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A Lower Risk of Dying from Urological Cancer in Down Syndrome: Clue for Cancer Protecting Genes on Chromosome 21

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Key Words
Bladder cancer · Chromosome 21 · Down syndrome · Nephroblastoma · Renal cancer · Tumor suppressor gene · Urinary tract

Abstract
Objective: It was the aim of this study to evaluate the risk of dying from bladder and kidney cancer in persons with Down syndrome (DS), as compared with the general population. ***Methods:*** Using data of the French national mortality statistics (INSERM) during a 21-year period, 1979–1999, we compared the observed number of deaths from renal and bladder cancer in DS subjects with the expected number of deaths from these cancers. The expected number of deaths was calculated taking into account the prevalence of DS at birth and the life expectancy of persons with DS, assuming the risk was identical to the one of the general population. ***Results:*** A significant 6-fold decreased risk of dying from urological cancer was found in persons with DS, with 5 cases observed, while 30 were expected. The relative risk of dying was 0.27 for bladder cancer ($p = 0.0017$) and 0.06 for kidney cancer ($p < 0.0001$). Other mortality studies provided similar values. ***Conclusions:*** Children and adults with DS have a decreased risk of dying from urological neoplasms. Genes on chromosome 21 could play a protective role against urological cancer.

Introduction

The life expectancy of persons with Down syndrome (DS, or trisomy 21) has greatly progressed during the last decades. The median age at death increased from 25 years in 1963 to 49 years in 1993 [1]. These patients now commonly reach the age when most cancers are diagnosed in the general population. Epidemiological studies have shown that cancer occurs in DS patients as frequently as in the general population [2, 3]. Nevertheless, the tumor profile of DS [4] corresponds to a very important excess of leukemia, with an increased risk of testicular tumors, while the frequency of many solid tumors, particularly in adults, is decreased. However, the relative importance of urological malignancies is not known. The aim of this study is to evaluate the risk of dying from kidney and bladder cancer in persons with DS.

Method

A mortality study of urological cancer in DS was conducted in the French population over a 21-year period, from 1979 to 1999, using data of the national mortality statistics (Department CepiDC) of the Institut National de la Santé et de la Recherche Médicale (INSERM, French NIH). The INSERM data cover the whole French population, i.e. 60 million persons, and register all deaths in the country, i.e. around 520,000 each year. We followed the

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methodology used for the evaluation of breast cancer mortality in a previous study [5]. The mortality statistics of INSERM used is limited to the French continental population (in the metropole). The observed number of deaths due to urological cancer in persons with DS was obtained by linking the international classification of disease (ICD) codes for the cause of death, bladder cancer (ICD-9: 188.0 to 9) and renal cancer (ICD-9: 189.0, 8, 9), to the code for comorbidity, DS (ICD-9: 758). The ICD codes for bladder and kidney cancers as well as for DS did not change during the period of the study. The observed number of deaths in people with DS was tabulated for each sex and age combination. The expected number of deaths from urological cancer was calculated separately for each sex and for each 10 years of age category using the mortality data in the general population and assuming that the specific cancer mortality rate is the same for DS and for the general population, after taking into account the evaluation of the population at risk, the prevalence of DS at birth and the life expectancy of persons with DS. In France, during the period 1978–2000, bladder cancer incidence increased from 7,184 to 10,771 cases, and renal cancer incidence increased from 3,689 to 8,293 annual cases. Similarly, during the same period, bladder cancer mortality increased from 3,596 to 4,558 deaths, and renal cancer mortality increased from 2,393 to 3,607 deaths [6]. The cumulative incidence of DS at birth has been estimated at 13 for 10,000 births (i.e. 1 for every 769 births) on the basis of European epidemiological data during the years 1974–1988 [7]. Since French life expectancy tables are not available for persons with DS, we chose to work with the data given by the Canadian population of British Columbia [8], as previously [5]. For old ages (>65 years), we used the data from an analysis of life expectancy of persons with DS in California [9]. The expected number of deaths for each type of cancer was obtained by multiplying the number of deaths in the general population by the cumulative incidence of DS at birth and for every 10 years of age category, by the percentage of persons with DS still alive. Observed and expected values were compared by computation of a standardized mortality ratio and 95% confidence intervals (CIs) determined under the assumption that the observed numbers of deaths in DS followed a Poisson distribution (the computed package SAS was used). If the CIs excluded unity, the standardized mortality ratio was considered to be statistically significant at the 0.05 level.

