The Incidence and Survival of Acute De Novo Leukaemias in Estonia and in a Well Defined Region of Western Sweden During 1982–1996: A Survey of Patients Aged 16–64 Years


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In the present work the incidence and survival of acute de novo leukaemias in two neighbouring countries, were studied retrospectively over three 5-year periods, 1982–1996. The aim was to compare the above variables, particularly with respect to political/socio-economic and environmental factors, in a well defined area of Sweden, the so-called Western Swedish Health Care Region, with Estonia. Population-wise the Western Swedish Region and Estonia are very similar; area-wise they are also well comparable. The present report covers only patients diagnosed between the ages of 16–64 years. The number of acute de novo leukaemias in the two regions was quite similar (Western Sweden n = 282 and Estonia n = 237). The age standardized incidence rate regarding total acute de novo leukaemias was slightly lower in Estonia than in Western Sweden (1.49/100,000 inhabitants/year for Estonia and 1.76 for Sweden, respectively), the difference being not statistically significant. However, the survival data for the two countries were highly different (P < 0.001). Thus, the relative survival for the total group of patients aged 16–64 years in Estonia at 1 year was 20.7% and at 5 years 3.6%, respectively. The corresponding figures for the Swedish patients were considerably higher, 65.2 and 29.4%, respectively. Further, the 5 year survival significantly (P < 0.05) increased for the Swedish patients over the 3 consecutive 5-year periods. No such improvement was recorded for the Estonian patients.

Keywords: Acute de novo leukaemia; Incidence; Survival; Estonia; Sweden

INTRODUCTION

Estonia was during five decades a part of the Soviet Union with accompanying weak economy in terms of gross national product (GNP) [1], with a low percentage of gross domestic product (GDP) allocated to health expenditure [2] and environmental pollution [2,3]. The country regained its independence in 1991. Thereby, a vivid reconstruction of the society was initiated. Sweden, on the other hand, is a part of the European Community since 1995, and is a member of the Organisation for Economic Co-operation and Development (OECD), i.e., a high-income economy with a well-developed health care system [1].

The present study was initiated to investigate the possible contribution of socio-economic and environmental factors to the development and outcome of malignant haematological disorders during a transitional period in modern European history, i.e., the years of 1982–1996. The aim was to investigate possible differences in the incidence and likely differences in survival of acute de novo leukaemias in two neighbouring European countries, in Estonia and in a well defined area of Sweden, i.e., the Western Swedish Health Care Region. These two areas are very similar as to population and are area-wise well comparable. It is firmly established that the incidence as well as the outcome of treatment and thereby survival in acute leukaemias is highly dependent upon the
age of the patients. We therefore decided to divide the study subjects into two groups: those diagnosed between the ages of 16–64 years, and those diagnosed at the ages ≥ 65 years. The present report deals only with the former group of subjects.

MATERIALS AND METHODS

The present retrospective study comprises all diagnosed patients with de novo acute leukaemias aged 16 – 64 years, registered as living in Western Sweden or Estonia between the years of 1982–1996.

Estonia covers an area of 45,000 km² and during the years of 1982–1996 the average population was 1.5 million inhabitants. The so-called Western Swedish Health Care Region covers an area of 27,000 km² and during the same period its population was 1.6 million inhabitants. For comparison it could be added that the total area of Sweden is 450,000 km² and that its population at the present is close to 9 million inhabitants.

The Structure of Specialized Haematological Care in Estonia

In Estonia all haematological care is, depending upon the patient’s domestic geographic area, referred either to the departments of haematology at Tallinn Central Hospital or at Tartu University Hospital. Tallinn Central Hospital covers a population of 0.9 million inhabitants whereas the remaining 0.6 million inhabitants are referred to Tartu University Hospital. Thereby, primary health care centres and local hospitals take no responsibility for patients with severe haematological disorders, particularly since no specialists in haematology are available at the different county or local hospitals.

The Structure of Specialized Haematological Care in the Western Swedish Health Care Region

The region has two university hospitals both of which do have highly specialized sections of haematology. Additionally, since the middle 1980-ties 6 county hospitals have had access to at least one, frequently two or three, specialists in haematology. Thereby, some non-university hospitals have been able to take care of most of their acute leukemias, whereas other hospitals have referred their patients to university hospitals. Hence, during the study period of 1982–1996 the number of acute leukemia patients referred from local hospitals to university hospitals has steadily decreased.

