Soft-Tissue Sarcomas, Breast Cancer, and Other Neoplasms

A Familial Syndrome?

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SUMMARY **Four families were identified in which a pair of children had soft-tissue sarcomas: three sets of sibs and one set of cousins. One parent of each affected child developed cancer; carcinoma of the breast occurred in three mothers under 30 years of age. Other young adults in these families had a high frequency of cancer, with no evidence of underlying genetic disorders known to carry a high risk of neoplasia. The increased familial susceptibility to cancer was manifested not only by the large number of members affected but by a seeming excess of multiple primary neoplasms. These findings suggest a new "familial" syndrome of neoplastic diseases in which heredity or oncogenic agents, or both, may have a causal role.**

RECENT INTEREST has focused on the familial aggregation of certain malignant neoplasms (1–6). In this paper we report four families in which soft-tissue sarcomas in related children were associated with cancers of the breast and other organs among parents and relatives. This constellation of neoplasms may represent a new familial syndrome, with opportunities for etiologic study and early detection of the component tumors.

METHODS

A kindred was referred for study when two cousins developed rhabdomyosarcomas in infancy (Family A). Interviews with parents and questionnaires mailed to other relatives provided a detailed family history.

We then reviewed the abstracts assembled from the medical charts of 280 children treated for rhabdomyosarcoma at 17 institutions (7). Two pairs of sibs with soft-tissue sarcomas were found, and with permission from their physicians the parents were interviewed to obtain additional genealogic data (Families B and C).

Family D was identified from the childhood cancer mortality registry described by Miller (8). When the records of the 418 children who died of rhabdomyosarcoma in the United States from 1960 through 1964 were matched by the child's last name and mother's maiden name, 1 sib pair was found. This family was not contacted, and further data were derived solely from hospital charts.

Efforts were made to confirm all reports of cancer by obtaining medical and mortality records and, whenever possible, by review of pathology specimens.

FINDINGS

First-degree relatives of the proband and portions of the extended family are shown in Figure 1 (Family A) and Figure 2 (Families B, C, and D). Individuals with cancer are listed on Table 1. The occurrence of tumors was restricted to the paternal line of the proband in Families A and C and to the maternal line in Familes B and D. There was no history of consanguinity or unusual environmental exposures. Parents with cancer were not exposed to therapeutic radiation or chemotherapy before the birth of an affected child.

FAMILY A (PATERNAL LINE)

The proband (V-1) developed rhabdomyosarcoma at 1 year of age. His father

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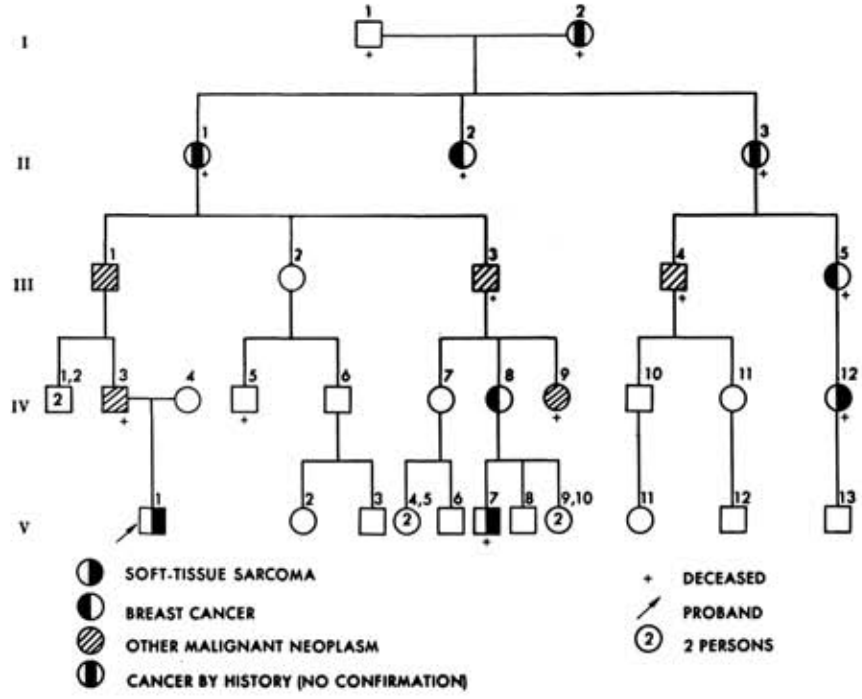

FIGURE 1. Pedigree of Family A.

