstukken 3 en 6**). In tegenstelling tot andere studies over borstkankeroverleving bij allochtonen, vonden wij een iets lagere overleving voor premenopauzale allochtone vrouwen maar een hogere overleving voor postmenopauzale vrouwen ten opzichte van autochtone Nederlandse vrouwen. Het feit dat de last van borstkanker bij vrouwelijke migranten naar verwachting zal toenemen, vraagt om meer regelmatige surveillance en herbeoordeling door middel van follow-up studies in de toekomst, mogelijk ook rekening houdend met potentieel beschikbare gegevens over leeftijd bij menarche en bij eerste geboorte.
Onder maagkanker patiënten was de sterfte bij migranten gemiddeld 30% lager dan onder autochtone Nederlanders (**hoofdstuk 6**). Verschillen in tumor histologie en erfelijke aanleg zouden dit resultaat kunnen beïnvloeden, net zoals methodologische aspecten, bijvoorbeeld door selectieve remigratie. Overleving van baarmoederhals- en darmkanker was iets beter bij alle migranten, met uitzondering van Indonesiërs. De overleving van patiënten met slokdarmkanker was iets slechter bij allochtonen dan bij autochtone Nederlanders (**hoofdstuk 7**).

Public Health aspecten
Migratie van laag naar hoog inkomen werd vertaald als 'tijdreizen' in termen van een versnelde overgang met betrekking tot gezondheid. In onze studie (**hoofdstuk 9**) hebben we betoogd dat terwijl de behandeling, toegang tot zorg en sanitaire omstandigheden vrijwel onmiddellijk na de migratie verbeteren, de gezondheidseffecten van de "westerse" risicofactoren -zoals ongezonde voeding en roken- pas op lange termijn zichtbaar zullen worden bij immigranten uit lage-inkomenslanden. Interessant is dat dit kan leiden tot (tijdelijke) voordelen in morbiditeit en mortaliteit bij immigranten uit lage-inkomenslanden in vergelijking met de autochtone bevolking van hoge-inkomenslanden. We ontdekten dat immigranten uit lage-inkomenslanden vaak niet in dezelfde mate kunnen profiteren van de algemene daling van sterfte aan niet-overdraagbare aandoeningen in hoge-inkomenslanden. Dit komt doordat deze immigranten een hoog risico hebben op een dubbele ziektelast, als gevolg van een onafgeronde gezondheidstransitie. Tijdelijke vooruitgang in de gezondheidszorg kan worden veroorzaakt door zowel selectie-effecten als een lange aanlooptijd tussen een verhoogde blootstelling aan nieuwe risicofactoren en het ontstaan van de ziekte. Daarom zullen niet-overdraagbare aandoeningen naar verwachting steeds vaker ziekten en doodsoorzaken worden onder immigranten woonachtig in hoge-inkomenslanden. Waarschijnlijk zullen de relatief kleinere dalingen van sterfte aan niet-overdraagbare aandoeningen, die onder immigranten werden waargenomen, bestaande ongelijkheden in gezondheid verhogen.

Methodologische aspecten
Studies naar kanker onder migranten zijn vaak onderworpen aan een aantal methodologische beperkingen met betrekking tot de beschikbaarheid, kwaliteit en consistentie van de gegevens, evenals door migratiespecifieke vertekeningen. Dit belemmert vooral vergelijkingen tussen landen (**hoofdstuk 5**). Een uniforme definitie van 'migranten' binnen Europa zou vergelijkingen tussen landen en databases vergemakkelijken. Veel landen registreren variabelen met betrekking tot migratie nog niet routinematig en het is waarschijnlijk nog een lange weg te gaan om dit (**hoofdstuk 2**) te bereiken. In Nederland is het geboorteland de meest gebruikte indicator voor etniciteit, ondanks aanzienlijke nadelen ten opzichte van etnische variatie binnen een geboorteland en de