Definition of Acute De Novo Leukaemia

The morphological diagnoses of acute leukaemia were made on May-Grünewald-Giemsa or Romanovsky stained blood and bone marrow smears obtained and prepared according to local traditions worked out at the different hospitals in the two countries. In Western Sweden immunophenotyping of blast cells came into routine use in 1987; in Estonia immunophenotyping was not in clinical use until 1993.

For the diagnosis of acute leukaemia at least one of the following criteria had to be fulfilled. The bone marrow smear should reveal > 30% blast cells, or > 50% blasts and promyelocytes/promonocytes, or the presence of Auer rods. In the few cases where a report of a bone marrow smear was lacking, > 30% blast cells should be present in the differential count of a peripheral blood smear [4–6].

Since the aim of the present work was to study only the incidence and survival of de novo acute leukaemias in the 2 countries the delineation of the diagnosis was critical. Therefore, patients with a history of pre-existing myelodysplasia, polycythaemia vera, essential thrombocythaemia, idiopathic myelofibrosis, chronic myeloid leukaemia or with a leukaemia secondary to chemo/radiotherapy were excluded from the study.

Identification of Patients with Acute De Novo Leukaemia

Due to differences in the structure of haematological care in the 2 countries the initial approach as to the identification of acute leukaemias differed. Inasmuch as all proven or potential acute leukaemias in Estonia were referred to and could be expected to be found at the departments of haematology either in Tallinn or Tartu we decided first to personally review all medical records in the two departments with the following ICD-8 codes: 204.0, 204.9, 205.0, 205.9, 206.0, 206.9, 207.0, 207.2, 207.3 and 207.9. During the study period the Estonian Cancer Registry had received a total of 587 reports under the above ICD codes; only 374 subjects fulfilled the criteria for the diagnosis of de novo acute leukaemia. However, a total of 18% of the patient records reported to the cancer registry were either missing or were lacking crucial information, and were therefore excluded from the analyses.

Since proven or potential acute leukaemias were spread over several county or local hospitals in Western Sweden, we decided to consult the Swedish Cancer Registry under the same codes as above. In Western Sweden the Cancer Registry identified a total of 1,059 patients with the above mentioned ICD-codes. Thereafter, we personally scrutinized all patient records at the different hospitals. Out of these medical records, a total 117 (11%) had to be excluded from the analyses for the same reason as above (missing or lacking crucial information). A total of 636 patients could be classified as acute de novo leukaemias.

The patients with acute de novo leukaemias were categorized into three different groups: those with unequivocal (i) acute myeloblastic leukaemia (AML), (ii) acute lymphoblastic leukaemia (ALL), and (iii) non-classifiable, undifferentiated or biphenotypic acute leukaemias (AL).
Treatment
Treatment was at the discretion of the haematologists in clinical charge of the patients in the two countries. In Estonia, during 1982–1990 the accessibility to chemotherapeutic agents was limited. When available, older patients frequently had to receive reduced doses of the cytostatic drugs. There was also lack of broad spectrum antibiotics for intravenous administration, and antifungal agents were not available. During 1992–1996 approximately 50% of AML patients received standard combination therapy programs, i.e., anthracycline and ARA-C, and 70% of ALL patients received combination treatment with anthracycline, vincristine, and corticosteroids. In parallel platelet transfusion therapy had become available and the accessibility to broad spectrum antibiotics, antifungal and antiviral agents had improved. In Western Sweden, during the whole study period, all hospitals had adhered to standard therapeutic protocols for AML and ALL. Thus, the vast majority of AML patients received combination therapy with anthracycline and ARA-C; consolidation therapy but no maintenance treatment was given. Patients with ALL received a combination of cyclophosphamide, vincristine, anthracycline, corticosteroids and L-asparaginase; they also received consolidation as well as maintenance therapy. Supportive care including platelet transfusion therapy, broad spectrum antibiotics, antifungal and antiviral treatment was instituted whenever needed.

In Estonia, during the study period only 1 patient received an allogeneic stem cell transplantation. In Western Sweden, a total of 17 study patients received allogeneic stem cell transplants.

Follow-Up
The identified acute de novo leukaemia patients were followed until December 31, 2000, i.e., the majority of patients were followed > 5 years. Only patients diagnosed in 1996 had a shorter follow-up. In the Swedish material no patient was lost during follow-up. In the Estonian material three patients aged 16–64 years were lost during the follow-up period and were therefore excluded in the survival analyses.

