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Follow-up Study of Twenty-four Families with Li-Fraumeni Syndrome

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ABSTRACT

The Li-Fraumeni cancer family syndrome is manifested by susceptibility to breast cancer, sarcomas, and other neoplasms in children and young adults. The present study utilized clinical follow-up data on 545 members of 24 Li-Fraumeni kindreds living and cancer-free at family ascertainment. Two hypotheses were tested based on a model of autosomal dominant genetic predisposition: (*a*) that syndrome cancers would continue to occur excessively during follow-up compared to the general population, and (*b*) that the tumors would occur primarily among those family members likely to carry the gene. Population cancer rates were compared with cancer rates in follow-up of the cohort from ascertainment to 1988. Risk of carrying the gene for the syndrome at the time of ascertainment was calculated for each family member under two models with somewhat different definitions of affection with the syndrome. Cancer occurrence after ascertainment was then analyzed according to the risks. Cancer did continue to occur excessively among the entire cohort during follow-up [relative risk (RR 2.1)]. The excess was greatest below age 20 (RR 21.1), declined with increasing age, and was most pronounced for neoplasms featured in the syndrome (RR 18.2). Among persons less than age 45, at least 87% of cancers occurred in those at higher risk of carrying the gene under both genetic models (RR 22.9 and 21.3). The clinical data, therefore, reliably identify individuals likely to carry a dominantly inherited gene conferring susceptibility to a specific constellation of neoplasms. Recent identification of a germ line mutation in the tumor suppressor gene *p53* in persons with the syndrome may, if confirmed, have implications for ultimately defining the component tumors of the syndrome and for the causes and prevention of those tumors arising outside these families.

INTRODUCTION

A familial cancer syndrome was initially recognized in 4 families with an autosomal dominant pattern of soft tissue sarcoma, breast cancer, and other neoplasms in young relatives (1). The disorder has been called the Li-Fraumeni syndrome or SBLA syndrome, which refers to several of the component tumors (1–3). Subsequent analyses of more than 50 affected families have expanded the tumor phenotypes to include osteosarcoma, brain tumors, leukemia, and adrenocortical carcinoma, and perhaps other cancers (2–9). The neoplasms in the syndrome tend to arise in children and young adults, often as multiple primary tumors. Epidemiological surveys have revealed an excess of breast cancer in the mothers of patients with childhood soft tissue sarcoma, osteosarcoma, and chondrosarcoma (10, 11). In addition, segregation analysis of several families of children with soft tissue sarcoma identified an autosomal dominant pattern of the diverse cancers featured in the Li-Fraumeni syndrome (12). Selection bias, referral bias, and small sample size have been issues in some of these studies.

In the present study, we report the results of follow-up observations on a series of 24 families previously diagnosed as having the Li-Fraumeni syndrome. This study is limited to blood relatives who were unaffected at the time of initial enumeration of family members. The restriction allows calculation of expected frequencies of cancers during follow-up of the cohort, and reduces the problem of selection bias. In addition, the probability of being a gene carrier was calculated for each family member based on two autosomal dominant inheritance models. Cancer occurrence during follow-up was analyzed for the data according to probability categories. The results under both models show an excess of the cancers featured in the syndrome among children and young adults likely to carry the gene.

SUBJECTS AND METHODS

The 24 kindreds with characteristics of the Li-Fraumeni syndrome were enrolled in the Cancer Family Registry of the Epidemiology and Biostatistics Program, National Cancer Institute, between 1968 and 1986 (1, 2). A descriptive report of cancers in the 24 pedigrees and the follow-up experience of 4 of these kindreds to 1981 have been previously published (2, 13). The proband of each family had a sarcoma before 45 years of age, and at least one first degree relative and one second degree relative with cancer before age 45 years or a sarcoma at any age.

Pedigrees were constructed at ascertainment of each family. A total of 842 blood relatives were enumerated within the affected lines. We reviewed the recorded demographic and medical data for each of them, and sought to update this information through 1988 by telephone interviews with family members. Demographic and follow-up data were available for 773 persons (92%) identified on the pedigrees. Among them, 190 had died and 38 others had developed cancer before their families were ascertained. The remaining 545 family members had no history of cancer prior to ascertainment of their kindreds and could therefore be followed for disease development. Reports of cancers in family members were confirmed by using medical charts or pathology records, death certificates, or pathology specimens. Six cancers in follow-up which could not be confirmed were excluded from analysis. Diagnosis of multiple primary neoplasms required documentation of each tumor.

