Cancer in immigrants as a pointer to the causes of cancer

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The early cancer studies on immigrants, which started to appear some 50 years ago, showed that the incidence in cancers changes to the level of the new host country in one or two generations. These findings were fundamental to the understanding of the environmental etiology of human cancer. Many immigrant groups originate from countries with no cancer registration, and, hence, the immigrant studies may provide estimates on the indigenous cancer rates. The Swedish Family-Cancer Database has been an important source of data for immigrant studies on various diseases. The Database covers the Swedish population of the past 100 years, and it records the country of birth for each subject. A total of 1.79 million individuals were foreign born, Finns and other Scandinavians being the largest immigrant groups. Over the course of years, some 30 publications have appeared relating to cancer in immigrants. In the present article, we will review more recent immigrant studies, mainly among Swedish immigrants, on all cancers and emphasize the differences between ethnic groups. In the second part, we discuss the problem of reliable registration of cancer and compare cancer incidence among non-European immigrants with cancer incidence in countries of origin, as these now have active cancer registries. We discuss the experiences in cancer registration in Morocco and Egypt. We show the usefulness and limitations in predicting cancer incidence in the countries of origin.

Introduction

The global cancer incidence varies extensively. According to the Cancer Incidence in Five Continents (CI5), the highest overall male incidence rates, ~500/100 000, are recorded among several US black populations.1 The highest female incidence rates, 370/100 000 are recorded for Swiss women in Geneva. The Swedish rates are ~250/100 000 for men and women. The lowest overall male and female incidence rates are <100/100 000 in some African and Indian populations. However, the differences between incidence rates at individual sites are usually much larger than those between overall rates because the developing countries, with low incidence rates for most cancers, show high risks for certain cancers, such as liver, esophageal, stomach and cervical cancers.1,2 The causes for these high-risk cancers are ascribed to microbial infections, nutritional imbalances and toxins, while the reasons for most high-risk cancers in the developed countries remain unknown beyond ‘western lifestyle’ and ‘affluence’.2,3 The vast increases in prostate and breast cancers and in melanoma and non-Hodgkin lymphoma over the past half century have remained largely unexplained. The reason for the high cancer incidence in the developed countries is the main challenge to the etiological cancer research.

‘Classical’ cancer studies on immigrants to USA and Australia showed that the incidence in common cancers changes to the level of the new host country in one or two generations.4 These findings were fundamental to the understanding of the environmental etiology of human cancer.2 Many immigrant groups originate from countries with no cancer registration, and, hence, the immigrant studies may provide estimates on the indigenous cancer rates. For example, the early Swedish studies showed high stomach cancer rates in Rumanians, among the world’s highest testicular cancer rates in Chileans, high non-Hodgkin’s lymphoma rates in Greeks and high thyroid cancer rates in former Yugoslav and Turkish women, which may signal truly elevated cancer risks in these countries lacking reliable cancer registration.5 In the present article, we will review more recent immigrant studies, mainly among Swedish immigrants, on all cancers. As a second part, we compare cancer incidence among non-European immigrants to cancer incidence in countries of origin, as these now have active cancer registries.

Swedish immigrant studies in the European perspective

Europe has witnessed historically extensive population movements. The Second World War and its consequences caused large shifts of population in Central Europe. After the War, demand of labour force and immigration from colonial countries gaining independence were the driving forces of immigration to Europe, counteracted by emigration to America and Australia. The spectrum of immigrants has been different in the European countries. France received large populations from North Africa, Algerians being the largest group. Germany received a large Turkish immigration, and Turks and other Eastern Mediterranean nationalities were the main non-European immigrants to Sweden. Moroccans immigrated to many countries on the other side of the Mediterranean Sea. Moroccans are also a large group in the Netherlands, together with Turks, Surinames, Indonesians and others from previous colonies. In UK, the dominant immigrant groups are Southern Asians and blacks from East Africa and the Caribbean. Spain has gained many immigrants from South America. This diversity is a great opportunity and a great challenge.

Donald Max Parkin, then at the International Agency of Cancer in Lyon, responded to these challenges, and he was in charge of a large number of immigrant studies both in Europe and outside. These were mainly published in the 1990s and summarized by him.6 In 2010, Arnold and co-workers reviewed 37 European cancer studies from years 1990 and 2010, and they published some of their own
studies on specific cancers. Most of these studies were based on first-generation immigrants because the tracking was based on the country of origin.

