

# A Cancer Family Syndrome in Twenty-four Kindreds<sup>1</sup>

Frederick P. Li,<sup>2</sup> Joseph F. Fraumeni, Jr., John J. Mulvihill, William A. Blattner, Margaret G. Dreyfus, Margaret A. Tucker, and Robert W. Miller

*Clinical and Environmental Epidemiology Branches, National Cancer Institute, Bethesda, Maryland 20892*

## ABSTRACT

A search of the Cancer Family Registry of the National Cancer Institute revealed 24 kindreds with the syndrome of sarcoma, breast carcinoma, and other neoplasms in young patients. Cancer developed in an autosomal dominant pattern in 151 blood relatives, 119 (79%) of whom were affected before 45 years of age. These young patients had a total of 50 bone and soft tissue sarcomas of diverse histological subtypes and 28 breast cancers. Additional features of the syndrome included an excess of brain tumors (14 cases), leukemia (9 cases), and adrenocortical carcinoma (4 cases) before age 45 years. These neoplasms also accounted for 73% of the multiple primary cancers occurring in 15 family members. Six of these patients had second cancers linked to radiotherapy. The diversity of tumor types in this syndrome suggests pathogenetic mechanisms which differ from hereditary cancers arising in single organs or tissues. The syndrome is presently diagnosed on clinical grounds; laboratory markers are needed to identify high-risk individuals and families and to provide insights into susceptibility mechanisms that may be shared by a wide variety of cancers.

## INTRODUCTION

In 1969, we described 4 families with an autosomal dominant pattern of soft tissue sarcoma, breast cancer, and other neoplasms in children and young adults (1). This cancer family syndrome (Li-Fraumeni syndrome; SBLA syndrome) has been observed in a few anecdotal reports and in the families of unselected series of children with sarcoma (2-16). Our analysis of 24 affected families extends the literature on the disorder and further defines its component neoplasms.

## SUBJECTS AND METHODS

We examined the Cancer Family Registry of the Epidemiology Branches, National Cancer Institute, for families with sarcoma, breast cancer, and other neoplasms occurring in children and young adults (17). Eligibility for this study was limited to families with 3 close relatives in whom cancer was documented by review of available hospital and pathology records, death certificates, and histopathology specimens. These family members included one individual, designated the proband, with a sarcoma before 45 years of age; a first degree relative with cancer in this age interval; and another close (first or second degree) relative in the lineage with either cancer at this age interval or a sarcoma at any age. For each study family, an abstract was made of the demographic and medical data for cancer patients in the affected lineage. The primary tumor site and histology were ascertained from the composite records. Patients were diagnosed with multiple primary cancers on the basis of review of the pathology slides or report for each neoplasm; bilateral breast carcinoma was counted as a single neoplasm. Records were unavailable for 27 patients, mostly elderly and distant relatives, who were thought to have developed cancer. These neoplasms were excluded from analysis, along with 3 skin carcinomas, 2 bilateral intraductal breast carcinomas, 1 *in situ* carcinoma of the cervix, and all benign tumors.

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<sup>2</sup> To whom requests for reprints should be addressed, at the Dana Farber Cancer Institute, 44 Binney Street, Boston, MA 02115.

A total of 24 families in the Registry (8 previously reported) were eligible for the study (Table 1) (1, 18-21). Twenty-one families are white, 2 are black, and 1 is American Indian. The pedigrees of these kindreds, as recorded in the Registry, were examined for cancer occurrence among the 923 enumerated blood relatives in the affected parental line; no excess cancers were discerned in the other parental line of the proband. After excluding the undocumented and noninvasive tumors, the study series was composed of 151 patients who developed a total of 169 neoplasms. The first cancers among the patients were examined separately from subsequent cancers. Initially, the analysis was limited to sarcoma and breast cancer before age 45 years, the cardinal features of the syndrome. To identify additional components of the syndrome, the distributions of other forms of cancers, before age 45 and  $\geq 45$ , were compared with corresponding data for the general population (22). Second and subsequent primary cancers were examined in particular for the carcinogenic effects of prior tumor therapy.

