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Occurrence of childhood cancers among sibs and estimation of familial risks

G. J. DRAPER, M. M. HEAF, AND L. M. KINNIER WILSON

From Childhood Cancer Research Group, Old Radcliffe Observatory, Woodstock Road, Oxford; and Epidemiology Unit, Marie Curie Memorial Foundation, The Chart, Oxted, Surrey

SUMMARY An analysis which includes the majority of the cases of childhood cancer occurring in Britain over a period of about 20 years suggests that there is a small familial element in the aetiology of these diseases; aggregations within sibships were observed more frequently than would be expected by chance. Possible explanations of these findings are considered. Some, perhaps many, of the cases within such sibships may be due to associations between malignant disease and various genetically determined conditions at a subclinical level or in the heterozygous state. Alternatively, the observed familial aggregations may be attributable to the fact that sibs share a common environment.

Childhood cancer in twins is discussed and findings compared with those from the United States.

Attention is drawn to a number of interesting combinations of tumours in sibs, particularly brain tumours and bone cancers.

The implications of the findings for genetic counselling are discussed; it is emphasized that, though there appears to be an increased risk that sibs of children with malignant disease will also be affected by such diseases, this amounts overall only to a doubling of the general population risk. Whether or not the explanation is a genetic one, the actual magnitude of the risk for such sibs is only about 1 in 300.

There are numerous case reports which suggest that there is a familial element in the aetiology of childhood cancers (e.g. Strøm, 1957; Fraumeni *et al.*, 1969; Wagget *et al.*, 1973). Estimates of the increased risk of such disease among families where one child is known to be affected have been obtained using data from Britain (Barber and Spiers, 1964) and the United States (Miller, 1971). Li *et al.* (1976) described a large series and studied the occurrence of additional cases in relatives of 'cancer-prone' families ascertained through already having more than one sib affected.

The data on which this paper is based are taken from the Marie Curie/Oxford Survey of Childhood Cancers, which contains records relating to about 20 000 cases of malignant disease occurring in England, Scotland, and Wales between 1953 and 1974. Information about the majority of these children has been obtained from hospital or general practitioner records, and the parents of about 15 000 of them have been interviewed. As a result of such inquiries, information has been collected on just over a hundred families in which two or more children are affected.

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We shall consider these findings from two points of view. First, we present data on families in which there are two or more children affected by malignant disease and discuss in detail certain diagnostic groups of particular interest and also the occurrence of cancer in twins. It is of course true that one would expect a number of families with more than one affected child to be observed purely as a result of chance. Secondly, we examine the question of whether our observations provide evidence that there is in fact a familial element in the aetiology of childhood cancer, i.e. whether there is an increased risk of cancer in general, or of certain tumours or combinations of tumours, occurring in some families. Estimates are given of the 'recurrence risk' for various types of tumour, i.e. of the chance that in a family with an affected child a subsequent child will also be affected. In this analysis we have included only those cases appropriate to a valid estimate of the familial risk; the rationale for excluding certain cases mentioned in the earlier part of the paper is discussed below.

Table 1 *Families in which there were 2 children affected*

Sib A / *Sib B*	*Leukaemia*	*Lymphoma*	*CNS tumour*	*Neuroblastoma*	*Wilms' tumour*	*Bone cancer*	*Other*
Leukaemia	12	7	6	3	2	2	5
Lymphoma		2	2	0	0	0	1
CNS tumour			7	3	1	2	7
Neuroblastoma				2	0	0	3
Wilms' tumour					0	0	0
Bone cancer						0	0
Other							3

Notes: (1) CNS tumours include non-malignant cases.
(2) Diagnostic categories with a known familial element, e.g. retinoblastoma, and sib pairs known to be affected with familial diseases, e.g. neurofibromatosis, are excluded from this table.

Method of ascertainment of cases

Death certificates of children dying from neoplastic disease in England, Scotland, and Wales have been received by the survey since 1953, and cancer registrations since 1962. The coverage in terms of age and diagnostic groups has changed from time to time.

For the majority of these children the parents have been interviewed, and at this interview information has been obtained concerning, *inter alia*, the family history of the affected child including, in particular, details of any sibs who have suffered from neoplastic disease. For cases where there has been no interview, other sources of medical information have usually been available, and in this way we have identified additional families in which there is another affected child among the sibs.