Results

During the period 1979–1999, 146,243 deaths from urological cancer (86,340 cancers of the bladder and 59,903 cancers of the kidney) were registered in the French INSERM mortality statistics. We observed 4 deaths due to bladder cancer, while 15.02 were expected, and 1 death due to kidney cancer, while 15.76 were expected. If the risk of dying from urological cancer would have been the same for DS, we should have found 30 deaths of persons with DS during this period. In fact, only 5 deaths were observed. This indicates a highly significant 6-fold decreased risk of dying from a urological cancer in DS. It resulted from a nearly 4-fold reduced risk of dying from bladder cancer and a nearly 15-fold reduced risk of dying from kidney cancer (table 1).

Table 1. Standardized mortality ratio (SMR) for bladder and kidney cancer among persons with DS in France 1979–1999

Sites of neoplasms	Observed deaths	Expected deaths	SMR	95% CI	p value
Bladder					
Men	3[1]	12.80	0.23	0.05–0.68	0.0024
Women	1[2]	2.21	0.45	0.01–2.51	0.7004
Total	4	15.02	0.27	0.07–0.68	0.0017
Kidney					
Men	1[3]	10.83	0.09	0.00–0.51	0.0005
Women	0	4.92	0.00	0.00–0.75	0.0145
Total	1	15.76	0.06	0.00–0.35	0.0000
Both sites					
Men	4	23.64	0.17	0.05–0.43	0.0000
Women	1	7.14	0.14	0.00–0.78	0.0128
Total	5	30.79	0.16	0.05–0.38	0.0000

[1] One man, age group 55–64 years, and 2 men, age group 65–74 years. [2] One woman, age group 55–64 years. [3] One man, age group 45–54 years.

Discussion

Our results indicate that mortality from bladder and kidney cancers is importantly decreased in persons with DS. Strengths of our study include (1) a large reference population of 60.10 million persons corresponding to the entire French continental population, i.e. a study done on a national scale. (2) The long period of 21 years covered by the study. (3) A single source of mortality information for both the studied population and the reference population. On balance, we believe our study offers compelling evidence of an importantly decreased risk of death from urological cancers in persons with DS.

Other studies [1, 10–13] (table 2) provided similar values of death deficit related to urological cancer. In the largest study [1], deaths from bladder cancer were 5-fold less frequent (standardized mortality odds ratio at 0.20) and deaths from renal tumors were 12-fold less frequent (standardized mortality odds ratio at 0.08). However, this study has the weakness of using proportional mortality odds ratios instead of standardized mortality ratios. Globally, epidemiological studies on cancer incidence [2, 3, 13–15] (table 3) also suggest a reduced risk.

Table 2. Epidemiological studies (including our study) reporting data on mortality from urological cancer in persons with DS

Authors	Country and period	Observed deaths	Expected deaths	SMR
Holland et al. [10], 1962	UK: 1946–1959	0	NA	0
Oster et al. [11], 1975	Denmark: 1960–1972	0	NA	0
Scholl et al. [12], 1982	USA: 1976	0	3.19	0
Yang et al. [1], 2002	USA: 1983–1997	bladder: 8	NA	0.20 (0.10–0.40)[1]
		kidney: 7	NA	0.08 (0.04–0.17)[1]
Hill et al. [13], 2003	Denmark and Sweden: 1965–1993	0	NA	0
Satgé et al., 2007	France: 1979–1999	bladder: 4	14.50	0.28 (1.1–10.2)
		kidney: 1	14.77	0.07 (0.0–5.6)

Figures in parentheses are 95% CIs. SMR = Standardized mortality ratio; NA = not available.
[1] Standardized mortality odds ratios.

Table 3. Epidemiological studies on urological cancer incidence in persons with DS

Authors	Country and period	Observed	Expected	SIR
Hasle et al. [2], 2000	Denmark: 1960–1994	bladder: 3[1]	1.78	1.69 (0.34–4.93)
		kidney: 1	1.19	0.84 (0.01–4.66)
Boker and Merrick [14], 2002	Israel: 1948–1995	bladder: 0	NA	0
		kidney: 0	NA	0
Hill et al. [13], 2003	Denmark and Sweden: 1965–1993	bladder: 0	NA	0
		kidney: 1	NA	0.6 (0.1–3.4)
Patja et al. [3], 2006	Finland: 1978–1986	bladder: 0	1.3	0
		kidney: 1	2	0.5 (0.0–2.8)
Sullivan et al. [15], 2007	Australia: 1982–2001	bladder: 0	NA	0
		kidney: 0	NA	0

Figures in parentheses are 95% CIs. SIR = Standardized incidence ratio; NA = not available.
[1] Three cancers, but only 2 patients.

