Rhabdomyosarcoma in Children: Epidemiologic Study and Identification of a Familial Cancer Syndrome [1]

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SUMMARY—To study the origins of childhood rhabdomyosarcoma, an examination was made of the 418 death certificates of U.S. children who died of this neoplasm, 1960–64, and of 280 medical charts from 17 hospital centers. Of exceptional interest was the presence in 5 families of a second child with a soft-tissue sarcoma, 3 sibs (vs. 0.06 expected by chance), and 2 cousins. The parents, grandparents, and other relatives of children in these families had a high frequency of carcinoma of the breast and diverse neoplasms (*e.g.*, acute leukemia and carcinomas of the lung, pancreas, and skin) at relatively young ages, suggesting a new familial syndrome of multiple primary cancers. Additional components of the syndrome were implicated by the occurrence of adrenocortical carcinoma and brain tumor in the first-degree relatives of 2 other children with rhabdomyosarcoma. While suggesting the role of inheritance, the familial patterns seen with rhabdomyosarcoma may result from an interaction of genetic and environmental (?viral) factors. The oncogenic agents and mechanisms in human cancer may be identified by the use of such family aggregations for laboratory studies and further epidemiologic studies. Like most childhood neoplasms, rhabdomyosarcoma showed a peak mortality before 4 years of age and occurred slightly more often in males. This neoplasm was diagnosed in 29 children in the hospital series before 1 year of age and in 9 within 1 month of birth; this indicates that rhabdomyosarcoma may arise *in utero*. Unlike most neoplasms of

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early inception, however, no association with congenital defects was detected. Rhabdomyosarcoma also showed no variations in time and/or space that might reflect environmental influences, such as viral or chemical agents which can induce this neoplasm in laboratory animals.—J Nat Cancer Inst 43: 1365–1373, 1969.

RECENT REPORTS indicate that viruses and chemical agents can induce rhabdomyosarcoma in animals (*1*, *2*). To study the role of environmental and other factors in the origin of rhabdomyosarcoma in children, we examined the epidemiology of this neoplasm as derived from a national registry of childhood cancer deaths and a multi-hospital survey of medical charts.

METHODS

We obtained from the National Vital Statistics Division, Public Health Service, copies of 21,659 death certificates for U.S. children under 15 years old who died of cancer, 1960–64. From the 418 certificates specifying rhabdomyosarcoma as the underlying cause of death, we abstracted the name of the child, race, sex, date of birth, age, date and State of death, and other listed diagnoses. Forty-nine of the records had a diagnosis of sarcoma botryoides, generally considered the polypoid form of rhabdomyosarcoma (*3*).

In addition to the National Cancer Institute and the National Cooperative Leukemia Survey, 15 institutions [4] provided the hospital charts of 280 children whose neoplasms were diagnosed as rhabdomyosarcomas before 16 years of age. These diagnoses were based on the pathology reports at each center. Of the 280 children, 50 died within the 1960–64 interval and were also in the mortality series. Data abstracted from each hospital record included the date of birth, clinical onset and diagnosis, and all disorders recorded in the medical and family histories, physical examination, laboratory reports, and autopsy protocols (83 cases). The frequency of associated disorders represents the minimum observed, due to the usual underreporting of such information on hospital charts. In selected instances, we obtained permission to contact the attending physician or the family for more detailed information and to request additional hospital records.

RESULTS

Patient's Age, Sex, and Color and Site of Tumor

The number of deaths and mortality rates for childhood rhabdomyosarcoma, 1960–64, by sex and color of patients are shown in table 1. There were 376 white, 40 Negro, and 2 other nonwhite (1 Japanese and 1 Portuguese-Japanese) children who died of rhabdomyosarcoma during the 1960–64 interval. The higher rates in whites than nonwhites may be partly attributed to more complete ascertainment of cases. The overall sex ratio (M/F) was 6:5 for whites and 1:1 for nonwhites. As shown in text-figure 1, the mortality for boys and girls peaked sharply at 3 years of age. The age at diagnosis (hospital series) showed a less distinct peak under 4 years of age, with a slight predominance of boys at most ages (text-fig. 2).