In this paper an 'affected' child is defined as one in whom a malignant disease, or any type of brain tumour, is diagnosed before the age of 15. All brain tumours are included because of the difficulty in distinguishing between benign and malignant tumours with the data available to us. All diagnoses have been confirmed by death certificates or, more often, by hospital records.

Families with more than one affected child

We have subdivided the families with two or more affected children into three groups: Table 1 includes all sib pairs except twins, Table 2 those with 3 or 4 affected children, and Table 3 includes only twins.

In considering Tables 1 and 2 we first draw attention to the occurrence within families of certain tumours and combinations of tumours which appear to be of particular interest, even though it is difficult to give an estimate of the degree of familial risk which is implied by such observations. In the following paragraphs we discuss a number of these.

Table 2 *Families with 3 or 4 affected children*

Diagnosis	*Sex*	*Age at diagnosis (y)*	*Age at death (y)*
Lymphosarcoma	M	1 10/12	1 11/12
Retroperitoneal sarcoma	M	—	2
Lymphatic leukaemia	M	5 9/12	5 10/12
Retroperitoneal sarcoma	M	—	2
Renal neoplasm	M	—	2
Neuroblastoma	M	1 3/12	2 1/12
Retinoblastoma	M	3/12	Alive age 9
Retinoblastoma	M	1/12	Alive age 7
Retinoblastoma	M	1/12	Alive age 5
Retinoblastoma	F	—	?
Retinoblastoma	F	—	Alive age 20
Retinoblastoma	F	—	Alive age 14
Retinoblastoma	F	8/12	Alive age 4

Table 3 *Twin pairs*

Diagnosis	*Sex*	*Age at diagnosis (y)*	*Age at death (y)* ‡
Malignant	M	3 1/12	3 11/12
oligodendroglioma	M	7 9/12	7 11/12
Multiple meningiomas	M	9 5/12	Alive age 16
cerebral and spinal	M	13	14
Wilms' tumour	M	1 3/12	1 8/12
	M	1 4/12	Alive age 8
Retinoblastoma	F	5/12	Alive age 6
	F	5/12	Alive age 6
Letterer-Siwe	M	11/12	11/12
	M	1 7/12	1 7/12

Note: Within each pair the diagnoses were identical.

Families with 3 or 4 sibs affected

In the course of the survey records have been collected relating to 4 families in which 3 or 4 children are each affected (Table 2). All of the children in 2 of these families have retinoblastoma, 4 being affected in 1 family; such occurrences are discussed below. The third family contains 3 boys with, respectively, lymphosarcoma, a retroperitoneal sarcoma, and lymphatic leukaemia; the fourth is one of 3 boys who all died at age 2 years with diagnoses of retroperitoneal sarcoma, renal tumour, and neuroblastoma. In most of these children the age at onset was below 2 years. Chatten and Voorhess (1967) describe a family of 4 children affected with neuroblastoma, and Meadows *et al.* (1974) one with 3 cases of Wilms' tumour. Li *et al.* (1976) discuss several families of this type.

Retinoblastoma families

The largest single category of familial cases is that consisting of sibs with retinoblastoma. In only one such family was a sib with a tumour of another type found; this child had an osteoclastoma of the leg.

There were 22 families in which 2, 3, or 4 sibs were affected by retinoblastoma. Such aggregations are well known and it is now generally accepted that a proportion of cases of retinoblastoma are genetic and the result of a dominant autosomal gene, the remainder being sporadic cases. The disease does not manifest in all carriers of the gene, but it is not clear whether this is because of incomplete penetrance (possibly attributable to modifying genes) or, as Knudson (1971) has suggested, because a somatic mutation is required for expression of the gene. In our data we estimate the penetrance to be about 80% or more. This is similar to estimates from other sources (Schappert-Kimmijser and Hemmes, 1966; Vogel, 1967). The detailed analysis of the families with retinoblastoma in the present study will be described in a separate paper dealing with the epidemiology of this disease.