## RESULTS

Among the 151 cancer patients, 119 (79%) were affected before 45 years of age (Table 1). The high proportion of young patients persisted after excluding the 72 cancer cases who qualified the 24 families for this study ( $119 - 72/151 - 72 = 59\%$  versus 10% of all cancers occurring before age 45 in the general population) (22). Breast cancers occurred only in females, and several other cancers showed a slight male predominance. There were 15 patients with multiple primary cancers.

The diverse forms of cancer in family members were analyzed individually, with attention to the neoplasms in children and young adults. The index tumor, sarcoma, developed as the first cancer in 55 patients (median, 2.3 sarcomas/family) (Table 2). Fifty of them (91%) were affected before age 45 years, often in childhood. The primary site was more often in soft tissues than in bone; both forms of sarcoma developed in 9 families. The soft tissue sarcomas arose at a wide range of ages and anatomic regions and were diverse in histology. Bone sarcomas in 19 of 23 patients arose in lower limbs between the ages of 5 and 28 years. There were 18 patients with osteosarcoma, but none had a Ewing's sarcoma which accounts for nearly one-third of bone sarcomas in the general population (23).

The other major component of the syndrome, breast carcinoma, developed as the first cancer in 36 members of 16 families. The majority (78%) was affected before age 45 years when, in the general population, only 12% of all breast cancers occur (22). Ten patients had bilateral metachronous breast cancers, usually starting at early ages (median, 33 years; range, 22-47). Infiltrating ductal carcinoma of the breast was the predominant histological type. Ten breast cancer patients (29%) had at least 1 offspring who developed a sarcoma.

Additional components of the syndrome were sought in the 41 patients under age 45 years whose first cancer was a neoplasm other than sarcoma and breast carcinoma. There were 14 patients with brain tumors, 8 with leukemia, and 4 with adrenocortical carcinoma (Table 2). Family members had an excess of these neoplasms when compared with persons before age 45 years in the general population (Table 3) (22). The syndrome appears to encompass these 3 cancers, but not other cancers in young patients.

Table 1 Cancer occurrence among 923 members of 24 families<sup>a</sup>

Family (no. in blood line) <sup>b</sup>	No. of patients with cancer <sup>c</sup> (no. affected before age 45 years)	
	Documented	Unconfirmed
1 (33)	16 (14)	3 (2)
2 (44)	5 (5)	3 (1)
3 (53)	7 (6)	2
4 (46)	5 (4)	3 (1)
5 (176)	17 (13)	3
6 (7)	5 (5)	0
7 (24)	3 (3)	0
8 (63)	8 (5)	0
9 (24)	7 (6)	1
10 (25)	3 (3)	1
11 (6)	4 (4)	0
12 (5)	4 (4)	0
13 (29)	5 (3)	1
14 (47)	5 (4)	0
15 (114)	13 (4)	0
16 (35)	5 (4)	2 (2)
17 (32)	8 (6)	2
18 (19)	7 (7)	1
19 (27)	7 (3)	0
20 (12)	5 (5)	0
21 (69)	3 (3)	1
22 (9)	3 (2)	0
23 (11)	3 (3)	4 (2)
24 (13)	3 (3)	0
Total (923) <sup>d</sup>	151 (119)	27 (8)

<sup>a</sup> Fifteen patients developed multiple primary cancers.

<sup>b</sup> Previous reports of Families 1–8: 1–4 (1, 31); 5 (20); 6 (19); 7 (21); and 8 (18).

<sup>c</sup> Skin and *in situ* carcinomas excluded.

<sup>d</sup> Includes persons born after initial ascertainment.