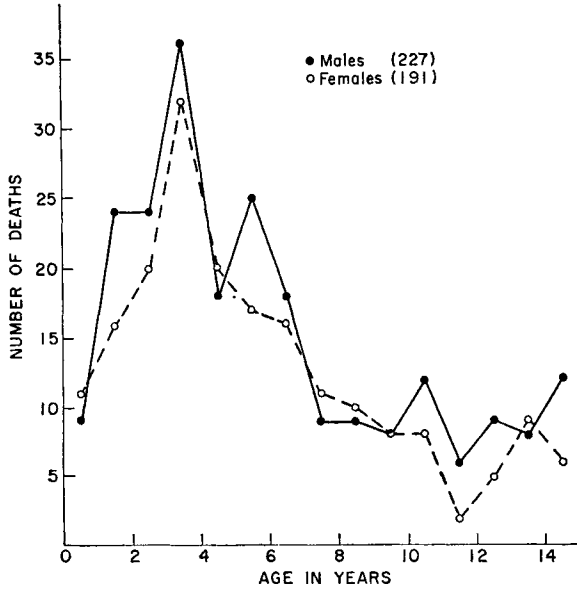
Rhabdomyosarcomas occurred most often in the head and neck areas, the urogenital organs, and the extremities (table 2). There were no clear age or sex differences by site, except that 18 of 21 children with tumors of the upper extremities were boys.

Time-Space Variation and Clustering

Table 3 compares the average annual death rate for the United States with that for each of the 9 geographic divisions by means of the standardized mortality ratio (*4*). The higher mortality in only one area—the Middle Atlantic division ($P<0.01$)—may be related to substantial variations existing in the diagnostic pathology of soft-tissue sarcomas. Perhaps for the same reason, the number of deaths from rhabdomyosarcoma increased during the 1960–64 interval. To evaluate the

TABLE 1.—Deaths and death rates, per million per year, for childhood rhabdomyosarcoma in the United States, by sex, color, and age group, 1960–64

Color	Sex	Age (yr)							
		0–4		5–9		10–14		0–14	
		Number	Rate	Number	Rate	Number	Rate	Number	Rate
White	Males	97	2.17	67	1.56	42	1.07	206	1.62
	Females	94	2.19	54	1.31	22	0.58	170	1.39
	Total	191	2.18	121	1.44	64	0.82	376	1.50
Nonwhite	Males	14	1.79	2	0.29	5	0.84	21	1.01
	Females	5	0.64	8	1.15	8	1.35	21	1.02
	Total	19	1.22	10	0.72	13	1.10	42	1.01



TEXT-FIGURE 1.—U.S. childhood mortality for rhabdomyosarcoma, 1960–64, by age and sex.

annual variation in mortality over the 9 geographic divisions of the United States, we used the Ederer-Myers-Mantel statistical procedure (*5*) for detecting clusters of rare events. Summation across the 45 (9 × 5) time-space units in the United States revealed no significant aggregation of cases. Only one division (South Atlantic) had a tendency for rhabdomyosarcomas to cluster in time (1962), but further study of these cases revealed no unusual geographic clustering.

Seasonal Distribution

To evaluate the possibility that rhabdomyosarcoma is induced during the prenatal or neonatal period by a seasonally prevalent agent, we applied an adaptation of the Ederer-Myers-Mantel clustering procedure (*6*) to the months of birth recorded among cases in the mortality series. For 3- and 4-month seasons and for months within seasons beginning alternatively in January, February, March, or April, no clustering was found for the entire United States or each of the 9 divisions. The procedure was also applied to the months of death, 1960–64, and there was no significant seasonal clustering. Furthermore, the hospital series showed no variations in the season of birth, clinical onset, or diagnosis.

Family History of Cancer

Table 4 lists the neoplasms reported in close relatives of children in the mortality and hospital series. Two sib aggregates from the mortality series (Cases 3 and 8) were included in the survey of Miller (*7*), and we are reporting others (Cases 1–3, 5, and 6) in greater detail elsewhere (*8*). In the present study, 6 mothers were known to have breast cancer during or before the child's hospitalization. Breast cancer occurred in 17 of 41 female relatives reported with specific cancers (41%); the usual relative frequency of breast cancer in women is 22% (*9*).

Three children with rhabdomyosarcoma (Cases 1–3) had a sib with soft-tissue sarcoma, and two (Cases 4 and 5) had cousins with soft-tissue sarcoma in childhood. As compared to the 3 sib pairs observed, only 0.06 sib pair would be expected on a chance basis, *i.e.*, if the 648 index cases in the entire study had an average of 2 sibs, each with a 3.2×10^{-6} annual risk of dying from soft-tissue sarcomas

TEXT-FIGURE 2.—Age at diagnosis of rhabdomyosarcoma, 280 U.S. children treated at 17 institutions.