Statistical Methods
For comparison of the incidence between different populations and time periods, age standardized rates were used. The World standard population was used as reference population. Exact confidence interval for the incidence rate ratio was calculated according to Rothmann [7].

Relative survival analyses were carried out by using the SURV3 computer package developed at the Finnish Cancer Registry by Hakulinen et al. [8]. Mortality data of the general population in Sweden and Estonia were used to estimate expected survival rates for the study populations. The mortality data contained the probability of death for single year age groups for both sexes in 5-year calendar periods. Testing relative survival rates between patient groups was done by the methods given by Hakulinen et al. [9].

RESULTS
The total number of acute de novo leukaemias encountered in the Estonian population comprising all patients ≥ 16 years of age was 374 (167 males and 207 females), the corresponding figure for the Western Swedish population being 636 (322 males and 314 females). A yearly age standardized incidence rate for acute de novo leukaemias of 1.9/100,000 inhabitants for Estonia and 2.4 for Sweden could thereby be calculated.

The Yearly Acute De Novo Leukaemia Incidence for Patients Aged 16–64 Years
The number of acute de novo leukaemias between the ages of 16–64 years was quite similar in the two regions (Western Sweden n = 282 and Estonia n = 237). The age standardized incidence rates as well as the crude incidence rates for patients in Western Sweden and Estonia are shown in Table I. The ratio of the age standardized incidence rate between the two regions was 0.85, indicating a small difference. However, the 95% confidence interval of the ratio ranged 0.71–1.01. Thus, no significant difference existed in the incidence of acute de novo leukaemias between the 2 regions. It is also seen that the incidence rates for AML and ALL were slightly lower in Estonia than in Western Sweden (Table I). However, as regards AL, i.e., non-classifiable, undifferentiated or biphenotypic acute leukaemias, the incidence rate was significantly (P < 0.001) higher for Estonian compared to Swedish patients (Fisher’s exact test). In both regions the incidence among males was generally higher than among females (Table I). Over the 3 consecutive 5-year periods the age standardized incidence rates remained largely unchanged (Table II).
ALL were similarly inferior to the Swedish results. However, as regards patients with AL the results for survival did not differ.

Over 3 consecutive 5-year periods the relative survival at 5 years after diagnosis increased significantly ($P < 0.05$) in Western Sweden, whereas no change in relative survival was observed in the Estonian patients over the same time period (Fig. 5). The relative survival at 5 years in Western Sweden during 1982–1986 was 20.3% (13.3–29.9%); during 1987–1991 the figure was 27.4% (19.0–37.8%), and during the last period, 1991–1996, the survival was 38.9% (30.0–48.7%). The corresponding figures for Estonia were 4.3% (1.5–11.8%), 1.5% (0.3–7.8%) and 4.9% (1.9–11.9%), respectively.

### TABLE I

Total number, crude and age-adjusted incidence rates (patients per 100,000 inhabitants per year), of acute de novo leukaemias in the population aged 16–64 years during 1982–1996

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<th>Crude</th>
<th>Age-adjusted</th>
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<tr>
<td></td>
<td>W Sweden</td>
<td>Estonia</td>
<td>W Sweden</td>
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<tr>
<td>AML</td>
<td>197</td>
<td>153</td>
<td>1.30</td>
</tr>
<tr>
<td>ALL</td>
<td>69</td>
<td>36</td>
<td>0.45</td>
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<tr>
<td>AL</td>
<td>16</td>
<td>48</td>
<td>0.11</td>
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<tr>
<td>Men</td>
<td>152</td>
<td>127</td>
<td>1.97</td>
</tr>
<tr>
<td>Women</td>
<td>130</td>
<td>110</td>
<td>1.74</td>
</tr>
<tr>
<td>Total population</td>
<td>282</td>
<td>237</td>
<td>1.85</td>
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Age-adjustment to the World standard population was applied.

### TABLE II

Age standardized (to the World standard population) incidence rates (patients per 100,000 inhabitants per year) of acute de novo leukaemias, in the population aged 16–64 years, over 3 consecutive 5-year periods

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<tr>
<td>Western Sweden</td>
<td>1.71</td>
<td>1.61</td>
<td>1.94</td>
</tr>
<tr>
<td>Estonia</td>
<td>1.48</td>
<td>1.39</td>
<td>1.63</td>
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FIGURE 1 Relative survival in patients 16–64 years old with acute de novo leukaemias diagnosed during 1982–1996. The difference between the two populations was statistically significant ($P < 0.001$).