Many immigrants have arrived as young couples to Sweden, whereby their Sweden-born children have a completely indigenous genotype. The earlier studies from Sweden, published in 2002 and 2003, showed that second-generation immigrants, those born in Sweden, already have largely adopted the Swedish cancer incidence. Such data led us to conclude that the childhood environment, rather than genotype, is important in setting the individual’s cancer destiny. However, these results hold to the immigrants that have arrived from European countries during 1940–70; these immigrants, who typically integrated quickly to the Swedish society, came from countries with not drastically different indigenous cancer incidence rates compared with Sweden. Furthermore, immigrant studies have also shown that biological reasons may be related to behaviours or access to knowledge and resources that have direct and indirect impacts on cancer survival.

For example, a significant difference on breast cancer age at diagnosis compared with matched Swedish controls was observed for women from Turkey (mean 5.5 years earlier than Swedes), Asian Arab and some African countries (5.1 years earlier than Swedes), Iran (4.3 years earlier than Swedes) and Iraq (4.0 years earlier than Swedes). These results may have implications to the organization of breast cancer screening programme in developing countries. The cancer experience of the large groups of Balkan and non-European immigrants was studied and reported in subsequent papers described below. In all, Sweden, in spite of the small population, is an excellent country to study cancer experience of the immigrants because of a uniform cancer registration and health-care system, and the large number of immigrants from practically around the world: in the Swedish Family-Cancer Database with 11.5 million individuals, 1.79 million (15%) are foreign born.

Limited numbers of survival studies have been done on immigrant populations, and, in general, these are more difficult to interpret than incidence studies. Despite the fact that Sweden has a system of universal health-care coverage, which in theory delivers a standardized quality of health care to all users, the data show that a socio-economic gradient exists in survival of many cancer. The reasons may be related to behaviours or access to knowledge and resources that have direct and indirect impacts on cancer survival. Understanding the underlying factors would help to boost survival probably not only for the poorest survivors but for all. The analysis of survival in immigrants would increase the understanding of the underlying factors. For example, what is the survival rate among the immigrant population whose prostate or melanoma risk is only 10–20% of the Swedish risk or, conversely, among those whose stomach cancer or lymphoma risks greatly exceeds the native Swedish levels.

Swedish data on all immigrants

In 2009, we launched a project to revisit immigrant cancers in Sweden based on the cancer data from the Swedish Cancer Registry up to year 2006 and after two updates up to 2010. The main difference to the studies from a decade earlier was that many of the non-European immigrant populations were reaching the age when cancers may occur, and thus the statistical power was boosted particularly for these populations. More than 20 papers were published mainly on the incidence differences compared with the native Swedes, reported as standardized incidence ratios (SIRs; standardized for age, period and region) and considering the SIR for Swedes as 1.0. We highlight some of the findings below and refer to the original studies for details.

In the analysis, immigrant groups were designated by the country of origin if the population was large enough for statistical analysis, as explained in the original papers. Else, the countries were pooled with their neighbouring countries. For some geographic areas, the Swedish registration system was non-specific, e.g. for North Africa, only Morocco is specified.

In Figure 1, we summarize results on male immigrants by showing the SIRs for the immigrants with the highest and lowest SIR; the SIRs are plotted on a logarithmic scale and the column on the right ‘Highest/Lowest’ gives the actual difference. The Swedish rate is shown as an SIR = 1.0. For some cancers, such as thyroid cancer, only the highest immigrant rate is shown; this implies that no immigrant group has a significantly lower SIR than the Swedes. The index ‘Highest/Lowest’ varies from 13.7 (nasopharyngeal cancer, Southeast Asia/former Yugoslavia, but the Swedish rate is even lower) and 11.1 (non-seminoma testicular cancer, Chile/other, which are diverse small immigrant groups) to small differences of 1.1 for oesophageal cancer and 1.4 for non-cardia gastric cancer.

Figure 2 shows similar data for female cancer. The largest difference of 14.9 was found for cervical cancer (Denmark/Iran). Other cancers with a difference of 10-fold or more were lung cancer (Finland/Indian subcontinent), gallbladder cancer (Indian subcontinent/Eastern Europe) and liver cancer (other Africa, i.e. other than North Africa/Baltic countries).