Table 2 Cancers in 151 patients, by tumor type and age at diagnosis<sup>a</sup>

First tumor	Age at diagnosis (yr)				All (0–44)
	0–14	15–29	30–44	>44	
Sarcoma					
Soft tissue <sup>b</sup>	17	4	7	4	32 (28)
Bone <sup>c</sup>	9	13	0	1	23 (22)
Breast <sup>d</sup>	0	10	18	8	36 (28)
Brain <sup>e</sup>	4	8	2	0	14 (14)
Leukemia <sup>f</sup>	7	1	0	1	9 (8)
Adrenocortical	4	0	0	0	4 (4)
Lung	0	1	1	5	7 (2)
Pancreas	0	0	1	3	4 (1)
Colorectal	1	0	0	2	3 (1)
Prostate	0	0	0	3	3 (0)
Lymphoma	0	2	0	1	3 (2)
Stomach	0	0	2	0	2 (2)
Other	2	3	2	4	11 (7)
All cancers	44	42	33	32	151 (119)

<sup>a</sup> Excludes unconfirmed and *in situ* cancers, benign tumors, and second and third primary cancers in 15 patients.

<sup>b</sup> Rhabdomyosarcoma in 11 patients, leiomyosarcoma in 9, liposarcoma in 2, fibrosarcoma in 2, and other and unspecified in 8.

<sup>c</sup> Osteogenic sarcoma in 18 patients, chondrosarcoma in 3, and giant cell tumor of bone in 2.

<sup>d</sup> Infiltrating ductal carcinoma in 24 patients, mixed tumors and unspecified carcinomas in 12.

<sup>e</sup> Gliomas in 9 patients and 1 each of medulloblastoma, ependymoma, spongioblastoma, choroid plexus tumor, and unspecified cerebellar tumor.

<sup>f</sup> Acute lymphocytic leukemia in 6 patients, acute myelocytic leukemia in 2, and chronic myelocytic leukemia in 1.

Among the 32 neoplasms in family members ages 45 years and over, 13 were sarcomas and breast cancers (Table 2). Most of the other tumors arose in the lung and digestive tract, as expected in an older population.

Abbreviated pedigrees show 148 of the 151 documented cancers in the affected lineage of the 24 families (Fig. 1); the other 3 cancers occurred in distant relatives. The pattern of multiple affected generations in all but one family (Family 7) is consistent with autosomal dominant transmission. Twenty-one families had diverse cancers affecting close relatives, and the remainder (Families 7, 21, and 22) had sarcoma only.

Table 3 Distribution of cancers other than sarcoma and breast cancer, ages 0–44 years, in 41 family members and the United States population<sup>a</sup>

Tumor	% of all cancers, ages 0–44 (no. of patients)	
	24 families	United States population
Brain	34 (14)	7
Leukemia	19 (8)	8
Adrenocortical	10 (4)	<1
Lung	5 (2)	7
Stomach	5 (2)	1
Lymphoma	5 (2)	5
Other <sup>b</sup>	22 (9)	72
Total	100 (41)	100

<sup>a</sup> Ref. 22.

<sup>b</sup> One each of Wilms' tumor, neuroblastoma, and carcinoma of the pancreas, thyroid, thorax, larynx, uterus, ovary, and colon.

Multiple primary cancers, excluding bilateral breast cancer, developed in 15 members of 11 families (Table 4). The first cancer was usually diagnosed at an early age (median, 22 years; range, 1–62 years), and in 11 patients (73%) it was a component tumor in the syndrome. These component tumors also comprised 12 of the 18 subsequent cancers (Cases 4, 5, and 15 each had a total of 3 primary cancers) among those with multiple primaries.

Seven of the subsequent cancers in 6 patients arose within the radiotherapy field. The cancers arose between 2 and 14 years after radiation exposure and were of histological types reported in other irradiated groups (24). These neoplasms are attributable to both host factors and radiation effects, suggesting that susceptibility to radiation carcinogenesis may be a feature of the syndrome.

The families had no identifiable exposures to environmental carcinogens other than radiation to account for the cancer cluster. None had a predisposing genetic disease such as hereditary retinoblastoma, von Recklinghausen's neurofibromatosis, and Werner's syndrome, but Family 7 had osteosarcoma associated with skeletal anomalies, macrocytosis, and suspected parental consanguinity (21, 25–27).

