Two families with the Li-Fraumeni cancer family syndrome

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SUMMARY The first two families to be identified in the United Kingdom with the Li-Fraumeni
syndrome of familial cancer are reported. The first family comprises breast carcinoma in the mother
and adrenocortical carcinoma, medulloblastoma, and rhabdomyosarcoma in three of her four
children, and the second family comprises breast carcinoma in the mother and adrenocortical
carcinoma and rhabdomyosarcoma in two of her three children. All three of the surviving children
with malignancy, and one other who has recently died, possess the tissue type antigen B12.

Childhood cancer is not evenly distributed among the population and familial aggregations sometimes
occur. Much of this familial clustering can be explained by known heritable diseases, for example,
some retinoblastomas and the frequency of malignancy in neurofibromatosis. In addition there seem
to be occasional families with a predisposition to various types of malignancy, the so-called 'cancer
families', and nine such families in the United States have been reported.1–7 We report two similar families
from the United Kingdom.

The families were identified through the population based Children's Malignant Disease Registries
of the Northern and North-Western Regions.8,9 In the Northern Region between 1968 and 1980
there have been five other sib pairs out of a total of 1100 cases notified to the Registry. Three of these
each had bilateral retinoblastoma but the other two were apparently unrelated malignancies with acute
lymphoblastic leukaemia (ALL) and retinoblastoma, and ALL and medulloblastoma. In the Manchester
Children's Tumour Registry there have been seven other sib pairs among a total of 2702 cases of malig
nant tumours registered from 1954 to 1980. These included two sib pairs of bilateral retinoblastoma.

Case reports

The immediate family pedigrees are shown in figs 1 and 2.

FAMILY A

The mother was born on 27.7.41. At the age of 33,
2 years after the birth of her fourth child, she
presented with a mass in the right breast. An infiltrat-
ing and intraduct poorly differentiated adenocarcin-
oma of the breast was found and, despite treatment,
she died 4 years later with metastatic disease in liver
and bone. There was no necropsy. She had been a
non-smoker.

The father was born on 22.7.36. He is a healthy, 45-
year-old, non-smoking office worker.

The first child was born on 29.9.63. She presented at
the age of 22 months with signs of virilisation.
Excessive levels of urinary hydroxy- and keto-
steroids suggested the presence of an adrenal tumour,
and this was confirmed at laparotomy where two
well encapsulated adrenal tumours were removed
from the left side, the right adrenal appearing normal.
Histology showed this to be an adrenocortical
carcinoma. She has had no further treatment and, at

FIG 1 Pedigree of family A. I.1 gastric carcinoma,
I.7 breast carcinoma, III.5 adrenocortical carcinoma,
III.6 medulloblastoma, III.8 rhabdomyosarcoma.

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the birth of her third child, she presented with a mass in her left breast. A poorly differentiated adenocarcinoma was confirmed at biopsy. Despite mastectomy and local radiotherapy she died a year later with widespread metastases. There was no necropsy.

The father was born on 17.12.51. He is a healthy, 29-year-old manual worker.

The first child by the first marriage was born on 18.12.71 and is a healthy 10-year-old boy.

The second child was born on 20.7.78. At the age of 16 months she presented with signs of virilisation. Investigations suggested an adrenal tumour and at laparotomy a well encapsulated left adrenal tumour was removed. Histology showed this to be an adrenal cortical tumour. Sixteen months later she has no evidence of recurrent disease.

The third child was born on 20.10.79. He presented at the age of 20 months with a progressive swelling of the right periauricular area, following which the tumour appeared extending from the middle ear. Biopsy showed this to be a botryoid rhabdomyosarcoma. He responded well to the first 4 months of chemotherapy, but then relapsed with widespread metastases and died.

Another unusual tumour has occurred in this family in the mother's cousin. This boy presented at the age of 22 years with a testicular seminoma and remains well with treatment. There are another eight family members with malignancy, but all occurred over the age of 60. Extensive tracing of family members, however, has not yet been completed.