Yet, a nonsignificantly raised standardized incidence ratio of 1.69 was established in a Danish study. However, 2 of the 3 cases of bladder cancer recorded were from the same patient [2]. None of the 4 other studies on cancer incidence conducted in Israel [14], Denmark and Sweden [13], Finland [3] and Australia [15] recorded any case of bladder cancer. Only 12 cases of bladder cancer have been shown in adults with DS in the reports we identified [1, 2, 16, 17]. Similarly, epidemiological studies on incidence indicate a 2-fold reduced risk of having renal cancer [2, 3, 13].

Taking together all the available data, we see that the risk of dying from urological cancer is importantly reduced, approximately 6 fold according to our estimation, whereas the risk of urological cancer is only reduced 2 fold at most. This apparent deficit could be due to methodological biases and, in particular, to a lack of ascertainment of cancer death in the DS population. Another potential explanation could be that persons with DS with a urological cancer have a better outcome compared with persons in the general population. This could be due to a higher relative frequency of less aggressive histological type of tumors compared with persons without DS.

Bladder Cancer

Persons with intellectual disabilities smoke tobacco much less frequently than persons in the general population [18]. They are not exposed to occupational carcinogens and do not use phenacetin in excess. This importantly reduced exogenous exposure to known bladder carcinogens [19] fits well with the reduced mortality from

bladder cancer in persons with DS. However, since the observed reduction in mortality is large, we suspect that other factors, particularly endogenous (genetic) ones, may be involved.

Currently, it is estimated that around 300 genes map to chromosome 21 [20]. Any gene protecting against cancer situated on chromosome 21 will be theoretically more efficient in persons with DS through the gene dosage effect [14], since these subjects have 3 copies of the gene. Cytogenetics of bladder cancer do not point to chromosome 21 [19]. However, an overexpression of genes such as ANA, TIAM1, ETS2, IFNAR, COL18A1 and CAR has been suggested to exert a protective effect against various cancers [5, 21, 22]. ANA impairs serum-induced cell cycle progression from the G0/G1 to the S phase. TIAM1 inhibits carcinoma metastases by acting on cell-cell adhesion mechanisms. ETS2, when overexpressed, inhibits the transcription of the RAS oncogene. The IFNAR gene, encoding type 1 interferon receptor, represses the tumorigenic phenotype and is particularly active at early stages of cancer development. Endostatin, the product of the COL18A1 gene, is a powerful antiangiogenic factor [for discussion, see ref. 5, 21]. The coxsackie and adenovirus receptor gene which codes for a transmembrane protein involved in cellular adhesion is particularly expressed in urothelial tumors and is often downregulated in transitional cell carcinoma [22].

Renal Cancer

Wilms' tumor, one of the most frequent solid tumors in children [23], has been reported only 5 times in DS [4, 24, 25]. Nephrogenic remnants have been described only once in an infant with DS [26]. Remarkably, renal hypoplasia is a frequent urological anomaly in DS [27, 28], whereas genetic conditions characterized by visceral overgrowth such as Beckwith-Wiedemann syndrome or Sotos syndrome are at a higher risk of developing Wilms' tumor [29]. Monosomy of chromosome 21 observed on Wilms' tumor tissue [30] supports the idea that genes on this chromosome could have an adverse effect on Wilms' tumor development.

In adults with DS, reduced use of tobacco should lower the risk of having renal cancer. However obesity, which is more frequent in persons with DS and dialysis used for renal disease, also more common in DS, enhance the risk of renal cancer. In the literature, we found only 10 cases of renal cancer reported in adults with DS [1–3, 13]. The constitutional upregulation of the Down syndrome critical region 1 gene which has a probable antiangiogenic effect on vascular endothelial growth factor [31] overexpressed throughout clear-cell renal carcinoma [32] could significantly inhibit tumor growth in persons with DS.

Considering possible methodological biases in our study, we do not think that a lack of diagnosis of urological cancer is likely to explain the greatly reduced number of cases we found. Bladder and kidney tumors give functional symptoms and abdominal masses at an advanced stage. Additionally, transabdominal ultrasonography is available in most institutions [19]. We do not believe that failure to register DS or tumors on death certificates could be significantly biasing our results since, using the same methodology, we found that leukemia accounted for 60.6% of deaths in DS due to cancer [5, 33], a value conformed to what is known [2, 9]. We are aware of a methodological weakness of our work since we evaluated life expectancy in persons with DS using data from Canada and the USA rather than from France. Nonetheless, as the medical care of persons with intellectual disabilities is similar in France and North America we do not feel that this could be responsible for important errors in estimating expected cases.

Conclusions

Our study and the current literature indicate a decreased risk of dying from bladder and kidney cancer in persons with DS. Following this observation, studies on urological cancer incidence in persons with DS should be encouraged. A protective role of genes on chromosome 21 against urological cancer should be considered while searching new therapeutic agents against these neoplasias.

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