The sib pair in which one child had a retinoblastoma and the other an osteoclastoma is exceptionally interesting because of the known association between retinoblastoma and osteosarcoma. It has been reported in various papers (Kitchin and Ellsworth, 1974; Lennox *et al.*, 1975) that retinoblastoma survivors have an enormously increased risk, as compared with the general population, of subsequently developing an osteosarcoma. We estimate the relative risk to be about 200. It seems probable that this risk is largely or entirely confined to the genetic cases of retinoblastoma. This suggests that the retinoblastoma gene may also be implicated in the aetiology of some cases of osteosarcoma and possibly other tumours (Kitchin and Ellsworth, 1974). It may also be that the sib with osteoclastoma is in fact a carrier of the retinoblastoma gene.

Sibs with leukaemia

The next largest group of concordant cases is that in which both children have leukaemia; there are 12 such pairs. Since leukaemia is the most common type of malignant disease in children, the number of sib pairs expected to occur simply by chance is also larger than for any other diagnostic group. The interpretation of these findings is discussed in more detail below. With the data available to us we cannot draw any conclusions as to concordance for cell type within families.

Sibs with lymphoma

In this group the most striking occurrence is that of a pair of brothers who were both diagnosed at ages 3 and 4, respectively, as having lymphosarcoma of the caecum and ileum. Such a disease is rare in children and, even allowing for the fact that observations of this type will occur from time to time purely by chance when a large number of diagnostic groups is being studied, this seems a remarkable event. The hospital records suggest the possibility of an immunological deficiency state.

Sibs with brain tumours

As shown in Table 4, there are 11 sib pairs in which both children have a brain tumour. These include two pairs of like-sex twins and a pair in which both sibs have neurofibromatosis and brain tumour. The latter family has a history of neurofibromatosis. One of the two affected children from another family was diagnosed as having tuberose sclerosis. Aita (1967) gives a detailed review of genetic aspects of tumours of the nervous system and their relation to certain diseases known to be of genetic origin.

The number of children with brain tumours who have a sib with another form of cancer is particularly striking. In our study there are 21 such pairs (see Table 5); in 6 of these the second child has leukaemia, in 3 neuroblastoma, and in 2 an osteogenic sarcoma. The sib of one child with a medulloblastoma had a carcinoma of the thymus and also suffered from Ehlers-Danlos disease.

Miller (1971) reported 8 sib pairs with brain tumours and a further 11 families in which one child had a brain tumour and the second another form of cancer. Of the latter, 3 were bone tumours, though it

Table 4 *Sib pairs with brain tumours in each child*

Diagnosis	*Sex*	*Age at diagnosis (y)*	*Age at death (y)*
Medulloblastoma	M	2 5/12	2 9/12
Medulloblastoma	M	3	3 6/12
Glioblastoma	F	8	9 6/12
Ependymoblastoma	M	2	3 4/12
Medulloblastoma	F	1	1 1/12
Glioma of the pons	F	4 9/12	5 7/12
Glioma of optic nerve	F	12 11/12	Alive age 17
Medulloblastoma	M	3 10/12	Alive age 13
Glioma of pineal region	F	9 11/12	10 1/12
Medulloblastoma	M	3 9/12	Alive age 8
Malignant oligodendroglioma	M } Twins	3 1/12	3 11/12
Malignant oligodendroglioma	M } Twins	7 9/12	7 11/12
Astrocytoma*	M	12 5/12	13
Glioblastoma multiforme*	F	3 11/12	3 11/12
Astrocytic glioma†	F	5 9/12	7 3/12
Astrocytic glioma	M	5 7/12	8 4/12
Medulloblastoma	M	1 8/12	1 8/12
Glioblastoma multiforme	F	6	6 8/12
Multiple meningiomas	M } Twins	9 5/12	Alive age 16
Multiple meningiomas	M } Twins	13	14
Medulloblastoma	F	5 2/12	5
Medulloblastoma	F	2 3/12	2 9/12

*Both children also had neurofibromatosis.
†Possible diagnosis of tuberose sclerosis.

was thought possible that one of these was a metastasis from a glioma.

Adrenocortical carcinoma

These tumours are exceedingly rare in children, representing perhaps 0·2% of tumours occurring below age 15. There appears to be a pronounced tendency for familial aggregations to occur; for instance, of the 26 children having this diagnosis in Miller's (1971) study 2 had sibs with rhabdomyosarcoma—a remarkable finding. In the present study one family was ascertained to have a child with this type of tumour and a sib with neuroblastoma, while in a second family a sib had medulloblastoma.

