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Cancer mortality in Down syndrome in California

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Abstract: Cancer in Down syndrome (DS) is characterized by a well known and marked excess of leukemia, whereas few studies are available on solid tumors in this population. *Objective*: To study the cancer mortality of DS in California. Study group: 16,808 DS cases (contributing 129,076 person-years) among 210,155 persons having received evaluations approximately annually from the California Department of Developmental Services over the period 1988-2002 were followed. *Methods*: Cancer mortality in DS was compared with the California general population using age- (and where significant sex) standardized mortality ratios (SMRs) computed for various cancer sites (ICD-9 codes 140-208). *Results:* An excess of overall cancer mortality (SMR 2.6, 95% CI 2.0-3.2) was found with overall SMR for neoplasms of the lymphatic and hematopoietic system of 10.3 (CI 7.5-13.9) [lymphomas: 3.7 (1.3-8.0), lymphoid leukemias: 27.6 (17.5-41.4), other specified leukemias: 51.1 (1.3-285.0) and unspecified leukemias: 25.4 (13.1-44.3)]. Deaths due to liver [5.6 (1.8-13.1)] and testicular cancer [12.5 (1.5-45.1)] were also more common in DS. No cancer deaths from lip, oral cavity, or pharynx were reported in DS. Other sites showed no significant differences. Excluding neoplasms of lymphatic and hematopoietic systems, the SMR for remaining cancers was 1.2 (0.8-1.7). *Conclusion:* Our findings do not support the hypothesis of a decreased risk of solid tumors in general in DS and confirm increased risk of testis and liver cancers. Further studies taking into account hormonal and genetic factors are needed to better understand the specific tumor profile in DS.

Keywords: Down syndrome, cancer, lymphoma, leukemia, mortality, testicular cancer, liver cancer

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INTRODUCTION

It is now generally recognized that the overall incidence and mortality related to cancer is either similar or greater among patients with Down syndrome (DS) than in the general population (1-7). The excess morbidity and mortality, however, may vary according to cancer site and possibly histology. Satgé et al (8,9) suggested that the excess cancer mortality in DS was mainly due to an excess of leukemias and was also accompanied by an under-representation of some solid tumors. These two results were also observed by others (6,7,10,11). The increase in life expectancy in DS patients (12,13) may lead to changes in the overall pattern of cancer mortality as more persons live to adulthood. As the results on mortality in past studies differ by cancer site and are possibly contradictory, the objective of this study was to examine in detail the mortality from cancer, according to site in a large population of persons with DS in California.

METHODS

Subjects were drawn from the 210,155 persons two years of age and older receiving services from the California Department of Developmental Services (DDS) between January 1, 1988 and December 31, 2002. Persons were identified as having DS based on ICD-9 (14) codes 758, 758.0, or 758.00 on the Client Development Evaluation Report (CDER) (15), an instrument completed annually for each person receiving services from the DDS. The CDER contains a variety of psychological, medical, functional, behavioral, and cognitive items. The reliability of the functional and clinical items has been assessed and judged satisfactory (16). As noted by Eyman et al (17), DDS Regional Center physicians are responsible for confirming, or making, the diagnosis of DS. If a karyotype has not been made the physicians arrange for the test to be performed. The DDS data on DS have been described in detail in Day et al (12).

Table 1. *Description of the 74 deaths caused by malignant neoplasms in the Down syndrome population, California, January 1, 1988 – December 31, 2002*

