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INCIDENCE OF LEUKEMIA AND OTHER CANCERS IN DOWN SYNDROME SUBJECTS IN ISRAEL

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Epidemiologic data have confirmed the high susceptibility of persons with Down syndrome (DS) to leukemia. The question of proneness to other kinds of cancer is still open. In this study we reassessed the incidence rates of leukemia and other malignancies in Israeli DS subjects, based on the total population. The target population consisted of all DS subjects in Israel in the period of 1948–1995. Due to incompleteness of data, the target population was not fully achieved, thus the study population was divided into 2 subgroups: subjects born in Israel between 1979 and 1995 (registry group) and currently or past-institutionalized subjects born before 1979 (institution group). The cohort was linked with the Cancer Registry, and cancer cases that had been diagnosed through December 1995 were subsequently identified. Observed incidence rates were compared with expected rates in the general population. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were computed for each disease category. Analyses were performed separately for each subgroup of the study population. In the registry group, 7 cancer cases were observed, compared with 1.5 expected (SIR = 4.67, 95% CI 1.9–9.6), all leukemia cases. For the institution group a total of 17 cancer cases were observed, compared with 12.8 expected. These included 4 cases of leukemia (SIR = 6.90, 95% CI 1.90–17.70). An excess of gastric cancer in male subjects (SIR = 11.9, 95% CI 1.3–42.9) was also observed. Significant excess of leukemia in DS population in Israel is in accordance with previously published data. An excess of gastric cancer in DS male subjects born before 1979, which has not been reported before, should be further explored.

Key words: *Down syndrome; cancer incidence; Israel*

Down syndrome is one of the most common conditions associated with mental retardation.[1,2] The association between DS and a higher incidence of leukemia is well established.[3–6] DS subjects are at a 10- to 30-fold higher risk for leukemia compared with the general population.[3,4] Leukemia morbidity in DS subjects is characterized by a peak in infancy that corresponds mostly to a transient leukomoid disorder (TLD); another peak at early childhood (3–6 years) that corresponds to acute leukemias, of which around 50% are acute lymphoblastic leukemias (ALL); and then a slight decrease in incidence that remains higher at all ages compared with the general population.[5,7] It has also been reported that DS children have a 400-fold higher risk of developing a unique subtype of an acute megakaryoblastic leukemia [French American British (FAB) classification: acute non-lymphoblastic leukemia-M7 (ANLL-M7)], compared with the general population.[7] This type of leukemia is considered to be similar to TLD, in that both diseases involve a megakaryoblastic displasia of bone marrow.[8–11]

The fact that Trisomy 21 is the most frequent chromosomal aberration in tumor 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 DS subjects to leukemia.[4,5,11] This hypothesis was later supported by the fact that several oncogenes were identified on the long arm of chromosome 21.[5,8,12] Current data regarding chromosomal background for many malignancies have raised the question whether DS subjects are prone to other kinds of cancer besides leukemia, as well. In the present study, our aim was to reassess the incidence of leukemia and other malignant diseases based on the total Israeli DS population. The study was approved by the Institutional Review Board (IRB) committee of the Chaim Sheba Medical Center.

METHODS

Study population

Target population consisted of all DS subjects in Israel between 1948 and 1995. As data for the early period (1948–1978) are incomplete, the study population consisted of 2 subgroups: all DS subjects born in Israel between the years 1979 and 1995 (registry group); and all DS subjects born before 1979, who are currently institutionalized, or were institutionalized in the past in 1 of the governmental or private institutions for developmentally disabled persons (institution group). Both subgroups totaled to 2,635 participants.

DS subjects born in Israel between the years 1979 and 1995 (1,846 subjects). Information regarding this subgroup was derived from the Israeli Registry of DS Births of the Israeli Ministry of Health. This registry was established in 1979, and is based on compulsory reports by law from all maternity and infant wards in Israel, and reports from licensed cytogenetic laboratories. Completeness, evaluated by comparison of hospitalization records from selected maternity and pediatric departments with the DS registry, was considered to be 95% and higher for Israeli Jews and somewhat lower for Israeli non-Jews. Demographic details and vital status are being ascertained regularly by matching to the Central Population Registry, using unique Israeli identity numbers.

