Cancer incidence in persons with Down syndrome in Israel

Lital Keinan Boker 1 and Joav Merrick 2

1 Julius Center for General Practice and Patient Oriented Research, University Medical Center Utrecht, The Netherlands
2 National Institute of Child Health and Human Development, Schneider Children’s Medical Center of Israel, Sackler School of Medicine, Tel Aviv University, Petah Tikva and Office of the Medical Director, Division for Mental Retardation, Ministry of Labour and Social Affairs, Jerusalem, Israel

Abstract- The purpose of this study was to assess the incidence rates of leukaemia and other malignancies in persons with Down syndrome in Israel. The target population consisted of all persons with Down syndrome in the period of 1948-1995 and the study population was divided into two subgroups: (1) Persons born in Israel between 1979-95 (registry group) and (2) Persons currently or past-institutionalised, born before 1979 (institution group). The study population was linked to the Cancer Registry and cases that had been diagnosed through December 1995 were subsequently identified. The observed incidence rates were compared to expected rates in the general population. Standardised Incidence Ratios (SIR) and 95% confidence intervals were computed for each disease category. Analyses of results were performed separately for each subgroup of our study population. In the registry group seven cancer cases were observed as compared to 1.5 expected (SIR=4.67 95% CI 1.9-9.6), all of which were leukaemia cases. For the institution group a total of 17 cancer cases were observed compared to 12.8 expected. These included four cases of leukaemia (SIR=6.90 95% CI 1.9-17.7). An excess of gastric cancer in males, based on two cases (SIR=11.9 95% CI 1.3-42.9) was also observed. The significant excess of leukaemia in the Down syndrome population in Israel is in accordance with other international studies. The excess of gastric cancer in males with Down syndrome, which has not been reported before, should be further explored.

Keywords: Down syndrome, cancer incidence, leukaemia, gastric cancer; Israel

Introduction

The cancer incidence of persons with intellectual disability has been poorly documented, but a recent study from Finland looked at a large representative nation wide cohort (2,173 persons with intellectual disability) and studied the cancer incidence for the years 1967-97. The incidence of cancer was comparable with the general population, but an elevated risk of cancer of the gallbladder and thyroid gland in the intellectual disability population was observed (Patja et al., 2001). In a study of mortality of persons with intellectual disability in residential care centres in Israel for the period 1991-97 (Merrick, 1999) the rate for cancer was found to be 1.17 per 1,000 compared to 1.27 for the general population.

In the Finnish study there were no cases of cancer in women with Down syndrome (a total of 93 men and 102 women in the cohort with Down syndrome), producing a significantly reduced risk of cancer for these persons (E=expected cases=3.9, SIR=standardised incidence ratio=0, 95% CI=confidence interval=0.0-0.9). Men with Down syndrome had the same risk as the general population (O=observed cases=3, E=2.6, SIR=1.1, 95% CI=0.2-3.3). One brain tumour, one undefined and one non-Hodgkin lymphoma were found (Patja et al., 2001).

The association between Down syndrome and a higher incidence of leukaemia has been reported (Evans & Stewart, 1972; Rowely, 1981; Fong & Brodeur, 1987; Levitt et al., 1990) and persons with Down syndrome are at 10-30 fold higher risk for leukaemia compared to the general population (Evans et al., 1972; Rowely 1981). Leukaemia is characterized by a peak in infancy, which mostly corresponds to a transient leukomoid disorder (TLD), another peak at early childhood (3-6 years) which corresponds to acute leukaemias (about 50% are lymphatic leukaemias [ALL]) followed by a slight decrease in incidence which still remains higher at all ages compared to the general population (Fong et al., 1987, Lange et al., 1998). It has also been reported that children with Down syndrome have a 400-fold higher risk of developing a unique subtype of an acute megakaryoblastic leukaemia (FAB classification: 

---

© 2002 The Down Syndrome Educational Trust. All Rights Reserved. ISSN: 0968-7912 http://www.down-syndrome.net/library/periodicals/dsrp/08/01/
ANLL-M7), compared to the general population (Lange et al., 1998). This type of leukaemia is considered to be on the same spectrum as TLD, as both diseases involve a megakaryoblastic displasia of bone marrow (Sacchi, 1992; Gassmann & Loffler, 1995; Zipursky et al., 1995; Bhatt et al., 1995).