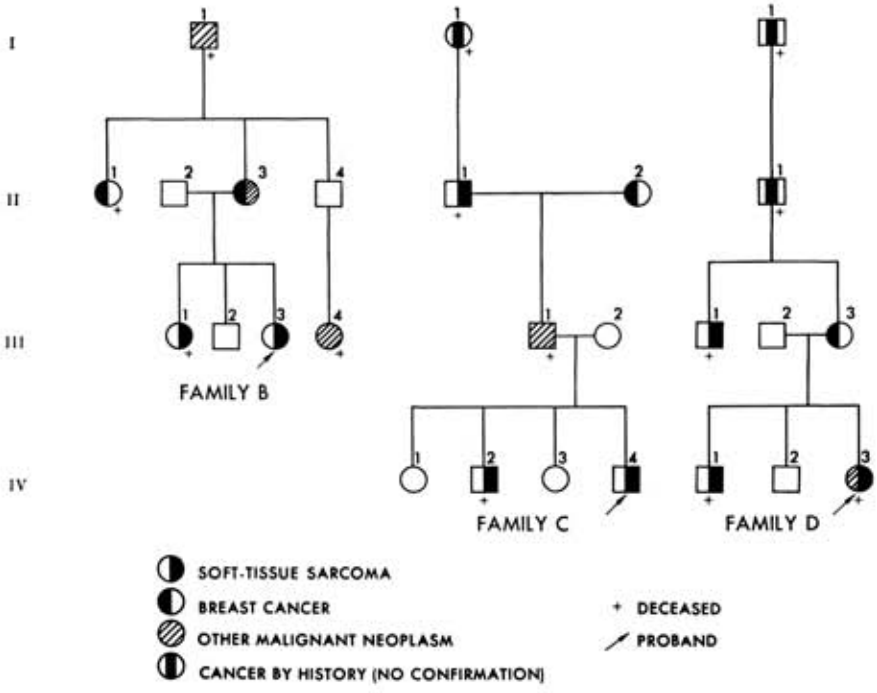

FIGURE 2. Pedigrees of Families B, C, and D.

TABLE 1. Cancers Among Members of Families A Through D

Case	Sex	Age at Diagnosis (and Death)	Type of Primary Neoplasm*	Other Neoplasms or Associated Conditions
		yr		
Family A				
V-1†	M	1	Rhabdomyosarcoma, biceps‡	Congenital pyloric stenosis
V-7	M	1 (2)	Rhabdomyosarcoma, deltoid‡	
IV-3	M	24 (25)	Acute myelocytic leukemia‡	
IV-8	F	28	Carcinoma of breast‡	
IV-9	F	23 (25)	Anaplastic neoplasm of lung‡	Turner's syndrome (45 X-0)
IV-12	F	32 (34)	Leiomyosarcoma, rectovaginal septum‡	
III-1	M	55	Squamous cell carcinoma of ear	Basal cell carcinoma of forehead, age 57
III-3	M	47 (48)	Alveolar cell carcinoma of lung‡	
III-4	M	30 (32)	Carcinoma of pancreas	
III-5	F	33 (46)	Carcinoma of breast	Carcinoma of opposite breast, age 41
II-1	F	? (41)	Carcinoma of breast§	
II-2	F	? (40)	Carcinoma of breast	
II-3	F	? (32)	Carcinoma of breast§	
I-2	F	Adult	Cancer, primary site unknown§	
Family B				
III-1	F	1 (1)	Undifferentiated sarcoma, retroperitoneal area‡	
III-3*	F	3	Rhabdomyosarcoma, thigh‡	Heterochromia of the irises
III-4	F	5 (6)	Acute lymphocytic leukemia	
II-1	F	32 (33)	Carcinoma of breast‡	
II-3	F	22	Carcinoma of breast‡	Carcinoma of opposite breast‡ and papillary carcinoma of thyroid‡, age 34
I -1	M	48 (50)	Carcinoma of pancreas‡	
Family C				
IV-2	M	2 (3)	Spindle cell sarcoma, calf‡	
IV-4†	M	11	Undifferentiated sarcoma, buttock‡	
III-1	M	47 (49)	Disseminated basosquamous carcinoma, scalp	
II-1	M	22 (23)	Poorly differentiated soft-tissue sarcoma, lower leg	
II-2	F	80	Carcinoma of breast‡	
I-1	F	Adult	Carcinoma of breast§	
Family D				
IV-1	M	1 (1)	Rhabdomyosarcoma, pelvis‡	
IV-3†	F	1 (6)	Rhabdomyosarcoma, eye	Died of brain stem astrocytoma, age 6
III-1	M	2 (2)	Angioendothelial sarcoma, mediastinum	
III-3	F	24	Carcinoma of breast‡	Thyroidectomy for thyrotoxicosis, age 22
II-1	M	? (40's)	Lung cancer§	
I-1	M	? (40's)	Lung cancer§	