No.	Sex	Age at death (years)	Year of death	Malignant neoplasm (ICD-9)
1	Female	47.1	1989	Long bone of lower limb (170.7)
2	Female	3.7	1989	Unspecified leukemia (208.9)
3	Female	56.2	1989	Acute leukemia NOS (208.0)
4	Female	2.3	1990	Megakaryocytic leukemia (207.2)
5	Female	2.7	1990	Unspecified leukemia (208.9)
6	Female	3.0	1990	Acute leukemia NOS (208.0)
7	Male	36.0	1990	Scalp and skin of neck (173.4)
8	Male	9.4	1991	Hodgkin's disease, unspecified (201.9)
9	Female	12.3	1991	Acute lymphoid leukemia (204.0)
10	Male	63.2	1991	Bladder, part unspecified (188.9)
11	Female	2.2	1992	Acute leukemia NOS (208.0)
12	Male	10.4	1992	Acute lymphoid leukemia (204.0)
13	Female	12.1	1992	Acute lymphoid leukemia (204.0)
14	Male	20.7	1992	Acute lymphoid leukemia (204.0)
15	Male	23.2	1992	Soft tissue, NOS (171.9)
16	Female	28.1	1992	Acute lymphoid leukemia (204.0)
17	Male	30.0	1992	Lymphoma NOS (202.8)
18	Female	48.4	1992	Breast, unspecified (174.9)
19	Male	3.4	1993	Acute lymphoid leukemia (204.0)
20	Female	11.0	1993	Acute leukemia NOS (208.0)
21	Male	3.4	1994	Acute lymphoid leukemia (204.0)
22	Female	4.1	1994	Acute leukemia NOS (208.0)
23	Male	14.7	1994	Acute lymphoid leukemia (204.0)
24	Male	17.3	1995	Unspecified leukemia (208.9)
25	Male	26.1	1995	Acute leukemia NOS (208.0)
26	Male	49.5	1995	Testis NOS (186.9)
27	Female	10.9	1996	Acute lymphoid leukemia (204.0)
28	Male	37.6	1996	Liver, primary (155.0)
29	Male	51.6	1997	Lymphoma NOS (202.8)
30	Female	3.9	1998	Acute leukemia NOS (208.0)
31	Female	7.3	1998	Unspecified leukemia (208.9)
32	Male	7.8	1998	Acute lymphoid leukemia (204.0)
33	Male	9.7	1998	Acute lymphoid leukemia (204.0)
34	Male	12.3	1998	Acute lymphoid leukemia (204.0)
35	Male	20.8	1998	Other, without specification of site (199.1)
36	Male	49.6	1998	Cerebrum (191.0)
37	Male	7.7	1999	Acute lymphoid leukemia (204.0)
38	Female	46.1	1999	Breast, unspecified (174.9)
39	Male	50.9	1999	Brain, unspecified (191.9)
40	Male	58.8	1999	Lymphoma NOS (202.8)
41	Female	7.3	2000	Acute lymphoid leukemia (204.0)
42	Male	12.5	2000	Soft tissue, NOS (171.9)
43	Female	19.1	2000	Other, without specification of site (199.1)
44	Male	21.4	2000	Lymphoma NOS (202.8)
45	Female	22.1	2000	Acute lymphoid leukemia (204.0)
46	Male	22.7	2000	Brain, unspecified (191.9)
47	Male	26.0	2000	Bronchus and lung NOS (162.9)
48	Male	43.0	2000	Liver cell (155.0)
49	Female	53.4	2000	Liver (155)
50	Female	54.6	2000	Meninges (192.1)

Table 1 (continued). *Description of the 74 deaths caused by malignant neoplasms in the Down syndrome population, California, January 1, 1988 – December 31, 2002*

No.	Sex	Age at death (years)	Year of death	Malignant neoplasm (ICD-9)
51	Female	3.3	2001	Acute myeloid leukemia
52	Male	5.7	2001	Acute leukemia NOS (208.0)
53	Female	8.3	2001	Lymphosarcoma (200.1)
54	Male	8.8	2001	Acute lymphoid leukemia (204.0)
55	Female	17.4	2001	Acute lymphoid leukemia (204.0)
56	Male	29.6	2001	Acute leukemia NOS (208.0)
57	Male	38.6	2001	Pancreas NOS (157.9)
58	Male	38.8	2001	Liver cell (155.0)
59	Male	41.5	2001	Testis NOS (186.9)
60	Male	44.0	2001	Esophagus NOS (150.9)
61	Male	44.6	2001	Liver cell (155.0)
62	Female	68.1	2001	Bronchus and lung NOS (162.9)
63	Male	76.5	2001	Bronchus and lung NOS (162.9)
64	Female	4.5	2002	Acute myeloid leukemia
65	Female	7.9	2002	Acute lymphoid leukemia (204.0)
66	Male	10.3	2002	Acute lymphoid leukemia (204.0)
67	Female	13.3	2002	Acute lymphoid leukemia (204.0)
68	Female	16.6	2002	Bone and cartilage NOS (170.9)
69	Female	34.6	2002	Acute lymphoid leukemia (204.0)
70	Male	35.8	2002	Acute lymphoid leukemia (204.0)
71	Male	38.2	2002	Liver NOS (155.2)
72	Female	41.4	2002	Other, without specification of site (199.1)
73	Female	44.6	2002	Acute lymphoid leukemia (204.0)
74	Female	52.0	2002	Skin NOS (173.9)

Mortality information was obtained from annual computer files from the State of California (18) with underlying causes of death identified according to the ICD-9 (14). When needed, ICD-10 codes were recoded into ICD-9 codes for uniform comparisons to be made. In California it is required that death certificates be filed with the state, and the electronic files are the state's official mortality record. Cancer-specific mortality rates in DS were compared with those in the California general population as follows:

- For each cause of death considered, age-specific mortality rates (deaths per 100,000 person-years) in the California general population were computed using state mortality (18) and population (19) data over the period 1988-2002. Sex was also adjusted for in some analyses.
- For the DS subjects the total number of person-years at risk of death, i.e. the observation time, was determined, based on the number identified with DS and their respective follow-up times.
- Mortality rates from step 1 were applied to the person-years at risk from step 2 to determine expected numbers of deaths due to each cause within each age group.
- The observed number of deaths in the DS population associated with each cause for each age group was noted.
- Standardized mortality ratios (SMRs) were computed for each age group as the ratio of the observed number of deaths to the expected number (20). By summing observed and expected numbers over age groups, overall SMRs for each cause were computed as the ratio of total number of observed to total number of expected deaths.
- Confidence intervals for the SMRs were determined based on the assumption that the observed number of deaths follows a Poisson distribution (20).