identificatie van de derde generatie migranten. Deze beperking is bijvoorbeeld duidelijk geworden bij migranten afkomstig uit Indonesië, een voormalige Nederlandse kolonie. Veel mensen die zijn geboren in Indonesië en zo'n 60 jaar geleden gemigreerd zijn naar Nederland, hebben Nederlandse voorouders of zijn autochtone Nederlanders. Dit feit verklaart niet alleen vergelijkbare resultaten voor Nederlanders en Indonesiërs in het risico op kanker, maar onderstreept ook de valkuilen die zijn verbonden aan het gebruik van geboorteland als proxy voor etniciteit (**hoofdstukken 2, 6 en 7**). In Duitsland, tot nu toe, kunnen alleen naamgebaseerde benaderingen worden gebruikt om Turkse migranten (**hoofdstukken 2 en 4**) te identificeren. Dit is deels te wijten aan het feit dat er geen nationale kankerregistratie bestaat en er geen routinematige registratie van migratiegevoelige indicatoren plaats vindt.
Het Verenigd Koninkrijk en de Scandinavische landen zijn pioniers als het gaat om etnisch uitgesplitste morbiditeit surveillancegegevens in Europa (**hoofdstuk 2**). Internationaal gezien kan een koppeling van gegevens het tekort aan informatie over gezondheidsgegevens naar etniciteit opvullen, gezien het feit dat er gestandaardiseerde informatie over etniciteit beschikbaar is in verschillende andere databases. Het gebruik van koppelingen is het meest effectief en nauwkeurig wanneer deze koppelingen gebaseerd zijn op een uniek persoonlijk identificatienummer. Het Burgerservicenummer (BSN) is een dergelijk nummer dat echter (nog) niet is goedgekeurd voor onderzoek. Op voorwaarde dat misbruik kan worden uitgesloten, kan het BSN een uiterst waardevol instrument zijn voor studies bij migranten. De uitgebreide informatie over migratie, die in het bevolkingsregister beschikbaar is, zou door middel van koppeling in veel verschillende settings bestudeerd kunnen worden, met inbegrip van studies over kanker.

De samenhang tussen sociaal-economische determinanten en gezondheid is bekend. Etnische verschillen in gezondheid zijn gedeeltelijk toe te schrijven aan sociaal-economische omstandigheden, waardoor ze nauw met elkaar verbonden zijn maar niet zozeer gelijkwaardige concepten vertegenwoordigen. Beiden zijn onafhankelijk van elkaar gerelateerd aan de incidentie, overleving en sterfte van kanker.
In Nederland wordt een ecologische proxy gebruikt om sociaal-economische status (SES) te kunnen meten. Deze weerspiegelt het gemiddelde inkomen per huishouden, het percentage huishoudens met een laag inkomen en het percentage huishoudens met een lage opleiding op basis van een viercijferige postcode op het moment van de diagnose. Allochtonen en mensen met een lage SES delen bepaalde risico's op kanker. Dit zijn vooral lagere risico's voor colon-, huid-, borst- en prostaatkanker, alsmede een hoger risico voor kanker van het hoofd-halsgebied, baarmoederhals en Hodgkin lymfoom. Hoewel personen met een lage SES hogere risico's vertonen op andere voornamelijk levensstijl-gerelateerde kankers, zoals van in de bovenste gastrointestinale tractus en de long, geldt het tegenovergestelde voor niet-westerse allochtonen. In tegenstelling tot de lage SES-groepen, vertonen niet-westerse migranten een hogere last met betrekking tot infectie-gerelateerde tumoren (zoals nasofarynx-, lever- en non-cardia carcinomen van de maag). Het is belangrijk om op te merken dat zowel allochtonen als personen met een lage SES zeer heterogene groepen vertegenwoordigen met verschillende prioriteiten op het vlak van kanker risico en preventie.

Conclusie en vooruitzichten

Vele vormen van kanker zijn in zekere mate te voorkomen. De bijdrage van omgevings- en gedragsdeterminanten bij de ontwikkeling van verschillende vormen van kanker wordt groter geschat dan eerder gedacht. Studies onder migranten hebben aanzienlijk bijgedragen aan deze kennis. Persoonlijke levensstijl keuzes werden derhalve geïdentificeerd als de belangrijkste oorzaak voor het ontstaan van kanker en de belangrijkste sleutel tot de preventie van kanker. Hoewel de sterfte aan kanker gedurende de afgelopen twee tot drie decennia in bijna alle westerse landen is gedaald , stijgt de ruwe incidentie van kanker nog steeds. Dit is grotendeels te wijten aan de vergrijzing maar kan mogelijk ook worden toegeschreven aan de nog niet optimale uitvoering van (effectieve) preventieprogramma's en aanhoudende hiaten in de kennis over kanker etiologie. Studies onder migranten hebben het potentieel om de kennis met betrekking tot de oorzaken van kanker te verfijnen en ook deze kennis in gerichte preventiestrategieën te vertalen. Daarnaast vereist een groeiend aantal oudere allochtonen in de West-Europese samenleving een heroverweging van de huidige praktijk in de richting van een meer op migranten toegespitste en migrantengevoelige gezondheidszorg.