* All diagnoses confirmed by hospital, pathology, or mortality records except as cited below.
† Proband.
‡ Diagnosis further confirmed by review of pathology specimen at National Institutes of Health, Bethesda, Md.
§ Diagnosis by history only.

(IV-3) died of acute myelocytic leukemia at age 25, and the grandfather (III-1) had a basal and a squamous cell carcinoma of the skin.

A second cousin (V-7) of the proband also had rhabdomyosarcoma at 1 year of age; his mother (IV-8) had breast cancer at age 28, an aunt (IV-9) died of an anaplastic lung tumor at age 25, and the grandfather (III-3) had alveolar cell carcinoma of the lung.

A second cousin once-removed (IV-12) of the proband had leiomyosarcoma of the pelvis at age 32; her mother (III-5) had bilateral breast cancer, and an uncle (III-4) had carcinoma of the pancreas. Cancers were also reported in earlier generations of the family, but only one case, of breast cancer (II-2), was verified.

FAMILY B (MATERNAL LINE)

Soft-tissue sarcomas developed in the proband (III-3) at age 3 and in her 1-year-old sister (III-1). The mother (II-3) had breast cancer at age 22, before the birth of these children, and at age 34 developed cancer in the opposite breast and papillary carcinoma of the thyroid. A first cousin (III-4) had acute lymphocytic leukemia at age 5, an aunt (II-1) had breast cancer at age 32, and the grandfather (I-1) had carcinoma of the pancreas.

TABLE 2. Soft-Tissue Sarcomas, Breast Cancer, and Other Neoplasms Verified in Four Families by Age at Diagnosis and Sex

Persons with Cancer, Age at Diagnosis (Sex)	Soft-Tissue Sarcoma	Breast Cancer	Other Neoplasms	Total
yr				
Under age 15 M	6	0	0	6
F	3	0	1	4
Age 15–40 M	1	0	2	3
F	1	6	1	8
Age 40 and over M	0	0	4	4
F	0	1	0	1
Total cases	11	7	8	26

FAMILY C (PATERNAL LINE)

Soft-tissue sarcomas were diagnosed in the 11-year-old proband (IV-4) and his 2-year-old brother (IV-2). Their father (III-1) died of disseminated basosquamous carcinoma of the scalp, the grandfather (II-1) had a poorly differentiated soft-tissue sarcoma of the lower leg at age 22, the grandmother (II-2) had breast cancer, and a great-grandmother (I-1) was reported to have breast cancer.

