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## Cancer mortality in Down syndrome in California

Annie J Sasco, MD, DrPH<sup>1</sup>, Steven M Day, PhD, FAACPDM<sup>2</sup>, Nicolas Voirin, PhD<sup>3</sup>, David J Strauss, PhD, FASA<sup>2</sup>, Robert M Shavelle, PhD, FAACPDM<sup>2</sup> and Daniel Satgé, MD, PhD<sup>4</sup>

<sup>1</sup>*Epidemiology for Cancer Prevention, Inserm CRE U 897, Bordeaux, France,*

<sup>2</sup>*The Life Expectancy Project, San Francisco, California, United States,*

<sup>3</sup>*Université de Lyon, Laboratoire de Biométrie et Biologie Evolutive, Equipe Epidémiologie et Santé Publique, Lyon, France and* <sup>4</sup>*Laboratory of Pathology, Centre Hospitalier, Tulle, France*

**Abstract:** Cancer in Down syndrome (DS) is characterized by a well known and marked excess of leukaemia whereas few cohort studies are available on solid tumours 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 annual evaluations from the California Department of Developmental Services over the period 1988-2002 were followed. Methods: Cancer mortality in DS was compared with the Californian general population using age-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 at 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)]. 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 tumours 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 tumour profile in DS.

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

**Correspondence:** Annie J Sasco, MD, DrPH, Director, Team of Epidemiology for Cancer Prevention, Inserm CRE U 897, Victor Segalen Bordeaux 2 University, 146 rue Leo Saignat, 33076 Bordeaux cedex, France. Office phone ++33 5 57 57 45 12. Cell phone ++33 6 74 25 43 93. Fax ++33 5 56 24 00 82. E-mail: [Annie.Sasco@isped.u-bordeaux2.fr](mailto:Annie.Sasco@isped.u-bordeaux2.fr)

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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 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 tumours. These two results were also observed by others (6,7, 10,11). The increase in life expectancy in Down syndrome (DS) patients (12,13) may lead to changes in the overall pattern of cancer mortality as more persons live to adulthood.

As results on mortality in past studies have differed by cancer site and are possibly contradictory, the objective of this study was to examine in detail the mortality due to 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 have been described in detail in Day et al (12).

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 to 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 time period 1988-2002.
- 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 (26). 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 and SD 14.8 and 14.9 years. 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 all malignant neoplasms. A statistically significant increase of cancer mortality (SMR 2.6, 95% CI 2.0-3.2) was found in persons with DS compared with the Californian 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 and not significant (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 from lip, oral cavity or pharynx sites was reported. A decrease in tobacco-related cancers (27) was observed, though this was not statistically significant. A similar decrease in deaths due to tumours 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 statistically significant 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, though the differences were not statistically significant.

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

## 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 which 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 tumours 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 a non-significant 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 but non-significant SIR (2.7; 95%CI: 0.3-2.6) (5). Interestingly, in the studies wherein sex is reported, the great majority of cases are males, as in our study.

Since immune deficiency is a well recognized risk factor for lymphomas, DS, with its associated immune deficiency (28), is theoretically a risk for solid hematopoietic tumours. The difference between most incidence studies compared to mortality ones could be explained by a worse prognosis. Many tumours are treated mainly by surgery in the general population as well as in DS. However, lymphomas and leukemias require principally chemotherapy and radiotherapy treatments. In patients with DS, compliance due to intellectual

deficiency may pose a problem, and different response and toxicity due to constitutional biological characteristics may also be factors.

An excess number of deaths due to liver cancer was also found, 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 (FSH) 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, Satge et al (31) suggested that some genes, for example Ets-2 on chromosome 21, could favor germ cell tumours.

Several authors (6-11) discussed the likelihood of a lower risk of mortality or incidence associated with solid tumours. This is in agreement with the lower PMR for neoplasms (other than leukemias) and solid tumours 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 women from fetal life onwards (34).

The non-significantly 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 a non-significant increase. A review on digestive tumours in DS did not find conclusive evidence of differences with general population rates (35).

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

Other cancer sites such as bone and cartilage, skin, brain and unspecified were found 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 non-statistically significant increase compared to the general population.

To our knowledge, this is the first study providing reliable site-specific cancer mortality estimates in a 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 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 pattern 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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