The fact that trisomy 21 is the most frequent chromosomal aberration in tumour cells of ANLL patients with a normal karyotype has led to an assumption that excess of chromosome 21 is a possible cause for the susceptibility of persons with Down syndrome to leukaemia (Rowely 1981; Fong et al., 1987; Bhatt et al., 1995). This hypothesis has been supported by the fact that several oncogenes were identified on the long arm of chromosome 21 (Fong et al., 1987; Papas et al., 1990; Sacchi 1992).

Current data regarding chromosomal background for many malignancies has raised the question whether persons with Down syndrome are prone to other kinds of cancer besides leukaemia. The purpose of this study was to establish the incidence of leukaemia and other malignant diseases in the population of persons with Down syndrome in Israel.

Methods

Our target population was all people with Down syndrome residing in Israel for the period 1948-1995 and the study population consisted of two groups. The registry group of all persons with Down syndrome born in Israel between the years 1979-1995 and the institution group of all persons with Down syndrome born before 1979, who are currently institutionalised, or were institutionalised in the past in one of the residential care centres for persons with intellectual disability in Israel. The combined groups totalled 2,635 persons. The study was approved by the Institutional Review Board (IRB) committee of the Chaim Sheba Medical Center, Tel Hashomer, Israel.

Information regarding the registry group (1,846 persons) was derived from the Israel Down Syndrome Register established in 1978 by the Israeli Ministry of Health. The register is based on legally compulsory reports from all maternity departments, paediatric departments and cytogenetic laboratories. Completeness, evaluated by comparison of hospitalisation records from selected maternity and paediatric departments to the Down syndrome registry, was estimated at 95% for Israeli Jews. Demographic details and vital status are being ascertained regularly by matching to the Central Population Register. Information concerning the institution group (789 persons) was derived from all residential care centres for persons with intellectual disability under the auspices of the Division for Mental Retardation, Ministry of Labour and Social Affairs and the Mortality Register of the Office of the Medical Director. Visits were made to 79 residential care centres (total population of close to 8,000 persons) and the files of 521 persons with Down syndrome examined. The Mortality Register contains all records of persons with intellectual disability, who died in residential care centres in Israel since 1948. All existing records – approximately 2,750 – were reviewed. Only 9.7% (268 persons) of them were persons with Down syndrome and a question-
naire containing demographic and medical data was filled out for each one.

Demographic details and vital status were ascertained for each person by matching their data with the Central Population Register. Altogether we located 789 cases of deceased or living institutionalised persons with Down syndrome born before 1979, of these 81% were born after 1948. In order to evaluate the completeness of this subgroup, we calculated a rough incidence rate of Down syndrome births in the years 1948-1978 according to the known number of persons with Down syndrome in residential care, using the number of total births as denominator, and compared it to the expected incidence rates according to Western trends, for Jews only (data not shown). The results reveal an estimated average annual Down syndrome incidence rate of 0.42 per 1,000 live births, a figure that is 3-fold lower than the conservative Western expected rate of 1.0-1.4 per 1,000 live births. We concluded therefore that the completeness of this set of data (institution group) is approximately 30%.

Linkage with the Israeli Cancer Register was accomplished by computer matching of the identification numbers of each person, as well as names and other demographic variables. The Israeli Cancer Register was established in 1960 and maintains data on all malignancies (excluding non-melanoma skin cancers) and some benign tumours (primarily of the central nervous system) in the country. It receives notifications of all malignancies from hospital discharged records, as well as oncology and pathology departments throughout the country, as is legally compulsory. The completeness of data is examined periodically and is approximately 90% for solid tumours and acute leukaemia. The Cancer Register provided cancer diagnosis, coded according to the International Classification of Diseases, Ninth Revision (ICD-9), along with date and place of diagnosis. Diagnoses were verified by reviewing the original histopathological report for each case.