Survival in cancer depends on many factors, including the level of health care and awareness of disease risks, but it is unclear whether differences in incidence rates may be related to survival. It is unlikely that subtle differences in cancer biology could be revealed in international comparisons. Instead, comparison of diverse immigrant groups in a country of uniformly accessible health-care system should enable conclusions to be made about ethnic determinants of cancer risk and survival. Thus, we address survival in two of our studies. Hazard ratios of death from female breast cancer were compared between immigrants and Swedes, but no evidence for ethnic differences in survival was found, except for lobular carcinoma, which may be related to treatment. However, we found a tendency of low-risk immigrants to present with higher T-class (in the Tumour, Node, Metastasis classification, T is related to tumour size), which may depend on their lower participation in the mammography screening programme. For prostate cancer, the results showed that the non-European immigrants, of mainly Middle East, Asian and Chilean origin, with the lowest risk of prostate cancer, also had the best survival in this cancer. It was suggested that the explanation could be a biological mechanism through a favourable androgenic hormonal host environment.

Cancer risk in immigrants compared with natives

The newest version of the CI5 of IARC (CI5-X, printed version to be published in year 2014) covers 290 population-based cancer registries from 68 of 196 countries in the world. The coverage is best in the developed countries and worst in the developing countries. However, another window into the cancer incidence variation may be through immigrants who have entered a new country in adult age. Their cancer incidence tends to deviate from that in the host country, usually towards the rates in their country of origin, given that data are available from CI5 or from extrapolated data assembled in the GLOBOCAN database. Many immigrant groups in countries like Sweden originate from regions with no cancer registration, and, hence, their cancer rates in the host country may provide estimates on the indigenous cancer rates. This would be most accurate for immigrants who have not stayed extended periods of time in the country because the differences to the natives may decrease with the length of time. As an example of a successful estimation, pointed out above, we reported in 2002 that Chilean immigrants in Sweden had testicular cancer rates matching Danish immigrants and Danish indigenous rates, known to be among the highest in the world. Chile had no cancer registration, but when the first regional rates were published in CI5-X for years
Figure 1 Summary of the highest and the lowest significant SIRs among immigrant men to Sweden. The highest to lowest ratio is shown in the right column. When only one bar is shown, the Swedish SIR is the lowest or the highest. Note the logarithmic x-axis.
Figure 2 Summary of the highest and the lowest significant SIRs among immigrant women to Sweden. The highest to lowest ratio is shown in the right column. When only one bar is shown, the Swedish SIR is the lowest or the highest. Note the logarithmic x-axis.
The NA immigrants (ASR = 190.9) had higher rates than Chilean immigrants (183.8) had decreased rates compared with Valdivia men rates compared with the residents in Izmir (286.0). Chilean measure of cancer incidence.

Morocco. We use age-standardized incidence rate (ASR) as the 05, CI5-X) and Casablanca (Casablanca registry report for 2004) for regional cancer registries of Algeria, Egypt and Tunisia (years 2003–

In the Swedish registration system, North Africans are assigned no expected large differences in incidence compared with Swedes. A decrease in the stomach cancer rate was seen among Moroccans (17.6) compared with the residents in Valdivia (35.2). The NA immigrants (13.5) had an increased rate of colon cancer compared with any NA residents (3.8–6.3). Lung cancer rate among Turks in Sweden (35.2) was lower compared with the residents in Izmir (90.1). All immigrants, except for Turks and Chileans, had an increased prostate cancer rate (ASR ranging from 37.4 to 69.9) compared with the residents in countries of origin.

Table 2 shows ASRs for all cancer and breast cancer among Table 2 ASRs (per 100 000) for selected cancers among Turkish, Chilean and NA immigrant women compared with the residents in countries of origin and the native Swedes

Table 1 Incidence (per 100 000) for selected cancers among Turkish, Chilean and NA immigrant men compared with the residents in countries of origin and the native Swedes