We postulated an autosomal dominantly inherited susceptibility to certain cancers in the families, and used the 545 previously unaffected relatives to test resultant hypotheses. The predictions were (*a*) that the neoplasms featured in the syndrome would continue to occur excessively during follow-up observation, and (*b*) that these tumors would tend to occur among those relatives who, by their positions in the pedigrees, were probable carriers of the gene for the syndrome.

The first prediction was examined by comparing observed numbers of cancers diagnosed during follow-up with the numbers expected based on sex-, age-, and calendar year-specific incidence rates by site from the Connecticut Tumor Registry (14). These rates were applied to the appropriate person-years at risk in the study population (15). Family members contributed person-years of risk from the time of ascertainment of their family until 1988 or until the development of a malignant tumor, death, or loss to follow-up, if sooner. Second cancers in these patients did not contribute to this analysis. Ratios of observed to expected cancers, expressed as RR,[2] were calculated for all cancers and specific sites of cancer in the total study population and subgroups by age, sex, and gene carrier probability. The relative risks and associated

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[2] The abbreviations used are: RR, relative risk; CI, confidence interval.

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95% confidence intervals were calculated by assuming an underlying Poisson distribution (16). Nonmelanomatous skin cancers and *in situ* cancers of the uterine cervix and breast were excluded from analysis because their rates are not included in the comparison data from the Connecticut Tumor Registry.

Testing of the second prediction (tumors would occur excessively during follow-up among family members at higher risk of carrying the gene for the syndrome) required identification of family members who were affected before the start of the follow-up period. "Affected" is used in the genetic sense, to signify cancer development attributable to carrying the gene for the cancer syndrome. Members considered affected had developed a cancer specified in the syndrome definition before ascertainment of the family and were assigned a probability of carrying the gene of 1.0. Obligate carriers were estimated to have a probability of carrying the gene near 1.0. Assuming a dominantly inherited susceptibility gene, siblings and offspring of affected family members were considered to have a 0.50 probability at birth; lower probabilities were calculated for more distant relatives. For those with probabilities 0.50 or less at birth, the risk of being a gene carrier then declined gradually for each cancer-free year of life until the start of follow-up. That is, as an individual aged without developing a cancer, the probability that he carried the gene decreased. The slope of the decline in risk was determined based on age-specific penetrance as specified in the models. The 545 members alive and unaffected at ascertainment were stratified by risk of carrying the gene at year of ascertainment. The observed number of cancers in each stratum was compared with the corresponding expected number for the years between initial ascertainment and close of follow-up in 1988. Risk estimates were not continually modified during the follow-up period.

The models used to calculate gene carrier status required specification of several parameters, including mode of inheritance, disease gene frequency in the population, gene penetrances, and definition of affection with the syndrome. The inheritance function was specified as autosomal dominant in accordance with results of a segregation analysis of the syndrome (12). A disease gene frequency of 0.0001 was selected to reflect the low frequency of disease in the general population. Uncertainty about the values of the other parameters led to the development of two genetic models. Both used age-specific penetrances which were the same for both sexes.

The more restrictive model is based on our observations of candidate families with the syndrome (2). In this model, the only cancers attributed to the influence of the gene were breast cancer, brain tumors, leukemia, or adrenocortical carcinoma diagnosed before age 45 years, sarcoma at any age, and multiple primary tumors at any age. A minimum penetrance of 15% at age 5 was selected and allowed to rise linearly to a maximum of 90% reached at age 45. After age 45, all cancers other than sarcoma were assigned to other causes. Under a more inclusive model, the spectrum of the syndrome was expanded to include: (*a*) the cancers used in the restrictive model and possible component cancers (melanoma, prostate, lung, larynx, and pancreas) diagnosed at any age, and (*b*) all other cancers diagnosed before age 45 years (3, 12). For this model, the minimum penetrance was also set at 15% at age 5, but the maximum penetrance of 90% was not reached until age 60. A low frequency of sporadic cancer cases was also incorporated after age 45, rising linearly to 10% for ages 60 and above. Relative to the restrictive model, the more inclusive model may overestimate the number of cancers attributable to the gene, if certain component cancers are improperly included in the definition. However, analyses showed that the actual differences are small. Only results based on the more conservative model, the restrictive model, are presented in detail.