Statistical methods

Standardised incidence ratios (SIR) were computed as a ratio of observed to expected cancers. Confidence intervals of 95% (95% CI) were estimated using the procedure described by Rothman and Boyce (1979). Person years at risk were computed from date of birth until December, 31st 1995 (last date of follow-up) or date of death for those dying of non-malignant causes or date of cancer diagnosis. The expected number of malignancies was computed by applying the appropriate age, sex, place of birth (for persons with Down syndrome born before 1979), nationality (for persons with Down syndrome born in 1979-1995) and year-specific national cancer incidence rates, to person-years at risk.

Results

A total of 24 cases of cancer were diagnosed over a follow up of 33,922 person years at risk. Seven cases were found in the registry group (10,964 person years at risk) and 17 in the institution group (22,958 person years at risk).

In the registry group the average age was six years (range 1-17), 55% were males, 72% were Jews and all were born in Israel (see Table 1). Among the cancer patients in this subgroup the average age was three years, 72% were males and 86% were Jews. Seven cancer cases were observed among persons born in 1979-95, as compared to 1.5 expected (SIR=4.7, 95% CI 1.9-9.6). Table 2 presents descriptive data of each case. All malignancies were cases of leukaemia, and included three ALL cases (compared to 0.05 expected, SIR=60.0, 95% CI 12.1-175.3), one case of ALL (compared to 0.2 cases expected, SIR=4.9, 95% CI 0.1-27.3) and three cases of non-specific leukaemia (compared to 0.023 cases expected, SIR=130.4, 95% CI 26.2-381.1) (see Table 2).

In the institution group the average age was 30 years, 51% were males, 87% were Jews and 78% were born in Israel (see Table 1). Among the cancer patients in this subgroup the average age was 33 years, 65% were males and 100% were Jews. A total of 17 cancer cases were observed in this subgroup, compared to 12.8 expected (SIR=1.3, 95% CI 0.8-2.1). Table 2 presents descriptive data of each case. Eleven of the malignancies occurred in males and six occurred in females. Only 4 out of the 17 cases were cases of leukaemia (compared to 0.6 expected, SIR=6.9, 95% CI 1.9-17.7) and the rest were solid tumours (see Table 5). In males with Down syndrome born before 1979, a statistically significant excess of gastric cancer (2 cases compared to 0.2 expected, SIR=11.9, 95% CI 1.3-42.9) was noted as well (see Table 6).

Discussion

In this study there was a marked and statistically significant excess of leukaemia in persons with Down syndrome. We found a 25-fold excess morbidity in the group born between 1979-1995 and a seven fold excess morbidity for persons with Down syndrome born before 1979. Such a 20-30 fold leukaemia risk for children with Down syndrome has been found by other researchers (Evans & Steward, 1972; Rowely 1981; Hasle et al., 2000) and also correspond to later works reporting a higher incidence of leukaemia in adults with Down syndrome (Fong et al., 1987).

A strong indication of an excess in certain types of cancers in general and particularly for gastric cancer was also found. Thase (1982) reviewed several studies addressing cancer morbidity and mortality among persons with Down syndrome. Apart from excess of leukaemia, persons with Down syndrome were also reported to be at higher risk for lymphoma and testicular carcinoma, and at an equivalent risk for upper and lower gastrointestinal tract tumours as compared with the general population (Thase, 1982). Scholl, Stein and Hansen (1982) reported that persons

http://www.down-syndrome.net/library/periodicals/dsrp/08/01/
with Down syndrome were at lower risk for gastrointestinal tract tumours, genital tumours and breast cancer.