FAMILY D (MATERNAL LINE)

The proband (IV-3) had rhabdomyosarcoma of the orbit at 1 year of age and died at age 6 of a brain stem astrocytoma. A brother (IV-1) died of rhabdomyosarcoma at 1 year of age, the mother (III-3) had breast cancer at age 24 after the birth of both children, and an uncle (III-1) died of an angioendothelial sarcoma at 2 years of age. The grandfather (II-1) and a great-grandfather (I-1) were said to have died of "lung cancer" in middle age.

DISCUSSION

The four kindreds described in this study appear to represent a familial syndrome of soft-tissue sarcomas in children and breast cancer and other neoplasms in young adults (Table 2). Each family had a pair of young children (three sets of sibs, one set of cousins) with soft-tissue sarcomas. The 3 sib pairs, ascertained from a survey of 649 children with rhabdomyosarcoma, surpass the occurrence of 0.06 pairs expected on a chance basis (7). In addition, a parent of each affected child had cancer—involving the breast in three mothers under 30 years of age and consisting of acute myelocytic leukemia and disseminated skin cancer, respectively, in two fathers. Relatives of the affected parents also had a high frequency of malignant neoplasms at a young age, particularly breast cancer and soft-tissue sarcomas. There were four instances of multiple primary neoplasms: bilateral breast carci-

noma, bilateral breast carcinoma with papillary thyroid carcinoma, rhabdomyosarcoma and astrocytoma, and basal and squamous cell carcinomas of the skin. In addition, three patients had congenital defects: congenital pyloric stenosis with rhabdomyosarcoma, heterochromia of the irises with rhabdomyosarcoma, and XO Turner's syndrome with anaplastic malignancy of the lung.

It is well known that breast cancer tends to cluster in certain kinships and, as in the families of this report, occurs at an earlier age than in sporadic cases of this cancer (9). A familial association with soft-tissue sarcomas has been reported in two instances: breast cancer in the mother of an infant with rhabdomyosarcoma (10), and a family with breast cancer, various sarcomas, and other neoplasms (11). Furthermore, a report of rhabdomyosarcoma in the orbit of two sibs (12) is the only evidence in the literature for familial aggregation of soft-tissue sarcomas during childhood. Sarcomas seem unduly frequent among individuals with inherited conditions such as tuberous sclerosis, multiple neurofibromatosis, basal cell nevus syndrome, Werner's syndrome (adult progeria), familial intestinal polyposis, and Gardner's syndrome (3, 13–16), but there were no typical manifestations of these disorders in the families studied. However, a forme fruste is suggested by one person with heterochromia of the irises, an abnormality reported with neurofibromatosis (17). In addition, the case with disseminated basosquamous carcinoma of the skin raises the possibility of an underlying condition predisposing to rhabdomyosarcoma and multiple skin cancers, such as the basal cell nevus syndrome (15). None of the congenital defects that occurred in a recently reported series (18) of children with soft-tissue sarcomas were found in these families.

The familial aggregation of these tumors cannot be explained by chance occurrence, since similar surveys conducted on a variety of other childhood neoplasms (19–22) uncovered no instances in which a sib and parent of the proband were reported to have neoplasms. An inherited predisposition for these tumors appears likely, although it is premature to assign a precise genetic mechanism. However, the pattern of involvement in these four families is compatible with transmission by a pleiotropic autosomal-dominant gene, with its expressivity limited by age and sex variations and by other modifying influences (environmental and genetic). A similar mechanism has been postulated for two other familial disorders of multiple neoplasms—pheochromocytoma with medullary thyroid carcinoma (4) and primary adenocarcinomas, especially of the colon and endometrium (6).

An environmental influence for the familial concentration of tumors should be considered, especially since viruses are causal agents for rhabdomyosarcoma, breast cancer, and other tumors in inbred strains of animals (23, 24). Since one child with soft-tissue sarcoma in each family died before the other was born, an environmental agent could not have been directly transmitted between affected children. The occurrence of cancer in both parent and child suggests the possibility of "vertical" transmission of an oncogenic agent between generations of *genetically susceptible* individuals. Laboratory studies are being conducted on surviving members of the families in an effort to evaluate genetic factors and viruses in the cause of the neoplasms.

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