FIGURE 2 Relative survival in patients 16–64 years old with de novo AML diagnosed during 1982–1996. The difference between the two populations was statistically significant ($P < 0.001$).

FIGURE 3 Relative survival in patients 16–64 years old with de novo ALL diagnosed during 1982–1996. The difference between the two populations was statistically significant ($P < 0.01$).
DISCUSSION

The results of the present study do not support the notion that adverse socio-economic and environmental factors, present in Estonia before and during the study period, did cause an increment of the incidence of acute de novo leukaemias. During the mentorship of Soviet Union, adverse socio-economic factors were present in Estonia in the form of low GNP and low health expenditure. In 1991 the GNP per capita in Estonia was USD 3,830 and in Sweden USD 25,110, respectively [1]. In 1989 the total health expenditure equalled 2.6% of GDP in Estonia; in 1990 the corresponding figure for Sweden was 8.8% [2]. Environmental problems during this period in Estonia were ascribed to the oil shale based power industry with high SO2 and CO2 emission, pollution of water supplies and causing waste materials; additionally, there was lack of wastewater treatment facilities and large amounts of hazardous waste was left behind by the Soviet army [2,3]. Although associations between general environmental exposures and acute leukaemia have been difficult to establish, there are some reports to suggest such relationships. In the work of Shore et al. [10], there was an association between ever living within 5 miles (8 km) from an industrial plant and leukaemia risk, for all acute leukaemias combined, for AML as well as ALL. Likewise, in the work of Linos et al. [11] there was an increasing risk for developing ALL and AML among individuals who lived \( \frac{1}{2} \) – 2 miles (0.8 – 3.2 km) from a factory.

In the present study, the total Estonian patient population of de novo leukaemias aged 16 – 64 years showed an age standardized incidence rate of 1.49/100,000/year, which was slightly lower than was encountered for the same time period in Western Sweden (1.76/100,000/year). The difference in the incidence of acute de novo leukaemias between the two regions did not differ statistically. In the present work we made major efforts to exclude possible secondary leukaemias from the two populations. However, particularly in retrospective studies, where immunologic and cytogenetic data may be missing it is almost impossible to ascertain that the diagnosis of de novo leukaemia is correct. In the present study therefore some secondary or post-myelodysplastic leukaemias could have been misdiagnosed as de novo leukaemias.

The incidence rates for acute de novo leukaemias in the present study are as a whole lower than encountered in other reports. Comparisons of incidence rates reported in earlier studies are difficult to interpret due to differences in methods of classifying leukaemias as well as differences in the reporting systems in terms of age and gender. Thus, in the survey of Åström et al. 2001 [12] the total crude yearly incidence rate for acute leukaemia for patients aged 15 – 59 years in a Swedish region was 2.7/100,000; sub-grouped were the figures for AML 2.0/100,000 and for ALL 0.7/100,000, respectively. Similarly, another Swedish study [13] showed a yearly incidence rate for all acute leukaemias of 2.7/100,000 for patients aged 15 – 59 years. A study from middle Norway [14] reported an annual incidence for all acute leukaemias of 4.6/100,000 in the adult population ( > 16 years). A French study of acute leukaemia in the total population [15] showed a crude annual incidence of 3.7/100,000 for females and 4.3/100,000 for males. McKinney et al. [16] found corresponding incidence rates for AML of 3.0/100,000 and 3.8/100,000, respectively, in England and Wales. As regards the three last reports [14 – 16] the age groups studied and sub-grouping of acute leukaemias with particular emphasis on de novo acute leukaemias did not enable comparison with the results of the present study. In the first two studies [12,13] the age groups were comparable with those of the present work but the
diagnoses differed; thus thereby, direct comparisons between incidence rates were not possible to carry out.