## DISCUSSION

Our study increases the literature on this cancer family syndrome from 21 to 45 reported kindreds (Table 5) (2–12). Both our series and the published data demonstrate the major features of the syndrome: autosomal dominant pattern of diverse neoplasms in children and young adults; predominance of soft tissue sarcomas, osteosarcoma, and breast cancer; excess of brain tumors, leukemia, and adrenocortical carcinoma; occurrence of the component neoplasms as multiple primary neoplasms in young family members (Tables 2, 4, and 5) (2–16, 28). Our data fail to show the finding in other published reports of associations with melanoma and carcinomas of the prostate, lung, and larynx, perhaps because of the small numbers of older family members in our series (7, 15).

Familial aggregates of cancer are often due to chance association. The lifetime risk of cancer exceeds 25% among the 240 million persons in the United States (29). Therefore, striking familial clusters of cancers may occur simply by random distribution. Chance aggregates are usually composed of older patients with the common cancers, such as carcinomas of the breast, respiratory tract, and digestive tract. In our families, chance is an unlikely explanation for the breast cancers which occurred predominantly in mothers of sarcoma cases and in young women as bilateral and multiple primary cancers. The

CANCER FAMILY SYNDROME

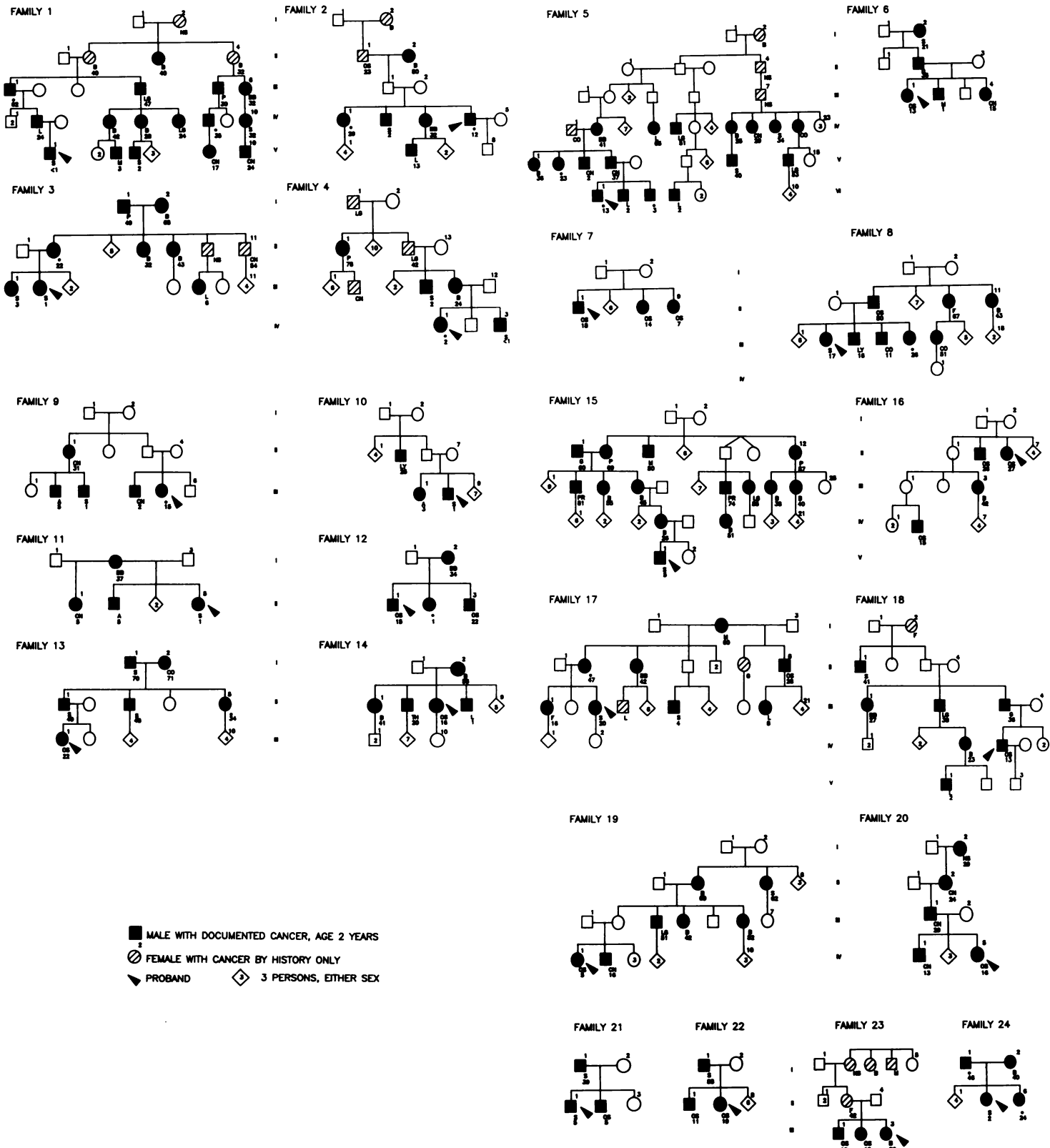


Fig. 1. Pedigrees of the 24 families. Shown are the proband in each family, all first-degree relatives and abridged portions of the extended pedigree of the affected blood line. Both spouses are shown in generation I and in each subsequent generation along the family line to the proband. Each patient is identified by a family, generation, and case number. Symbols for the cancer types are: \*, multiple primary cancer (see Table 4); A, adrenocortical carcinoma; B, breast cancer, unilateral; BB, breast cancer, bilateral; CN, central nervous system (brain) tumor; CO, colon cancer; F, female