RESULTS

Among the 210,155 persons age 2 years and older who received services between 1988 and 2002, 16,808 (8.0%) were diagnosed as having DS, among whom 9,119 (54%) were male. They contributed 129,076 person-years at risk of death during the study period. The median age of the DS subjects at first evaluation was 7.1 years, with mean 14.8 (SD = 14.9) years.

Table 2. *Standardized mortality ratios for cancer among persons with Down syndrome, California, January 1, 1988 – December 31, 2002*

Cause of death	ICD9 Codes	Deaths		SMR‡	95% C.I.§
		Obs*	Exp†		
All malignant neoplasms	140-208	74	28.84	2.6	2.0-3.2
Lip, oral cavity, and pharynx	140-149	0	0.58	0.0	0.0-6.4
Digestive organs and peritoneum	150-159	8	5.70	1.4	0.6-2.8
Colon	153	1	1.64	0.6	0.0-3.4
Liver	155	5	0.89	5.6	1.8-13.1
Gallbladder	156	0	0.14	0.0	0.0-26.4
Respiratory, intrathoracic organs	160-165	3	6.07	0.5	0.1-1.4
Nasal, larynx	160-161	0	0.20	0.0	0.0-18.6
Trachea, bronchus, lung	162	3	6.00	0.5	0.1-1.5
Bone, connective tissue, skin, breast	170-176	8	5.20	1.5	0.7-3.0
Bone and cartilage	170	2	0.33	6.0	0.7-21.7
Skin	172-173	2	0.89	2.3	0.3-8.1
Breast	174	2	3.42	0.6	0.1-2.1
Genitourinary organs	179-189	3	3.15	1.0	0.2-2.8
Testis	186	2	0.16	12.5	1.5-45.1
Ovary and other uterine adnexia	183	0	0.79	0.0	0.0-4.7
Bladder	188	1	0.25	3.9	0.1-21.9
Other and unspecified sites	190-199	8	3.90	2.1	0.9-4.0
Brain	191	4	1.8	2.2	0.6-5.7
Without specification of site	199	3	1.45	2.1	0.4-6.0
Lymphatic and hematopoietic tissue	200-208	44	4.26	10.3	7.5-13.9
Lymphomas	200-202	6	1.64	3.7	1.3-8.0
Leukemias	204-208	38	2.26	16.8	11.9-23.1
Lymphoid leukemia	204	23	0.83	27.6	17.5-41.4
Myeloid leukemia	205	2	0.92	2.2	0.3-7.9
Other specified leukemia	207	1	0.02	51.1	1.3-285.0
Leukemia of unspecified cell type	208	12	0.47	25.4	13.1-44.3
Tobacco-related cancers‖	See footnote	13	12.24	1.1	0.6-1.8
All malignant neoplasms other than those of lymphatic and hematopoietic tissue	140-199	30	24.58	1.2	0.8-1.7

* Obs = number of observed deaths among 14,781 persons with Down syndrome in California, 1988-2002.
† Exp = expected numbers of deaths based on age-adjusted cause-specific mortality rates in the California general population, 1988-2002.
‡ Ratio of observed to expected number of deaths, obs/exp.
§ Confidence interval based on the assumption that the observed deaths follow a Poisson distribution.(20)
‖ Tobacco related cancers from Monograph 83 of the IARC on tobacco smoking(38): lung, trachea, bronchus (ICD9 codes 162), oral cavity (140-145), pharynx (oro-, naso-, hypo-) (146-148), larynx (161), oesophagus (150), pancreas (157), bladder and renal pelvis (188), nasal cavities and sinuses (160), stomach (151), liver (155), kidney (189), uterine cervix (180), myeloid leukemia (205)

Among the 924 who died during this period, 74 were identified as having a malignant neoplasm (ICD-9 codes 140-208) as underlying cause of death. Table 1 describes these 74 individuals. The median age at death was 21 years, and 40 were males (54%). Among all cancer deaths, 44 (59%) were related to malignant neoplasms of the lymphatic and hematopoietic system, among which 38 (86%) were due to leukemias.

Table 2 gives the observed and age-adjusted expected numbers of deaths due to various sites of malignant neoplasms. An increase of cancer mortality overall (SMR 2.6, 95% CI 2.0-3.2) was found in persons with DS compared with the California general population. When neoplasms of the lymphatic and hematopoietic system (ICD9 codes 200-208) were excluded, the SMR for the remaining cancer sites was only 1.2 (95% CI 0.8-1.7).