There are several explanations to the comparably low rates of incidence for acute de novo leukaemia in the present report. It is well recognized that undernotifications do occur in cancer registries. Indeed, in a recent report it was shown that undernotification in the Swedish Cancer Registry was as high as 15.4% for acute leukaemias, greater for AML and unspecified AL than for ALL [12]. The study also pinpointed the issue of undernotification among elderly leukaemia patients. Herein, 21.4% of patients over 80 years compared to 7.8% of patients under 60 years, were not notified. In the experience of Bowie [17] where the South Western Regional cancer register in Great Britain was investigated, it was found that 23% of leukaemia cases were not included in the register. Further, 7% of those registered as leukaemia did not have leukaemia and 3% had the wrong type of registered leukaemia. However, in one Swedish study [18] of undernotification to a Regional Cancer Registry it was estimated that the deficit was 4% for the total cancer incidence and 10% as regards leukaemias. A recent study showed an undernotification of 11.7% of thyroid cancer in the Estonian Cancer Registry [19].

Another explanation for the rather low incidence rates of acute de novo leukaemias encountered in the present work could be the exclusion of patients where the records were either missing or were lacking crucial information; this was true for 18% of the acute leukaemia associated diagnoses in the Estonian Cancer Register and for 11% in the Western Swedish Cancer Register.

Finally, it should be kept in mind that in the current report we decided to investigate only the incidence of acute de novo leukaemias. In the total Estonian material of acute leukaemia patients, aged ≥16 years, 22.2% were shown not to fulfil the criteria for acute de novo leukaemia; the corresponding figure for the Swedish material was as high as 32.5%. This latter figure is obviously in contrast to the report of Åström et al. [12] in which only 20% of the acute leukaemias were considered to be secondary.

As already stated above, the rates as to yearly incidence of acute de novo leukaemia between the two countries did not differ. There were, however, major differences as regards the results for short term as well as long term survival in between the Estonian and Swedish patients (Figs. 2–5). Thus, the relative survival for the total group of Estonian patients at 1 year was 20.7% and at 5 years 3.6%, respectively. The corresponding figures for the Swedish patients were significantly higher (62.5 and 29.4%, respectively). In both countries, however, the group of AL patients showed a similar dismal survival.

In the literature, survival data from comparable unselected patient populations with de novo acute leukaemia are lacking. It would, however, appear that the Swedish results do approach the best possible which could be achieved at the time of the study period. Indeed, in 3 large randomized clinical trials [20–22] on AML carried out between the years of 1986–1994 the results for overall survival at 4 or 5 years were reported to range 11–41%. The age distributions for patients contained in the three clinical studies were roughly similar to those for the patients of the present work. However, whereas the three clinical studies were carried out on selected patients with AML, the present study patients were unselected de novo patients not only with AML but also with ALL and AL. Indeed, in even most recent major reports the survival rates for patients with AML and ALL agree closely with those reported for the Swedish patients of the present work [23–26].

The difference in survival between the two regions reported in the present study is in line with other works that compare survival of cancer in former East bloc countries with Western countries. One study from Estonia and Sweden [27] investigated the pattern of cancer survival in Estonians who during the end of the Second World War in 1944–1945 took refuge in Sweden. The study showed that Estonians in Estonia had lower cancer survival rates than Estonians in Sweden, whereas the cancer survival rates for Estonians in Sweden and the total Swedish population were similar. This finding suggested that differences in survival were due to delay in diagnosis and inferior treatment, explained by lag in socio-economic development in Estonia.

Considering the results of the present work it appears that the demonstrated differences as to survival are mainly accounted the fact that the Estonian haematologists during these years, for economic reasons, did not have access to the therapeutic measures readily available for Swedish haematologists whenever dealing with qualified haematology. Herein are included chemotherapeutic agents, antibiotics, platelet transfusion therapy and other supportive measures normally available in modern Western haematology. Additionally, an explanation for the poorer outcome for Estonian patients could be difficulties in subgrouping the leukaemias due to lack of diagnostic devices, e.g., immunophenotyping did not come in routine use until 1993, compared to 1987 in Western Sweden; this might also explain why the incidence for Estonian patients is higher as to AL when compared with Swedish patients.

Most importantly, as regards Swedish patients, the present study did demonstrate that the survival at 5 years increased significantly over the three consecutive 5-year periods. No such increment was seen in the Estonian patients. It is evident that access to the above therapeutic facilities in Estonia will improve the outcome for patients with acute leukaemias.

It therefore appears that the present report should also be regarded as a historical document reflecting how political/socio-economic factors may influence the survival of acute leukaemia patients in two neighbouring countries. Currently, we are in the process to prospectively compare the results for the incidence and outcome of de novo acute leukaemia between the two regions over forthcoming 5-year periods.
Acknowledgements

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References


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