genital tract; G, gastric; H, head and neck; K, kidney; L, leukemia; LG, lung; LY, lymphoma; M, miscellaneous types of cancers; NS, not specified; OS, osteosarcoma; P, pancreas; PR, prostate; S, soft tissue sarcoma; TH, thyroid. Number below each tumor type represents age at diagnosis or death if available (age at first cancer is shown for those with bilateral breast cancer and multiple primary tumors).

other components of the syndrome are uncommon neoplasms with population incidence rates that range from 0.3/million for adrenocortical carcinoma to 4/100,000 for leukemia in childhood (30). Nevertheless, our series of families was highly se-

lected for the occurrence of sarcoma, breast cancer, and other neoplasms in children and young adults. Anecdotal reports of affected families in the literature may also have similar biases. Analytical epidemiology studies have formally excluded

Table 4 Multiple primary cancers in 15 family members

Family-generation-patient no. (see Fig. 1)	First tumor (age in yr)	Subsequent tumors (age in yr)
1-IV-8	Larynx carcinoma (35)	Lung carcinoma (39)
1-III-1	Prostate carcinoma (62)	Leiomyosarcoma <sup>a</sup> (66)
2-IV-4	Liposarcoma (12)	Leiomyosarcoma <sup>a</sup> (26)
2-IV-1	Bilateral breast carcinoma (29, 36)	Mesothelioma <sup>a</sup> (40)
		Fibrosarcoma <sup>a</sup> (41)
3-II-2	Bilateral breast carcinoma (22, 36)	Thyroid carcinoma (30)
		Ovarian carcinoma (50)
4-IV-1	Rhabdomyosarcoma (2)	Glioma (5)
5-VI-1	Osteosarcoma (13)	Brain tumor (25)
5-VI-3	Schwannoma (3)	Osteosarcoma <sup>a</sup> (13)
5-V-2	Leiomyosarcoma (23)	Bilateral breast carcinoma (25)
8-III-10	Glioblastoma (26)	Acute leukemia <sup>a</sup> (28)
9-III-5	Osteosarcoma (15)	Soft tissue sarcoma (18)
12-II-2	Adrenocortical carcinoma (1)	Glioma (19)
13-II-5	Leiomyosarcoma (34)	Leiomyosarcoma (41)
17-II-2	Duodenal carcinoma (47)	Bladder carcinoma (52)
24-II-6	Breast carcinoma (24)	Ovarian granulosa cell tumor (28)
		Glioblastoma (29)

<sup>a</sup> Subsequent cancer arose within the field of radiotherapy for the first cancer.