The SMR for neoplasms of the lymphatic and hematopoietic system was 10.3 (95% CI 7.5-13.9). Contributing to this global excess were lymphomas

(SMR 3.7, 1.3-8.0), lymphoid leukemias (SMR 27.6, 17.5-41.4), other specified leukemias (SMR 51.1, 1.3-285.0), and unspecified leukemias (SMR 25.4, 13.1-44.3).

No cancer death was reported for lip, oral cavity, or pharynx sites. A decrease in tobacco-related cancers (27) was observed. A similar decrease in deaths due to tumors of the trachea, bronchus and lung was also observed, and interestingly all 3 of these observed in the DS population occurred in the last three years of the study period.

A 12-fold excess of mortality from testis cancer was observed (SMR 12.5, 1.5-45.1, based on 2 observed deaths). Deaths from colon (SMR 0.6, 0.0-3.4) and breast cancer (SMR 0.6, 0.1-2.1) were found less frequently than expected.

Finally, the mortality rates associated with cancers from bone and cartilage, skin, and other or unspecified sites were higher than expected (SMRs 6.0, 2.3, and 2.1, respectively, not statistically significant).

DISCUSSION

The overall SMR of 2.6 for cancer mortality is consistent with some previous studies (1-4). The majority of this observed excess was due to lymphatic and hematopoietic tissue tumours, while the overall SMR for remaining sites was 1.2 and not statistically significant. Clear excesses were observed for testis and liver cancer. As the life expectancy of persons with DS has improved in recent years, more deaths due to solid tumours may be observed in this population in the future.

We compared our results with 12 previous studies (1-7,11,21-24). Nine of these reported SMRs or standardized incidence ratios (SIRs), and their results are summarized in Table 3. Absent in the table are the results from Scholl et al (24), which reported proportional mortality ratios (PMRs) and Yang et al (21), who reported standardized mortality odds ratios (SMORs). The interpretation of PMRs and SMORs is difficult as their values depend on the relative distribution of causes of death, with a decrease in non-cancer deaths leading to an apparent increase in cancer deaths. Although PMRs and SMORs are not directly comparable to SMRs or SIRs, directions of effects among all of these measures are in general agreement.

The excess mortality in DS associated with leukemia and lymphoma is dramatic and, at least for leukemia, not unexpected. Two deaths due to myeloid leukemia were observed, and none due to monocytic leukemia, though some may have been included among the high number of unspecified leukemias (n=12). In our study, 10 deaths from leukemia were observed among patients aged below five years, representing 26% of the deaths from leukemia. This is consistent with Hasle et al (11), who reported that leukemia incidence in DS varied with age and occurred more frequently during the first 4 years of life. Scholl et al (24) and Yang et al (21) reported significantly higher number of deaths from leukemia, a pattern also well reported elsewhere (see Table 3). Chromosome 21, which when there is trisomy is responsible for DS, has been sequenced by Hattori et al (25) in 2000. More than 15 supposed leukemic oncogenes have been identified (26) including RUNX1 (or AML1), which is a transcription factor involved in the generation of the hematopoietic lineages, suggesting that an increased gene dosage due to trisomy could explain the predisposition to leukemia of persons with DS. In addition to these genes, Gurbuxani et al (26) also hypothesized that trisomy 21 might predispose persons to a genetic instability leading to an increase of mutations in other genes, such as GATA-1, located on the X chromosome, which is required for the maturation of erythroid cells and megacaryocytes.

Our study found a 3.7 fold excess of death from lymphoma compared with the general population. This result agrees with other mortality studies in persons with DS that also pointed to lymphomas. An old study on 52 children with DS who died before the age of 10 years from cancer found two "lymphosarcomas" which was about eight times as many as expected (27). In Scholl et al (24), which included children and adults, lymphomas were the only type of solid tumors over-represented as a cause of death in comparison with the general population. The proportional mortality ratio was 1.3. Similarly, authors from Sweden and Denmark (1), and Great Britain (4) estimated the SMR respectively at 3.9 (95% CI 0.5-14.2) and 2.08 (CI not given). On the contrary, three incidence studies (6,7,11) did not find any case of lymphoma in DS. The same Nordic study cited above (1) that found an SMR of 3.9 for lymphomas found an SIR of 1, indicating no difference in incidence with the general population, whereas a UK study found an elevated SIR (2.7; 95%CI: O.3-2.6) (5). Interestingly, in the studies where sex is reported, the great majority of cases are males, as in our study.