TABLE 2.—Primary sites of rhabdomyosarcoma in children

Primary sites	Mortality series	Hospital series
Head and neck (total)	92	127
Orbit	24	49
Oronasopharnyx	37	47
Other	31	31
Extremities (total)	28	51
Upper	7	*21
Lower	21	†30
Pelvis and abdomen (total)	84	91
Urinary bladder	22	17
Prostate and testicular area	27	17
Vagina and uterus	11	14
Other	24	43
Thorax (total)	8	7
Unspecified or undetermined (total)	206	‡4
Total	418	280

*Right arm, 9 cases; left, 12.
†Right leg, 13 cases; left, 17.
‡Widely disseminated disease prevented identification of primary site.

(U.S. rate, 1960–64) during the 15 years of childhood ($648 \times 2 \times 15 \times 3.2 \times 10^{-6}$). Further investigation of these 5 families, through questionnaires and personal interviews, revealed the occurrence of neoplasia in at least one grandparent of each child and in a parent of all but one of the affected children. Carcinoma of the breast developed in 3 mothers under 30 years old and was unusually prevalent in other female relatives (*8*). There was also a high frequency of soft-tissue sarcomas and a range of other cancers among young adults in these families (table 5). In addition, 4 family members had multiple neoplasms: 1) bilateral breast carcinoma, 2) bilateral breast carcinoma and papillary thyroid carcinoma, 3) rhabdomyosarcoma and astrocytoma (Case 3), and 4) basal and squamous cell carcinomas of the skin. None of the 5 families presented evidence of unusual environmental exposures, consanguinity, or underlying genetic disorders known to carry a

TABLE 3.—Deaths, death rates (per million per year), and standardized mortality ratios (SMR)* for childhood rhabdomyosarcoma in geographic divisions of the United States, 1960–64

Geographic divisions	Deaths						Average annual death rate (per million)	SMR
	1960	1961	1962	1963	1964	1960–64		
New England	3	6	6	2	7	24	1.50	105
Middle Atlantic	12	15	22	29	20	98	1.94	†136
East North Central	17	17	15	19	12	80	1.35	94
West North Central	5	9	7	13	8	42	1.70	119
South Atlantic	5	13	19	3	13	‡53	1.21	85
East South Central	3	3	4	6	9	25	1.22	85
West South Central	8	7	5	8	9	37	1.26	88
Mountain	4	3	4	1	5	17	1.33	93
Pacific	12	11	7	3	9	42	1.20	84
U.S. total	69	84	89	84	92	418	1.43	100

*SMR = (observed/expected) × 100.
†Significant at 1% level.
‡Significant at 5% level.

TABLE 4.—Neoplasms reported in parents and sibs of children with rhabdomyosarcoma

Case No.	Sex	Series*	Relative	Neoplasms
1	F	H	Sister Mother	Undifferentiated soft-tissue sarcoma† Breast carcinoma and papillary thyroid carcinoma†
2	M	H	Brother Father	Soft-tissue sarcoma† Disseminated basosquamous carcinoma of skin†
3	F	M	Brother Mother	Rhabdomyosarcoma† Breast carcinoma†
4‡	M	H	Father	Carcinoma of pancreas†
5§	M	M	Mother	Breast carcinoma†
6§	M	H	Father	Acute myelocytic leukemia†
7	F	H	Mother	Brain tumor and breast cancer
8	M	M	Brother	Medulloblastoma†
9	F	M	Sib (?sex) Brother	Brain cancer Adrenocortical carcinoma†
10	M	H	Sister	Acute lymphocytic leukemia†
11	M	H	Mother	Breast cancer†
12	M	H	Mother	Breast tumor
13	F	H	Mother	Carcinoma of cervix
14	M	H	Mother	Thyroid tumor
15	M	H	Mother	Tumor of jaw

*H = hospital series; M = mortality series.
†Diagnosis verified by hospital or mortality record.
‡A 5-year-old male cousin had a soft-tissue sarcoma, with no history of parental cancer.
§Cases 5 and 6 were cousins.

TABLE 5.—Soft-tissue sarcoma, carcinoma of the breast, and other neoplasms verified in 31 members of 5 families, by age at diagnosis and sex*

Age (yr)	Sex	Soft-tissue sarcoma†	Carcinoma of breast	Other neoplasms‡	Total§
<15	M	8	0	0	8
	F	3	0	2	5
15–40	M	1	0	3	4
	F	1	6	2	9
>40	M	0	0	4	4
	F	0	3	0	3
		13	9	11	33

*Omitted are unconfirmed reports of lung cancer (4 cases), breast cancer (3 cases), and other neoplasms (3 cases).

†Includes Cases 1–6 (table 4).

‡Three instances of carcinoma of the pancreas; 2 each with leukemia (1 myelocytic and 1 lymphocytic), carcinoma of the skin, and carcinoma of the lung; and 1 each with thyroid carcinoma and astrocytoma.