Institutionalized DS subjects born before 1979 (789 subjects). Information concerning this subgroup was derived from all private and governmental institutions for the developmentally disabled in Israel, which are supervised by the Israeli Ministry of Work and Welfare (IMWW), and from the IMWW archives, which keep all files of deceased institutionalized DS subjects. Data, therefore, were collected in 2 tracks: First, all 79 IMWW supervised institutions for the developmentally disabled in Israel were approached in search for currently institutionalized DS subjects, because guidelines for institutionalization are based on the level of retardation, not its etiology. For each DS subject identified, a file review was conducted. The number of DS subjects currently institutionalized totaled 521. Second, the IMWW's archive contains all records of institutionalized developmentally disabled sub-

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jects who died in 1 of the supervised institutions in Israel since 1948. All existing records—approximately 2,750—were reviewed; only 9.7% of the records were of DS subjects. For those, a questionnaire containing demographic and medical data was filled out. A total of 268 deceased institutionalized DS subjects were identified.

Demographic details and vital status were ascertained for each participant by matching our data to the Central Population Registry, using the participant's unique Israeli identity number. Of the 789 cases of deceased or living institutionalized DS subjects born before 1979, 81% were born after 1948. To evaluate the completeness of this subgroup, we calculated a rough incidence rate of DS births in the years 1948–1978 according to the known number of institutionalized DS subjects, using the number of total births as denominator, and compared this estimated rate with the expected incidence rates according to Western trends, for Jews only (data not shown). The results indicated an estimated average annual DS incidence rate of 0.42/1,000 live births, a figure that is 3-fold lower than the conservative Western expected rate of 1.0–1.4/1,000 live births. We concluded therefore that the institution group represented approximately 30% of the total DS population in Israel at this period.

Linkage with the Israeli Cancer Registry

Record linkage was accomplished by matching of the patients' unique Israeli identity numbers, as well as names and other demographic variables, with the Cancer Registry Database through a specifically adjusted software. The Israeli Cancer Registry was established in 1960 and maintains data on all malignancies (excluding non-melanoma skin cancers) and some benign tumors (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 compulsory by law. The completeness of data is examined periodically and is approximately 90% for solid tumors and acute leukemia. The Cancer Registry provided cancer diagnosis, coded according to the International Classification of Diseases, Ninth Revision, along with date and place of diagnosis. Diagnoses were verified by reviewing the original histo-pathologic report for each case.

Statistical analyses

Standardized incidence ratios (SIR) were computed as a ratio of observed to expected cancer; 95% confidence intervals (95% CI) were estimated using the procedure described by Rothman and Boice.[13] Person-years at risk were computed from date of birth until December 31, 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 DS subjects born before 1979), nationality and year-specific national cancer incidence rates, to person-years at risk.

RESULTS

Twenty-four cancer cases were diagnosed in the total study group, over a follow-up of 33,922 person-years at risk: 7 in the registry group (more than 10,964 person-years at risk) and 17 in the institution group (more than 22,958 person-years at risk).

DS subjects born in 1979–1995 (registry group)

In this subgroup the average age was approximately 6 years (range <1–17 years), 55% were males, 72% were Jews, and all were born in Israel. At cancer diagnosis in this subgroup, the average age was approximately 3 years, 72% of the cases were males, and 86% were Jews. Seven cancer cases were observed among DS subjects born in 1979–1995, as compared with 1.5 expected (SIR = 4.67, 95% CI 1.9–9.6). All malignancies were cases of leukemia, and included 3 ANLL cases (compared with 0.05 expected, SIR = 60.00, 95% CI 12.06–175.31), 1 case of ALL (compared with 0.2 cases expected, SIR = 4.90, 95% CI 0.06–27.27) and 3 cases of non-specific leukemia (compared with 0.023 cases expected, SIR = 130.43, 95% CI 26.2–381.1) (Table I).