The computer program LIPED (17), modified to allow for variable age at diagnosis (18), was used to calculate genetic risks for all unaffected cohort members. To calculate the genotype probability under each model for an individual, given all the family data, three likelihood computations were conducted and the results were combined as follows. Assume the disease locus has two alleles D and d, where D is the disease allele and d is the normal allele. Then, for each unaffected individual, the three genotype risks for D/D, D/d, and d/d are computed. The risk of an individual being a gene carrier for the disease allele D is given by

$$\frac{L(DD) + L(Dd)}{L(DD) + L(Dd) + L(dd)}$$

where L(DD), L(Dd), and L(dd) denote the likelihoods for the genotypes DD, Dd, dd, respectively (19, 20).

Analyses were performed of cancer occurrence during follow-up by genetic risk group. Family members were categorized by the probability of being a gene carrier into 5 strata (0.00–0.09, 0.10–0.24, 0.25–0.34, 0.35–0.49, 0.50–1.00) in each of the 2 models. In both models, the majority of the cohort were in the lowest probability group (0.00–0.09) because members of the extended families were studied, and previously affected carriers were excluded from the analysis. Small numbers and the absence of significant differences among the four higher-risk groups for each model led to consideration of these groups as a single category with probability 0.10–1.00 (Wilcoxon test for ordered alternatives) (21).

RESULTS

The 545 family members who were alive and free of cancer at ascertainment have been followed for 2 to 20 years (total person-years, 7606; median follow-up, 14.1 years). The excess cancer occurrence during follow-up was greatest among younger members of the study population and showed a progressive decrease with age (Table 1). Relative risk of cancer was 21.1 at ages 0–19 years, 6.2 in the 20–44 year age group, and 2.4 for those 45–59 years. Each of these differences is significant at $P < 0.05$. The absence of excess cancer occurrence among persons age 60 or older during the follow-up period influenced the overall relative risk for the cohort, which was 2.1 (95% CI, 1.6 to 2.8). Test for trend in relative risk is significant at $P < 0.001$. There was no significant difference in the age pattern of cancer occurrence for male *versus* female family members with the exception of breast cancer in women aged 20–44 years (10 observed, 0.6 expected, RR 18.1; 95% CI, 8.6 to 33.2). No male member of our pedigrees has developed breast cancer.

Neoplasms previously defined as components of the syndrome (breast cancer, brain tumors, adrenocortical carcinomas, and leukemia before age 45, and osteosarcomas and soft tissue sarcomas at any age) were also analyzed separately. These tumors comprised 20 of the 52 neoplasms occurring among the entire cohort during follow-up (1.10 expected, RR 18.2; 95% CI, 11.1 to 28.1) (Table 2). The excess was significant for each component tumor, although numbers are small. These 20 tumors occurred before age 45 and account for nearly the entire cancer excess in that age interval (RR 20.3; 95% CI, 12.4 to 31.4). The three other tumors before age 45 were one each laryngeal carcinoma, ovarian germ cell neoplasm, and Wilms' tumor. After age 45, relative risks were not significantly increased.

Table 3 shows the cancer occurrence in follow-up by estimate of the risk of carrying the gene for the syndrome under both models. For persons below age 45, with the restrictive model,

Table 1 *Observed and expected numbers of cancers during follow-up, by age at diagnosis*

Age (yr)	Persons at risk[a]	No. of cancers		
		Observed	Expected	RR (95% CI)
0–19	249	6	0.3	21.1 (7.7–46.0)
20–44	375	17	2.8	6.2 (3.6–9.9)
45–59	154	14	5.8	2.4 (1.3–4.1)
60+	101	15	15.7	1.0 (0.5–1.6)
All ages	545	52	24.5	2.1 (1.6–2.8)

[a] Number of persons contributing person-years of observation within the age category. During the follow-up period, some persons contribute to more than one age category. Therefore, the numbers do not sum to 545.