Further family studies

The HLA types of the surviving family members and

<table>
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<tr>
<th>HLA typing</th>
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<tr>
<td>Family A</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>First child (adenocarcinoma)</td>
</tr>
<tr>
<td>Third child (unaffected)</td>
</tr>
<tr>
<td>Fourth child (rhabdomyosarcoma)</td>
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<tr>
<td>By deduction, mother</td>
</tr>
<tr>
<td>Family B</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>First child (unaffected)</td>
</tr>
<tr>
<td>Second child (adenocarcinoma)</td>
</tr>
<tr>
<td>Third child (rhabdomyosarcoma)</td>
</tr>
<tr>
<td>Maternal grandmother</td>
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<tr>
<td>By deduction, mother</td>
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one child who has now died are shown in the table. The first and fourth children in family A (as well as being identical at HLA loci A, B, and C) are mutually non-responsive in mixed lymphocyte culture suggesting that they are also D locus identical.

Chromosome analysis of the peripheral blood leucocytes of the same surviving family A members showed no evidence of chromosomal damage, aneuploidy, fragile sites, or banding polymorphism. Markers (specific satellites) for a chromosome 14 were present in the father and child 4, and for a chromosome 21 in the father and child 3 and 4.

Discussion

It has previously been reported by Draper et al. that even when known inherited diseases are excluded, there is an increased risk of other sibs developing malignancy if one child presents with cancer, the risk being I in 300 as compared with I in 600 for the general population. Some of this increase may be accounted for by a genetic component. We believe families A and B are examples of the Li-Fraumeni syndrome. This was first described in 1969 in four families in which sibs or cousins had a rhabdomyosarcoma and there was malignancy at a young age in one of the parents. This constellation of tumours was extended to include brain tumour and adrenocortical carcinoma and later leukaemia in children, and other adult tumours. The characteristics of the syndrome appear to be an aggregation of childhood tumours with an increased incidence of malignancy in young adult family members. Both the child and the adult malignancies usually present at a younger age than that of the general population. There is also a tendency for multiple primary neoplasms and the second tumour tends to be of the same type as that in the sib. It has been suggested that an autosomal dominant gene with variable expressivity, modified perhaps by an environmental agent, may be responsible and that the agent is an oncogenic virus. This could explain the explosive nature, in time, of the syndrome which is very apparent in both the families, with all the malignancies presenting within 9 years in family A and within 19 months in family B.

Family A shows a very compact manifestation of the syndrome, although there is no increased incidence of malignancies in the extended family. The four identified members with malignancy are not significantly different from the nine which would be expected as calculated from Serial Mortality Tables. This suggests that if there is dominant transmission the mother may have possessed a new mutant gene. The absence of chromosomal abnormalities in the surviving members of the family conflict with the findings of Bottomley et al. of an increased incidence of aneuploidy in the cultured peripheral blood leucocytes of the family.

Although HLA typing has been performed in other cancer family syndromes, it has not been reported in families with the Li-Fraumeni syndrome. There appeared to be no common HLA haplotype but the antigen B12 occurred in all three surviving members with a malignancy and one who has subsequently died, and by deduction must have occurred in the mother in family A.

Although the antigen B12 occurs in 30% of the population, it has not previously been described as being associated with any neoplasm. However, there is an increased incidence of the antigen B12 in the longer term survivors of acute myeloid leukaemia. Although certain antigens (A24, A28, A29, B15, B35) have been seen with increased incidence in families prone to breast cancer, no definite association has been proved. It would be of interest if B12 occurred in members of other families with the Li-Fraumeni syndrome and if children with adrenocortical carcinoma associated with the syndrome possessed the antigen, while sporadic cases did not.

Adrenocortical carcinoma is extremely rare, accounting for only 0.2% of all childhood malignancies, but it is over-represented in families with more than one childhood malignancy and as a second primary tumour. Its occurrence should alert clinicians to the possibility of this being a manifestation of a family cancer syndrome.

The importance of 'cancer families' is twofold. Firstly, they may prove to be a cornerstone in the investigation of the aetiology of malignancy, in particular the interplay of inherited and environmental factors. Secondly, having identified the families, they pose a challenge in terms of cancer surveillance. Not only may other sibs have an increased chance of malignancy but affected family members may have a risk of developing further primary tumours. Close surveillance and screening procedures, especially of the breast, can thus be directed at a high risk population.

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