DS subjects born before 1979 (institution group)

In this subgroup the average age was approximately 30 years, 51% were males, 87% were Jews, and 78% were born in Israel. At diagnosis in this subgroup, the average age was approximately 33 years, 65% of cases were males, and 100% were Jews. Seventeen cancer cases were observed in this subgroup, compared with 12.8 expected (SIR = 1.33, 95% CI 0.77–2.12). Only 4 of the 17 cases were cases of leukemia (compared with 0.58 expected, SIR = 6.90, 95% CI 1.86–17.66), and the rest were solid tumors. Table II shows observed and expected rates of certain malignancies according to age groups. In DS males born before 1979, a statistically significant excess of gastric cancer (2 cases compared with 0.17 expected, SIR = 11.9, 95% CI 1.3–42.9) was noted as well (data not shown).

DISCUSSION

Our study confirms a marked and statistically significant excess of leukemia in DS subjects; A 25-fold excess morbidity for DS subjects born between 1979 and 1995 and a 7-fold excess morbidity for DS subjects born before 1979, mostly noted for the age groups of 0–19 and 20–39 years. These findings are in agreement with former studies reporting a 20- to 30-fold leukemia risk in DS children compared with normal-karyotype counterparts.[3,4,14] These findings also correspond to those in studies reporting a higher incidence of leukemia in adult DS subjects as compared with the general population.[5] In addition, we found a significant excess of gastric cancer in males.

Apart from excess of leukemia, DS subjects were reported to be at higher risk for lymphoma and testicular carcinoma, and at an equivalent risk for upper and lower gastrointestinal tract tumors as compared with the general population.[15] However, it was also reported that DS subjects were at lower risk for gastrointestinal tract tumors, genital tumors, and breast cancer in comparison with normal individuals.[16] Satge *et al.*,[17,18] who reviewed the issue, suggested that some tumors are over-represented and some are under-represented in DS subjects. Accordingly, the DS tumor profile includes n excess of leukemia, lymphoma, gonadal tumors, extra-gonadal germ cell tumors, retinoblastoma and benign skin syringoma; and a lower incidence of central and peripheral neural system tumors, pediatric nephroblastoma, ear nose and throat

TABLE I – OBSERVED AND EXPECTED CANCER CASES AMONG DS INDIVIDUALS BORN IN 1979–1995

	N	Observed (*n*)	Expected (*n*)	SIR (95% CI)
All sites	1,846	7	1.50	4.67 (1.90–9.60)
Total leukemias	1,846	7	0.27	25.18 (10.40–53.40)
ALL	1,846	3	0.05	60.00 (12.06–175.31)
ANLL	1,846	1	0.20	4.90 (0.06–27.27)
Other and non specific leukemias	1,846	3	0.02	130.43 (26.20–381.10)

DS, Down syndrome; ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphoblastic leukemia; SIR, standardized incidence ratio; CI, confidence interval.

TABLE II – OBSERVED AND EXPECTED CANCER CASES AMONG DS INDIVIDUALS BORN BEFORE 1979

Age group (years)	*n*	Observed (*n*)	Expected (*n*)	SIR (95% CI)
All sites				
0–19	225	3	0.21	14.8 (2.8–41.1)
20–39	302	7	1.97	3.55 (1.4–3.7)
40–59	248	7	8.46	0.83 (0.3–1.7)
60+	14	0	2.17	—
Total leukemias				
0–19	225	2	0.04	50.0 (5.6–180.5)
20–39	302	2	0.23	8.7 (1.0–31.4)
40–59	248	0	0.38	—
60+	14	0	0.07	—
ALL				
0–19	225	1	0.024	41.7 (0.7–278.2)
20–39	302	1	0.11	9.1 (0.1–50.6)
40–59	248	0	0.20	—
60+	14	0	0.03	—
ANLL				
0–19	225	0	0.01	—
20–39	302	1	0.09	11.1 (0.2–61.8)
40–59	248	0	0.20	—
60+	14	0	0.03	—
Other and nonspecific leukemias				
0–19	225	1	0.005	200.0 (1.3–556.4)
20–39	302	0	0.03	—
40–59	248	0	0.04	—
60+	14	0	0.01	—