As immune deficiency is a well-recognized risk factor for lymphomas, DS, with its associated immune deficiency (28), is theoretically a risk for solid hemato-poietic tumors. The difference between most incidence studies compared with mortality studies could be

Table 3. *Comparison of SMRs and SIRs between the present study and selected other studies*

	Present study		Hill et al. 2003 [3]		Hermon et al. 2001 [6]		Oster et al. 1975 [7]	Holland et al. 1962 [25]	Boker et al. 2001, 2002 [4,5]	Hasle et al. 2000 [10]	Goldacre et al. 2004	Patja et al. 2006	Sullivan et al. 2007
Cause of death (ICD-9 codes)	Obs	SMR (95% CI)	SMR (95% CI)	SIR (95% CI)	SMR (95% CI)	SIR (95% CI)	SMR (95% CI)	SMR (95% CI)	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)
All malignant neoplasms	74	2.6 (2.0-3.2)	3.9 (1.9-5.0)	1.7 (1.3-2.1)	1.87 (1.21-2.76)	1.27 (0.86-1.82)	3.39§ (NA) 1.35‖ (NA)	---	1.33¶ (0.77-2.12) 4.67** (1.90-9.60)	1.20 (0.92-1.55)	2.7 (1.80-3.90)	0.9 (0.7-1.1)	1.1 (0.68-1.68)
Lip, oral cavity, pharynx (140-149)	0	0.0 (0.0-6.4)	---	---	---	---	---	---	---	0.00 (0.00-2.88)		0.0 (0.0-2.6)	
Digestive organs and peritoneum (150-159)	8	1.4 (0.6-2.8)	---	---	---	---	---	---	---	0.61 (0.17-1.57)		1.3 (0.6-2.2)	
Colon (153)	1	0.6 (0.0-3.4)	3.3 (0.7-9.6)	2.1 (0.6-5.3)	---	---	---	---	---	0.89 (0.10-3.23)	3.1 (0.4-11.1)	1.5 (0.4-3.9)	
Liver (155)	5	5.6 (1.8-13.1)	7.2 (0.9-26.1)	6.0 (1.2-17.5)	---	---	---	---	---	---		2.4 (0.1-13.2)	
Gallbladder (156)	0	0.0 (0.0-26.4)	8.2 (1.0-29.6)	---	---	---	---	---	---	---		6. (0.7-21.6)	13.56 (0.34-75.6)
Respiratory and intrathoracic organs (160-165)	3	0.5 (0.0-1.4)	---	---	---	---	---	---	---	0.20 (0.00-1.12)		0.0 (0.0-0.9)	
Nasal, larynx (160-161)	0	0.0 (0.0-18.6)	---	---	---	---	---	---	---	---			
Trachea, bronchus, lung (162)	3	0.5 (0.0.1-1.5)	---	---	---	---	---	---	---	0.24 (0.00-1.32)			

Cause of death (ICD-9 codes)	Obs	Present study SMR (95% CI)	Hill et al. 2003 [3] SMR (95% CI)	Hill et al. 2003 [3] SIR (95% CI)	Hermon et al. 2001 [6] SMR (95% CI)	Hermon et al. 2001 [6] SIR (95% CI)	Oster et al. 1975 [7] SMR (95% CI)	Holland et al. 1962 [25] SMR (95% CI)	Boker et al. 2001, 2002 [4,5] SIR (95% CI)	Hasle et al. 2000 [10] SIR (95% CI)	Goldacre et al. 2004 SIR (95% CI)	Patja et al. 2006 SIR (95% CI)	Sullivan et al. 2007 SIR (95% CI)
Bone, connective tissue, skin, breast (170-176)	8	1.5 (0.7-3.0)	---	---	---	---	---	---	---	---			
Bone and cartilage (170)	2	6.0 (0.7-21.7)	---	---	---	---	---	---	---	---		2.1 (0.1-11.9)	
Skin (172-173)	2	2.3 (0.3-8.1)	---	---	---	---	---	---	---	0.25 (0.03-0.89)			
Breast (174-175)	2	0.6 (0.1-2.1)	---	0.5 (0.1-1.4)	0.62 (NS)	---	---	---	---	0.00 (0.00-0.41)		0.4 (0.1-0.8)	
Genitourinary organs (179-189)	3	1.0 (0.2-2.8)	---	---	---	---	---	---	---	---			
Testis (186)	2	12.5 (1.5-45.1)	25.2 (3.0-90.9)	3.7 (1.0-9.4)	8.40 (NS)	3.46 (NA)	---	---	---	1.86 (0.50-4.77)	12.0 (2.5-35.6)	4.8 (1.8-10.4)	1.94 (0.05-10.83)
Ovary and other uterine adnexa (183)	0	0.0 (0.0-4.7)			4.05 (NS)	3.83 (NA)	---	---	---	1.97 (0.40-5.77)		0.5 (0.0-3.0)	
Bladder (188)	1	3.9 (0.1-21.9)	---	---	---	---	---	---	---	1.69 (0.34-4.93)		0.0 (0.0-2.9)	
Malignant neoplasms of other and unspecified sites (190-199)	8	2.1 (0.9-4.0)	---	---	---	---	---	---	---	---			
Brain (191)	4	2.2 (0.6-5.7)	---	0.7 (0.1-2.4)	---	---	---	---	---	0.30 (0.00-1.68)		0.4 (0.0-1.3)	1.6 (0.04-8.92)
Without specification of site (199)	3	2.1 (0.4-6.0)	---	0.6 (0.1-3.2)	---	---	---	---	---	3.27 (0.66-9.56)		0.0 (0.0-4.5)	