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Table 2 *Observed and expected numbers of cancers diagnosed during follow-up, ages 0 to 44 and >45, by tumor type*

Tumor	No. of cancers					
	Age < 45 yr		Age > 45 yr		Total	
	Observed/expected	RR (95% CI)	Observed/expected	RR (95% CI)	Observed/expected	RR (95% CI)
Component tumor types[a]	*20/0.99*	20.3 (12.4–31.4)	8/3.73	2.1 (0.9–4.2)	28/4.71	5.9 (3.9–8.6)
Sarcomas	*3/0.11*	27.8[b]	*0/0.12*	0.0	3/0.22	13.4[b]
Breast	*10/0.56*	17.9[b]	5/2.81	1.8	15/3.37	4.5[b]
Central nervous system	*4/0.16*	25.5[b]	1/0.28	3.6	5/0.43	11.5[b]
Leukemia	*2/0.15*	13.1[b]	2/0.52	3.9	4/0.67	6.0[b]
Adrenal cortex	*1/0.01*	111.1[b]	0/0.01	0.0	1/0.02	45.5[b]
Other tumors	3/2.06[c]	1.5 (0.3–4.4)	21/17.76	1.2 (0.7–1.8)	24/19.81	1.2 (0.8–1.8)
Total	23/3.04	7.6 (4.8–11.4)	29/21.49	1.3 (0.9–1.9)	52/24.53	2.1 (1.6–2.8)

[a] Tumors in the syndrome defined by site and age under the restrictive model are *italicized*. Sarcomas are included at any age, while the 4 other tumor types must be diagnosed before age 45 years.
[b] 95% confidence interval does not include 1.0; $P < 0.05$.
[c] Laryngeal carcinoma, ovarian germ cell neoplasm, and Wilms' tumor (1 each).

Table 3 *Observed and expected numbers of cancers in follow-up, age 0–44 and >45, by carrier probability under restrictive and inclusive models*[a]

Gene carrier probability	Persons at risk[b]		No. of cancers					
			Age < 45 yr			Age > 45 yr		
	<45	>45	Observed	Expected	RR (95% CI)	Observed	Expected	RR (95% CI)
Restrictive model								
0.00–0.09	296	176	3	2.2	1.4 (0.3–4.1)	23	19.5	1.2 (0.8–1.8)
0.10–1.00	139	31	20	0.9	22.9 (14.0–35.4)	6	2.0	3.0 (1.1–6.6)
Inclusive model								
0.00–0.09	266	148	2	2.1	1.0 (0.1–3.5)	16	15.8	1.0 (0.6–1.7)
0.10–1.00	169	59	21	1.0	21.3 (13.2–32.6)	13	5.7	2.3 (1.2–3.9)

[a] See text for descriptions of the models.
[b] Number of persons contributing person-years of observation within the category. During the period of follow-up, some persons contribute to both age categories. Therefore, the numbers do not sum to 545.

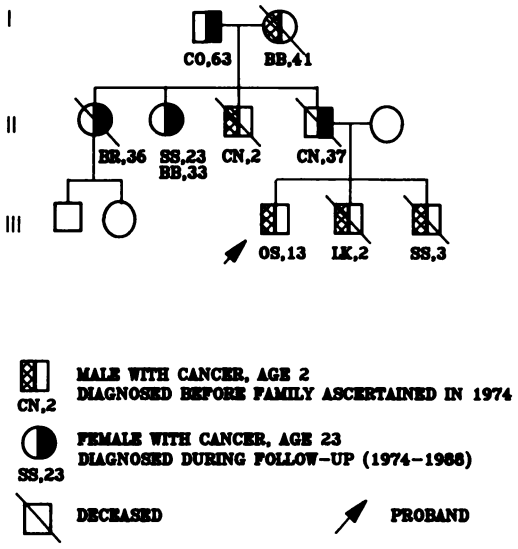

Fig. 1. A portion of the pedigree of a family. Symbols for the cancer types are: *BB*, bilateral breast cancer; *BR*, unilateral breast; *CN*, central nervous system tumor; *CO*, colon carcinoma; *LK*, leukemia; *OS*, osteosarcoma; *SS*, soft tissue sarcoma. Probabilities at ascertainment of carrying the gene: II-1, $P = 0.27$; II-2, $P = 0.35$; II-4, $P = 1.00$.

20 of the 23 tumors (87%) occurred among the group with greater probability of carrying the gene (0.9 expected, RR 22.9; 95% CI, 14.0 to 35.4). Eighteen of the 20 were component neoplasms. No significant excess was present for the group with a carrier probability below 10%. The small excess cancer occurrence in persons older than 45 years was also limited to those more likely to be gene carriers (RR 3.0; 95% CI, 1.1 to 6.6). Data analysis performed with the second, more inclusive model, yielded similar results. This model shifted some study subjects from low to high probability of being a carrier. However, expected frequencies of cancer among probable carriers increased correspondingly, leaving the relative risks essentially unchanged.