Table 1

<table>
<thead>
<tr>
<th>Birth region</th>
<th>All</th>
<th>Stomach</th>
<th>Colon</th>
<th>Lung</th>
<th>Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ASR (95% CI)</td>
<td>N</td>
<td>ASR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Sweden</td>
<td>121,290</td>
<td>287.4</td>
<td>2909</td>
<td>6.9</td>
<td>8,594</td>
</tr>
<tr>
<td>Turkish immigrants</td>
<td>552</td>
<td>190.0 (172.7–207.3)</td>
<td>31</td>
<td>9.7 (5.8–13.6)</td>
<td>30</td>
</tr>
<tr>
<td>Turkey, Izmir residents</td>
<td>26,461</td>
<td>286.0</td>
<td>1282</td>
<td>13.6</td>
<td>1,161</td>
</tr>
<tr>
<td>Chilean immigrants</td>
<td>353</td>
<td>183.8 (158.2–209.4)</td>
<td>33</td>
<td>17.6 (10.4–24.8)</td>
<td>16</td>
</tr>
<tr>
<td>Chile, Valdivia residents</td>
<td>2,356</td>
<td>229.8</td>
<td>365</td>
<td>35.2</td>
<td>90</td>
</tr>
<tr>
<td>NA immigrants</td>
<td>252</td>
<td>190.9 (154.8–227.0)</td>
<td>11</td>
<td>8.4 (2.9–13.9)</td>
<td>19</td>
</tr>
<tr>
<td>Moroccan immigrants</td>
<td>81</td>
<td>149.3 (106.1–192.5)</td>
<td>2</td>
<td>5.3 (0.0–12.7)</td>
<td>7</td>
</tr>
<tr>
<td>Other NA immigrants</td>
<td>171</td>
<td>200.0 (158.0–242.0)</td>
<td>9</td>
<td>10.3 (2.5–18.1)</td>
<td>12</td>
</tr>
<tr>
<td>Algeria, Setif residents</td>
<td>2,403</td>
<td>94.4</td>
<td>141</td>
<td>5.7</td>
<td>125</td>
</tr>
<tr>
<td>Egypt, Gharbiah residents</td>
<td>9,661</td>
<td>132.6</td>
<td>216</td>
<td>2.9</td>
<td>290</td>
</tr>
<tr>
<td>Tunisia, north</td>
<td>8,465</td>
<td>122.6</td>
<td>407</td>
<td>5.8</td>
<td>433</td>
</tr>
<tr>
<td>Casablanca</td>
<td>1,503</td>
<td>100.3</td>
<td>62</td>
<td>4.1</td>
<td>56</td>
</tr>
</tbody>
</table>

Notes: Bold type: The 95% confidence interval (CI) of ASR for immigrants does not overlap with the 95% CI of ASR for residents in countries of origin. In NA, only comparisons among Moroccans are considered. Shaded line indicate immigrants to Sweden.

2003–07, the highest global rate of 13.7/100 000 was recorded for Valdivia, Chile. The data in Figure 1 show additionally that the high incidence is true for both seminoma and non-seminoma histologies. The advantage of using incidence rates in the host country is that they are based on a uniform cancer registration system, not distinguishing natives and immigrants. The caveat is that immigrants are always a selected population whose cancer rates may deviate from the virtual mean rates in the country of origin.

Here we compare cancer incidence in non-European immigrants with the rates in the countries of origin and in Sweden. The particular immigrants were selected for the comparison because of a reasonable number of cancer cases in immigrants, availability of population-based incidence data in the country of origin and expected large differences in incidence compared with Swedes. In the Swedish registration system, North Africans are assigned no specific country of origin, except for Moroccans. Thus, we consider regional cancer registries of Algeria, Egypt and Tunisia (years 2003–05, CI5-X) and Casablanca (Casablanca registry report for 2004) for Morocco. We use age-standardized incidence rate (ASR) as the measure of cancer incidence.

The ASRs for all cancer and the selected cancers among men are shown in Table 1. Turkish male immigrants (ASR = 190.0) had decreased all-cancer rates compared with the residents in Izmir (286.0). Chilean immigrants (183.8) had decreased rates compared with Valdivia men (229.8). The NA immigrants (ASR = 190.9) had higher rates than Algerian men (94.4) or other North African men. Overall, all immigrants had lower rates than Swedish men (287.4); however, the overall rate in Izmir equalled the Swedish rate. A decrease in the breast cancer rate was seen among Moroccans (17.6) compared with the residents in Valdivia (35.2). The NA immigrants (13.5) had an increased rate of prostate compared with any NA residents (3.8–6.3). Lung cancer rate among Turks in Sweden (35.2) was lower compared with the residents in Izmir (90.1). All immigrants, except for Turks and Chileans, had an increased prostate cancer rate (ASR ranging from 37.4 to 69.9) compared with the residents in countries of origin.

Table 2 shows ASRs for all cancer and breast cancer among women. Turkish women (130.7) showed a significant difference with the rates of residents in Izmir (163.2). Chilean women (151.2) had decreased rates compared with female Valdivia residents (184.4). NA women (136.7) had increased rates compared with Tunisian (94.0) and Algerian women (95.8). Overall, all immigrants had lower rates than Swedish women (245.8). An increased breast cancer rate was seen among NAs (54.0) compared with NA residents (29.9–45.4).