§Multiple neoplasms of different organs occurred in two persons: 1) primary carcinomas of breast and thyroid; and 2) rhabdomyosarcoma and astrocytoma.

high risk of neoplasia. The parents with cancer had no therapeutic radiation or chemotherapy before the birth of an affected child.

Three children with rhabdomyosarcoma (Cases 7–9 in table 4) had a close relative with a brain tumor (1 mother and 2 sibs). The mother with a brain tumor (Case 7) subsequently developed breast cancer, and the sibship of Case 9 also included a child with adrenocortical carcinoma. Another sibship with a rhabdomyosarcoma and an adrenocortical carcinoma was identified from the childhood cancer mortality registry after the 1960–64 study period; the mother of this sib pair had an astrocytoma at 30 years of age.

Congenital Defects

Table 6 lists the associated diagnoses among children with rhabdomyosarcoma, as recorded on the hospital records. No disorder was clearly in excess of normal expectation. Only 1 child had prior therapeutic irradiation, implicated in certain instances of rhabdomyosarcoma (*10*, *11*), but the tumor occurred at an unrelated site.

DISCUSSION

Rhabdomyosarcoma in children occurred mostly in the very young, slightly more often in males than in females. It was diagnosed before 1 month of age in 9 of 280 children (3%) in the hospital series; this finding and the peak occurrence from infancy through 3 years of age suggest that a substantial proportion of tumors originate during prenatal life. The common sites of involvement (head and neck, extremities, and urogenital organs) had similar age and sex patterns, though the preponderance of males with tumors diagnosed in the upper limbs (18 boys vs. 3 girls) suggests a sex-related influence at this site.

An age peak in early childhood has been reported with other malignant neoplasms, such as leukemia, brain tumors, neuroblastoma, Wilms' tumor, and liver cancer (*4*, *12–15*). Except for neuroblastoma (*13*), these tumors have occurred excessively with specific congenital defects. Although an excess of congenital defects was reported recently in a small series of children with a variety of soft-tissue sarcomas (*16*), the anomalies observed were of diverse types. Our survey of rhabdomyosarcoma, in which the frequency of concurrent defects was compatible with chance occurrence, adds to the evidence that a neoplasm with an age peak in early childhood and apparent prenatal inception is not necessarily related to a specific congenital malformation (*13*). The possible association of other childhood sarcomas with congenital defects requires further investigation.

This survey uncovered 5 families with an aggregation of soft-tissue sarcomas in children. On the ancestral line of one parent in each family was a high concentration of cancers of diverse

TABLE 6.—Associated disorders among 280 children with rhabdomyosarcoma (hospital series)

Case No.	Sex	Age at diagnosis (yr)	Associated diagnosis
			Musculoskeletal (*see also* #50)
16	M	1	Extra finger on left hand and talipes varus
17–21	5 M	1, 1, 3, 8, 12	Inguinal hernia (5 cases), 3 surgically treated
22–24	3 M	1, 1, 7	Umbilical hernia (3 cases), 1 surgically treated
25, 26	M, F	9, 1	Spina bifida occulta, adduction spasm of hips (1 case each)
			Gastrointestinal
6	M	1	Congenital pyloric stenosis, surgically treated
27	M	3	Congenital esophageal atresia, surgically treated
28	F	6	Pneumatosis cystoides enteralis and unexplained hepatomegaly at autopsy
			Genitourinary (*see also* #50)
29, 30	M, F	3, 8	Double ureter, unilateral
31, 32	2 M	6, 14	Undescended testis (2 cases), 1 treated with hormones
			Eye (*see also* #50)
33–37	3 M, 2 F	4, 8, 10, 2, 8	Congenital strabismus (5 cases), 2 treated surgically
38	M	1	Congenital ptosis, left eye
1	F	3	Heterochromia of the irises
			Tumors
3	F	1	Astrocytoma diagnosed at age 6 years, causing death
39	M	10	Hamartoma of liver (3 cm in diameter) at surgery for rhabdomyosarcoma
40	F	2	Meningioma (0.7 cm in diameter) at autopsy
			Cutaneous
41	M	5	Large nevus on forearm
42, 43	M, F	2, 1	Café-au-lait spot on abdomen and on forearm (2 × 3 cm in diameter)
44	M	1	Capillary hemangioma on tibial area (4 × 1 cm in diameter)
			Other defects within one organ system
45–48	4 M	2, 8, 9, 12	Sickle cell anemia, surgically treated atrial and ventricular septal defects, mental retardation, and diabetes mellitus (1 each)
			Defects of multiple organs
49	M	5	Complete situs inversus
50	M	13	Bilateral congenital ptosis, unilateral clubfoot, and cryptorchidism