Cause of death (ICD-9 codes)	Obs	Present study SMR (95% CI)	Hill et al. 2003 [3] SMR (95% CI)	Hill et al. 2003 [3] SIR (95% CI)	Hermon et al. 2001 [6] SMR (95% CI)	Hermon et al. 2001 [6] SIR (95% CI)	Oster et al. 1975 [7] SMR (95% CI)	Holland et al. 1962 [25] SMR (95% CI)	Boker et al. 2001, 2002 [4,5] SIR (95% CI)	Hasle et al. 2000 [10] SIR (95% CI)	Goldacre et al. 2004 SIR (95% CI)	Patja et al. 2006 SIR (95% CI)	Sullivan et al. 2007 SIR (95% CI)
Malignant neoplasms of lymphatic and hematopoeitic tissue (200-208)	44	10.3 (7.5-13.9)	---	9.1 (6.4-12.4)	---	---	---	---	---	---			
Lymphomas (200-202)	6	3.7 (1.3-8.0)	3.9* (0.5-14.2)	1.0* (0.1-3.5)	2.08* (NS)	---	---	---	---	0.00* (0.00-2.13)	2.7 (0.3-9.6)	0.6 (0.1-2.3)	
Lymphoid leukemia (204)	23	27.6 (17.5-41.4)	33.2† (23.1-46.2)	24.2 (15.2-36.6)	13.04† (6.51-23.34)	17.26† (0.96-29.61)	2† cases significantly more than expected	17.95† (S)	6.7¶ (0.7-24.2) 60.0** (12.1-175.3)	24.36 (14.9-37.6)	22.2 (10.9-40.6)		
Myeloid leukemia (205)	2	2.2 (0.3-7.9)	---	28.2‡ (15.7-48.3)	---	---	---	---	3.0¶ (0.0-16.6) 4.90** (0.06-27.27)	20.28 (10.5-35.4)	17.2 (5.5-40.9)		
Other specified leukemia (207)	1	51.1 (1.3-285.0)	---		---	---	---	---	---	---			
Leukemia of unspecified cell type (208)	12	25.4 (13.1-44.3)	---	33.3 (0.8-185.6)	---	---	---	---	12.0¶(0.2-67.0) 130.4** (26.2-381.1)	1.93 (0.03-10.8)			
Tobacco related cancers	13	1.1 (0.6-1.8)	---	---	---	---	---	---	---	---			

Obs. Number of observed deaths among the Down syndrome population, California, January 1, 1988 – December 31, 2002; * Non Hodgkin lymphomas only (202); † All leukemia (204-208); ‡ Nonlymphocytic acute leukemia; § Period 1949-1959; || Period 1960-1971; ¶ Period before 1979; ** Period 1979-1995; NS. Not significant (p>0.05), exact p-value not given; S. Significant (p<0.05), exact p-value not given
NA. Not available

explained by a worse prognosis. Many tumors are mainly treated by surgery in the general population, as well as in DS. However, lymphomas and leukemias principally require chemotherapy and radiotherapy treatments. In patients with DS, compliance due to intellectual deficiency may pose a problem, and a different response and toxicity due to constitutional biological characteristics may be factors as well.

We also found an excess number of deaths due to liver cancer, and this is in agreement with Hill et al. (1). Because institutionalized individuals might be more exposed to transmissible agents, the elevated probability of transmission and infection with hepatitis B and C viruses (29), which are known liver carcinogens (30), might explain an increased incidence of liver cancer among persons with DS.

Testicular cancer was associated with a 12.5-fold excess of mortality. This result is in agreement with published studies (1,4-7,11,21). Cryptorchidism, associated with an increased risk of transformation of the germ cells, and higher gonadotropins, such as Follicle-Stimulating Hormone concentrations, were suggested as possible explanations for the high rate of testis cancer (31). Smucker et al (32) suggest a possible excess of dysgerminoma in females with DS. Similarly, Satgé et al (31) suggested that some genes, for example Ets-2 on chromosome 21, could favor germ cell tumors.

Several authors (6-11) discussed the likelihood of a lower risk of mortality or incidence associated with solid tumors. This is in agreement with the lower PMR for neoplasms (other than leukemias) and solid tumors observed by Scholl et al (24) and the low SMORs reported by Yang et al (21). In our study, no cancer deaths related to lip, oral cavity, or pharynx were found, a result also reported by Hasle et al (11).

