Original articles

The French Wilms' tumour study: no clear evidence for cancer prone families

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Abstract

Wilms' tumour of the kidney is known to occur in Beckwith-Wiedemann syndrome. It has also been described in four cancer prone families displaying Li-Fraumeni syndrome but it is not usually considered to be part of this syndrome. In order to detect particular familial cancer aggregations associated with this tumour, we studied the cancer incidence and mortality among relatives of the 501 Wilms' tumour patients in the French Wilms' Tumour Study. We found no familial association with breast cancer or soft tissue sarcomas which are the most common cancers in the Li-Fraumeni syndrome. However, we found two significant familial associations of Wilms' tumour with bone cancers on the one hand and with brain tumours on the other hand. These associations could reflect a small proportion of families segregating for some susceptibility gene. This should then be confirmed at the molecular level.

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Wilms' tumour (WT) of the kidney (or nephroblastoma) is an embryonal tumour affecting young children, usually before the age of 10.¹ Since there are several similar epidemiological features in retinoblastoma and Wilms' tumour (existence of both unilateral and bilateral cases with earlier age at onset for bilateral cases, familial occurrence), Wilms' tumour was thought for a long time to arise from the same mechanism as retinoblastoma which is a paradigm of childhood cancers.² Wilms' tumour was thus thought to occur after two mutations at homologous loci of a tumour suppressor gene resulting in loss of normal gene function.^{3,4} By this hypothesis, most unilateral cases are sporadic resulting from two somatic events whereas all bilateral and rare unilateral cases are the result of one inherited

(or new germline) altered gene followed by a somatic event. In fact, WT carcinogenesis seems to be more complex than previously thought. Molecular studies have shown that at least three loci are probably involved in WT carcinogenesis⁵: WT1 at 11p13 in patients displaying WAGR syndrome (Wilms' tumour, Aniridia, Genitourinary abnormalities, and mental Retardation), WT2 at 11p15.5 in patients with Beckwith-Wiedemann syndrome (multiorgan developmental abnormalities and predisposition to cancers including WT), and WT3, still unmapped and involved in a substantial amount of familial WT since linkage analyses of three families segregating for WT excluded tight linkage with 11p13 and 11p15.5.⁶⁻⁸ Furthermore, all bilateral cases being hereditary has been questioned.^{2,9,10} Non-random loss of maternal alleles at 11p15 in sporadic WT¹¹⁻¹³ and an excess of transmitting females in BWS¹⁴⁻¹⁶ suggest genomic imprinting in WT. Our recent findings using genetic epidemiological methods on the data of the French Wilms' tumour study are in agreement with this hypothesis.¹⁰ The human H19 gene, located at 11p15, monoallelically expressed,¹⁷ and whose active allele is lost in some WT,¹⁸ is a good candidate for a WT2 susceptibility gene.

Familial occurrence of WT is rare and the frequency of WT in relatives of patients is low. In the French Wilms' tumour study, frequencies of WT were estimated to be less than 0.4% in sibs, 0.06% in first cousins, and 0.04% in uncles and aunts.¹⁹

Wilms' tumour is well known to occur in Beckwith-Wiedemann syndrome or in the WAGR syndrome. It has also exceptionally been described in cancer prone families and especially in Li-Fraumeni syndrome (LFS), described as the familial aggregation of sarcomas, breast cancers, leukaemias, brain tumours, and adrenocortical carcinomas, usually occurring before the age of 45. Wilms' tumour is not considered to be part of the LFS but this remains to be confirmed, especially since four LFS families were described with a case of Wilms' tumour.²⁰⁻²³

The purpose of this study is to search for a global excess of cancers among the relatives of Wilms' tumour patients and to detect particular familial cancer aggregations suggesting an inherited susceptibility.

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Material

Between 1982 and 1989, complete family histories and clinical data were collected for 501 children with Wilms' tumour from several departments of pediatric oncology in France: 337 from the Institut Gustave Roussy in Villejuif, 56 from the Institut Curie in Paris, and 108 from other centres in France.¹⁹ Respectively, four, three, and two patients were diagnosed as having WAGR, BWS, and Drash syndrome. Familial data were obtained either by direct interview with the parents, or by a self-questionnaire given to the parents and brought back at the next visit. Family information consisted of sex, date of birth, eventual occurrence of tumours or anomalies, and eventual date and cause of death among patients' relatives including sibs, parents, grandparents, uncles, aunts, and first cousins.

Methods

Two different approaches were used to search for an excess of cancers among relatives of Wilms' tumour patients. On the one hand, we dealt with cancer mortality, and on the other with cancer incidence.