Sib pairs with other malignant neoplasms

For one pair of sibs in the study the first child was stated in our original records to have had a neuroblastoma and the other a Wilms' tumour. However,

Table 5 *Sib pairs in which one child had a brain tumour*

Diagnosis	*Sex*	*Age at diagnosis (y)*	*Age at death (y)*
Midbrain glioma	M	4	4
Lymphatic leukaemia	F	4 11/12	5
Medulloblastoma	M	6 10/12	7 5/12
Lymphatic leukaemia	M	3 10/12	4 11/12
Astrocytoma	F	4 2/12	4 3/12
Acute leukaemia	F	4 7/12	4 8/12
Cerebral tumour	F	—	2 5/12
Lymphatic leukaemia	F	4 10/12	8 1/12
Glioma of fourth ventricle	F	5 8/12	5 9/12
Erythraemic myelosis	F	6 9/12	7 11/12
Astrocytoma	F	11 11/12	?
Acute lymphatic leukaemia	M	11 4/12	11 8/12
Brain-stem glioma	M	7 10/12	7 11/12
Neuroblastoma	M	2 5/12	2 7/12
Astrocytoma	F	5 9/12	6 6/12
Neuroblastoma	M	3	3 1/12
Benign astocytoma	F	12+	Alive age 15
Neuroblastoma	F	2 11/12	3 6/12
Glioblastoma of the basal ganglia	F	2 10/12	3 7/12
Osteogenic sarcoma of humerus	M	10 5/12	11 1/12
Glioma of temporal lobe	F	7 4/12	9 1/12
Osteogenic sarcoma of tibia	M	11 4/12	11 9/12
Glioma of fourth ventricle	F	4 8/12	Alive age 12
Fibrosarcoma leg	M	3 1/12	Alive age 10
Medulloblastoma	F	8/12	10/12
Sarcoma neck	F	—	3 10/12
Medulloblastoma	F	3/12	8/12
Embryonic sarcoma neck	F	1 2/12	1 6/12
Medulloblastoma	F	10 7/12	11 2/12
Lymphosarcoma nasopharynx	M	5 10/12	6 7/12
Glioma of third ventricle	M	1	1 6/12
Reticulosarcoma neck	M	6/12	7/12
Medulloblastoma	M	9/12	2 4/12
Wilms' tumour	F	2 1/12	2 3/12
Medulloblastoma	M	12 4/12	12 11/12
Carcinoma of thymus	M	14 1/12	Alive age 21
Malignant glioma of left temporal lobe	M	1 2/12	1 6/12
Malignant dermoid cyst of ovary	F	5/12	Alive age 3
Medulloblastoma	M	5 1/12	6 1/12
Orchioblastoma	M	1 6/12	1 11/12
Medulloblastoma	M	3 7/12	4
Carcinoma of adrenal cortex	F	2 6/12	Alive age 9

in a detailed investigation of this family described by Wagget *et al.* (1973) the tumour in the second sib was subsequently reclassified as a neuroblastoma. These authors reviewed earlier reports and pointed out that at that time these were only the fifth and sixth families in which neuroblastoma had been conclusively shown to occur in sibs. (This does not appear to include a report by Miller (1971) of neuroblastoma occurring in twins.) The most remarkable report is that by Chatten and Voorhess (1967) describing 4 sibs with neuroblastoma, only 1 child in a family of 5 being free of the disease.

The group of 'other' cancers in Table 1 includes tumours at various sites and of various histological types. One particularly noteworthy family is that in which a primary hepatoma and a carcinoma of the pancreas occurred in 2 brothers who both died when less than 2 years old.

The findings for Wilms' tumour are of some interest. Only one sibship with more than one affected child has been observed in the course of the survey and these children were in fact twins. The mother of one child with a Wilms' tumour had herself had a similar tumour in childhood. Several families with two or more cases of Wilms' tumour have been previously reported (e.g. Strøm, 1957; Cochran and Froggatt, 1967).

Knudson and Strong (1972) have suggested that there might be an important genetic component in the aetiology of Wilms' tumour and that familial aggregations of this disease have been uncommon, in contrast with retinoblastoma, because of the high mortality rate. If their estimates are correct it is to be expected that more familial cases will be observed in the next generation now that more children are being cured of Wilms' tumour. However, it seems possible that they may have overestimated the magnitude of the genetic risk.