De meeste vormen van kanker komen bij migranten minder vaak voor en hun overlevingskansen zijn gelijk of beter dan die van de algehele populatie. Sommige tumoren komen in deze groep echter vaker voor, in het bijzonder kankers met een infectieuze oorsprong. Deze verdienen speciale aandacht bij professionele zorgverleners, om diagnosen in een laat stadium te voorkomen. In de praktijk moet zo lang mogelijk voortgebouwd worden op gunstige risico's bij allochtonen terwijl ongunstige risico's moeten worden verminderd door middel van adequate en op de doelgroep gerichte preventie. Omdat het moeilijk is om levensstijl-gerelateerd gedrag te veranderen, moet de nadruk liggen op het verhogen van het bewustzijn over kanker, vroege opsporing en gerichte zorg onder immigranten en andere etnische groepen. Verdere inspanningen om het toegenomen aantal gevallen van overgewicht en roken onder allochtone jongeren en andere potentieel kansarme groepen terug te dringen, zijn solide uitgangspunten voor de preventie van kanker. De heterogeniteit van het risico op kanker onder migranten vraagt om subgroep-specifieke aanbevelingen en richtlijnen voor de zorg. Het verhogen van culturele en etnische gevoeligheid, in plaats van gelijkheid, moet het hoofddoel in de zorg en de preventie zijn. Er zijn nog steeds veel inspanningen nodig om dit onderwerp meer te laten meewegen in het onderzoek en de zorg in Nederland. Dit geldt vooral voor de verbetering van de migratiegevoelige kankerregistratie en kwalitatief onderzoek naar sociaal-culturele aspecten die het gebruik van zorg, de kwaliteit van zorg en de kwaliteit van leven beïnvloeden. Ook zou specifieke informatie over allochtone kankerpatiënten moeten worden opgenomen in de opleiding van professionals in de gezondheidszorg.

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My first *thank you* goes to my two promoters, prof. dr. Jan Willem Coebergh and prof. dr. Oliver Razum. They equipped me with just the right portion of criticism, self-esteem and passion that it took in order to write this thesis and to keep me going. Their critical comments helped me a lot in finding my way and I am more than thankful for that.

Jan Willem, you gave me the chance to finish my PhD in your working group in Rotterdam. Thank you for believing in me and for being such a great and extraordinary promoter. I've never talked about German history as much as I did with you since leaving high school. Thank you for all those great talks. From you I've also learned that chocolate can solve many (but not all) conflicts in life and discovered that its impact on the writing of a thesis can be substantial - probably even statistically significant but (luckily) not clinically relevant in my case.

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My time at Bielefeld University also had a big influence on the writing and the contents of this thesis. Without the AG3-warmth (in Dutch I would definitely say *gezelligheid*, an expression for which there is no simple translation), an essential part of it would not be here today. Jacob, my very first tutor and companion ever since. Your humor and easiness, but above all your skills and expertise have certainly contributed to this book. Eva and Kati, we went this (sometimes stony) way together from the very start of our studies and I am so grateful for having you around. Not only as colleagues, but most of all as

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Thanks also to my roommates. Kevin, for all the funny jokes and talks that we shared. And Suzette, for lighting up so many days, for all the lunches and discussions. Thanks to the other girls, especially to Fenna, Liz, Inge and Astrid. You are great! Maggie, thank you for the high-teas, talks and for sharing all sorts of sorrows in the life of a German expat with me, amongst which the greatly feared *M-formulier* (which actually stands for *migration* and made me aware of the fact that I am a migrant myself).