DS, Down syndrome; ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphoblastic leukemia; SIR, standardized incidence ratio; CI, confidence interval.

tumors, lung cancer, urinary tract tumors, endometrial adenocarcinoma, breast cancer and malignant skin tumors. It was also stated that most of the DS tumors occur at an earlier age than in the general population, that some may have a potential for regression (*i.e.*, TLD) and that DS males are more susceptible to some of the tumors (such as ANLL-M7 and lymphoma) than DS females.

Results of a recent study, investigating leukemia and solid tumor incidence in Danish DS population,[14] confirmed the excess in leukemia incidence in DS subjects up to the age of 29 years, as well as a non-significant excess of testicular cancer in males, ovary cancer in females and retinoblastomas in children.[14] Our results basically correspond to the scheme offered by Satge *et al*.[17,18]: A significant excess of leukemia was observed in both subgroups; a non-significant excess of Hodgkin's lymphoma was also observed in the institution group as well as a non-significant excess of testicular cancer in males and ovary cancer in females. In addition, breast cancer in females occurred in lower rates than expected (1 case *versus* 2.60 expected, SIR = 0.38, 95% CI 0.01–2.10) and childhood neuroblastoma was not observed at all.

However, we have also observed a statistically significant excess of gastric cancer in DS males, a finding that was not described before. Gastric cancer has been found to be twice as common among male patients compared with female patients.[19] Risk factors for the disease include, among others, exposure to nitrites, which are produced by certain bacteria. Exogenous sources of nitrate-converting bacteria include bacterially contaminated food (salted, smoked or dried foods, common in lower socioeconomic classes) and possible exposure to *Helicobacter pylori.*[19,20] It is possible that the subgroup of the institutionalized DS subjects might have been exposed to some of these risk factors. In addition, the well-established proneness of DS subjects to gastrointestinal and respiratory infections[1,2,15,21–23] might have put this institutionalized subgroup at a higher risk for a *H. pylorii* 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.[24,25] Therefore, it may be that certain genes on the long arm of chromosome 21 are involved with the oncogenesis of gastric adenocarcinoma.

Study limitations

Whereas the subgroup of DS subjects born in 1979–1995 included about 95% of the target population in Israel, the institution subgroup contained only about 30% of the target population. The latter group may be selected, as it is based on individuals who have survived long enough after birth to be admitted into one of the supervised institutions for the developmentally disabled in Israel and does not include those who were raised by their families or those hospitalized for long periods. This may have lead to an under-representation of childhood cancers in this subgroup as many institutionalized children died of congenital and infectious causes before developing cancer, and those who were institutionalized at a later age were a selective group of survivors.

This possible selection bias may have lead also 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 SIRs observed in this subgroup. However, although such a misclassification is possible, the high completeness of the Israeli Cancer Registry data confirms that the possible selection bias could not have a heavy impact on our results.

In addition, the entity of "non-specific and other leukemia" is problematic as it contains both ANLL and ALL and thus dilutes the observed rates for the 2 latter entities. It may also be that DS subjects were selectively misclassified and grouped under this entity. Unfortunately, we were unable to ascertain the specific leukemia type in the 4 reported cases of non-specific leukemias in our study because of lack of medical records.

Conclusions

In this study we confirmed a statistically significant excess of leukemia in the DS population in Israel. In addition, we also observed an excess of gastric cancer in institutionalized DS males born before 1979. A further investigation into cancer incidence in an adult DS population is called for, and may be best achieved by a future follow-up of the DS subjects born in 1979–1995 cohort, because of that group's data completeness.

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