Satge et al. (1998), who recently reviewed this issue, suggested that some tumours are over-represented and some are under-represented in persons with Down syndrome. Accordingly, the Down syndrome tumour profile includes: (I) An excess of leukaemia, lymphoma, gonadal tumours, extra-gonadal germ cell tumours, retinoblastoma and benign skin syringoma; (II) A lower incidence of central and peripheral neural system tumours, pediatric nephroblastoma, ear nose and throat tumours, lung cancer, urinary tract tumours, endometrial adenocarcinoma, breast cancer and malignant skin tumours. It was also stated that most of the tumours in people with Down syndrome occur at an earlier age as compared to the general population, some may have a potential for regression (i.e. TLD), and that males with Down syndrome are more susceptible to some of the tumours (such as ANLL-M7 and lymphoma) compared with females. The basis for this theory is that due to the primary chromosomal aberration, certain tissues are extremely vulnerable in persons with Down syndrome, whereas others offer an additional degree of resistance to oncogenesis (Satge et al., 1998). Results of a recent study, investigating leukaemia and solid tumour incidence in the Danish Down syndrome population (Hasle et al., 2000), confirmed the excess in leukaemia incidence up to the age of 29 years, as well as a non-significant excess of testicular cancer in males, ovarian cancer in females and retinoblastomas in children (Hasle et al., 2000). Our results correspond only partially to the scheme offered by Satge et al. (1998): More males (five cases, 71%) than females (two cases, 29%) had leukaemia in the institution group, but the corresponding M:F ratio of 2.5 was quite different from the general M:F ratio of 1.05 in this subgroup. We have also observed a non-significant excess of lymphoma and testicular cancer in males of the institution group, as well as non-significant excess of ovarian cancer in females of the institution group. In addition, breast cancer in females of the institution group occurred in lower rates than expected (one case as compared to 2.60 expected, SIR=0.38, 95% CI 0.01-2.10).

The finding of a statistically significant excess of gastric cancer in males with Down syndrome was investigated by Table 4. Descriptive aspects of cancer cases in Down syndrome population born before 1979.

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Age at diagnosis (yrs)</th>
<th>Vital status</th>
<th>Gender</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>15</td>
<td>Alive</td>
<td>F</td>
<td>ANLL</td>
</tr>
<tr>
<td>1977</td>
<td>18</td>
<td>Alive</td>
<td>M</td>
<td>Pituitary tumour</td>
</tr>
<tr>
<td>1959</td>
<td>20</td>
<td>Dead</td>
<td>M</td>
<td>ALL</td>
</tr>
<tr>
<td>1960</td>
<td>22</td>
<td>Dead</td>
<td>M</td>
<td>ALL</td>
</tr>
<tr>
<td>1947</td>
<td>23</td>
<td>Dead</td>
<td>M</td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>1949</td>
<td>25</td>
<td>Dead</td>
<td>F</td>
<td>Ovary cancer</td>
</tr>
<tr>
<td>1950</td>
<td>27</td>
<td>Dead</td>
<td>F</td>
<td>Non-specific leukaemia</td>
</tr>
<tr>
<td>1956</td>
<td>27</td>
<td>Dead</td>
<td>M</td>
<td>Gastric adenocarcinoma</td>
</tr>
<tr>
<td>1966</td>
<td>28</td>
<td>Alive</td>
<td>F</td>
<td>Ovary cancer</td>
</tr>
<tr>
<td>1957</td>
<td>29</td>
<td>Dead</td>
<td>M</td>
<td>Seminoma</td>
</tr>
<tr>
<td>1956</td>
<td>38</td>
<td>Alive</td>
<td>F</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>1953</td>
<td>41</td>
<td>Alive</td>
<td>F</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>1953</td>
<td>42</td>
<td>Alive</td>
<td>M</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>1939</td>
<td>43</td>
<td>Dead</td>
<td>M</td>
<td>Intrahepatic biliary tumour</td>
</tr>
<tr>
<td>1947</td>
<td>44</td>
<td>Alive</td>
<td>M</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>1936</td>
<td>45</td>
<td>Dead</td>
<td>M</td>
<td>Gastric adenocarcinoma</td>
</tr>
<tr>
<td>1944</td>
<td>49</td>
<td>Dead</td>
<td>M</td>
<td>Extrahepatic biliary tumour</td>
</tr>
</tbody>
</table>