A special thanks goes to my two paranymphs who are standing beside me today. Jolien, it always astonishes me when I think about what we went through together in the past four years. Thank you so much for your support, our countless talks and for your friendship. And Inge, thank you for your friendship, your support and for being such a good listener. It's an honor to have the two of you at my side on this special day!

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Melina

Curriculum Vitae

Melina Arnold was born on June 28, 1987 in Vorwerk, Germany. In 2005, she completed her secondary education (Abitur) at the Zinzendorfschule in Tossens (Germany) and started studying *Health Communication* at Bielefeld University. During that time, she completed two academic internships, one at the 'Self-help Resource Centre of Greater Toronto' in Canada and one at the Federal Statistical Office of Germany in Bonn, before she obtained her Bachelor's degree in 2008.

In the same year, she moved to the Netherlands to study *Clinical Epidemiology* at the Netherlands School of Health Sciences (NIHES). Her research project focused on cancer patterns in migrants in the Netherlands and was conducted in the Cancer Surveillance section, headed by Prof. dr. Jan Willem Coebergh at the Department of Public Health. Meanwhile, she continued working as a part-time research assistant at Bielefeld University where she was involved in the EU-funded MEHO (Migrant and Ethnic Health Observatory) project, resulting in a book publication (*Migration-sensitive Cancer Registration in Europe*) that Melina co-edited in 2011.

After receiving her Master's degree in 2010, she returned to Bielefeld to work as a full-time researcher at the Department of Epidemiology and International Public Health, headed by Prof. dr. Oliver Razum. At Bielefeld University, Melina was responsible for several projects, amongst others a Health Technology Assessment (HTA) of positron-emission-tomography (PET) in the detection and prognosis of breast cancer. She was also the main coordinator of the 'European Master of Public Health' program of the faculty and taught courses on epidemiology and biostatistics on the Master's level.

In October 2011, Melina joined the Department of Public Health of the Erasmus University Medical Center in Rotterdam as a researcher and continued her work on ethnic heterogeneity in cancer with a focus on studies among migrants in the Netherlands, resulting in this thesis.

List of publications

Publications in this thesis

1. Arnold M, Razum O, Coebergh JW (2010). Cancer risk diversity in non-Western migrants to Europe: An overview of the literature. Eur J Cancer. 2010 (46). 2647-2659.
2. Spallek J, Arnold M, Hentschel S, Razum O (2009). Cancer incidence rate ratios of Turkish immigrants in Hamburg, Germany: A registry based study. Cancer Epidemiol. 2009 (33). 413-418.
3. Spallek J*, Arnold M*, Razum O, Juel K, Rey G, Deboosere P, Mackenbach JP, Kunst AE. Cancer mortality patterns among Turkish immigrants in four European countries and in Turkey. European Journal of Epidemiology. In press. (*shared first authorship)
4. Arnold M, Aarts MJ, Van der Aa M, Visser O, Coebergh JW. Investigating cervical, oesophageal and colon cancer risk and survival among migrants in the Netherlands. European Journal of Public Health. In press.
5. Arnold M, Aarts MJ, Siesling S, Van der Aa M, Visser O, Coebergh JW. Diverging breast and stomach cancer incidence and survival in migrants in the Netherlands, 1996-2006. Acta Oncologica. In press.
6. Arnold M, Wildeman MA, Visser O, Karim-Kos HE, Middeldorp JM, Fles R, Bing Tan I, Coebergh JW. Lower mortality from nasopharyngeal cancer in the Netherlands since 1970 with differential incidence trends in histopathology. Oral Oncol. 2012 Oct 19. [Epub ahead of print]
7. Arnold M, Razum O. Migration conceptualized as high-speed Health Transition: do new Data support this Hypothesis? *Submitted*.

Book publication

1. Razum O, Spallek J, Reeske A, Arnold M (eds). Migration-sensitive Cancer Registration in Europe. Challenges and Potentials. Frankfurt: Peter Lang Verlag. 2011.