Among the children included in the present study there are over 1200 cases of Wilms' tumour, having between them over 2800 sibs; there has not been a single report of a sib pair being affected, apart from the pair of twins discussed below. This suggests that the genetic component in the aetiology is small. However, it is true that because of the high mortality rate of the disease until recently and because the familial cases may tend to be bilateral and to have a worse prognosis there may in fact be a more substantial proportion of cases with a genetic origin than these data appear to indicate. It does, however, seem that Knudson and Strong's estimate that 38% of Wilms' tumours arise from the inheritance of a dominant gene, and that 37% of carriers do not develop a tumour, is unlikely to be correct, though it is not clear which of these estimates needs adjusting, or whether both do.

It is well known that there is an association between Wilms' tumour and aniridia, a condition that can be genetically transmitted as an autosomal dominant. However, it appears from published reports that the association is usually with 'sporadic' aniridia, though of course such cases could be new mutations rather than phenocopies. In the present study there is no record of aniridia being associated with the familial cases of Wilms' tumour.

Sib pairs excluded from the main analysis

A number of interesting familial aggregations are excluded from Table 1 and the main analysis because at least one of the diagnoses was in a non-malignant category or because the disease was associated with a syndrome well known to have a genetic basis.

(a) NEUROFIBROMATOSIS

Several families with this condition are included in the study. Among these are one with 2 children who developed brain tumours and are included in Table 4, a family with a known history of neurofibromatosis in which one child developed an optic nerve glioma, and another in which a child developed a fibrosarcoma of the chest wall.

(b) LETTERER-SIWE, FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS, AND ASSOCIATED CONDITIONS

Several families with these conditions were found. Evidence for familial aggregation in Letterer-Siwe disease has been presented by Glass and Miller (1968). An unusual family in the present series is one in which one child has Letterer-Siwe disease and the other a Wilms' tumour.

(c) XERODERMA PIGMENTOSUM

One family in the series had 2 children diagnosed as having squamous epithelioma; both of these children were stated also to have xeroderma pigmentosum.

Twins

The five families in which cancer was observed in each of a pair of twins are listed in Table 3. In all cases the twins were like-sexed.

The twins with Wilms' tumour were both born with mild hypospadias and were diagnosed at ages 15 and 16 months, respectively. One pair of twins with brain tumours was diagnosed as having gliomas with oligodendroglial and astrocytic elements; the other pair had multiple meningiomas. The first pair have been described by Fairburn and Urich (1971) and the second by Sedzimir *et al.* (1973). The father of the

twins with retinoblastoma had bilateral retinoblastoma, treated by enucleation, as a child; in this family there had previously been twin stillbirths and one other sister with mild hydrocephalus. Both twins with Letterer-Siwe disease presented with a generalized rash, with lymphadenopathy, simulating rubella. One died within 24 hours of onset; the other was admitted to hospital at the same time and discharged with the diagnosis of rubella as most likely. At necropsy of the first twin there was evidence of Letterer-Siwe disease; the diagnosis was made in the second twin only when he became fatally ill again 8 months later.

We have no record of any like-sex twin pair whose disease is not concordant and no record of any unlike-sex twins both with a neoplasm. Miller (1971) and R. W. Miller (1976, personal communication) mentions a pair of twins with neuroblastoma and another pair in which there was one child with glioblastoma multiforme, the other having an osteosarcoma in 1965 followed 2 years later by leukaemia. No radiotherapy was used in treating the osteosarcoma; we do not have information regarding any drug treatment.

Our series does not include any pairs of twins with leukaemia, whereas Miller mentions 7 pairs of like-sex-twins with leukaemia and at least a further 5 pairs are known to have occurred in the United States (MacMahon and Levy, 1964). From their data MacMahon and Levy estimated that the concordance rate for childhood leukaemia among identical twins was 25%.

There are insufficient data available to calculate concordance rates for any single diagnostic group in the present study, and in view of the heterogeneity of the diagnostic categories and the probable diversity of aetiological factors, it is doubtful if a single figure for concordance rates covering all childhood cancer has any useful meaning. Moreover, since the twins with retinoblastoma, and perhaps those with Letterer-Siwe disease, reflect a specific mode of inheritance, and in addition the latter should arguably not be included as a malignant neoplasm, there are only 3 pairs on which an estimate of concordance rates could be based. Such an estimate would be hard to interpret and subject to considerable statistical error.