Table 4. Descriptive aspects of cancer cases in Down syndrome population born before 1979
syndrome, which has not been reported before and appears at a relatively young age for this tumour, warrants a very cautious interpretation. In general, gastric cancer is twice as common among males compared to females (Mayer, 1998). Risk factors for the disease include, among others, exposure to nitrites, which are produced by special bacteria. Exogenous sources of nitrate converting bacteria include bacterially contaminated food (salted, smoked or dried, common in lower socio-economic classes) and – possibly – exposure to Helicobacter pylori. Endogenous factors favouring growth of nitrate-converting bacteria in the stomach are, among others, decreased gastric acidity, prior gastric surgery, atrophic gastritis and/or pernicious anaemia. Gastric ulcers, adenomatous polyps and blood group A were also identified as risk factors for the disease (Mayer, 1998; Tominaga, 1999). It is more than likely that the institution subgroup might have been exposed to some of these risk factors (contaminated foods, lower socioeconomic status). In addition, the well-established proneness of persons with Down syndrome to gastrointestinal and respiratory infections (Thase, 1982; Pueschel, 1990; Ugazio et al., 1990; Cooley et al., 1991; Hayes et al., 1993; Cuadrado & Barrena, 1996) might have put this institutionalized subgroup at a higher risk for a Helicobacter pylori infection than the general population. Moreover, it has been reported that certain regions on 21q were deleted, causing loss of heterozygosity, in isolates from differentiated human gastric adenocarcinoma cells (Sakata et al., 1997; Monakhov et al., 1997). Therefore, it may be that certain genes on the long arm of chromosome 21 are involved with the oncogenesis of gastric adenocarcinoma.

Our study has some limitations that should be taken into account, when using the data. One subgroup of persons with Down syndrome born in 1979-95 represented about 95% of the target population in Israel, whereas the institution subgroup contained only about 30% of the target population. The latter group may be selective, as it is based on individuals, who have survived long enough and does not include those who were raised by their families or those hospitalised for long periods. This possible selection bias may have led to a misclassification due to under-diagnosis and under-reporting of malignant diseases in the institution group to the Israeli Cancer Registry. Such an under-reporting may be responsible for the non significant SIR’s observed in this subgroup. However, although such a misclassification is possible, the high level of completeness of the Israeli Cancer registry data makes it unlikely that it would have much effect on our results.

Conclusions

In this study we have confirmed a statistically significant excess of leukaemia in the Down syndrome population in Israel. In addition, we have also observed an excess of gastric cancer in institutionalised males with Down syndrome born before 1979. Further investigation into the incidence of cancer in the adult Down syndrome population is called for, and may be best achieved by a future follow-up of the Down syndrome subjects born in 1979-1995 cohort.

Acknowledgements

Edna Ekstein of the National Down Syndrome Register at Chaim Sheba Medical Center, Ministry of Health, the colleagues at the Department of Clinical Epidemiology, Chaim Sheba Medical Center, the personnel of the residential care centres for persons with intellectual disability and colleagues of the Office of the Medical Director, Ministry of Labour and Social Affairs are thanked for their help and assistance. This paper is based on the work accepted for the first author's Master of Public Health by the Hadassah Braun School of Public Health and Community Medicine, Hebrew University, Jerusalem and is an updated and revised version of the following paper:


Correspondence

Lital Keinan Boker • Julius Center for General Practice and Patient Oriented Research, University Medical Center Utrecht (DOI:335, UMCU), P.O.B. 85500, 3508 GA Utrecht, The Netherlands  E-mail:L.K.Boker@jc.azu.nl

Professor Joav Merrick • Division for Mental Retardation, Box 1260, IL-91012 Jerusalem, Israel  E-mail: jmerrick@aquanet.co.il

References