CANCER MORTALITY

Although cancer mortality is an indirect measure of the frequency of cancer, it uses good population data. French statistics for mortality^{24,25} have effectively been registered since 1945 which allows birth cohort effects to be taken into account. However, we could not confirm causes of death mentioned by persons interviewed since death certificates are anonymous in France. Subjects who were known to have cancer but had died from another cause were counted as not cancer. The expected number of cancer deaths was calculated from French statistics for each class of relatives, for each sex, for each five year age group and each one year period from 1943 to 1990. Two indicators were used to calculate expected values: (1) the Standardised Mortality Ratio (SMR) based on the number of cancer deaths in the general population: $SMR = \frac{d}{D_E}$ where d is the observed number of cancer deaths and D_E the expected number of cancer deaths based on applying the cancer mortality rates to the number of people in each of the classes; (2) the Standardised Proportional Mortality Ratio (SPMR) based on the number of cancer deaths among dead persons in the general population: $SPMR = \frac{d}{D_{EP}}$ where D_{EP} is the expected number of cancer deaths based on applying proportional cancer mortality ratio in each of the classes.

Expected and observed values were compared by a classical χ^2 test. When the expected number of cancer deaths was too small to perform a χ^2 test, the exact probability was computed using binomial distribution.

Comparison of observed and expected values was first performed for cancers of all sites. Since breast cancer is frequent and is a major feature of LFS, we also studied mor-

talities from breast cancer in our sample of relatives.

CANCER INCIDENCE

Cancer incidence is the exact measure of cancer frequency and requires knowledge of age at diagnosis which implies ascertainment of the diagnosis. Unfortunately, French incidence data²⁶ are recent and birth cohort effect cannot be taken into account. Searching for familial cancer aggregation was performed treating each family separately. For one family i , the probability P_i to have at least one affected relative before the age of 45 is:

$$P_i = 1 - \sum_{j=1}^k 1 - cr_j$$

where k is the number of relatives and cr_j the cumulative risk of subject j , according to age and sex, and given by French statistics.²⁶ The expected number of families with at least one affected relative before the age of 45 among n families is:

$$P = \sum_{i=1}^n P_i$$

Observed and expected values were compared by a classical χ^2 test. This test was performed using incidence data for all types of cancer and then for each cancer included in the Li-Fraumeni syndrome (that is, soft tissue sarcomas, breast cancer, bone cancer, brain tumours, and leukaemias). Adrenocortical carcinoma was not considered since it is too rare in the population as well as in the LFS.

Results

MORTALITY

Comparison between observed and expected numbers of cancer deaths applying the SPMR and the SMR is shown in tables 1 and 2 respectively. When using the SPMR, a significant excess is observed for grandfathers ($p < 0.001$) and for parents ($p = 0.003$). There is also an excess among fathers and aunts but this may not be significant given the number of tests performed. When using the SMR, there is a non-significant excess of cancer deaths in almost all categories of relatives. The validity of these tests will be discussed later.

INCIDENCE

The results of comparisons between observed and expected numbers of families with at least one relative diagnosed as having cancer before the age of 45 are shown in table 3. When dealing with all types of cancer, there is no excess of such families. One can even note a deficit (39 observed families versus 78 expected). There is also no excess of breast cancers, soft tissue sarcomas, or leukaemias. Our analysis, however, concludes that there is a significant association between WT and either bone cancers ($p = 0.028$) or brain tumours ($p = 0.014$). Pedigrees with relatives

Table 1 Observed and expected number of cancer deaths with the SPMR methods

	Total deaths	Observed cancer deaths	Expected cancer deaths	SPMR	Probability
Grandparents	493	172	133.1	1.29	p < 0.001
M	317	116	84.51	1.37	p < 0.001
F	176	56	48.59	1.15	p = 0.66
Aunts and uncles	162	28	19.6	1.43	p = 0.04
M	100	14	11.4	1.23	p = 0.45
F	62	14	8.2	1.71	p = 0.04
Parents	11	8	3.13	2.56	p = 0.003
M	9	6	2.32	2.59	p = 0.012
F	2	2	0.81	2.47	p = 0.164
Sibs	22	1	0.87	1.15	p = 0.588
M	12	0	0.44	0	—
F	10	1	0.43	2.33	p = 0.356
Cousins	62	5	2.58	1.94	p = 0.115
M	34	2	1.13	1.77	p = 0.312
F	28	3	1.45	2.07	p = 0.175
All relatives	850	214	159.3	1.34	p < 0.001
M	472	138	99.81	1.38	p < 0.001
F	378	76	59.49	1.28	p = 0.04

In italics: exact probability using binomial distribution.