There is also a further difficulty. Stewart (1973) suggested that twins with malignant disease have an increased chance of dying *in utero* and that this would affect monozygotic more than dizygotic conceptions. Thus the number of cases in which twins from like-sex pairs are recognized as having malignant disease will be less than the true total, since some will have died *in utero* and, possibly, for others the co-twin may have died so that some twins are thought to be singletons. One consequence of this suggestion is that there may be unrecognized twin concordant cancers.

A conclusion of more practical importance is that even the small number of twin pairs with cancer reported here implies that if a twin is affected by cancer then a like-sex co-twin has a greatly increased risk of being found to be also affected.

Estimation of familial recurrence risks

A number of familial aggregations of the type described in this paper would be expected purely as a result of chance. In this section we consider the problem of comparing our observed results with what would be expected to occur by chance if there were no familial element in the aetiology of childhood cancer. We also derive estimates of the familial recurrence risk, that is, the probability that a child will develop cancer if another child in the same family is already known to be affected. More precisely, we estimate recurrence risks defined as follows:

The (*absolute*) *risk of recurrence* of diagnosis B given the occurrence of diagnosis A is the probability that a sib will develop disease B given that one child in a family has disease A, and nothing is known about any other children in the family.

The *relative risk of recurrence* is the ratio of this probability to the probability that a child chosen at random will develop disease B.

In a prospective epidemiological study relative risks are estimated as the ratio of the observed to expected number of affected cases. However, in a study of the type described here an affected child X may be ascertained through being a sib of an index case Y and, contrariwise, Y may be ascertained as an affected sib of index case X. It is necessary to allow for such double counting in the analysis by working in terms of numbers of *ascertainments* of affected sibs, and standard methods are available for investigating diseases for which there is a relatively simple genetic explanation (see, e.g. Bailey, 1961). These methods have to be modified before they can be applied to the problem discussed here. It is necessary to compare the observed and expected numbers of ascertainments of affected sibs; the essential requirements are to define precisely the index cases, or probands, to be included and then to estimate the total number of sibs at risk, the period during which each was effectively observed, and the number of cancers occurring among these sibs. Certain probands and sibs included in Tables 1 and 2 are excluded from this more formal analysis of recurrence risks.

A detailed discussion of the statistical problems will be presented elsewhere.

For the purpose of this analysis the various types

of childhood neoplasms have been divided into seven diagnostic categories: (1) Leukaemia; (2) lymphomas, i.e. all other diagnoses in ICD 200-209; (3) brain tumours, malignant and benign; (4) neuroblastoma; (5) Wilms' tumour; (6) bone tumours; (7) other malignant tumours, but excluding retinoblastoma.

Retinoblastoma for which some cases are known to have a genetic explanation, and malignant tumours associated with syndromes known to be of genetic origin, e.g. neurofibromatosis, have been excluded from the analysis of recurrence risks since we wish to determine whether there is a familial element in the aetiology of the remaining cases. For similar reasons, and because of the problem of classification, we have also excluded Letterer-Siwe disease and similar syndromes. Twins with cancer have also been omitted since such occurrences also presumably represent a different type of risk.

The observed total and expected numbers of ascertainments of affected sibs, and the numbers in each combination of categories 1 and 2 and 3 to 7 combined, are given in Table 6. In Table 7 the same data are given for the 5 diagnostic groups comprising the cancer category.

From these data it is possible to compile a table of recurrence risks and hence of relative recurrence risks. The absolute risks of recurrence are given in Table 8 and the relative risks in Table 9. Standard errors are given in brackets. The method of calculation is described in detail elsewhere (Draper, 1977).

In interpreting these tables we see, for instance, from Table 8 that if a child has leukaemia then the probabilities that a sib will have (a) leukaemia, (b) lymphoma, (c) cancer, or (d) any of the tumours covered by this table are respectively 110, 53, 116, and 278 per 100 000. From Table 9 the corresponding relative risks are respectively 2·3, 2·9, 1·2, and 1·7.