The lower than expected breast cancer mortality reported here has been seen in other studies as well (1,4,6,11,33). This apparent protective effect against breast cancer may be explained in part by the hypo-oestrogeny in DS females from fetal life onwards (34).

The low colon cancer mortality is consistent with Hasle et al (11) and Yang et al (21) but disagrees with the results of Hill et al (1) and Goldacre et al (5) who reported an increase. A review on digestive tumors in DS did not find conclusive evidence of differences with general population rates (35).

Lower mortality rates associated with some solid tumors might be expected based on the probable presence of tumor-suppressor genes on chromosome 21 (36,37). The increase due to the trisomy of some products issued from these tumor suppressor genes could induce a decrease of the incidence of solid tumors.

Other cancer sites, such as bone and cartilage, skin, brain and unspecified, were associated with higher mortality rates and contributed to the overall excess of malignant neoplasms in DS. The increases of deaths related to skin and brain cancers were not significant and contradicted the results from Hasle et al (10) and Hill et al (1). This may be the first time that an estimation of the mortality rate from bone and cartilage cancer is provided for persons with DS, the result being a 6-fold increase compared with the general population.

To our knowledge, this is the first study providing reliable site-specific cancer mortality estimates in a large, well-defined DS population. The detailed information on the underlying causes of deaths is a strength of our study. It permitted comparison of site-specific cancer mortality rates within the DS population with those of the general population. Another strength of this work is the use of identical sources of mortality information to determine causes of death in the DS group and in the comparison group (California general population), thus minimizing the effect of various potential sources of reporting bias on the resulting SMRs .

This study has several limitations. First, although it is believed that the majority of persons with DS are enrolled in the State system, this is difficult to verify directly and we do not know the percentage of coverage of the DS population by the DDS. This limits the generalization of our results to all persons with DS. Second, despite being the largest cohort study available on this topic with substantial follow-up, the cohort is quite young by comparison with the California general population, and the small numbers of cases observed for many cancer sites decreased the power of our study to detect significant differences between the DS and general populations. Lastly, we did not have information on other exposures such as infectious diseases prevalence, alcohol and tobacco use, or diet.

Differences in lifestyles exist between the DS and general populations, which could explain in part why the mortality due to specific cancers is higher or lower in DS. Information on smoking, alcohol or diet habits would facilitate the identification of the causes of cancers in DS. Data on the residence type, especially institutionalization, may also be useful to clarify factors associated with cancers among this population.

CONCLUSIONS

This study confirms previously reported patterns of cancer deaths within the DS population, identifying

clear site-specific differences in mortality rates compared with the general population. An excess of deaths due to lymphatic and hematopoietic neoplasms, especially leukemia and lymphoma, was observed in the DS population. Mortality rates associated with several solid tumours were lower than expected. Lifestyle factors and habits might partly explain these results, but the genetic information on chromosome 21 could also play a role. Further research on these issues would increase our understanding of cancer pathogenesis.

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REFERENCES

1. Hill DA, Gridley G, Cnattingius S, Mellemkjaer L, Linet M, Adami HO, et al. Mortality and cancer incidence among individuals with Down syndrome. Arch Intern Med 2003;163(6):705-11.
2. Boker LK, Blumstein T, Sadetzki S, Luxenburg O, Litvak I, Akstein E, et al. Incidence of leukemia and other cancers in Down syndrome subjects in Israel. Int J Cancer 2001;93(5):741-4.
3. Boker LK, Merrick J. Cancer incidence in persons with Down syndrome in Israel. Downs Syndr Res Pract 2002;8(1):31-6.
4. Hermon C, Alberman E, Beral V, Swerdlow AJ. Mortality and cancer incidence in persons with Down's syndrome, their parents and siblings. Ann Hum Genet 2001;65(Pt 2):167-76.
5. Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. Arch Dis Child 2004;89(11):1014-7.
6. Patja K, Pukkala E, Sund R, Iivanainen M, Kaski M. Cancer incidence of persons with Down syndrome in Finland: a population-based study. Int J Cancer 2006;118(7):1769-72.
7. Sullivan SG, Hussain R, Glasson EJ, Bittles AH. The profile and incidence of cancer in Down syndrome. J Intellect Disabil Res 2007;51(Pt 3): 228-31.
8. Satgé D, Sasco AJ, Lacour B. Are solid tumours different in children with Down's syndrome? Int J Cancer 2003;106(2):297-8.
9. Satgé D, Sommelet D, Geneix A, Nishi M, Malet P, Vekemans M. A tumour profile in Down syndrome. Am J Med Genet 1998;78(3):207-16.
10. Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. Lancet Oncol 2001;2(7):429-36.
11. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355(9199):165-9.
12. Day SM, Strauss DJ, Shavelle RM, Reynolds RJ. Mortality and causes of death in persons with Down syndrome in California. Dev Med Child Neurol 2005;47(3):171-6.
13. Leonard S, Bower C, Petterson B, Leonard H. Survival of infants born with Down's syndrome: 1980-96. Paediatr Perinat Epidemiol 2000;14(2): 163-71.
14. Practice Management Information Corporation., United States. Health Care Financing Administration. ICD-9-CM: international classification of diseases, 9th revision, clinical modification, fifth edition, color coded, volumes 1 and 2. Hospital ed. Los Angeles, CA: PMIC (Practice Management Information Corp.), 2000.
15. California Department of Developmental Services. Client Development Evaluation Report (CDER). Sacramento, CA: Calif Dept Devl Serv, 1986.
16. Citygate Associates. Independent evaluation of the Department of Developmental Services—community placement practices: final technical report. Sacramento, CA: Citygate Associates, 1998.
17. Eyman RK, Call TL. Life expectancy of persons with Down syndrome. Am J Ment Retard 1991;95(6):603-12.
18. State of California, Department of Health Services, Center for Health Statistics, Office of Health Information and Research. Annual electronic death records, 1988-2002.
19. State of California, Department of Finance. Race/ Ethnic Population with Age and Sex Detail, 1970-2040. Sacramento, CA: Dept Finance, 1988.
20. Kahn HA, Sempos CT, Kahn HA. Statistical methods in epidemiology. New York: Oxford Univ Press, 1989.
21. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 2002;359(9311):1019-25.