Other publications

1. De Vries E, Arnold M, Altsitsiadis E, Trakatelli M, Hinrichs B, Stockfleth E, Coebergh JW (2012). Potential impact of interventions resulting in reduced exposure to ultraviolet (UV) radiation (UVA and UVB) on skin cancer incidence in four European countries, 2010–2050. BJD. 2012 167 (Suppl. 2), 53–62.
2. Arnold M, Moore S, Bray F. The unequal burden of stomach cancer in indigenous populations: a global synthesis. Manuscript in preparation.
3. Arnold M, Liu L, Soerjomataram I, Coebergh JW. What influences the risk of second primary tumours after cervical cancer. Manuscript in preparation.
4. Arnold M. “Cancer Mortality”. Encyclopedia of Immigrant Health (Springer, New York 2012)
5. Arnold M, Razum O. “Cancer Prevention”. Encyclopedia of Immigrant Health (Springer, New York 2012)

PhD Portfolio

Name PhD student:	Melina Arnold
Erasmus MC Department:	Public Health (Cancer Surveillance Section)
PhD period:	September 2010 – January 2013
First promoter:	Prof. dr. Jan Willem Coebergh
Second promoter:	Prof. dr. Oliver Razum

	Year	Workload hrs (ECTS)
Courses		
'Quality of Life Measurement', Netherlands Institute for Health Sciences	2012	24 hrs (0.9 ECTS)
'Statistical Methods for Population-based Cancer Survival Analysis', Summer School on Modern Methods in Biostatistics and Epidemiology, Veneto, Italy	2012	40 hrs (1.4 ECTS)
Seminars and Workshops		
Symposium 'Geneesmiddelen en Kanker', Rotterdam	2011	4 hrs (0.1 ECTS)
Life course epidemiology, Bielefeld University	2011	8 hrs (0.3 ECTS)
DG EPI Nachwuchstreffen, Charité Berlin	2011	16 hrs (0.6 ECTS)
MEHO Meeting, AMC Amsterdam	2009	16 hrs (0.6 ECTS)
Teaching		
Lecture during the MSc course 'Public Health in low and middle income countries: Causes and consequences', Erasmus University Rotterdam, The Netherlands	2012	8 hrs (0.3 ECTS)
Full lectureship for the MSc course "Methods of Epidemiology and Statistics", Bielefeld University, Germany	2011	100 hrs (3.6 ECTS)
Full lectureship for the MSc course "Epidemiology and Biostatistics", Bielefeld University, Germany	2010 2011	100 hrs (3.6 ECTS)
Presentations		
1 Poster presentation AACR Conference	2012	32 hrs (1.1 ECTS)
1 Oral presentation ENCR Meeting	2012	32 hrs (1.1 ECTS)
1 Poster presentation WEON	2011	32 hrs (1.1 ECTS)
1 Oral presentation WEON	2011	32 hrs (1.1 ECTS)
2 Oral presentations Department of Public Health, Bielefeld University	2011	64 hrs (2.3 ECTS)
1 Oral presentation EUPHA	2010	32 hrs (1.1 ECTS)
1 Oral presentation EUPHA	2009	32 hrs (1.1 ECTS)
Conferences		
AACR Cancer Disparities Conference, San Diego, USA	2012	32 hrs (1.1 ECTS)
ENCR Meeting, Cork, Ireland	2012	8 hrs (0.3 ECTS)
WEON 2012, Rotterdam, The Netherlands	2012	16 hrs (0.6 ECTS)
WEON 2011, Ijmuiden, The Netherlands	2011	16 hrs (0.6 ECTS)
DG EPI 2010, Münster, Germany	2010	24 hrs (0.9 ECTS)
EUPHA 2010, Amsterdam, The Netherlands	2010	24 hrs (0.9 ECTS)
EUPHA 2009, Lodz, Poland	2009	24 hrs (0.9 ECTS)
Other		
Project on second malignancies, Erasmus MC (2011-2012)		80 hrs (3.0 ECTS)
Project on skin cancer trends and prevention potential, Erasmus MC (2011)		80 hrs (3.0 ECTS)
Coordination of European Master of Public Health Program, Bielefeld University (2010-2011)		80 hrs (3.0 ECTS)
HTA PET and breast cancer, Bielefeld University (2010-2011)		240 hrs (8.6 ECTS)
MEHO Project, Bielefeld University (2009-2011)		240 hrs (8.6 ECTS)
Total		**1436 hrs (51.8 ECTS)**