Table 6 *Ascertainments of pairs of sibs with childhood cancers*

Total number of ascertainments	103
Number expected if there were no familial effect	54·7

Observed and expected numbers in three diagnostic groups:

	Leukaemia	*Lymphoma*	*Cancer*
Leukaemia	15 (6·6)	10 (3·8)	27 (21·1)
Lymphoma		3 (0·6)	4 (6·0)
Cancer			44 (16·6)

Notes: 1. Expected numbers, on hypothesis of no familial effect, are in brackets.
2. Twins and cases where there is a known genetic component are excluded.
3. 'Cancer' includes non-malignant CNS tumours.

Table 7 *Detailed diagnosis for 44 sib pair ascertainments where both sibs had cancer*

	CNS	*Neuroblastoma*	*Wilms' tumour*	*Bone*	*Other*
CNS	8 (2·8)	5 (2·0)	2 (1·7)	4 (0·8)	11 (3·5)
Neuroblastoma		3 (0·4)	0 (0·6)	0 (0·3)	7 (1·3)
Wilms' tumour			0 (0·3)	0 (0·2)	0 (1·1)
Bone				0 (0·1)	0 (0·5)
Other					4 (1·1)

Notes: 1. Expected numbers, on hypothesis of no familial effect, are in brackets.
2. Twins and cases where there is a known genetic component are excluded.
3. 'CNS' includes non-malignant CNS tumours.

The main conclusion to be drawn is that if a child is diagnosed as having any of the neoplasms considered here there is in general a small increase in the risk that a sib will also develop one of these diseases, and that it is likely that the two diagnoses will be concordant. In particular, the impression gained from Table 1, that there is a tendency for brain tumours to occur among sibs more often than would be expected by chance, is confirmed.

The estimates in Tables 8 and 9 quantify the extent

Table 8 *Risk per 100 000 for sibs of probands with given diagnosis*
(Standard errors are in brackets)

Risk to sib of having:	*Proband diagnosis*						*Population risk*
	Leukaemia		*Lymphoma*		*Cancer**		
Leukaemia	110	(40)	113	(56)	65	(19)	49
Lymphoma	53	(22)	100	(81)	13	(9)	18
*Cancer**	116	(30)	59	(42)	248	(53)	93
*Any malignant neoplasm**	278	(54)	271	(107)	326	(57)	160

*Includes non-malignant CNS tumours.

Table 9 *Relative risks for sibs of probands with given diagnosis*
(Standard errors are in brackets)

Sib diagnosis	*Proband diagnosis*					
	Leukaemia		*Lymphoma*		*Cancer**	
Leukaemia	2·3	(0·8)	2·3	(1·2)	1·3	(0·4)
Lymphoma	2·9	(1·2)	5·4	(4·4)	0·7	(0·5)
Cancer*	1·2	(0·3)	0·6	(0·4)	2·7	(0·6)
Any malignant neoplasm*	1·7	(0·3)	1·7	(0·7)	2·0	(0·4)

*Includes non-malignant CNS tumours.

of the familial element in childhood cancer and can be used in problems of genetic counselling as described below.

As can be seen from the estimates of standard errors given in brackets, there is considerable uncertainty as to the exact value of the risks, but considering the data here, together with that given by Miller (1971), the approximate level of risk seems fairly well established. In both studies there may be a tendency to underestimate the familial risk since certain sib pairs will not be identified. However, in the present study much of the information was obtained from interviews with the parents, and it seems unlikely that a substantial number of cases have been missed.

Discussion

COMPARISON WITH EARLIER STUDIES

The recurrence risks found in this paper are lower than those given by Barber and Spiers (1964) in an earlier analysis of the same survey. Their analysis was based on smaller numbers, and the difference could in part be the result of sampling fluctuation; the difference may arise in part also from the fact that they included diseases which have been excluded from the present analysis.

Miller (1971) performed a similar analysis, using an entirely different method, for deaths from childhood cancer in the United States. It should be noted that in estimating the relative recurrence risk the ratio of observed to expected numbers given by Miller should be doubled when considering pairs of sibs having the *same* type of tumour, in order to allow for the fact that each pair in his group is actually ascertained twice. With this adjustment the results are very similar to those presented here. In particular, the number of pairs in which both sibs had brain tumours or both had leukaemia is greater than expected, and there is also an association between brain and bone tumours, and between brain and other types of tumour.