Table 5 Published descriptions of the cancer syndrome in 21 families<sup>a</sup>

Tumor	No. of patients, by age (no. with second cancers)			Total
	0-44	>44	Unknown	
Sarcoma				
Soft tissue	14 (6)	3 (2)		17 (8)
Bone	17 (5)	1		18 (5)
Unknown site	9 (2)			9 (2)
Breast	28 (2)	13	5	46 (2)
Brain	19	4	2	25
Leukemia	7 (1)	2	1	10 (1)
Adrenocortical	9			9
Other <sup>b</sup>	9 (1)	29 (5)	3	41 (6)
All cancers	112 (17)	52 (7)	11	175 (24)

<sup>a</sup> Refs. 2-12.

<sup>b</sup> Ten colon cancers; 4 ovarian; 3 lung; 3 prostate; 2 each of melanoma, larynx, liver, and lymphoma; 1 each of pancreas, gallbladder, testis, kidney, and thyroid; and 8 unspecified tumors.

chance as the explanation for the familial association of sarcoma with other cancers. Williams and Strong (15) showed by segregation analysis that 9 of 159 families of children with sarcoma had an autosomal dominant pattern of cancers. Cancer developed in one-half of these high-risk family members by age 30 years and in 90% by age 60. Other population-based studies of children with soft tissue and bone sarcomas (osteosarcoma and chondrosarcoma) have shown that their mothers have a 3-fold excess of breast cancer at young ages (13, 14). In addition, a follow-up study of our original 4 families (Families 1-4) from 1969 to 1981 has shown that 16 new cancers developed among family members when less than 1 case was expected (31). A similar follow-up of this series of 24 families should provide additional data on cancer risk in the syndrome.

The locus of the gene(s) for this inherited cancer syndrome is unknown. Cytogenetic analyses of somatic cells from affected family members have been unrevealing, and fresh sarcoma tissue from affected families are rarely available for study. However, cytogenetic studies of sporadic soft tissue sarcomas have shown nonrandom translocations that correlate with the histological subtype (32, 33). In addition, molecular studies have revealed loss of heterozygosity on the short arm of chromosome 11 in childhood rhabdomyosarcomas and homozygous deletions involving the locus of the retinoblastoma (*Rb-1*) gene on chromosome 13q14 among soft tissue sarcomas in several adults (34, 35). Loss of alleles in chromosomes 11p and 13q has also been found in breast cancers but has not been shown to be involved in the syndrome affecting our families (36, 37).

This cancer family syndrome is composed of at least 6 forms of cancer and differs from the majority of hereditary cancers which tend to be tissue-, histology-, and site-specific (38, 39). Knowledge of the biological basis of this unusual syndrome will enhance understanding of the pathogenesis of several childhood cancers and breast cancer, the commonest neoplasm among women in the United States and elsewhere. Progress depends in part on the availability for study of affected families and their tumor specimens. For these families and perhaps other kindreds with less conspicuous manifestations, identification of a predisposing gene(s) or other markers of susceptibility may be useful in early cancer detection, genetic counseling, and prenatal diagnosis.