types. Soft-tissue sarcomas and carcinoma of the breast were the most common neoplasms, and there were multiple instances of acute leukemia and carcinomas of the pancreas, lung, and skin. Family aggregates of soft-tissue sarcomas have been recorded infrequently (*17–19*), and there are only scattered case reports of childhood soft-tissue sarcoma associated with other cancers in the same kinship (*20, 21*). In the only previous report of familial sarcoma with other cancers, Fraumeni, Vogel, and Easton (*22*) presented a kinship in which a father and his child died of soft-tissue sarcomas, while 2 other offspring (both with colonic polyps) died, respectively, of carcinoma of the colon and reticulum cell sarcoma.

The familial occurrence of neoplasms originating at discordant sites may represent a counterpart of the tendency for a single individual to develop multiple primary tumors. Thus it is of interest that breast cancer has been found as a double primary tumor in 2 of 24 women with liposarcoma (*23*), and has also been linked to lymphangiosarcoma of the arm following mastectomy (Stewart-Treves syndrome) (*24*). These findings suggest that factors causing carcinoma of the breast may also have sarcomatous potential, particularly within lymphedematous tissue (*24*).

The familial constellation of neoplasms associated with rhabdomyosarcoma may also include brain tumors and adrenocortical carcinoma—cancers

which occurred in close relatives of 2 other children in this study. Miller described the aggregation of soft-tissue sarcomas and brain tumors among sibs dying of cancer (*7*), and a recent observation suggests that close relatives of children with adrenocortical tumors have an excess of certain cancers (*25*). As multiple primary neoplasms in children, rhabdomyosarcoma has been observed with astrocytoma (Case 3 in our series), and adrenocortical carcinoma with brain tumors (*26*). To our knowledge, soft-tissue sarcoma has not yet been reported with an adrenocortical tumor, which would complete the possible combinations of double primary tumors among children with these neoplasms.

The increased frequency of cancers of the breast and other sites among the relatives of children with familial sarcoma cannot be explained on a chance basis. To date, similarly conducted surveys of other childhood neoplasms (*4*, *13*, *14*, *26*) have uncovered no instance in which cancer affected sib *and* parent. It is likely, therefore, that genetic or environmental influences, or both, are responsible for the family aggregates of cancer. The lineal involvement of family members with a spectrum of neoplasms is consistent with transmission by an autosomal dominant gene that is variably expressed. This mode of inheritance has been proposed for other familial syndromes of neoplasms affecting different sites—pheochromocytoma and medullary thyroid carcinoma (*27*) and primary adenocarcinoma of the endometrium, colon, and other sites (*28*). These syndromes have been described in adults and do not include childhood cancers as a component; yet they resemble the familial occurrences in our study in that they tend to develop at an earlier age than usual and to occur sometimes as multiple primary tumors in the same individual. Furthermore, soft-tissue sarcomas are known to be associated occasionally with genetically transmitted diseases, such as the basal-cell nevus syndrome (*29*), multiple neurofibromatosis (*30*), tuberous sclerosis (*31*), Werner's syndrome (*32*), intestinal polyposis, and Gardner's syndrome (*22*). Though not clinically observed among families in our study, these conditions indicate the plausibility of genetic mechanisms in familial occurrences of sarcoma. However, since genetic disorders predisposing to sarcoma do not increase the risk of breast cancer, inheritance *alone* appears to be an insufficient explanation for the range of neoplasms seen with familial sarcoma.

Environmental factors in human rhabdomyosarcoma are implicated by the viral and chemical induction of this neoplasm in susceptible strains of animals (*1*, *2*). Although we found no temporal or spatial clustering of children with this tumor to suggest the role of extrinsic agents, the family aggregates of rhabdomyosarcoma and other neoplasms may reflect an environmental influence on genetically susceptible individuals. Observations on laboratory animals show that an oncogenic virus (*33*) or chemical (*34*) can produce a wide variety of tumors in a single host, so that the range of familial neoplasms in this study may indicate an agent with similar potentialities. One might speculate that the lineal pattern of familial tumors and the early childhood peak of rhabdomyosarcoma are human counterparts to animal tumor models, in which oncogenic viruses are transmitted vertically (from one generation to another) and are especially active in the newborn host or fetus (*35*). Further studies of these family aggregates are needed to distinguish genetic factors from viral or other environmental carcinogens. Familial cancer syndromes involving multiple sites suggest that the component tumors share etiologic influences, and that these influences may be clarified by the fullest possible use of such occurrences for laboratory and epidemiologic research.

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