Experiences in setting up cancer registries in Egypt and Morocco

In Egypt, the first initiative for cancer registry was the establishment of the Cancer Registry for the Metropolitan Cairo Area in early
Cancer patterns in NA

According to the Casablanca Registry, the five most common cancers in women were breast (ASR 35.0/100 000), cervix (15.0), thyroid (6.7), colorectum (5.8) and ovary (5.3). In men, the ranking was lung (25.5), prostate (9.6), bladder (8.7), colorectum (8.1) and non-Hodgkin lymphoma (7.2).37 Cancers at young ages are particularly common in women: 67% of the cases were under 50, which is internationally a high level. In Morocco, only hospital-based registries were available. The first initiative for establishment of a cancer registry was in 1986 in the form of a hospital-based registry in the National Institute of Oncology. Cancer Registry of Greater Casablanca with a population base of 3.7 million is the first population-based registry in Morocco. It was founded in 2003 by a team of medical professors of the University of Casablanca and the Ministry of Health. It has developed into an independent department and is a member of the International Agency of Cancer Registries. Data are actively collected from 17 pathology laboratories (2 public ones and 15 private ones), 11 public hospitals and 10 private hospitals of the region and forms are filled in the registry for all medical records/pathology reports mentioning cancer. Data from death certificates were not used, as in 90% of cases the real cause of death was not mentioned. The Registry receives financial support from Lalla Salma Foundation against Cancer. The first registry report from 2007 covered newly diagnosed cases of cancer in 2004. Another population-based registry in Morocco is the Rabat Cancer Registry (population base 60 000), set-up in 2005 as part of a cooperative project between the Moroccan Ministry of Health and the World Health Organization. Data quality in the Casablanca Registry has been reviewed by international experts and described as adequate. The proportion of cases with histological confirmation (all sites except skin cancers) was 98%, which is internationally a high level. In Morocco, underdiagnosis is relatively frequent among elderly who are reluctant to consult physicians or to pursue with full diagnosis once cancer is suspected.37

1970s, then Alexandria cancer registry in 1980, that was followed by the registry of the National Cancer Institute in Cairo. All these were hospital-based, and the first attempt towards population-based registration was launched in Gharbia with a population base of 30 000 in 1998. The National Cancer Registry Program of Egypt decided to start population-based registration of incident cancer cases and to explore the possibility of establishing a national cancer database through eventual inclusion of hospital-based cancer registries. The registry programme started in 2008 and covered Asswan Governorate (with the largest population base of 1 million) followed by Menia, Beheira and Damietta. Egypt will thus be covered by a network of population-based registries geographically in several locations. The Metropolitan Cairo is not covered by population-based registration due to logistic difficulties. The National Cancer Registry Program is supported by a strong technical unit, which is responsible for the establishment of the Egypt National Cancer Registry Portal for programme sustainability. The Gharbia data are included in CI5-X, as referred to above.
Conclusions

The incidence rates for most cancers are low in developing countries, but for a few cancers the rates are high. These include liver, nasopharyngeal, oesophageal, stomach and cervical cancers. The causes for these cancers are usually known, and they are related to microbial infections, nutritional imbalances and toxins, and the risks of these cancers tend to be high in first-generation immigrants to Sweden; the exception is cervical cancer. Cancer rates are high in native Swedes for most cancers in agreement with most developed countries. The reason for the high risk is referred to as ‘western lifestyle’ and ‘affluence’, but more precisely, the reason is probably excess energy intake. Overweight and obesity are risk factors for many cancers, as discussed elsewhere in this special issue. A pooled analysis of prospective studies on type 2 diabetes has shown a continuous association between fasting glucose levels and cancer mortality; many cancers are increased in diabetics, and such associations provide strong evidence in support of the direct role of hyperglycaemia, i.e. excess energy. An important conclusion from the Swedish immigrant studies in which a large proportion of the present immigrant population had entered Sweden in their early 20s is that the cancer pattern or destiny is set before the age of 20 years. Those who lived in a low-risk country until adulthood remain at low risk and, vice versa, youth in a high-risk country destines a high risk for the rest of one’s life. This is highly relevant for cancer prevention, which should target early years of life. In the same vein, the growing problem of obesity and excess energy intake in the developing countries will predict increasing cancer rates in some segments of the population that had traditionally low rates of cancer.

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Conflicts of interest: None declared.

Key points

- Immigrant studies have shown that incidence of cancer changes when people move to a new environment.
- Time in the new environment influences cancer risk.
- By the age of 20 years, much of the cancer pattern or the related habits have been set.
- Cancer risks in adult immigrants are informative of the incidence in the country of origin.

References