POSSIBLE EXPLANATIONS OF FAMILIAL AGGREGATIONS

The results of the present study and those of Miller suggest that within certain families there may be a generally increased susceptibility to cancer and also, in view of the number of families in which the two cancers are concordant as to type, that in some cases a particular gene may be involved in the aetiology of certain cancers. Miller discusses this in some detail. Grundy *et al.* (1973) suggested that subclinical immunological defects may underlie family aggregations of lymphoma with other tumours. A similar possibility, which is discussed by Fraumeni (1973), is that there is in some affected families, particularly those with brain tumours, an underlying, possibly subclinical, genetically determined disorder such as tuberose sclerosis or neurofibromatosis. Swift (1971) suggests that heterozygotes for the gene for Fanconi's anaemia may have an increased susceptibility to cancer.

However, as has already been pointed out, the existence of familial aggregation does not necessarily imply that there is a genetic component in the aetiology. Other possible explanations are considered below.

(a) *Possible association with antenatal x-rays*

It is known, for instance, that a proportion of childhood cancers are caused by antenatal *x*-rays, and it is in theory possible that the aggregations are because certain mothers are more likely to be *x*-rayed than others.

The data on obstetric *x*-raying provide no evidence in favour of this hypothesis. First, as regards the twins, if we assume that the effects of radiation on the 2 fetuses are independent, the probability of observing even 3 pairs of twins with concordant tumours as a result of radiation is so small that it can be ignored. Secondly, though in the remainder of the sib pairs the proportion of children reported to have been irradiated *in utero* is slightly greater than that for the survey as a whole, it is still too small to account for the results presented here.

(b) *Other environmental factors*

No other environmental factor which could account for the observed familial aggregations has yet been identified in childhood cancer.

(c) *Possible transmission from one sib to another*

Transmission between cases has been suggested for both leukaemia and Hodgkin's disease. The evidence for the former is equivocal, while in the case of Hodgkin's disease the only controlled study—that by Pike *et al.* (1975)—has produced negative conclusions. No sib pairs with Hodgkin's disease were observed in the present study; however, since the total number of cases of this disease in our records is only about 600, and since the incidence in this age range is only about 6 to 9 per 100 000 births, even a tenfold increase in risk for the sibs could easily escape detection.

RELEVANCE TO GENETIC COUNSELLING

For the purposes of genetic counselling we require an estimate of the magnitude of the risk of cancer of any form for sibs of children with cancer, and the increase in this risk as compared with the general population.

These risks can be taken from Table 8 as explained at the end of the section on 'Estimation of familial recurrence risks'. The conclusions can be summarized by saying that, excluding neoplasms with a known genetic component, and families with genetically determined syndromes known to predispose to malignant disease, the risk to a sib of a proband with malignant disease is about 1 in 300 as compared with a risk to the general population of about 1 in 600. This is true irrespective of whether the proband has leukaemia, lymphoma, or other cancer. Obviously in any particular family situation many other factors will have to be taken into account in deciding on the appropriate guidance to be given to the parents; the main conclusion to be drawn from the data presented here is a reassuring one.

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Appendix

CALCULATION OF RECURRENCE RISKS

Standard methods of analysis of sibship data are available (see for example Bailey, 1961) for estimating familial recurrence risks, or segregation ratios, if

(a) a relatively simple genetic explanation for the disease is postulated, and in affected families there is a well-defined risk of the disease occurring among sibs;

(b) all affected cases are recognizable as such and all have the same probability of being included as index cases;

(c) ascertainment of cases takes place during a limited period of time, during which there are no changes in the sizes of the families included in the analysis;

(d) all affected sibs are recorded.

None of the above conditions holds for the data analysed in this paper; we have used a modification of Weinberg's general proband method (Draper, 1977) in which

(a) no simple genetic model is proposed and there is no well-defined recurrence risk for sibs. Instead we estimate the *average* recurrence risk, that is the average probability that in a family in which just one child is known to be affected (and no information is available on the other children) any given sib will also be affected.

(b) the probability of an affected child being included as an index case depends on the year of birth of the child.

(c) the size of some families may change during the course of the study.

(d) the disease may not become manifest in some affected sibs until after the study is completed.

These factors have to be taken into account in calculating the expected numbers of sibs who would be affected if there were no increased familial risk. The relative recurrence risks are calculated as the ratio of observed to expected numbers of *ascertainments* of affected sibs. The details of the method for calculating these observed and expected numbers are described elsewhere (Draper, 1977).

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