Table 2 Observed and expected number of cancer deaths with the SMR methods

	Person years	Observed cancer deaths	Expected cancer deaths	SMR	Probability
Grandparents	54 470	172	150.14	1.15	p = 0.08
M	25 705.5	116	97.98	1.18	p = 0.07
F	28 764.5	56	52.42	1.08	p = 0.66
Aunts and uncles	83 541.5	28	24.8	1.13	p = 0.52
M	43 534	14	15.48	0.9	p = 0.71
F	39 917.5	14	9.32	1.5	p = 0.13
Parents	11 858	8	7.45	1.07	p = 0.467
M	6146	6	5.29	1.7	p = 0.435
F	5712	2	2.16	0.9	p = 0.635
Sibs	11 669	1	0.85	1.18	p = 0.568
M	5858	0	0.49	0	—
F	5811	1	0.36	2.78	p = 0.261
Cousins	48 142	5	3.68	1.36	p = 0.305
M	24 693.5	2	2.25	0.89	p = 0.657
F	23 448.5	3	1.43	2.1	p = 0.057
All relatives	209 590.5	214	187.19	1.14	p = 0.05
M	105 937	138	121.5	1.14	p = 0.15
F	103 653.5	76	65.69	1.16	p = 0.20

In italics: exact probability using binomial distribution.

affected by bone or brain tumours are shown in figs 1 and 2 respectively. There is no histological homogeneity among bone cancers (fig 1): one osteosarcoma (family 3), one Ewing's tumour (family 2), one ameloblastoma (family 5), and two unspecified bone tumours (families 1 and 4). There is only one affected relative in all the families except in family 2 where a case of bilateral WT has two cousins from the same sibship with Hodgkin's disease and Ewing's tumour respectively. Moreover their mother and the proband's mother are twins. When dealing with families with at least one relative diagnosed as having a brain tumour (fig 2), it can be seen that only one family has more than two cancers (family 6): the proband's WT, one brain tumour in a first cousin, and two early onset breast cancers in aunts.

Discussion

There is no significant excess of cancer deaths among relatives of Wilms' tumour patients

except among grandfathers and parents, but this excess is only found by using the Standardised Proportional Mortality Ratio (SPMR). However, this estimator is often biased since it is based on the ratio between the number of cancer deaths and the total number of deaths. The denominator may be underestimated since non-cancer deaths may be unknown because of lack of follow up. SPMR can thus lead to an overestimation of cancer deaths.²⁷ The Standardised Mortality Ratio (SMR), based on the whole set of at risk persons (alive and dead), is not affected by this bias and is a better indicator for cancer mortality. Note that the excess of cancer deaths previously shown in relatives of retinoblastoma patients²⁸ and in a preliminary analysis of the first set of WT patients²⁹ was found using the SPMR methods and may be because of an overestimation of cancer versus non-cancer deaths. There is no excess of breast cancer deaths which does not support the hypothesis that WT is part of the LFS.

Incidence analysis confirms part of the results obtained with mortality ratios but, even if there is no excess of cancer among the whole set of relatives, we found a significant familial association between Wilms' tumour and bone cancers on the one hand and brain tumours on the other hand. This association may be even stronger for two reasons. First, since our data on cancer occurrence only result from family interview, there could be a deficit of cancer

Table 3 Observed and expected numbers of families with at least one relative diagnosed as having cancer before the age of 45

	Observed	Expected	
Breast	3	3.75	NS
Bone	5	1.93	p = 0.028
Brain	5	1.74	p = 0.014
STS	1	2.12	NS
Leukaemia	8	9.39	NS
All cancers	39	78.25	NS

Figure 1 Pedigrees with relatives diagnosed with bone cancer before the age of 45.

diagnosis and especially of recent cancers which may be still unknown by family members. The observed number of cancers might thus be greater than it is. Second, since cancer incidence has been increasing with time, our recent population data may lead to an overestimation of the expected number of families with at least one relative diagnosed as having cancer before the age of 45. This could explain the deficit of families when we deal with all types of cancer (39 observed versus 78 expected). We thus reduced the possibility of showing an excess.

Soft tissue sarcomas and breast cancers are the most common features of the LFS. Analysis of 501 families showed no excess when testing for these cancers. These results provide no evidence for WT being part of this cancer syndrome. However, the excess of bone and brain tumours could reflect a very small proportion of families in which a susceptibility gene segregates. Two families (families 2 and 6) could be the result of such a mechanism and it would be interesting to investigate them at a molecular level to confirm this hypothesis.

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