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REFERENCES

- Li, F. P., and Fraumeni, J. F., Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? *Ann. Intern. Med.*, 71: 747-752, 1969.
- Pearson, A. D. J., Craft, A. W., Ratcliffe, J. M., Birch, J. M., Morris-Jones, P., and Roberts, D. F. Two families with the Li-Fraumeni cancer family syndrome. *J. Med. Genet.*, 19: 362-365, 1982.
- Epstein, L. I., Bixler, D., and Bennett, J. E. An incident of familial cancer. *Cancer (Phila.)*, 25: 889-891, 1970.
- Duncan, M. H., and Miller, R. W. Another family with the Li-Fraumeni cancer syndrome. *JAMA*, 249: 195, 1983.
- Meisner, L. F., Gilbert, E., Ris, H. W., and Haverly, G. Genetic mechanisms in cancer predisposition. Report of a cancer family. *Cancer (Phila.)*, 43: 679-689, 1979.
- Bottomly, R. H., Trainer, A. L., and Condit, P. T. Chromosome studies in a "cancer family." *Cancer (Phila.)*, 28: 519-528, 1971.
- Lynch, H. T., Mulcahy, G. M., Harris, R. E., Gurgis, H. A., and Lynch, J. F. Genetic and pathologic findings in a kindred with hereditary sarcoma, breast cancer, brain tumors, leukemia, lung, laryngeal, and adrenal cortical carcinoma. *Cancer (Phila.)*, 41: 2055-2064, 1978.
- Lynch, H. T., Krush, A. J., Harlan, W. L., and Sharp, E. A. Association of soft tissue sarcoma, leukemia, and brain tumors in families affected with breast cancer. *Am. Surg.*, 39: 199-206, 1973.
- Little, J. B., Nove, J., Dahlberg, W. K., Troilo, P., Nichols, W. W., and Strong, L. C. Normal cytotoxic response of skin fibroblasts from patients with Li-Fraumeni familial cancer syndrome to DNA-damaging agents *in vitro*. *Cancer Res.*, 47: 4229-4234, 1987.
- Miller, C. W., and McLaughlin, R. B. Osteosarcoma in siblings. Report of two cases. *J. Bone Joint Surg. A*, 59: 261-262, 1977.
- Lynch, H. T., and Gurgis, H. A. Childhood cancer and the SBLA syndrome. *Med. Hypotheses*, 5: 15-22, 1979.
- Smith, J. W., Ali, K., Caces, J. N., Coburn, T. P., Kumar, A. P. M., and Mauer, A. M. Familial cancer: the occurrence of bone cancer in male