The follow-up data are illustrated by the very severely affected pedigree shown in Fig. 1. Five relatives (marked with *cross-hatches*) were affected at the time of ascertainment of the family in 1974 (22). The proband had osteosarcoma diagnosed at age 13 and close relatives had sarcoma, leukemia, brain tumor, and breast cancer at very young ages. The probabilities of carrying the gene for the unaffected family members (see Fig. 1 legend) were calculated under the restrictive model. The proband's father (*II-4*) was estimated to be an obligate carrier (gene carrier probability near 1.0) because of having an affected parent, sibling, and offspring when the family was identified. His two unaffected sisters, *II-1* and *II-2*, were ages 27 and 21 years, respectively, at ascertainment. They were calculated to have gene carrier probabilities at ascertainment that had decreased from approximately 0.5 at their births to 0.27 and 0.35, respectively. Tumors occurred during the follow-up period (*solid symbols*) in these 3 previously unaffected family members: brain tumor at age 37 in the father, breast cancer at 36 in one sister, and sarcoma at 23 and bilateral breast cancer by 33 in the other sister. The first cancers in these 3 relatives contributed to the analysis as component tumors in probable gene carriers. Individual *I-1* is presumed to be outside the affected blood line.

DISCUSSION

Interpretation of the original description of the Li-Fraumeni syndrome in four kindreds and subsequent reports of affected families has been obscured by a potential ascertainment bias. Because dramatically affected kindreds are most likely to come

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to the attention of investigators, the possibility of chance association of cancers in rare families could not be excluded. In addition, the prevalence of the syndrome in the population cannot be estimated. Uncertainties remain in defining the spectrum of cancers in the syndrome and the penetrance of the predisposing gene.

To minimize selection bias, this study of 24 families was limited to an evaluation of cancers that occurred on follow-up of all relatives who were unaffected at the time the syndrome was recognized in the kindred. Family members who were not individually identified in the original pedigree were excluded from the cohort analysis. This restriction prevents overestimation of the cancer risk by selective reporting of relatives who developed cancer during follow-up. Our findings revealed continued expression of the dominantly inherited syndrome among young family members, with excesses confined to the 6 previously described tumor types: breast carcinomas, soft tissue and osteosarcomas, leukemia, brain tumors, and adrenocortical carcinomas. Furthermore, the tumors aggregated in those with higher probabilities of carrying the gene under two genetic models.

This study has limitations that might introduce errors in the estimations of risk. Overestimation of cancer risk might have resulted from exclusion of the 69 persons who were lost to follow-up, errors in the genetic model, and small numbers. Firstly, assuming no cancers occurred among the persons lost during follow-up, cancer occurrence in the entire cohort would remain in significant excess. Secondly, two genetic models with different definitions of affection were used to calculate carrier probabilities. However, stratified analyses using these different probabilities yielded virtually identical results. The parameters specified for the two models, including autosomal dominant transmission, gene frequency, and penetrance functions, were based on data from prior analyses of the syndrome (2, 10, 12). These assumptions could not be formally tested in our analysis. Finally, the number of persons with higher probabilities of carrying the gene was relatively small. This necessitated aggregation of the higher probability categories, and loss of precise information on individual risk groups. In aggregate, the numbers suffice to show that specific cancers developed much more frequently in probable gene carriers than in noncarriers. Underestimation of the true risk might have occurred due to exclusion of the six unconfirmed cancers that occurred during the follow-up period.

This study shows that previously recognized features of the Li-Fraumeni syndrome have continued to arise excessively in affected families, but fails to implicate any additional tumors as syndrome components. A clearer definition of the syndrome will emerge when the defective gene is identified. Recently, we have detected germ line mutations of the tumor suppressor gene, *p53*, in several affected families (23). If confirmed, the observation will allow accurate identification of gene carriers among living members and future generations of these kindreds, as well as families less severely affected with the syndrome. It may also find more general application in the detection of carriers of a new germ line *p53* mutation among patients with a component tumor of the Li-Fraumeni syndrome, but no family history of cancer. On the other hand, not all cancers among gene carriers may be due to the mutant *p53* gene. To distinguish these chance events from additional components of the syndrome, continued follow-up observation for cancer development in affected kindreds will be required.

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