22. Oster J, Mikkelsen M, Nielsen A. Mortality and life-table in Down's syndrome. Acta Paediatr Scand 1975;64(2):322-6.
23. Holland WW, Doll R, Carter CO. The mortality from leukaemia and other cancers among patients with Down's syndrome (mongols) and among their parents. Br J Cancer 1962;16:177-86.
24. Scholl T, Stein Z, Hansen H. Leukemia and other cancers, anomalies and infections as causes of death in Down's syndrome in the United States during 1976. Dev Med Child Neurol 1982;24 (6): 817-29.
25. Hattori M, Fujiyama A, Taylor TD, Watanabe H, Yada T, Park HS, et al. The DNA sequence of human chromosome 21. Nature 2000;405(6784): 311-9.
26. Gurbuxani S, Vyas P, Crispino JD. Recent insights into the mechanisms of myeloid leukemogenesis in Down syndrome. Blood 2004; 103(2):399-406.
27. Barber R, Spiers P. Oxford Survey Of Childhood Cancers; Progress Report II. Mon Bull Minist Health Public Health Lab Serv 1964;23:46-52.
28. Nespoli L, Burgio GR, Ugazio AG, Maccario R. Immunological features of Down's syndrome: a review. J Intellect Disabil Res 1993;37 (Pt 6):543-51.
29. Vellinga A, Van Damme P, Meheus A. Hepatitis B and C in institutions for individuals with intellectual disability. J Intellect Disabil Res 1999;43 (Pt 6):445-53.
30. International Agency for Research on Cancer. IARC Monogr Eval Carcinog Risks Hum Volume 59: Hepatitis viruses. Geneva: WHO, 1994;1-286.
31. Satgé D, Sasco AJ, Cure H, Leduc B, Sommelet D, Vekemans MJ. An excess of testicular germ cell tumours in Down's syndrome: three case reports and a review of the literature. Cancer 1997;80(5):929-35.
32. Smucker JD, Roth LM, Sutton GP, Hurteau JA. Trisomy 21 associated with ovarian dysgerminoma. Gynecol Oncol 1999;74(3):512-4.
33. Satge D, Sasco AJ, Pujol H, Rethore MO. (Breast cancer in women with trisomy 21). Bull Acad Natl Med 2001;185(7):1239-52; discussion 1252-4.
34. Cento RM, Ragusa L, Proto C, Alberti A, Romano C, Boemi G, et al. Basal body temperature curves and endocrine pattern of menstrual cycles in Down syndrome. Gynecol Endocrinol 1996;10(2): 133-7.
35. Satgé D, Sasco AJ, Vekemans MJ, Portal ML, Flejou JF. Aspects of digestive tract tumours in Down syndrome: a literature review. Dig Dis Sci 2006;51(11):2053-61.
36. Lee EB, Park TI, Park SH, Park JY. Loss of heterozygosity on the long arm of chromosome 21 in non-small cell lung cancer. Ann Thorac Surg 2003;75(5):1597-600.
37. Yamamoto N, Uzawa K, Miya T, Watanabe T, Yokoe H, Shibahara T, et al. Frequent allelic loss/imbalance on the long arm of chromosome 21 in oral cancer: evidence for three discrete tumour suppressor gene loci. Oncol Rep 1999;6(6):1223-7.
38. International Agency for Research on Cancer. IARC Monogr Eval Carcinog Risks Hum Volume 83. Tobacco smoke and involuntary smoking. Lyon: IARC Press 2004;83:1-1438.