- members of a family in multiple generations. *Clin. Res.*, 28: 869A, 1980.
13. Hartley, A. L., Birch, J. M., Marsden, H. B., and Harris, M. Breast cancer risk in mothers of children with osteosarcoma and chondrosarcoma. *Br. J. Cancer*, 54: 819-823, 1986.
  14. Birch, J. M., Hartley, A. L., Marsden, H. B., Harris, M., and Swindel, R. Excess risk of breast cancer in the mothers of children with soft tissue sarcomas. *Br. J. Cancer*, 49: 325-331, 1984.
  15. Williams, W. R., and Strong, L. C. Genetic epidemiology of soft tissue sarcomas children. In: H. R. Muller and W. Weber (eds.), *Familial Cancer, First International Research Conference*, pp. 151-153. Basel: S. Karger AG, 1985.
  16. Go, R. C. P., King, M.-C., Bailey-Wilson, J., Elston, R. C., and Lynch, H. T. Genetic epidemiology of breast cancer and associated cancers in high-risk families. I. Segregation analysis. *J. Natl. Cancer Inst.*, 71: 455-461, 1983.
  17. Greene, M. H., Goldin, L. R., Clark, W. H., Jr., Lovrien, E., Kraemer, K. H., Tucker, M. A., Elder, D. E., Fraser, M. C., and Rowe, S. Familial cutaneous malignant melanoma: autosomal dominant trait possibly linked to the *Rh* locus. *Proc. Natl. Acad. Sci. USA*, 80: 6071-6075, 1983.
  18. Fraumeni, J. F., Jr., Vogel, C. L., and Easton, J. M. Sarcomas and multiple polyposis in a kindred. *Arch. Intern. Med.*, 121: 57-61, 1968.
  19. Li, F. P., Tucker, M. A., and Fraumeni, J. F., Jr. Childhood cancer in sibs. *J. Pediatr.*, 88: 419-423, 1976.
  20. Blattner, W. A., McGuire, D. B., Mulvihill, J. J., Lampkin, B. C., Hananian, J., and Fraumeni, J. F., Jr. Genealogy of cancer in a family. *JAMA*, 241: 259-261, 1979.
  21. Mulvihill, J. J., Gralnick, H. R., Whang-Peng, J., and Leventhal, B. G. Multiple childhood osteosarcomas in an American Indian family with erythroid macrocytosis and skeletal anomalies. *Cancer (Phila.)*, 40: 3115-3122, 1977.
  22. Young, J. L., Perry, C. L., and Asire, A. J. (eds.). *Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-1977*. National Cancer Institute Monograph, Vol. 57, pp. 70-73. Washington, DC: United States Government Printing Office, 1977.
  23. Miller, R. W. Contrasting epidemiology of childhood osteosarcoma, Ewing's tumor and rhabdomyosarcoma. *Natl. Cancer Inst. Monogr.*, 56: 9-14, 1981.
  24. Boice, J. D., Jr., and Fraumeni, J. F., Jr. (eds.). *Radiation Carcinogenesis: Epidemiology and Biological Significance*. New York: Raven Press, 1984.
  25. Shimke, R. N., Lowman, J. T., and Cowan, G. A. B. Retinoblastoma and osteogenic sarcoma in siblings. *Cancer (Phila.)*, 34: 2077-2079, 1974.
  26. Usui, M., Ishi, S., Yamawaki, S., and Hirayama, T. The occurrence of soft tissue sarcomas in three siblings with Werner's syndrome. *Cancer (Phila.)*, 54: 2580-2586, 1984.
  27. Sorensen, S. A., Mulvihill, J. J., and Neilsen, A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. *N. Engl. J. Med.*, 314: 1010-1015, 1986.
  28. Hartley, A. L., Birch, J. M., Marsden, H. B., Reid, H., Harris, M., and Blair, V. Adrenal cortical tumors: epidemiological and familial aspects. *Arch. Dis. Child.*, 62: 683-689, 1987.
  29. Costanza, M. E., Li, F. P., Greene, H. L., and Patterson, W. B. Cancer prevention and detection. Strategy for the office practice. In: B. Cady (ed.), *Cancer Manual. A Manual for Practitioners*, Ed. 6, pp. 1-21. Boston: American Cancer Society, 1982.
  30. Young, J. L., Ries, L. G., Silverberg, E., Horm, J. W., and Miller, R. W. Cancer incidence, survival, and mortality for children younger than age 15 years. *Cancer (Phila.)*, 58: 598-602, 1986.
  31. Li, F. P., and Fraumeni, J. F., Jr. Prospective study of a family cancer syndrome. *JAMA*, 247: 2692-2694, 1982.
  32. Van Den Berghe, H. Chromosome anomalies in solid tumors and their significance. *Cancer Genet. Cytogenet.*, 28: 49-54, 1987.
  33. Turc-Carel, C., Dal Cin, P., Limon, J., Rao, U., Li, F. P., Corson, J. M., Zimmerman, R., Parry, D. M., Cowan, J. M., and Sandberg, A. A. Involvement of chromosome X in primary cytogenetic change in human neoplasia: nonrandom translocation in synovial sarcoma. *Proc. Natl. Acad. Sci. USA*, 84: 1981-1985, 1987.
  34. Koufos, A., Hansen, M. F., Copeland, N. G., Jenkins, N. A., Lampkin, B. C., and Cavenee, W. K. Loss of heterozygosity in three embryonal tumours suggests a common pathogenic mechanism. *Nature (Lond.)*, 316: 330-334, 1985.
  35. Friend, S. H., Horowitz, J. M., Gerber, M. R., Wang, X. F., Bogeman, E., Li, F. P., and Weinberg, R. A. Deletions of a DNA sequence in retinoblastomas and mesenchymal tumors: organization of the sequence and its encoded protein. *Proc. Natl. Acad. Sci. USA*, 84: 9059-9063, 1987.
  36. Lundberg, C., Skoog, L., Cavenee, W. K., and Nordenskjold, M. Loss of heterozygosity in human ductal breast tumors indicates a recessive mutation on chromosome 13. *Proc. Natl. Acad. Sci. USA*, 84: 2372-2376, 1987.
  37. Ali, I. U., Lidereau, R., Theillet, C., and Callahan, R. Reduction to homozygosity of genes on chromosome 11 in human breast neoplasia. *Science (Wash. DC)*, 238: 185-188, 1987.
  38. Knudson, A. G., Jr. Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res.*, 45: 1437-1443, 1985.
  39. Knudson, A. G., Jr. Retinoblastoma: a prototypic hereditary neoplasm. *Semin. Oncol.*, 5: 57-60, 1978.